Sub-Lingual Immunotherapy

World Allergy Organization Position Paper 2009

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European Academy of Allergy and Clinical Immunology (EAACI).
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Australasian Society of Clinical Immunology and Allergy.
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International Primary Care Respiratory Group (IPCRG).
Global Allergy and Asthma European Network (GA^2LEN).
National Institutes of Health (NIH).

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Colombian Allergy, Asthma, and Immunology Association.
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Indian College of Allergy, Asthma and Applied Immunology.
Mongolian Society of Allergology.
Norwegian Society of Allergology and Immunopathology.
Peruvian Society of Allergy and Immunology.
Russian Association of Allergology and Clinical Immunology.
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PREFACE

Sublingual immunotherapy (SLIT) has gained wide acceptance in many European countries and has raised the level of interest in immunotherapy among practicing allergists and primary care physicians. Large pivotal double-blind, placebo-controlled, randomized clinical trials have confirmed the efficacy and safety of SLIT, although some negative trials have also been published. In 2008, the World Allergy Organization (WAO) Board of Directors decided that it was important and timely to advise our global constituents on the current State of the Art on SLIT, to offer consensus on its use based on currently available evidence and expert opinion, and to develop practice parameters. Unmet needs would be identified by analysis of recent and ongoing SLIT clinical trials, then recommendations for further studies needed, and suggestions for the appropriate methodology to conduct them, would be offered.

To ensure a truly global consensus on SLIT, a meeting was held on 22–23 January 2009 in Paris, France. WAO invited its Regional, National, and Affiliate Member Societies to participate actively by sending representatives to the meeting. Non-Governmental Organizations working in the field of allergy were also invited to attend and Allergic Rhinitis and its Impact on Asthma (ARIA), European Federation of Allergy and Airway Diseases Patients Association (EFA), International Primary Care Respiratory Group (IPCRG), International Association of Asthmology (Interasma), Global Allergy and Asthma European Network (GA^2LEN), et al were represented.

The meeting and its outcomes remain totally independent from the interest/influence/funding of the pharmaceutical or the allergen extract/vaccine industry.

Abbreviations:

AAAAI:	American Academy of Allergy and Clinical Immunology
ACAAI:	American College of Allergy and Clinical Immunology
ADR:	Adverse Drug Reaction
AE:	Adverse Event
AMP:	Adenosine Monophosphate
ARIA:	Allergic Rhinitis and its Impact on Asthma
AUC:	Area under Curve
BHR:	Bronchial Hyperresponsiveness
CHMP:	Committee for Human Medicinal Products
CIS:	Commonwealth of Independent States
CMD:	Cumulative Monthly Dose
CONSORT:	Consolidated Standards of Reporting Trials
DBPCFC:	Double-blind placebo-controlled food challenge
DBPC-RCT:	Double-blind, placebo-controlled–randomised clinical trial
EAACI:	European Academy of Allergy and Clinical Immunology
EBM:	Evidence-based Medicine
ECP:	Eosinophil Cationic Protein
EFA:	European Federation of Allergy and Airway Diseases Patients Association
EMEA:	European Medicines Agency
EU:	European Union
FDA:	(US) Food and Drug Administration
FeNO:	Fraction of exhaled Nitric Oxide
FEV_1:	Forced Expiratory Volume in One Second
FVC:	Forced Vital Capacity
GA^2LEN:	Global Allergy and Asthma European Network
GP:	General Practitioner
GRADE:	Grading Recommendations, Assessment, Development and Evidence
HCP:	Health Care Professional
HDM:	House Dust Mite
ICAM-1:	Intercellular Adhesion Molecule-1
ICER:	Incremental Cost-Effectiveness Ratio
IDO:	Indoleamine 2,3-dioxygenase
Ig:	Immunoglobulin
IL:	Interleukin
Interasma:	International Association of Asthmology
IPCRG:	International Primary Care Respiratory Group
IT:	Immunotherapy
LLR:	Large Local Reactions
MedDRA:	Medical Dictionary for Regulatory Activities
MHC:	Major Histocompatibility Complex
mRNA:	Messenger Ribonucleic Acid
NIH:	National Institutes of Health
PAT:	Preventive Allergy Treatment (study)
PEF:	Peak Expiratory Flow
QoL:	Quality of Life
RCT:	Randomized Controlled Trial
RQLQ:	Rhinoconjunctivitis Quality of Life Questionnaire
SAE:	Serious Adverse Event
SCIT:	Subcutaneous Immunotherapy
SCORAD:	Score in Atopic Dermatitis
SCUAD:	Severe Chronic Upper Airway Disease
sECP:	Serum Eosinophil Cationic Protein
SIT:	(allergen-) Specific Immunotherapy

(*Continued*)

Abbreviations: Continued

SLIT:	Sublingual Immunotherapy
SMD:	Standardized Mean Differences
SPT:	Skin Prick Test
SR:	Systemic Reaction
T regs:	Regulatory T Cells
TGF:	Transforming Growth Factor
Th:	T Helper Cells
VAS:	Visual Analogue Scale
WAO:	World Allergy Organization
WHO:	World Health Organization

REGULATORY PERSPECTIVE

Historical Perspective

Before the 1980s there was no allergen standardization; this resulted in marked variations in allergenic strength among allergen vaccine batches produced in different phases.

Until 1991 allergen vaccines were considered "Galenic" drugs, because they were prepared upon request of the physician for a specific patient. Specific immunotherapy was administered through the injective route only, and the available allergen preparations were used both in diagnosis and therapy. Most firms produced batches of ready-to-prepare extracts and the final phase of production consisted of matching the name of a patient with a specific pre-prepared vaccine. Leading up to 1991, the companies active in the allergen manufacturing sector noticed that physicians had changed their prescribing patterns, and were now requesting single specific allergens for immunotherapy, rather than the allergen mixtures that had previously been supplied.

In the 1990s, when sublingual immunotherapy first appeared on the market, the available vaccines for SLIT were only single allergen preparations, as required by the first guideline in this field. It immediately became evident to the regulatory authorities that documents pertaining to the production of allergens and their standardization method were needed; it is important not only to prepare extracts that are always equivalent between different batches, but also to prepare an initial reference extract (the standard extract) that is allergenically/biologically active, to provide a comparison with subsequent production batches.

Current Situation

According to Guideline 2001/83/EC, allergens are immunologic medicinal products and therefore, in general, require a marketing authorization. However, in several countries national regulations are implemented that still allow marketing of allergen products as "named patient preparations" (NPPs) without a marketing authorization. For example, in Germany it has been estimated that approximately 50% of the market for allergen products are NPPs. This market segment includes the majority of allergen products for SLIT.

From the regulatory point of view, there is no difference between allergen products for SLIT and SCIT. By contrast a clear difference exists between the requirements on natural allergen extracts versus recombinant allergens, in particular regarding acceptance criteria for product quality.[1–3] In Germany, 4 products for SLIT were authorized up to mid-2009, whereas more than 200 allergen products for SCIT had a marketing authorization. Of the SLIT products, one grass pollen allergen tablet successfully passed a mutual recognition procedure and is available in the majority of European Union (EU) countries.

Recent Phase III clinical trials performed with 2 grass pollen tablets involved hundreds of patients in each

Why Sublingual Immunotherapy Vaccines Should Be Licensed

For the Physician

- The prescription of nonauthorized products weakens the role of the allergy specialist, and may have contributed to the current paucity of allergy specialists available to treat the estimated figure of 20% of the world population that suffers from allergies.
- The prescription of products not sold in pharmacies creates difficulties for the global management of vaccines (from the point of ordering, up to receipt and storage).

For the Patient

- The use of products that are not distributed in pharmacies weakens the credibility of the product itself; it precludes any patient interaction with the pharmacist (a traditional counselor of patients) and weakens the image of the product, which has to be used for years.
- An authorized pharmaceutical product offers the patient more guarantees, consequently increasing compliance with treatment (at present only 30% of vaccinated patients complete at least 3 years of treatment in accordance with the recommended guidelines for duration of therapy).

For the Industry

- A nonregulated sector makes possible the use of "low quality" products, and fails to give adequate recognition to the ethical manufacturers who conduct scientific research and employ good manufacturing practices. A more regulated sector attracts the increasing interest of ethical and qualified investors.

For the Regulatory Agencies

- Marketing of nonregulated products precludes correct pharmacovigilance and, in consequence, precludes all the activities connected with an open and transparent dialogue among the stakeholders, eg, pre- and post-registration clinical trials, professional training, and congress activities.

trial and were performed according to an adequate double-blind, placebo-controlled–randomized clinical trial (DBPC-RCT) design. These studies and others showed that particularly for SLIT, parameters such as determination of an adequate pretreatment period in seasonal rhinoconjunctivitis trials, and exploratory studies for determination of the dose resulting in the most favorable risk:benefit ratio, are of major importance. A recent WAO statement[4] and the European Medicines Agency (EMEA) Guideline[5] define for the first time the regulatory requirements for clinical trials in SIT, and will lead to improved harmonization of assessments by regulatory agencies of data obtained from clinical trials.

Increased availability of authorized allergen products with proven quality, safety and efficacy will lead to an improved benefit for allergic patients and may also improve the general acceptance of SIT as an established treatment by regulatory agencies.

Sublingual vaccines seem to have heralded a new era in specific allergen desensitization; because of their efficacy and safety, they have been considered eligible for submission for registration by many regulatory authorities. New products registered for respiratory allergopathologies approach this pathology in an etiologic way; they may act as real biologic modifiers, and have long-lasting effects. This benefit is interesting not only clinically, but also in terms of their pharmacoeconomic profile.

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CHAPTERS

CHAPTER 1: INTRODUCTION AND HISTORICAL BACKGROUND TO SUBLINGUAL IMMUNOTHERAPY

- Subcutaneous immunotherapy (SCIT) currently represents the standard immunotherapy modality, with well ascertained clinical efficacy.
- The first SLIT randomized DBPC-RCT was published in 1986. The rationale proposed for SLIT was to improve the safety and to make the treatment more convenient.
- The first DBPC-RCT trial with tablets was published in 1986.
- SLIT was firstly accepted as a viable alternative to SCIT in the World Health Organization (WHO) position paper, published in 1998, and then included in the ARIA guidelines.
- Since 1986, 60 DBPC-RCT trials have been published.
- The available meta-analyses are in favor of SLIT (rhinitis in adults, asthma, and rhinitis in children), although the conclusions are limited by the great heterogeneity of the studies.
- Adequately powered, well-designed DBPC-RCTs involving hundreds of patients, published in the last 3 years have clearly confirmed the efficacy and the dose-dependent effect of SLIT for grass allergens in both adults and children.

Allergen-specific immunotherapy (SIT), or allergen vaccination is the practice of administering to allergic subjects increasing amounts of allergen(s) (the allergenic extract or vaccine) to achieve hyposensitization, that is to reduce the symptoms occurring during the natural exposure to the allergen(s) itself. The history of SIT began in the first years of the twentieth century, based on the idea of the vaccination against infectious agents. In fact, Leonard Noon[1] aimed at achieving a vaccination against "airborne toxins," and for this reason he chose the subcutaneous route of administration. Although the theoretical background was incorrect, SIT was immediately found to be effective in reducing symptoms of hay-fever, its use spread rapidly, and the subcutaneous route (SCIT) remained therefore the standard practice.

Indeed, the idea of administering the allergenic extracts via noninjection routes is not as recent as commonly believed. The first descriptions of the "oral" route of administration also appeared in the early 1900s[2] and the first clinical attempts with this administration were carried out only a few years later.[3,4] Subsequently, other routes of administration

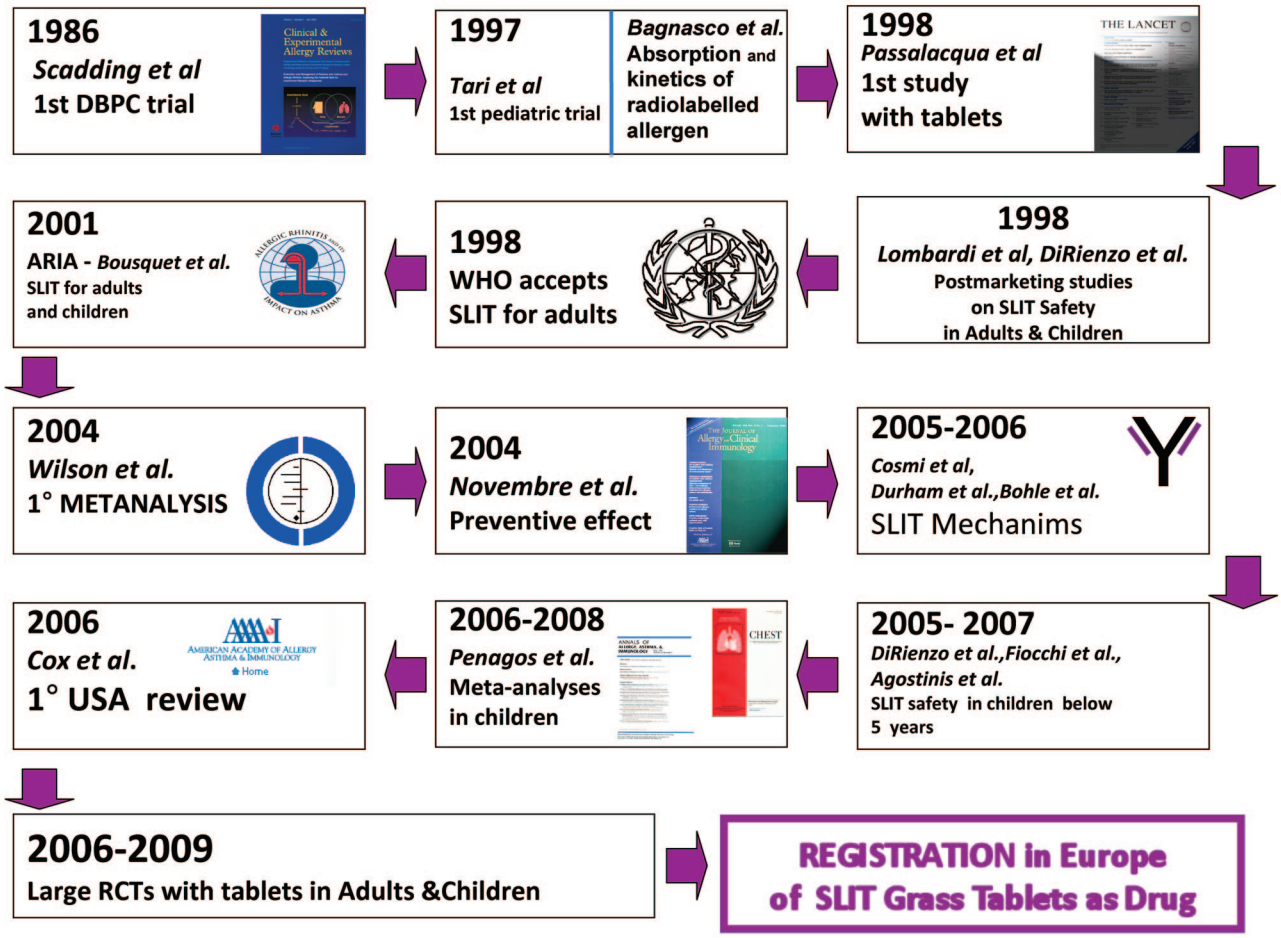
were proposed, that is, local bronchial during the 1950s[5,6] and local nasal[7,8] during the 1970s. The overall rationale of these attempts was of course that of finding a safer and more convenient route of administration for SIT. Those routes have been variously named, that is, *alternative*, *nonparenteral*, *noninjection*, or *local* routes. Presently, it is agreed that the most proper terms are *local* and *noninjection*, which are equivalent; whereas the word *alternative* has been abandoned because it might generate confusion with other unconventional medicines. The oral route was investigated in several clinical trials performed during the 1980s,[9–12] but the clinical results were controversial and, in some cases, important gastrointestinal adverse events were reported. For these reasons, oral administration was gradually abandoned. In 1986, the British Committee for the Safety of Medicines[13] reported several deaths caused by SCIT, and raised serious concerns about the safety and the risk/benefit ratio of SIT, also because cheaper and effective drugs (eg, oral H1-antihistamines and topical corticosteroids) had become available for the treatment of respiratory allergy. In this scenario, the interest in noninjection routes of immunotherapy (IT) increased again,[14] and in 1986 the first randomized controlled trial with the sublingual route (SLIT) was published.[15] This study was conducted with very low doses of a mite extract. The original idea supporting SLIT was to achieve a prompt absorption of the vaccine through the sublingual mucosa as happens, for instance with nitroglycerine or nifedipine. Indeed, 10 years later, biodistribution studies with radiolabeled allergens in humans,[16,17] consistently showed that the direct absorption of the extract through the oral mucosa is absent or negligible, and that the clinical effect should be rather ascribed to the interaction of the allergen with the mucosal immune system. Nonetheless, from a clinical point of view, SLIT was confirmed to be effective in several controlled studies utilizing either drops or tablets,[18,19] and the first pediatric study appeared in 1990.[18]

In the subsequent years, the number of DBPC-RCTs of SLIT rapidly increased, and SLIT began to be mentioned in official documents. In 1993 the European Academy of Allergy and Clinical Immunology (EAACI) stated in its position paper that SLIT could be regarded as a "promising route" for desensitization.[14] Five years later, the WHO, based on the results of 8 DBPC-RCTs, stated that SLIT "may be considered as a viable alternative to the injection route in adults."[20] In the same year, EAACI produced a position paper on noninjection routes, stating that the use of SLIT in clinical practice is justified because of the ascertained efficacy and the favorable safety profile.[21] In 2001, the ARIA position paper accepted the use of SLIT in adults and children, as a valid alternative to SCIT[22] and this was confirmed by the ARIA update in 2008.[23] In SLIT, the allergen extract (prepared as drops or tablets) is kept under the tongue for 1 to 2 minutes and then swallowed; thus, this route is also called *sublingual-swallow*. In some studies a different method was adopted, the allergen was kept under the tongue and then spat out (*sublingual-spit*).[24] Presently, only the sublingual-swallow route is used, therefore the acronym SLIT refers to the sublingual-swallow modality.

Nowadays, more than 50 DBPC-RCTs are available in the literature.[25] Their results were also pooled and evaluated in several meta-analyses, which concluded that SLIT is significantly efficacious compared with placebo for rhinitis and asthma in adults and children.[26–29] In the last 2 years, some adequately powered, well-designed DBPC-RCTs with grass drops[30] or tablets[31–33] including hundreds of patients, were published. These studies have confirmed the efficacy of SLIT for these allergens and, more importantly, have demonstrated a dose-effect relationship. In parallel to the clinical trials, postmarketing surveys,[34] mechanistic investigations,[35,36] prevention studies,[37,38] and pharmaco-economic assessments[39] were also published in the last 10 years, so that several aspects of SLIT were gradually clarified. Concerning safety, all clinical trials and postmarketing surveys have consistently agreed that SLIT is safe, and the majority of side effects are local and mild. In more than 20 years of clinical trials and everyday use, only 6 cases of anaphylaxis with SLIT have been reported, some of which were with mixtures of multiple unrelated allergens using nonstandardized extracts, but 2 patients had a severe reaction after the first dose of a grass tablet. It has also been reported that use of multiple allergens for SLIT does not increase the rate of side effects in children.[40] Furthermore, it has been suggested[41] that the safety profile of SLIT does not differ in children below the age of 5 years (a relative contraindication to SCIT).

