



Lack of evidence for use of glatiramer acetate in multiple sclerosis

Of the treatments for multiple sclerosis (MS) aimed at prevention of relapse or disease progression, there is only regulatory approval for beta interferons and glatiramer acetate. Treatment with either interferon beta-1a or interferon beta-1b is established, although their beneficial effects have been challenged by our systematic review of randomised trials in relapsing-remitting MS.¹ The alternative treatment is glatiramer acetate, a synthetic amino-acid polymer shown to suppress experimental allergic encephalomyelitis in animals. Although glatiramer acetate's mechanism of action is not fully understood, molecular similarities to myelin basic protein suggest competition with myelin in binding to T lymphocytes; this may improve the course of the disease.

Glatiramer acetate is now routinely prescribed for MS and it is the fastest growing product in its market. However, our systematic review of all randomised controlled trials of glatiramer acetate² found little support for use of this drug in patients with MS.

The efficacy of glatiramer acetate has been assessed in only four studies with a total of 646 patients: 540 with relapsing-remitting and 106 with chronic progressive MS. Whatever the disease course, glatiramer acetate is no better than placebo in preventing clinical progression at 2 years. Furthermore, all studies assessing this outcome³⁻⁵ defined progression as an increase of at least 1 point on the Expanded Disability Status Scale (EDSS), maintained for 3 months. This is probably too short a follow-up period to exclude relapse. Research shows that at least 1 year of follow-up is needed to confirm disease progression and most clinicians would not agree with a shorter period. Other studies have characterised patients' disability by measuring EDSS changes over time. Unfortunately, EDSS is an ordinal scale and comparison of mean scores with the baseline has limited validity as an outcome measure. Therefore a slight decrease in the mean EDSS score up to 3 years, shown by a

single major study, has questionable clinical importance.⁵

The effect of glatiramer acetate on the risk of relapse has also been studied. Three studies measured decreases in the average number of exacerbations during follow-up.^{3,5,6} Patients enrolled in these trials, however, were not homogeneous in their risk profile. When pooled estimates of treatment effect are adjusted for heterogeneity across studies, there is no difference between relapse rates for patients taking glatiramer acetate compared with those taking placebo up to 2 years. After almost 3 years of treatment with glatiramer acetate there is a significant reduction in exacerbations from 1.98 to 1.34. This difference, however, could hardly be accepted as a relevant benefit for patients. Relapse-free survival is a better outcome measure. Unfortunately, if glatiramer acetate does reduce patients' risk of developing exacerbations, available studies do not have adequate statistical power to detect this. Up to 35 months, the relative risk of at least one clinical relapse is not significantly decreased with glatiramer acetate; the results of a small pilot trial are an exception.³ The median time to first relapse has also been studied,⁵ and no significant difference was shown between the treatment and control groups.

Glatiramer seems to be a safe drug. The incidence of reported adverse events is not consistent with major toxicity. However, a transient and self-limiting patterned reaction of flushing, chest tightness, sweating, palpitations, and anxiety associated with glatiramer acetate dosage was common, as well as local injection-site reactions (eg, itching, swelling, erythema, or pain). Even if not harmful to the patient, these side-effects cast doubts on the possibility of a blind outcomes assessment of glatiramer acetate.

Resource-use data suggest that treatment with glatiramer may decrease hospital admission rates and the need for steroids. However, these outcomes depend on the local healthcare financing system and reflect the choices of individual physicians.

MRI has been suggested as an objective measure of treatment effect. But MRI measurement is a surrogate of therapeutic efficacy and not a therapeutic goal. According to Prentice's validity criteria,⁷ we should trust surrogate endpoints only if they fully capture the net effect of treatment on clinical outcomes.

And here we return to the clinical outcomes issue. The natural course of MS spans 30–40 years, therefore treatment effectiveness should relate to the delaying of disease progression. We still lack evidence to prove that glatiramer acetate improves the outcomes in patients with MS. New clinical trials need to be planned and must develop a reliable working definition of progression, concealed assessment methods for patients with injection-site reactions, and a comprehensive and relevant measure of disability over time. Finally, patients' quality of life should be included among the primary endpoints of future studies.

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Conflict of interest

We have no conflicts of interest.

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