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Pharmacogenetic Predictors of Response to Interferon Beta Therapy in Multiple Sclerosis

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Abstract

First-line therapy with interferon beta (IFN-β), involved in gene expression modulation in immune response, is widely used for multiple sclerosis. However, 30–50% of patients do not respond optimally. Variants in *CBLB*, *CTSS*, *GRIA3*, *OAS1* and *TNFRSF10A* genes have been proposed to contribute to the variation in the individual response. The purpose of this study was to evaluate the influence of gene polymorphisms on the IFN-β response in relapsing–remitting multiple sclerosis (RRMS) patients. *CBLB* (rs12487066), *GRIA3* (rs12557782), *CTSS* (rs1136774), *OAS1* (rs10774671) and *TNFRSF10A* (rs20576) polymorphisms were analysed by Taqman in 137 RRMS patients. Response to IFN-β and change in the Expanded Disability Status Scale (EDSS) after 24 months were evaluated using multivariable logistic regression analysis. Carriers of at least one copy of the C allele of *CTSS*-rs1136774 had a better response to IFN-β (p = 0.0423; OR = 2.94; CI95% = 1.03, 8.40). Carriers of TT genotype of *TNFRSF10A*-rs20576 had a higher probability of maintaining their EDSS stable after 24 months of IFN-β treatment (p = 0.0251; OR = 5.71; CI95% = 1.39, 31.75). No influence of *CBLB* (rs12487066), *OAS1* (rs10774671) and *GRIA3* (rs12557782) gene polymorphisms in the variation of the individual response to IFN-β was shown. Our results suggest that the *TNFRSF10A*-rs20576 and *CTSS*-rs1136774 gene polymorphisms influence the response to IFN-β after 24 months, while the *CBLB* (rs12487066), *OAS1* (rs10774671) or *GRIA3* (rs12557782) gene polymorphisms had no effect on the variation of the individual response to IFN-β.

Keywords Multiple sclerosis · Interferon beta · Response · Polymorphisms

Introduction

Multiple sclerosis (MS) is one of the most common neurological diseases causing permanent disability among young adults [1, 2]. Epidemiological data indicate an estimated total prevalence of 83 affected per 100,000 people, an estimated annual average incidence rate of 4.3 cases per 100,000 inhabitants and a ratio female:male of ≈ 2.0 in the last three decades in the European continent, with the highest rates corresponding to Northern countries [3]. Although there are different types of MS, defined by the course of the disease [4], the relapsing–remitting multiple sclerosis (RRMS) pattern, manifested by 85% of patients, is characterized by the recurrence of weakening and recovery episodes [5, 6].

The mechanisms underlying the immunopathogenesis of MS have not yet been fully determined, despite the intense research [7, 8]. Some evidence points to autoimmune processes involving several cell subtypes and proinflammatory substances [8]. The process occurs through the production of cytokines by dendritic cells and lymphocytes; when the dendritic cells cross the blood–brain barrier reaching the central nervous system (CNS), induce polarization and activation of T helper cells (Th1 and Th17) [9, 10]. Both IFN gamma and interleukin 17 (IL-17), produced by Th1 and Th17 cells respectively, are active during the disease, promoting CNS inflammation and axonal damage [11–13].

Most MS patients are treated with first-line disease-modifying drugs, such as IFN-β, a natural polypeptide highly synthesized by fibroblasts with anti-inflammatory properties. IFN-β modulates the expression of certain genes, interfering with the antigen presentation process, inhibiting the activation and proliferation of T cells [14] and also reducing

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the expression of proinflammatory cytokines [15]. It has important effects on the molecules involved in the permeability of the blood–brain barrier, preventing the adhesion of T lymphocytes to the endothelium and their extravasation to the CNS [16, 17].

