Journal of Neuroimmunology 303 (2017) 62–65

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Short communication

Chitinase 3-like 1 is associated with the response to interferon-beta treatment in multiple sclerosis

Clara Matute-Blanch [a,*], Jordi Río [a], Luisa M Villar [b], Luciana Midaglia [a], Sunny Malhotra [a], José C Álvarez-Cermeño [b], Angela Vidal-Jordana [a], Xavier Montalban [a], Manuel Comabella [a,*]

[a] Servei de Neurologia-Neuroimmunologia, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Institut de Recerca Vall d'Hebron (VHIR), Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain
[b] Departments of Neurology and Immunology, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigacion Sanitaria, Madrid, Spain.

ARTICLE INFO

Article history:
Received 3 October 2016
Received in revised form 2 December 2016
Accepted 12 December 2016
Available online 19 December 2016

Keywords:
Chitinase 3-like 1
Interferon-beta
Glatiramer acetate
Biomarkers
Multiple sclerosis

ABSTRACT

Chitinase 3-like 1 (CHI3L1) plays a prognostic role in patients with multiple sclerosis (MS). Here, we investigated a potential association between CHI3L1 and the response to interferon-beta (IFNβ) and glatiramer acetate (GA). Serum CHI3L1 levels were measured by ELISA in 117 relapsing-remitting MS (RRMS) patients, 76 IFNβ-treated and 41 GA-treated patients. CHI3L1 levels were increased by GA ($p = 0.014$) but unchanged by IFNβ ($p = 0.830$). CHI3L1 was associated with IFNβ response and levels were higher in non-responder group ($p = 0.020$), while GA showed no responder effect ($p = 0.943$). These results suggest a role for CHI3L1 as response biomarker to IFNβ in RRMS patients.

1. Introduction

Chitinase 3-like 1 (CHI3L1) is a member of the glycoside hydrolase 18 chitinase family that targets chitin but lacks enzymatic activity (Renkema et al., 1998). It is produced by a wide range of cells such as macrophages, chondrocytes, synovial cells, osteoblasts, neutrophils, and vascular smooth muscle cells (Hakala et al., 1993; Johansen, 2006; Kawada et al., 2007). Although its physiological function remains elusive, recent studies point to a clear prognostic role for CHI3L1 in patients with multiple sclerosis (MS), particularly at the time of the first neurological event or clinically isolated syndrome (CIS). In this regard, high cerebrospinal fluid CHI3L1 levels in CIS patients have been associated with the conversion to MS (Canto et al., 2015; Hinsinger et al., 2015; Modvig et al., 2015) and with the development of neurological disability (Canto et al., 2015). Studies of CHI3L1 in peripheral blood of MS patients are scarce. In a previous study conducted by our group in plasma samples from MS patients, CHI3L1 levels were found elevated in patients with primary progressive and secondary progressive MS, suggesting a role for CHI3L1 in the progressive forms of the disease (Canto et al., 2012). In this same study (Canto et al., 2012), plasma levels of CHI3L1 were also measured in a cohort of relapsing-remitting MS (RRMS) patients before and after treatment with interferon-beta (IFNβ). The finding of a trend towards decreased CHI3L1 in treated patients suggested that peripheral blood CHI3L1 levels could also be modulated by IFNβ treatment. However, the response to IFNβ treatment was not specifically addressed in this particular study (Canto et al., 2012). Building on these previous observations, in the present study we aimed to investigate a potential association between CHI3L1 and the response to first-line disease modifying therapies (DMT) such as IFNβ and glatiramer acetate (GA).

2. Methods

2.1. Ethics statement

The study was approved by the Hospital ethics committee, and all patients gave their informed consent.

2.2. Patients

This is a prospective study of naive RRMS patients treated with IFNβ or GA at the outpatient clinic of the Centre d'Esclerosi Multiple de Catalunya (Cemcat) and the Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS) and included into a follow-up protocol collecting

Abbreviations: CHI3L1, chitinase 3-like 1; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; CIS, clinically isolated syndrome; DMT, disease modifying therapies; IFNβ, interferon-beta; GA, glatiramer acetate.

