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Interferon in relapsing-remitting multiple sclerosis (Review)

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[Intervention Review]

Interferon in relapsing-remitting multiple sclerosis

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A B S T R A C T

Background

Recombinant interferons have been shown to suppress both the clinical and magnetic resonance imaging (MRI) measures of disease activity in patients with relapsing remitting multiple sclerosis (RRMS).

Objectives

The objective of this review was to assess the effects of recombinant interferons in adults with RRMS.

Search methods

We searched the Cochrane Multiple Sclerosis Group trials register (April 2007), MEDLINE (January 1966 April 2007), EMBASE (January 1985 to April 2007) and reference lists of articles. We also contacted manufacturers and researchers in the field

Selection criteria

The trials selected were double-blind, placebo-controlled, randomised trials of RRMS patients who were treated with recombinant interferon, given by the subcutaneous or the intramuscular route.

Data collection and analysis

All reviewers independently assessed trial quality and extracted data. Study authors were contacted for additional information. Adverse effects information was collected from the trials.

Main results

Although eight trials involving 1301 participants were included in this review, only 919 (71%) contributed to the results concerning exacerbations and progression of the disease at two years. Specifically interferon significantly reduced the occurrence of exacerbations (Relative risk [RR] 0.80, 95% confidence interval [CI] 0.73 to 0.88, p < 0.001) and progression of the disease (RR 0.69, 95% CI 0.55 to 0.87, p = 0.002) two years after randomisation. However, the correct assignment of dropouts was essential to the demonstration of efficacy, most conspicuously concerning the effect of the drug on disease progression. If interferon-treated participants who dropped out were deemed to have progressed (worst case scenario) the significance of these effects was lost (RR 1.31, 95% CI 0.60 to 2.89, p = 0.5). The evolution in magnetic resonance imaging (MRI) technology in the decade in which these trials were performed and different reporting of data among

trials made it impossible to perform a quantitative analysis of the MRI results. Both clinical and laboratory side effects reported in the trials were more frequent in treated participants than in controls; there was no information after two years of follow-up. The impact of interferon treatment (and its side effects) on the quality of life of patients was not reported in any trial included in this review.

Authors' conclusions

The efficacy of interferon on exacerbations and disease progression in patients with relapsing remitting MS was modest after one and two years of treatment. Interferon administered by the oral route was not effective for prevention of relapses. Longer follow-up and more uniform reporting of clinical and MRI outcomes among these trials might have allowed for a more convincing conclusion.

P L A I N L A N G U A G E S U M M A R Y

The use of interferons for treating people with the relapsing-remitting form of multiple sclerosis

Multiple sclerosis (MS) is a chronic disease of the nervous system which affects young and middle-aged adults. Repeated damage to the myelin sheaths and other parts of the nerves can lead to serious disability. MS may be related to the immune system. Interferons have several effects on the immune system, and act against viruses. Interferons can help to reduce disability and attacks for people with multiple sclerosis, but there is not enough evidence about their usefulness in the long term. The review of trials found that interferons administered intramuscularly or subcutaneously can lead to a moderate reduction in recurrences and disability in people who have MS with remissions. Interferon-1a administered by the oral route was not effective for prevention of relapses. Side effects were usually influenza-like symptoms, injection site-reactions, pains in the joints and muscles, fatigue and headache.

BACKGROUND

Description of the condition

Multiple sclerosis (MS) is the commonest seriously disabling disease of young adults. Although the etiology is largely unknown, it is believed that MS develops in genetically predisposed individuals and that autoimmune mechanisms play a central role in its pathogenesis (Noseworthy 1999). Environmental factors are suspected to play a role, but the magnitude of their effect has not been clearly elucidated.

Description of the intervention

Interferons have been studied extensively in MS for more than 20 years, reflecting both the desperate need for an effective treatment for MS and the desire to expand the role for interferons, which had been found helpful only in some malignancies and viral hepatitis. It could be conceded that the development of interferon in recent years was largely fuelled by the success of the drug in a few early pilot trials (Jacobs 1981; Knobler 1984a).

