Glatiramer in the treatment of multiple sclerosis

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Abstract: Multiple sclerosis (MS) is a disease of the central nervous system with both an inflammatory and degenerative component. The disease primarily affects young adults and results in significant physical and cognitive disability. Several disease-modifying agents are currently used in the management of multiple sclerosis. Glatiramer acetate (GA, Copaxone®, co-polymer 1) is a disease-modifying agent approved for the treatment of relapsing remitting multiple sclerosis. Apart from its unique mode of action, there is evidence pointing toward a possible neuroprotective role. This review will critically discuss GA's potential mechanisms of action, the results of clinical trials, safety profile, and future directions of treatment.

Keywords: multiple sclerosis, disease-modifying agents, glatiramer acetate, clinical trials, MRI, neurodegeneration

Introduction

Most patients with multiple sclerosis (MS) present with an initial inflammatory phase manifested by relapses and gadolinium-enhancing lesions on magnetic resonance imaging (MRI) followed by a gradually progressive degenerative phase. A minority of patients have the progressive form of the disease from the onset. Even though the etiology and pathogenesis of the disease are largely unknown, several clinical trials have confirmed a favorable response to treatment with immunomodulating and immunosuppressive agents. Several disease-modifying agents are currently available for the treatment of relapsing remitting multiple sclerosis (RRMS). These include interferon-β1a (Rebif® and Avonex®), interferon-β1b (Betaseron®), and glatiramer acetate (Copaxone®). Mitoxantrone (Novantrone®), an immunosuppressant, is used for the treatment of worsening MS. Natalizumab (Tysabri®), a selective adhesion molecule inhibitor, was approved for a short period of time prior to being withdrawn because three patients, two of whom were in MS trials and one of whom was in a Crohn's disease study, developed progressive multifocal leukoencephalopathy (PML) (Yousry et al 2006). At the time of writing this review, natalizumab is being re-evaluated for approval. However, if approved, it will likely initially be utilized in a select group of patients.

All these agents have a marked effect on the inflammatory component of the disease and have been shown to alter the natural history of MS. Unfortunately, effects on the degenerative aspect of the disease have not been consistently demonstrated. Glatiramer acetate (GA) is different from the interferons in having a unique mechanism of action and there is emerging evidence that it may also have an effect on the neuro-degenerative aspect of MS. This article reviews the available data supporting the use of glatiramer acetate in relapsing remitting MS.

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Immunology of MS

Current hypotheses support the idea that MS is an immunologically mediated disease. Although the etiology is unknown, it is likely that exposure to a variety of antigens, including viruses and toxins, results in activation of T cells. These T cells (T helper 1) recognize antigens presented by antigen-presenting cells and subsequently release pro-inflammatory cytokines, such as tumor necrosis factor (TNF), inferferon-γ, and IL-12, and then subsequently invade the central nervous system (CNS). In the CNS, T cells are further activated by antigens found on antigen-presenting cells, which leads to further secretion of pro-inflammatory cytokines and chemokines. A variety of proposed mechanisms may then lead to demyelination and axonal transaction (Martin et al 2001) (Table 1).

Table 1 Possible mediators of neuronal demyelination and degeneration in MS

T-cell mediated
Antibodies
Cytokines
Complement
Nitric oxide
Others (viruses, bacteria, free radicals)

History of GA and mechanism of action

An important step in understanding the immune mechanisms in MS was the development of an animal model of demyelination. Experimental allergic encephalomyelitis (EAE), a T cell-mediated disease, can be induced in susceptible animals by inoculating them with CNS tissue such as myelin basic protein (MBP) (Bernard et al 1992). Copolymers (copolymer 1 up to copolymer 11) were synthesized with amino acid composition similar to MBP. None of them were able to induce EAE but several were able to prevent or minimize EAE in animals inoculated with MBP. Copolymer 1 (L-glutamate, L-tyrosine, L-alanine, and L-lysine) appeared to be the most potent and showed a consistent effect in several animal models, including primates (Teitelbaum et al 1971). It was also shown to be safe.

Effect of GA on T cells

GA is a synthetic molecule composed of four amino acids (L-alanine, L-glutamic acid, L-lysine, and L-tyrosine). These are the same amino acids represented in MBP. GA was originally designed as a synthetic model of MBP for the purpose of inducing EAE, an experimental animal model of MS. However, in vitro studies proceeded to show the opposite effect, as GA appeared to prevent the induction of EAE.

