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Spasticity improvement in patients with relapsing–remitting multiple sclerosis switching from interferon-β to glatiramer acetate: The Escala Study

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ABSTRACT

Background: A recent pilot study suggested spasticity improvement during glatiramer acetate (GA) treatment in multiple sclerosis (MS) patients who previously received interferon-β (IFN-β).
Objective: To evaluate changes in spasticity in MS patients switching from IFN-β to GA.
Methods: Observational, multicentre study in patients with relapsing–remitting MS (RRMS) and spasticity switching from IFN-β to GA. The primary endpoint comprised changes on Penn Spasm Frequency Scale (PSFS), Modified Ashworth Scale (MAS), Adductor Tone Rating Scale (ATRS), and Global Pain Score (GPS) at months 3 and 6 after starting GA.
Results: Sixty-eight evaluable patients were included (mean age,41.7 ± 9.5 years; female,70.6%; mean time from MS diagnosis to starting GA,7.6 ± 5.7 years). Previous treatments were subcutaneous IFN-β1a in 42.6% patients, intramuscular IFN-β1a in 41.2% and IFN-β1b in 32.4%, whose mean durations were 3.5 ± 3.3, 2.7 ± 2.5 and 4.4 ± 3.6 years, respectively. Statistically significant reductions in mean scores on all spasticity measurements were observed from baseline to month 3 (PSFS, 1.7 ± 0.9 vs 1.4 ± 0.6, $p<0.01$; MAS, 0.7 ± 0.5 vs 0.6 ± 0.5, $p<0.01$; highest MAS score, 1.9 ± 0.8 vs 1.7 ± 0.8, $p<0.01$; ATRS, 1.6 ± 0.6 vs 1.4 ± 0.6, $p<0.01$; GPS, 29.4 ± 22.1 vs 24.7 ± 19.4, $p<0.01$) and from baseline to month 6 (PSFS, 1.7 ± 0.9 vs 1.3 ± 0.6, $p<0.01$; MAS, 0.7 ± 0.5 vs 0.5 ± 0.5, $p<0.01$; highest MAS score, 1.9 ± 0.8 vs 1.5 ± 0.9, $p<0.01$; ATRS, 1.6 ± 0.6 vs 1.3 ± 0.6, $p<0.01$; GPS, 29.4 ± 22.1 vs 19.1 ± 14.8, $p<0.01$).
Conclusion: Spasticity improvement in terms of spasm frequency, muscle tone and pain can be noted after three months and prolonged for six months of GA treatment.

1. Introduction

Spasticity is a well-known symptom of multiple sclerosis (MS) that may affect up to 80% of patients [1]. Spasticity increases from painful cramps, spasms or transient clonus to persistent stiffness as the disease progresses. Thus, worsening of spasticity might require additional symptomatic treatment and lead to a significant disability that often impairs activities of daily living and patients' quality of life.

Current MS treatments have considerably improved the course of disease, but they might also influence negatively the degree of spasticity. In fact, interferon-β (IFN-β), one of the most common agents for long-term treatment of MS, has been associated with worsening of spasticity, affecting 13–15% of treated patients [2,3], especially those with pre-existing pronounced spasticity [4], and with a significant effect approximately two months after starting treatment [5].

Glatiramer acetate (GA) is a widely used and effective drug indicated for treatment of relapsing–remitting MS (RRMS) that does not appear to be associated with worsening of spasticity [2,6]. However, the information available about its influence on spasticity is very limited. To date, there is only one report of a pilot study which specifically approached the effect of GA on spasticity in patients with RRMS [7]. This effect was evaluated in 15 treatment-naïve patients and 13

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patients switching from IFN-β who started GA at the approved dosage and were followed for 12 and 18 months, respectively. The results obtained did not show any evidence of worsening of spasticity in treatment-naïve patients, and they even revealed a significant improvement in spasticity among patients with RRMS switching from IFN-β to GA.

In view of the above, the purpose of this study was to broaden the information available about the impact of GA treatment on spasticity, evaluating the change in spasticity measurements in patients with RRMS switching from IFN-β to GA administered under clinical practice conditions.

2. Patients and methods

This observational multicentre post-marketing study was conducted in accordance with the Helsinki Declaration of the World Medical Association, all of its amendments, and national regulations. The study was approved by the ethics committees and all patients gave their written informed consent prior to study enrolment.

2.1. Patient population

The main eligibility criteria included patients between 18 and 60 years old, with diagnosis of RRMS, a score of ≤5.5 on the Kurtzke Expanded Disability Status Scale (EDSS), and spasticity confirmed by any of the scales specified in the study protocol. Patients should also have switched from IFN-β to GA and received GA for at least 24 weeks. Patients' medical charts should contain information of patients' clinical follow-up and evaluation of spasticity every three months after starting GA. Patients under treatment with stable spasmolytic therapy during the last 12 weeks were allowed to participate in the study.