Two therapeutic options of recombinant IFN-β are used in the treatment of MS. IFN-β 1a is obtained from hamster ovary cells, with identical amino acid sequence to native IFN, which may be administered intramuscularly (IM) or subcutaneously (SC) [18]. The second form of recombinant IFN-β is the pegylated IFN 1a (PEG 1a), obtained by conjugation with polyethylene glycol molecules. The pegylation contributes to a reduction in antigenicity and immunogenicity, as well as increased exposure, half-life and serum concentrations of the therapeutic agent [19, 20]. IFN-β 1b, administered SC, is synthesized by *Escherichia coli,* has significant differences in certain amino acids compared to IFN-β of natural origin and is not glycosylated. These differences influence the specific biological activity, and therefore, a higher dose is required [18], which implies a greater probability of developing neutralizing antibodies (NAbs) [21].

The efficacy of IFN-β as first-line therapy has been demonstrated in different studies [22, 23]. However, approximately 30 to 50% of patients do not respond optimally to IFN treatment, showing no indication of response in some cases [24, 25]. The influence of genetic variants on MS susceptibility and/or in the response to IFN-β therapy has been investigated in several genome-wide association (GWA) and candidate gene association studies [26–35], revealing potential roles for different genes in the response to IFN-β [26–30, 36–38]. Although many single-nucleotide polymorphisms (SNPs) have been proposed, there is in general a lack of replication in other studies. Among them, we selected SNPs in *GRIA3*, *TNFRSF10A*, *CTSS*, *OAS1* and *CBLB* genes, previously identified with potential roles in response to IFN-β [30], as response modifiers [28], increased disease activity [29] or mechanistically involved in IFN treatment [26]. In a GWAS evaluating 428,867 SNPs in 210 RRMS patients of Caucasian origin, the most significant SNP associated with response to IFN-β was rs12557782 in *GRIA3* gene [30]. The *GRIA3* gene (glutamate receptor ionotropic Ampa 3), located on the X chromosome, plays an important role in the synaptic transmission in the CNS [39, 40]. The rs12557782 (G allele) variant of this gene was identified as a possible biomarker of response to IFN-β therapy in 144 Spanish RRMS women ($p = 0.002$; $OR = 2.7$; $CI_{95\%} = 1.5, 5.2$) [30]. The *TNFRSF10A* (tumour necrosis factor receptor superfamily 10A) gene encodes a protein that induces cellular apoptosis [41] and is involved in autoimmune diseases mediated by T cells, such as MS [42]. The rs20576 polymorphism (CC genotype) was identified as a predictor of positive response to IFN-β ($p = 8.88 \cdot 10^{-4}$; OR: 0.30; $CI_{95\%} = 0.14, 0.63$) in the joint analysis of an original cohort of 509 and a validation cohort of 226 Spanish RRMS patients [38]. The C allele carriers of the rs1136774 polymorphism, located in the *CTSS* (cathepsin S) gene [43], encoding a protease involved in the degradation of antigens from antigen-presenting cells [44], showed a greater response to IFN-β in 230 RRMS patients from Belfast, UK ($p = 0.02$; $OR = 0.38$; $CI_{95\%} = 0.18, 0.84$) [28]. The *OAS1* gene (oligoadenylate synthetase 1) is induced by IFN and encodes a protein involved in mechanisms of regulation of viral infection [45]. The presence of the AA genotype in the rs10774671 variant of this gene conferred susceptibility to MS in 401 RRMS patients treated with IFN-β and 394 healthy controls from Dublin, Ireland, while the GG genotype protected against disease activity ($p = 0.04$; hazard ratio = 1.47; $CI_{95\%} = 1.01, 2.16$) [29]. The *CBLB* gene (Casitas B-lineage lymphoma proto-oncogene B gene) is a key regulator of the activation thresholds of the peripheral immune system and T lymphocytes, involved in immunological tolerance and autoimmunity [26, 36, 37]. In 37 RRMS patients from Hamburg, Germany, T allele carriers of *CBLB* rs12487066 polymorphism showed a reduction in *CBLB* expression compared to CC homozygotes in the presence of IFN ($p = 0.012$), not inhibiting the proliferation of T lymphocytes [26].

Given the evidence of a potential role of genetics on the variability of the response to IFN-β in MS, the objective of this study was to investigate the influence of five polymorphisms (*CBLB*-rs12487066, *GRIA3*-rs12557782, *CTSS*-rs1136774, *OAS1*-rs10774671 and *TNFRSF10A*-rs20576) in the response to IFN-β in RRMS patients.

