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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

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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.

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 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

Trademark: Copaxone® (Teva Pharmaceuticals, Petah Tikva, Israel).
†Trademark: Copamer® (Zahravi Pharmaceutical Company, Tehran, Iran).
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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). Accordingly, the final sample size was 200 patients considering loss to follow-up.

Categorical variables are reported as number and percentage, and quantitative variables are presented as a mean (SD). Survival

Table 1
Patient and disease characteristics.

Characteristic	Result
Age*, y	33.5 (7.6)
Weight*, kg	70.5 (8.8)
Time from diagnosis year*	4.3 (3.8)
Baseline Kurtzke Expanded Disability Status Scale score*	1.97 (0.75)
Abnormal lab finding over 1 y†	0
Number of cities of residence†	21
Sex‡	
Men	31 (16.8)
Women	154 (83.2)
Medical history‡	
Diabetes	4 (2.2)
Ovary cancer	1 (0.5)
Hypertension	10 (5.4)
Rheumatoid arthritis	1 (0.5)
Hepatic disorder	45 (24.3)
Renal disorder	2 (1.1)
Thyroid disorder	6 (3.2)
Depression	38 (20.5)
Others	13 (7.0)

* Values presented as mean (SD).
† Values presented as number.
‡ Values presented as number of patients (%).

analysis was conducted for time-dependent variables such as relapse rate. To compare efficacy parameters from the baseline to the end of the follow-up period, conditional logistic regression or paired *t* test were performed according to the type of dependent variables. All patients who signed informed consent were included in the final analysis (intention to treat analysis).

Results

Two hundred patients were screened and 185 eligible trial patients were enrolled. Basic and disease characteristics and medical history of patients who gave informed consent were collected from their medical records (**Table 1**). Regarding medical history, the mean (SD) EDSS score was 1.97 (0.75) at the time of screening, and all patients experienced 1 relapse during 1 year before screening (**Table 1**). One hundred seventy (91.9%) patients completed the study up to Month 12, but 15 patients (8.1%) discontinued treatment with Copamer 40 due to ADRs (1%) and pregnancy (7%) (Fig.). The most common disorders found in their medical history were hepatic disorders (24.3%) and depression (20.5%) (**Table 1**). Other patients' characteristics are listed in **Table 1**, as well.

The injection site reactions experienced by patients using Copamer 40 were local pain (45.41%), erythema (38.92%), inflammation (16.76%), itching (16.76%), lipoatrophy (1.62%), and hypersensitivity at the site (0.54%). In addition, immediate postinjection reactions included dyspnea (10.27%), anxiety (9.73%), palpitation

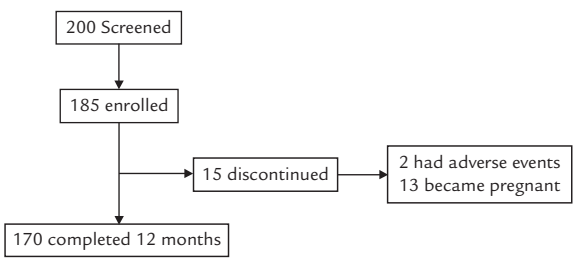

Fig. Participant flow of patients with RRMS over 1 year of glatiramer acetate (Trademark: Copamer® (Zahravi Pharmaceutical Company, Tehran, Iran) administration. *Two patients discontinued treatment due to intolerability (dyspnea, urticaria, and flushing).

Table 2
Adverse drug reactions reported by patients with relapsing-remitting multiple sclerosis over 1 year of glatiramer acetate (Copamer 40*) administration.