SLIT is currently commercialized and used in most European and South American countries, and in Australia and Asian countries, but not in the United States. After an initial skepticism, because of the paucity of data, the US scientific community also acknowledged the efficacy and safety of SLIT.[42] Nevertheless, because there is so far no Food and Drug Administration (FDA)-approved product for SLIT, this modality is not currently recommended in clinical practice in the US, where the Practice Parameter states that "…there is no US Food and Drug Administration (FDA)-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time."[43] Clinical trials for FDA registration in the US are currently ongoing.

There are several aspects of SLIT still needing investigation and confirmation, including the optimal dose, the long-lasting effect, the preventive action and the exact mechanisms of action. This relative lack of information is not surprising if we consider that the history of SLIT is only 20 years in duration, and that the majority of studies were aimed at demonstrating the efficacy and safety of the treatment. Furthermore, despite the number of clinical trials available, the value of SLIT in pediatric patients was a matter of debate,[44] until the new positive adequately powered, well-designed DBPC-RCTs in children were reported.[45,46] The most important concern that still remains is to determine the optimal dose of allergen for SLIT, because the treatment has been shown effective over a very large range of doses (from 5–300 times the dose used for SCIT). However, it is clear that the effective doses of allergens for SLIT must be higher than for SCIT (in fact, we commonly speak of high-dose SLIT). On the other hand, the recently published large trials have indicated the correct direction for research; that is, dose-finding studies, standardization, and uniformization of admin-



SLIDE 1. History of sublingual immunotherapy.

istration schedules, and the use of no-updosing regimens, which are more simple and patient-friendly. In the meantime, new opportunities are being explored with SLIT, including the possibility of using it in conditions other than respiratory allergy, namely food allergy[47] or Hymenoptera venom allergy[48] and the use of adjuvants and mucoadhesive substances. Other issues concern the indication of SLIT because there is no study assessing its efficacy in patients uncontrolled despite optimal pharmacotherapy (Slide 1).

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CHAPTER 2: ALLERGEN SPECIFIC IMMUNOTHERAPY

An update on subcutaneous immunotherapy, other routes of immunotherapy administration, different allergens and impact of immunotherapy on the natural history of disease.

- Many double-blind, placebo-controlled studies confirm the efficacy of subcutaneous immunotherapy for treatment of allergic rhinitis, allergic asthma, and Hymenoptera venom hypersensitivity.
- Studies are lacking that support immunotherapy with fungal extracts, other than for *Alternaria* and *Cladosporium*, and with cockroach extracts.
- Although limited in number, some controlled studies have demonstrated efficacy of subcutaneous immunotherapy with multiple allergen mixes. However, there have also been negative studies.
- There seem to be 2 distinct and perhaps sequential immunologic responses to immunotherapy, generation of regulatory T-cells (T regs) secreting interleukin (IL)-10 and transforming growth factor (TGF)-β and immune deviation from T_H2 to T_H1 responses.
- Subcutaneous immunotherapy has reduced the development of new sensitizations in monosensitized patients and, in a few studies, has reduced the development of asthma in children who only have allergic rhinitis.
- The beneficial effects of subcutaneous immunotherapy persist for years after discontinuation.
- The use of subcutaneous immunotherapy is limited by the occurrence of local and systemic reactions (SRs) and the prolonged period required for build-up to maintenance dosing.

Historical Development

Subcutaneous administration of increasing doses of a grass-pollen extract to treat allergic rhinitis was introduced by Leonard Noon in 1911,[1] with completion of his studies by John Freeman.[2] Timothy grass was administered preseasonally or seasonally. This treatment was subsequently extended to other seasonal and perennial allergens and to the treatment of allergic asthma and rhinitis.[3] Perennial administration largely replaced preseasonal treatment. While immunotherapy was initially used based on the clinical impression of efficacy, in the 1960s, definitive double-blind studies using ragweed pollen extract established that this was an effective form of treatment.[4,5]

Clinical Efficacy

Many double-blind, placebo-controlled studies confirm the efficacy of subcutaneous injection allergen specific immunotherapy (SCIT) for treatment of both allergic rhinitis[6] and allergic asthma.[7] These studies showed efficacy with extracts of various pollens, animal danders, HDMs, and fungi. For most classes of allergens, results support efficacy. However, although a few small size studies report positive results treating patients with *Cladosporium*[8] and *Alternaria*,[9] studies supporting immunotherapy with many of the other available fungal allergen extracts are lacking.[10]

Most controlled studies included in SCIT meta-analyses that show clinical efficacy of SCIT for allergic rhinitis and asthma include only a single allergen extract. Although there are controlled studies that demonstrate efficacy for multiple allergen mixes for treatment of both allergic rhinitis[4] and allergic asthma,[11] the studies are more than 40 years old and there are no recent studies.

Mechanisms of Action

Along with evidence of the efficacy has come an understanding of the probable mechanisms by which SCIT alters the disease processes. The earliest objective evidence of an immune response was the observation by Noon that immunotherapy reduced conjunctival sensitivity to timothy grass extract.[1] Subsequent observations confirm a reduction of sensitivity to the injected allergen in the skin, or topical allergen on the conjunctivae, nasal mucosa and lungs.[12,13] Humoral responses were also observed, with first an increase and later a decline in specific immunoglobin(Ig)E[14] and the generation of a blocking IgG antibody.[15] However, studies failed to correlate these responses with clinical improvement.[16]

Research today is focused on changes in T-lymphocyte responses and 2 distinct patterns of change, which may occur sequentially. An event that occurs within 7 days at high allergen doses[17] and 2–4 weeks at low allergen doses[18,19] is the generation of regulatory T-cells secreting IL-10 and TGF-β[19] accompanied by suppression of allergen-induced late cutaneous responses.[17,18] This is followed at 6–12 weeks after initiating therapy by corresponding elevations in allergen-specific IgG4 and IgA that parallel a more delayed suppression of allergen-induced early cutaneous responses.[18,19] A second and probably later immunologic response is immune deviation with a shift in the allergen specific T-cell response from predominantly T_H2 to T_H1.[20]

Impact on Natural History

Considering the profound effect on the immune response to the administered allergen, it is not surprising that SCIT alters the natural course of allergic diseases. Several studies have demonstrated that SCIT, when administered to monosensitized patients, reduces the likelihood of developing new sensitivities.[21–23] Furthermore, the reduction in new sensitivities persists for at least 3 years after discontinuation of treatment.[22,23] A similar inhibitory effect occurs for the progression to asthma in children suffering from only allergic rhinitis.[24] Timothy or birch pollen SCIT reduced the development of new onset asthma during the course of 3 years of treatment[25] and reduced the incidence of asthma with little loss of effect more than 7 years of posttreatment observation. The beneficial effects of SCIT on allergy symptoms persist for years after its discontinuation. In a prospective, placebo-controlled trial, subjects who discontinued timothy grass SCIT after 3 to 4 years of treatment had the same level of symptoms during the next 3 grass pollen seasons as did the group who continued on monthly maintenance injections.[26]

Alternative Approaches to Immunotherapy

Despite its clinical and disease-modifying efficacy, SCIT has some disadvantages: it is not 'patient friendly' because of the regular injections, which may arouse fear among children and some adults, and it has some indirect costs such as travel to the doctor's office and lost work/school hours. The use of SCIT is also limited by the prolonged time for build-up required to reach maintenance levels of treatment and by adverse reactions. Attempts to improve the former have lead to trials with accelerated treatment schedules, while the latter has been addressed by modifying the allergen extracts or administering them by routes other than injection. Alternatives to the weekly build-up include administering clusters of 2 or 3 injections, usually 30 minutes apart, during a single clinic visit with visits spread over several weeks.[27] This cluster schedule is not associated with an increased incidence of adverse reactions.[28] However, a more rapid build-up, in which maintenance is achieved in just one or a few days, is associated with an increased incidence of reactions even when treatment subjects are premedicated.[29] Extract modification includes adsorption of the extract to aluminum to achieve a depot effect[30] and modifying the extracts with formaldehyde[31] or glutaraldehyde[32] to reduce reactivity with specific IgE. Recombinant technology is currently being used to produce altered proteins[33] or peptides[34,35] that retain T-cell epitopes but are no longer recognized by the specific IgE. Another approach is to combine the allergen with products, most extensively with monophosphoryl lipid A[36] or CpG motifs,[37] that stimulate the innate immune system thereby favoring a T_H1 response.

Another approach is to administer the extracts by an alternative route, for example, orally[38] or sublingually[39] slowing absorption and presenting the extract to a different component of the immune system. Other alternative approaches are to administer the extract directly on to the respiratory

mucosa, either into the upper or lower respiratory tracts.[40,41] This approach can induce allergic respiratory symptoms, therefore, either modified extracts with decreased allergenicity are used[42] or cromolyn sodium is applied to the mucosa before the allergen is administered to block the allergic reaction.[43]

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CHAPTER 3: MECHANISMS OF SUBLINGUAL IMMUNOTHERAPY

- Allergen immunotherapy provides an opportunity to study antigen-specific tolerance in man.
- Subcutaneous immunotherapy suppresses allergic 'T_H2-mediated' inflammation and increases antigen-specific IgG probably by induction of T regs, immune deviation ($T_H2 \rightarrow T_H1$) and/or apoptosis of T cells.
- Oral mucosa is a natural site of immune tolerance (Langerhans cells, FcεR1, IL-10, IDO [indoleamine 2,3-dioxygenase]).
- Sublingual immunotherapy in optimal doses is effective and may induce remission after discontinuation and prevent new sensitizations, features consistent with induction of tolerance.
- Sublingual immunotherapy is associated with:
  - Retention of allergen in sublingual mucosa for several hours.
  - Marked early increases in antigen-specific IgE, blunting of seasonal IgE.
  - Modest increases in antigen-specific IgG4 and IgE-blocking activity.
  - Inhibition of eosinophils, reduction of adhesion molecules in target organ.
  - Some evidence of increase in peripheral T cell IL-10.
- SLIT induces modest systemic changes consistent with SCIT, but additional local mechanisms in oral mucosa and/or regional lymph nodes are likely important.

Immunotherapy provides a unique opportunity to study the evolution of antigen-specific tolerance in man. Understanding the underlying mechanisms may lead to the development of vaccines with greater efficacy and allow the identification of biomarkers that may predict the clinical response to treatment. Whereas there is considerable knowledge concerning mechanisms of SCIT, information on the mechanisms of SLIT[1,2] is less well advanced.

Subcutaneous Immunotherapy

Subcutaneous immunotherapy in patients with pollen rhinitis is associated with transient increases in allergen-specific IgE, blunting of seasonal increases in IgE,[3] and increases in allergen-specific IgG, particularly IgG4,[3–5] and IgA.[5,6] Serum antibody concentrations seem to relate more to the dose of allergen administered rather than correlate with clinical improvement.[7] Immunoreactive IgG populations include antibodies with a wide range of clonality and/or affinity. In contrast, functional assays of IgG are more likely to represent that proportion of circulating IgG that is biologically (and therefore clinically) relevant. For example, serum obtained after SCIT has been shown to inhibit allergen-IgE binding to B-cells,[8] an effect mediated largely by IgG4. This system has provided an in vitro assay of the ability of 'blocking' antibodies to inhibit IgE-facilitated antigen presentation. Similarly, basophil histamine release can be used to measure the functional ability of IgG to inhibit IgE-dependent activation and mediator release,[9] either via competition with IgE for allergen and/or by stimulation of surface IgG-inhibitory receptors present on basophils and mast cells.[10] Whereas postimmunotherapy serum IgA is unable to block allergen-IgE binding to B cells, by triggering surface IgA receptors on monocytes, IgA releases the inhibitory cytokine IL-10[6]. Subcutaneous immunotherapy has been shown to decrease the numbers of effector cells at mucosal sites, both during seasonal allergen exposure[11] and after allergen challenge,[12] and reducing effector cell reactivity in vitro.[9]

It has been suggested that allergic disease may result from a relative imbalance between the effects of T regs and T_H2 cells.[13] T regs can be divided into 'naturally occurring', thymus derived CD4+ CD25+ cells, which are positive for the transcription factor Foxp3, and 'adaptive' regulatory cells, either Tr1 IL-10 secreting cells, or Th3 TGF-β secreting cells.[14] Subcutaneous immunotherapy in patients with grass pollen[15] and mite[5] allergy results in increased IL-10 in allergen-stimulated peripheral T cell cultures. Additionally, subcutaneous immunotherapy has been associated with immune deviation in favor of T_H1 responses.[16,17] However, changes in T cell responses to allergen have not been universally observed in cells derived from peripheral blood.[18,19] Studies of local nasal T cell responses have identified skewing of cytokine profiles in favor of T_H1 responses[20,21] and local increases in IL-10+[3] and TGF-β+ T cells[6] and Foxp3+ phenotypic T regs[22] within the nasal mucosa.

The Oral Mucosa as a Tolerogenic Organ

The local environment in the mouth is regarded as a site of natural immune tolerance.[2] Despite continued exposure to micro-organisms and multiple foreign substances, the oral mucosa remains noninflamed with a relative paucity of effector cells compared with other mucosal sites. The presence of a sophisticated network of Langerhans cells, epithelial cells and monocytes capable of producing IL-10, TGF-β, and activins[23,24–26] may play a role in the maintenance of oral tolerance. Local secretory IgA may also have an antiinflammatory effect.[6]

Human oral Langerhans cells constitutively express FcεR1, Major Histocampatibility Complex (MHC) class I and II, and costimulatory and coinhibitory molecules,[27] properties consistent with highly efficient antigen presentation to T cells. Cross-linking of FcεR1 on monocytes induces production of IL-10[28] and indoleamine 2,3-dioxygenase,[29] the latter associated with reduced tryptophan levels and consequent impaired T-cell stimulatory capacity. Human oral mucosal Langerhans cells produce substantial IL-10. Ligation of Toll-like receptor 4 on isolated human oral Langerhans cells enhanced IL-10 production[30] and in coculture experiments decreased T-cell proliferation (in mixed lymphocyte reactions) with a parallel induction of T-cells with a regulatory phenotype. One hypothesis is that innate receptors enhance the tendency toward tolerance to antigens presented in the

microbe-rich oral environment. Interaction between dendritic cells, Langerhans cells and T cells may occur locally within the oral mucosa[27,30] whereas animal studies[26] imply that the principle site for such interactions is within the regional lymph nodes. It is possible that oral Langerhans cells interact with naive T-cells, resulting in the generation of allergen-specific regulatory T-cells. Alternatively, interaction with allergen-specific memory T_H2 cells may result in down-regulation of function or redirection to a regulatory or T_H1 phenotype. Downstream events, as in subcutaneous immunotherapy, may include B-cell class-switch to IgG4 and IgA rather than IgE, and down-regulation of mucosal effector cells. It remains to be determined whether such mechanisms operate in vivo during sublingual immunotherapy.

Immunologic Effects of Sublingual Immunotherapy in Man

Clinical studies of sublingual immunotherapy are heterogeneous, involving different allergens, doses, and durations of therapy. A wide range of laboratory techniques has been used to measure putative immunologic mechanisms: this may explain, at least in part, the variability of results obtained. Tracer studies of radio-iodine labeled allergen have shown that allergen may be retained within the oral mucosa for at least 2 hours[31] and up to 18–20 hours[32] after sublingual administration, affording opportunities for both local and systemic effects on the immune system.

Specific Antibody Levels

During pollen SLIT, increases in allergen-specific IgE occur within weeks although do not seem to be associated with adverse events. These early increases are followed by blunting of seasonal rises in IgE. There follows an increase in allergen-specific IgG/IgG4. These elevations are both time- and allergen-dose dependent[33] and progressive for at least 2 years[34] although of lower magnitude than observed during SCIT.[3,35] Some studies have shown increases in specific IgG4 in the absence of demonstrable efficacy,[36] whereas others have shown no difference in IgG levels, likely related to the lower allergen doses employed,[37] particularly in relation to mite SLIT.[38–41] These findings raise the issue of causality verses bystander effects. In functional assays, a serum obtained after grass pollen SLIT was able to inhibit IgE-binding in vitro.[34]

Effector Cells

Sublingual mite immunotherapy[42] was associated with decreases in conjunctival eosinophils, neutrophils and epithelial expression of intercellular adhesion molecule-1 (ICAM-1) and accompanied by a reduction in circulating eosinophil cationic protein (ECP). Similarly, SLIT in *Parietaria*-sensitive patients reduced eosinophils, neutrophils, and ICAM-1 expression in the nasal mucosa.[43] Decreases in ECP[42,44] and eosinophils have been observed in several but not all[40] studies. One study investigated the effects of high dose grass pollen SLIT on immune cells within the sublingual mucosa.[45] No differences in total T-cells, CD1a+ dendritic cells or macrophages were detectable and no differences in IL-12 messenger ribonucleic acid (mRNA)+ cells, whereas the T reg phenotype was not assessed. Interestingly, mast cells and eosinophils are present, albeit in low numbers, within the buccal/sublingual mucosa[46,47] and corresponding activation markers such as tryptase and ECP are detectable within salivary secretions,[48] providing a plausible explanation for local itching and swelling that may occur after sublingual allergen administration.

T Cells and Cytokines

Studies of peripheral T cell responses to inhalant allergens, before or after SLIT have been highly variable. Decreased T cell proliferative responses in birch[49] and grass-treated[50] patients have been observed in some but not other studies[37,51] and even less convincing trends for HDM-treated patients.[52,53] Similarly results for T cell cytokine production at both messenger RNA and protein levels have been highly variable, with some studies showing an increase in interferon gamma and/or decreases in T_H2 cytokines[49,51,53–55] whereas others show no changes.[37,41,50] A more consistent finding (as in SCIT) has been increases in peripheral T cell IL-10 production which have been observed at protein[49,56,57] and mRNA levels[54] in several, but not all, studies.[37] An elegant study by Bohle[49] on small numbers of birch-treated patients showed a reduction in proliferative responses to Bet v1 that was accompanied by increases in IL-10. This suppression was reversed by anti-IL-10 or depletion of CD25+ cells from the cultures that implied involvement of reg T cells. Further immunologic studies on larger numbers of subjects using validated clinical protocols are needed. One such recently published DBPC-RCT evaluated HDM SLIT in 30 HDM-allergic subjects for more than 12 months. The study reported suppression of IL-5 production and allergen specific CD4+T cell proliferation via TGF-β, transient increase in CD4+ CD25+Foxp3+/CD127lo T regs with functional suppressor activity and allergen specific antibody isotype switching to IgG4 in clinically effective HDM SLIT.[58]

Conclusion

A consensus is emerging that SLIT may involve similar mechanisms to SCIT with allergen-driven altered T cell responses underlying suppression of allergic inflammation and the modest changes observed in circulating antibody levels, particularly allergen-specific IgG4. Although results vary, the underlying event is likely to involve induction of a population of IL-10 producing regulatory T cells. Alternative mechanisms include immune deviation in favor of T_H1 responses and apoptosis and/or anergy of antigen-specific T cells. Studies of local T cell responses in the allergic mucosa may yield more definitive information. In contrast to murine studies, it is difficult to assess in man the likely additional local mechanisms involving T cell-dendritic cell interactions within the oral mucosa and/or local lymph nodes.