How the intervention might work

Interferons have many actions of potential relevance to MS. Antiviral effects, pleiotropic effects on the immune system and blood brain barrier could all contribute to a benefit in patients with MS (Hohlfeld 1997). It is not known which of these mechanisms underlies the reported efficacy of interferons in the disease. Although tantalizing immunological effects of interferons in MS have been reported (induction of interleukin-6, 10), readers should be reminded that these observations are established only for certain populations of treated patients, compared to controls. No single biochemical marker has been linked to a clinical or magnetic resonance imaging (MRI) response in individual patients, although research in this area is promising (vanBoxel-Dezaire2000).

Why it is important to do this review

Recombinant interferons have been approved by the regulatory authorities of many countries for the treatment of relapsing remitting MS (RRMS) but many questions remain concerning their efficacy in preventing progression of the disease and increased disability in the long term, the optimum dose and duration of treatment and the consequences of discontinuation of the drug. No systematic reviews of this subject are known to exist.

OBJECTIVES

The efficacy and safety of recombinant interferons in the treatment of patients with relapsing remitting MS (RRMS) were evaluated. The primary questions were whether recombinant interferon was more effective than placebo in decreasing the number of patients who experience clinical relapses and disease progression.

The secondary objectives were:
(1) To examine the efficacy of recombinant interferon in reducing the need for corticosteroid treatment and hospitalisation of RRMS patients;
(2) To evaluate the incidence and seriousness of side effects and adverse events;
(3) To assess the effect of interferon on magnetic resonance imaging (MRI) which is a surrogate outcome.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised, double blind, placebo-controlled trials of recombinant interferons. Uncontrolled and non-randomised trials were excluded. We excluded trials which were confounded by other treatments such as immunosuppressive drugs. Trials which addressed the efficacy of interferons in progressive forms of MS will be reviewed at a later date.

Types of participants

The diagnosis of multiple sclerosis was accepted on the basis of established clinical and paraclinical evidence. The definition of Poser was most commonly applied (Poser 1983). Patients in a relapsing-remitting phase were included. This is defined as the phase of the disease characterised by one or more exacerbations followed by complete or partial recovery. Patients are clinically stable between exacerbations.

Types of interventions

We considered all trials in which alfa- or beta- recombinant interferons had been compared to placebo. Trials were not excluded on the basis of dose, duration of treatment, route of administration or length of follow up. For trials in which treatment effects were reported for more than one dose, we restricted the analysis to the higher dose (which is the dose most frequently used in clinical practice).

Types of outcome measures

Primary outcomes

The primary outcome measures included:

(1) the number of patients who continued to experience exacerbations during the scheduled treatment period and the follow-up period. Exacerbation was defined as newly developed or recently worsened symptoms of neurologic dysfunction that lasted more than 24 hours, with or without objective confirmation, and that stabilised or resolved either partially or completely;
(2) the number of patients who progressed during the first two years of treatment. The definition of progression was taken from the original articles. Most studies used the Expanded Disability Status Scale (EDSS) (Kurtzke 1983) and the definition of progression was a sustained (three or six months) increase in EDSS of at least one point recorded out of exacerbation. EDSS is the most widely used disability measure in clinical trials of MS. It is based on the results of a neurologic examination and the patient's ability to walk. Scores range from 0 (no neurologic abnormality) to 10 (death from MS) (Table 1);
(3) mean change in disability score (EDSS) in treatment groups at the end of the follow-up period;
(4) the number of patients who were unable to walk without aid (EDSS greater than 5.5) at the end of the follow-up period.

Secondary outcomes

The secondary outcome measures included:

(1) time to first exacerbation;
(2) time to progression in disability;

(3) the number of patients who underwent steroid administration during interferon treatment and follow-up;

(4) the number of patients who were hospitalised during treatment and follow-up;

(5) the number of patients experiencing side effects or adverse events;

(6) the effect of treatment on the magnetic resonance imaging which is considered a surrogate outcome. It included:

(a) the mean change of total lesion load on T2-weighted images during treatment and follow-up;

(b) the number of patients who continued to show gadolinium-enhancing lesions during treatment and follow-up. Gadolinium is a paramagnetic contrast agent for magnetic resonance that identifies deficiencies in the blood brain barrier.

