Patient Preference and Adherence

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REVIEW

Two decades of subcutaneous glatiramer acetate injection: current role of the standard dose, and new high-dose low-frequency glatiramer acetate in relapsing–remitting multiple sclerosis treatment

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Abstract: Glatiramer acetate, a synthetic amino acid polymer analog of myelin basic protein, is one of the first approved drugs for the treatment of relapsing–remitting multiple sclerosis. Several clinical trials have shown consistent and sustained efficacy of glatiramer acetate 20 mg subcutaneously daily in reducing relapses and new demyelinating lesions on magnetic resonance imaging in patients with relapsing–remitting multiple sclerosis, as well as comparable efficacy to high-dose interferon beta. Some preclinical and clinical data suggest a neuroprotective role for glatiramer acetate in multiple sclerosis. Glatiramer acetate is associated with a relatively favorable side-effect profile, and importantly this was confirmed also during long-term use. Glatiramer acetate is the only multiple sclerosis treatment compound that has gained the US Food and Drug Administration pregnancy category B. All these data support its current use as a first-line treatment option for patients with clinical isolated syndrome or relapsing–remitting multiple sclerosis. More recent data have shown that high-dose glatiramer acetate (ie, 40 mg) given three times weekly is effective, safe, and well tolerated in the treatment of relapsing–remitting multiple sclerosis, prompting the approval of this dosage in the US in early 2014. This high-dose, lower-frequency glatiramer acetate might represent a new, more convenient regimen of administration, and this might enhance patients' adherence to the treatment, crucial for optimal disease control.

Keywords: glatiramer acetate, disease modifying treatment, efficacy, safety

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease involving the white and gray matter of the central nervous system (CNS), causing neurological dysfunction.[1] It affects predominantly females, and has a prevalence varying from five to 80 per 100,000 persons worldwide.[2] It is thought to be a multifactorial disease resulting from an autoimmune reaction to self-antigens in genetically predisposed individuals, and probably involving additionally several environmental factors, such as vitamin D deficiency, sun exposure, smoking, and infections. Evidence for a concomitant neurodegenerative component has been highlighted to be present already at disease onset;[3] however, this prevails in the later phases of the disease.[4,5]

Multifocal localized inflammation of the CNS leading to demyelination, axonal damage, and astrocytosis pathologically characterizes the disease and causes impaired nerve conduction,[5] leading to MS symptoms commonly involving sensory, motor, visual, balance, sphincteric, and cognitive functions, as well as fatigue.

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Relapsing–remitting (RR) is the most common (80%–85%) MS subtype, characterized by flares and remissions.[6,7] The first MS relapse is currently referred to as clinically isolated syndrome (CIS), corresponding to a typical clinical and paraclinical early RRMS picture that cannot however fulfill current MS diagnostic criteria.[8] Approximately 60%–70% of patients with RRMS evolve to secondary progressive MS over time, and around 10% of patients can be classified as having a primary progressive or progressive relapsing course.

Though incurable, MS is currently treatable, with the aim of delaying as much as possible disability progression that may derive principally from unrecovered relapses and progressive neurological deterioration. To this end, several immunomodulating, immunosuppressive, and immunobiological agents have been developed to control inflammatory activity, prevent relapses, and possibly delay disability progression, particularly in the early phase of the disease.

Glatiramer acetate (GA; Copaxone®; Teva Pharmaceutical Industries, Petah Tikva, Israel) and beta-interferons (IFNβs) have been traditionally considered first-line treatments of RRMS, and represent the cornerstone in MS therapy.[9] Until recently, these two drug types were the only immunomodulatory therapies available for the treatment of RRMS. However, these drugs are not always sufficiently efficacious to suppress inflammatory activity in all MS patients. Moreover, they may not be well tolerated due to side effects or frequent injections, which sometimes preclude adequate adherence.[10] The advent of second-line drugs, such as natalizumab,[11] fingolimod,[12] teriflunomide,[13] and dimethyl fumarate,[14] as well as alemtuzumab[15] in some countries, is promising both for possible higher anti-inflammatory efficacy and a more convenient way of administration (ie, either intravenous injections or oral). These advantages have, however, the price of a variable but overall less favorable safety and side-effect profile.[16] Nevertheless, the approval of these new compounds changed the MS therapeutic landscape and the first-line drug-decision process in a newly diagnosed MS patient.