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CHAPTER 4: CLINICAL EFFICACY OF SUBLINGUAL IMMUNOTHERAPY

- Up to June 2009, there were 60 DBPC-RCTs of SLIT, of which 41 conducted with grass or HDM extracts. The majority of these studies is heterogeneous for allergen dose, duration and patients' selection.
- Forty eight trials provided overall positive results and 12 were totally or almost totally negative.
- The literature suggests that overall, SLIT is effective, although differences exist among allergens.
- The available meta-analyses are in favor of SLIT (rhinitis in adults, asthma, and rhinitis in children), although the conclusions are limited by the great heterogeneity of the studies.
- The clinical efficacy and dose dependency have been demonstrated, in adequately powered, well-designed DBPC-RCTs, for rhinoconjuntivitis because of grass pollen.
- Dose finding trials and large studies with properly defined outcomes and sample size are needed for the other relevant individual allergens.

General Aspects

As in the case of SCIT, the evaluation of the clinical efficacy of SLIT relies on the assessment of symptom severity and rescue medication use during the natural exposure to allergens. This requires the adoption of a rigorous methodological design, which is the DBPC-RCT. Furthermore, as suggested by WAO,[1] an ideal study should include:

- Only monosensitized patients.
- A baseline assessment (ie, a run-in pollen season).
- Adequate pollen counts in trials on pollen-allergic subjects.
- A sample size calculation for adequate power of the study.
- A balanced symptom/medication score evaluation.
- An adequate duration and allergen dose.

For practical (time consumption, budget, and rarity of monosensitized subjects) and historical reasons (the earliest studies were performed more than 10 years ago), only few recent trials fulfill the above-mentioned criteria. Therefore, the majority of the published Randomized Controlled Trials (RCTs) can be considered as suggestive, rather than demonstrative. Nonetheless, the RCTs taken together provide relevant and reliable information.

DBPC-RCTs (Table 4-1)

The number of DBPC-RCTs is increasing: as shown in Table 4-1, there were 60 DBPC-RCTs performed since 1986,[2–61] when the first controlled trial appeared.[2] Of these, 26 trials were performed with grass extracts, 15 with mite, 5 with *Parietaria*, 3 with cat, and the remaining 11 trials with other pollen extracts. The duration of the trials ranged between 4 months and 4 years, 19 of them being of 6

TABLE 4-1. Placebo-Controlled Studies

Author[ref], Year	Age range	Patients A/P *	Dropout A/P*	Allergen	Duration	Dose Preparation	Dose vs SCIT	Disease**	Manufacturer	Main Positive Results	No Change
Scadding[2], 1986		20/20	0/0	HDM			NA	R		Reduction in symptoms in 72% patients	
Tari[3], 1990	5–12	30/28		HDM	18 m	15.4 mg Der p 1/m Aqueous/ phenol	5	RA	ALK	Symptom score 12 m: ($P < 0.05$); 18 m: ($P < 0.001$). Drug score 20%	
Nelson[4], 1993	20–55	20/21		Cat	3.5 m	1.2 mg Fel d 1/m	40	RA	HS	Drugs/symptoms not evaluated	Symptoms on challenge
Sabbah[5], 1994	13–51	29/29		Grass	4 m	210 μg Dac g 5 glycerosaline	50	R	STA	Rhinitis ($P < 0.05$) Ocular ($P < 0.01$) Drugs ($P < 0.01$)	Patient's assessment $P = 0.16$
Feliziani[6], 1995	14–48	18/16	0/0	Grass	4 m	19 μg grass/m glycerol-phenol	6	RA	ALK	Symptoms Asthma ($P = .026$); Rhinitis ($P = .01$) Overall ($P = 0.008$), Medications: Overall ($P = .002$) Asthma ($P = .049$) Rhinitis ($P = .002$)	
Troise[7], 1995	17–60	15/16	0/0	*Parietaria*	10 m	1 μg Par j 1/m	20	R	ALK	$P < 0.05$ VS placebo in pollen season	Monthly clinical score
Hirsch[8], 1997	6–16	13/14		HDM	1 year	48 μg Der p 1/m Cumulat: 570 μg Glycerol	5	RA	ALP	$P = 0.05$ vs placebo for asthma only	Medication score, Rhinitis score, Self assessment
Passalacqua[13], 1998	15–46	10/10	0/1	HDM (monoid)	2 years	18.000 AU/m Tablets	20	R	LOF	Rhinitis symptoms in winter ($P < 0.05$). Meds not assessed	
Vourdas[11], 1998	7–17	34/32	1/2	Olive	2 season	1,215 μg Ole e 1/m Glycerophenol	300	RA	STA	Dyspnea score (0.04 1st year and 0.03 2nd year). Conjunctivitis $P < 0.05$ 2nd season.	Medication score, PEF, Rhinitis score, Global assessment
Clavel[9], 1998	8–55	62/58		Grass	6 m	288 μg Phl p 5/m Aqueous	100	R	STA	Medication score ($P < 0.01$), Oral steroids ($P < 0.05$), Asthma symptoms (p 0.02)	Rhinitis score, Conjunctivitis score
Horak[10], 1998	16–48	18/16		Birch	4 m	62 μg Bet v 1/m Glycerophenol	NS	R	ALK	Anterior rhinomanom. Vienna Challenge Chamber. Symptom-medication not evaluated	
Hordijk[12], 1998	18–45	27/30		Grasses	6 m	4,250 BU/m Glycerinated	NS	R	ART	Symptom decreased 29% at peak season (0.03)	Medication score, Symptom score whole season

(*Continued*)

TABLE 4-1. Continued

Author[ref], Year	Age range	Patients A/P *	Dropout A/P*	Allergen	Duration	Dose Preparation	Dose vs SCIT	Disease**	Manufacturer	Main Positive Results	No Change
Bousquet[15], 1999	15–37	32/33	17/18	HDM	2 years	300 μg Der p 1/m Glycerosaline	200	A	STA	at 24 months asthma symptoms (0.02), FEV_1 (0.01), PEF, (0.01), QoL.	Mean daily drug score; asthma symptom score; patients evaluation
Passalacqua[14], 1999	15–42	15/15	1/2	*Parietaria*	8 m	3.6 μg Par j 1/m., Cumulat: 16 μg , Glycerophenol	7	R	ALK	vs baseline: symptoms ($P = 0.16$) drug intake ($P = 0.08$)	
Pradalier[17], 1999	6–25	60/59	2/4	Grass	5 m	255 μg Phl p5/m Cumulat: 935 μg, Glycerophenol	150	RA	STA	Asthma symptomatic days (0.02); % patients with asthma (0.05); ocular symptoms (0.05); albuterol (0.01).	Total medication score; oral steroids (P 0.059); patients' assessment
La Rosa[18], 1999	6–14	20/21	4/4	*Parietaria*	6 m 2 seasons	2,730 μg Par j 1/m Cumulat: 52.5 mg Glycerophenol	375	RA	STA	Rhinitis score 2 years (0.02)	Medication scores, Rhinitis score 1st year
Purello[16], 1999	14–50	14/16	0/0	*Parietaria*	8 m	1.5 μg Par j 1/m Cumulat: 12 μg	3	RA	ALK	Rhinitis and asthma scores ($P = 0.01$); medication score ($P = 0.05$)	
Pajno[21], 2000	8–15	12/12	0/3	HDM	2 years	10.4 μg Der p 1/m Cumulat: 360 μg Aqueous	4	A	ALK	Asthma symptom score 2nd year ($P < 0.01$) night symptom (0.01) medication score 1st and 2nd year (<0.01) VAS 2nd year (<0.01)	Asthma symptoms 1st year; VAS 1st yr
Guez[20], 2000	6–51	38/37	8/15	HDM	2 years	91 μg Der p 1/m Cumulat: 2.2 mg Aqueous	2	R	STA	Higher dropout rate in placebo	Total symptom score, Medication score, VAS score
Caffarelli[22], 2000	4–14	24/20	0/4	Grass (monoid)	3 m	12,000 AU/m, 37,000 AU	5	RA	LOF	Total symptom score (<.05), Asthma score (<.05), Symptom-med scores for high pollen count.	Medication score, Ocular score
Yuksel[19], 1999	5–15	21/18	NS	Grass	4 m	Cumulat 210 μg Dac g 5 Glycerosaline	NS	RA	STA	Antihistamine (<0.05), Rhinitis score (<0.01), Overall efficacy by physician ($P = 0.04$)	Beta2 use, Asthma scores, PEF
Ariano[23], 2001	19–50	10/10	0/0	Cypress	8 m	30,000 RU/m, Cumulat 300,000, Glycero-Aqua	5	RA	ANA	Symptoms and medications score (<0.05)	

(*Continued*)

TABLE 4-1. Continued

Author[ref], Year	Age range	Patients A/P *	Dropout A/P*	Allergen	Duration	Dose Preparation	Dose vs SCIT	Disease**	Manufacturer	Main Positive Results	No Change
Bahceciler[24], 2001	7–15	8/7	0/0	HDM	6 m	72 μg Der p 1/m; Cumul: 0.56 mg Aqueous	NS	RA	STA	Asthma score ($P = 0.05$), Beta2 ($P = 0.028$), PEF ($P = 0.049$), Exacerbation ($P = 0.007$)	Nasal symptom score, ICS ($P = 0.06$), NCS vs placebo
Voltolini[25], 2001 (2nd yr open)	15–52	15/15 1st, 24/10 2nd	0/1	Birch	24 m	90 μg Bet v 1/m Glycerophenol	5	RA	ALK	Symptoms vs baseline ($P = 0.001$); drugs vs baseline ($P = 0.007$). 2nd yr: combined scores vs baseline and placebo	Symptoms and drugs scores vs placebo
Sanchez[26], 2001	18–50	20/20	0/0	Cat	1 year	0.3 μg Fel d 1/d Glycero-saline	NS	RA	CBF	Symptom score (<0.01)	Medication not assessed
Lima[27], 2002	16–48	26/23	2/1	Grass	18 m	0.9 mg Phl p 5/m Glycerinate	50	R	ALK	Patient assessment ($P = 0.02$)	Rescue meds, Symptom score
Mortemousque[28] 2003	6–60	26/19	4/11	HDM	24 m	Cumulat:2.2 mg Der p 1, Glycero-aqueous	NS	C	STA	Conjunctival provocation, Conjunctival score, Nasal score	
Andre[29] 2003	6–55	48/51	7/4	Ragweed 3doses	7 m	1.4–4.0 mg Amb a 1/m Solution/tablets	NS	R	STA	Only highest dose:, Rhinitis score ($P = 0.05$), Ocular score ($P = 0.04$), Oral steroids ($P = 0.05$)	In all dose groups:, Symptoms and drugs, combined
Ippoliti[30] 2003	5–12	47/39	0/0	HDM	6 m	10.4 μg Der p 1/m Cumulat: 57 μg Glycerophenol	5	AR	ALK	Asthma score (<0.01), Rhinitis score (<0.01), FEV_1 (<0.01), Drugs not assessed	
Pajno[31] 2003 (vs placebo and control)	8–14	15/15	1/2	*Parietaria*Add onto ICS	13 m	1.56 μg Par j 1/m Cumulat: 23 μg Glycerosaline	NS	RAC	ALK	Ocular score 0.025 vs controls; VAS ($P = 0.037$) vs placebo	Bronchial, nasal scores
Wuthrich[32] 2003	6–13	10/12	4/2	Grass	2 years	6μg /m Glycerophenol	NS	RA	ALK	Drug score 2nd yr (0.05)	Drug score 1st yr Symptom score
Tonnel[33] 2004	7–45	15/17	5/9	HDM	2 years	53 μg Der p 1/m Cumulat: 57 μg Solution-tablets	NS	R	STA	Rhinitis score 1st yr (<.03): 2nd yr (<.02)	Drug score
Bufe[34] 2004	6–13	68/74	0/10	Grass	1 year + 2 years open	273 μg Phl p 5/m Cumulat: 9.6 mg Solution	10	RA	HAL	Symptom+drug score $P = 0.046$ vs placebo: only 3rd year and only most severe group	Symptom + drug scores

(*Continued*)

TABLE 4-1. Continued

Author(ref), Year	Age range	Patients A/P *	Dropout A/P*	Allergen	Duration	Dose Preparation	Dose vs SCIT	Disease**	Manufacturer	Main Positive Results	No Change
Smith[35] 2004	18–60	49 1 year, 46 2 years, 46 placebo	35	Grass	1 year, 2 years	329 μg Dac g 5/m Solution-tablets	300	R	STA	2nd year: sneezing (0.05) and rhinorrhea (0.001)	Nasal score 1st year: Drug scores all study
Rolinck-Werninghaus[36] 2004	3–14	39/38	1/1	Grass	3 years	6 μg major/m Glycerophenol	NS	RA	ALK	Drug score (.025), Symptom+drug score (0.049)	Ocular, nasal, bronchial symptom score
Bowen[37] 2004	6–52	36/40	8/11	Ragweed 3 doses	4 m	3.1–9.4 mg Amb a 1 /m Solution	NS	R	STA	Sneezing and itching (0.04); investigator's evaluation	Drug score Conjunctivitis score
Durham[41] 2006	18–66	569/286	39/26	Grass 3 doses	6 m	15 μg (136 pts), 150 μg (139 pts), 450 μg (294 pts), Phl p 5/m Tablets	NS	R	ALK	Drug score –28% (0.012):, Symptoms –21% (0.002): QoL , Only highest dose	Symptoms and drug scores for the 2 low doses
Passalacqua[40] 2006	14–56	34/34	6/6	HDM (monoid)	2 years	8.000 AU/m Tablets	10	R	LOF	1st year: total symptoms (0.03), obstruction (0.05), medication (0.03). 2nd year: medications (0.03); General wellbeing	Symptom score and obstruction at 2nd year. Satisfaction profile.
Niu[38] 2006	6–12	56/54	7/6	HDM	6 m	320 μg Der p 1/m Cumulat 1.7 mg, Glycerosaline	100	A	STA	Nighttime (.002), daytime (.009), total (.01) asthma score; FEV_1, FVC vs baseline (<.05). Global assessment	Oral steroids, PEF (0.07), FEV1 and FVC between groups
Dahl[39] 2006	18–64	74/40	13/8	Grass	5 m	450 μg Phl p 5/m, Cumulat. 2.7 mg, Tablets	NS	RCA	ALK	RC symptom –37% (.004), RC drugs –41% (.03), Well days –52% (.004)	Asthma symptoms and medications
Valovirta[42], 2006	6–14	65/33	8/6	Hazelnut, birch, elm (two doses)	18 m	Weekly dose of major allergens, group 1 3.6 μg, group 2: 30 μg	NS	RC	ALK	With higher dose: total symptoms (.001), nose, lung, eye symptoms during birch season (<.05)	Total drug score, Methacholine, Skin test
Dahl[43], 2006	23–35	316/318	42/46	Grass	6 m	450 μg Phl p 5/m, Cumulat. 2.7 mg, Tablets	NS	RC	ALK	RC symptom –30% (.001), RC drugs –38% (.001), Well days –52% (.004), VAS	
Lue[44] 2006	6–12	10/10	0/0	HDM	8 m	Cumulat: 1.7 mg Der p 1, Glycerosaline	NS	A	STA	Night symptoms (.04) vs pl Day symptoms (.04), FEV_1, drugs (.01) vs b/line	Day symptoms, drugs, FEV_1, PEF vs placebo

(*Continued*)

TABLE 4-1. Continued

Author(ref), Year	Age range	Patients A/P *	Dropout A/P*	Allergen	Duration	Dose Preparation	Dose vs SCIT	Disease**	Manufacturer	Main Positive Results	No Change
Palma-Carlos[45] 2006	19–43	17/16	4/9	Grass(monoid)	2 years	8,000 AU/m Tablets	NS	RC	LOF	Conjunctivitis, rhinorrhea, sneezing (<.05) at the 2nd year; nasal reactivity (.03) at the 2nd year	Symptoms and nasal reactivity at the 1st year
Pham-Ti[46] 2007	5–11	55/56	11/8	HDM	18 m	810 μg Der p 1/m Cumulat 6.9 mg, Glycerosaline	NS	A	STA	SPT ($P = 0.01$) , QoL ($P < 0.01$)	Asthma symptoms, Asthma medication, Asthma free days, (low: both groups)
Vervloet[48] 2007	19–60	38/38	2/4	Juniper	4 m , 2 seasons	6 mg Jun a 1/m, Glycero-aqueous	NS	A	STA	1st and 2nd season: Nasal steroids (.01), Total medications (.04), IgE and IgG4	Both seasons: Total and single symptom scores. Single medication
Roeder[47] 2007	6–18	108/96	26/24	Grass	2 years	168 μg Lol p 5/m Cumulat: 4.5 mg Solution	NS	RC	ARTU		Mean daily score, Symptom-free days, Medication free days, QoL
Alvarez-Cuesta[49] 2007	16–51	25/25	8/9	Cat	1 year	Cumulat: 17.1 μg Fel d 1 Glycerosaline	2	RC	CBF	Bronchial, nasal, conjunctival symptoms and PEF vs baseline (<.05) at room challenge	
Didier[50] 2007	25–47	472/156	59/10	Grass, 3 doses	6 m	240 μg (157 pt)/m, 750 μg (155 pt)/m, 1.2 mg (160 pt)/m Tablets	NS	RC	STA	For 300 & 500 IR, Total/individual symptom/drug scores (<.001); RQLQ; medication-free days	
Horiguchi[51] 2007	18–50	43/24	2/2	Jap cedar	7 m	6 μg Cry j 1/m Solution. Spit	100	RC	TORI	Symptoms+drugs (<.05); sneezing, obstruction, rhinorrhea ($P < 0.05$). IgG4	
De Blay[52], 2007	12–41	61/57	8/8	Grass	10 m	250 μg group 5/m Cumulat: 2.5 mg, Solution	NS	RC	ALB	Medications (.02); symptoms in pats without asthma (.01): QoL; IgG4	Global symptoms score, Global medication score
Moreno[53], 2007	14–55	51/49	11/9	Olive+, Grass	10 m	60 μg group 5, 90 μg Ole e 1/m, Solution	NS	RC	ALK	vs 1st season: eye, nose, lung and total symptoms (<.01); symptom+drugs (.02) VAS (.01); QoL (.01)	Symptom and drug active vs placebo
Mosges[54], 2007	18–50	48/53	6/5	Grass	9 m	Cumulative 3.5 mg Phl p 5	NS	RC	STA	Nasal+ocular symptom -37% (.03) Eye symptoms -47% (.003)	Nasal symptoms (.08), IgE, IgG4

