Benefit-risk analysis of glatiramer acetate for relapsing-remitting and clinically isolated syndrome multiple sclerosis
Qizilbash N, Mendez I, Sanchez-de La Rosa R

CRD summary
The authors concluded that glatiramer acetate had a similar risk and benefit profile to other available treatments for multiple sclerosis. The authors' conclusions reflected the evidence presented but limitations in the quality of the included studies and heterogeneity in some meta-analyses suggest the findings should be interpreted with caution.

Authors' objectives
To examine the risks and benefits of glatiramer acetate for relapsing-remitting multiple sclerosis (RRMS) and clinically isolated syndrome (CIS).

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials were searched up to January 2011 for articles written in English, French and Spanish. Search terms were reported. Reference lists of included studies and the United States Food and Drug Administration website were searched. The World Health Organisation global spontaneous adverse reaction reports database was used to complement the analysis of adverse events.

Study selection
Eligible studies were RCTs or comparative prospective cohort studies that included patients (aged 18 or over) with RRMS or CIS who received glatiramer acetate (20mg daily subcutaneous dose). Studies were excluded if they did not provide data on clinical outcomes, did not analyse glatiramer acetate separately, used routes of administration or doses not described in the summary of product characteristics or included patients with primary progressive multiple sclerosis or other diseases.

Most studies focused on patients with RRMS (82%). Mean age ranged from 30 to 46.9 years. More than half of the included studies were RCTs and the most common comparators were interferon 1a, interferon 1b and placebo. Most patients in all studies were female. Included outcomes were percentage change of relapse-free patients, mean number of relapses, clinical progression, Expanded Disability Status Scale (EDSS) score, adverse events leading to discontinuation, any injection site reaction and any systemic reaction. EDSS score was used to define disease progression in just over half of included studies. Study duration ranged from nine to 36 months.

It was unclear how many reviewers selected the studies.

Assessment of study quality
The Jadad scale (for trials) and Scottish Intercollegiate Guidelines Network quality checklist (for non-randomised studies) were used to quality assess the studies.

Two reviewers independently assessed study quality and any disagreements were resolved through discussion.

Data extraction
Data were extracted from dichotomous outcomes to enable the calculation of risk ratios (RR) and absolute risk differences, with 95% confidence intervals (CI). For continuous outcomes, change from baseline data were extracted to calculate mean differences with 95% CIs.

Data extraction was conducted by two reviewers independently and any differences were resolved through discussion.

Methods of synthesis
Risk ratios and standardised mean differences (SMDs) were each pooled using the random-effects inverse variance method. Heterogeneity was assessed using I². Small study effects or publication bias were assessed using a funnel plot and Egger's test. Studies were stratified by patient population (RRMS, CIS and mixed), comparator (placebo, untreated...
and interferon) and length of follow up (zero to 12 months, 13 to 24 months and >24 months).

**Results of the review**

Twenty-four studies were included but data were reported only on the 11 studies that were entered into the meta-analysis (4,759 patients). Seven of the 11 studies were RCTs (four double blind, one single blind and two not blinded); two were rated high, two good and three fair. There were also four comparative cohort studies; one was rated fair and three were rated low quality. Efficacy outcomes were derived from RCTs in patients with RRMS. The analysis of adverse events included all studies and all patients. Drop-out ranged from 5.9% to 26%.

**Relapse-free:** No statistically significant differences were found between glatiramer acetate and placebo (moderate to high heterogeneity, $I^2=44.5\%$; four studies) or between glatiramer acetate and interferon (no heterogeneity, $I^2 = 0\%$; two studies).

**Mean number of relapses:** There was a reduced mean number of relapses for patients who received glatiramer acetate compared with placebo (SMD -0.54, 95% CI -0.89 to -0.19; three studies; $I^2=67.5\%$) but with high statistical heterogeneity.

**Clinical progression:** There was a statistically significant benefit for glatiramer acetate compared with interferon (RR 0.82, 95% CI 0.68 to 0.98; two studies; $I^2=0\%$) but not when compared to placebo.

**Change in EDSS scale:** Change from baseline was statistically significantly higher for glatiramer acetate compared with placebo at 13 to 24 months (SMD -0.25, 95% CI -0.49 to -0.04; two studies; $I^2$ not reported) and at 24 months follow-up (SMD -0.39, 95% CI -0.66 to -0.11; one study).

**Adverse events:** Receiving glatiramer acetate was associated with a statistically significant increased risk of discontinuation due to adverse events compared with placebo (RR 3.13, 95% CI 1.38 to 7.12; four studies; $I^2=0\%$) but not compared with interferon (four studies; $I^2=0\%$). Glatiramer acetate was associated with a statistically significant increased risk of any injection site reaction compared with placebo (RR 1.88, 95% CI 1.24 to 2.86; two studies; $I^2=87.5\%$) but there was very high statistical heterogeneity. No statistically significant difference for injection site reaction was found compared with interferon (two studies; no statistical heterogeneity). For post-injection reaction, there was a greater risk in patients receiving glatiramer acetate compared with placebo (RR 3.39, 95% CI 2.34 to 4.90; four studies) with no statistical heterogeneity. There was also a statistically significant increased risk of post-injection reaction compared with interferon (RR 3.45, 95% CI 1.44 to 8.22; three studies; $I^2=67.5\%$) but with high statistical heterogeneity.

No evidence was found to indicate the presence of publication or small study biases. Further results at specific follow-up periods were reported in the paper.

**Authors’ conclusions**

Glatiramer acetate was associated with a reduced relapses compared with placebo and less clinical progression compared with interferon. Adverse events were comparable with interferon. Glatiramer acetate had a similar risk and benefit profile to other available treatments for multiple sclerosis including interferon 1a and 1b.

**CRD commentary**

The review question was clear and inclusion criteria were adequately specified. The range of electronic databases searched was adequate and included attempts to identify unpublished data. It was unclear whether language restrictions were applied. Appropriate procedures were applied to minimise error and bias for data extraction and quality assessment; it was unclear whether this was also the case for study selection. Studies varied in quality including whether blinding or randomisation were used. Studies varied in terms of length of follow-up and in sample size. There were some discrepancies between tables and text. Meta-analysis appeared appropriate although there was high heterogeneity in some calculations.

The authors’ conclusions reflected the evidence presented but limitations in the quality of the included studies and heterogeneity in some meta-analyses suggest the findings should be interpreted with caution.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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