This paper reviews relevant data concerning the mechanism of action, efficacy, and safety of GA administered at the licensed (20 mg daily) dose, summarizes more recent data concerning the administration of GA at higher doses with lower frequency, and aims to define its current role as a treatment option in MS.

PubMed was searched for abstracts using the terms "glatiramer acetate AND multiple sclerosis" and "glatiramer acetate AND adherence". Only articles written in English were considered, and there was no time-period restriction. The references of the resulting studies were used to identify additional articles to be included in the review (Table 1).

Glatiramer acetate

GA (Copaxone) is a synthetic amino acid polymer analog of myelin basic protein (MBP), an antigen thought to be involved in the pathogenesis of MS.[17–21] It consists of a standardized combination of four amino acids (L-alanine, L-glutamic acid, L-lysine and L-tyrosine) randomly combined to form a polymer with an average length of 40–100 amino acids.[17–20]

It has been empirically found to suppress autoimmune encephalomyelitis in mice,[22] possibly due to a displacement of immune cells targeting native myelin components. Clinical results consistent with this rationale have also been shown in humans, leading to its licensing for MS treatment in 1997 in the US and 2000 in Europe. Initially, GA was approved as first-line treatment in RRMS at a dose of 20 mg subcutaneous (SC) injection daily. More recently, further approval was obtained for the treatment of CIS patients.[23]

Mechanism of action

It is believed that GA has a multifaceted mechanism of action, involving both immunomodulation and neuroprotection (Figure 1). It is basically an immunomodulator capable of modifying the immune responses that drive MS pathogenesis.[17–20,24] It binds to major histocompatibility complex (MHC) class II molecules on MBP-specific antigen-presenting cells, preventing MBP itself from binding to and stimulating these cells.[18,20,24] A body of preclinical and clinical data support a role of GA in inducing a T-helper (Th)-1 to Th2-cell phenotype shift. In other words, GA-reactive T cells predominantly secrete anti-inflammatory cytokines, such as IL-1, IL-4, and IL-10, characterizing Th2 regulatory cells instead of typical Th1, and proinflammatory cytokines, such as IL-2 and IL-12.[18,20,24] It has to be underlined that GA per se is not able to penetrate the CNS blood–brain barrier. Its immunomodulatory function is carried out by peripheral GA-induced Th2 cells that enter the CNS, recognize myelin antigens, and are thus reactivated, ultimately reducing inflammation associated with MS.[24–26] This mechanism of action is known as "bystander suppression".[27]

In addition, several studies have suggested further effects on the immune system mediated by GA.[17,24] GA induces T-regulatory cells, such as $CD4^+$, $CD8^+$, and $CD4^+CD25^+$ T cells, while it downregulates Th17 cells that have been associated with MS disease activity. Moreover, GA drives monocytes, dendritic cells, and microglia to preferential anti-inflammatory responses.[24,25,28–34]

