Glatiramer Acetate in the Reduction of Relapse Frequency in Multiple Sclerosis

Augusto Miravalle2, Barry Hendin3, Timothy L. Vollmer2 and Mrinalini Kala1,3

1Division of Neurology, Barrow Neurological Institute, St. Joseph’s Hospital and Medical Center, 350 West Thomas Road, Phoenix, AZ 85013, USA. 2Department of Neurology, University of Colorado Health Sciences, 12631 East 17th Avenue, Aurora Colorado 80045, Mail Stop B 182. 3University of Arizona College of Medicine, Phoenix, AZ, USA. Corresponding author email: mrinalini.kala@chw.edu

Abstract: Glatiramer acetate (GA; Copaxone®) is a heterogeneous polymer of four amino acids. It is one of the therapies approved by the Food and Drug Administration in 1996 for treatment of relapsing remitting multiple sclerosis (RRMS). GA reduces the relapse rate for RRMS, and has a good safety profile and moderate efficacy. Preclinical and clinical studies reveal that GA plays a role in modulating the cells of the immune system as well as in neuroprotection. In this article, we review the role of GA in reducing the frequency of relapses in MS, as well as its efficacy, safety, and current place in therapy.

Keywords: multiple sclerosis, glatiramer acetate, relapse rate
Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, immune-mediated, demyelinating disorder of the central nervous system (CNS) with a heterogeneous clinical presentation and pathology. MS is a leading cause of disability among young adults in North America and Europe (MS Society web site). Most patients with MS experience periods of well-defined neurological deficits (relapses) followed by complete or partial functional recovery (remissions). The first clinical event is referred to as clinically isolated syndrome (CIS) and usually involves sensory, motor, and brainstem symptoms, in order of decreasing frequency respectively. Despite apparent clinical improvement after attacks, most untreated patients with MS will eventually develop a continuous, progressive, and usually irreversible accumulation of disability known as secondary progression. Approximately 10%–15% of patients do not exhibit the relapsing-remitting form of the disease and present with continuous disease progression.

The FDA-approved treatments for MS currently being used include β-interferons, glatiramer acetate (GA), mitoxantrone, natalizumab, and the recently approved oral drug, fingolimod. Significant changes have been made in recent years in the treatment of relapsing-remitting multiple sclerosis (RRMS) and several new treatments including oral therapies are in late phase clinical trials or are under review by the FDA.

Apart from β interferon, GA was one of the earliest drugs used to treat MS. GA reduces the relapse rate in pivotal trials and a long term observational trial showed improved disability outcome in patients with RRMS. GA is administered by subcutaneous injection at a dose of 20 mg per day.

Several clinical trials have shown the long-term efficacy and safety of GA in treating MS. Preclinical and clinical studies show that GA modulates the immune system (T cells, monocytes, dendritic cells, B cells and natural killer (NK) cells) has neuroprotective properties and is immunosuppressive. These characteristics of GA may contribute to its clinical efficacy.

Metabolism and Pharmacokinetic Profile

GA was designed to stimulate myelin basic protein (MBP). It is a complex mixture of heterogeneous polypeptides composed of four amino acids: L-glutamic acid, L-alanine, L-lysine, and L-tyrosine (GALT). GA has a molecular weight in the range of 5000 to 9000 daltons and an average polypeptide length of 60 amino acids. When injected subcutaneously, a considerable fraction of GA is hydrolyzed locally at the injection site (Copaxone injection prescribing information). Intact or partially hydrolyzed GA fractions may enter the lymphatic system and reach the lymph nodes, and some GA may enter the systemic circulation. Although GA’s rapid degradation makes it difficult to estimate metabolite concentrations in the systemic circulation, even the availability of such a test would not reveal the degree to which the immune system is exposed to GA.