Evidence suggests that the structural similarity between GA and MBP may be partly responsible by way of competitive mechanisms and/or cross-reactivity for the therapeutic benefit of GA. EAE studies suggest that GA may compete with MBP for antigenic binding to the MHC II complex on antigen-presenting cells in the CNS. This mechanism alone is unlikely to function in vivo because GA is rapidly degraded after subcutaneous administration before it can enter the CNS (Lobel et al 1996). However, this competition may function in vivo if it occurs in the periphery or at subcutaneous SC injection site where GA may confront MBP-specific T cells before GA is degraded. The resulting GA/MHC complex may then bind preferentially to MBP-specific T cells over MBP/MHC complexes and induce alterations to the T cells. One such alteration may be a phenotypic shift in the T cells from Th1 to Th2 cells, thus increasing anti-inflammatory mechanisms (Duda et al 2000; Chen et al 2001; Neuhaus et al 2001). After activation in the periphery by daily immunization, GA has been demonstrated to selectively promote trans endothelial migration of Th2 cells across the blood–brain barrier (BBB) (Prat et al 2005). It is postulated that when the GA-specific Th2 cells are reactivated in the CNS by the presentation of degraded myelin components, they are stimulated to release anti-inflammatory cytokines such as IL-4, IL-6, and IL-10 (Neuhaus et al 2001). The release of anti-inflammatory cytokines then nonspecifically decreases the pathological inflammation in MS (Miller et al 1998; Brenner et al 2001; Dhib-Jalbut 2002; Yong 2002) (Figure 1).

GA and neuroprotection

The burden of disease in MS appears to be propagated by more than just inflammation and secondary demyelination from acute relapses. An important mechanism in MS appears to be a parallel ongoing process of neuro-degeneration. Data pointing towards neurodegeneration as a significant component of the immunopathology of the initial phases of MS are increasing (Trapp et al 1998). The mechanism of this neuronal degeneration is unknown and represents an important area of interest and a potential target for future therapeutics (Neuhaus et al 2003).

Much of the interest in potential mechanisms of neuroprotection surround the role of neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF). BDNF is up-regulated in response to neuronal damage and may have a protective role against neuro-degeneration. BDNF is hypothesized to influence the neuronal response to trauma or degeneration via inhibition of cell death and