Material and Methods

An ambispective cohort study was carried out.

Study Population

This study was carried out at the Virgen de las Nieves University Hospital (VNUH) in Granada, Spain, during the period from May 2016 to June 2020. One hundred thirty-seven RRMS patients over 18 years old and treated with IFN-β therapy were included and followed for 24 months. No patients with clinically or radiologically isolated syndrome were included. This study was approved by the VNUH Ethics and Research Committee and performed conform the declaration of Helsinki. All patients signed an informed consent.

Clinical and Sociodemographic Variables

The clinical and sociodemographic data were collected by reviewing and monitoring the medical records of the patients included in the study. The variables included were gender, family history of cancer, age at the time of the diagnosis of

MS, duration of disease (years), Expanded Disability Status Scale (EDSS) [46], Multiple Sclerosis Severity Score (MSSS), Progression Index (EDSS/years of disease) [47] and treatment (IFN1a IM, 1a SC, 1a PEG, 1b SC) [18].

Two outcome variables were considered: response to IFN-β, as described by Rio et al. [48, 49], and change in the EDSS. For the variable response to IFN-β, patients were classified as non-responders if there was evidence of magnetic resonance disease activity and/or increase of at least one point on the EDSS scale and/or had one or more relapses that persisted for a minimum of two consecutive scheduled visits separated by a 6-month interval and/or the medication was discontinued in absence of toxicity [48, 49].

The variable change in the EDSS was defined as a variation or not in the EDSS after 24 months.

Genetic Variables

Analysis of Gene Polymorphisms

The following SNPs were determined, using real-time PCR with TaqMan probes (Supplementary Table 1), according to previously described protocols [50]: *CBLB* (rs12487066), *GRIA3* (rs12557782), *CTSS* (rs1136774), *OAS1* (rs10774671), *TNFRSF10A* (rs20576). DNA extraction from saliva samples was performed using the QIAamp Mini Kit (Qiagen Gmbh, Hilden Germany), according to the extraction protocols indicated by the manufacturer.

Statistical Analysis

Quantitative data were expressed as the mean and standard deviation for variables with a normal distribution or median and 25th and 75th percentiles for variables with a non-normal distribution. The Lilliefors test (Kolmogorov–Smirnov) was used to assess the normality of the variables.

To analyse the association between response and polymorphisms (genotypic, additive, allelic, dominant and recessive models), a bivariate test was performed using Pearson's chi-square with Yates' correction or the Fisher test for expected frequencies below 5%. The relative risk (RR) and its 95% confidence interval ($CI_{95\%}$) were also calculated. The genetic models were defined as follows: genotypic (mm vs. Mm vs. MM), dominant (mm and Mm vs. MM), recessive (mm vs. Mm and MM) and allelic (M vs. m), m being the minor allele and M being the major allele. Bivariate analysis for independent quantitative variables was carried out using the Wilcoxon test.

To verify the influence of SNPs on response to IFN-β, a multivariable logistic regression model was applied, taking a level for significance of $p < 0.05$. Statistical analyses were carried out using R 3.0.1 [51]. Hardy–Weinberg equilibrium was estimated using the free, open-source whole-genome association analysis toolset PLINK 1.9 [52].

The statistical analysis of rs12557782 polymorphism in the *GRIA3* gene (X chromosome) was stratified by sex.

Results

Clinical Characteristics of Patients

We included a total of 137 patients of Caucasian origin diagnosed with RRMS who had been treated with IFN-β (1a, PEG 1a, 1b).