Studies show that GA-specific nonneutralizing immunoglobulin’s (IgGs) are detected in all RRMS patients treated with GA, favoring a Th1 to Th2 shift in antibody responses. Similarly, GA stimulates GA-specific peripheral blood lymphocytes in MS patients and in healthy donors, and repeated exposure to GA skews the responses of T cells to anti-inflammatory Th2-type cells. GA also competes with MBP for binding to the major histocompatibility complex (MHC) and modulates a variety of cells in the immune system. Some of these indicate a possible requirement for a systemic concentration of GA. On the other hand, studies where the adoptive transfer of T cells, type II monocytes, and B cells from GA-treated animals into EAE recipient animals produced the immunomodulating effect of GA favor the concept that the therapeutic efficacy of GA may be unrelated to its systemic concentrations.

Mechanism of Action

Studies show that GA has immunomodulatory and neuroprotective effects. GA binds MHC class II molecules on human antigen-presenting cells (APC) with high affinity. Since GA mimics MBP it competes with MBP at the MHC binding site, which may lead to reduced expansion of MBP-specific T cells. It is becoming clear that GA modulates several arms of the immune system, including T cells, dendritic cells, type II monocytes, B cells, NK cells, and CD8+ T cells. Immune modulation of GA is generally with reduced secretion of pro-inflammatory cytokines and enhanced secretion of anti-inflammatory cytokines. In addition, the main immunomodulatory effect of GA is to skew T cell responses from the Th1 type to
the Th2 type.\textsuperscript{34,39,40–45} GA may restore the number and function of regulatory T cells\textsuperscript{10,12,13} and maintain the anergy of pathogenic T lymphocytes.\textsuperscript{46,47}

GA-reactive Th2/Th3 cells accumulate in the CNS of GA-treated mice.\textsuperscript{48} Recent studies in humans also show GA-reactive Th2 cells in the CSF of GA-treated MS patients.\textsuperscript{49,50} Based on these studies and sequence similarities between MBP and GA, it is possible that cross-recognition of MBP may account for the reactivation of GA-reactive T cells in the CNS. Alternatively, secretion of anti-inflammatory cytokines may mediate bystander suppression of nearby pathogenic T cells within the CNS, thus accounting for the therapeutic effect of GA. However, other unknown mechanisms may be responsible.

GA also confers a neuroprotective effect. GA-reactive T cell lines from MS patients and healthy controls secrete brain-derived neurotrophic factor (BDNF) at low levels, which is enhanced by GA stimulation.\textsuperscript{18–21} In a murine model, the secretion of BDNF by GA-reactive T cells was associated with reduction in neuronal damage as well as an increase in neuronal proliferation.\textsuperscript{22,22a} Finally, treatment with GA has been shown to induce remyelination in EAE mice.\textsuperscript{23,24}

**Clinical Studies/Efficacy**

GA was initially studied in a small group of patients with advanced MS and acute disseminated encephalomyelitis (ADE). Even though there was no clear benefit noted, it was found to be safe and well tolerated.\textsuperscript{51} A preliminary phase 1 open trial has demonstrated that GA is capable of suppressing EAE in laboratory animals, and is nonencephalitogenic and nontoxic.\textsuperscript{26} The first double blind, randomized, placebo-controlled pilot trial suggested a significant reduction in clinical exacerbations as well as relapse rate in 50 patients with relapsing forms of MS (56% vs. 26% relapse-free patients respectively \( P = 0.045 \)). Interestingly, there was a trend of more benefit in the less disabled patients, suggesting greater efficacy early in the course of the disease (Bornstein et al, 1987). The same group\textsuperscript{52} then studied the clinical benefits of GA (15 mg twice daily) vs. placebo in 106 chronic progressive MS patients at 2 different sites. When data from both sites were pooled, the results were not statistically significant. However, when the results were analyzed by individual centers, there was a statistically significant benefit in one center (Albert Einstein, Bronx, NY) with an almost 19% \( (P = 0.03) \) lower probability of progression in patients who received GA. It is possible; however, that patients enrolled in the placebo arm at this center had a much more aggressive course of the disease.\textsuperscript{52} The first multicenter phase III, double-blind, placebo-controlled clinical trial\textsuperscript{7} demonstrated a 29% reduction in relapse rate over 2 years in 125 patients receiving GA \( (P = 0.007) \). Patient withdrawals were slightly more common for the GA group. In general, the treatment was well tolerated, with injection-site reaction being the most commonly reported adverse event.\textsuperscript{3}

