REVIEW ARTICLE

Drug Safety 2001; 24 (13): 979-990
0114-5916/01/0013-0979/$22.00/0

Risk-Benefit Assessment of Glatiramer Acetate in Multiple Sclerosis

Tjalf Ziemssen,[1] *Oliver Neuhaus*[2] and *Reinhard Hohlfeld*[1,3]

1 Department of Neuroimmunology, Max Planck Institute of Neurobiology, Martinsried, Germany
2 Department of Neurology, Karl-Franzens University, Graz, Austria
3 Institute for Clinical Neuroimmunology and Department of Neurology, Klinikum Grosshadern, Ludwig Maximilians University, Munich, Germany

Contents

Abstract

Glatiramer acetate, formerly known as copolymer 1, is a mixture of synthetic polypeptides composed of four amino acids. Glatiramer acetate has been shown to be effective in preventing and suppressing experimental autoimmune encephalitis (EAE), the animal model of multiple sclerosis (MS). Therefore it was tested in several clinical studies, where it was found to slow the progression of disability and to reduce the relapse rate and the magnetic resonance imaging (MRI)–defined disease activity and burden in relapsing-remitting MS. As a daily standard dose, 20mg of glatiramer acetate is injected subcutaneously. After injection, glatiramer acetate undergoes rapid degradation to amino acids and shorter peptides; so it is not possible to measure any systemic plasma concentrations or excretion rates. Two major mechanisms have been proposed to explain the effects of glatiramer acetate in EAE and MS: the induction of glatiramer acetate-reactive T helper 2 (Th2)-like regulatory suppressive cells and the interference with T cell activation

as an altered peptide ligand. The most common adverse effects were mild injection site reactions (erythema, inflammation and induration). The most remarkable adverse event is the acute and transient immediate postinjection reaction manifested by flushing, chest tightness, palpitations and dyspnoea. Other reported adverse effects are transient chest pain and lymphadenopathy. Antibodies to glatiramer acetate induced during treatment do not interfere with its clinical effects. In several controlled clinical studies, glatiramer acetate has been shown to provide consistent, reproducible clinical benefits in the target population of patients with relapsing-remitting MS. The safety profile and risk-benefit ratio are excellent. Overall, glatiramer acetate is very well tolerated and has an excellent risk-benefit profile in patients with relapsing-remitting MS.

Glatiramer acetate, formerly known as copolymer 1, is the acetate salt of a standardised mixture of synthetic polypeptides containing the four amino acids L-alanine, L-glutamic acid, L-lysine and L-tyrosine with a defined molar ratio of 0.14 : 0.34 : 0.43 : 0.09 and an average molecular mass of 4.7 to 11.0kD, i.e. an average length of 45 to 100 amino acids.[1,2] In the 1960s Drs Sela, Arnon and their colleagues at the Weizmann Institute in Israel were involved in studies on the immunological properties of a series of polymers and copolymers which were developed to resemble myelin basic protein (MBP), a myelin protein. MBP in Freund's complete adjuvant induces experimental allergic encephalitis (EAE), the best animal model of multiple sclerosis (MS). They were interested in evaluating the extent to which these polypeptides could simulate the ability of MBP and of fragments and regions of the MBP molecule to induce EAE.[3-6] None of these series was capable of inducing EAE, but several polypeptides were able to suppress EAE in guinea-pigs. Copolymer 1, later known as glatiramer acetate, was shown to be the most effective polymer in preventing or decreasing the severity of EAE.[6] The suppressive effect is a general phenomenon and not restricted to a particular species, disease type or encephalitogen used for EAE induction.[7]

Abramsky et al.[8] were the first to treat a group of patients with severe relapsing-remitting MS with intramuscular glatiramer acetate 2 to 3mg every 2 to 3 days for 3 weeks, then weekly for 2 to 5 months. No conclusions could be drawn regarding drug efficacy but there were no significant adverse effects. Three clinical trials performed in the 1980s showed some evidence of efficacy that was adequate to support US Food and Drug Administration (FDA) approval and a good safety profile.[9-11] However, the results of these studies must be interpreted with caution because before 1991 production of the drug was not standardised.[2,12] Different batches had variable suppressive effects on EAE, which could also imply variable effects in MS patients. In 1991 a phase III multicentre trial with a daily 20mg dose of subcutaneously administered, highly standardised glatiramer acetate preparation was started in the US. This double-blind, placebo-controlled study demonstrated that glatiramer acetate significantly reduced the relapse rate without significant adverse effects.[13] In 1996 glatiramer acetate was approved by the FDA as a treatment for ambulatory patients with active relapsing-remitting MS.[7] Since then, glatiramer acetate has been licensed for approval in many other countries.