(*Continued*)

TABLE 4-1. Continued

Author[(ref)], Year	Age range	Patients A/P *	Dropout A/P*	Allergen	Duration	Dose Preparation	Dose vs SCIT	Disease**	Manufacturer	Main Positive Results	No Change
Panzer[55], 2008	15–50	45/30	4/0	Grass, SLIT or supraling.	1 year	38 μg Lol p 5 /m Cumulat: 456 μg Solution	NS	RC	SEVA	Symptoms –38% (supralingual); -67% SLIT; drugs –67%	IgE; SPT
Okubo[56] 2008	25–55	38/23	1/1	Cedar	5 m	2000 JAU	NS	RC	TORI	Symptoms and med better in SLIT in 4 days of season; QoL	Overall season symptoms and medications
Pfaar[57] 2008	17–59	94/91	17/9	Grass	2 years	1.2 mg/m, Solution	NS	RCA	ALP	Symptoms + med scores AUC (<.01), VAS	
Wahn[58] 2008	4–17	139/139	4/8	Grass	8 m	600 μg major allergen/mo, Tablets	NS	RC	STA	Rhinitis score -28% (.01); Meds -24% (.006); Med. free days (.01)	
Ott[59], 2009	20–50	142/67	3/1	Grass	5 years, 4 seas	Cumulative 1.5 mg major allergen/ season	NS	RC	STA	Combined and symptoms score sig. reduced from 1st seas. Symptoms decrease from -33% to 47% (3rd season)	Medication score all seasons
Bufe[60], 2009	5–16	126/127	12/7	Grass	6 m	450 μg Phl p 5/m	NS	RC	ALK	Sig reduction in RC symptoms score (-24%), asthma score (-64%) RC meds (-34%), well days (+28%). All $P <$ 0.03	
Stelmach[61] 2009	6–17	25/25	5/10	Grass	6 m, 2 seas	3.65 mg Phl p 5 cumulat.	NS	A	STA	Sig reduction in asthma score (-40%) asthma med (-10%)	Eye symptoms

months duration or less. The majority of studies was conducted in patients with rhinitis or rhinitis plus asthma. Only a few studies[15,21,31,38,44,46,61] were specifically designed to evaluate the efficacy in asthma, and one study dealt with allergic conjunctivitis.[28] When stated, the dose used in the clinical trials ranged between 5 and 375 times that used in an equivalent SCIT course, but the monthly and cumulative doses of major allergen(s) was largely variable from trial to trial. The majority of the clinical trials used the traditional symptom score assessment (graded from 0 to 3) plus recording of doses of rescue medications. In some trials, other evaluation parameters were applied, including visual analogue scale (VAS), combined score, symptom-free days and medication-free days. Out of 60 DBPC-RCTs, 18 enrolled more than 100 patients.[9,17,34,35,38,39,41,43,46,47,50,52,57–60] Of these, ten had a formal sample size calculation.[41,43,46,47,50,52,57–60] Twenty DBPC-RCTs involved only pediatric subjects (less than 18 years of age). As shown in Table 4–1, in the majority of the trials, the results were overall positive for one or more of the parameters investigated. On the other hand, there were 4 totally negative studies[4,20,47,56] and 8 trials reported only partial or negligible clinical efficacy.[8,9,11,27,34,36,46,52]

During the last 3 years, adequately powered, well-designed DBPC-RCTs involving several hundreds of patients and using standardized grass pollen tablets, were published.[39,41,43,50,58–60] In those studies the magnitude of the effect, defined as the reduction in diary symptoms and rescue medication scores compared with placebo was reported as 16% and 28%,[41] 30% and 38%,[43] 35% and 46%,[50] 28% and 24%,[58] 24% and 34%,[60] respectively. All these trials followed the established methodological criteria, had a power calculation and clearly defined outcomes and statistical analyses. So far, these large trials represent the best evidence available on the efficacy of SLIT. According to these trials, a dose-dependency of the efficacy of SLIT was observed, and the optimal monthly maintenance dose for grasses was identified as about 600 μg of the major allergen(s). One large DBPC-RCT[47] of grass extract, with 164 patients from general practice, screened and selected by researchers and specialists from a university allergy department, failed to demonstrate any difference between active and placebo. In another large trial with grass extract,[52] a significant difference in rhinitis scores could be seen only for those patients without asthma. Most of the DBPC-RCTs were designed to assess the efficacy of SLIT in rhinoconjunctivitis, and asthma was sometimes evaluated as a secondary outcome. Only 8 studies were specifically designed to assess the effect of SLIT in asthma,[15,21,31,38,39,44,46,61] and the majority confirmed a significant effect on symptoms and/or medication intake. In the 3 asthma studies that reported negative results,[39,44,46] the patients were almost completely free of asthma symptoms at enrolment and remained so during the trial, so that the absence of efficacy is not substantiated. Only 2 DBPC-RCTs assessed the efficacy of multiple non cross-reacting allergens.[53,62] The first one used grass and olive extracts, and confirmed the efficacy of SLIT in rhinitis. The second one compared the efficacy of SLIT with grass alone or with grass plus 9 other pollens and found that the treatment with a single allergen had more effect on immunologic parameters than that with multiple allergens. Because of the low pollen count, no clinical difference between the 2 groups and placebo was seen in this study.

Meta-Analyses

The first meta-analysis of SLIT for allergic rhinitis included 22 trials and 979 patients up to September 2002. It concluded that SLIT was significantly more effective than placebo,[63] but the studies in allergic asthma were too few to perform a meta-analysis. A meta-analysis in asthma was recently repeated, including 25 trials (either open or blinded) and involving more than 1,000 adults and children.[64] This meta-analysis demonstrated a significant effect of SLIT for most of the considered outcomes (symptoms + medications, pulmonary function, overall improvement), with the exception of asthma symptoms alone. Another meta-analysis[65] of SLIT for allergic rhinitis in pediatric patients (aged 4–18 years) involved 10 trials and 484 subjects. It showed that SLIT was significantly more effective than placebo, as assessed by the reduction in both symptom scores and rescue medications usage. Although all the studies were of high methodological quality, there was a relevant heterogeneity ($I^2 > 80\%$), because of the large variability in study design, duration, outcome measures and inclusion criteria. Finally, a meta-analysis was also performed for asthma in pediatric patients.[66] This review included 9 DBPC trials and 441 patients, and found a significant effect of SLIT on both asthma symptoms and rescue medication usage. In addition, in this case, the heterogeneity of the trials was very large ($I^2 > 90\%$). The meta-analyses mentioned pooled together all the allergens, whereas a systematic evaluation of the efficacy of one specific allergen is available only for HDM,[67] with positive results. In summary, the available meta-analyses involve very heterogeneous trials, often without a proper sample size calculation: publication biases and discrepancies in data collection are additional concerns.[68] Thus, meta-analyses provide only suggestive evidence.

Other Controlled Studies (Table 4-2)

There are 8 randomized open controlled trials[69–76] assessing the clinical efficacy of SLIT, mostly compared with control groups receiving drugs only. All these studies provided positive results for clinical scores and/or medication intake, and 2 of them[71,74] also demonstrated a significant reduction in nonspecific bronchial hyperresponsiveness (BHR). One trial[75] was specifically designed to evaluate the safety of a no-updosing regimen, rather than the efficacy, and another[76] demonstrated that SLIT with 2 noncross-reacting allergens (birch and grass) is overall more effective than SLIT with the single allergens in both pollen seasons.

Comparison with SCIT (Table 4-3)

When comparing 2 different routes of administration, the gold standard methodology is the use of a double-blind, double-dummy design. One double-dummy study, although without a placebo group, conducted in grass pollen allergic patients, showed that the clinical efficacy of SLIT (symptoms

TABLE 4-2. Randomized Controlled Not Double-Blind

Author,[ref] Year	Description	Age Range	Patients	Allergen	Duration	Dose Preparation	Disease	Manufacturer	Main Results
D'Ambrosio,[69] 1996	Randomized open. Controls with drugs only	18–56	20 SLIT 20 Control	*Parietaria*	6 m	NS	R	ALK	Lower symptom score (P = 0.032) and drug+symptom score (P = 0.037)
Gozalo,[70] 1997	Randomized open. Controls with drugs only	18–50	35 SLIT 19 Control	Grass	2 years	NS	R	ALK	Lees medications in SLIT group in first (.05) and second (.01) pollen season
Lombardi,[71] 2001	Randomized open. Controls with drugs only	18–55	26 SLIT 25 Control	Grass	6 m 3 seas	8,000 AU/mo Allergoid	RA	LOF	Decreased rhinitis/asthma medication (.01), rhinitis/ asthma scores (0.01), nonspecific bronchial reactivity (0.01)
Marogna,[72] 2004	Randomized, open controlled	18–62	390 SLIT 192 Control	HDM Grass *Parietaria* Birch	3 years	32 μg Der p 1/mo 5.8 μg Phl p1/mo 5.8 μg Par j1/mo 8.3 μg Bet v1/mo	RC	ANA	Clinical scores improvement at 1, 2 and 3 years vs baseline and controls (<.01). New sensitizations at 3 years in 5.9% SLIT and 38% controls (<0.01)
Marcucci,[73] 2005	Randomized, open, two different doses	6–14	100IR = 32 300IR = 42	Grass	6 m	100 IR 300 IR Glycerosaline	RC	STA	Higher dose better for overall score (P = 0.024), symptoms (0.03), and medications (0.04) during peak pollen. No change in IgE
Marogna,[74] 2005	Randomized open. Controls with drugs only	18–65	39 SLIT 40 Control	Birch	5 years 5 seas	8.5 μg Bet v 1 glycerinated	RA	ANA	From 2nd season: reduction asthma/rhinitis symptoms (.01), salbutamol intake (0.001), methacholine reactivity (.01). No change in the 1st season.
Guerra,[75] 2006	Randomized, open. Comparison traditional vs no updosing	18–45	10 tradition 10 no updosing	*Parietaria*	3 m	90 μg Par j 1 cumulative Solution	R	ALK	No difference in side effects between the two regimens
Marogna,[76] 2007	Randomized open. 4 groups: birch, grass, birch+grass, controls	19–43	11 birch,12 grass, 13 birch+grass 12 Control	Birch Grass	2 season 2nd and 4th yr	100 μg Bet v1 80 μg Phl p1	RA	ANA	Single allergens effective on symptoms and medication scores in the specific season and other season. Combined SLIT significantly more effective in both seasons.

and medication use) was equivalent to that of SCIT.[77] Another rigorous double-blind, double-dummy, placebo-controlled trial with birch pollen extract, compared SLIT and SCIT. Symptoms and medication use were reduced by about one third in the SLIT group and by one half in the SCIT group, with no significant difference evident between treatments. However, there were 6 grade 3 and 4 adverse reactions in the SCIT group and none in the SLIT group.[78] Four other comparative studies have been published, but they were all conducted in an open fashion. Bernardis et al[79] performed an open comparative 12 months study in *Alternaria tenuis* allergic patients and found a clinical improvement in symptoms (mainly rhinitis) and medication use in both groups with a statistically significant difference in favor of SLIT. In another study,[80] the clinical efficacy of SLIT, SCIT, and nasal immunotherapy was assessed in 43 patients with rhinitis because of mites. This study considered only the immunologic changes, which were significant only for SCIT. An open comparison,[81] again in mite-allergic patients, showed that the clinical improvement was more prompt with SCIT, especially for asthma symptoms, although SLIT controlled rhinitis symptoms well. Finally, Mauro et al,[82] compared SCIT and SLIT in 47 patients with birch allergy and found no difference between the 2 treatments in seasonal symptom

TABLE 4-3. Comparisons Between SLIT and SCIT

Author,[ref] Year	Design	Patients	Allergen	Duration	Dose	Manufacturer	Main Results
Quirino,[77] 1996	Randomized DB double-dummy without placebo arm	10 SLIT 10 SCIT	Grass	12 m	6.4 μg major allergen/m for SCIT. SLIT = 3 X SCIT	ALK	Significant reduction in symptom and drug intake score ($P <$ 0.01) in both groups versus baseline. No change in IgE. Increase in IgG and reduction of skin reactivity only in SCIT group
Bernardis,[79] 1996	Randomized, open, without placebo	SCIT SLIT	Altern			ALK	
Piazza,[80] 1993	Randomized, open, SLIT and SCIT vs nasal IT and controls	17 SCIT 14 SLIT 12 LNIT 14 Controls	HDM	2 years	SCIT: 4.8 μg/m SLIT: 12 μg/m LNIT: 32 ng/m	ALK	SLIT: decrease in symptoms at 3 months (.01) but not 12–24 months SCIT: decrease in symptoms at 3, 12, 24 months (<.01) IgE, IgG, and IgG4 changed only in SCIT. No change at all in LNIT
Mungan,[81] 1999	Randomized open, placebo-SLIT controlled	15 SLIT 10 SCIT 11 Placebo	HDM	1 year	Der p 1 SLIT: 21.6 μg/m SCIT: 0.6 μg/m	STA	Reduction in rhinitis score for SLIT (<.01) and SCIT (<0.05). Asthma score reduction only SCIT (<.05). Reduction drug score for both SLIT and SCIT. Reduction SPT diameter only in SCIT.
Khinchi,[78] 2002	Randomized DB double-dummy placebo contr	21 SCIT 18 SLIT 19 Placebo	Birch	2 seasons	Bet v 1/m SCIT: 3.28 μg SLIT: 738 μg	STA	Reduction of rhinitis score in SLIT (0.36) and SCIT (0.75). No significant difference between treatments, both superior to placebo ($P = 0.002$). Medication scores SLIT and SCIT vs placebo ($P = 0.02$). No change in QoL.
Mauro,[82] 2007	Randomized open SLIT vs SCIT	19 SCIT 15 SLIT	Birch	4 m	Cumulative 50.65 IR SCIT 4653.1 IR SLIT	STA	During pollen season, no difference SLIT-SCIT in symptoms + drug scores. Specific IgG4 significantly increases with SCIT only

score, although specific IgG4 significantly increased only with SCIT.

DBPC-RCTs of SLIT in Other Diseases (Table 4-4)

The efficacy of SLIT was investigated, as proof of concept, in DBPC-RCTs in diseases other than respiratory allergy, namely food allergy,[83,84] latex allergy,[85,86] atopic dermatitis,[87] and Hymenoptera venom allergy.[88] The results of all these trials were clearly in favor of SLIT. Enrique[83] found that SLIT was able to significantly increase the oral provocation threshold in patients with hazelnut allergy and the same was shown by Fernandez et al with peach.[84] Pajno et al[87] showed that in patients allergic to mites and with mild-moderate atopic dermatitis, SLIT after 9 months significantly reduced the SCORAD score. Severino et al, in 30 patients with honeybee allergy, demonstrated that a 6-month course of SLIT with a maintenance dose of 525 μg venom significantly reduced the severity of LLRs to sting challenge.[88]

Unmet Needs

- Recent large trials with grass extracts have identified the optimal dose for this allergen: similar studies (dose-finding, DBPC-RCT) are mandatory for the other relevant allergens, that is, HDM, *Parietaria*, ragweed, and cat dander, but should take into account the variability of potency of extracts among manufacturers.[89]
- According to press releases and one abstract,[90] some US clinical trials failed to reach the primary outcome, thus, FDA approval is still pending. Possible reasons for those results, including inappropriate patient selection and low

TABLE 4-4. DBPC-RCTs in Diseases Other Than Respiratory Allergy

Author,[ref] Year	Age Range	Patients A/P*	Dropout A/P*	Allergen	Duration	Dose	Disease	Manufacturer	Main Results
Enrique,[83] 2005	19–53	12/11	1/0	Hazelnut	6 m	188 μg Cor a1/d	Food allergy		Significant increase in the food challenge provocation dose ($P = 0.02$). 50% active subjects tolerated maximum dose. No change IgG4 and skin test.
Fernandez Rivas,[84] 2009	20–40	37/19	4/3	Peach	6 m	300 μg Pru p 3/m	Food allergy	ALK	Significant increase (3–5 times) of the provocation dose at DBPCFC
Bernardini,[85] 2006	5–14	12/14	0/0	Latex	1 year		Skin, respiratory and oral allergy due to latex	ALK	Active group: Improvement glove test at 3 months and 1 year ($P < 0.01$), Reduction oral allergy syndrome
Pajno,[87] 2007	5–16	28/28	2/6	Mite	18 m	3.3 μg Der p 1/week	Atopic dermatitis	ANA	Only in mild-moderate subjects: Reduction SCORAD starting from month 9 ($P = 0.025$). Reduction rescue medications (p.02)
Nettis,[86] 2007	18–47	20/20	2/3	Latex	12 m	1,200 μg /m	Latex allergy, Urticaria, asthma	ALK	Active group: Decreased reactivity glove test ($P < 0.05$), Decreased bronchial reactivity to latex (<0.05), Symptoms and rescue medication scores at 6 and 12 months
Severino,[88] 2008	18–65	15/15	1/3	Honey bee	6 m	525 μg venom/m	Hymenoptera, allergy, Large local reactions	ANA	Reduction peak diameter LLR ($P = 0.014$) at sting challenge. Increase specific IgG4 (0.03)

*Active/placebo; **rhinitis, asthma, conjunctivitis.
ALK = Alk-Abellò, ANA = Anallergo; ALB = AllerBio; ALP = Allergopharma; ART = Artu Biologicals; CBF = CBF Leti; HS = Hollister-Stier; LOF = Lofarma; STA = Stallergenes; SEVA = Seva Pharma; TORI = Torii Pharmaceuticals.

pollen counts, have been extensively analyzed by a WAO task force,[91] who also provided recommendations for future trials.

- Current data on the clinical efficacy of SLIT in asthma are controversial: it is essential that RCTs with appropriate sample sizes are conducted in patients symptomatic for asthma under natural allergen exposure. Symptom and rescue medication intake scores are a reasonable outcome measure, but objective parameters (FEV_1, PEF) should be included as coprimary endpoints.
- Experimental data on mixtures of unrelated allergens are very scarce, thus, properly conducted clinical trials evaluating this are needed (the safety aspect is of primary relevance). Because the EMEA recommends against mixing different allergens in a single preparation,[92] there may be problems with the feasibility of clinical studies with such mixtures
- Other relevant questions are the optimal duration of a SLIT course, the duration of the preseasonal induction and the efficacy/safety of the no-build up regimens.
- Oral allergy symptoms are commonly reported in many studies and it is not possible to control for this side-effect. This fact could influence results.
- Although positive results on the use of SLIT in latex allergy, food allergy, atopic dermatitis, and Hymenoptera venom allergy have been reported, these should be considered as investigational: further data on efficacy and safety are needed.
- No clinical data are available for nickel-induced SRs.

