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ADIS DRUG EVALUATION

Glatiramer Acetate 40 mg/mL in Relapsing–Remitting Multiple Sclerosis: A Review

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Abstract Glatiramer acetate (Copaxone®) is a synthetic analogue of myelin basic protein, which is thought to be involved in the pathogenesis of multiple sclerosis (MS). The therapeutic effects of the drug in the treatment of MS are thought to be via immunomodulation and neuroprotection. Subcutaneous glatiramer acetate 20 mg/mL once daily is approved in several countries for the treatment of relapsing forms of MS. Recently, a high-concentration formulation of glatiramer acetate 40 mg/mL administered three times weekly was approved in the USA and several European countries in the same indication. This article reviews the efficacy and tolerability of the high-concentration regimen. In the randomized, phase III GALA study in patients with relapsing–remitting MS (RRMS), glatiramer acetate 40 mg/mL three times weekly reduced annualized relapse rates significantly more than placebo, and indirect comparisons indicate that the efficacy of the three-times-weekly regimen is similar to that of the 20 mg/mL once-daily regimen. Results of the randomized, phase IIIb GLACIER study in patients with RRMS demonstrated that the three-times-weekly regimen reduced the risk of injection-site reactions by 50 % and was associated with numerically greater patient convenience scores than the once-daily regimen. Thus, in the treatment of RRMS, glatiramer acetate 40 mg/mL three times weekly is effective and provides a better tolerated and possibly more convenient option than the once-daily regimen.

Glatiramer acetate 40 mg/mL in relapsing–remitting multiple sclerosis (RRMS): a summary

Administered three times weekly

Reduced annualized relapse rate more significantly than placebo in patients with RRMS

Indirect comparisons suggest similar efficacy to that of the once-daily regimen (20 mg/mL)

Reduced the incidence of injection-site reactions by 50 % compared with the once-daily regimen

May be more convenient than the once-daily regimen

Associated with more favourable outcomes than placebo on brain magnetic resonance imaging assessments

1 Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated disease characterized by multifocal demyelination in the CNS with progressive neurodegeneration in genetically susceptible individuals [1]. The disease is estimated to

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affect more than 2 million people worldwide [2]. MS phenotypes vary, but most patients (≈80–85 %) are classified as having relapsing–remitting MS (RRMS), which presents with a clinically isolated syndrome (CIS) followed by episodes of acute worsening then recovery [1, 3]. Over a variable period and subsequent to the relapsing course, progressive accumulation of clinical disability may lead to progressive disease, termed secondary progressive MS [1, 3].

Subcutaneous glatiramer acetate (Copaxone®) was approved in the USA for the treatment of RRMS almost two decades ago. More recently, with an improved understanding of the importance of early treatment, the drug was also approved in CIS. The glatiramer acetate dosage of 20 mg/mL once daily, until recently, was the only regimen available and the efficacy and tolerability of this regimen is well proven [4].

This article focuses on the efficacy and tolerability of a new dosage regimen comprising high-concentration subcutaneous glatiramer acetate 40 mg/mL administered three times weekly.

2 Pharmacodynamic Properties

The pharmacodynamic properties of glatiramer acetate have been reviewed in detail previously [4–6]. Briefly, the drug is a synthetic analogue of myelin basic protein, an antigen believed to be involved in the pathogenesis of MS [4, 7]. The drug's mechanism of action in the treatment of

immunomodulation and neuroprotection [7]. Table 1 provides a summary of selected pharmacodynamic properties.

Although glatiramer acetate is rapidly degraded in the periphery and does not cross the blood–brain barrier, glatiramer acetate-induced T helper-2 cells migrate into the CNS, leading to the subsequent downregulation of CNS-based inflammation associated with MS (Table 1) [4, 6, 8].

Glatiramer acetate-reactive antibodies produced in response to treatment are of the IgG subtype and do not affect the clinical efficacy of the drug [4].

3 Pharmacokinetic Properties

The pharmacokinetic properties of subcutaneous glatiramer acetate (reviewed previously [4, 9]) have not been fully characterized in patients. Limited data are available from preclinical studies and healthy controls. The drug is rapidly absorbed and most of the dose is rapidly hydrolysed in subcutaneous tissue [10, 11]. Some of the injected drug, either intact or partially hydrolysed, reaches regional lymph nodes (presumably via the lymphatic circulation) and some may enter the systemic circulation intact [10, 11]. Fragments of glatiramer acetate can be detected as glatiramer acetate-reactive antibodies [10].