On the basis of this trial, GA was approved for the treatment of RRMS. GA is now licensed in much of the world to reduce the frequency of relapses in RRMS. After this initial study, all patients were offered treatment with GA as part of a 10 year ongoing prospective study, becoming the longest prospective organized evaluation of clinical efficacy and safety data of a continuous immunomodulatory treatment in MS.\textsuperscript{4} Close to 50% of patients who began GA therapy remained in the study. Relapse rates decreased by approximately one half in the first year of treatment. This decline was maintained, or even improved, in the long term follow up, with up to an 80% reduction in relapse rate at 10 years. Previous natural history studies in MS patients suggest a decline in relapse rate with increasing disease duration, even without treatment.\textsuperscript{4} However, untreated patients show a commensurate accumulation of disability. The majority of patients receiving long-term GA therapy exhibited stable, or improved, Expanded Disability Status Scale (EDSS) scores, suggesting that the decline in relapse and stabilization or improvement of the underlying disease process reflects the clinical efficacy of GA over placebo. The most commonly reported adverse reactions in patients receiving long-term GA included local injection-site reactions (erythema, pain, and edema). Symptoms related to immediate post-injection reactions, like chest pain, vasodilatation, palpitations, tachycardia, and dyspnea were also reported.\textsuperscript{4}

GA has also been shown to slow the progression to clinical definitive MS (CDMS) in CIS patients. A recent clinical trial demonstrated that the rate of progression to CDMS was reduced by 45 percent in patients with CIS receiving GA versus a placebo \( (P = 0.0005) \). In addition, MRI activity, including the number of enhancing lesions and the number
of new T2 lesions, was significantly lower in the glatiramer-acetate group (58% reduction of new T2 lesions \( P = 0.0001 \)).

GA was also studied in primary progressive MS, but a large controlled trial failed to provide any evidence for benefit in this population. The study randomized 943 patients to either GA or placebo for 36 months, with a placebo-controlled extension phase. The primary endpoint was the progression of disease measured by a 3 or 6 month sustained increase in EDSS scores. Secondary endpoints included the proportion of progression-free patients, changes in EDSS scores, number and volume of various lesions on MRI, black hole lesion burden, and changes in brain volume. The study was discontinued early because the progression rate in the placebo group was unexpectedly small. This situation prevented demonstration of a clear treatment effect on the primary endpoint.

**Paraclinical Evidence of Clinical Efficacy**

The first study on the effects of GA on serial MRI involved 10 RRMS patients compared before and after treatment. Monthly gadolinium (Gd)-enhanced MR imaging was performed for 9–27 months in the pretreatment period followed by 10–14 additional months during GA treatment. GA-treated patients had a 57% lower frequency of new Gd-enhancing lesions, as well as decreased accumulation of T2-weighted lesion area when compared with the pretreatment period, \( P = 0.1 \). The decrease in T2 lesions was significant for the patient group with a longer pretreatment period (\( P = 0.05 \)).

A larger trial, the Pivotal US Trial, included 135 patients undergoing MRI with initial imaging sessions performed at 2447 ± 61 days after initial treatment and demonstrated a reduction in enhancing lesions. It also showed that delay in treatment was associated with increased progression on MRI. The European/Canadian MRI study examined the effects of GA on MRI outcomes. Two hundred and thirty nine RRMS patients were randomized to either GA or placebo. In patients in the treatment arm, there was a significant reduction in the frequency and volume of new enhancing lesions, with an overall 30% reduction in the number of enhancing lesions and new T2-weighted lesions. Further analysis of this study also showed that the percentage of new lesions evolving into so called “T1-black holes” was lower in the GA-treated group compared to the placebo group (15% vs. 31% respectively, \( P = 0.002 \)). There was also a significant reduction in the rate of re-enhancement of previous lesions. Thus, in addition to slowing the formation of new MS lesions, GA may also limit permanent damage from new lesions by protecting axons and promoting lesion recovery. This evidence was one of the first indications for a neuroprotective effect for GA.