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CHAPTER 5: SAFETY OF SUBLINGUAL IMMUNOTHERAPY

- SLIT appears to be better tolerated than SCIT.
- SLIT should only be prescribed by allergy-trained physicians.
- Specific instructions should be provided to patients regarding the management of adverse reactions, unplanned interruptions in treatment and situations when SLIT should be withheld.
- The majority of SLIT adverse events appears to occur during the beginning of treatment.
- A few cases of SLIT-related anaphylaxis have been reported but no fatalities.
- Risk factors for the occurrence of SLIT severe adverse events have not yet been established.
- There is a need for a generally accepted system of reporting adverse reactions/anaphylaxis.

Classification and Frequency of SLIT Adverse Events

One of the purported advantages of SLIT over SCIT is greater safety, which may allow for administration of this treatment outside of the medical setting. In a comprehensive review of 104 articles on SLIT, there were 66 studies that provided some information on safety and tolerance, representing 4,378 patients who received approximately 1,181,000 SLIT doses.[1] The amount of information on the adverse events (AE) in these studies varied greatly, ranging from general summary statements, such as "no relevant side effects," to a detailed analysis of the AEs. One consideration with SLIT is that the majority of doses are administered outside of the clinic setting with no direct medical supervision, and the accuracy of the AE reporting is dependent on the patient and/or family's interpretation of the event and recall. The vast heterogeneity in classifying and reporting immunotherapy (SCIT and SLIT) AEs in the published clinical trials makes comparisons and analysis of safety difficult. Recognizing the need for a uniform classification of immunotherapy AEs, a Joint Task Force (representing members of the American College of Allergy and Clinical Immunology [ACAAI], American Academy of Allergy and Clinical Immunology [AAAAI], EAACI, and WAO immunotherapy committees) was formed with the purpose of developing a uniform classification system for anaphylaxis. This grading system is referred to as the World Allergy Organization Subcutaneous Immunotherapy SR Grading System, and a paper is in press in the *Journal of Allergy and Clinical Immunology*, 2009.

Only 10 studies in this review classified the severity of the AE according to varying criteria. Three studies classified the reactions according to the recommendations of EAACI, which have subsequently been modified and were originally intended as a classification system for SCIT reactions.[2] Oral-mucosal reactions, considered a SLIT local reaction, were relatively common, affecting up to 75% of patients, and seen most frequently in the build-up phase. In the studies that specified the type of reaction, 169 of 314,959 (0.056% of doses administered) were classified as SR. There were 244 moderate AEs requiring dose adjustment or causing withdrawal from the study in 2,939 patients treated for 4,586 treatment years with 810,693 doses of SLIT (50 studies). The majority of these reactions were gastrointestinal symptoms, rhinoconjunctivitis, urticaria, or some combination of these symptoms.

In the 38 placebo-controlled studies, there were ~282,894 SLIT doses administered to 1,688 patients, which resulted in 353 (21%) patients reporting 823 AEs (2.9 per 1,000 doses) and 226,261 placebo doses administered to1,302 patients, resulting in 152 (11.7%) patients reporting 207 AEs (0.9 per 1,000 doses). AEs accounted for withdrawal in 3% of the SLIT patients compared with 1.4% of the placebo-treated patients. To provide some perspective, in one review of 38 SCIT studies, the SR rate with nonaccelerated schedules (single dose increase per visit) ranged between 0.05 to 3.2% of injections and 0.8 to 46.7% of patients (mean, 12.92%).[3]

SLIT Serious Adverse Events

In the SLIT comprehensive review, there were no fatalities or events described as anaphylaxis, although there were 14 probable SLIT-related serious adverse events (SAE) in 3,984 patients treated with a total of 1,019,826 doses in 58 studies. This represents 1.4 SAEs per 100,000 SLIT doses and one SLIT-related SAE per 384 treatment years or 285 patients. The most common SLIT-related SAEs were asthmatic reactions (7), one of which required hospitalization: the others were abdominal pain/vomiting (3), uvula edema (1), and urticaria lasting 48 hours. Subsequent to this review, there have been 4 case reports of SLIT-associated anaphylaxis:

- One occurred on the 3rd day of build-up with a multiallergen SLIT extract in a 31-year-old woman with allergic rhinitis and asthma.[4]
- One occurred in a 11-year-old girl with allergic rhinitis and asthma shortly after administration of mixed pollen

SLIT at the height of pollen season, 1 month after beginning maintenance.[5]

- One occurred on the 4th day of a latex rush protocol.[6]
- One occurred after a 3-week gap in maintenance treatment after taking a dose 6 times higher than prescribed HDM SLIT (60 drops of 100 IR instead of 10 drops) in a 16-year-old girl with allergic rhinitis and asthma. She had 2 previous episodes of wheezing related to SLIT within the first 3 months of maintenance. This reaction resulted in loss of consciousness and admission to the intensive care unit.[7]
- Two cases of anaphylaxis occurring with the first dose of a sublingual grass tablet have recently been reported.[8] Both of these individuals had previously discontinued grass-pollen SCIT because of SRs. One reaction was urticaria in a 13-year-old boy with allergic rhinitis, who developed periorbital angioedema and urticaria within 15 minutes of administering the grass tablet. The other case involved a 27-year-old woman with allergic rhinitis and asthma, who began to experience asthma symptoms, generalized itching, faintness, and abdominal cramps immediately after the first grass tablet dose. She was wheezing and hypotensive (blood pressure 90/50) when she arrived in her general practionioner's (GP) office, where she was treated with subcutaneous epinephrine.
- In comparison, SCIT fatalities, although rare, have been reported at a rate of one in 2 to 2.5 million injections in 3 surveys of AAAAI members that date from 1945 to 2001.[9–11] The most recent survey also assessed the frequency of SCIT near-fatal reactions, defined as severe respiratory compromise and/or fall in blood pressure requiring emergency treatment with epinephrine.[12] The incidence of unconfirmed near-fatal reactions during the period of 1990 to 2001 was 23 per year or 5.4 events per one million injections.

Risk Factors for SLIT Adverse Events

No clear predictors for SLIT AEs have been identified although some of the factors in the SLIT anaphylaxis case reports are recognized as risk factors for SCIT: ie, height of season,[12] history of previous SRs,[13] dose[14] and accelerated schedules.[15] In addition, most of the patients with SLIT-related SAEs or anaphylaxis had asthma, which has been identified as a risk factor.[16]

Dose and Adverse Reaction Rate

There does not seem to be a consistent correlation between the adverse reaction rate or severity and the administered SLIT dose. In an 18-month study of 58 asthmatic children with dust mite allergy treated with relatively low-dose SLIT (1.2 mg of Der p 1 3 times a week or 15.4mg of Der p 1 cumulative monthly dose [CMD]), there were 32 SRs in ~6,933 administered doses (0.46% per dose).[17] Seventeen of these reactions were classified as severe and because of exceeding "maximum tolerated dose." In contrast, a multicenter study of 97 dust-mite allergic children with mild-to-moderate asthma who received high-dose SLIT (20 drops of 300 IR/ml = approximately 783 mg cumulative monthly dose [CMD] of mixed mites), there were no incidences of serious SLIT-related AEs or a significant difference in the incidence of AEs between the SLIT and placebo groups.[18] The CMD dose in this study was about 50 times the dose used in the study that reported 17 severe dose-related reactions, and the daily dose appeared to be equal to the amount taken by the 16-year-old, who developed anaphylaxis after taking 6 times her usual dose after a 3-week gap in treatment. However, in some large dose response studies, a relationship between dose and frequency and severity of AE has been demonstrated.[19,20]

Induction Schedule

Unlike SCIT, which appears to be associated with a greater incidence of AEs during some accelerated induction schedules such as rush, there does not seem to be a relationship between the type of induction schedule and AEs with SLIT. Rush, ultra-rush and no-induction schedules seem to be equally well tolerated with SLIT. In a study of 679 patients with allergic rhinitis, asthma, or both, who underwent a 20- to 25-minute ultra-rush SLIT induction, during which increasing doses of allergen were administered every 5 minutes, the cumulative allergen doses achieved after half an hour were in the range of 4.7 to 525 μg of major allergens.[21] All patients were reported to have tolerated the treatment well, with 17.96% of patients reporting mild local symptoms, primarily oral pruritis. Two patients experienced urticaria 2 and 3 hours after the ultra-rush induction and one patient had urticaria and rhinitis 3 hours later.

In 2 large multicenter dose response studies of 855 and 628 patients with grass-pollen allergic rhinitis, treated with grass tablets containing up to 15 μg of Phl p 5[22] or 41 μg of the group 5 major allergens,[20] respectively, administered with no induction phase, there was only one serious SLIT-related AE. One patient in the middle-dose treatment group (~5 μg Phl p 5) was hospitalized for observation with "mild uvula edema"[22]: the patient continued the study without any further complications.

Although the induction phase does not seem to influence the SLIT AE rate, many studies reported that the majority of AEs occurred during the induction phase as compared with the maintenance phase.

SLIT in Young Children

SCIT is not generally prescribed to young children, primarily because of safety concerns.[23] It has been suggested that children less than 5 years of age may have difficulty cooperating in an immunotherapy program, particularly, in communicating symptoms of SRs.[24] It has also been suggested that injections can be traumatic to very young children.

Three studies, 2 observational and one postmarketing survey, specifically designed to assess the safety of SLIT in young children, included a total of 231 children younger than 5-years-old, who were treated with various pollen and mite allergens (33 patients received allergoid).[25–27] AEs were reported in 5 to 15% of patients in a total of 68,975 doses with rates of 0.268, 0.0766, and 1.767 AEs per 1,000 doses in the 3 studies. Most reactions appeared to be mild or moderate and resolved without treatment. Dose reduction by changing from a sublingual-swallow to a sublingual-spit method controlled

gastrointestinal reactions in one study.[27] One further Randomized Controlled Trial (RCT) with HDM SLIT in 138 children aged 2–5 years with asthma or rhinitis showed only mild to moderate local AEs.[28]

Multiallergen SLIT

Two of the case reports of SLIT anaphylaxis involved multiallergen SLIT and most of the SLIT studies employed single allergens. Two studies have investigated the safety of multiallergen SLIT in adults and children.[29,30] There was no significant difference in AEs in a study of 159 adult patients with allergic rhinitis ± asthma (age 16–59 years), who were treated with either a single allergen ($n = 76$) or multiple allergens ($n = 83$), with 45 AEs occurring in 42 patients who received 7,296 single allergen doses and 51 AEs reported in 47 patients, who received 8,051 multiallergen doses.[29] Similar results were found in a study of 355 children (age 3–18 years) who received either single allergen SLIT ($n = 179$) or multiallergen SLIT ($n = 254$) with 76 AEs reported in the single allergen group (42.46% patients, 4.43/1,000 doses) and 102 AEs in the multiallergen group (40.3% patients, 4.42/1,000 doses) ($P = NS$).[29]

SLIT Safety: Special Considerations

Because this treatment is administered at home without direct medical supervision, patients should be provided with specific instructions regarding: how to manage adverse reactions, unplanned treatment interruptions, when and what to report to the prescribing physician, situations when SLIT should be withheld (eg, oropharyngeal infection, oral abrasion, acute gastroenteritis, asthma exacerbation, etc).[2] Careful consideration should also be given to the ability of the patient and/or their family to adhere to these instructions and the treatment regimen.

SLIT Safety Summary

In general, SLIT appears to be associated with fewer and less severe AEs than SCIT. Oropharyngeal reactions are the most common AEs but other reactions, such as asthma, urticaria and abdominal pain have been reported with SLIT. There have been a few case reports of anaphylaxis with SLIT, including 2 reports of anaphylaxis with the first dose. Risk factors for SLIT AEs have not been clearly established. Some studies suggest a greater frequency of AEs during the induction phase compared with the maintenance phase, but there does not seem to be a relationship between induction schedule and SLIT AEs, with ultra-rush and no-induction schedules reported as being well tolerated in several studies.

Further studies are needed to identify and characterize SLIT risk factors and patients who should initially receive this treatment in a medically supervised setting.

Unmet Needs

- The safety of SLIT in moderate to severe asthmatics.
- The safety of SLIT in patients who have had SRs with SCIT.
- The safety of SLIT with multiple allergens.
- Interruptions in treatment: how long between doses is it safe to administer usual dose?.
- This might also include treatments with no induction phase: once treatment has begun and there is a gap in treatment, the response to reintroduction is not known.
- Can someone stop eg, daily grass tablets for a few weeks then restart and stop periodically as patients often do in real life?.
- If so would it be safe to start midseason if they are most symptomatic in season?.
- Is it safe to administer SLIT with no induction with all formulations? Or do some require an updosing phase?.
- Are oropharyngeal infections or lesions (eg, ulcers, gingivitis, paradentosis) risk factors for SLIT SRs?.
- Under which clinical situations should a SLIT dose be withheld (eg, recent respiratory tract infection, recent exacerbation of asthma, gastroenteritis)?.
- The safety of SLIT in pregnant or breast-feeding women.
- The safety of SLIT in patients on beta-blockers.
- Are there any risk factors that identify which patients may experience a SR with SLIT?.

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CHAPTER 6: IMPACT OF SUBLINGUAL IMMUNOTHERAPY ON THE NATURAL HISTORY OF RESPIRATORY ALLERGY

- Allergen specific immunotherapy may alter the natural history of respiratory allergy by preventing the onset of new skin sensitizations and/or reducing the risk of asthma onset.
- There are two randomized open controlled studies suggesting that SLIT reduces the risk of asthma onset in children with rhinitis.
- Two open randomized studies show that SLIT reduces the onset of new allergen sensitizations.
- One DBPC-RCT and one nonrandomized prospective study suggest the persistence of the clinical effects for 3–5 years after discontinuation.

Introduction

Respiratory allergy (allergic rhinitis, allergic asthma, united airways disease) is not a static entity, but may change in its clinical presentation over time. Apart from changes in environmental exposure, which can modify the severity and presentation of the disease, there seems to be a "natural history" of the disorder. One of the paradigmatic examples of this is the so-called "atopic march" in children.[1] It is also well known, for instance, that allergic rhinitis is an independent risk factor for developing asthma and that allergic rhinitis often precedes asthma. It has been shown that 16% to about 40% of subjects with rhinitis develop asthma later in life,[2–5] that the relative risk of rhinitis patients developing asthma varies from 2.2 to 5.4 (review[6]) and that rhinitis independent of atopy is a good predictor of adult onset asthma.[7] Identically, prospective studies have shown that allergic rhinitis may precede the development of BHR.[8,9] On the other hand, it has been shown that in children, asthma may precede rhinitis.[10] Another well recognized aspect of the natural history of respiratory allergy is the trend to develop new skin sensitization over time,[9] and this has been consistently demonstrated in both adults and children. On one hand, this development testifies for an evolution of the immune response to allergens; on the other hand, it has relevant clinical implications, because the severity of the disease directly correlates in part with the number and size of positive skin tests.[11,12]

Interventions that can alter the natural history of respiratory allergy may reduce the risk of developing asthma or prevent the onset of new allergen sensitizations. Presently, none of the currently available medications, including H1-antihistamines and inhaled steroids, display such properties.[13–16] Conversely, the disease-modifying effect of SCIT was described more than 40 years ago. In an observational study, Johnstone[17] observed that a significantly smaller proportion of children receiving SCIT developed asthma, versus children treated with medications only, over a period of 14 years. Subsequently, the Preventive Allergy Treatment (PAT)[18] study suggested the preventive effect of SCIT on the development of asthma in children with rhinitis, and this effect was shown to persist 7 years after discontinuation.[19] In parallel, it was consistently shown that SCIT was able to reduce the onset of new sensitizations in both adults and children.[20,21] The long-lasting persistence of the clinical effects of SCIT after discontinuation is an additional indirect confirmation of the effect on the natural history.[22–25]

The disease-modifying effects of SLIT have only been apparent in the past 10 years because the previous clinical trials were aimed at demonstrating the clinical efficacy and the safety of the treatment. Furthermore, studies assessing long-term and preventive effects require several years of follow-up of the patients. Nonetheless, there are some interesting and promising data on the preventive effects of SLIT.

Prevention of Asthma

The first study showing that SLIT may prevent the onset of asthma in children with rhinitis was published in 2004.[26] This randomized, open, controlled study involved 113 children aged 5–14 years suffering from seasonal rhinitis because of grass pollen at enrolment. Of these children, 54 were randomly allocated to drug treatment plus SLIT and 59 to standard symptomatic therapy alone. After 3 years, 99 children were re-evaluated: development of asthma was 3.8 times more frequent (95% CI,

1.5–10.0) in the control subjects. Another randomized, open, controlled trial[27] involved 216 children (age 5–17 years) suffering from allergic rhinitis with or without intermittent asthma. They were randomly allocated 2:1 to drugs plus SLIT or drugs only, and followed for 3 years. Symptoms and medication scores were recorded yearly during the period of exposure, whereas the presence of persistent asthma was assessed at 3 years. There was a significant reduction of symptom-medication scores only in the SLIT group throughout the study. There were 196 patients evaluated at 3 years, and the occurrence of persistent asthma was 2/130 (1.5%) in the SLIT group and 19/66 (30%) in the control group, with a number to treat of four. Overall, the rate of prevention of the onset of asthma in children, as reported in the aforementioned trials, is quite similar to that described for SCIT in the PAT study.

Concerning BHR, Pajno et al[28] demonstrated in a double-blind placebo-controlled study of 30 children with *Parietaria*-induced asthma, that SLIT was capable of preventing the onset of BHR to methacholine during the *Parietaria* pollen season. In an open randomized controlled study[29] of 52 birch-monosensitized patients (29 SLIT + 23 controls; followed for 5 pollen seasons) with allergic rhinitis and asthma, there was a significant and progressive increase in the methacholine provocation dose in the SLIT group (that became near normal at the fifth pollen season), with no change in the control group. As for the PAT study, the severity of asthma in the control groups was never presented.

Prevention of New Skin Sensitizations

There is no double-blind study with SLIT specifically designed to study the preventive effect on the development of new allergen sensitizations. However, some randomized controlled open trials have suggested this preventive effect with SLIT. Marogna et al[30] assessed the onset of new allergy skin test sensitizations after 3 years in 511 patients, randomly allocated to SLIT (319 subjects) or drugs alone (192 subjects). SLIT was given for mites (166), grass (89), or trees (64). At the end of the study, new sensitizations, compared with baseline, appeared in 64/170 (38%) of controls and 16/271 (5.9%) of SLIT patients ($P < 0.001$). In the study mentioned earlier, conducted in children,[27] at the 3rd year of follow-up, the rate of onset of new sensitizations was 4/130 in the SLIT group and 23/66 in the control group.