End point	Copamer n (%)	% Glatiramer acetate†
Primary end points		
Injection site reaction		
Local pain	84 (45.41)	10-40
Erythema	72 (38.92)	22-43
Inflammation	31 (16.76)	2-49
Itching	31 (16.76)	6-27
Lipoatrophy	3 (1.62)	≤ 2
Hypersensitivity	1 (0.54)	4
Immediate postinjection hypersensitivity		
Dyspnea	19 (10.27)	2-16
Anxiety	18 (9.73)	2-16
Palpitation	15 (8.11)	2-16
Urticaria (pruritus)	10 (5.41)	2-16
Flushing	6 (3.24)	2-16
Chest pain	4 (2.16)	2-16
Throat constriction	1 (0.54)	2-16
Secondary end points		
Headache	12 (6.49)	≥ 10
Ecchymosis	6 (3.24)	1-10
Tremor	3 (1.62)	1-10
Lightheadedness	3 (1.62)	Not reported
Hypertonia	2 (1.08)	1-10
Edema	1 (0.54)	8
Fever	1 (0.54)	3-6
Nausea	1 (0.54)	2-15
Facial edema	1 (0.54)	3
Neck pain	1 (0.54)	8
Fluctuation blood pressure	1 (0.54)	Not reported

* Trademark: Copamer® (Zahravi Pharmaceutical Company, Tehran, Iran).
† Source: Drugs Fact & Comparisons, 2015.

(8.11%), urticaria (5.41%), flushing (3.24%), chest pain (2.16%), and throat constriction (0.54%) (**Table 2**). Furthermore, headache, ecchymosis, tremor, lightheadedness, and hypertonia were reported by more than 1% of patients. **Table 2** shows the incidence and spectrum of ADRs for Copamer.[8]

The annual relapse rate was 0.134 and the percentage of relapse-free patients at Month 12 was 87% during 1-year of treatment with Copamer 40. The EDSS score increased in 20% of patients and T2 lesion augmentation, and gadolinium-enhancing lesions were found in 34.7% and 9.4% of patients, respectively. Gadolinium-enhancing lesions decreased in 22.4% of patients (**Table 3**). Treatment failure during 1 year of Copamer 40

Table 3
Kurtzke Expanded Disability Status Scale (EDSS), relapse, and magnetic resonance imaging (MRI) analysis obtained from patients with relapsing-remitting multiple sclerosis (RRMS) over 1 year of glatiramer acetate (Copamer*) administration.

End point	Patients (%)
Increased EDSS	37/185 (20.0)
Stable EDSS	148/185 (80.0)
Annualized relapse rate	0.134
Relapse-free patients	161/185 (87.0)
Relapse rate ≥ 1	24/185 (13.0)
Time to first relapse (mo)	
≤ 6	3 (1.6)
7-9	5 (2.7)
10-12	16 (8.6)
MRI end points	
Increased new T2 lesion	59/170 (34.7)
Increased GAD enhancing	16/170 (9.4)
Decreased GAD enhancing	38/170 (22.4)

GAD = gadolinium.
* Trademark: Copamer® (Zahravi Pharmaceutical Company, Tehran, Iran).

Table 4
Treatment failure over 1 year of glatiramer acetate (Copamer*) administration according to Rio score† and Modified Rio score‡.

Patients (%)	Magnetic resonance imaging criterion = 1	Relapse criterion = 1	Kurtzke Expanded Disability Status Scale score = 1	Treatment failure (2+ points)
	10 (5.4)	24 (12.9)	0 (0)	8 (4.3)
	2 (1.08)	23 (12.4)	1 (0.54)	3 (1.6)

* Trademark: Copamer® (Zahravi Pharmaceutical Company, Tehran, Iran).

† Rio score: - Magenetic resonance imaging criterion = 1 (≥2 active T2 lesions), - Relapse criterion = 1 (≥1 relapse), and - Kurtzke Expanded Disability Status Scale criterion =1 increase in EDSS score ≥1 point (sustained over at least 6 mo).

‡ Modified Rio score: - Magnetic resonance imaging criterion = 1 (≥4 new T2 lesions), and - Relapse criterion = 1 (1 relapse), relapse criterion = 2 (≥2 relapses).

administration was 4.3% according to the Rio score and 1.6% according to the Modified Rio score (Table 4).