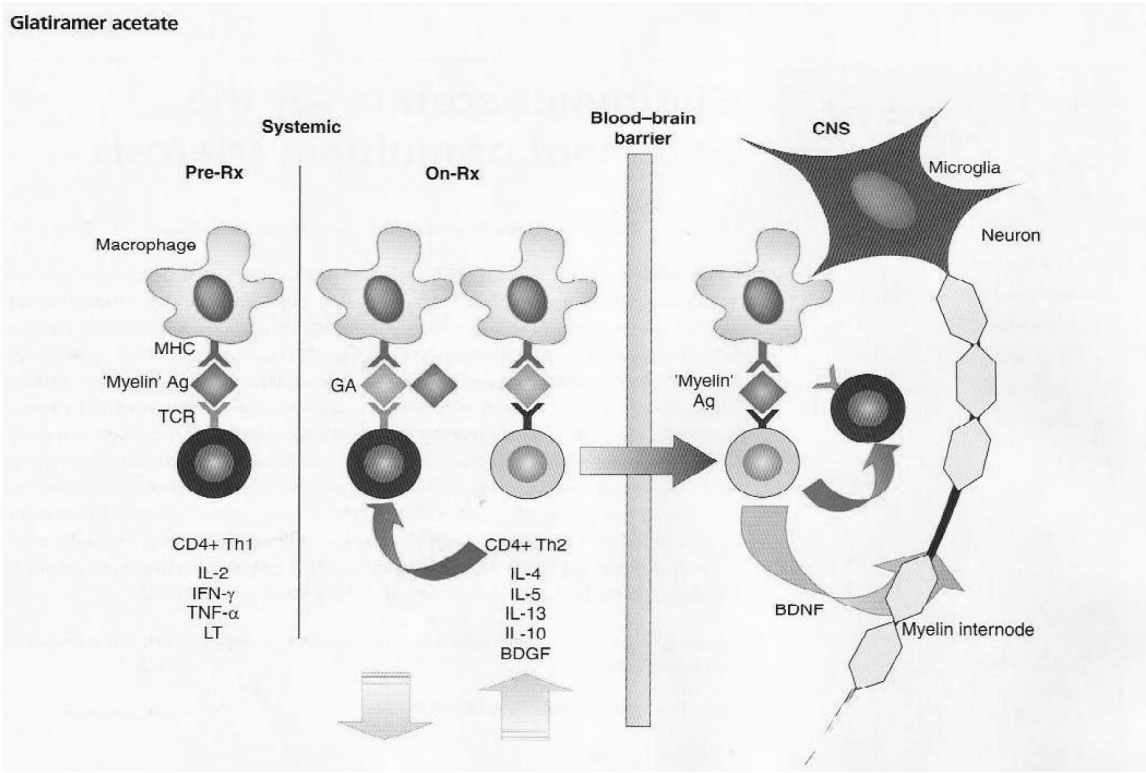

Figure 1 A simplified diagrammatic representation of the immunopharmacology of GA in MS therapeutics. The Pre-Rx portion of the panel emphasizes the baseline state in MS with CD4+ Th1 myelin antigen-reactive cells being activated by systemic antigen processing cells, including macrophages, that present foreign antigens that are myelin-like ('myelin' Ag) in the context of surface MHC to TCR; invoking the concept of molecular mimicry. Stimulated CD4+ Th1 'myelin' Ag-reactive cells secrete a number of pro-inflammatory cytokines (IL-2, IFN-γ, TNF-α, and LT). With GA therapy, GA may displace some 'myelin' Ag. More importantly, on presentation and stimulation of GA and 'myelin' Ag-reactive CD4+ Th1 cells, GA silences cross-reacting CD4+ Th1 'myelin' Ag-reactive cells through anergy, apoptosis, or antigen-specific mechanisms. Concomitantly, GA stimulates and expands a population of GA-reactive CD4+ Th1 cells (dark grey curved arrows). With continued therapy the net result is a reduced proportion of CD4+ Th1 and an increased proportion of GA and 'myelin' cross-reactive CD4+ Th2 cells. When these GA and 'myelin' cross-reactive CD4+ Th2 cells gain access to the CNS by trafficking across the blood–brain barrier, they are re-stimulated by true myelin Ags processed and presented by microglia, a brain-resident macrophage. On re-stimulation, the GA-reactive CD4+ Th2 cells secrete anti-inflammatory cytokines to inhibit 'myelin' Ag-reactive CD4+ Th1 cells within the CNS and also secret topic factors, such as BDNF that may facilitate neuronal survival (light grey curved arrow). Reproduced from Wolinsky JS 2004a. Glatiramer acetate for the treatment of multiple sclerosis. *Expert Opin Pharmacother*, 5:875–91. Copyright © 2004 with permission from Ashley Publications.

Abbreviations: Ag, antibody; BDNF, brain-derived neutrophic factor; GA, glatiramer acetate; IFN, interferon; LT, leukotriene; MHC, major histocompatibility complex; MS, multiple sclerosis; Rx, treatment; TCR, T cell receptor; TNF, tumor necrosis factor.

axonal degeneration, and via support of oligodendrocytes and remyelination. Studies have shown BDNF's ability to rescue degenerating neurons by inducing axonal outgrowth, remyelination, and regeneration (Gravel et al 1997; Yan et al 2002).

In situ data have demonstrated increased BDNF expression from immune cells isolated from MS lesions (Kerschensteiner et al 2003) and studies on interferon-β-treated MS patients show higher BDNF production compared with healthy volunteers (Petereit et al 2003). Given these observations, BDNF may be a potent neurotrophic factor with the ability to greatly impact neuronal repair and regrowth (Thoenen 1995; Barde 1997).

It is possible that GA may also mediate a neuroprotective role via increased production of neurotrophic factors such as BDNF. Evidence has shown that locally activated GA-reactive Th2 cells produce BDNF (Ziemssen et al 2002). In GA-treated EAE-induced mice, brain regions demonstrating high populations of GA-specific T cells also had high levels of BDNF and Th2 anti-inflammatory cytokines (Aharoni et al 2003). Another study found a reduced level of BDNF in the serum and CSF of RRMS patients which was reversed after therapy with GA (Azoulay et al 2005).

GA antibodies

Neutralizing antibodies to interferons is associated with worsening clinical efficacy and MRI parameters. Although patients treated with GA develop binding antibodies, there is no evidence that the antibodies influence the therapeutic effect of the drug (Farina et al 2002).

Clinical trials

Copolymer 1 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 (Abramsky et al 1977). Another preliminary trial (Phase 1, open-label) suggested a beneficial effect and no significant toxicity (Bornstein et al 1982).

