Current Therapeutic Research 88 (2018) 47–51

Contents lists available at ScienceDirect

Current Therapeutic Research

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

Tolerability and Safety Profile of a New Brand-Generic Product of Glatiramer Acetate in Iranian Patients with Relapsing-Remitting Multiple Sclerosis: An Observational Cohort Study☆,†

Roya Abolfazli, MD[1,*], Shirin Pournourmohammadi, PharmD, PhD[2], Ahmadreza Shamshiri, MD, PhD[3], Sara Samadzadeh, MD[1]

[1] Neurology Department, Tehran University of Medical Sciences, Amiralam Hospital, Tehran, Iran.
[2] Medical Affairs Department, Zahravi Pharmaceutical Company, Tehran, Iran.
[3] School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.

ARTICLE INFO

Article history:
Received 10 December 2017
Revised 8 May 2018
Accepted 21 May 2018

Keywords:
adverse drug reaction
efficacy
glatiramer acetate
multiple sclerosis
safety
tolerability

ABSTRACT

Background: The aim of this study was to evaluate the safety, tolerability, and efficacy of a brand-generic glatiramer acetate product in patients with relapsing-remitting multiple sclerosis over a 12-month period. A noninterventional cohort study was conducted on 185 patients. The patients had a confirmed and documented diagnosis of relapsing-remitting multiple sclerosis as defined by the Revised McDonald Criteria (2010), were ambulatory with a Kurtzke Expanded Disability Status Scale score of 0 to 5.5, and their treatment by glatiramer acetate 40 mg/mL was just started.

Methods: Adverse drug reactions, relapse rate, magnetic resonance imaging parameters, and Expanded Disability Status Scale score were evaluated over 1 year.

Results: Of 185 enrolled patients from 21 different cities, 170 completed the study. The mean (SD) Expanded Disability Status Scale score was 1.97 (0.75) at the time of screening. The mean age was 33 years with an average of 4-year multiple sclerosis history, and 83% were women. Hepatic disorder and depression were the most frequent medical history. The most common adverse drug reactions were local pain (45.4%) and erythema (38.9%). The immediate postinjection reactions included dyspnea (10.3%), anxiety (9.7%), palpitation (8.1%), urticaria (5.4%), flushing (3.24%), chest pain (2.16%), and throat constriction (0.54%). The percentage of relapse-free patients at Month 12 was 87%, and the annual relapse rate was 0.134. An increase in the Expanded Disability Status Scale score was observed in 20% of patients, and new T2 and gadolinium-enhancing lesions were found in 34.7% and 9.4%, respectively. The rate of treatment failure was 1.6% and 4.3% according to the Modified Rio and Rio scores, respectively.

Conclusions: The 40 mg brand-generic glatiramer acetate product was well tolerated in this selected group of Iranian patients with relapsing-remitting multiple sclerosis, and patient adherence was favorable over 1 year. (*Curr Ther Res Clin Exp*. 2018; 79:XXX–XXX).

Introduction

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease of the central nervous system. Relapsing-remitting MS (RRMS) is characterized by clearly defined relapses with full recovery or with sequelae and residual deficits upon recovery without disease progression between relapses. There are 10 US Food and Drug Administration-approved products for the treatment of RRMS, including interferon-beta-1a, interferon-beta-1b, glatiramer acetate (GA) (Copaxone*), dimethyl fumarate, fingolimod, teriflunomide, natalizumab, daclizumab, alemtuzumab, and ocrelizumab.

GA is the acetate salt of synthetic polypeptides, including L-glutamic acid, L-lysine, L-alanine, and L-tyrosine with a complex mechanism of action. It is a well-intentioned option as a first-line treatment in RRMS.[1,2] GA was approved by the US Food and Drug Administration for treatment of RRMS in 1996 based on a

☆ Trademark: Copaxone® (Teva Pharmaceuticals, Petah Tikva, Israel).
† Trademark: Copamer® (Zahravi Pharmaceutical Company, Tehran, Iran).
* Address correspondence to: Roya Abolfazli, MD, Neurology Department, Amiralam Hospital, Tehran University of Medical Sciences, Saadi St, Tehran, Iran 1435915371.
E-mail address: abolfazl@sina.tums.ac.ir (R. Abolfazli).
URL: http://dx.doi.org/10.1016/j.curtheres.2018.05.001 (R. Abolfazli)

multicentric, Phase III trial of patients with RRMS in which 251 patients were randomized to receive Copaxone (n = 125) or placebo (n = 126) at a dose of 20 mg/mL by daily subcutaneous injection for 2 years. The results showed the number of relapses was reduced by 29% with GA versus placebo.[3] In 2013, higher dose with less frequently dosed 3 times a week version of GA was evaluated in a multinational (142 sites in 17 countries), randomized, Phase III GALA study in patients with RRMS (n = 943 in GA and n = 461 in the placebo group) for 12 months. GA 40 mg/mL 3 times weekly reduced annualized relapse rates significantly more than placebo, and indirect comparisons indicated that the efficacy of the 3-times-weekly regimen was similar to that of the 20 mg/mL once-daily regimen. GA 40 mg/mL reduced the risk of relapse (34%) in addition to a cumulative number of Gd-enhancing (44.8%) and new or newly enlarging T2 lesions (34.7%). Seventy-seven percent of patients were relapse-free at Month 12. In terms of safety, injection site reaction was the most common adverse drug reaction (ADR).[4] Treatment of patients with RRMS with GA 20 mg in a European/Canadian multicenter trial showed a significant reduction in disease activity monitored with magnetic resonance imaging (MRI) compared with placebo.[5] Another multicenter trial conducted in 16 countries showed GA 20 mg could reduce the risk of developing clinically defined MS by 45% compared with placebo over 3 years.[6]