The clinical characteristics and sociodemographic data are detailed in Table 1. The median age of diagnosis was 31 years, with a mean duration of the disease of 2 years. The proportion of women was 65.7% (90/137). Sixty-nine patients maintained their EDSS stable after 24 months of therapy (84.2%) and the remaining 15.9% increased their EDSS score in a median of 0.5 points (Table 1). Good response to IFN-β therapy was shown by 77.3% of patients (Table 1). There were no differences in the distribution of

Table 1 Sociodemographic and clinical characteristics of the 137 multiple sclerosis patients treated with interferon beta

Characteristic	N (%)	P_{50} [P_{25}, P_{75}]
Gender		
Female	90 (65.7)	
Male	47 (34.3)	
Family history of cancer		
Yes	6 (4.4)	
No	131 (95.6)	
Age at multiple sclerosis diagnosis		31 [5, 39]
Duration of disease (years)		2 [2, 4]
Expanded Disability Status Scale		1 [0, 1]
Baseline Expanded Disability Status Scale		1 [0, 1.5]
Change in the Expanded Disability Status Scale		0 [0, 2]
No change	69 (84.2)	0 [0, 0]
Increase	13 (15.9)	0.5 [0.5, 1.0]
Multiple Sclerosis Severity Score		1.92 [0.53, 2.01]
Progression index		0.25 [0, 0.50]
Response to interferon beta		
Yes	106 (77.3)	
No	31 (22.6)	
Treatment type		
1a Intramuscular	54 (39.4)	
1a Subcutaneous	46 (33.6)	
1a Pegylated	5 (3.6)	
1b Subcutaneous	14 (10.2)	
Unspecified	18 (13.1)	

responders and non-responders to IFN-β or change in the EDSS among different IFN-β therapeutic options (Table 2).

Baseline EDSS was the only clinical variable associated with response to IFN-β (p = 0.008) and change in the EDSS (p = 0.036) (Table 2).

Influence of SNPs and the Response to IFN-β

The bivariate analysis of genetic polymorphisms and the response to IFN is detailed in Table 3. Bivariate analysis showed that patients with CC genotype in the rs1136774 polymorphism of the *CTSS* (recessive model) gene had greater response to IFN-β (Table 3: p = 0.047; RR = 1.3; $CI_{95\%}$ = 1.0, 1.7); women with the GG genotype of the rs12557782 polymorphism in the *GRIA3* gene (recessive model) showed greater response to IFN-β (Table 3: p = 0.033; RR = 1.4; $CI_{95\%}$ = 1.0, 2.1). The *CBLB*-rs12487066 and *TNFRSF10A*-rs20576 gene polymorphisms showed a trend to association with change in the EDSS after 24 months of IFN treatment, but non-significant (p < 0.1; Table 3). The *OAS1*-rs10774671 gene polymorphism did not predict the variation of the individual response to IFN-β or change in the EDSS.

Multivariable logistic regression analysis showed that patients with lower baseline EDSS (p = 0.0694; OR = 0.06; $CI_{95\%}$ = 0.34, 1.04) and carriers of at least one copy of the C allele of *CTSS*-rs1136774 had a better response to IFN-β (p = 0.0423; OR = 2.94; $CI_{95\%}$ = 1.03, 8.40). Patients with lower baseline EDSS (p = 0.0060; OR = 0.36; $CI_{95\%}$ = 0.016, 0.71) and carriers of TT genotype of *TNFRSF10A*-rs20576 had a higher probability of maintaining their EDSS stable after 24 months of treatment with IFN-β (p = 0.0251; OR = 5.71; $CI_{95\%}$ = 1.39, 31.75) (Table 4). The *GRIA3*-rs12557782 association with response in women and trend shown by *CBLB*-rs12487066 on change in the EDSS in the bivariate analysis were not confirmed as independent associations after multivariable analyses.

Discussion

IFN-β is one of the most used first-line treatment therapies for MS. Although its mechanism of action is not yet fully known, several studies indicate that it plays a role in modifying the expression of genes involved in the immune

Table 2 Association of clinical and sociodemographic characteristics with change in the Expanded Disability Status Scale (EDSS) and response to IFN-β in 137 multiple sclerosis patients treated with interferon beta (bivariate analysis)

