Annualized relapse rate of first-line treatments for multiple sclerosis: a meta-analysis, including indirect comparisons versus fingolimod
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CRD summary
This review found that first-line treatment in patients with multiple sclerosis with fingolimod was associated with significant decreases in relapse rates compared to beta interferon and glatiramer acetate. The results were derived from indirect comparisons between the treatments but the authors’ cautious conclusions are likely to be reliable.

Authors’ objectives
To compare the annualised relapse rates after treatment with beta interferon, glatiramer acetate and fingolimod in patients with multiple sclerosis.

Searching
MEDLINE, EMBASE, DARE and The Cochrane Library were searched to April 2010 for relevant studies in English; search terms were reported. Reference lists of identified review articles were checked to identify additional studies. Conference abstracts from five relevant organisations were searched from January 2008 to April 2010.

Study selection
Eligible studies were randomised controlled trials in patients with relapse-remitting multiple sclerosis. Patients received first-line treatment of interferon beta 1a 30mcg (6 MIU) intramuscular once weekly; interferon beta 1a 22mcg subcutaneously three times per week; interferon beta 1a 44mcg subcutaneously three times per week; interferon 1b 250mcg subcutaneously once every two days; glatiramer acetate 20mg subcutaneously once daily; or fingolimod 0.5mg oral once daily. Eligible trials were required to evaluate annualised relapse rate defined as the total number of relapses divided by the total person-time at risk of relapse.

The mean age of the included patients ranged from 30 to 39 years and the mean duration of multiple sclerosis ranged from 0.9 to 8.3 years. Where reported, 60% to 74.9% of patients in the trials were female. Disease severity was typically measured using the Expanded Disability Scale Score. Scores at baseline ranged from 1.96 to 3.20. Definitions of relapse varied across the trials and included appearance of a new neurological symptom or worsening of an old symptom that lasted a minimum of 24 hours to at least 48 hours.

Two reviewers performed the study selection; any disagreements between the reviewers were resolved by discussion with a third reviewer.

Assessment of study quality
Methodological quality was assessed using criteria recommended by the Centre for Reviews and Dissemination (CRD) in terms of randomisation, allocation concealment, use of appropriate blinding, similarity of treatment groups at baseline and use of intention-to-treat analyses.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data were extracted by one reviewer and checked by a second reviewer and used to calculate annualised relapse rates and 95% confidence intervals (CI) for each intervention in each study. Imputations were performed in some trials to calculate relapse rates.

Methods of synthesis
The results were combined using a mixed treatment comparison framework to estimate the relative effects of treatment and corresponding 95% CIs with each of the first-line interventions. Relapse rates were annualised as Poisson outcomes using the total number of relapses observed within a treatment group out of the total person-time of follow-up for that treatment group. A mixed Poisson regression was fit for the outcomes and the Χ² statistic was used to assess the
goodness of fit of the model. The results from this model were compared with head-to-head comparisons for these active treatments. Covariate mixed treatment comparison analyses were performed for mean number of relapses in the previous two years, mean baseline Expanded Disability Scale Score, year of publication, disease duration, mean age, percentage of females and time point of analysis.

**Results of the review**

Fourteen trials (6,717 participants, range 50 to 1,345) were included in the review. Ten trials reported allocation concealment and 12 studies used intention-to-treat analyses. Most studies were reported to be appropriately blinded. Baseline characteristics for the treatment groups were described as similar across the studies.

Results of the mixed treatment comparison found that fingolimod administered at 0.5mg conferred significantly greater benefits than all comparators, with lower annualised relapse rates (ARR) compared to interferon beta 1a 30mcg (6 MIU) (ARR 1.67, 95% CI 1.32 to 2.10), interferon beta 1a 22mcg (ARR 1.55, 95% CI 1.26 to 1.90), interferon beta 1a 44mcg (ARR 1.93, 95% CI 1.59 to 2.34), interferon 1b 250mcg (ARR 1.51, 95% CI 1.22 to 1.860) and glatiramer acetate (ARR 2.32, 95% CI 1.95 to 2.77).

Covariate analyses showed significant effects of baseline Expanded Disability Scale Scores (ARR 1.63, 95% CI 1.04 to 2.56; 13 trials) and year of publication (ARR 0.96, 95% CI 0.94 to 0.98). Repeat mixed treatment analyses with adjustments for each covariate found no differences between actual relative treatment effects for the unadjusted models.

There were no significant differences in results from the mixed-treatment comparison model and those from head-to-head comparisons. Estimates provided by the reduced X² statistic indicated a reasonably good fit for both the adjusted and unadjusted models. Informal assessment of the model fit showed that the mixed-treatment comparison-derived relative rates closely matched to rates from head-to-head trials.

**Authors' conclusions**

Treatment with fingolimod was associated with significant reductions in relapse when used as first-line treatment in patients with relapse-remitting multiple sclerosis compared with beta interferon and glatiramer acetate.

**CRD commentary**

The review outlined a defined question and criteria for the inclusion of studies in the review were outlined. The search was comprehensive; various appropriate databases were searched for relevant studies and attempts were made to identify unpublished studies. The search was performed without language restrictions but articles in languages other than English were excluded from the review and this may have introduced language bias. Steps were taken to minimise errors and bias during study selection and data extraction but were not reported for the assessment of methodological quality. The reviewers assessed study quality using sensible criteria and the quality of the included trials was generally good.

The authors acknowledged limitations of the review due to variation of definitions of relapse across the trials and use of indirect comparisons to provide estimates of efficacy. The study was funded by Novartis Pharmaceuticals (manufacturer of fingolimod).

The authors' cautious conclusions reflected the evidence presented and are likely to be reliable.

**Implications of the review for practice and research**

The authors did not state any implications for practice and further research.

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**Bibliographic details**

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.