This review considers the long-term risks of glatiramer acetate therapy of multiple sclerosis and also attempts to assess the benefit of glatiramer acetate. Because there are several recent studies on the immunobiological consequences of treatment with glatiramer acetate, this review places emphasis on the possible mechanisms of action. Data was retrieved using a literature search of Medline up to August 2001 using the key words: glatiramer acetate, coploymer 1 and multiple sclerosis treatment.

1. Mechanism of Action

Until recently the effects of glatiramer acetate on the human immune system and its mechanisms

of action were largely unknown. Most data so far have been obtained in animal models. Several new papers, however, have shed light on the mechanisms of glatiramer acetate in MS and suggest several major effects on human T cells.[14]

In contrast to its lack of effect on immune cells isolated from untreated animals, glatiramer acetate induces vigorous polyclonal proliferation of peripheral blood lymphocytes from untreated (unprimed) human donors.[15-20] In glatiramer acetate–treated patients, the proliferative response to the agent decreases with time.[21] Recent results from our group indicate that this decrease is specific to glatiramer acetate, as it is not observed with recall antigens such as tetanus toxoid and tuberculin.[19] Theoretically, the observed decrease in glatiramer acetate–reactive T cells could be due to anergy induction or activation-induced cell death of glatiramer acetate-specific T cells.

Glatiramer acetate binds to major histocompatibility complex (MHC) class II and perhaps to MHC class I molecules, thereby competing with the MHC binding of other antigens.[22-24] This effect, which by its nature is antigen-nonspecific, is unlikely to play a role *in vivo*, since after subcutaneous administration, glatiramer acetate is quickly degraded and thus it is not likely to reach the CNS, where it could compete with the relevant auto-antigens for MHC binding. Complexes of glatiramer acetate/MHC can compete with MBP/MHC for binding to the antigen-specific surface receptor of MBP-specific T cells (T cell receptor antagonism).[25] The experimental evidence supporting this effect is controversial.[26] If it occurs, it is unlikely to be relevant *in vivo*, since glatiramer acetate is unlikely to reach sites where it could compete with MBP.

On the other hand, glatiramer acetate could act in the periphery as an 'altered peptide ligand' relative to MBP.[27-31] As a consequence, some of the circulating myelin-specific, potentially pathogenic T cells might become 'anergic' or be otherwise changed in their properties, e.g. in their migratory potential. This effect would be relatively antigen-specific and presumably occur in the periphery at the injection sites or in the corresponding draining lymph nodes, where MBP-specific T cells might be confronted with glatiramer acetate. Although some *in vitro* findings support this mechanism, it is not yet known whether the functional properties of MBP-specific T cells are altered in glatiramer acetate–treated patients. It may be relevant in this connection that we were unable to isolate MBP-specific T cell lines from glatiramer acetate–treated patients.[32]

Glatiramer acetate treatment induces an *in vivo* change of the cytokine secretion pattern and the effector function of glatiramer acetate–reactive T helper (Th) cells, a so-called Th1 to Th2 shift.[18,19,32-36] Th cells can be divided into several types based on their characteristics.[37-39] Th1 cells produce pro-inflammatory cytokines such as interleukin (IL)-2, IL-12, interferon (IFN)-γ and tumour necrosis factor (TNF)-α. In contrast, Th2 cells produce down-regulatory cytokines such as IL-4, IL-5, IL-6, IL-10 and IL-13. Different lines of evidence suggest that glatiramer acetate treatment changes the properties of the glatiramer acetate–reactive T cells in such a way that they increasingly become Th2-like with time. Using intracellular double-immunofluorescence flow cytometry, we demonstrated that long-term glatiramer acetate–reactive T cell lines from untreated MS patients and healthy controls predominantly produce IFNγ and are to be classified as Th1 cells, whereas glatiramer acetate-reactive T cell lines from glatiramer acetate–treated MS patients predominantly produce IL-4, i.e. behave like Th2 cells.[32]

