Journal of Clinical Neuroscience 21 (2014) 2212–2218

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

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

Clinical Study

Long-term effectiveness of glatiramer acetate in clinical practice conditions

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ARTICLE INFO

Article history:
Received 17 December 2013
Accepted 25 May 2014

Keywords:
Clinical practice
Disability
Long-term effectiveness
Glatiramer acetate
Multiple sclerosis
Relapse

ABSTRACT

Glatiramer acetate currently represents one of the main treatments for relapsing-remitting multiple sclerosis (RRMS). However, the information available about its long-term effect in clinical practice is still limited. Thus, this multicenter retrospective cohort study aimed to assess the long-term effectiveness of glatiramer acetate in this setting. The study population included RRMS patients treated with glatiramer acetate for at least 5 years after its marketing authorization and the primary endpoint was long-term clinical effectiveness, defined as absence of disability progression for at least five consecutive years. A total of 149 patients were included into the study, who had received glatiramer acetate for a mean of 6.9 ± 1.4 years (5 years, n = 149; 6 years, n = 112; 7 years, n = 63; 8 years, n = 32; 9 years, n = 21). More than 85% of patients remained free from disability progression through years 1 to 9 of glatiramer acetate treatment, and 75.2% showed absence of disability progression for at least five consecutive years. Expanded Disability Status Scale (EDSS) scores were maintained, with most patients showing stable/improved EDSS and 92.6% sustaining EDSS <6. Decreased annual relapse rates and increased proportion of relapse-free patients were maintained during the whole glatiramer acetate treatment compared to the year prior to its authorization ($p < 0.001$). The number of gadolinium-enhanced T1-weighted lesions also decreased from pre-glatiramer-acetate assessment to last follow-up whilst on glatiramer acetate ($p < 0.05$). In conclusion, administration of glatiramer acetate shows long-term clinical effectiveness for RRMS treatment; its effect under clinical practice conditions slowed disability progression and reduced relapse occurrence for up to 9 years.

1. Introduction

Multiple sclerosis is a lifelong inflammatory demyelinating disease of the central nervous system with the first symptoms usually appearing in young adults, representing the major cause of non-traumatic disability in this group [1]. The development of disease-modifying therapies has improved the prognosis of the disease but no cure is available yet. Therefore, the main goals of current treatments are to control relapses and to prevent long-term accumulation of disability.

Glatiramer acetate is one of the main immunomodulatory drugs used for multiple sclerosis treatment. It has been approved in many countries worldwide for the reduction in frequency of relapses in ambulatory patients with relapsing-remitting multiple sclerosis (RRMS). Apart from the reduction in the number of relapses, glatiramer acetate has also been shown to slow disability progression and disease activity measured by MRI [2–7]. Even though the efficacy of glatiramer acetate has been mainly assessed after 9 to 42 months of treatment, the extension phases of the pivotal clinical trials of glatiramer acetate have shown that its beneficial effect may be maintained long-term [8,9].

The extension phase of the USA pivotal trial of glatiramer acetate reported that patients with a mean duration of multiple sclerosis of 22 years having continuously received glatiramer acetate for up to 15 years maintained low relapse rates, as well as slow disability progression and transition to secondary progressive multiple sclerosis [8]. In addition, the long-term follow-up of a European/Canadian glatiramer acetate trial also showed delayed accumulation of disability, and a small MRI lesion burden after a

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http://dx.doi.org/10.1016/j.jocn.2014.05.045
0967-5868/

mean of 5.8 years on glatiramer acetate treatment [9]. However, the information available about the long-term effect of glatiramer acetate is still limited, and the highly controlled conditions and homogeneous patient population characteristic of clinical trials may entail differences in the effectiveness observed in clinical practice [10].

In light of the above, the objective of this study was to increase the currently available knowledge on the long-term effectiveness of glatiramer acetate administered to RRMS patients under clinical practice conditions.

2. Patients and methods

This study was approved by the ethics committee of Hospital Universitario Virgen de las Nieves (Granada, Spain), and conducted according to the World Medical Association Declaration of Helsinki, all its amendments and national regulations.

2.1. Patient population

All patients meeting selection criteria who gave their written informed consent to participate in the study were consecutively recruited between June 2012 and February 2013. The inclusion criteria were patients aged 18 to 60 years with a diagnosis of RRMS who had received glatiramer acetate (Copaxone, Teva Pharmaceuticals Ltd., London, UK) for a minimum of 5 years after its marketing authorization in Spain in 2002. The exclusion criteria included patients whose medical charts lacked scores on the Expanded Disability Status Scale (EDSS) or number of relapses at the time of commencing glatiramer acetate and follow-up while on glatiramer acetate for at least 5 years.

