Network analysis of randomized controlled trials in multiple sclerosis

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CRD summary
This review found that natalizumab (300mg) and fingolimod (0.5mg) were better than placebo, and alemtuzumab may be better than interferon beta-1b (250μg) in the treatment of multiple sclerosis. The review was well conducted and the results may be reliable, but the reliance on indirect comparisons of treatments means that the results should be interpreted with some caution.

Authors' objectives
To investigate the relative effectiveness of treatments for multiple sclerosis.

Searching
PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to December 2010. Only articles in English were considered. Some search terms were reported. References of eligible articles were also searched.

Study selection
Randomised controlled trials (RCTs) that compared at least two pharmaceutical therapies in patients with relapsing multiple sclerosis were eligible. Only studies with sufficient data to calculate odds ratios for the outcomes of interest were included. Trials of treatment during acute relapse, trials that compared two different formulations of the same drug and follow-up or extension trials were excluded.

Outcomes of interest were: incidence of relapse, disease progression, progression identified by magnetic resonance imaging scans (MRI progression) and incidence of adverse events.

The trials included patients with relapsing-remitting multiple sclerosis, primary and secondary progressive multiple sclerosis, with relapsing and patients with combinations of these. The mean ages ranged from 22 to 52 years, 64% were female and most were Caucasian. The average disease activity at baseline according to the Expanded Disability Status Score varied from 1.2 to 6.2, mean relapse rate from 0.6 to 3.4 and number of MRI lesions from 0.36 to 9.6.

Two reviewers independently performed the selection.

Assessment of study quality
Quality was assessed by determining whether trials were double-blind, whether articles described withdrawals, described how randomisation was implemented and whether intention-to-treat analyses were performed.

Data extraction
Data were extracted sufficient to calculate odds ratios (OR) and their respective 95% confidence intervals (CI) for each of the outcomes of interest. Trials with more than two treatments had each pair-wise comparison treated as a separate study. Trials that presented results for different types of multiple sclerosis were also counted as separate studies for each multiple sclerosis type.

The data extraction was performed independently by two reviewers with discrepancies resolved by a third.

Methods of synthesis
Where at least two trials compared the same treatments, odds ratios for the comparison between treatments were pooled using a DerSimonian and Laird random-effects meta-analysis. Heterogeneity was assessed using the I² statistic. Where treatments were not compared directly in trials, an indirect treatment comparison was performed using network meta-analysis methods. Direct and indirect evidence was then combined.

Subgroup analyses were performed according to date of publication and use of intention-to-treat analyses.
Results of the review
There were 109 eligible RCTs, involving 26,828 patients and 145 different treatments. Of these 82 reported incidence of relapse, 48 disease progression, 29 MRI progression and 25 adverse events. Most trials were double-blind (at least 72%, depending on outcome), most described patient withdrawals (also at least 72%, depending on outcome), about half reported randomisation details and 49% used an intention-to-treat analysis.

Comparison with placebo
Eleven treatments were significantly better than placebo for patient relapse, levamisole was best (OR 6.00, 95% CI 1.54 to 23.40). Seven treatments reduced the incidence of disease progression, levamisole was best (OR 11.7, 95% CI 2.44 to 55.8). Seven treatments reduced the incidence of MRI progression, intravenous immunoglobulin (0.4g/kg) was best (OR 27.00, 95% CI 1.04 to 698.8). Only natalizumab (300mg) and fingolimod (0.5mg) were significantly better than placebo for all three outcomes. Six treatments increased adverse events, levamisole was worst (OR 80.6 95% CI 4.26 to 1523).

Comparison with interferon beta-1b (250μg)
Based on indirect analyses, sixteen treatments (or treatment combinations) were better than interferon beta-1b (250μg) for patient relapse, interferon beta-1a (44μg) with methylprednisolone (200mg/day) was best (OR 10.77 95% CI 6.38 to 19.4). Six treatments reduced the incidence of disease progression, levamisole was best (OR 5.05 95% CI 2.67 to 9.53). Only alemtuzumab (12 mg and 24mg) and levamisole were significantly better for both patient relapse and disease progression. No treatment was significantly better than interferon beta-1b for MRI progression.

Authors’ conclusions
Some treatments may have greater efficacy in the treatment of multiple sclerosis than either placebo or interferon beta-1b (250μg). The results should be interpreted with caution because of the use of indirect treatment comparisons.

CRD commentary
The review was generally well conducted. Appropriate searches were made, although articles not in English were excluded and it was unclear whether unpublished trials were sought. Action was taken to minimise reviewer error and bias. The quality of included trials was assessed and trials were generally of good quality. A large number of relevant trials were included. Suitable methods were used to synthesise the data, but as the authors noted, many of the results were based on indirect treatment comparisons which have the potential for bias, so some caution in interpreting the results was needed. In general the authors’ cautious conclusions are appropriate, and the results probably reliable.

Implications of the review for practice and research
Practice: The authors made no recommendations for practice.
Research: The authors suggested that large trials were needed that make head-to-head comparisons of treatments to identify the optimal treatment for multiple sclerosis.

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