Long-Lasting Effect

Few studies have investigated the long-term effect of SLIT. Di Rienzo et al,[31] in a prospective controlled open study, followed 60 children (mean age 8.5 years) with asthma/rhinitis because of dust mites, for 10 years. They were subdivided into 2 matched groups with 35 subjects undergoing 4–5 years of SLIT and 25 subjects receiving only drug therapy. The patients were evaluated at baseline, at the end of SLIT and 4 to 5 years after SLIT discontinuation. In the SLIT group there was a significant difference compared with baseline for the presence of asthma ($P \leq 0.001$), whereas no difference was observed in the control group. This difference was also seen 5 years after the SLIT discontinuation.

A 15-year follow-up of mite-allergic patients treated with SLIT for 3, 4, or 5 years has suggested that a 4-year course represents the best combination of clinical efficacy and long-term effect.[32] Patients who received 4 years of SLIT had significantly better monthly symptom scores 7 years after discontinuation compared with the groups that were treated with 1 or 3 years of SLIT and the untreated control group. Again, a retrospective study on 59 patients allergic to HDM[33] suggested that 4 years of SLIT achieved a long-lasting effect of 7–8 years, whereas this effect was lost with shorter courses of treatment. Tahamiler et al,[34] in a 6-year randomized prospective trial, evaluated 2 groups of patients up to 3 years after SLIT discontinuation. One group of 67 patients received SLIT for 2 years and placebo in the subsequent year. The other group (70 patients) received SLIT for 3 years. Symptoms and specific nasal reactivity improved in both groups during treatment. The improvement was maintained 3 years after stopping SLIT, although the 3-year group displayed a more pronounced, long-term effect.

Unmet Needs

- The available experimental data suggest that SLIT can exert some effects on the natural history of respiratory allergy, resembling those of SCIT. These studies can be considered suggestive, but not conclusive, because of the relatively small number of subjects and the methodological problems.
- In particular, the long-term effect of SLIT after its discontinuation needs to be confirmed in randomized controlled trials, possibly double-blinded in the first years, and involving large numbers of patients.[35]
- The demonstration of a preventative effect on the onset of asthma would also require DBPC-RCTs, where objective respiratory parameters are assessed.
- The severity of asthma in patients on placebo needs to be assessed.
- Specific factors that can predict those patients that are protected against new sensitizations and new development of asthma, need to be identified: this issue also applies to SCIT.

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CHAPTER 7: SUB-LINGUAL IMMUNOTHERAPY IN CHILDREN

- SLIT is effective in allergic rhinitis in children ≥5 years of age.
- SLIT may be safe in allergic rhinitis in children ≥3 years of age.
- SLIT can be used for allergic rhinitis in children with asthma.
- SLIT should not be suggested as monotherapy for treating asthma.
- There are many unmet needs with SLIT in children.
- More studies are needed with SLIT in children in large randomized trials.

The first study on SLIT in children was published in 1990[1]: since then many studies have been published showing the efficacy and safety of SLIT in allergic children with rhinitis (rhino-conjunctivitis) and some sporadic papers of SLIT in children with other allergic diseases.

Rhinitis

Tari′s study[1] was the first showing the efficacy of SLIT in reducing the symptom score for rhinitis and significantly increasing nasal patency measured by rhinometry. Some studies have been published since then and a recent meta-analysis of 10 DBPC-RCT (that met the meta-analysis criteria out of 70 studies reviewed) found a significant improvement in those children receiving standardized allergen extract compared with placebo, and a decrease in medication use,[2] even though the heterogeneity among the studies was high and the dosages used were diverse. However, a systematic review of the literature reported that there was no evidence of effect for SLIT in terms of efficacy in rhinitis in the pediatric age group,[3] but the studies analyzed in this review were those

published up until 2005, when study design and dosing were still not optimal.[4]

The first evidence of the effect of SLIT in children came from an 18-month study of 2 different doses of SLIT for tree-pollen allergy in 88 children suffering seasonal allergic rhinitis, confirmed by skin prick test, specific serum IgE, and conjunctival allergen challenge. Eighteen months of SLIT with tree pollen extract provided dose-dependent benefits in terms of significantly reduced symptoms and medication use.[5]

Two adequately powered, well-designed DBPC-RCTs have now been published, both showing a clear effect of allergen tablets in childhood. A statistically significant reduction in rhinitis symptoms (28%) and medication (64%) score was shown during the pollen season in 114 children receiving active grass allergen tablets (with 15 μg Phl p 5) compared with 120 children in the placebo group.[6] The other DBPC-RCT evaluated the efficacy of 5-grass tablets (with 25 μg group 5 major allergen) administered pre- and coseasonally to 227 children with seasonal allergic rhino-conjunctivitis. In those receiving the 5-grass tablets a significant improvement was found in symptom and medication scores.[7] All these studies performed by specialists clearly show the efficacy of SLIT in reducing the symptom score during pollen season in children with rhinitis; furthermore, there were also a significant reduction in medication use. On the contrary a study of SLIT in a primary care setting did not show any differences at all for symptoms, rescue medication-free days, and disease-specific quality of life (QoL) between active and placebo groups, not even when subgroup analysis was carried out.[8] The studies suggest that SLIT is effective for the management of rhinitis in children selected and followed up by specialists.

The allergens that have been used with success in SLIT in the pediatric age group for rhinitis are pollen from *Phleum pratense*, 5-grass mix, *Parietaria* and *Betulaceae* pollens and HDM. SLIT with olive pollen showed only improvement in symptoms[9] and one grass study was negative.[10]

Asthma

Tari′s study also looked at the effect of SLIT in asthma in children. SLIT induced an improvement in both specific and non specific bronchial hyperreactivity.[1] An Italian double-blind, placebo-controlled study evaluated the efficacy and safety of SLIT after 2 years of treatment: there was a significant decrease in symptoms of asthma ($P = 0.0001$) and medication use ($P = 0.0001$) in the active group ($n = 12$) compared with the placebo group ($n = 12$). The visual analogue score on overall asthma symptoms improved in the SLIT group ($P = 0.0001$), but not in the placebo group.[11] Other studies have been published showing the efficacy and safety of SLIT in HDM sensitive children with asthma.[12] A study in 97 HDM-sensitive asthma children from Taiwan has shown that SLIT was effective in improving not only day and night symptom scores but also lung function.[13] However, 2 other DBPC studies of HDM SLIT in children were negative.[14,15] In olive pollen sensitive children the dyspnoea score, but not the medication score, improved with SLIT.[9] More recently a meta-analysis of DBPC-RCT of SLIT in asthma in children was published.[16] Symptom scores and the use of rescue medication were calculated with standardized mean differences (SMDs) using the random-effects model. The statistical software package (RevMan, 4.2.8; The Cochrane Collaboration; Oxford, UK) was used to perform the meta-analysis after the recommendations of the Cochrane Collaboration and the Quality of Reporting of Meta-analyses guidelines. Overall, there was a significant reduction in both symptoms ($P = 0.02$) and medication use ($P = 0.007$) after SLIT compared with placebo. However, all of these studies were small in size (total number of patients 441) and the size of effect was at best moderate.

One of the recent large trials on SLIT has assessed the effect of the grass tablets on asthma in children 5 to 16 years of age. Asthma symptoms (coughing, wheezing, shortness of breath, and exercise-induced symptoms) were significantly reduced, whereas use of rescue medication was reduced, but not significantly.[6] There is no clear consensus as to the use of SLIT in allergic children with asthma symptoms, particularly those with pollen allergy and concomitant allergic rhinitis.[17,18] The allergens that have been used with success in SLIT in the pediatric age group for allergic asthma are pollen from *Phleum pratense* and *Betulaceae* pollen; pollen extract from *Parietaria* did not show efficacy.[19] Furthermore, none of the studies reported objective parameters, and the clear-cut diagnosis of pollen asthma in these patients is questionable.

SLIT in Other Allergic Processes in Children

A single study in children with atopic dermatitis[20] and a preliminary report in those with IgE-mediated cow milk allergy[21] suggested that SLIT had given positive results. A DBPC-RCT study showed efficacy in children with cutaneous and respiratory symptoms induced by natural rubber latex.[22] At 1 year, latex SLIT reduced the symptom score in treated patients and prevented reactions induced by cross-reacting fruits. All of these studies open an avenue to study the efficacy and safety of SLIT in children suffering allergic symptoms beyond traditional seasonal or perennial aeroallergens. However, more studies are needed to confirm further clinical indications.

Safety in Children

The sublingual route was introduced with the aim of reducing side effects and increasing the safety of immunotherapy. This aspect has been reviewed recently. There is no difference in the incidence of AEs between children and adults[23] and SLIT has been shown to be safe. The most frequently reported AEs (mostly self-limiting) are local in the oral mucosa (itching and swelling) and of the digestive system. Just a few cases were considered moderate/severe and requiring medical intervention. Experience must be gained in the use of single versus multiple-allergens. SLIT with a single allergen is the most common practice in Europe whereas multiple allergens are used mainly in USA, Latin America and some other parts of the world. In adults, in one study, use of SLIT with multiple allergens was reported to be as safe as SLIT with a single allergen.[24]

Unmet Needs of SLIT in Children

Although recent adequately powered, well-designed DBPC-RCTs with grass tablets in children have shown effi-

cacy, there is no dose-ranging study and the optimal dose is still a matter of debate. Recent meta-analyses indicate that SLIT has a significant effect on symptoms and medications use in allergic rhinitis and asthma and the treatment is shown to be safe, though severe AEs may occur (see section on SLIT safety). There are still unmet needs for SLIT in children:

- Optimal dose and dosing frequency of allergen administration.
- Efficacy in patients unresponsive to pharmacotherapy.
- Drops versus tablets.
- Duration of treatment.
- Long-term efficacy.
- Preventive capacity.
- Other allergic processes beyond respiratory allergy.
- SLIT in preschool children.

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CHAPTER 8: GUIDELINES AND RECOMMENDATIONS ON SUBLINGUAL IMMUNOTHERAPY

- Several adequately powered, well-designed, randomized clinical trials have been published on sublingual immunotherapy.
- High-dose sublingual specific immunotherapy is effective in carefully selected patients with rhinitis, conjunctivitis and/or asthma caused by pollen and/or HDM allergy.
- Randomized clinical trials have confirmed that sublingual immunotherapy is safe. However, many patients report local side effects.
- SRs have only been reported rarely.

Many consensus documents and guidelines for immunotherapy have followed the WHO consensus meeting on immunotherapy,[1] the first EAACI guidelines on immunotherapy,[2] and the WHO Position Paper on immunotherapy.[3] In all of these articles, SLIT was not recognized as an effective and/or safe treatment of allergic diseases. In 1998, an EAACI consensus on local immunotherapy[4] suggested that SLIT may be effective but its safety was questioned. Only 4 trials met the requirements for inclusion in this document. The first ARIA guidelines[5] found that 12 trials could be analyzed and proposed use of SLIT both in children and adults. However, SLIT was still a matter of debate, in particular in the USA,[6]

and is not FDA approved. In their review for the ARIA 2008 Update,[7,8] Passalacqua and Durham listed 23 new RCTs.[7] Other RCTs have been reported more recently.[9–13]

Guideline Development: From Evidence-Based Medicine to Patients' Views

A consensus is "a document that represents the collective opinion of a convened expert panel." The opinions expressed in the statement do not reflect a formal evidence review and were not developed in accordance with the process outlined for evidence-based clinical practice guidelines. Early guidelines were predominantly derived from such unsystematically compiled opinions of experts based on clinical trials and mechanistic approaches (opinion-based medicine).[14] The terms "recommendation," "evidence-based," and "guideline" should not be used in the context of consensus statements.

The development of evidence based clinical guidelines, on the contrary, follows transparent processes.[15] "Evidence-based-medicine" (EBM) has become an essential component in the preparation of guidelines. It is the ability to track down, critically appraise (for validity and usefulness) and incorporate data obtained from the best available evidence (ideally DBPC-RCTs) to establish the clinical bases for diagnosis, prognosis and therapeutics.[16,17] Evidence-based medicine attempts to provide a logical, transparent and applicable framework from which the quality and relevance of clinical studies may be assessed in an unbiased manner.[18] Systematic reviews contribute to resolving uncertainty when original research, reviews and editorials disagree.[19]

The efficacy of SLIT has been assessed in RCTs. Around 50 SLIT RCTs have been carried out. Systematic reviews and meta-analyses have been completed.[20–23] However, their results are difficult to interpret for many reasons (Table 8-1).

Although there is increasing agreement upon the components of proper clinical practice guidelines and what constitutes high quality evidence, it is also clear that the highest quality evidence from DBPC-RCTs is often based on selected patients. Therefore, they may fall short of representing the entire population.[24] However, RCTs offer the most methodological rigorous approach to establishing cause and effect, thereby providing the highest quality evidence. A number of approaches have been used to grade the quality of evidence and the resulting strength of recommendations.[25,26] The large number of systems for measuring the quality of evidence and recommendations is confusing[27] and all previously used approaches for grading levels of evidence and the strength of recommendations have important shortcomings.[14,25]

At present, the identification, interpretation, and reporting of harmful effects is incomplete in RCTs.[28,29] Thus, there is a need to obtain better evidence about side effects (risks).[27] Evidence is required throughout the entire spectrum of the treatment life cycle, from the premarketing to the postmarketing phase. Drug safety and effectiveness need to be assessed in the real world, where outcomes may differ from those of controlled clinical trials that provide premarket test results. Drug regulatory initiatives include data mining, active adverse drug reaction (ADR) surveillance, independent, multidisciplinary evaluation of suspected ADRs, and formal pharmaco-epidemiology studies.

TABLE 8-1. Points to Consider for Inclusion of SLIT RCTs in Meta-analyses

The number of patients needed to enroll should be clearly stated in the protocol considering expected effect size and drop-out rates. Analysis should be done according to the intention to treat principle
Most RCTs carried out before 2005 were underpowered and could only be considered as proof-of-concept studies
Extracts may not be compared between manufacturers and the labeled content may not be the exact content in micrograms of major allergen
Vehicles differed and there may be large pharmacokinetic differences between drops and tablets and between tablets themselves. Appropriate analyses of this difference is required
The allergens may differ for a given indication. Some manufacturers use a single allergen whereas others a mixture of a few major grass pollens
The raw materials, preparation and standardization of allergens differ widely between manufacturers
A number of standardized allergens, allergoids and others have been studied
The dosing schedule is specific to each manufacturer: maintenance dose, weekly dose, total cumulative dose, pre- and co-seasonal administration
Primary and secondary outcomes may differ between trials
Emphasis should be placed on registered trials (when started after registries were available) and publication biases should be evaluated carefully

More recently, the "Guidelines for WHO guidelines" recommended using a specific, uniform grading system.[30] The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach is one of the recommended systems[26] and is being used increasingly by a number of organizations. The GRADE working group has published the results of its work.[31] It grades recommendations in 2 levels (strong and weak) and quality evidence into 4 categories (high, moderate, low, and very low)[26,27] based on the evidence, the quality of evidence, safety, costs, and patients' views.

Guidelines and Consensus Document in Sublingual Immunotherapy

The first guidelines on immunotherapy were opinion-based.[3] Subsequently, most guidelines and consensus documents used the Shekelle et al method[32] (Table 8-2).

The ARIA guidelines were the first to develop an evidenced-based model.[5,8] Adequately powered, well-designed DBPC-RCTs have been performed with SCIT[35] and SLIT[10,36–38] in patients suffering from pollen induced allergic rhinitis. In the population selected, they confirmed the efficacy of immunotherapy (Evidence A[32]). In children, one systematic review suggested that SLIT is not effective,[22] but a large RCT in birch pollen allergy[39] and 2 very recent adequately powered, well-designed DBPC-RCTs in grass pollen allergy convincingly showed efficacy.[40,41] More studies are however needed to demonstrate the efficacy of SLIT to other allergens in rhinitis and SLIT in asthma.[42] The methodology of RCTs is critical[43,44] and only trials after an optimal study design should be considered.[45,46] Practice parameters for immunotherapy have been published by EAACI[47,48] and AAAAI/ ACAAI.[34]

SLIT is safer than SCIT although some rare severe reactions may occur.[49–51] SLIT is administered at home and patients

TABLE 8-2. Evidence Models of Guidelines in Sublingual Immunotherapy

			SLIT	
	Year	Evidence Model	RCT No.*	Recommendation
WHO consensus[1]	1988	None	0	None
EAACI 1988 guidelines[2]	1988	None	0	None
EAACI 1992 guidelines[33]	1992	None	0	None
WHO Position Paper[3]	1998	None	2	None
EAACI Local Immunotherapy[4]	1998	None	4	Suggested in adults
ARIA[5]	2001	Shekelle et al[32]**	12	Recommended in adults, suggested in children
AAAAI/ACAAI Practice parameters[34]	2007	Shekelle et al[32]**	18	SLIT as investigational (in the US, not FDA approved)
ARIA Update[8]	2008	Shekelle et al[32]**	36	Recommended in adults and children

*Number of DBPC-RCTs considered in the paper; **the Shekelle et al[32] grading system only considers efficacy.

should be educated on how to recognize and treat a reaction if it occurs. It is also important to improve the study of the time course of severe reactions after immunotherapy.[52] The safety of SLIT in preschool children needs more attention before being widely used[53] or proposed in guidelines. Postmarketing surveillance studies are needed to compare the safety of different forms of immunotherapy.