As a first-line treatment, Copaxone is costly for long-term consumption, and its availability is limited, particularly in Iran. Zahravi Pharmaceutical Company was interested in developing a brand-generic version of GA called Copamer† containing 20 or 40 mg/mL GA in prefilled syringes. Both dosage forms are available on the market. This study aimed to investigate the safety, tolerability, and efficacy of Copamer 40 mg/mL in patients with RRMS over 1 year of treatment. Copamer 20 mg/mL was not considered in this investigation because few patients used it and adequate sample size could not be achieved. It is necessary to mention that this study was just a postmarketing study and not for the purpose to obtain marketing approval.

Materials and Methods

Study design

This study was a cohort, observational, 1 arm, open-label clinical trial approved by the Ethics Committee of Pharmaceutical Sciences Research Center of Tehran University of Medical Sciences (code: IR.TUMS.PSRC.REC.1395.379). The study was conducted according to the International Conference on Harmonisation in compliance with Good Clinical Practice guidelines and the Declaration of Helsinki. Two hundred trial patients from 4 hospitals and 1 private office were screened according to the following inclusion criteria: man or woman, aged at least 18 years, a confirmed and documented diagnosis of RRMS as defined by the Revised McDonald Criteria (2010), with a relapse-onset or relapsing-remitting disease course, being ambulatory with a Kurtzke Expanded Disability Status Scale (EDSS) score of 0 to 5.5 in both screening and baseline visits, having a stable neurologic condition and being relapse-free and free of any corticosteroid treatment (intravenous, intramuscular, and/or oral) or adrenocorticotrophic hormone 30 days before recruitment, being a candidate for GA 40 mg/mL according to MRI and clinical findings assessed by a neurologist, providing written informed consent. The following patients were excluded: women who were either pregnant or breastfeeding or became pregnant during the study; patients with a clinically significant or unstable medical or surgical condition that would interfere with study results; patients with a history of drug or alcohol abuse within the past year; and patients who used corticosteroid, interferon, or immunosuppressive drugs within 30 days before recruitment.

The main study end point was the rate of injection-related ADRs over 1 year, including all local injection-site reactions and events related to immediate postinjection reactions (eg, flushing, chest pain, palpitation, anxiety, dyspnea, throat constriction, and urticaria). The secondary end points were treatment failure, efficacy (based on EDSS score, relapse, and MRI findings), and other ADRs, including expected and unexpected drug-related ADRs other than injection-related reactions according to the product monograph.

Data collection and management

The trial patients who had a confirmed and documented RRMS diagnosis defined by the Revised McDonald Criteria (2010) with a relapse onset or relapsing-remitting course and were ambulatory with a Kurtzke EDSS score of 0 to 5.5, were enrolled in the trial according to the inclusion criteria mentioned earlier during 7 months (April–November 2015). The trial study patients were trained for self-subcutaneous injection of prefilled Copamer 40 mg/mL syringes (sites for self-injection were the abdomen, arms, hips, and thighs).

The criteria for the evaluation of safety included the history of ADRs, vital signs such as blood pressure, heart rate, and body temperature (sudden clinical changes in vital signs during treatment were considered adverse events), and laboratory tests such as blood biochemistry, hematology, and urinalysis. Regarding ADRs, reports were collected by a neurologist at each visit using an ADR form at Months 6, 9, and 12. Patients were asked to report any adverse event in the meantime.

The criteria for the evaluation of efficacy included medical history and physical exam, EDSS score at baseline; Month 6, 9, and 12; annualized relapse rate (ie, total number of confirmed relapses during the study divided by the sum of the number of days on study then multiplied by the number of days in the year); number of relapse-free patients at Month 12 (relapse defined as the appearance of 1 or more new neurologic abnormalities or the appearance of 1 or more previously observed neurologic abnormalities lasting at least 48 hours and proceeded by an improving neurologic state of at least 30 days from the onset of previous relapse); and MRI parameters collected at baseline and Month 12 (MRI was taken any time according to physician's decision when a relapse or serious problems occurred), including new T2 lesions, enlarging lesions, and enhancing lesions. The MRI protocol included dual echo T2-weighted image (W1), 3-dimensional inversion recovery spoiled-gradient recalled T1-W1, fluid-attenuated inversion recovery, and spin-echo T1-W1 with and without Gd contrast. Brain MRI was done in a medical diagnostic imaging center in Tehran, Iran (Dr Athari Imaging Center) and the MRI findings were confirmed by 2 radiologists. Treatment failure during 1 year of GA administration was evaluated with regard to the Rio and modified Rio score.[7] Withdrawal conditions were defined based on pregnancy, ADRs, concomitant medication, intolerance, and consent withdrawal.

Statistical analysis

The sample size was calculated based on the most common ADR. Injection site reactions were reported by 36% of patients receiving Copaxone 40 mg/mL during a 12-month follow-up in a study conducted by Khan et al.[4] A sample size of at least 181 patients was calculated to estimate the same frequency with 7% precision and 95% confidence (type 1 error = 0.05). Immediate postinjection reaction was reported by 8% of patients receiving Copaxone 40 mg/mL in the study conducted by Khan et al.[4] So, a sample size of at least 177 patients was calculated to estimate the same frequency with 4% precision and 95% confidence (type 1 error = 0.05).