REVIEW ARTICLE

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Risk-Benefit Assessment of Glatiramer Acetate in Multiple Sclerosis

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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

preferably be done under medical observation to reassure the patient.[49]

3.4 Transient Chest Pain

Approximately 26% of glatiramer acetate–treated patients in the multicentre controlled trial (compared with 10% of the placebo-treated patients) experienced at least one episode of what was described as transient chest pain.[50] Although some of these episodes occurred in the context of the immediate postinjection reaction described above, many did not. The pain was transient, often unassociated with other symptoms and appeared to have no important clinical sequelae. Electrocardiographic monitoring did not reveal any cardiac abnormality.[13] The pathogenesis of this symptom is unknown.

3.5 Immunological Effects

Studies in both rat and monkey have suggested that immune complexes are deposited in renal glomeruli.[50] In three different clinical studies, all patients (n = 130) developed glatiramer acetate–reactive antibodies.[13,21,60,61] Maximum levels were attained after an average treatment duration of 3 to 4 months; thereafter antibodies declined, but remained positive (about 50% greater than the baseline). No such antibodies were detected in placebo patients. Immunoglobulin (Ig) G1 antibody levels were 2 to 3 times higher than those of IgG2. The preferential production of IgG1 over IgG2 antibodies may indicate that Th2 responses are involved in mediating the clinical effect of glatiramer acetate.[14,21] The continued clinical benefit, observed in long-term studies, suggests that the modifying effect of glatiramer acetate in relapsing-remitting MS is not compromised by the appearance of neutralising antibodies.[59,62] Because levels of glatiramer acetate–specific antibodies have not been determined after the 24-month point, no direct information is currently available.[59] The presence of anti-glatiramer acetate antibodies did not influence the clinical efficacy of the drug, as these antibodies did not reduce the effect of glatiramer acetate in mice with EAE or the proliferation of a glatiramer acetate–specific T cell line.[49,63] Furthermore, the humoral and cellular immunological responses to glatiramer acetate do not correlate with the observed side effects of glatiramer acetate treatment. Antibodies and T cell responses to MBP were low and did not change significantly during treatment.[21]

Anaphylaxis can be associated with the administration of almost any foreign substance, and the protein nature of glatiramer acetate certainly entails the risk of anaphylaxis. Up to now, three nonfatal anaphylactic reactions have been reported.[50,64] Bayerl et al.[64] described a 30-year-old woman who developed an immediate postinjection reaction 2 months after starting glatiramer acetate treatment. She continued the daily glatiramer acetate injections without further notable adverse effects; 6 weeks later she developed a second, this time systemic, allergic reaction with nausea, a sensation of heat, pressure and drowsiness in the head, generalised erythema and wheals on the trunk. She felt cold perspiration, collapsed and experienced gastric spasms and diarrhoea. After resting on the floor for half an hour she recovered, with wheals remaining for 4 hours. In this patient, there might have been an exaggerated specific activation of the humoral immune reaction against glatiramer acetate. In summary, anaphylactic reactions to glatiramer acetate are rare but need to be taken seriously.

There was one published report of the onset of myasthenia gravis during treatment with glatiramer acetate in a patient with MS.[65] Heesen et al.[66] reported another autoimmune phenomenon during glatiramer acetate treatment. They describe the case of a 30-year-old woman with MS who developed autoimmune hyperthyroidism after receiving glatiramer acetate treatment for 3 years. Although it is not possible to derive a clear causal relationship from these case reports and one cannot exclude a coincidental occurrence of autoimmune phenomena, the treating physician should pay attention to complaints suggesting additional autoimmune diseases during glatiramer acetate treatment. Perhaps autoantibody production is somehow stimulated by the enhanced Th2 cell response that develops during glatiramer acetate treatment.

Windhagen et al.[67] showed that glatiramer acetate induced a mild to moderate tender lymphadenopathy in 9 of 27 glatiramer acetate–treated patients. Symptoms included touch sensitivity or mild pain. The size of the swollen lymph nodes ranged from 2 to 5cm. A lymph node biopsy in one patient with severe generalised lymphadenopathy revealed strong immune stimulation with lymphofollicular hyperplasia but no atypical cells. In 7 of these 9 patients the lymphadenopathy remained localised to the draining lymph nodes.

3.6 Pregnancy and Breastfeeding

No adverse effects on embryofetal development occurred in reproduction studies in rats and rabbits receiving subcutaneous doses up to 37.5 mg/kg glatiramer acetate during the period of organogenesis.[50] Because animal reproduction studies are not always predictive of human response, glatiramer acetate should not be used during pregnancy. Thus far, however, there is no evidence that glatiramer acetate is toxic for the fetus or embryo.[51] It is not known whether glatiramer acetate is excreted in human milk. Because many drugs may be excreted in human milk, caution should be exercised when glatiramer acetate is administered to a woman who is breastfeeding.