Characteristic	N	Expanded Disability Status Scale		p	N	Response		P
		Change	No change			Yes	No	
Gender								
Female	53	47 (68.1)	6 (46.2)	0.204*	90	63 (63.0)	27 (73.0)	0.374
Male	29	22 (38.9)	7 (53.8)		47	37 (37.0)	10 (27.0)	
Family history of cancer								
Yes	4	2 (2.9)	2 (15.4)	0.116*	6	4 (4.0)	2 (5.4)	0.661*
No	78	67 (97.1)	11 (84.6)		131	96 (96.0)	35 (94.6)	
Age at multiple sclerosis diagnosis	82	30 [24, 38]	31 [26, 37]	0.380	137	31 [24, 38]	31 [25, 40]	0.767
Duration of disease (years)	82	2 [2, 4]	2 [2, 3]	0.917	137	2 [2, 4]	2 [2]	0.217
Baseline Expanded Disability Status Scale	82	1 [0, 1]	1.5 [0, 2]	**0.036**	137	1 [0, 1]	1 [1, 2]	**0.008**
Treatment								
Type								
1a	71	9 (69.2)	62 (91.2)	0.050	105	86 (88.7)	19 (86.4)	0.721
1b	10	4 (30.8)	6 (8.8)		14	11 (11.3)	3 (13.6)	
All options								
1a Intramuscular	35	6 (46.2)	29 (42.6)	0.070	54	45 (46.4)	9 (40.9)	0.770*
1a Subcutaneous	31	2 (15.4)	29 (42.6)		46	36 (37.1)	10 (45.5)	
1a Pegylated	5	1 (7.7)	4 (5.9)		5	5 (5.2)	0 (0)	
1b Subcutaneous	10	4 (30.8)	6 (8.8)		14	11 (11.3)	3 (13.6)	

*p-value for Fisher's exact test. p-value for the chi-squared test otherwise in qualitative variables. p-value for the Wilcoxon test. Significant p-values are shown in bold

Frequencies are expressed as number (%)

Quantitative variables are expressed as P_{50} [P_{25}, P_{75}]

Percentages shown are calculated per column

Table 3 Association of gene polymorphisms with response and change in the Expanded Disability Status Scale (EDSS) after 24 months of interferon beta