Search methods for identification of studies

A systematic search without language resctrictions was conducted to identify all relevant publisched and unpublished randomised controlled trials. We identified 125 articles in MEDLINE, a further 23 in EMBASE, 46 by handsearching and 14 in the Cochrane Controlled Trials Register. We did not identify any unpublished trials.

Electronic searches

We searched the following databases:
1. Cochrane Multiple Sclerosis Group trials register (April 2007)
2. MEDLINE January 1966 to April 2007 (Appendix 1)
3. EMBASE January 1988 to April 2007 (Appendix 2)

Searching other resources

4.Handsearching of the references quoted in the identified trials, symposia reports (1990 to 2007) from the most important neurological associations and MS Societies in Europe and America;
5. contact with researchers who were participating in trials on interferons; and
6. contact with the following companies in order to identify unpublished trials or data missing from articles: Biogen (Avonex: interferon beta-1a), Ares Serono International SA (Rebif: interferon beta-1a), Schering AG (Betaseron or Betaferon: interferon beta-1b), Berlex Laboratories (Betaseron or Betaferon: interferon beta-1b), Roche (Roferon: interferon alfa- 2a).

Data collection and analysis

STUDY SELECTION
The reviewers independently scrutinised the trials and decided which trials met the inclusion criteria. We resolved all disagreement about including or excluding a trial by discussion among the reviewers.

QUALITY ASSESSMENT
The trials were judged on the reported method of allocation concealment as: adequate (A), unclear (B) or inadequate (C) as outlined in the "Cochrane Reviewers' Handbook " (Clarke 2000). The assessment also included the adequacy of blinding, the definition and clinical relevance of outcomes, the number of participants who withdrew or were withdrawn from the trial after randomisation and the number with incomplete follow-up. We also addressed whether an intention-to treat analysis was done or could be done. When this information was not reported, we submitted a formal request to the trial sponsors. When investigators did not respond, the item was considered unclear.

We extracted data concerning side effects or adverse events for each effect or event whenever possible. For trials in which they were reported for more than one dose, we reported the data pertaining to the higher dose.

DATA EXTRACTION
The reviewers extracted the data independently: characteristics of participants, interventions (type of interferon, type of placebo, dose, duration of treatment, length of follow-up), outcome measures, use of corticosteroids and need for hospitalisation during the scheduled treatment and follow up, side effects and adverse events. We also extracted the date and location of trial, sponsor of trial (specified, known or unknown) and publication status. Disagreement about quality assessment and data were resolved by discussion among the reviewers. All data were registered on a collection form.

DATA ANALYSIS
We sought data on the number of participants in the treatment groups and with each outcome, irrespective of compliance or completeness of follow-up, in the articles or requested from the authors in order to do an "intention-to-treat" analysis.

We analysed binary outcomes by calculating relative risks for each trial with the uncertainty in each trial being expressed using 95% confidence intervals (CI). We analysed continuous outcomes according to the difference between their means. For each outcome we calculated a weighted treatment effect across trials. We expressed results as a weighted estimate of relative risk with the relative 95% CI for binary outcomes, and difference between means across trials for continuous outcomes. We performed statistical analyses with the Review Manager software developed by the Cochrane Collaboration (4.1).

We considered the number of participants who need to be treated (NNT) to prevent one event for the following outcomes:

- participants who continued to experience exacerbations during the first year;
- participants who continued to experience exacerbations during the first two years;
- participants who progressed during the first two years.

The NNT has been calculated as the reciprocal of the absolute risk reduction (1/ARR). ARR is the risk difference between participants treated with interferon and controls. It is known that ARR is sensitive to factors that change the baseline risk such as the outcome considered, participants' characteristics and the clinical setting (Smeeth 1999). Since the baseline risk often varies appreciably between the trials, we calculated ARR according to different levels of baseline risk (BR), ranging from 0.1 to 0.9, as follows: ARR = BR- (RR x BR), where RR is the relative risk resulting from meta analysis.