* Corresponding authors at: Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Institut de Recerca Vall d'Hebron (VHIR), Hospital Universitari Vall d'Hebron, Pg. Vall d'Hebron 119-129, 08035 Barcelona, Spain.
E-mail addresses: clara.matute@vhir.org (C. Matute-Blanch), manuel.comabella@vhir.org (M. Comabella).

http://dx.doi.org/10.1016/j.jneuroim.2016.12.006
0165-5728/

Table 1
Demographic and baseline clinical characteristics of the whole cohort of MS patients treated with GA.

Characteristics	R	NR	P values[c]
N	28	13	–
Age (years)	38.6 (10.4)	32.1 (9.8)	0.064
Female/male (% women)	17/11 (60.7)	7/6 (53.8)	0.678
Duration of disease (years)	6.5 (6.0)	4.7 (3.8)	0.276
EDSS[a]	1.8 (1.5–2.0)	1.7 (1.0–2.5)	0.561
Number of relapses[b]	1.7 (0.9)	1.8 (1.1)	0.674
Number of Gd-enhancing lesions	8.1 (10.7)	12.1 (9.4)	0.286

Data are expressed as mean (standard deviation) unless otherwise stated.
[a] Data are expressed as mean (interquartile range).
[b] Refers to the number of relapses in the two previous years. EDSS: Expanded Disability Status Scale. Gd: gadolinium. R: responders to GA. NR: non-responders to GA.
[c] P values: Refers to *p* values obtained following comparisons between responders and non-responders by means of Student-*t*-test or Mann-Whitney's test depending on the applicability conditions (age, duration, EDSS, and number of relapses) and chi-square test (gender).

basal and longitudinal clinical data. Clinical and radiological response to first-line DMT was assessed after 1 year of treatment (Rio et al., 2009; Rio et al., 2014). Non-responders to DMT were patients fulfilling 2 or 3 of the following criteria: (i) presence of 1 or more relapses; (ii) confirmed increase at 6 months of 1 or more points in the EDSS score; (iii) presence of 3 or more active lesions (gadolinium enhancing lesions or new or enlarging T2 lesions) on the 1-year brain MRI. The remaining patients were considered responders to DMT. A total of 117 RRMS patients were included in the study, 76 treated with IFNβ and 41 with GA. Of these, 14 patients were classified as non-responders to IFNβ and 13 to GA. Tables 1 and 2 and Supplementary Tables 1 and 2 summarize demographic and main clinical characteristics of patients stratified by treatment and inclusion center.

2.3. Determination of CHI3L1 levels in serum samples by ELISA

Peripheral blood was collected by standard venipuncture and allowed to clot spontaneously for 30 min. Serum was obtained by centrifugation and stored frozen at −80 °C until used. CHI3L1 levels were determined in serum samples at baseline and after 12 months of treatment with DMT by enzyme-linked immunosorbent assay (ELISA; MicroVue YKL-40 EIA Kit, Quidel) according to the manufacturers' recommendations. Undiluted serum samples were measured in duplicate and the intra-assay and inter-assay coefficients of variation were 7.7% and 11.7% respectively.

Table 2
Demographic and baseline clinical characteristics of the whole cohort of MS patients treated with IFNβ.