Gene	SNPs Minor allele	Genetic Model	Expanded Disability Status Scale					Response			
			Genotype	N	Change N (%)	No Change N (%)	p-value	N	Yes N (%)	No N (%)	p-value
CBLB	rs12487066 C	Genotypic	CC	7	3 (42.9)	4 (57.1)	0.130*	10	9 (90.0)	1 (10.0)	0.568*
			CT	28	3 (10.7)	25 (89.3)		48	34 (70.8)	14 (29.2)	
			TT	47	7 (14.9)	40 (85.1)		79	57 (72.2)	22 (27.8)	
		Dominant	C-	35	6 (17.1)	29 (82.9)	1	58	43 (74.1)	15 (25.9)	0.949
		Recessive	CC	7	3 (42.9)	4 (57.1)	0.075*	10	9 (90.0)	1 (10.0)	0.287*
		Allelic	C	42	33 (78.6)	9 (21.4)	0.251	68	52 (76.5)	16 (23.5)	0.456
CTSS	rs1136774 C	Genotypic	CC	24	2 (8.3)	22 (91.7)	0.487*	33	29 (87.9)	4 (12.1)	0.083
			CT	40	7 (17.5)	33 (82.5)		68	47 (69.1)	21 (30.9)	
			TT	18	4 (22.2)	14 (77.8)		36	24 (66.7)	12 (33.3)	
		Dominant	C-	64	9 (14.1)	55 (85.9)	0.467*	101	76 (75.2)	25 (24.8)	0.437
		Recessive	CC	24	2 (8.3)	22 (91.7)	0.327*	33	29 (87.9)	4 (12.1)	**0.047**
		Allelic	C	88	77 (87.5)	11 (12.5)	0.205	134	105 (78.4)	29 (21.6)	0.050
OAS1	rs10774671 G	Genotypic	AA	30	5 (16.7)	25 (83.3)	0.914*	51	37 (72.5)	14 (27.5)	0.714*
			AG	42	6 (14.3)	36 (85.7)		69	49 (71.0)	20 (29.0)	
			GG	10	2 (20.0)	8 (80.0)		17	14 (82.4)	3 (17.6)	
		Dominant	G-	52	8 (15.4)	44 (84.6)	1*	86	63 (73.3)	23 (26.7)	1
		Recessive	GG	10	2 (20.0)	8 (80.0)	0.655*	17	14 (82.4)	3 (17.6)	0.559*
		Allelic	G	62	52 (83.9)	10 (16.1)	0.940	103	77 (74.8)	26 (25.2)	0.609
TNFRSF10A	rs20576 G	Genotypic	GG	2	1 (50.0)	1 (50.0)	0.101*	3	1 (33.3)	2 (66.7)	0.227*
			GT	37	8 (21.6)	29 (78.4)		60	43 (71.7)	17 (28.3)	
			TT	43	4 (9.3)	39 (90.7)		74	56 (75.7)	18 (24.3)	
		Dominant	G-	39	9 (23.1)	30 (76.9)	0.161	63	44 (69.8)	19 (30.2)	0.566
		Recessive	GG	2	1 (50.0)	1 (50.0)	0.293*	3	1 (33.3)	2 (66.7)	0.177*
		Allelic	G	41	31 (75.6)	10 (24.4)	0.083	66	45 (68.2)	21 (31.8)	0.312
GRIA3	rs12557782 G		Women (n = 53)					Women (n = 90)			
		Genotypic	AA	16	2 (12.5)	14 (87.5)	0.456*	30	17 (56.7)	13 (43.3)	**0.034***
			AG	27	2 (7.4)	25 (92.6)		45	32 (71.1)	13 (28.9)	
			GG	10	2 (20.0)	8 (80.0)		15	14 (93.3)	1 (6.7)	
		Dominant	G-	37	4 (10.8)	33(89.2)	1*	60	46 (76.7)	14 (23.4)	**0.087**
		Recessive	GG	10	2 (20.0)	8 (80.0)	0.315*	15	14 (93.3)	1 (6.7)	**0.033***
		Allelic	G	51	45 (88.2)	6 (11.8)	0.889	81	64 (79.0)	17 (21.0)	**0.010**
			Men (n = 29)					Men (n = 47)			
			A	13	5 (38.5)	8 (61.5)	0.192*	23	18 (78.3)	5 (21.7)	1*
			G	16	2 (12.5)	14 (87.5)		24	19 (79.2)	5 (20.8)	

*p-value for Fisher's exact test. P-value for the chi-squared test otherwise. Significant p-values are shown in bold

Percentages shown are calculated per row

response [18, 53–56], by inhibiting the synthesis of inflammatory cytokines (IL-12, IL-17, IL-23), and favouring the production of anti-inflammatory cytokines (IL-4, IL-10) and Th2 type cells [57]. The response to IFN-β has also been suggested to be determined by certain genetic variants in the *GRIA3*, *CBLB*, *CTSS*, *OAS1* and *TNFRSF10A* genes, among others [26–30, 36–38]. Our results point at the TT genotype for rs20576 in *TNFRSF10A* as a possible indicator of better response to IFN-β since it was associated with stability in the EDSS score after 24 months (p = 0.0251; OR = 5.71; CI95% = 1.39, 31.75). However, this was not reflected in an association with response to IFN-β when defined as the compound EDSS/relapse/imaging variable. The beneficial effect of the TT genotype found in our study is in contrast with the findings of a previous study including 509 MS patients of Spanish origin treated with IFN-β and an additional validation cohort of 226 patients, which showed an association of the CC genotype with a positive

Table 4 Association of gene polymorphisms with response to interferon beta and change in the Expanded Disability Status Scale

	Reference category	p-value	Odds ratio	Confidence interval (95%)
Response to interferon beta				
Baseline EDSS		0.0694	0.60	0.34, 1.04
CTSS rs1136774 (C-)	TT	0.0423	2.94	1.03, 8.40
Change in EDSS				
Baseline EDSS		0.0060	0.36	0.16, 0.71
TNFRSF10A rs20576 (TT)	G-	0.0251	5.71	1.39, 31.75