An open label extension of this trial evaluated the clinical benefits (as measured by various MRI outcomes) of switching to GA in patients originally enrolled in the placebo arm. Patients who started GA had a significant reduction in the number of new enhancing lesions (54%, \( P = 0.03 \)). In addition, there was a 24% reduction in the number of new enhancing lesions in patients initially enrolled in the treatment group (\( P = 0.001 \)). The difference between the T2 lesion burden in the two groups suggested that the benefits of early treatment with GA was not regained in those patients who switch from placebo to GA, supporting the need to start treatment early in the course of the disease.

Changes in brain volume may indicate the extent of neuronal degeneration. In addition, factors other than neuronal degeneration can lead to changes in brain volume, particularly alterations in water content or pseudoatrophy. One of the difficulties in assessing brain volume is the limitations and accuracy of different volumetric analysis techniques. For example, when the European/Canadian MRI data were analyzed by a semi-automated segmentation technique, no significant difference in atrophy was found. However, when the same MRI data were re-analyzed using a fully automated, normalized technique, the analysis demonstrated a slightly lowered, but not significantly different, brain volume change in the GA group. In addition, when using a more sophisticated measure during the open-label phase, there was a significant reduction in atrophy for the group initially treated with GA. These data suggest that GA may have a delayed but significant effect on brain atrophy.

A recent study evaluated the clinico-radiological parameters of neuroprotection in 18 treatment-naive RRMS patients who received GA therapy over 2 years compared to 4 patients who remained untreated. The integrity of neurons and axons and subsequent axonal metabolic recovery was demonstrated by
analyzing variations in N-acetylaspartate (NAA) levels using magnetic resonance spectroscopy (MRS). A sustained increase in NAA levels was demonstrated in RRMS patients receiving GA therapy. This neuroprotective effect may be partially explained by the production of brain-derived neurotrophic factor (BDNF) induced by GA.

Comparison of Relapse Frequency with Other Immunomodulatory Drugs
A 3-year study of Copaxone and betaferon treatment of 280 patients with a definite diagnosis of MS was done at the Moscow MS center by Boiko et al 2006. One hundred sixty-six patients regularly received drugs for at least 3 years. Patients who had received betaferon previously had a severe MS course with frequent relapses, making direct comparison of data for the two treatment groups difficult. Treatment with GA reduced the annual relapse rate from 1.45 to 0.27 during the first year (P < 0.001), and this reduced rate remained stable for the rest of the study period. For 36 months, 40.4% of patients were relapse-free, with no disease progression in 80% of these patients. Treatment with betaferon reduced the relapse rate from 1.84 to 0.69 per year, and 8 patients (26%) with RRMS were relapse free for 36 months. In 31 patients with secondary progressive MS, the relapse rate was reduced from 1.80 to 0.49 per year (P < 0.001). Seventy one percent of patients with secondary progressive multiple sclerosis (SPMS) had no disease progression for 36 months.

Another 24-month comparison trial was done that was an open label study in 308 RRMS patients treated with beta interferons or GA. This trial showed that relapse rate was reduced after 6 months for the treatment groups and was sustained over 24 months when compared with baseline. Although the studies showed no differences in the relapse rate among patients treated with different beta interferon preparations, a significant reduction was seen with GA-treated patients compared to beta interferons (P < 0.001). However, this study had its limitations in design that make comparison difficult.

The BEYOND (Betaferon Efficacy Yielding Outcomes of New Dose) trial was a large, prospective multicenter, randomized study involving 2244 RRMS patients that compared patients treated with two subcutaneous IFN-β1b doses (250 or 500 µg) administered daily to patients treated with 20 mg of GA administered subcutaneously. Study duration was between 2 and 3.5 years. The primary outcome was a change in the relapse rate. Results showed no difference in clinical efficacy (relapse rate or EDSS changes) between GA and IFN-β1b at either dose. Both drugs were equally well tolerated.