Table 1 Reviewed studies

Article	Patients	Treatment arm	Comparison	Length of follow-up	Main outcome
Pivotal trials					
Bornstein et al[38]	RRMS	GA 20 mg/day SC (n=25)	Placebo (n=23)	2 years	No relapse in 56% of GA-treated subjects versus 26% in placebo (P=0.045)
Johnson et al[39]	RRMS	GA 20 mg/day SC (n=125)	Placebo (n=126)	2 years	29% reduction in relapse rate compared to placebo (P=0.007)
Comi et al[45]	RRMS	GA 20 mg/day SC (n=119)	Placebo (n=120)	9 months	Reduced number of GdE lesions compared to placebo (P=0.003)
Comi et al[23]	CIS	GA 20 mg/day SC (n=243)	Placebo (n=238)	Up to 36 months	45% reduced risk of conversion to CDMS compared to placebo (HR 0.55, 95% CI 0.40–0.77; P=0.0005)
Extension studies					
Johnson et al[40]	RRMS	GA 20 mg/day SC (n=99) since study initiation	Placebo (n=104) since study initiation	Johnson et al[39] extended for additional 1–11 months	32% reduction in relapse rate compared to placebo (P=0.002)
Johnson et al[41]	RRMS	GA 20 mg/day SC (n=83, end of 6th year) since study initiation	GA 20 mg/day SC after placebo for 30 months (n=86, end of 6th year)	Johnson et al[39] extended to 6 years	No difference in relapse rate between the two groups after placebo-treated patients' switch to GA
Johnson et al[42]	RRMS	GA 20 mg/day SC (n=72, end of 8th year) since study initiation	GA 20 mg/day SC after placebo for 30 months (n=70, end of 8th year)	Johnson et al[39] extended to 8 years	No difference in relapse rate between the two groups after placebo-treated patients' switch to GA
Ford et al[43]	RRMS	At least one dose of GA 20 mg/day SC (n=232)	–	Johnson et al[39] extended to 10 years	Decreased relapse rate from 1.18/year prestudy to approximately 1/5 years during study
Ford et al[44]	RRMS	GA 20 mg/day SC (n=100, end of 15th year) since study initiation	–	Johnson et al[39] extended to 15 years	Decreased relapse rate from 1.12/year prestudy to 0.25/year during study 57% stable/improved EDSS
Wolinsky et al[46]	RRMS	GA 20 mg/day SC (n=111) since study initiation	GA 20 mg/day SC after placebo for 9 months (n=113)	Comi et al[59] extended for additional 9 months	54% reduction in mean number of GdE lesions in patients switching to GA
Rovaris et al[47]	RRMS	GA 20 mg/day SC (n=73) since study initiation	GA or other/no treatment after placebo for 9 months (n=69)	Comi et al[59] extended to a mean of 5.8 years	No difference in MRI measures between the two groups
Head-to-head trials					
Mikol et al[48]	RRMS	IFNβ-1a 44 μg 3 times/week SC (n=386)	GA 20 mg/day SC (n=378)	96 weeks	No difference in time to first relapse (HR 0.94, 95% CI 0.74–1.21; P=0.64) between the two groups
O'Connor et al[49]	RRMS	IFNβ-1b 250 μg/2 days SC (n=888) and 500 μg/2 days SC (n=887)	GA 20 mg/day SC (n=445)	2.0–3.5 years	No difference in relapse risk (P=0.48 and P=0.74) between the groups
Cadavid et al[50]	RRMS or CIS	IFNβ-1b 250 μg/2 days SC (n=36)	GA 20 mg/day SC (n=39)	Up to 2 years	No significant difference in combined active lesions (P=0.58) between the two groups
Studies with high-dose GA					
Cohen et al[58]	RRMS	GA 40 mg/day SC (n=46)	GA 20 mg/day SC (n=44)	9 months	Trend to lower number of GdE lesions in the 40 mg group (38% reduction, P=0.089)
Comi et al[59]	RRMS	GA 40 mg/day SC (n=569)	GA 20 mg/day SC (n=586)	12 months	No difference in relapse rate between the two groups (P=0.49)
Khan et al[62]	RRMS	GA 40 mg 3 times/week SC (n=943)	Placebo (n=461)	12 months	34% reduction of annual relapse rate compared to placebo ($P<0.0001$)

Abbreviations: RRMS, relapsing–remitting multiple sclerosis; CIS, clinically isolated syndrome; CDMS, clinically definite multiple sclerosis; GA, glatiramer acetate; SC, subcutaneously; HR, hazard ratio; CI, confidence interval; GdE, gadolinium-enhancing; IFNβ, interferon beta; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging.