EDSS, Expanded Disability Status Scale

response to IFN-β, defined in a similar way to ours and also after 24 months (OR: 0.30; CI95% = 0.14–0.63; $p = 8.88 \cdot 10^{-4}$) [38]. The clinical characteristics of the patients were also similar. Another study with 73 Iranian MS patients did not found a significant association of rs20576 with IFN-β response (p = 0.87) [58]. No other studies have explored the influence of rs20576 on IFN-β response in MS patients. In follicular lymphoma, no association with response to first-line rituximab was found either in 125 patients [59]. Its role as a susceptibility marker for systemic lupus erythematosus [60], hepatocellular carcinoma [61], Alzheimer's disease [62] or lymphomas [63] has also been investigated, although unsuccessfully.

Our patients also showed a better response to IFN-β for the C allele of the rs1136774 *CTSS* in the multivariable analysis (Table 4: p = 0.042; OR: 2.94; $CI_{95\%}$: 1.03, 8.40), in line with the results of a study with 230 RRMS patients of European origin (UK) in which C allele carriers had a better response to IFN-β after 2 years of follow-up (p = 0.02; OR: 0.38; $CI_{95\%}$: 0.18, 0.84) [28]. The *CTSS* protein (lysosomal cysteine proteinase) has been suggested to participate in the presentation of microglia antigens through MHC II-associated invariant chain degradation [64] and the degradation of myelin basic protein in vitro [65]. Serum cathepsin S and cystatin C levels influenced disease activity in 73 RRMS patients, specifically in those responding to IFN-β, through the reduction of the levels of serum cathepsin S [66].

We could not find any association of response to IFN-β or change in EDSS with gene polymorphisms in *GRIA3*, *CBLB* or *OAS1*. RRMS women carrying the G allele in rs12557782-*GRIA3* responded better to IFN-β (p = 0.002; OR = 2.7; $CI_{95\%}$ = 1.5, 5.2) in a GWAS including 106 RRMS patients of Caucasian origin (Spanish) that evaluated 428,867 SNPs [30]. No association was found in men [30]. Despite the size, follow-up period of 24 months and female:male ratio (2:1) in our study being very similar and GG women showing greater response to IFN-β in our bivariate analysis, this association did not prove to be independent after multivariable analysis (Table 3: p = 0.033). No association with response to IFN-β was shown in 73 MS patients of Iranian origin, neither in females or males (p = 0.15 and 0.4, respectively), although we cannot rule out a lack of statistical power, given the limited size of the study [58]. The *GRIA3* gene encodes an AMPA-type glutamate receptor, which participates in most excitatory synaptic transmissions of the CNS, potentially explaining a relationship between the response to IFN-β and genes encoding channels activated by neurotransmitters [27]. The rs12487066 polymorphism of the *CBLB* gene was associated with MS risk in a GWAS in which 334,923 SNPs were evaluated in 931 family trios of European origin (UK = 928 cases and 1475 controls) and American (US = 1394 cases and 1512 controls) [67]. The replication study showed an increased risk of MS in T allele carriers (p = 0.035; OR: 1.08; CI95% = 1.03, 1.16) [67]. Another study with 342 patients of Saudi origin (99 MS with no antecedents of MS, 22 with a family member with MS, 89 controls related to MS and 132 independent controls) showed rs12487066 associated with MS when compared to the independent control group [68]. This SNP has been suggested to regulate the expression of the *CBLB* gene so that in carriers of the T allele, *CBLB* is inhibited by transcription factors, and lymphocytic proliferation does not cease [26]. In our study, *CBLB*-rs12487066 had no influence on response to IFN-β in RRMS patients, but we cannot compare it to other populations since this is the first study evaluating its possible predictive value for response in MS. The role of *OAS1*-rs10774671 polymorphism in disease activity in MS patients treated with IFN-β was investigated in 198 RRMS Irish patients and 394 controls [29]. The relapse time after treatment with IFN-β was significantly shorter in patients with AA genotype (hazard ratio: 1.47; CI95% = 1.01–2.16; p = 0.04) [29]. RRMS patients were divided into two groups according to disease activity (low and high); those with low activity were defined as those who had a maximum relapse after 24 months of treatment with IFN-β and did not have a sustained increase in disability. High activity was for those who had two or more relapses in the 24-month follow-up, with or without a sustained increase in disability (EDSS) [29]. This approach is similar to the response criteria applied in our study; however, *OAS1*-rs10774671 did not show an influence on response to IFN-β in our RRMS patients. There

are no more studies of rs10774671 related to response to IFN.