The main exclusion criteria included patients with surgically treated spasticity, any concomitant disease leading to short-term fatal outcome, severe refractory epilepsy, depression or drug abuse.

2.2. Study treatment

Patients received GA (Copaxone®, Teva Pharmaceuticals Ltd., London, United Kingdom) from commercial sources administered according to the Summary of Product Characteristics, and under clinical practice conditions.

No restrictions regarding other treatments or changes in any spasmolytic medications were specified in the study protocol.

2.3. Assessments

All information about patients' medical history, physical condition and treatment when starting GA and in the following three and six months were retrieved from patients' medical charts. Spasticity assessments included Penn Spasm Frequency Scale (PSFS) [8], Modified Ashworth Scale (MAS) [9], Adductor Tone Rating Scale (ATRS) [10], and Global Pain Scores [11,12]. Quantification of patients' disability was performed according to scores on the EDSS [13]. Information about the number of MS relapses, working days' leave, and concomitant medications during the study period were also collected. Data about patients' quality of life according to the questionnaire Multiple Sclerosis Quality of Life-54 (MSQOL-54) [14] at baseline and month 6 was also retrieved, as well as all the adverse events reported during the whole study period.

2.4. Statistical considerations

Sample size determination was based on a pilot study that evaluated the effects of GA on spasticity in patients with RRMS [7]. The scale with the lowest variation during the study was considered to guarantee statistical significance of the variable with the lowest change. Thus, the selected variable was the ATRS, whose mean absolute change ranged from 0.55 to 0.20. The most conservative value (0.20) was used to calculate the sample size, together with the standard deviation (SD) of patients previously treated with IFN-β (0.69).

The primary efficacy endpoint was the change in spasticity in patients with RRMS switching from IFN-β to GA. Analysis of this primary efficacy endpoint included comparison of scores on PSFS, MAS, ATRS and GPS at baseline, month 3 and month 6 using a general linear model. An additional sub-analysis of the change in spasticity scores was also performed comparing patients receiving and not receiving spasmolytic treatment at baseline. Differences between these subgroups were evaluated using a general lineal model and the Mann–Whitney test for independent samples.

Secondary efficacy endpoints included the change in disability and number of relapses during the study period, the influence of disease relapses and spasticity on working days' leave, the use of spasmolytic medications, and the tolerability of GA according to the adverse events reported during the study period. Descriptive analyses of these secondary endpoints were performed. EDSS scores at baseline, month 3 and month 6 were compared using t-tests for dependent/related samples. An additional evaluation of patients' quality of life was also assessed based on the scores on the MSQOL-54 questionnaire (Spanish validated version) at baseline and month 6. Comparison of scores between baseline and month 6 was performed using t-tests for dependent/related samples. The magnitude of the difference between baseline and month 6 was determined by the formula for Cohen's effect size, considering d values of 0.2 ± 0.15, 0.5 ± 0.15 and 0.8 ± 0.15 as small, medium and large effect sizes, respectively.

Missing data were not considered in the analyses and a significance level of 0.05 was used for statistical testing. The statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc, Chicago, USA).

3. Results

3.1. Patient characteristics

Patient data from September 2009 to January 2011 was collected from a total of 75 patients recruited in 27 Spanish hospitals. Seven of them were screening failures and 68 patients comprised the evaluable population.

Baseline characteristics of evaluable patients are described in Table 1. The mean (SD) age was 41.7 (9.5) years, 48 patients (70.6%)

Table 1
Demographic and clinical characteristics of patients at baseline (N = 68).

Patient characteristics	Value
Mean age, years (SD)	41.7 (9.5)
Gender, n (%):	
Female	48 (70.6)
Male	20 (29.4)
Ethnicity, n (%):	
Caucasian	66 (97.1)
Arab	2 (2.9)
Family history of MS, n (%)	4 (5.9)
Previous treatments of MS, n (%):	
IFN-β 1a sc	29 (42.6)
IFN-β 1a im	28 (41.2)
IFN-β 1b	22 (32.4)
Mean time from diagnosis to the last relapse of MS, years (SD)[a]	7.0 (5.4)
Mean time from diagnosis of MS to starting GA, years (SD)[b]	7.6 (5.7)
Mean number of relapses from diagnosis of MS to starting GA (SD)[c]	4.1 (3.4)

GA: glatiramer acetate; im: intramuscular; MS: multiple sclerosis; N: number in sample; n: number in subsample; sc: subcutaneous; SD: standard deviation.
[a] Missing data, n = 17.
[b] Missing data, n = 5.
[c] Missing data, n = 2.