Homogeneity among trial results was evaluated using a standard chi squared test and we rejected the hypothesis of homogeneity if the p value was less than 0.10. Trial outcomes were combined using a fixed effect approach (Yusuf 1985) unless there was a significant heterogeneity, in which case we summarised results using a random effects model (DerSimonian 1986c).

We did subgroup analyses because we hypothesised a priori that responses might differ according to: (1) type of interferon; (2) dose; (3) duration of treatment; and (4) length of follow-up.

We evaluated heterogeneity in the effect of treatment between studies by meta-regression in order to analyse associations between treatment effect and study characteristics. Meta-regression was done in STATA.

We conducted a sensitivity analysis to address the effect of withdrawn and lost to follow-up on the major outcomes. The best case scenario (with regards to treatment) assumed that none of the patients who were excluded from the analysis in the interferon-treated group had the outcome of interest, while all those excluded from the control group did and vice versa for the worst case scenario.

RESULTS

Description of studies

For the first version of this review 208 articles identified by the search strategy, eighteen articles were selected provisionally, on the basis of the inclusion criteria mentioned above.

We excluded eleven studies after reading the full published papers: two studies were open-label (Rudick 1998; Herndon 1999); in three studies participants were treated with natural interferon-alfa (IFN-alfa) (Knobler 1984; AUSTIMS 1989; Milanese 1990); in one study only immunological, not clinical, outcomes were reported (Hirsch 1986); one study was a dose-comparison trial of interferon beta-1a without a placebo group (Pozzilli 1997); one study was performed on progressive MS participants and included only two participants with relapsing-remitting MS (Rudge 1995); one study reported data only relating to the placebo group of a RCT on interferon beta-1a (IFNB-1a) (Simon 1999) and in one study (Jacobs 2000) participants were treated after a first exacerbation, prior to a definite diagnosis of MS. Finally, one study was excluded because neither blinding criteria nor clinical outcomes were clearly described (Schwartz 1997). (See table of excluded studies).

During the update of the review we first identified two studies that met the inclusion criteria. One of them (Granger 2003) was excluded because it is a secondary analysis of a study already included in this review (The MSCRG 1996) using FIM instrument instead of EDSS to assess disease progression.

Thus eight trials contributed to this review: the earliest was published in 1993 and the most recent in 2003 (Knobler 1993; IFNB MS Group 1993; Durelli 1994; The MSCRG 1996; The PRISMS 1998; Myhr 1999; The OWIMS 1999; Polman 2003). A total of 1301 experimental participants (in the higher dose arms which were compared with placebo treated participants), including 658 treated with interferon and 643 randomised to placebo, were included in this review. One multicenter study of subcutaneous IFNB-1a (The PRISMS 1998) accounted for 371 (30.5%) participants while a study of intramuscular IFNA-2a (Durelli 1994) accounted for only 20 (1.6%) participants. All studies included only relapsing-remitting MS participants. (See table of included studies).

THE AGENTS COMPARED WITH PLACEBO WERE:

- IFNA-2a: 9.0 MIU self-administered intramuscularly every other day for six months (Durelli 1994), 4.5 or 9.0 MIU administered by study physician subcutaneously three times weekly for six months (Myhr 1999). The dose of 9.0 MIU was used for comparison.
- IFNB-1a: 6.0 MIU administered once weekly by the intramuscular route for 104 weeks, by study nurses or local health professionals under the supervision of study personnel (The MSCRG 1996), 6.0 or 12.0 MIU self-administered subcutaneously once a week for 48 weeks (The OWIMS 1999), 6.0 or 12.0 MIU self-administered subcutaneously three times weekly for two years (The PRISMS 1998). In the last two studies the dose of 12.0 MIU was used for comparison with placebo. In one study (Polman 2003), 0.06, 0.6, or 6 MIU were administered every day by the oral route.
- IFNB-1b: 1.6 or 8.0 MIU self-administered subcutaneously every other day for two years (IFNB MS Group 1993); 0.8 or 4.0 or 8.0 or 16.0 MIU self-administered subcutaneously three times weekly for three years (Knobler 1993). The doses of 8.0 MIU and 16.0 MIU were used in the first and second study respectively.