Other SNPs have been proposed as indicators of response to IFN-β in Caucasian patients in various studies, some of them as response predictors (*FHIT*, *GAPVD1*, *ZNF697* [35], *GPC5*, *COL25A1*, *HAPLN1* [27], *IRF5* [31], *CD46* [32], *PELI3*, *GABRR3* [33]), or other signs of response, as lower relapse rates (*IFNAR1*) [34]. Some of these results were not adjusted by multiple comparisons [27] or have not been replicated in other studies [28, 34].

The main limitation of our study was the sample size. In our study, 160 patients treated with IFN-β were included as an initial cohort, 23 were excluded due to unavailability of their clinical history for follow-up, leaving an even smaller sample size. However, our population has a great homogeneity in terms of the definition and application of the response criteria since these are patients treated in the same hospital, evaluated, monitored and treated according to the same protocols by the same team of physicians.

It has been shown that patients treated with IFN-β could develop neutralizing antibodies that can negatively affect the therapeutic response. In Korea, a study was conducted with 150 patients from nine different centres to evaluate the development of NAbs in MS patients treated with IFN-β-1a and IFN-β-1b. NAbs were found in 35% of patients treated with IFN-β-1b, 15% with IFN-β-1a SC and 0% with IFN-β-1a IM. Persistent NAb positivity was associated with disease activity in MS patients treated with IFN-β ($p = 0.004$) [69]. The frequency of MS patients developing NAbs against IFN-β was also significantly higher with IFN-β-1b therapy compared with IFN-β-1a therapy [70]. In our study, with only 14 patients (Table 1, 10.2%) treated with IFN-β 1b SC, the influence of NAbs development could not be well-powered investigated. Consequently, a further limitation of our study would be that patients were not screened for NAbs.

It is therefore necessary that future studies include larger cohorts that allow greater statistical power to elucidate associations, not only to warrantee sufficient statistical power for the investigation of a greater number of SNPs, but also to include different therapeutic forms of IFN-β or several follow-up periods, which would allow to explore the effect of the different genetic variants on the short or long-term response, as well as the need for a change in therapy and the moment during the follow-up when this occurs, which will allow a better therapeutic control of these patients.

Conclusions

Our results suggest that treatment of RRMS patients with IFN-β for 24 months helps maintaining EDSS score in TT carriers of the *TNFRSF10A*-rs20576 gene polymorphism, whereas carriers of the C allele of *CTSS*-rs1136774 show a better response. A lower baseline EDSS is associated with a better response to IFN-β and EDSS stability, while *CBLB* (rs12487066), *OAS1* (rs10774671) or *GRIA3* (rs12557782) gene polymorphisms did not influence the variation of the individual response to IFN-β after 24 months.

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Author Contributions All authors are accountable for all aspects of the work, contributed to data interpretation, revised the manuscript critically and gave final approval. Additional contributions are as follows:

M.I.C.C.: Drafting the manuscript, conception and design of the work, data acquisition and analysis
C.P.R.: Data analysis
E.M.C.: Data acquisition
A.S.P.: Drafting the manuscript
C.A.G.: Data acquisition
M.A.C.H.: Funding acquisition
A.J.M.: Funding acquisition
M.C.G.: Drafting the manuscript, conception and design of the work, data acquisition and analysis

Data Availability All data generated or analysed during this study are included in this published article and its supplementary information files. The datasets generated during and/or analysed during the current study cannot be publicly available due to that option was not included in the informed consent for participants.

Declarations

Ethics Approval This study was approved by the VNUH Ethics and Research Committee and performed conform the declaration of Helsinki. All patients signed an informed consent.

Consent to Participate Written informed consent was obtained from all patients.

Consent to Publish Not applicable.

Conflict of Interest The authors declare no competing interests.

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