A systematic review on the efficacy of interferon beta in relapsing remitting multiple sclerosis: comparison of different formulations

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CRD summary
This review concluded that subcutaneous interferon-beta-1a (Rebif) or subcutaneous interferon-beta-1b (Betaferon) worked better than intramuscular interferon-beta-1a (Avonex), whilst Betaferon was even better than Rebif in management of relapsing-remitting multiple sclerosis, although the results were not statistically significant. These conclusions should be interpreted with caution, given the limitations of the included studies.

Authors' objectives
To compare the efficacy of three different formulations of interferon-beta including intramuscular interferon-beta-1a (Avonex), subcutaneous interferon-beta-1a (Rebif) and subcutaneous interferon-beta-1b (Betaseron or Betaferon) for the treatment of patients with relapsing-remitting multiple sclerosis.

Searching
The following databases were searched for English language studies from 1966 to July 2009: PubMed, Scopus, Web of Science and Cochrane Central Register of Controlled Trials. Search terms were reported. The reference lists from retrieved publications were also screened. Conference proceedings were also considered for inclusion (details not reported).

Study selection
Controlled studies that compared three different formulations of interferon-beta, including intramuscular interferon-beta-1a (Avonex), subcutaneous interferon-beta-1a (Rebif) and subcutaneous interferon-beta-1b (Betaseron or Betaferon), in patients with multiple sclerosis were eligible for inclusion. Studies that compared any formulations of interferon-beta with only placebo were excluded.

The eligible outcomes were mean change in Expanded Disability Status Scale and number of patients with at least one relapse.

For included studies that compared Avonex with Rebif, the dosage regimen of Avonex was 30µg per week and the dosage regimen of Rebif ranged from 22 to 44µg three times per week. For included studies that compared Avonex with subcutaneous Betaseron, the dosage regimen of Avonex was 6MIU per week and the dosage regimen of Betaseron was 8MU on alternate days. For included studies that compared Rebif and Betaseron, the dosage regimen of Rebif ranged from 22 to 44µg once to three times per week and the dosage regimen of Betaseron was 250µg on alternate days. The duration of treatment in included studies ranged from 48 weeks to two years. All the included patients had relapsing-remitting multiple sclerosis. The patients' mean age in included studies ranged from 28 to 38 years; most included patients were females. The included studies were published from 2001 to 2007.

Three reviewers independently assessed studies for inclusion, with any disagreement resolved by consensus.

Assessment of study quality
The quality of studies was assessed using the Jadad scale, a 5-point scale evaluating randomisation, blinding and withdrawals. Studies scoring at least 5 were classified as high quality.

The authors did not report how many reviewers performed the validity assessment.

Data extraction
For dichotomous outcomes, event rates were extracted to enable the calculation of relative risks (RRs) with 95% confidence interval (CIs). For continuous outcomes, means and standard deviations were extracted to enable the
calculation of mean differences (MDs) and 95% confidence intervals.

Three reviewers independently performed the data extraction, with any disagreement resolved by consensus.

**Methods of synthesis**

The included studies were combined in meta-analyses. The pooled relative risks and 95% confidence intervals were calculated using the DerSimonian-Laird random-effects model. The authors reported that there were insufficient data to pool mean change in Expanded Disability Status Scale. Statistical heterogeneity was assessed using the Cochran Q test. The heterogeneity of effect estimates was explored using the L’Abbe plot. Publication bias was assessed using a funnel plot and Kendall’s test.

**Results of the review**

Six studies (four clinical controlled trials and two observational cohort studies) were included in the review (n=5,266 patients). The quality score of trials ranged from 0 to 4 points. Only one trial was classified as high quality.

There was a marginally significant reduction in the rate of patients with at least one relapse for subcutaneous interferon-beta-1a (Rebif) compared with subcutaneous interferon-beta-1b (Betaferon) (RR 0.90, 95% CI 0.82 to 1.00; three studies). No significant heterogeneity was observed in this outcome (p=0.32).

No significant differences in the rate of patients with at least one relapse were observed for intramuscular interferon-beta-1a (Avonex) compared with subcutaneous Rebif (RR 0.85, 95% CI 0.57 to 1.25; three studies; p<0.0001) and for Avonex compared with Betaferon (RR 0.91, 95% CI 0.75 to 1.10; four studies; p=0.03). Significant heterogeneity was observed for both outcomes.

There was some evidence of publication bias among studies that compared Avonex with Betaferon. It was not possible to assess publication bias for the remaining comparisons.

**Authors’ conclusions**

Although the results were not statistically significant, subcutaneous interferon-beta-1a (Rebif) or subcutaneous interferon-beta-1b (Betaferon) worked better than intramuscular interferon-beta-1a (Avonex), whilst Betaferon was even better than Rebif in management of relapsing-remitting multiple sclerosis.

**CRD commentary**

The inclusion criteria of the review were clear. Relevant databases were searched. Efforts were made to find both published and unpublished studies, minimising the potential for publication bias. Publication bias was assessed where possible, but use of a funnel plot to assess publication bias in the small number of included studies might not have been appropriate. Only English-language studies were sought, introducing the potential for language bias. Steps were taken to minimise reviewer biases and errors by having more than one reviewer undertake the study selection and data extraction, but it was unclear whether the process of validity assessment was performed in duplicate.

Relevant criteria were used to assess the quality of clinical controlled trials, but no formal validity assessment was performed for observational studies. Given the diversity of included studies, pooling the results from studies with different types of study design might not have been appropriate. The authors reported that there was insufficient data to pool mean change in Expanded Disability Status Scale; however, some data were presented in tables, but no narrative was provided.

Given the limited quality and small number of included studies, and high levels of statistical heterogeneity between studies for some outcomes, the authors’ conclusions should be interpreted with caution.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further clinical trials are required to gain more conclusive results for the evaluation of...
the efficacy and safety of interferon-beta in patients with relapsing-remitting multiple sclerosis.

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