In addition, the study of Farina et al.[19] demonstrated that an automated ELISPOT assay, which is able to detect cytokine production of individual peripheral blood lymphocytes, allows the correct identification of glatiramer acetate–treated and untreated donors in most cases. Glatiramer acetate–treated MS patients show: (i) a significant reduction of glatiramer acetate-induced proliferation of peripheral blood mononuclear cells; (ii) a positive IL-4 ELISPOT response mediated predominantly by CD4+ T cells after *in vitro* stimulation with a wide range of glatiramer acetate concentrations; and (iii) an elevated IFNγ response partially mediated by CD8+ T cells after stimulation with high

glatiramer acetate concentrations. Glatiramer acetate–reactive T cells seem to not be physically deleted, but rather they are modified in such a way that they respond to *in vitro* challenge with glatiramer acetate by secretion of cytokines but not by proliferation. This ELISPOT assay may help to distinguish between immunological responders and nonresponders to glatiramer acetate treatment.

In summary, the following scenario has the strongest experimental support:[14] glatiramer acetate–reactive Th2-like T cells are able to cross the blood-brain barrier, since they are activated by daily immunisation.[40] Inside the CNS, glatiramer acetate–reactive T cells may cross-react with products of the local myelin turnover presented by local antigen-presenting cells.[41] Thus, some of the glatiramer acetate–reactive Th2 cells may be stimulated to release anti-inflammatory cytokines and even neurotrophic factors.[42-44] Schori et al.[45] were able to demonstrate in an animal model different from EAE that immunisation with glatiramer acetate protected retinal ganglion cells against death from glutamate cytotoxicity and ocular hypertension. Subsequently, the production of proinflammatory cytokines by other inflammatory cells is reduced via a suppressive bystander effect.[33,34,46,47]

2. Pharmacokinetics

Glatiramer acetate is administered daily as a subcutaneous injection of 20mg of a standardised mixture of the described polypeptides.[48,49] Injection sites should be rotated between the upper arms, thighs and abdomen. After subcutaneous administration, glatiramer acetate is quickly absorbed with only 10% remaining at the injection site after 1 hour. It undergoes rapid degradation to amino acids and shorter peptides. No systemic plasma concentrations nor any urinary or faecal excretion can be detected.[50]

There are only a few studies *in vivo*, using radioactive labelling methods, on the pharmacokinetics of glatiramer acetate in mice, rats and monkeys.[51] The radioactivity in serum reaches a maximum after 1 to 2 hours in rats and after 2 to 4 hours in monkeys. Long-term administration in rats did not affect the pharmacokinetic parameters of glatiramer acetate. The curves of plasma radioactivity are similar after oral administration and after intramuscular or subcutaneous injections. The distribution of iodinated material showed the highest level in stomach and thyroid and the lowest in the brain, probably because the penetration through the blood-brain barrier is impeded by the high polarity and the hydrophilic nature of glatiramer acetate. Urinary excretion is the major elimination pathway for the radioactive labels, and faeces contained only trace amounts. One should be aware of a general methodological problem of radioactive labelling: it is not known whether the widely distributed radioactive label is still attached to intact glatiramer acetate or to fragments of glatiramer acetate.