The costs of treatment are key factors in the therapeutic decision. They should include short-term effects and long-term effects and the preventive effect of immunotherapy that is always difficult to assess or to model.[54] Some large carry-over studies assessing the effect after treatment interruption will soon be available. SLIT was proposed to be cost-effective[55–57] but these analyses suggest a very high annual cost and there are some concerns.[58] Furthermore, there may be some misconceptions about immunotherapy cost-effectiveness. Many studies are now using the quality-adjusted-life years to make pharmacoeconomic decisions.[59] It is usually accepted that for severe and/or life-threatening diseases the ICER (incremental cost-effectiveness ratio) threshold is up to 50,000 € per year. This is the case for omalizumab in severe asthma or many biologicals in cancer or neurodegenerative diseases.[60] Thus, some authors have proposed that a similar ICER threshold may be used for immunotherapy.[60] However, the majority of patients suffering from allergic diseases have a mild to moderate form of the disease and cost-effectiveness needs to take into consideration the preventive effect of immunotherapy using models such as Markov.[54,60]

One of the remaining problems is that the selection of patients for immunotherapy RCTs does not necessarily reflect the current suggestions[5,8] (Table 8-3). For allergic rhinitis, immunotherapy is commonly indicated in patients who have long-lasting symptoms during the year and/or who were not well controlled by optimal pharmacotherapy (SCUAD, Severe Chronic Upper Airway Disease) and/or who have had side effects from pharmacotherapy and/or who do not wish pharmacotherapy.[5,8] However, these patient characteristics are not included in the published RCTs. One study approached these recommendations and showed that SLIT can reduce medication needs in patients receiving immunotherapy while maintaining disease control.[61]

The age of the patients is still a matter of debate. New adequately powered, well-designed DBPC-RCTs have found that SLIT is effective in school children.[41,42,62] However, there is no study in preschool children. The guidelines on immunother-

TABLE 8-3. Recommendations to Minimize Risk and Improve Efficacy of Immunotherapy (From EAACI[33], GINA[63], and ARIA[5,8])

Considerations for Initiating Immunotherapy (Updated From the WHO Position Paper on Allergen Vaccines[3])

1. Presence of a demonstrated IgE-mediated disease:
   - Positive skin tests and serum specific IgE to an allergen concordant to clinical symptoms
2. Documentation that specific sensitivity is involved in symptoms:
   - Exposure to the allergen(s) determined by allergy testing related to appearance of symptoms
   - If required, allergen challenge with the relevant allergen(s) (optional)
3. Severity and duration of symptoms:
   - Subjective symptoms for rhinoconjunctivitis: patients should have symptoms of sufficient severity and duration
   - For asthma: control questionnaire should not show uncontrolled asthma
   - Objective parameters, for example, work loss, school absenteeism
   - In asthmatics pulmonary function (*essential*): exclude patients with severe asthma
   - Monitoring of pulmonary function
4. Availability of standardized or high quality vaccines
   - Specific immunotherapy needs to be prescribed by specialists
   - SCIT needs to be administered by physicians trained to manage systemic reactions if anaphylaxis occurs
   - SLIT is administered at home and patients should be informed of possible risks and how to control eventual side effects
   - Patients with multiple sensitivities may not benefit from specific immunotherapy as much as patients with a single sensitivity. More data are necessary
   - Patients with non-allergic triggers will not benefit from specific immunotherapy
   - It is essential, for safety reasons, that asthmatic patients should be asymptomatic at the time of the injections because lethal adverse reactions are more often found in asthma patients with severe airways obstruction
   - In asthmatics, FEV_1 with pharmacological treatment should reach at least 70% of the predicted values, for both efficacy and safety reasons

apy recommend starting the treatment after the age of 5 years.[3] In preschool children, safety has to be evaluated in Phase I trials before large RCTs are started. Furthermore, the diagnosis of allergy in preschool children may need some attention.[64]

Unmet Needs

- SCUAD patients should be tested using chamber studies to show that SLIT can add efficacy to current treatment in patients uncontrolled despite intranasal corticosteroids and oral H1-antihistamines.
- If the above study shows that SCUAD patients are improved by SLIT, an appropriate RCT should be carried out.
- Studies in asthma should be done. To get registration for asthma, objective measures should be used [forced expiratory volume in 1 second (FEV_1) and peak expiratory flow (PEF)] as coprimary or major secondary outcomes. The definition of "seasonal asthma" needs better characterization.
- Studies on prevention should be started (see prevention and methodology).
- After analysis of HDM studies, new studies are needed with improved or different outcomes.

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CHAPTER 9: DEFINITION OF SUBLINGUAL IMMUNOTHERAPY PATIENT SELECTION

- To be eligible for SLIT, patients should have:
  - A clinical history of allergy.
  - Documented ALLERGEN SPECIFIC IgE positive test.
  - The allergen used for immunotherapy must be clinically relevant to their clinical history.
- Age does not seem to be a limitation.
- Monosensitized patients are ideal candidates for SLIT, and recently single allergen SLIT has been demonstrated to be effective in polysensitized patients.
- Presently use of SLIT in Latex Allergy, Atopic Dermatitis, Food Allergy and Hymenoptera Venom Allergy is under investigation: more demonstrations are needed to support clinical use.
- There is no indication whatsoever for treating non-IgE-mediated hypersensitivity (for instance nickel sensitivity) with SLIT.
- SLIT may be considered as initial treatment. Failure of pharmacological treatment is not an essential prerequisite for the use of SLIT.
- SLIT may be proposed as an early treatment in respiratory allergy therapeutic strategy.
- Special SLIT indications exist in the following patients.
  - Patients uncontrolled with optimal pharmacotherapy (SCUAD).
  - Patients in whom pharmacotherapy induces undesirable side effects.
  - Patients refusing injections.
  - Patients who do not want to be on constant or long-term pharmacotherapy.

SIT is a highly effective treatment in patients with IgE-mediated diseases, asthma, rhinoconjunctivitis, insect venom SRs, and probably atopic dermatitis and food allergy.

Patients must have IgE sensitization to an allergen demonstrated either by skin tests or serum IgE antibodies and a relationship between symptoms and exposure to an allergen to which the patient is sensitive. Immune modulation by administration of increasing doses of specific allergens provides protection against allergy symptoms on natural exposure to the allergen but only if the allergen is clinically relevant. Many people may have IgE antibodies (a positive skin test or serum specific IgE$>$ 0.35 kU/L) though do not develop symptoms.

Patient selection is important, and efficacy must always be balanced against the risk of side effects. The necessity for initiating SIT depends on the degree to which symptoms can be reduced by medication, the amount and type of medication required to control symptoms, and whether effective allergen avoidance is possible. Therefore, it is essential to consider

SIT based on allergen sensitization rather than on a particular disease manifestation.[1,2]

Although the majority of subjects is polysensitized, monosensitized patients or patients concomitantly sensitized to noncross-reacting allergens are ideal for a single allergen vaccine study and are more likely to demonstrate the beneficial effects of SIT. Inclusion criteria should be defined in relation to age, sex, disease, disease severity, comorbid conditions, and previous SIT. Concomitant medications for nonallergic diseases, other illnesses, and undesirable daily activities are examples of exclusion criteria.[3]

Age

There is no specific upper or lower age limitation for SIT. SLIT may be a safe and effective treatment for all ages if an atopic mechanism is involved in the pathogenesis of disease, although efficacy in children less than 5 years of age is not documented. A meta-analysis showed that SLIT is effective in children 3–18 years of age with allergic rhinitis.[4]

To evaluate the clinical efficacy of SLIT in respiratory allergy in children, 8 DBPC-RCTs on SLIT were selected. Five studies were run with HDM, one with olive pollen, one with wall pellitory (*Parietaria*) pollen, and one with grass pollen. SLIT could be currently considered to have low to moderate clinical efficacy in children of at least 4 years of age, monosensitized to HDM, and suffering from mild to moderate persistent asthma.[5]

Children with asthma or persistent rhinitis, aged 1 year and 11 months to 3 years and 10 months were treated with a monomeric allergoid. The mean follow-up was 22.3 months and 30/36 children were highly or moderately improved. SLIT was safe in these very young children.[6]

Asthma

Patients allergic to mites may be candidates for SLIT if they have significant symptoms of rhinitis or asthma when they are exposed to domestic mite allergens.

A meta-analysis of DBPC-RCTs evaluated SLIT efficacy in the treatment of allergic asthma in children. Nine studies reported 441 subjects who had concluded treatment and had received a final clinical assessment. SLIT with standardized extracts (mainly mites) reduced both symptom scores and rescue medication use in children with allergic asthma compared with placebo.[7]

An asthma expert panel recommends that allergen immunotherapy be considered for patients with persistent symptoms and in patients whose asthma is not well controlled by pharmacotherapy, or in whom multiple medications are required.[8]

Immunotherapy can prevent the development of asthma in allergic rhinitis patients and new sensitivities in monosensitized children and adults. As in the case of rhinitis, SIT is indicated when there is a significant allergic contribution to the patient's symptoms.[9]

Although efficacy of SIT has been shown for treatment of allergic asthma, there is a risk of acute asthma in patients with severe asthma. Thus, severe or uncontrolled asthma is a contraindication for SIT.[8,10]

Allergic Rhinitis

Allergen immunotherapy is an effective treatment for allergic rhinitis and can potentially modify the disease. Clinical benefits may be sustained years after discontinuation of treatment, may prevent the development of new allergen sensitization and reduce the risk for the future development of asthma in some patients. As for asthma, SLIT should be considered if: 1) symptoms are persistent or severe, despite pharmacological and nonpharmacological measures; 2) medications cause unacceptable side effects; 3) patients or parents unwilling to use intranasal corticosteroid; or 4) asthma is present. Again, allergen immunotherapy should only be considered if there is clear evidence of a relationship between symptoms and exposure to an allergen to which the patient is sensitive.[11–13]

Special Considerations

Venom

In a proof-of-concept study, honeybee SLIT significantly reduced the extent of LLRs to honeybee in monosensitized adult patients, and its safety profile was good. Local reactions are not an indication for venom IT and the efficacy of venom SLIT should be assessed in patients with SRs.[14]

Atopic Dermatitis

SLIT with a standardized mite extract showed efficacy in children with mild-moderate allergic atopic dermatitis, whereas the benefit was variable in the severe form. Children aged 5 to 16 years with atopic dermatitis [Scoring Atopic Dermatitis (SCORAD) >7] and sensitized to dust mites (mean mite specific IgE: 10.6 kU/L) received SLIT for 18 months.[15] Further studies in atopic dermatitis are necessary before recommendations can be made regarding effectiveness.

Food Allergy

The efficacy and tolerance of SLIT with a standardized hazelnut extract were evaluated in 23 patients allergic to hazelnut in a randomized, double-blind, placebo-controlled study. SRs were observed in only 0.2% of the total doses administered. After 8–12 weeks treatment, efficacy was assessed by double-blind, placebo-controlled food challenge: almost 50% of patients who underwent active treatment, but only 9% in the placebo group reached the highest food challenge dose (20 g) provoking objective symptoms. IgG4 and IL-10 levels after SLIT increased only in the active treatment group.[16] None of these last 3 diseases should be presently considered indications for clinical use of SLIT.

Latex Allergy

Patients with latex-induced urticaria may benefit from latex SLIT.[17] In an open trial designed to evaluate tolerance, SLIT (4 days) with a standardized NRL extract was followed by a 9-week maintenance treatment. In 26 patients, the glove-use test improved significantly after 5 days and 10 weeks of treatment ($P = 0.003$, $P = 0.0004$, respectively), the rubbing test also improved significantly.[18]

Finally, consideration should be given to the possibility to predict responder patients to SIT, including SLIT; recently the evaluation of serum s-IgE/total IgE ratio has been proposed.[19] Further studies are needed to better predict SLIT responders.

Summary

SLIT is indicated for treatment of different allergic conditions following the general criteria of selecting patients for SIT; mild to moderate IgE-mediated disease, clinically relevant allergens, exhausting pharmacological and nonpharmacological therapeutic options, and unavoidable side-effects of medication.

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CHAPTER 10: THE FUTURE OF IMMUNOTHERAPY IN THE COMMUNITY CARE SETTING

- **The significance of primary care:** Globally, allergic disease is under-recognized, under- or mis-diagnosed and under- or maltreated, because the symptoms of IgE mediated allergic disease (rhinitis, asthma, eczema, conjunctivitis, etc) overlap with many other conditions. The majority of patients who seek medical advice are seen in primary care.
- **Allergy education:** Allergy teaching needs to become a core part of under- and postgraduate curricula. Primary care teams in particular require further training in the early detection, diagnosis, management and treatment of allergic disorders. Pragmatic programs need to be developed for a better Patient-Physician Partnership.
- **Delivery of SLIT in the community setting:**
  a. Primary Care Physicians/GPs should be armed with the knowledge of selecting the appropriate treatment relevant to the patient's illness and should be trained to make a comprehensive assessment, recognise treatment failure (inadequate therapy, mal-administered therapy, inadequate control) and exacerbations of illness.
  b. They should be trained in all aspects of SLIT, including assessment of patients and administration of SLIT. Emphasis should be placed on detection and management of untoward side effects, possible local and SRs, adverse effects and other untoward incidents in detail, and taught how to manage such incidents.
- **Collaboration between primary care team and allergists:** Primary Health Care Workers (including physicians, nurses, and others) should be able to administer SLIT under the mentorship of a trained allergist, and maintain regular liaison with the allergist. In collaboration, the allergist and the GP will commence, devise and plan SLIT for the patient, and follow up as and when needed: they will also jointly decide when to discontinue therapy. However, the decision whether or not to initiate SLIT (as for SCIT) should be made by the allergist.

Introduction

Allergic diseases are increasing worldwide. They are manifest in many different organ systems, often causing distressing and disabling symptoms for the sufferer and their

families alike. Allergy is currently managed suboptimally[1,2] in the community setting and allergy specialists are often difficult to access.

It is important that health care professionals (HCPs) working in the community have a clear understanding of allergy to differentiate the problem from nonallergic causes, such as sensitivity or intolerance, for which allergy medicines have limited effectiveness. Nonetheless, H1-antihistamines and other agents may benefit the patient in conditions mimicking allergy (eg, where pharmacological, hormonal, neurogenic, or other stimuli initiate direct degranulation of the mast cell). Many patients' problems can be managed with the judicious use of medications but for some, particularly where medications are not effective, SIT offers the prospect of a cure. The advent of SLIT now offers the possibility of once again providing immunotherapy in the community setting.

Background

Globally, over the last 50 years or so, allergic diseases have increased to epidemic proportions, as clearly demonstrated in longitudinal population studies,[3] with a concomitant rise in hospital admissions for severe disease.[4] Many people consult their primary health care teams with wide ranging symptoms, which may or may not be because of allergy, the most common manifestations of which are rhinitis, asthma, and eczema. Allergy is a set of signs and symptoms caused by mast cell degranulation in response to crosslinking of IgE molecules bound to the membrane of these mast cells by an allergen. The term "allergy" is loosely used by both patients and HCPs, with patients ascribing many symptoms to an allergic cause when a carefully taken history reveals this is not the case.[5] Most patients with allergic diseases consult primary care physicians.[6]

Similarly lax use of the term by HCPs creates further anxiety and misunderstanding, for example, the watering of eyes while cutting onions; or explaining the diarrhea caused by antibiotics as an allergy instead of as an alteration in bowel flora. It is clear that we have a duty of care to our patients to attempt to make the correct diagnosis by taking a careful history and performing appropriate examinations and investigations.[7] Failure to meet patients' needs leads them to seek help from alternative practitioners who may do more harm than good, and often at great expense to the patient.

Educational Needs

In many medical schools allergy is not given a high priority or even included in the medical curriculum. This fact is compounded by the paucity of allergy education given to or acquired by those working in the community setting.[8,9] A description of those needs is beyond the scope of this statement but has been addressed elsewhere.[10] It is imperative that clear educational messages are made available to the general public concerning what is and is not allergic disease and what treatments are and are not effective.

Allergy Management

This consists of a variety of strategies, foremost of which is avoidance of the offending allergen. This of course may not be possible for example with the ubiquitous HDM[11] but for other allergens, for example, peanuts, is currently the only reasonable course of action. Many allergies can be managed by the judicious use of medications and for some diseases such as rhinitis and asthma, there are clear guidelines eg, ARIA,[12] GINA,[13] and IPCRG.[14]

Rescue medications may be needed to treat some allergic conditions, for example, use of adrenaline in acute anaphylaxis or oral corticosteroids for an exacerbation of asthma or severe acute intermittent rhinitis. Similarly, routine medications such as antihistamines and intranasal steroids may provide adequate control of many allergic problems such as urticaria or intermittent rhinitis.

Immunotherapy

Before the mid-1980s many patients received SCIT in the community setting and were assessed, by skin prick testing, before administration of allergen extract solutions. Anecdotally many of these patients benefited from this therapy, although it was delivered in a haphazard, random fashion with no true systematic evaluation. This results in a number of deaths and leads to an abandonment of immunotherapy in primary care, coupled with a loss of confidence in this treatment modality, especially in the UK.[15] However the use of allergen immunotherapy in the Primary Care setting[16–19] and also the use of allergen extracts for the diagnosis of allergic disease,[20] has been well documented.

More recently both subcutaneous (SCIT)[21,22] and sublingual (SLIT)[23–28] immunotherapy have been found to be effective treatment for allergies.

For the near future, some forms of immunotherapy (Hymenoptera venom) will have to continue to be administered in specialist units, because of the risk of anaphylaxis. On the other hand SLIT offers an effective,[29,30] safe[31–34] and easy-to-use form of treatment which may be administered by or through primary care.[35–38] Fatal anaphylaxis has yet to be encountered, although local side effects are relatively common. Because patients self administer at home, there is little drain on the time of the primary care team who only have to supervise the first dose: it is also cost effective to the patient.[39–42] There is now a wide range of allergens available for SLIT, for example, grass[43] and HDM[44–50] and the evidence for cumulative benefit is emerging.[51,52]

The current challenge is to identify those patients who are most likely to benefit from the administration of SLIT, what are the steps necessary to identify likely candidates, what investigations are needed to validate that choice and what mechanisms need to be made available to ensure efficient, effective, cost effective and safe delivery of this new technology. One suggestion is the creation of a GP with a special interest who would have a higher level of allergy training and greater resources to assess and investigate patients needs, especially where access to specialist care is difficult.[53] However, for the immediate future, it would still be advisable that the decision whether or not to initiate SLIT (as for SCIT) should be made by the allergist.

The IPCRG and WAO could join together, as organizations that encompass the generalism of primary care with the specialism of secondary and tertiary care to endorse a course of action that will lead to greater accessibility and

availability of these medications coupled with an initiative to meet the educational needs of patients and providers alike.

Unmet Needs

- HCPs should learn to differentiate between allergic and nonallergic rhinitis.
- HCPs should be able to use readily available pharmaceutical agents to ameliorate the symptoms of allergic rhinitis.
- HCPs need educational initiatives to help them to understand immunotherapy.
- It is important to recognize which patients might benefit from SLIT.

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CHAPTER 11: METHODOLOGY OF CLINICAL TRIALS IN SUBLINGUAL IMMUNOTHERAPY

- The methodology of randomized clinical trials is essential to critically assess and register treatment interventions.
- Recently, large well-performed randomized clinical trials have been published for specific sublingual immunotherapy.
- Requirements for conducting trials in SLIT include. Allergen standardization.
- Patient's inclusion and exclusion criteria.
- Phase I trials to assess safety.
- Dose-ranging studies.
- Adequate pollen counts in trials on pollen allergic patients.
- Pivotal trials that should be of randomized, parallel-group, placebo-controlled design: the number of patients should be adequate.
- Primary and secondary outcome measures are identified.
- There are needs for specific trials in asthma, food allergy, disease-modifying efficacy, cost-effectiveness, and children
- In all trials, safety should be carefully monitored.

Introduction

The efficacy and safety of SLIT were until recently a matter of debate. The methodology of many SIT trials was insufficient.[1]

Meta-analyses could not reach a clear conclusion because they included RCTs of insufficient methodology, which were not always devoid of defects and the new adequately-powered, well-designed DBPC-RCTs were published later.[2–5] The major issues that can be addressed to currently available meta-analyses on SLIT relate to the high level of interstudy heterogeneity (clinical, methodological, and statistical) and the size of the studies included. Trials administering different allergens, with different schedules, in different cumulative doses, to different kinds of patients and for different durations were analyzed together. Open or single-blind studies were included. The quality of trials measured by accepted evaluation scales, detected defects regarding allocation concealment, blinding, randomization, and patient selection in most of the trials, especially in the pediatric population. Therefore, small studies are potentially misleading for the risk of overestimating the size effect of intervention or missing moderate/low effects. Finally, most studies included symptoms as a primary outcome without taking into account the concomitant rescue medications inducing misinterpretation.