3.7 Other Effects

Compared with placebo, glatiramer acetate did not increase the incidence of flu-like syndrome, depression or suicidal ideation.[52]

4. Clinical Studies

4.1 Preliminary Trials

Four early exploratory open studies were performed in the late 1970s and early 1980s to obtain indications of dosing and safety.[8-10,68] In total, 41 patients with relapsing-remitting or secondary progressive MS were enrolled in these studies. The treatment schedules, doses of glatiramer acetate and treatment duration were quite variable from study to study. The maximum dose of 20 mg/day was well tolerated and no severe adverse effects were detected in these studies.

4.2 Phase II Studies

Because there was evidence of some potential benefit, Bornstein et al.[60] started a double-blind, placebo-controlled pilot trial. 50 patients with MS received either 20mg glatiramer acetate dissolved in 1ml saline or just saline for 2 years. There were 62 relapses in the placebo group (average 2.7 per patient) and 16 among patients in the glatiramer acetate treated group (average 0.6 per patient). In addition, the proportion of relapse-free patients was twice as great in the glatiramer acetate-treated group. Only five patients of the treatment group showed a confirmed progression of disability, compared with 11 patients in the placebo group ($p = 0.005$). The effects on relapse rate and on disability were more pronounced in patients who had the least disability at entry. This study also reported the occurrence of a postinjection systemic reaction in two patients.

In the mid 1980s a subsequent double-blind, randomised study in 106 patients with primary and secondary progressive MS was conducted.[11] No distinction was made between primary and secondary MS courses or between progression due to incomplete recovery from a relapse and progression unrelated to relapses. The differences between the overall survival curves were not significant. The progression rates at 12 and 24 months were nonsignificantly higher for the placebo group ($p = 0.088$) with 2-year probabilities of progressing of 20.4% for glatiramer acetate and 29.5% for placebo. Only at one of the two centres was a significant difference at 24 months detectable between placebo and glatiramer acetate. In conclusion, there was no evidence of efficacy of glatiramer acetate in patients with progressive MS, although a favourable trend was more marked in those whose disability was less at the time of beginning treatment. Currently the effect of glatiramer acetate on progressive MS is being addressed in a large controlled study of efficacy in primary progressive MS.

4.3 Phase III Studies

For a more comprehensive assessment of the efficacy of glatiramer acetate in patients with relapsing-remitting MS, a definitive phase III trial was conducted at 11 US medical centres with a total of 251 patients with relapsing-remitting MS who received glatiramer acetate 20mg or placebo by daily subcutaneous injection for 2 years.[13] As the primary end-point, the mean annualised relapse rates were 0.59 for the glatiramer acetate-treated group and 0.84 for the placebo group; a 29% reduction was statistically significant ($p = 0.007$). Trends in the proportion of relapse-free patients and median time to first relapse favoured glatiramer acetate treatment. Patients in both groups with higher disability at entry, measured by the Expanded Disability Status Scale (EDSS),[69] had a higher relapse rate, while the largest reduction in relapse rate between groups occurred in patients with a baseline EDSS of 0 to 2 (33% versus a reduction of 22% in patients with an EDSS score at entry >2). When the proportion of patients who improved, were unchanged, or worsened by ≥1 EDSS step from baseline to end of study (2 years) was evaluated, significantly more patients on glatiramer acetate improved and more on placebo worsened ($p = 0.037$). The effect of treatment was constant throughout the entire study duration. Patient withdrawals were 19 (15.2%) from the glatiramer acetate group and 17 (13.5%) from the placebo group at approximately the same intervals. The treatment was well tolerated. The most common adverse event was the injection-site reaction. Rarely, the transient self-limited immediate postinjection reaction followed the injection in 15.2% of those treated with glatiramer acetate and 3.2% of those treated with placebo.

In an extension of this study up to 35 months with unchanged blinding and study conditions, the clinical benefit of glatiramer acetate for both the relapse rate and neurological disability was sustained.[12,58] Thus, the reduction of annual relapse rate was 32% in favour of glatiramer acetate ($p = 0.002$). The results of this extension study confirmed the excellent tolerability and safety profile of glatiramer acetate.

This study was further extended as an open-label study with all patients receiving active drug.[59] The reported data from approximately 6 years of organised evaluation showed a mean annual relapse rate of the treated patients of 0.42. The rate per year continued to drop and for the sixth year it was 0.23. After 6 years of observation, 152 of 208 patients (73%) were still participating. Of the group who have remained taking glatiramer acetate without interruption for 5 or more years, 69.3% were neurologically unchanged or improved from baseline by at least one step on the EDSS scale.