EXCLUSION CRITERIA

Exclusion criteria were specified in seven trials (IFNB MS Group 1993; Durelli 1994; The MSCRG 1996; The PRISMS 1998; Myhr 1999; The OWIMS 1999; Polman 2003). The first trial (IFNB MS Group 1993) excluded participants who had been treated with ACTH or prednisone during the 30 days prior to entry or who had received any previous treatment with azathioprine or cyclophosphamide. The second trial (Durelli 1994) excluded participants who had other severe illnesses, participants who had been treated previously with interferon or cytostatic drugs or with ACTH or corticosteroids during three months before entry, and women who were pregnant. The MSCRG (The MSCRG 1996) excluded patients with prior therapy with immunosuppressants, interferon or ACTH/steroids within two months before study entry; patients with infection or other active disease; patients with progressive MS; those who were pregnant or breastfeeding and those unwilling to practice contraception during the study. The fourth study (The PRISMS 1998) excluded patients who had previously received interferon, lymphoid irradiation, cyclophosphamide or immunomodulatory or immunosuppressive drugs in the 12 months prior to the study. The fifth study (Myhr 1999) excluded patients who were pregnant or breastfeeding; those who were unwilling to practice contraception; those previously treated with interferon or immunosuppressants during the previous year or steroids in the month before randomisation; patients experiencing significant concomitant disease and those who were in the progressive phase of the disease. The OWIMS study (The OWIMS 1999) excluded patients who were pregnant or lactating, patients who were concomitantly ill with other conditions and those who had previously been treated with interferon, cyclophosphamide, lymphoid irradiation or any immunosuppressive or experimental therapy in the preceding twelve months. In the trial testing oral interferon (Polman 2003) patients were excluded if any previous parenteral IFN treatment had been terminated due to inefficacy. In only one study (Knobler 1993) exclusion criteria were not reported.

All trials applied diagnostic criteria for MS (Poser 1983).

Data on the time period of patient recruitment were missing in the Myhr study (Myhr 1999) and in the Polman study (Polman 2003). The scheduled follow-up periods were six months (Durelli 1994), 48 weeks (The OWIMS 1999), 12 months (Myhr 1999), two years (IFNB MS Group 1993; The MSCRG 1996; The PRISMS 1998) and three years (Knobler 1993).

OUTCOMES

A clinical outcome was the primary outcome measure in five studies: clinical relapse (IFNB MS Group 1993; Knobler 1993; Durelli

1994;The PRISMS 1998) or disability progression (The MSCRG 1996).

Magnetic resonance imaging was used as the primary outcome measure in two studies (The OWIMS 1999; Myhr 1999) in which clinical outcomes were reported as the secondary outcomes. In the Polman study (Polman 2003) primary outcome was the cumulative number of newly active lesions seen on brain MRI scans; secondary outcomes included volume of enhancing lesions on TI-weighted images each month, lesion volume on T2-weighted images at month 3 and 6 and safety measures.

CLINICAL OUTCOME
In five trials (Knobler 1993; Durelli 1994; The PRISMS 1998; Myhr 1999; The OWIMS 1999) data were available on the number of participants who continued to experience exacerbations during the first treatment year; and in three trials (IFNB MS Group 1993; The MSCRG 1996; The PRISMS 1998) exacerbations were reported over the two years following randomisation. Comparable definitions of relapse were used in the trials and included:

- acute or subacute objective deterioration of neurological status attributable to the disease, lasting at least 24 hours in the absence of fever and followed by complete or partial resolution (described by Poser 1983)(Durelli 1994);
- a new symptom or worsening of an old symptom accompanied by a new neurologic abnormality, lasting at least 24 hours in the absence of fever and preceded by stability or improvement for at least 30 days (described by Schumacher 1968) (IFNB MS Group 1993; Knobler 1993; The PRISMS 1998; Myhr 1999; The OWIMS 1999);
- a new symptom or worsening of an old symptom of at least 48 hours, which followed clinical stability or improvement of at least 30 days duration (described by Jacobs 1995) (The MSCRG 1996).

