Interferon therapy in relapsing-remitting multiple sclerosis: a systematic review and meta-analysis of the comparative trials

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CRD summary
The review concluded that treatment with high-dose beta-interferon in patients with relapsing-remitting multiple sclerosis was more beneficial for relapse control and MRI stability compared with low-dose treatment. These conclusions should be interpreted with caution, given lack of clarity of the review methodology, and the variable quality and small numbers of the included studies.

Authors' objectives
To compare the efficacy of different beta-interferon treatments in adults with relapsing remitting multiple sclerosis.

Searching
MEDLINE and the Cochrane Library were searched from 1966 to January 2009 for articles published in English. Search terms were reported. Bibliographies of included studies were handsearched.

Study selection
Head-to-head studies that compared the efficacy of at least two commercially available beta-interferon agents in patients (aged 18 or over) with a diagnosis of relapsing remitting multiple sclerosis were eligible for inclusion. Studies also had to report baseline patient profile data. Eligible outcome measures were magnetic resonance imaging (MRI), relapse rate and Extended Disability Status Scale (EDSS) scores.

The characteristics of included patients were not reported. In addition to the outcome measures, some included studies reported side effects.

The drug dosages used in the included studies were: low-dose beta-interferon-1a (30μg weekly); half of high-dose beta-interferon-1a (22μg three times weekly); high-dose beta-interferon-1a (44μg three times weekly); and high-dose beta-interferon-1b (250μg every other day). The low-dose beta-interferon-1a was given by intra-muscular injection; all the high-dose treatments were given by subcutaneous injection. Some studies also included a glatiramer acetate (non-interferon treatment) arm.

It was not clear whether study duration ranged from six to 24 months or from 12 months to five years. Only one study had over 100 patients in each treatment arm. The included studies were conducted in Western Europe, North America and Argentina (where reported) and were published between 2002 and 2008.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Studies were assessed using the US Preventive Services Taskforce (USPST) grading recommendations, based on the presence or absence of randomisation, study design, and study quality. Blinding, attrition and group assignment were also reported for some studies.

The authors did not state how the validity assessment was performed.

Data extraction
Event rates were extracted to calculate relative risks (RRs) and absolute risk differences (RDs) with 95% confidence interval (CIs).

EDSS stability was defined as the percentage of participants free from EDSS progression during the study period, with progression used as defined in each of the primary studies. MRI stability was defined as no new lesion activity at study
completion compared to baseline.

Three reviewers independently abstracted the data, with disagreements resolved by consensus.

Methods of synthesis
The included studies were combined in meta-analyses, using fixed-effect models. Statistical heterogeneity ($\chi^2$ and $I^2$) was reported under each forest plot.

A description of the change in mean EDSS scores in each study was included, but this was not subjected to meta-analysis. β

Results of the review
Seven studies (three randomised trials, three retrospective cohorts, and one prospective and retrospective observational study) were included in the review. The exact number of participants was not clear, but it appeared that 1,513 patients were treated with low- or high-dose beta-interferon-1a, or high-dose beta-interferon-1b. Limitations of the included studies identified in the review were lack of randomisation (four studies), disproportionate group assignment (two studies) and disproportionate attrition (two studies). All studies were reported as either not blinded or not double blinded.

Although the authors stated that all studies provided data in a suitable format for relative risk and risk difference pooling, the forest plots showed some studies were not estimable.

Relapse status: High-dose beta-interferon-1b (RR 0.75, 95% CI 0.60 to 0.93; RD -0.12, 95% CI -0.21 to -0.03; four studies; 450 patients) and high-dose beta-interferon-1a (RR 0.88, 95% CI 0.79 to 0.98; RD -0.07, 95% CI -0.13 to -0.01; four studies; 919 patients) were associated with a lower relapse rate than low-dose beta-interferon-1a. There was no evidence of heterogeneity for beta-interferon-1b studies, but there was strong evidence of heterogeneity between studies for beta-interferon-1a. When the two high-dose treatments were combined and compared with the low-dose treatment, similar patterns for the effect on relapse were found. The two studies (n=100 patients) that compared the two high-dose treatments (beta-interferon-1a versus beta-interferon-1b) found no difference in relapse rates between the two treatment arms.

Progression-free status - Extended Disability Status Scale (EDSS) stability (two studies; 344 patients): High-dose beta-interferon-1b was associated with a lower EDSS stability than low-dose beta-interferon-1a, which approached but did not meet statistical significance (RR 0.90, 95% CI 0.79 to 1.01; RD -0.08, 95% CI -0.17 to 0.01); there was heterogeneity between studies. There was no difference in EDSS stability between interferon-beta-1a at high or low dose, and no difference between combined high-dose treatments or low-dose beta-interferon-1a ($I^2=54%$ for RR analysis; $I^2=57%$ for RD analysis).

MRI stability (two studies; 865 patients): Total combined high-dose treatments were associated with a lower relapse rate than low-dose beta-interferon-1a (RR 0.61, 95% CI 0.53 to 0.71; RD -0.22, 95% CI -0.29 to -0.16). There was some evidence of heterogeneity between studies ($I^2=56%$ for RR analysis; $I^2=23%$ for RD analysis).

Some studies reported on adverse events. Patients treated high-dose beta-interferon had higher rates of injection-site reactions, white blood cell dyscrasias and liver function test elevations.

Authors' conclusions
Treatment of patients with relapsing remitting multiple sclerosis with high-dose beta-interferon was more beneficial for relapse control and MRI stability compared with low-dose treatment.

CRD commentary
The inclusion criteria of the review were clear. Two relevant databases and one other appropriate source were searched. Six articles written in languages other than English were eliminated, so language bias was possible. No attempt was made to search for unpublished data; publication bias was not assessed. Multiple reviewers performed the
data extraction, but it was unclear whether this applied to study selection and quality assessment, which meant that reviewer error and bias could not be ruled out.

The authors acknowledged some of the limitations of the included studies. The review included randomised and non-randomised studies, and no attempt to differentiate the results from different study designs was made. Insufficient information was provided to assess whether the statistical methods used were appropriate. The studies used different definitions for outcomes, such as EDSS progression. Statistical heterogeneity was reported under each forest plot; Despite heterogeneity being significant for many of the outcomes, random-effects models were not used. The authors did not appear to investigate the reasons for the heterogeneity.

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

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

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