The REGARD (Rbif vs. Glatiramer Acetate in RRMS) study was a multicenter, randomized, comparative, parallel-group, open label study evaluating the clinical efficacy of treatment with 20 mg of GA injected subcutaneously daily compared to 44 µg of IFN-β1a injected subcutaneously three times per week for 96 weeks in 746 RRMS patients. The primary endpoint was time to first relapse. The study found no difference in terms of the time to first relapse, proportion of patients free from relapses, relapse rate, or disability progression.

The BECOME (Betaseron vs. Copaxone in MS with Triple-Dose Gadolinium and 3-Tesla MRI Endpoints) study was the first head-to-head, prospective, randomized clinical trial to compare the effects of GA and IFN-β1b on MRI indices of MS. 75 RRMS patients were randomized to receive 20 mg of GA subcutaneously once daily or 250 µg of IFN-β1b subcutaneously every other day. Patients underwent monthly MRI of the brain for the first year of treatment, an exit MRI at the end of 2 years, and optional monthly MRI scans during year 2. The primary end point was the number of combined active lesions (CAL; all enhancing and nonenhancing new T2 fluid-attenuated inversion recovery (FLAIR) lesions). Secondary outcomes included the number of new lesions and the relapse rate over the 2 year study period. Like other comparative studies, the results showed no differences between GA and IFN-β1b in the median number of CAL or in other MRI measures. Similarly, there was no difference in relapse rate between the two treatments.

Safety
Because GA is an exogenous polypeptide, it may be immunogenic. Indeed, GA-specific antibodies are produced by all patients treated with GA, but these antibodies do not neutralize the therapeutic effect of GA. Because GA was created to mimic MBP, such crossreactivity with self protein may lead to the generation of a severe autoimmune disease. However, clinical studies for short- and long-term GA use since its FDA approval have shown only therapeutic efficacy in MS; they have not shown the
accumulation of toxicities, late-emerging AEs, or patient deaths related to GA.

**Place in Therapy**

MS is a complex and highly heterogeneous disease with marked differences in clinical presentation, amount of disability accumulation among patients, and an often unpredictable disease course. Therefore, in order to achieve meaningful results, clinical trials must enroll large numbers of patients, last many years and use MRI abnormalities such as Gd-enhanced areas and T2 lesions as more sensitive marker to judge efficacy of therapies. For that reason, physicians often choose therapies based on an individual’s disease course and tolerances.

Several agents are currently approved as first-line treatment for the prevention of clinical relapses. These drugs are considered first-line therapies based on their safety and efficacy record.

In selected head-to-head comparison trials, GA showed comparable efficacy in terms of relapse rate, accumulation of disability, and MRI parameters, with only minor differences in terms of adverse reactions when compared to subcutaneously injected interferon. While some of the earlier studies comparing GA with other immunomodulatory drugs showed a significant (0.001) reduction in relapse rate for patients treated with GA, some recent studies showed no difference in relapse rate. In addition, the REGARD and the BEYOND trials showed no significant clinical advantage for interferon compared to GA. Therefore, most clinicians view interferon and GA as comparable in clinical efficacy.

Even though there is no consensus on the use of a particular disease-modifying therapy as first line agent, in general it is reasonable to consider using a personalized treatment for patients whether it is with an immunomodulatory agent such as interferon or GA or with fingolimod or natalizumab.

In the future, it is hoped that we may be able to personalize medicine by using markers for the efficacy of individual drugs matched to individual patients.

**Conclusions**

MS is a heterogeneous disease mediated by a variety of immune cells. Research on GA suggests that despite its heterogeneous and complex constitution and rapid hydrolysis at the injection site, treatment with GA supports anti-inflammatory responses and the growth of nervous tissue. These immunomodulatory and possibly neuroprotective effects of GA may explain the observed long-term clinical efficacy. Observational trials in RRMS patients suggest that GA delays the progression of disability, reduces the relapse rate, and reduces inflammation. Although GA may have no significant adverse effects and may be cost-effective relative to its benefit, it is becoming clear that the complexity of MS demands individualized therapy, since each patient responds to therapies differently.

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