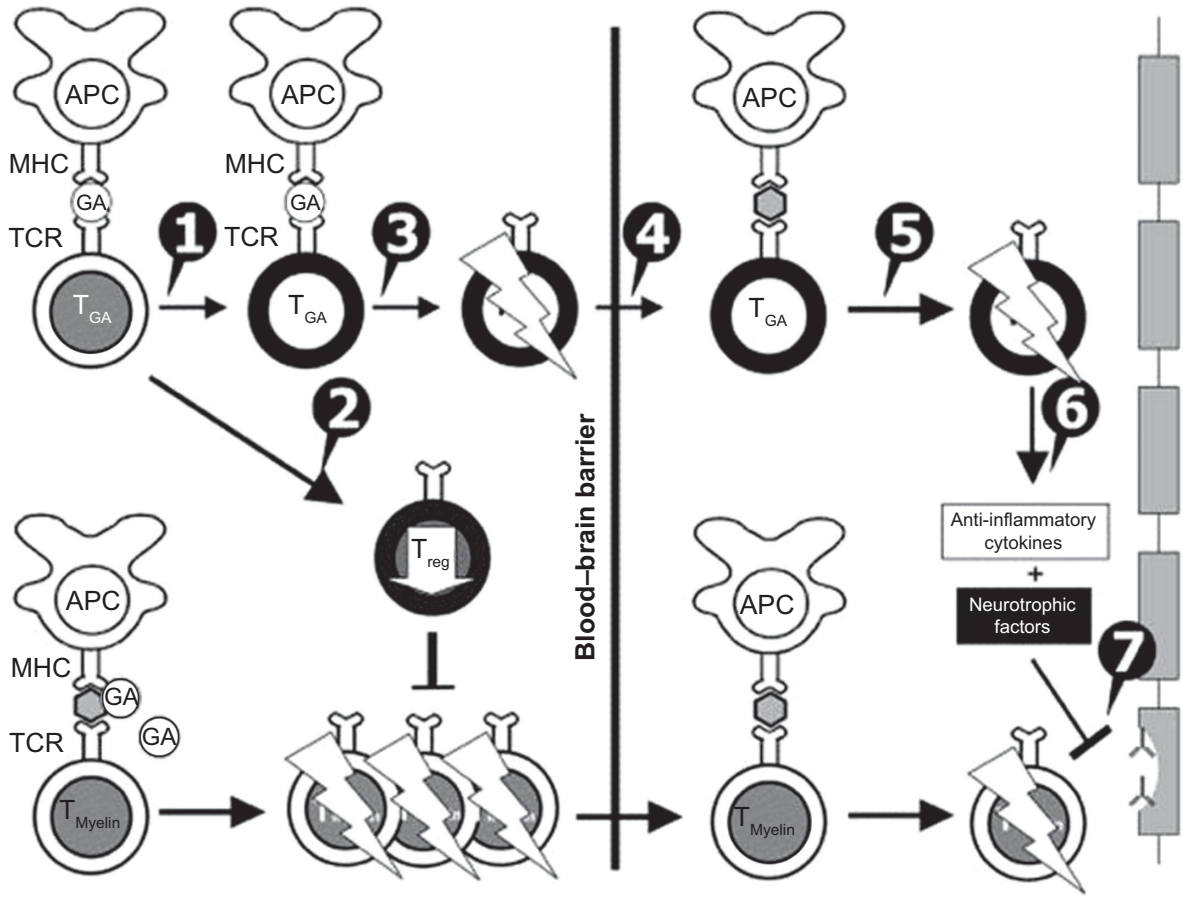

Figure 1 Mechanisms of action of glatiramer acetate (GA) in multiple sclerosis. GA exhibits competitive binding at the MHC-II complex and T-cell receptor (TCR) antagonism. GA is able to displace myelin basic protein from the binding site on MHC-II molecules. Treatment with GA leads to the induction of antigen-specific TH2 T cells in the periphery (**1**). In addition $CD8^+$ and $CD4^+CD25^+$ regulatory T cells are induced by GA therapy (**2**). The constant activation seems to have an important impact on the induction and maintenance of the regulatory/suppressive immune cells (**3**). Because of the daily activation, GA T cells are believed to be able to cross the blood–brain barrier (**4**). Inside the central nervous system, some GA-specific T cells cross-react with products of local myelin turnover presented by local antigen-presenting cells (APCs) (**5**). In response, anti-inflammatory cytokines are secreted, which dampen the local inflammatory process (bystander suppression) (**6**). Furthermore, GA-specific T cells secrete neurotrophic factors that might favor remyelination and axonal protection (**7**). Reprinted from *Autoimmun Rev*. 2007;6(7). Schrempf W, Ziemssen T. Glatiramer acetate: mechanisms of action in multiple sclerosis. 469–475. Copyright © 2007, with permission from Elsevier.[78]

Finally, GA seems to induce neuroprotective and/or neuroregenerative effects at the preclinical level.[17,18,24,25] For instance, it increases neurotrophic factors like brain-derived neurotrophic factor, involved in neuronal and glial cell survival, and may mediate neuroprotection. There is also evidence that GA induces remyelination and enhances neurogenesis.[17,18,21,24,25]

The majority of patients treated with GA develop GA-reactive IgG antibodies. However, these do not appear to be related to clinical or radiological clinical course measures of efficacy.[35–37]

Clinical efficacy: data from clinical trials

Pivotal trials