In radiolabelling studies in animals, the major elimination pathway of glatiramer acetate was urinary excretion, and only trace amounts of the drug were detected in the faeces [4].

Drug interaction studies with glatiramer acetate and

formally conducted [10, 11]. However, no significant interactions have been observed in clinical trials in which glatiramer acetate was coadministered with other drugs commonly used in MS, including corticosteroids and IFNβ-1a [10, 12]. Glatiramer acetate is highly bound to plasma proteins, but is not thought to displace or be displaced by phenytoin or carbamazepine [4]. No well controlled studies have been performed with glatiramer acetate in pregnant women [10, 11].

4 Therapeutic Efficacy

The efficacy of subcutaneous glatiramer acetate 20 mg/mL once daily is well established and was reviewed in this journal previously [4]. Briefly, in clinical trials in patients with RRMS, once-daily glatiramer acetate 20 mg/mL reduced annualized relapse rates (ARRs) and the burden and activity of disease on magnetic resonance imaging (MRI) more effectively than placebo ($p \leq 0.01$) [13, 14] and demonstrated generally similar efficacy, with regard to these endpoints, to subcutaneous IFNβ-1a 44 μg three times weekly and subcutaneous IFNβ-1b 250 or 500 μg every other day [15–17]. However, in a combination therapy trial in patients with RRMS, glatiramer acetate 20 mg/mL once daily plus intramuscular IFNβ-1a 30 μg once weekly was no more effective than glatiramer acetate plus placebo, but was more effective than IFNβ-1a plus placebo, in terms of reducing ARRs [12]. Long-term extension studies have shown that the beneficial effects of glatiramer acetate 20 mg/mL once daily are sustained over the long term, including up to 20 years of treatment [18, 19]. Furthermore, in patients with CIS, glatiramer acetate 20 mg/mL once daily significantly reduced the risk of developing clinically definite MS compared with placebo ($p = 0.0005$) [20]. Results of a phase III dose-comparison study in patients with RRMS demonstrated that there was no gain in efficacy with glatiramer acetate 40 mg once daily compared with 20 mg once daily [21]. However, less frequent administration (of a high-concentration 40 mg/mL formulation) may be associated with fewer localized injection-site reactions than once-daily administration.

This section focuses on the efficacy of subcutaneous glatiramer acetate 40 mg/mL three times weekly in adults (aged ≥18 years) with RRMS in the randomized, phase III, double-blind, placebo-controlled, multinational GALA (Glatiramer Acetate Low-frequency Administration) study [22].

4.1 GALA Study

Patients with a confirmed diagnosis of RRMS and an Expanded Disability Status Scale (EDSS) score of ≤5.5 who were relapse free for ≥30 days were eligible for inclusion [22]. Patients were also required to have had ≥1 relapse in the previous 12 months, ≥2 relapses in the previous 24 months, or 1 relapse between 12 and 24 months previously with ≥1 T1 gadolinium-enhancing (GdE) lesion on MRI in the previous 12 months. MS phenotypes other than RRMS, and recent treatment with immunomodulators or immunosuppressive agents were among exclusion criteria [22].

Patients received glatiramer acetate 40 mg/mL or placebo three times weekly for 12 months, and the primary endpoint was the total number of confirmed relapses (Table 2) [22]. Brain MRI parameters were evaluated in secondary analyses. Patients underwent a complete neurological assessment, including Kurtzke's EDSS and functional system assessment, at screening, baseline and months 3, 6, 9 and 12 [22]. If a relapse was suspected, patients were assessed within 7 days. Brain MRI studies were performed at baseline and months 6 and 12.

The mean age of patients was ≈38 years, and most (68 % of patients) were female [22]. At baseline, the mean time from the onset of MS symptoms was ≈8 years in both groups, and the mean volume of T2 lesions in the glatiramer acetate and placebo groups was 19.7 and 17.4 mL, respectively. The number of exacerbations experienced over the 12 months prior to the study was 1.3 in both groups [22].