Discussion

Because MS is a lifelong disease with disability and inflammation of the central nervous system, inexpensive and well-tolerated disease-modifying treatment remains the best option for many patients. Copaxone (20 and 40 mg) was initially introduced to the market by Teva Pharmaceuticals[9]; then, generic versions—glatopa and copemyl 20 mg—were developed in the United States and Europe to expand the availability of GA for patients at a lower price, although there are other generic GAs in Argentina, Mexico, and India.[10,11] In Iran, there are more than 70,000 patients with MS, and the cost of long-term treatment with Copaxone is unaffordable for Iranian patients despite the fact that Copaxone is not registered in Iran. Because this immunomodulatory and disease-modifying agent can be used as a first-line treatment for RRMS, Zahravi Pharmaceutical Company developed a brand-generic of GA locally. Therefore, we were interested in investigating the tolerability and safety profile of the product in Iranian patients after marketing approval. Some parameters, like the inclusion/exclusion criteria and safety, were designed based on the GALA study, a Phase III clinical trial comparing GA 40 mg versus placebo in RRMS.[4] The incidence and spectrum of ADRs observed in this small, selected group of Iranian patients were similar to GA in the reference book[8] except for local pain, which was higher (45.4% vs 40%) and it might influence the compliance of patients despite reasonable efficacy. More pain might be due to the sensitivity of Iranian patients or the quality of the needles. Among trial patients, 13 women became pregnant and discontinued the treatment but they were followed by 1 gynecologist, and the results showed that both the mothers and newborn infants were safe and no ADR was reported. Two patients discontinued treatment due to intolerability (ie, dyspnea, urticaria, and flushing). Of 185 patients treated with Copamer 40 mg, 44.3% (82 patients) experienced at least 1 ADR over the first 6 months, 62.2% (115 patients) experienced at least 1 ADR over 1 year, among whom 98.3%, 71.3%, 43.5%, and 31% reported ADRs during the first month, between 2 and 6 months, between 7 and 9 months, and between 10 and 12 months of treatment, respectively.

The results of Phase IIIb GLACIER study[12] in 108 patients with RRMS who converted from using GA 20 mg to GA 40 mg demonstrated that 58.3% of patients experienced at least 1 injection-related adverse event and 56.5% of patients experienced at least 1 injection-site reaction. The annualized rate of the injection-related adverse event was 35.3 associated with GA 40 mg. Most of the injection-related adverse events were injection-site reactions, among which pain and erythema were most frequent.[12]

Regarding relapse profile of Copamer 40 mg, the annual relapse rate was 0.134 and the percentage of relapse-free patients at Month 12 was 87%. Regarding efficacy of Copamer 40 mg, the rate of treatment failure reported in our study was clinically acceptable considering the outcome of the previous reports. Concerning the diversity of ethnicities and geographic areas, the enrolled patients (referred to 4 hospitals and the private office of a neurologist) were from 21 cities; 68% were inhabitants in the capital (Tehran) and 32% were from other cities around the country.

Concerning limitations of our study, we were interested in conducting a comparison study, but we had no chance to do so because Copaxone is not registered and not available in our market. This study was conducted in this small, selected group of Iranian patients for 1 year, and an extended study is required to confirm its safety and efficacy profile.

Conclusions

The results of our study of 185 Iranian patients showed that the new brand-generic version of GA (Copamer 40) was well tolerated in this small, selected group of Iranian patients with RRMS and the patient adherence was favorable over 1 year.

Acknowledgments

This study was a cohort, observational, 1 arm, open-label clinical trial approved by Ethics Committee of Pharmaceutical Sciences Research Center of Tehran University of Medical Sciences (code: IR.TUMS.PSRC.REC.1395.379) and funded by Zahravi Pharmaceutical Company, which also supported all investigators and study staff to enroll, evaluate, and-follow up the study patients. It was conducted according to International Conference on Harmonisation in compliance with Good Clinical Practice guidelines and Declaration of Helsinki. The authors thank Dr. Jaleh Alaghehbandi for providing data entry and assistance to the trial documentation, the patients and neurologists who participated in this study, as well as Dr. Athari of the Imaging Center for kind cooperation. All named authors have seen and agreed with the contents of the manuscript. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. All named authors take responsibility for the integrity of the work as a whole and have given final approval for the version to be published. All authors contributed equally.

Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Appendix A. Supporting information

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.curtheres.2018.05.001.

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