Definitions of disease progression were also similar:

- deterioration from baseline = 1.0 point or more on the Expanded Disability Status Scale (EDSS) persisting for at least six months (The MSCRG 1996);
- increase in EDSS of at least 1.0 point sustained over at least three months (IFNB MS Group 1993; The PRISMS 1998).

In two trials (IFNB MS Group 1993; The PRISMS 1998) the mean disability score (EDSS) was reported as a change of disability with respect to the baseline.

The number of patients who were unable to walk without aid (EDSS score greater than 5.5) at the end of the follow-up period was not reported in any trial.

Time from randomisation to first exacerbation was reported as the median time.

Two studies (Durelli 1994; Myhr 1999) reported the number of participants who underwent steroid treatment in the first year after randomisation and one study (The PRISMS 1998) reported participants with steroid treatment within two years of randomisation.

Hospitalisation within two years was included as an outcome in two studies (Durelli 1994; The PRISMS 1998).

SIDE EFFECTS AND ADVERSE EVENTS
Data concerning the numbers of participants with side effects or adverse events (attributed to interferon during the study according to the authors) were reported in six trials (IFNB MS Group 1993; Durelli 1994; The MSCRG 1996; The PRISMS 1998; Myhr 1999; The OWIMS 1999). One study (Knobler 1993) did not report data for each treatment group, but only gave cumulative numbers for groups that had received different doses of interferon. Finally, it was not possible in any of the trials to assess the length of time for the development of side effects or adverse events, either due to short follow-up periods or because of incomplete reporting.

MAGNETIC RESONANCE IMAGING (MRI)
Seven trials reported MRI data using a number of different assessments, measures and time of follow-up. One study (IFNB MS Group 1993) reported MRI data for only 60% of the randomised participants. In another study (The OWIMS 1999) the authors reported the results of MRI, but without the numbers of participants who underwent complete MRI evaluations.

Risk of bias in included studies

RANDOMISATION
Concealment of treatment allocation had been adequate in three trials (Durelli 1994; The PRISMS 1998; The OWIMS 1999) and unclear in the other five (Knobler 1993; IFNB MS Group 1993; The MSCRG 1996; Myhr 1999; Polman 2003).

BASELINE PARTICIPANTS' CHARACTERISTICS
All participants were clinically stable at study entry except in one study which did not report whether or not participants were in a stable phase (The PRISMS 1998). Equivalence between treated and control participants for age, disability score at entry and frequency of exacerbations in the pre-study period was confirmed in all studies except in one which did not report clinical characteristics for each arm (The MSCRG 1996). Disease duration was longer in treated than in control participants in three studies (IFNB MS Group 1993; The PRISMS 1998; Myhr 1999).

BLINDING
All trials were intended to be double-blind. However the well documented side effects of interferon injection, mainly injection-site reactions and influenza-like symptoms, make it likely that patients could become unblinded during trials. Analysis of blinding in two studies (IFNB MS Group 1993; The MSCRG 1996) identified a strong tendency for treated patients to become unblinded. Specifically, 80% of participants in the 8.0 MIU IFNB-1b arm, 51% in the 1.6 MIU IFNB-1b arm and 30% in the placebo arm had correctly guessed their treatment at the end of follow-up (IFNB MS Group 1993). Thus many, if not most, treated patients had become aware of the treatment they were receiving during the course of the trial, and these trials should be regarded as single-blind.

PARTICIPANTS LOST TO FOLLOW-UP
Overall, 246 (19%) participants were excluded after randomisation or were lost to follow-up (Table 2). In one study (The MSCRG 1996), 73 (46%) of the 158 randomised participants in the treatment group and 56 (39%) of the 143 in the control group did not complete the scheduled two years of follow-up because the study ended prematurely. In this study, the occurrence of acute exacerbations or disease progression were not reported at one year; at two years these primary outcomes were available for only 57% of the randomised participants. In one trial (IFNB MS Group 1993),

withdrawals and losses to follow-up were agglomerated into a single figure: 48 participants (19%).

Participant- or investigator- perceived worsening and side effects or adverse events were the most frequent causes of withdrawn or loss to follow-up in all trials.