Pivotal trials have shown consistent efficacy of GA in the treatment of RRMS patients. The first study assessing the efficacy of GA in RRMS was published more than 25 years ago.[38] It was a double-blind, randomized, placebo-controlled pilot trial involving 50 RRMS patients who were treated either with daily GA 20 mg or daily placebo over 2 years. Twenty-six percent of placebo- and 56% of GA-treated patients experienced no relapses over the study period (P=0.045). Among less disabled patients (Kurtzke disability score 0–2), those taking GA improved (+1.2 Kurtzke units), while placebo-treated patients worsened (–0.5 Kurtzke units, P=0.012). In contrast, more disabled patients in both groups showed an increase in Kurtzke disability score. Limited by the small sample size, this pivotal trial provided the first clinical evidence for a role of GA in the treatment of RRMS. A number of subsequent larger multicenter trials confirmed these results.

The first large Phase III double-blind, placebo-controlled study included 251 RRMS subjects 18–45 years old, with an Expanded Disability Status Scale (EDSS) score of 0–5.0, a history of at least two relapses in the 2 years prior to study entry, and a disease duration of at least 1 year. Participants were

randomized to receive GA or placebo by daily SC injection for 2 years, with a reduction of 29% in the annualized relapse rate (ARR; primary end point) in favor of the GA group (0.59 versus 0.84, respectively; P=0.0007).[39] Among secondary clinical outcomes, median time to first relapse from baseline and the proportion of relapse-free patients over 2 years showed a trend favoring GA over placebo (287 versus 198 days, P=0.097; 33.6% versus 27.0%, P=0.098; respectively). Overall, parameters of disability change also favored GA over placebo (EDSS change from baseline −0.05 versus 0.21, P=0.023), though the proportion of patients who were free from disability progression was similar between groups (78.4% versus 75.4%, not significant). The main limitation of this trial was the absence of magnetic resonance imaging (MRI) monitoring.