The first randomized study of copolymer 1 involved 48 patients in 24 pairs matched for age, sex, and disability. Two additional unmatched patients were also enrolled, raising the total number of patients to 50. Patients on copolymer had fewer relapses and more patients remained relapse-free (Bornstein et al 1987). Copolymer was then tested in a more disabled chronic progressive population consisting of both secondary progressive and primary progressive patients. After a pretrial observation period, 106 out of 169 patients were noted to have progression and were entered in the trial. Although the results were not statistically significant there was a trend favoring the patients who received copolymer (Bornstein et al 1991).

In 1991, a Phase 3, double-blinded, placebo-controlled study began with 251 patients. The primary endpoint was the mean number of relapses in subjects receiving GA compared with placebo. The Expanded Disability Status Scale (EDSS) range was 0–5.0. The mean annualized relapse rate was 0.59 for patients receiving GA and 0.84 for patients receiving placebo (29% reduction) (Johnson et al 1995). On the basis of this trial, GA was approved for treatment of RRMS. After 10 years of open label extension, patients originally randomized to GA continue to do better than patients who were originally on placebo. Patients continuing GA for 10 years had an average disease duration of 18 years, yet nearly all remained ambulatory. Only 108 of the original 251 patients remained in the study and the annualized relapse rate in both (GA-GA, placebo-GA) declined to 0.2 (Ford et al 2006).

MRI effects of GA therapy

MRI provides a non-invasive surrogate marker of pathology, and is the only way subclinical disease activity can be detected. MRI has improved diagnostic accuracy, advanced the understanding of immunopathology of MS, and has become an essential tool in clinical drug trials. The first study of the effects of GA on serial MRI involved 10 RRMS patients compared before and after treatment. GA reduced both frequency and area of new lesions (Mancardi et al 1998). The larger US Pivotal Trial included only a few patients undergoing MRI but did demonstrate a reduction in enhancing lesions, and it also showed that delay in treatment was associated with increased progression on MRI (Wolinsky et al 2001). Since the Phase 3 trial of GA did not include a significant MRI component, a large randomized, double-blinded, placebo-controlled MRI trial was initiated in Canada and Europe. A total of 239 patients were randomized to GA or placebo for 9 months followed by an open-label phase for an additional 9 months. The European/Canadian MRI study demonstrated a reduction in frequency and volume of new enhancing lesions, with a 29% reduction in the number of enhancing lesions for the treatment arm. This study also observed an intriguing difference in the rapidity of resolution of gadolinium (Gd)-enhancing activity between GA-treated patients and interferon-β-treated patients. Enhancing activity resolved much more slowly in the GA-treated group (Comi et al 2001; Wolinsky et al 2002). This slower resolution may provide further support for current theories on the differential mechanisms of GA and interferon-β. Gd-enhancing MRI activity generally corresponds with BBB disruption (Bakshi et al 2004). While interferon-β functions by reducing lymphocytic infiltration across the BBB, GA activity is dependent upon the entry of GA-reactive Th2 cells beyond an intact BBB. From within the CNS, GA-reactive Th2 cells then decrease inflammation and repair the BBB. This mechanism of repair from within the CNS is proposed to take a longer time, as reflected by the delayed change in MRI activity (Dhib-Jalbut 2002).

Several recent MRI studies raise the possibility of neuroprotection as a potential mechanism of GA. Axonal degeneration in MS is represented on MRI by atrophy and the conversion of hyperintense T2 lesions into persistent hypointense T1 lesions. In the natural history of MS, 20%–60% of new lesions will degenerate into persistent hypointense T1 lesions (van Waesberghe et al 1998). The European/Canadian study demonstrated that the percentage of new lesions evolving into so called "T1-black holes" was more than 50% lower in the GA-treated group (Filippi et al 2001). Thus, in addition to slowing the formation of new MS lesions, GA may also limit permanent damage of new lesions by protecting axons and promoting lesion recovery.

The effects of GA on generalized brain atrophy in RRMS have also come under recent attention. The pilot study (27 patients from the pivotal Phase III trial) to assess MRI-measured atrophy demonstrated a significantly lower mean reduction in brain volume in patients on GA. The placebo group had a three-fold greater decline in brain volume compared with the GA group (Ge et al 2000). This study was limited because of relatively small number of patients and

lack of baseline data. In a larger study population (European/Canadian trial), the findings were mixed depending on the MRI brain volume measurement techniques. When the European/Canadian MRI data were analyzed by a semi-automated segmentation technique, no significant difference in atrophy was found (Rovaris et al 2001). However, when the same MRI data were re-analyzed using a fully automated, normalized technique, the analysis demonstrated a slight but not significantly lowered brain volume change in the GA group. However, during the open-label phase, there was a significant reduction in atrophy for the group initially treated with GA (Sormani et al 2004). These data may suggest a delayed but significant effect of GA on brain atrophy. Further research may better answer this question.