INTENTION-TO-TREAT ANALYSIS

Although an intention-to-treat analysis was mentioned in seven trials (IFNB MS Group 1993; Durelli 1994; The MSCRG 1996; The PRISMS 1998; Myhr 1999; The OWIMS 1999; Polman 2003) in most cases patients who were withdrawn and lost to follow-up had been excluded from the analyses.

Effects of interventions

PRIMARY OUTCOMES

(1) THE NUMBER OF PARTICIPANTS WHO CONTINUED TO EXPERIENCE EXACERBATIONS DURING THE FIRST YEAR OF TREATMENT

This information was available from five trials (Knobler 1993; Durelli 1994; The PRISMS 1998; Myhr 1999; The OWIMS 1999) and 667 participants representing 51% of those included in this review. Eighty five per cent of these participants were from two trials (The PRISMS 1998; The OWIMS 1999). Overall, the risk of new exacerbations in participants receiving interferon was 50% and the risk of new exacerbations in participants not receiving interferon was 68%. There was significant heterogeneity among the trials (chi 2 = 8.54, df = 4, p = 0.07). Using a random effects model the pooled relative risk with interferon administration was 0.73, 95% CI 0.55 to 0.97, p = 0.03, and the pooled risk difference was -23%, 95% CI -8% to -39% which means that if 100 MS patients were treated with interferon, 23 (95% CI 8 to 39) would be free from exacerbations during the first year.

Univariate meta-regression analysis, performed by STATA, identified that the length of interferon administration (number of weeks up to one year) and dose (interferon MIU/week) explained the heterogeneity between the studies. We found no evidence that the type of interferon administered had any effect on the outcome. A subgroup analysis based on the five trials identified little benefit with interferon administered for six months (relative risk 0.82, 95% CI 0.66 to 1.02, p = 0.08) (Durelli 1994; Myhr 1999; The OWIMS 1999) than treatment for one year (relative risk 0.69, 95% CI 0.59 to 0.80, p < 0.001) (Knobler 1993; The PRISMS 1998). In four of the trials, the exception was (Durelli 1994), the participants were followed at least for one year. In four of the five studies, participants had MS for five to seven years at randomisation; in the other study (Durelli 1994) mean disease duration was nine years. All participants had a disability score (EDSS) at randomisation between 0 and 5.5.

The results of the Polman study (Polman 2003) did not indicate a benefit for oral interferon-1a: approximately two-thirds of patients in each group remained relapse free at 6 months follow-up.

(2) THE NUMBER OF PARTICIPANTS WHO CONTINUED TO EXPERIENCE EXACERBATIONS DURING THE FIRST TWO YEARS OF TREATMENT

Data from three trials (IFNB MS Group 1993; The MSCRG 1996; The PRISMS 1998) involving 919 participants (71% of participants included in this review) were available for this outcome measure. The pooled relative risk of exacerbations despite interferon administration was 0.80 (95% CI 0.73 to 0.88, p < 0.001), a decrement of 20% in the treatment group compared to the control group. There was no heterogeneity between the three trials (chi2 = 0.43, df = 2, p = 0.81). Overall, the risk of exacerbations during the first two years in participants receiving interferon was 55% and the risk in placebo-treated participants was 69%. The pooled risk difference was -14% (95% CI -8% to -19%) using a fixed effect model.

The reduction in exacerbations disappeared if interferon-treated participants who dropped out were assumed to have had exacerbations (worst case scenario). In this case, there was a significant heterogeneity between the trials (chi2 = 46.15, df = 2, p < 0.001). This was explained by the fact that in one study (The MSCRG 1996) 43% of the randomised participants did not contribute to the two year data. Using a random effects model the pooled relative risk of exacerbation for participants treated with interferon was 1.11, 95% CI 0.73 to 1.68, p = 0.6.