Characteristics	R	NR	P values[c]
N	62	14	–
Age (years)	35.0 (8.7)	36.7 (8.7)	0.496
Female/male (% women)	45/17 (72.6)	12/2 (85.7)	0.305
Duration of disease (years)	4.2 (4.6)	6.3 (5.4)	0.138
EDSS[a]	1.8 (1.0–2.0)	2.6 (1.4–3.6)	0.062
Number of relapses[b]	1.6 (1.1)	1.4 (1.1)	0.632
Number of Gd-enhancing lesions	9.0 (12.2)	11.3 (14.3)	0.536
Type of IFNβ [n (%)]			
IFNβ 1a IM	30 (48.4)	6 (42.9)	
IFNβ 1b SC	10 (16.1)	5 (35.7)	0.271
IFNβ 1a SC	22 (35.5)	3 (21.4)	

Data are expressed as mean (standard deviation) unless otherwise stated.
[a] Data are expressed as mean (interquartile range).
[b] Refers to the number of relapses in the two previous years. EDSS: Expanded Disability Status Scale. Gd: gadolinium. IM: intramuscular. SC: subcutaneous. R: responders to IFNβ. NR: non-responders to IFNβ.
[c] P values: Refers to *p* values obtained following comparisons between responders and non-responders by means of Student-*t*-test or Mann-Whitney's test depending on the applicability conditions (age, duration, EDSS, and number of relapses) and chi-square test (gender and type of IFNβ).

2.4. Statistical analysis

Statistical analysis was performed by using the IBM SPSS Statistics for Windows version 20.0 (IBM Corp, Armonk, NY). An analysis of variance (ANOVA) for repeated measures was used to analyze: (i) time effect, which addresses the question whether CHI3L1 protein levels are modified by treatment during the follow-up period; (ii) responder effect, which addresses the question whether responders and non-responders to DMT differ in the mean CHI3L1 protein levels; and (iii) responder by time interactions, which addresses the question whether responders and non-responders differ in the CHI3L1 protein levels during the follow-up period. Comparisons of mean serum CHI3L1 levels before and after treatment with DMT in responders and non-responders were assessed using a paired Student-*t*-test.

3. Results

3.1. Serum levels of CHI3L1 are increased by GA

We first investigated whether serum CHI3L1 protein levels were modulated by first-line DMT in RRMS patients. As shown in Fig. 1, a statistically significant time effect was observed for GA, and CHI3L1 levels were significantly increased by the effect of GA ($F = 6.604$, $p = 0.014$). In contrast, time effect was not statistically significant for IFNβ and mean serum CHI3L1 levels were similar between the baseline and the 12 months time point in the whole group of IFNβ-treated patients ($F = 0.046$, $p = 0.830$; Fig. 1).

3.2. Serum CHI3L1 levels are associated with the response to IFNβ treatment

We next assessed whether mean serum CHI3L1 levels differed between responders and non-responders during the first year of treatment with DMT. As shown in Fig. 2, a statistically significant responder effect was observed for IFNβ ($F = 5.652$, $p = 0.020$). Mean CHI3L1 levels were significantly higher in non-responders compared to responders after 12 months of IFNβ treatment ($p = 0.013$), whereas a trend towards increased serum CHI3L1 levels was already observed at baseline in the non-responder group ($p = 0.055$).

When we investigated the responder effect of CHI3L1 in GA-treated patients, mean CHI3L1 levels in serum did not significantly differ over time between responders and non-responders ($F = 0.005$, $p = 0.943$; Fig. 2).

Finally, when the group by time interactions were analyzed no statistically significant differences were observed between responders and non-responders to IFNβ ($F = 0.392$, $p = 0.533$) or GA ($F = 0.289$, $p = 0.594$).

4. Discussion

CHI3L1 measured in the CSF represents a promising prognostic biomarker in patients with CIS (Canto et al., 2015). Here, we aimed to investigate the role of CHI3L1 measured in peripheral blood with the response to IFNβ and GA, two established first-line DMT known to be partially effective and associated with a significant proportion of MS patients who do not respond to treatment (Rio et al., 2002; Rio et al., 2014). CHI3L1 levels were measured in serum samples at baseline and after 12 months of treatment, the latter corresponding to the time point at which the response to IFNβ and GA was evaluated by applying both clinical and radiological criteria (Rio et al., 2009; Rio et al., 2014).

Regarding GA, CHI3L1 levels were modulated by the effect of treatment, and serum protein levels were significantly increased in the treated time point compared with the baseline. However, despite the