2.2. Study design

This was a retrospective cohort study carried out at 28 Spanish hospitals. The study follow-up comprised the whole duration of glatiramer acetate treatment, from its start (or patients' enrollment into the study) to its end (if this had occurred).

All treatments were administered according to routine clinical practice and no restrictions regarding patient treatment were specified in the study protocol.

2.3. Assessments

Patient information was retrospectively retrieved from their medical charts from the first to the last assessment available whilst on glatiramer acetate treatment. These data included demographics, medical history of multiple sclerosis and its treatment, EDSS scores, and the number of relapses experienced by patients. Data on the last MRI assessment performed before starting glatiramer acetate and at last follow-up available whilst on glatiramer acetate treatment were also collected.

Patient disability was quantified using the EDSS, with greater scores representing increased disability [11]. Patients were classified as stable/improved if their EDSS increased $\leqslant$0.5 points, did not change or decreased from treatment onset. Progression of disability was defined as an increase in EDSS $\geqslant$1.0 points for patients with EDSS <5.5, or $\geqslant$0.5 points for patients with EDSS $\geqslant$5.5, persisting on a second examination performed 3 to 6 months later. Long-term clinical effectiveness was defined in terms of disability progression, namely the absence of disability progression for at least five consecutive years.

A relapse was defined as the appearance of a new neurologic symptom or worsening of a pre-existing one, not attributable to fever or infections, which persisted for more than 24 hours and became evident during a neurological examination.

Table 1
Patient characteristics at the time of glatiramer acetate commencement (n = 149)

Patient characteristics	Value
Age at multiple sclerosis diagnosis, years[a]	32.5 ± 7.8
Age, years	36.3 ± 7.6
Sex	
Female	105 (70.5)
Male	44 (29.5)
Previous multiple sclerosis treatment	
Patients previously treated for multiple sclerosis	63 (42.3)
Treatment prior to GA onset	
Subcutaneous interferon β-1a	22 (14.8)
Intramuscular interferon β-1a	21 (14.1)
Interferon β-1b	13 (8.7)
Mitoxantrone	6 (4.0)
Azathioprine	1 (0.7)
Duration of multiple sclerosis, years[b]	3.8 ± 3.8
EDSS score	2.2 ± 1.3
Relapse rate in year previous to GA	1.5 ± 1.0
Number of MRI lesions[c]	
Gadolinium-enhanced T1 lesions	0.7 ± 1.5
New T2 lesions	3.5 ± 6.0

Data are presented as mean ± standard deviation or number (%).
[a] Missing data, n = 1.
[b] Missing data, n = 7.
[c] Missing data, n = 42.
EDSS = Expanded Disability Status Scale, GA = glatiramer acetate.

2.4. Statistical considerations

Sample size was calculated taking into account the 69% and 57% of patients maintaining/improving their EDSS scores reported by the 6 and 15 year follow-up of the USA glatiramer acetate trial [8,12]. Considering a 65% rate of progression-free patients, a

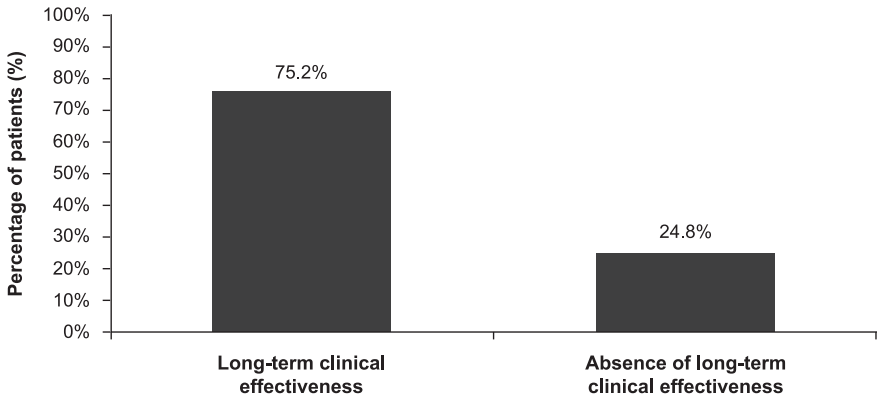

Fig. 1. Distribution of relapsing-remitting multiple sclerosis patients with long-term clinical effectiveness of glatiramer acetate (n = 149).