So far there is no evidence of relevant drug interactions in humans. Results from existing clinical trials do not suggest any significant interactions of glatiramer acetate with therapies commonly used in patients with MS, including the concurrent use of corticosteroids, antihistamines, antidepressants and muscle relaxants up to 28 days.[50,52] A clinical trial of combined treatment with IFNβ and glatiramer acetate is currently in progress. Animal experiments with a combination of IFNα and glatiramer acetate indicate that such a combination may not be beneficial.[53]

3. Risks Associated with Glatiramer Acetate

3.1 Toxicological Data

Toxicological studies indicate that glatiramer acetate is well tolerated at the currently used dose (20 mg/day) with an adequate safety margin. Reproduction studies in rats and rabbits showed no impairment of fertility and no fetal loss or fetal abnormalities. *In vitro* and *in vivo* studies demonstrated that glatiramer acetate is devoid of any mutagenic or carcinogenic potential. Serial analysis of urine and blood revealed no changes in liver, spleen, kidney, bone marrow, gastrointestinal, circulatory or pulmonary function.[13,50,52]

3.2 Local Site Effects

As glatiramer acetate is given by daily subcutaneous injection administered by the patient or carer, this route of administration itself will inevitably result in local adverse effects. Across all trials, the most commonly reported local adverse events were, in isolation or combined, local reactions such as erythema, itching, burning, pain, inflammation, oedema and/or swelling.[52] The local adverse effects seem not to be related to the dose per injection. In controlled studies, local adverse effects were overall reported in 82% of the glatiramer acetate–treated group and in 48% of the placebo group.[12,13,49,54] Only 2% of patients receiving glatiramer acetate for injection in controlled clinical trials had local adverse effects that were graded severe (compared with 1.2% on placebo). In controlled studies, 2.1% of the glatiramer acetate–treated patients discontinued treatment because of local injection site reactions (compared with 1.1% of patients receiving placebo). There were isolated reports of injection site fibrosis, injection site atrophy, abscess and injection site necrosis.[50] The frequency of injection site effects generally decreases with time except, most notably (as would be expected), the rare events of atrophy and fibrosis, which tend to occur later.[52]

Mancardi and co-workers described a localised lipoatrophy in 4 of 27 patients after prolonged treatment with glatiramer acetate.[55,56] After 3 years of treatment, well circumscribed areas of skin depression were visible at the injection sites with a normal-appearing overlying skin. One erythematous indurated skin area showed perivascular infiltrates of lymphocytes and rare eosinophils in both superficial and deep dermis on biopsy. In the other three cases, skin samples from atrophic areas showed fibrosis of the dermis and subcutis with a reduction in the size of fat lobules and only minimal inflammation. It is therefore possible that in some cases the drug itself induces a local inflammatory reaction with subsequent dermal fibrosis and fat atrophy.

Hofstadt et al.[57] reported 3 of 33 glatiramer acetate–treated patients who developed subcutaneous masses with a diameter of 5cm or more. Skin biopsies showed lymphocytic and eosinophilic infiltration. Epicutaneous tests were negative, and prick scratch and intracutaneous tests were positive at a dilution of 1 : 2000 in a crescendo reaction until 72 hours. This reaction seems to be compatible with a delayed type hypersensitivity (type IV allergy). Glatiramer acetate should be discontinued in affected patients. The incidence of potentially serious reactions to glatiramer acetate (3 in 33) in this report was much higher than that encountered in clinical practice and controlled trials.

3.3 Immediate Postinjection Systemic Reaction

Apart from local injection site adverse events, the most common treatment-related adverse events were symptoms of immediate postinjection reactions that occurred in about 10% of the patients.[12,52,58] This infrequent adverse experience reported by patients treated with glatiramer acetate includes, in isolation or combined, facial or more generalised flushing (vasodilation), chest discomfort (pain) and perceived shortness of breath (dyspnoea). These symptoms generally appear within minutes of an injection and resolve spontaneously in 5 to 15 minutes, but in some situations they can last for more than 1 hour. The reaction typically occurs at home soon after injection and resolves spontaneously before it can be observed by a health professional. No long-term or permanent sequelae of the immediate postinjection reaction have been reported.[50,58,59] Nearly half of all patients who developed one episode of this type eventually experience it again. One patient had seven such reactions over approximately 30 months of using the drug.[52] However, on average, it occurred only once in approximately 840 daily injections. Whether any of these symptoms actually represent a specific syndrome is unclear. The cause of this systemic reaction is unknown. Because it is self-limited and without relevant consequences there is no reason to stop treatment. Patients should be informed that this reaction may occur, in order to reduce the emotional effect; moreover, re-injection after such a reaction should

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.