Meta-analysis, comparative, combination, and other trials

When data from three clinical trials (Bornstein pilot trial, US pivotal trial, and European Canadian study) were compiled for meta-analysis, an annualized relapse rate reduction of 28% was noted for GA compared with placebo (Boneschi et al 2003).

Several comparative open label trials have supported the use of GA as a first-line agent (Table 2). These trials should be interpreted with caution since biases are unavoidable. Controlled trials comparing the efficacy of GA and inteferon-β are underway. Data for use as combination treatment are lacking, but a large NIH-funded trial looking at the efficacy of a combination of GA and interferon-β1a is currently underway.

When all the randomized and controlled GA trials were analyzed in a Cochrane database review, GA did not show a significant effect on disease progression as measured by a worsening on EDSS score. The authors could not support GA as first-line treatment in MS (Munari et al 2004). This study's reliability could have been limited for several reasons including the variability of disease course (a mixture of RRMS, secondary progressive MS, and primary progressive MS) and the reliability of EDSS as a primary outcome measure.

GA was also studied in primary progressive MS and a large controlled trial failed to provide any evidence for benefit in this population (Wolinsky 2004b; Wolinsky et al 2004). Similarly, an oral form of GA studied in a controlled population did not show any significant evidence of efficacy.

Safety

The most common adverse reaction is a local injection-site reaction of erythema and induration. In one trial, 90% experienced at least one such reaction compared with 69% of placebo patients. GA is less frequently associated with a transient post-injection systemic reaction of flushing, chest tightness, dyspnea, chest palpitations, and anxiety. This self-limited systemic reaction was experienced in 15%. The reactions typically resolve within 15–30 minutes without sequelae. No significant laboratory abnormalities

Table 2 Comparative open-label trials on the use of GA as a first-line agent

Author	Nr patients	Comparative treatment groups	Duration	Results
Khan et al 2001	156	IFN β1a 30 μg/week IM (n = 40) IFN β1b 250 μg/qod SC (n=41) GA 20 mg/day SC (n=42) No treatment (n=33)	18 months	Relapse rate reduction was significant in the GA and IFN β1b groups
Carra et al 2003	134	IFN β1a 30 μg/week IM (n=26) IFN β1a 44 μg 3x/week (n=20) IFN β1b 250 μg/qod SC (n=20) GA (n=30) daily SC No treatment (n=38)	16 months	Significant decline in relapse rates in all patients with the largest reduction in the GA group
Fletcher et al 2002	58	GA daily SC GA qod SC Untreated	2 years	All patients showed similar reduction in relapse rates compared to 2 years prior to immunomodulating therapy
Haas et al 2003	283	IFN β1a 30 μg/week IM (n=79) IFN β1a 22 μg 3x/week SC (n=48) IFN β1b 250 μg/qod SC (n=77) GA daily SC (n=79)	2 years	Significant reductions from pre-study to on-study relapse rates for all of the IFN preparations with superior reduction in GA relapse rate compared with interferons at month 24

Abbreviations: GA, glatiramer acetate; IFN, interferon; IM, intra-muscular; SC, subcutaneous.

were found. According to the manufacturer, rare cases of non-fatal anaphylaxis have also been reported. Sixty-six non-fatal anaphylactic reactions in about 80 000 treated patients have been reported worldwide (Rauschka et al 2005). GA is a pregnancy category B drug. Although its use is not recommended in pregnancy, there is no evidence to suggest increased risk of adverse fetal or pregnancy outcome (Coyle et al 2003).

Conclusion

Since the initial pilot trial of GA published in 1987, numerous clinical trials have consistently established its safety and efficacy as a first-line treatment of RRMS. Its role in reducing clinical activity of disease has also been supported by parallel MRI data. Laboratory and clinical studies have also helped to define its potential mechanisms of action, including a potentially unique mechanism of neuroprotection. Results of ongoing clinical trials may define its role in combination therapy as well as its efficacy in comparison with other established therapies. Future studies may also help to define other potential clinical applications of GA in the treatment of MS and other autoimmune disorders.

Disclosures

SAR is currently doing clinical trials (funded by research grants) with Teva (makers of glatiramer acetate), Genentech, Biogen, and Berlex. He has been a consultant to and has received honoraria from Teva, Berlex, Genentech, Biogen, and Serono. EK and JM have no conflicts of interest to disclose.

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