A meta-analysis of the efficacy and tolerability of interferon-beta in multiple sclerosis, overall and by drug and disease type

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CRD summary
This review concluded that interferon-beta was associated with prevention of relapse compared with placebo across all types of multiple sclerosis, but effects appeared to vary with the type of interferon-beta and with the subtype of multiple sclerosis. Differences between trials and lack of significant effect in some multiple sclerosis subtypes mean the authors’ conclusions should be interpreted with caution.

Authors’ objectives
To determine the efficacy and tolerability of interferon-beta in the maintenance of remission of multiple sclerosis and to assess variations in efficacy by type of interferon-beta and subtype of multiple sclerosis.

Searching
PubMed, Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL) were search from 1966 to May 2010. Search terms were reported. Web of Science was searched for meeting abstracts. References of identified studies were checked. Only published English language studies in were eligible for inclusion.

Study selection
Trials with placebo control that assessed interferon-beta for the treatment of multiple sclerosis and reported on efficacy or tolerability were eligible for inclusion. Trials that reported only magnetic resonance imaging outcomes were excluded.

Outcomes assessed were mean change in the Expanded Disability Status Scale (EDSS) score, number of patients with at least one relapse, discontinuations due to adverse events, deaths, completed or attempted suicide attempts, and a range of individual adverse events.

Most patients in the included trials had secondary progressive multiple sclerosis (SPMS); most of the other patients had relapsing remitting multiple sclerosis (RRMS). The mean age of patients was 40.6 years and just under two thirds were women. Approximately half the patients were randomised to interferon-beta-1a or placebo and half to interferon-beta-1b. Baseline EDSS scores ranged from 2.3 to 5.5. Trial duration ranged from one to three years.

Three reviewers independently assessed the studies for inclusion in the review.

Assessment of study quality
The trials were assessed for validity using the Jadad scale, awarding up to 5 points for the criteria of randomisation, blinding and treatment of withdrawals and drop-outs. Trials that scored 3 or more points were considered to be high quality; those that scored 2 or fewer points were considered low quality.

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

Data extraction
Baseline and outcome data were extracted to permit the calculation of the mean change in EDSS score and number of patients with at least one relapse.

Three reviewers independently extracted the data, with disagreements resolved through consensus.

Methods of synthesis
Trials were combined using both fixed-effect and random-effects meta-analyses to calculate pooled relative risks (RRs)
and effect sizes with 95% confidence intervals (CIs); a Mantel-Haenszel fixed-effect model was adopted unless statistically significant heterogeneity was detected, in which case a DerSimonian and Laird random-effects model was used. Heterogeneity was assessed using Cochran's Q. A L’Abbe plot was used to calculate the relative event rates. Publication bias was assessed through funnel plot analysis.

Results of the review
Nine randomised controlled trials (RCTs) were included in the review (n=3,980 patients). Sample sizes ranged from 50 to 939. All the RCTs were double-blind and had Jadad scores of 3 or higher.

Number of multiple sclerosis patients with at least one relapse: The pooled relative risk showed a statistically significant benefit with interferon-beta treatment (RR 0.86, 95% CI 0.76 to 0.97; seven RCTs), but there was statistically significant heterogeneity (p = 0.006). In three RCTs using interferon-beta-1a, there was no benefit compared with placebo (but substantial heterogeneity). Three RCTs of interferon-beta-1b showed a statistically significant benefit with a fixed-effect model (RR 0.92, 95% CI 0.85 to 1.00; no significant heterogeneity), but not with a random-effects model. In patients with secondary progressive multiple sclerosis, there was no statistically significant benefit of treatment either overall or with interferon-beta-1b (three RCT; significant heterogeneity, p<0.001); this was also the case in patients with relapsing remitting multiple sclerosis (two RCTs; significant heterogeneity, p=0.004).

Mean change in Expanded Disability Status Scale (EDSS) score: There was no statistically significant benefit of treatment for either the 22μg or the 44μg dose of interferon-beta (two RCTs; significant heterogeneity, p<0.001).

Tolerability: There was a statistically significantly higher rate of discontinuations due to adverse events in the interferon-beta groups (RR 2.76, 95% CI 1.97 to 3.89) with no significant heterogeneity. There were no statistically significant differences between groups in deaths or completed or attempted suicides or depression (three RCTs). There were statistically significantly higher rates of flu like symptoms (six RCTs), injection-site reactions (five RCTs), injection-site inflammation (four RCTs), myalgia (five RCTs), leucopenia (three RCTs), lymphopenia (four RCTs) and increased alanine aminotransferase (three RCTs). The analyses did not show significant heterogeneity, except for injection site reactions and depression.

Authors’ conclusions
Interferon-beta was associated with prevention of relapse compared with placebo across all types of multiple sclerosis, but the efficacy appeared to vary with the type of interferon-beta used and with the subtype of multiple sclerosis.

CRD commentary
The review question was clear and the inclusion criteria were specific. Several relevant databases were searched, but the decision to limit the review to published studies reported in English may have led to the omission of some relevant studies and the potential introduction of selection biases. The authors reported using methods designed to reduce reviewer bias and error in the selection of studies and the extraction of data, but they did not report whether similar measures were applied to the assessment of validity.

The quality assessment of included trials was based on relevant criteria. Significant heterogeneity was found for several analyses, which suggested that the treatment effects were not consistent across trials. In two analyses (risk of at least one relapse with any type of interferon-beta and risk in patients with secondary progressive multiple sclerosis), trials showed different directions of treatment effect; pooling these trials may not have been appropriate, particularly given that potential reasons for heterogeneity among trials were not discussed.

The authors’ conclusions appeared to reflect the results of the review, but statistically significant benefits were not found for either of the subgroups of patients with secondary progressive multiple sclerosis and relapsing remitting multiple sclerosis; this means that 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 trials are required to clarify the efficacy and tolerability of various types of
interferon-beta in specific subtypes of multiple sclerosis.

**Funding**
Not stated.

**Bibliographic details**

**PubMedID**
21095482

**DOI**
10.1016/j.clinthera.2010.10.006

**Original Paper URL**
http://www.clinicaltherapeutics.com/article/S0149-2918(10)00345-0/abstract

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Female; Humans; Immunologic Factors /adverse effects /therapeutic use; Interferon beta-1a; Interferon beta-1b; Interferon-beta /adverse effects /therapeutic use; Male; Multiple Sclerosis /drug therapy /physiopathology; Multiple Sclerosis, Relapsing-Remitting /drug therapy /physiopathology; Randomized Controlled Trials as Topic; Remission Induction /methods

**AccessionNumber**
12010008208

**Date bibliographic record published**
13/04/2011

**Date abstract record published**
20/10/2011

**Record Status**
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.