4.1.1 Relapse Rate

Patients receiving glatiramer acetate 40 mg/mL three times weekly experienced significantly fewer relapses than patients receiving placebo, equating to a mean ARR risk reduction of 34 % ($p < 0.0001$) (Table 2) [22]. With regard to exploratory endpoints, the mean annualized severe relapse rate was significantly lower and the time to first relapse significantly longer in the glatiramer acetate group than in the placebo group (Table 2). Moreover, more patients remained relapse free following glatiramer acetate versus placebo (77.0 vs. 65.5 %, respectively; $p < 0.0001$). EDSS progression was similar in the two groups [22].

Initiating treatment with glatiramer acetate early was associated with a lower risk of relapse than delayed initiation in an open-label extension of the GALA study (reported in an abstract) [23]. Patients continued to receive glatiramer acetate 40 mg/mL three times weekly ($n = 716$; early initiation group) or switched from placebo to glatiramer acetate 40 mg/mL three times weekly ($n = 325$; delayed initiation group) for a further 2 years. The adjusted mean ARR from baseline to month 36 was significantly lower in the early than the delayed initiation group (0.23 vs. 0.30; $p = 0.0052$) [23].

Table 2 Clinical efficacy of glatiramer acetate 40 mg/mL three times weekly in the treatment of adults with relapsing–remitting multiple sclerosis. Results of the randomized, double-blind, 12-month GALA study [22]

Treatment	No. of pts[a]	Relapse endpoints				MRI endpoints	
		Mean ARR[b]	RR (95 % CI)	Mean ASRR[c]	Time to first relapse[c] (days)	Cum. GdE T1 lesions at 6 and 12 months[d]	Cum. new[e] T2 lesions at 6 and 12 months[d]
GLA 40 mg tiw	943	0.331*	0.656 (0.539–0.799)	0.301*	393*	0.905*	3.650*
PL	461	0.505		0.466	377	1.639	5.592

ARR annualized relapse rate, *ASRR* annualized severe relapse rate, *Cum* cumulative, *GdE* gadolinium enhancing, *GLA* glatiramer acetate, *MRI* magnetic resonance imaging, *PL* placebo, *pts* patients, *RR* risk ratio, *tiw* three times weekly

* $p < 0.0001$ vs. PL

[a] Intent-to-treat population, used for primary analysis

[b] Primary endpoint. Relapse was defined as the appearance of ≥1 new neurological abnormality or the reappearance of ≥1 previously observed neurological abnormality lasting ≥48 h and subsequent to an improved neurological state of ≥30 days from the onset of previous relapse

[c] Exploratory endpoint

[d] Secondary endpoint

[e] New or newly enlarging

4.1.2 MRI-Assessed Outcomes

With regard to MRI endpoints, results were also significantly more favourable in the glatiramer acetate group than in the placebo group, with a 45 % reduction in the cumulative number of GdE T1 lesions and a 35 % reduction in the cumulative number of new or newly enlarging T2 lesions (Table 2) [22]. There was no difference between the respective groups in the percentage change in normalized brain volume at 12 months (−0.706 and −0.645).

Treatment with glatiramer acetate 40 mg/mL three times weekly was associated with a significantly lower rate of new active MRI lesions converting to black holes than placebo in an analysis of GALA data [24]. Among 1292 patients in the GALA study with complete MRI data available at baseline and months 6 and 12, the adjusted mean number of GdE T1 or new T2 lesions at month 6 that were not present at baseline and that had converted to black

4.2 Indirect Comparison of Glatiramer Acetate 40 mg/mL Three Times Weekly and 20 mg/mL Once Daily

Results of a systematic review and meta-analysis [25], and a predictive statistical model [26] (both reported in abstracts) indicate that, based on indirect comparisons, glatiramer acetate 40 mg/mL three times weekly has similar efficacy to that of glatiramer acetate 20 mg/mL once daily. In the meta-analysis, statistical adjustments and weighting were used to account for differences in study design, patients numbers and drug exposure [25]. Pooled individual data from four placebo-controlled studies showed an ARR reduction of 28 % with glatiramer acetate 20 mg/mL once daily versus placebo ($p = 0.0112$), compared with an ARR reduction of 34 % with glatiramer acetate 40 mg/mL three times weekly versus placebo ($p < 0.0001$) in the GALA study. Compared with placebo, new T2 lesions were reduced by 43 % ($p = 0.002$) and

well tolerated [4, 19]. The most common treatment-emergent adverse events are injection-site reactions and vasodilation, with most events being mild in severity. The theory that fewer injections would lead to fewer injection-site reactions was evaluated in the randomized, open-label, phase IIIb, multicentre GLACIER study that compared the tolerability of glatiramer acetate 40 mg/mL three times weekly with that of 20 mg/mL once daily in patients with RRMS [27].