A pivotal GA study by Johnson et al was followed by a prospective, open-label study replicating the benefits of early versus delayed GA at 3, 6 and 8 years.[41,42] Further 10-year extension data were obtained from 47% of the original cohort,[43] and showed that continuous GA treatment led to more than 80% decline in relapse rate (from 1.18 relapses/year prestudy to one relapse/5 years), with no significant disability progression, evaluated using the EDSS score. Recently, data concerning 15-year extension were published.[44] Of the initially randomized subjects, 43% were still on GA treatment, and had received only this immunomodulator during the disease course. Of those, two-thirds had not reached secondary progression, 57% had stable or improved EDSS, and 82% of patients could still walk. The comparator cohort that had interrupted GA obtained fairly good results as well; however, the mean disease duration in these patients was much shorter (13 versus 22 years).

The clinical efficacy of GA was replicated in a European/Canadian trial[45] involving 239 RRMS subjects, and extended results toward a benefit on MRI disease activity. Main inclusion criteria were age between 18 and 50 years, a disease duration of at least 1 year, an EDSS score up to 5.0, and documented disease activity (at least one relapse in the preceding 2 years, and at least one gadolinium-enhanced [GdE] lesion on their screening brain MRI). Patients were randomized to either daily injections of GA 20 mg or placebo and treated for 9 months, and were followed with monthly brain MRIs. GA-treated patients showed a significant reduction in total GdE lesions (primary end point −10.8 versus −18.0, P=0.003), number and volume of new T_2 lesions, and brain-atrophy progression, as well as clinical efficacy measured by reduction of mean relapse rate. Interestingly, the treatment effect of GA on the mean number of GdE lesions per patient per month, as well as mean number of relapses per patient, consistently appeared only from month 6 after GA start. However, the short duration of the study prevented assessment of treatment effects on disability progression, especially in light of the delayed onset of GA action.

In the 9-month, open-label phase of the European/Canadian study[45] involving 94% of the original cohort, the effect of GA treatment was sustained: a 54% reduction in the mean number of GdE lesions for those switching from placebo to GA and a further 24.6% reduction for those remaining on GA were observed.[46] A 5.8-year extension phase[47] involving 63.4% of the original cohort showed that 66% of the patients were still on GA and had the highest relapse-free period, compared either to IFN switchers or to untreated patients (3.5 versus 1.3 versus 2.9, respectively). No significant differences for any MRI parameters were found at 5 years between originally GA- or placebo-treated subjects. However, the proportion of patients not requiring walking aids was lower in the first group (P=0.034), suggesting that an earlier initiation of GA might have a favorable impact on long-term disease evolution.

In conclusion, between the late 1980s and early 2000s, the results of three pivotal trials were published, which consistently assessed the efficacy of GA in the treatment of patients with RRMS, showing an approximately 30% reduction in relapse rate and consistent benefits on MRI for surrogates of disease activity compared to placebo. Open-label extension studies consistently showed a sustained efficacy of GA up to 15 years in a subgroup of patients participating in pivotal trials, though these were limited by several factors, including absence of a placebo arm and positive selection of responders.

CIS trial

GA has been recently labeled for CIS based on the favorable results of the PreCISe (Evaluate Early Glatiramer Acetate Treatment in Delaying Conversion to Clinically Definite Multiple Sclerosis of Subjects Presenting with Clinically Isolated Syndrome) trial.[23] This involved 481 subjects presenting with a monofocal CIS and two or more T_2 brain lesions (≥6 mm), that were randomly assigned to either SC GA 20 mg per day or placebo. A significant delay in conversion to clinically definite MS (722 versus 336 days in the treatment versus placebo groups, P=0.0005), as well as consistent benefits on radiological parameters (number/volume of new T_2, number of new T_1 GdE and T_1 hypointense lesions) were observed after approximately 2.4 years of treatment. The study included only a restricted subgroup of CIS subjects, and did not provide information concerning the impact of GA on disability progression. In conclusion, the PreCISe trial provided substantial information in favor of the effectiveness of GA in the treatment of early forms of MS.

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