Although there are negative DBPC-RCTs[6] (unpublished data), adequately-powered, well-designed DBPC-RCTs have recently confirmed the efficacy and safety in adults and children with pollen-induced rhinitis.[7–13] It is therefore important to propose guidelines for the performance and evaluation of RCTs in SLIT to optimize the quality and reporting of RCTs and guidelines.[14]

A paper under the auspices of the WAO[15] on the methodology of RCTs has been used as a basis for the present paper. Furthermore, the EMEA Committee For Medicinal Products For Human Use (CHMP) Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases and other related European regulatory issues were carefully studied.[16,17]

Diseases and Allergens to Be Investigated

The clinical efficacy of SLIT is well established for grass pollen rhinitis and conjunctivitis but more studies are needed for other allergens and asthma. For other allergic diseases such as atopic dermatitis,[18] latex,[19] or food allergy,[20,21] SIT is still not recommended and adequately-powered, well-designed DBPC-RCTs need to be carried out to critically assess efficacy and safety. Immunotherapy using venoms will not be considered in this chapter.

Quality and Standardization of Allergen Vaccines

The quality of the allergen vaccine is critical. Whenever possible, standardized vaccines of known potency and shelf-life should be used.[22,23]

The potency of allergen vaccines depends on the type of vaccine (allergen extract, recombinant allergen, allergoids) and should follow recommendations such as the recent CHMP guideline on allergen products.[24] In any RCT using allergen extracts, the characteristics of the vaccine need to be included, namely the content of representative major allergens in mass units (micrograms per milliliter).[22,23] However, comparison between different manufacturer labeling may be difficult because of differences in assays and methodologies for measurement of the major allergens.[25,26] For mixtures, the principle of homologous groups is advised in Europe,[27] to-

gether with the careful assessment of the stability of the extracts when mixing together different allergens.

Placebo

Double-blind, placebo-controlled, SLIT studies have found that up to 65% of subjects on active treatment with allergen versus less than 30% on placebo have had local allergy symptoms allegedly associated with absorption of the allergen. This imbalance of adverse local/regional reactions in these studies makes the blinding of the study difficult.

Collins English Dictionary defines placebo as "an active substance or other form of therapy administered to a patient usually to compare its effects with those of a real drug or treatment . . ." The use of a placebo is essential in any study, and appears particularly important in SLIT. Ideally, the placebo should have the same characteristics as the active allergen in appearance, smell, taste, consistency, and cause local symptoms consistent with an allergen extract.

However, the choice for a placebo in SLIT is unclear. Histamine, under the tongue, does not elicit itching; nor are there any other substances that produce similar symptoms to an allergen extract in a person allergic to a given allergen. Therefore, it would be difficult to manufacture a placebo that causes local allergy symptoms. In addition, from some studies, the adverse local effects from SLIT typically remit within a week or two. Because it is not feasible to devise an active placebo, any analysis of efficacy should take into account the incidences of side effects in assessing efficacy. However, in a study, the level of local/regional side reactions was not associated with efficacy.[9]

Patient Characteristics

a. Selection of Patients

Many subjects with positive skin tests and/or serum specific IgE do not present with symptoms.[28] Thus, only patients with an accurate diagnosis of an allergic disease, and in whom the allergen sensitization is correlated with the time of symptoms should be included in RCTs. The diagnosis of allergy should be based on skin prick tests and/or the measurement of allergen-specific IgE in serum. It is not clear whether both tests are needed. Additionally, nasal and/or conjunctival allergen provocation tests can be used to establish the relevance of the allergen. The history of allergic diseases should cover at least 2 consecutive years.[16]

Allergic diseases should be classified in terms of duration and severity (or control) according to the most recent guidelines: ARIA for allergic rhinitis[29] and GINA for asthma.[30] Small studies in patients with perennial rhinitis showed usually less efficacy[31] than those in persistent rhinitis.[32] Therefore, it is advised to study patients with persistent rhinitis.

Patients enrolled in SIT studies should have a minimal level of symptoms (historical for pollen trials or at baseline). The maximum mean (or median) symptom score of patients receiving placebo is usually low in SIT studies by comparison to drug trials. These low scores do not reflect the severity of the disease but may be associated with low allergen exposure of patients during the season.

Because most allergic patients are polysensitized,[33] it is important to characterize the different inhalant allergens to which the patients are sensitized, to differentiate mono- and polysensitized subjects, and to consider cross-reactivities between allergens. The exposure to relevant allergens overlapping with the allergen used in a SLIT trial, can cause misleading results. Comorbidities should be clearly stated and eventually used in multivariate analyses. Patients should not have had any form of immunotherapy within the past 5 years.[16]

b. Comedication and Allergen Avoidance

The indication of SIT with inhalant allergens is not to replace pharmacologic treatment, but to improve the control of patients who are insufficiently controlled using drugs.[22] Concomitant medications are therefore needed in most patients. In most SIT trials, rescue medications are proposed, and should be administered in a standard way to calculate a medication score.[34] In a study, patients were instructed to use medications to control symptoms as best as possible and the primary end point was the medication score.[35] In patients with high morbidity, preventer medication should be considered in accordance to ARIA and GINA guidelines. A composite score that includes medication can be considered.

Allergen avoidance is a matter of discussion because single measures to avoid mites are not effective in asthma.[36] However, it has been proposed that patients should have a control of mites in SLIT trials.[16]

Design of Clinical Trials

a. Phase I Studies

The methodology of Phase I studies should follow strict recommendations.[16] Only allergic patients should be included in Phase I trials. Some SLIT trials have been published.[37–39]

TABLE 11-1. Surrogate or Paraclinical Parameters

Target Organ Allergen Specific Reactivity	Immunological Parameters
• Skin: end point skin test, late cutaneous response	• Total and allergen specific IgE and IgG subclasses
• Nose, eye, and bronchi: allergen specific provocation test	• Mucosal IgA
Allergen chambers	• Lymphocyte subsets and cytokines (eg, IL-12, IFNγ, IL-5, IL-10)
Non specific organ reactivity:	• Local and systemic inflammatory markers (eg, adhesion molecules, urinary leukotrienes, sECP**, tryptase)
• Bronchial challenge with methacholine, carbachol, histamine, AMP*	

*Adenosine monophosphate; **serum eosinophil cationic protein.[40]

b. Phase II Studies

i. Outcomes to be Measured. Many different outcomes may be examined in Phase II studies to support the efficacy of SIT. They are detailed in the WAO Paper (Table 11-1).[15]

ii. Dose-Finding Studies. One important issue is the optimal dose of allergen that should be used to obtain the maximal efficacy without side effects. Dose-finding studies are therefore required. It has been suggested that challenge studies may be used[16] but RCTs may be needed.[9]

iii. Pharmacodynamic Studies. The first experimental basis for exploring the in vivo kinetics of allergen administered through noninjectable routes was achieved by radiolabeled allergens, scintigraphic images and chromatography.[41,42] Pharmacodynamic studies can be performed assessing changes on immunologic markers or allergen challenge.[16]

c. Phase III Studies

i. Baseline Assessment. In pollen allergy, the inclusion of a baseline period of observation, for example, one pollen season before randomization would be optimal. However, because of the unpredictability and variability of allergenic exposure to pollen allergens this baseline period cannot be used to compare with treatment years.[43,44] This baseline season may be used to exclude patients who do not present a clear increase in symptoms during the season. During patient selection, attention should be paid to the out of season level of symptoms in active and control groups to check the correlation between increase in symptoms and in pollen counts.

In HDM allergy, a baseline may be used,[45] and the fluctuations in the levels of indoor allergens may be observed throughout the studies.[32] In the case of corticosteroid-withdrawal studies, a baseline observation period is needed to stabilize asthma and to assess the baseline level of inhaled corticosteroids.

ii. Randomized Clinical Trial in Rhino-Conjunctivitis. A randomized, parallel group, placebo-controlled and double-blind design remains the gold standard to determine efficacy and safety of allergen products.[15,46] Superiority studies need to be carried out.[16] Trials should be registered.

Many SLIT studies have methodological flaws:

- Inclusion of a small number of participants.
- Studies of unmatched groups with respect to disease severity.
- Undefined primary outcome.
- Nonsignificant primary outcome and significant secondary outcomes.

1. Assessment of Allergen Exposure

In pollen RCTs, pollen counts should be measured and pollen traps should be located to match the pollen season of all patients of the study. However, it is almost impossible to have a sufficient number of pollen traps in multinational trials. Furthermore, the local exposure of patients is very important and cannot be assessed using pollen traps. Thus, there is only a poor association between pollen counts and individual patients' symptoms.

In mite studies, the association between household mite allergen levels and symptoms is questionable at best; major allergen content of house dusts in patients' homes may be measured serially during the trial. However, the levels of mite allergens often decrease during the trial.[47]

2. Number of Patients Needed to be Treated

Phase III trials for registration will need a large number of perfectly characterized subjects. From the recent Phase III trials in SLIT, it seems that a number of 150–200 patients[36] per group is adequate.[7–9] However, an appropriate calculation is necessary depending on the primary outcome chosen and the magnitude of effect desired.[48,49]

3. Primary Outcome Parameters

The primary end point should, if possible, be a single end point giving a global assessment of the patient. In the case of allergic rhinitis induced by pollens, it is advisable to use the total symptom score including all nasal symptoms (nasal obstruction, rhinorrhoea, sneezing, and pruritus) with one or more ocular symptoms.[7–9] The use of electronic devices to assess the daily symptom score is recommended. There is no universally accepted system to measure symptoms: ordinal scales, days free of symptoms, days free of medications, symptom scores corrected for medications, etc. The most frequently used approach in SIT clinical trials is a 4-point rating scale (from 0= absent to 3 = severe) applied to each symptom.

The minimal relevant magnitude of efficacy has been proposed to be at least 20% higher than placebo[14] and this level appears to be clinically relevant.[50]

The use of rescue medication has an impact on symptom severity. Therefore, a primary end point reflecting both symptom severity and intake of rescue medications is favored. Different approaches to combine the 2 scoring systems have been proposed but there is no standardized method as yet.[51] Any analysis of such a combined score should be supported by a responder analysis.[16] A consensus to standardize nasal symptoms or combined scores is still needed.

4. Secondary Outcome Parameters

Several secondary outcome parameters can be used:

- Rescue medications or score if they are not included in a global score.
- Individual symptoms.[52]
- Visual analogue scale (VAS).
- QoL.[50]
- Symptom-free days.
- Physician and patient rated clinical global improvement.[7–9]
- There is however no objective measurement for rhinitis or conjunctivitis.

5. Exploratory Outcome Parameters

Exploratory outcomes include:

- Evolution of nasal or conjunctival challenges.
- Chamber studies.
- Evolution of skin tests to allergens.
- Allergen-specific antibodies[7–9] and other immunologic parameters.[53–55]

6. Methodological Aspects[56]

Some characteristics of the trials need to be defined before starting the trial and considered until the end of the study:

- Allocation needs to be guaranteed very strictly and verified. At best, a centralized randomization using permutation blocs, generated by computer with a specific list (different random order and/or bloc size) has to be carried out for each center (allocation within site). Any stratification, justification and method should be explained.
- The double-blind method has to be described, especially for placebo, which has to be strictly similar to active vaccine (same composition, aspect, color, taste…) except for allergens.[57] However, for SLIT, there are no defined placebo local side effects similar to allergen. Finally, usually in RCTs, double-blind methodology should be maintained and confirmed during administration of intervention, data collection, and analysis of results. This has to be discussed, especially for long-term RCTs.
- Drop-outs are difficult to avoid because of the usual length of the trials (months or even years). Attempts to reduce drop-outs are essential to reduce a potential attrition bias. Drop-out rates should be less than 20%.[58] If the drop-out rate is over this level, a sensitivity analysis is needed to evaluate the reliability of the results.[59]
- The analysis has to be conducted as intent-to-treat.[59] This approach is often inadequately described and inadequately applied. Deviations from allocation and missing responses have to be described and their potential effect discussed in the final report and publications. RCTs are conducted to respond to one objective. Post hoc analyses are commonly performed. However, these analyses must be declared before starting patient inclusion.

7. Safety

Safety is a key factor for any SLIT trial and may differ depending on the sensitization of the patient.[60] ADR should be codified using MedDRA (Medical Dictionary for Regulatory Activities).[61] At least during the first month of use, safety should be recorded every day.

It is recommended that anaphylactic ADRs should be defined according to the definition of anaphylaxis,[62] and the ADR severity needs to be reported using the proposals of EAACI.[25]

8. Study Duration

For pollen allergy, the pollen count is important and the clinical effects of SLIT should be recorded during the entire pollen season. However, the primary outcome anal-

TABLE 11-2. Points to Consider for RCTs in SLIT

Allergen Vaccine		
	Composition[24]	Single allergen Mixtures
	If mixture[27]	Homologous allergens
	Standardization[24]	Defined Differ depending on vaccine
	Daily dose[22,23]	Micrograms of major allergen
	Cumulative dose[22,23]	Micrograms of major allergen
	Weekly dose[22,23]	Micrograms of major allergen
Patient selection		
	Demographic characteristics[16,17]	
	Assess all sensitizations (mono or polysensitization): For EU[63]	Panel of allergens Skin prick tests
	Prove concordance of sensitization and symptoms as not all sensitizations are clinically relevant[16,17]	Skin prick tests and serum specific IgE Optional: Allergen challenge
	Assess severity of symptoms[16,17]	Historical or run-in
	Report comorbidities[16,17]	May be used in the analysis
	Exclude patients who received SIT within 5 years[16,17]	

(*Continued*)

TABLE 11-2. Continued

RCT[16,17]	• Randomized • Double-blind • Placebo-controlled • Superiority trial • Intent-to-treat analysis	
	Objective of the study[16,17]	• Treatment of allergic symptoms: short term trial • Sustained clinical effect: 2–3 years trial • Disease modifying effect: 3 years trial and efficacy after discontinuation
	Protocol of the trial	• Maximum daily dose (if possible μg allergen) • Protocol to reach maintenance • Number of doses per week • Duration of the study • Co-seasonal administration
	• Rescue medication	• Standardized list • Weighted medication score
	• Primary outcome	• Total symptom score • Combined symptom-medication score • For asthma: co-primary: FEV_1 or PEF
	• Secondary outcomes	• Rescue medications • Individual symptoms • Visual analogue scale (VAS) • Quality-of-life (QOL) • Asthma control • Symptom-free days • Physician and patient rated clinical global improvement
	• Exploratory analyses	• Evolution of nasal or conjunctival challenges. • Evolution of skin tests to allergens. • Specific immunoglobulins • Other immunologic parameters • Nonspecific BHR (asthma) • Inflammatory biomarkers: induced sputum, FeNO (asthma)
	• Assess exposure to allergen	• Pollen counts • Mite allergen content in individual homes
	• Safety	MedDRA[61] Anaphylactic reactions[62] Severity of reactions[25]
	• Number of patients needed to be treated[48,49]	
Statistical analysis		Depends on study objectives
Publication of results		CONSORT statement[73,74]

ysis can be made for the peak of the pollen season, represented for instance by the weeks including 50% of the total pollen load. HDMs and animal dander can induce both intermittent and persistent symptoms, thus, patients with persistent rhinitis and/or asthma should be carefully selected.

The duration of the treatment needs to be carefully defined.[64–66]

9. Compliance to Immunotherapy

Compliance to treatment, a major problem of allergy and asthma management, is far better in RCTs than in real life. Thus, "real life" or pragmatic trials are needed[67] but are rarely available for allergic diseases.[68] If initiated, such trials should include pharmacoeconomic analyses.

Very few studies have assessed the compliance to immunotherapy. It was found that compliance to SCIT and

SLIT is adequate[69–72] although some studies were based on low numbers of patients. On the other hand, in a few patients, compliance to intranasal immunotherapy was found to be low.[69] In a "real life" situation, the Florida Medicaid database, it was found that among the 3,048 children who were prescribed SCIT, only 16% were still on treatment after 3 years of treatment.[73] The real compliance with SLIT is therefore unknown and "real life" studies should be carried out for assessment.

10. Publication of the Results

The publication of the RCTs should follow the Consolidated Standards of Reporting Trials (CONSORT) statement whenever possible.[74,75] Funding of the trial should be clearly stated.[76] To improve transparency, the results should be reported both numerically and with graphs.

iii. Randomized Clinical Trials in Asthma. For a claim of efficacy in asthma, specific trials should be performed (Table 11-2).

Bronchial symptoms (wheezing, shortness of breath, cough) may be used as a primary outcome, but they should be associated as a coprimary end point with FEV_1 or PEF, which can be measured serially using electronic diaries. As secondary outcomes, the control of the disease and QoL seem to be the most important parameters. Exploratory outcomes, for example, nonspecific BHR may complement the study. Furthermore, patients should have sufficient symptoms to demonstrate a significant difference between placebo and SLIT.[77]

Most guidelines propose to avoid SIT in moderate to severe asthmatics because of the increased rate of severe asthmatic reactions. However, a recent SCIT study suggested that patients with moderate asthma may be safely treated by SCIT.[78] If new studies are carried out, it will be of great importance to carefully scrutinize the safety.

In asthma, many studies have attempted to find a sparing effect of treatments, on asthma control or symptoms. However, many of these studies were inconclusive with medications because the placebo effect is significant.[43,79]

d. Studies in Children

Despite limitations because of the limited number of patients studied in many reports, recent reviews and meta-analyses[3,4] usually, but not always[5] showed positive effects of SLIT in children. Furthermore, recent large RCTs provided final evidence of effectiveness of SLIT in children.[11–13] The European Medicines Agency (EMEA Directive 2001/20/EC) and FDA state clearly that "children are not small adults" and that specific trials should be conducted in this age group. Allergy is difficult to demonstrate in preschool children and SLIT trials may be very difficult to carry out. Special ethics should be considered since children cannot usually give their informed consent.

Immunotherapy is not recommended in children less than 5 years of age because of the possible severity of side-effects. A postmarketing surveillance safety study on 126 3- to 5-year-old children (73% with asthma) demonstrated the safety of SLIT prescribed mostly for mite allergy.[80]

e. Preventative Studies

Studies assessing long-term efficacy with sustained clinical effect after immunotherapy is stopped (disease-modifying effect) should be specifically designed. Specific trials for this claim need to be carried out.[16] Some studies suggest that this effect may be observed during SLIT,[81] but more data in sufficiently powered placebo-controlled RCTs are needed.

f. Cost-Effectiveness Studies

New studies will need to incorporate cost-effectiveness parameters in their design[40,82–84] and comparison with other forms of SIT.[85]

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