5.1 GLACIER Study

Adults with an EDSS score of ≤5.5 who had been receiving glatiramer acetate 20 mg/mL once daily for ≥6 months were randomized to continue the same treatment or switch to glatiramer acetate 40 mg/mL three times weekly for 4 months [27]. Patients were assessed at baseline and at months 1, 2 and 4; to date, all data are available in abstracts and/or posters.

The primary endpoint was the annualized rate of injection-related adverse events (i.e. including localized reactions and generalized symptoms), based on patients' diary cards [27]. Convenience was assessed with the validated Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9). Most (82 %) patients were female, the average age was approximately 51 years, and the mean time since MS diagnosis was 11.5 years [27, 28].

5.1.1 Injection-Related Adverse Events

At 4 months, there was a significantly lower mean annualized rate of injection-related adverse events in the 40 mg/mL three-times-weekly group than in the 20 mg/mL once-daily group, equating to a 50 % rate reduction (Table 3) [27]. Similarly, there was a 60 % reduction in the mean annualized rate of moderate or severe injection-related adverse events with glatiramer acetate three times weekly compared with once daily (Table 3) [27].

With regard to local injection-site reactions only, the mean annualized event rates with glatiramer acetate 40 mg/mL three times weekly and 20 mg/mL once daily [35.2 vs. 70.4; risk ratio (RR) 0.50; $p = 0.0006$] were almost identical to the event rates in the respective groups for all injection-related adverse events (Table 3) [28]. The proportion of patients reporting moderate or severe local injection-site reactions was 9.2 % in the three-times-weekly group compared with 15.4 % in the once-daily group. When common injection-site reactions were compared based on MedDRA preferred terms (version 16.0), annualized rates for pain, erythema, mass, swelling and pruritus were numerically lower in the three-times-weekly group than in the once-daily group, and moderate or severe rates of these events were either similar in both groups (pain, erythema, mass) or numerically lower in the three-times-weekly group (swelling and pruritus) [28].

In an extension of the GLACIER study, in which all patients ($n = 198$) received glatiramer acetate 40 mg/mL three times weekly for a further 18 weeks, the mean annualized event rate was generally similar in the group that received the three-times-weekly regimen from the start of the GLACIER study and the group that switched to the three-times-weekly regimen at the start of the extension study (23.1 vs. 28.0 events/year) [29].

5.1.2 Patient Well-Being and Convenience

An assessment of patient-reported physical and psychological well-being in the GLACIER study using the MS Impact Scale-29 questionnaire found no difference between the glatiramer acetate 40 mg/mL three-times-weekly and 20 mg/mL once-daily treatment regimens at month 4 with regard to this endpoint [30]. Therefore, because of the predefined statistical testing hierarchy, treatment differences for subsequent secondary endpoints (including the TSQM-9) could not be tested for significance.

Table 3 Injection reactions associated with glatiramer acetate 40 mg/mL three times weekly or 20 mg/mL once daily in adults with relapsing–remitting multiple sclerosis. Results of the randomized, open-label, 4-month GLACIER study (reported in an abstract) [27]

Treatment (mg/mL)	No. of pts[a]	Mean annualized rates of injection reactions[b]			
		IRAE[c]	RR (95 % CI)	Moderate to severe[d] IRAE	RR (95 % CI)
GLA 40 tiw	108	35.3	0.50 (0.34–0.74)**	0.88	0.40 (0.23–0.72)*
GLA 20 od	101	70.4		2.20	

GLA glatiramer acetate, *IRAE* injection-related adverse event, *od* once daily, *pts* patients, *RR* risk ratio, *tiw* three times weekly

* $p < 0.0021$, ** $p < 0.0006$ vs. GLA 20 od

[a] All randomized patients who received at least one dose of GLA

[b] Includes local injection-site reactions and symptoms relating to immediate post-injection reactions, such as flushing, palpitations, anxiety and dyspnoea. Based on patients' diary cards

[c] Primary endpoint

[d] Moderate (interferes with normal daily activities) and severe (prevents normal daily activities) IRAEs were assessed in a post hoc analysis

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