4.4 Other Studies

As part of the US pivotal trial, the effects of glatiramer acetate on cognition were studied in a 2-year placebo-controlled longitudinal study with 248 patients. This study showed no effect of glatiramer acetate therapy on cognitive function in relapsing-remitting MS.[70] The results, however, do not exclude a beneficial effect of glatiramer acetate on cognitive function, because there was no measurable decline in the placebo group.

4.5 Magnetic Resonance Imaging Studies

Several early magnetic resonance imaging (MRI) studies indicated a trend toward benefit with glatiramer acetate, but were limited by the small number of evaluated patients.[71-73] Wolinsky et al.[73] were able to demonstrate a definite, but modest effect of glatiramer acetate on MRI enhancements of MS patients in the US open-label glatiramer acetate extension MRI trial for relapsing multiple sclerosis. A large randomised, double-blind, placebo-controlled MRI trial involving 239 patients with relapsing-remitting MS was conducted to determine the effect, onset and durability of any effect of glatiramer acetate on disease activity monitored with MRI.[74] Treatment with glatiramer acetate, compared with placebo, showed as a primary outcome measure a significant reduction of 30% in the total number of enhancing lesions on T1-weighted images ($p = 0.003$); as a secondary outcome measure there was a significant reduction of the number of new enhancing lesions ($p < 0.003$), the

monthly change in the volume of enhancing lesions ($p = 0.01$) and the change in the volume ($p = 0.006$) and the number ($p < 0.003$) of new lesions seen on T2-weighted images. The relapse rate was also significantly reduced by 33% for glatiramer acetate–treated patients ($p = 0.012$). All described effects increased over time. Compared with effects observed in MRI studies with various formulations of IFNβ, the effects of glatiramer acetate on clinical and MRI-defined disease activity are delayed.[73,74] This delay is consistent with the time course of the glatiramer acetate–induced immunological changes (induction and expansion of a glatiramer acetate-specific, protective T cell population).[14]

The percentage of new lesions that evolved into 'black holes' was lower in glatiramer acetate–treated than in placebo-treated patients on scans at 7 (18.9 and 26.3%; $p = 0.04$) and 8 (15.6 and 31.4%; $p = 0.002$) months after lesion appearance.[75] Glatiramer acetate seems to have a favourable effect of tissue disruption in MS lesions once they are formed.

5. Risk-Benefit Assessment

The requirement for long-term therapy dictates that a successful drug should have sustained safety, tolerability and efficacy. Tolerability is especially important to achieve continued patient compliance. An ideal drug for MS should also be useful for patients with a wide range of disabilities.

The proposed indication for the use of glatiramer acetate is to reduce the relapse rate in patients with relapsing-remitting MS, which has been linked adversely with long-term outcome. Several clinical trials have shown a consistent effect of a reduction of the relapse rate by approximately 30% and of the accumulation of disability in patients with relapsing-remitting MS treated with glatiramer acetate. The clinical benefit was supported by positive MRI effects. Clinical experience shows that glatiramer acetate is usually well tolerated and suitable for self-administration by patients with MS.

In general, the local adverse events have rarely limited treatment. The immediate postinjection reaction is unpleasant but transient. The low dropout rate in clinical studies provides further reassurance. The commonly observed adverse effects of glatiramer acetate do not therefore appear to constitute a substantial 'risk'. In a progressive, disabling disease such as MS, the benefits of glatiramer acetate treatment clearly far outweigh the relatively benign adverse effect profile. In summary, the risk-benefit assessment for glatiramer acetate is excellent.

It is difficult to compare the beneficial effects of glatiramer acetate with those of the different IFNβ preparations because there is no comparative trial. Laboratory studies indicate that IFNβ and glatiramer acetate produce their effects by different immunological mechanisms.[39,47] Compared with those of IFNβ, the beneficial effects of glatiramer acetate treatment have a delay in onset which may be related to the protracted time course of the glatiramer acetate–induced immunological changes (induction and expansion of a glatiramer acetate-specific protective T cell population).[14,74,76] The time course of the immunological changes is consistent with the delayed effect on MRI.

Comparing the adverse effects, glatiramer acetate is at least as acceptable to patients as IFNβ. For both glatiramer acetate and IFNβ, there are clinical responders and nonresponders who at present can be defined only by the clinical course. In the future it will be important to develop laboratory tests that help to identify the nonresponders.

There is evidence that in addition to the subcutaneous route of administration, oral application of glatiramer acetate is beneficial in EAE.[46,77] This beneficial effect in the animal model has led to the ongoing placebo-controlled study with an oral glatiramer acetate formulation. The results of this trial will be available in the near future.

6. Conclusion

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.

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