(3) THE NUMBER OF PARTICIPANTS WHOSE CONDITION PROGRESSED DURING THE FIRST TWO YEARS OF TREATMENT

Data from three trials (IFNB MS Group 1993; The MSCRG 1996; The PRISMS 1998) involving 919 (71%) participants were available for this outcome. Overall, MS progressed in 20% of the participants in the interferon arm and 29% in the placebo arm over two years. There was no heterogeneity between the three trials. This result underlined a benefit of interferon in reducing progression of the disease (relative risk 0.69, 95% CI 0.55 to 0.87, p = 0.002). It implies that for every 100 people treated, 9 (95% CI 3 to 14) would be expected to remain stable over two years. However, the assignment of dropouts (to progression or not) was essential to the demonstration of efficacy. If interferon-treated participants who dropped out were assumed to have progressed (worst case scenario) there was a significant heterogeneity between the trials (chi2 = 30.99, df = 2, p < 0.001) explained by the MSCRG study (The MSCRG 1996) and the treatment no longer produced a significant benefit (relative risk 1.31, 95% CI 0.60 to 2.89, p = 0.5).

(4) MEAN CHANGE IN DISABILITY SCORE (Expanded Disability Status Scale) AT TWO YEARS

This outcome was available from only two trials (IFNB MS Group 1993; The PRISMS 1998) involving 618 (51%) participants included in this review. The effect of the treatment on patient disability (as assessed by Expanded Disability Status Scale) was statistically significant (weighted mean difference = -0.25, 95% CI -0.05 to -0.46, p = 0.01). There was no significant heterogeneity between the two studies for this outcome. It should be emphasised that this result is of questionable clinical importance because it would be impossible to measure this very low degree of change on the Expanded Disability Status Scale in the clinical practice.

(5) THE NUMBER OF PARTICIPANTS WHO WERE UNABLE TO WALK WITHOUT AID (Expanded Disability Status Scale greater than 5.5) AT TWO YEARS

No data were available for this outcome.

SECONDARY OUTCOMES

(a) TIME FROM RANDOMISATION TO THE FIRST EXACERBATION

No data were available.

(b) TIME FROM RANDOMISATION TO PROGRESSION IN DISABILITY

No data were available.

(c) THE NUMBER OF PARTICIPANTS WHO UNDERWENT STEROID TREATMENT

This information was available during the first year from only two small trials (Durelli 1994; Myhr 1999) involving 85 (7%) participants included in this review. These two trials differed in duration of follow-up (six months in Durelli and 12 months in Myhr). It is not surprising to find that the results of these two trials were different from one another: the first study showing a reduction (not significant) in the use of steroids in participants receiving interferon and the second study not confirming this beneficial effect.

The frequency of steroid administration over the first two years from randomisation was available from only one study (The PRISMS 1998) and 371 (29%) participants included in this review. The result was significant (relative risk 0.70, 95% CI 0.56 to 0.87, p = 0.001).

(4) THE NUMBER OF PARTICIPANTS WHO WERE HOSPITALISED OVER TWO YEARS

This information was available from only two trials (Durelli 1994; The PRISMS 1998) involving 391 (30%) participants included in this review. Again there was heterogeneity between these two trials (chi2 = 3.48, df = 1, p 0.06). There was no significant reduction in the frequency of hospitalisation between participants treated with interferon and those treated with placebo (relative risk 0.44, 95% CI 0.08 to 2.36, p = 0.3). Data from another study (IFNB MS Group 1993) were available only after three years. Participation in the third year was optional in that study.

(5) THE NUMBER OF PARTICIPANTS WITH SIDE EFFECTS OR ADVERSE EVENTS ATTRIBUTED TO TREATMENT

The definitions of side effects or adverse events, as reported by the study authors, are listed in Table 3 .

(a) PARTICIPANTS WHO HAD CLINICAL SIDE EFFECTS OR ADVERSE EVENTS DURING TREATMENT

Not all results concerning side effects and adverse events were described, monitored and reported in a uniform manner. There were some deviations among studies in the timelines against which side effects were measured and in the definition of composite syndromes, such as "flu-like syndrome" or "flu-like symptoms". This likely accounts for the heterogeneity (chi2 = 12.37, df = 3, p = 0.006) in the observation of this syndrome, which was interpreted rather vaguely. Heterogeneity was not encountered when its component symptoms (fever, myalgia, fatigue and nausea) were considered individually.

A constellation of "flu-like symptoms" was reported by four studies (IFNB MS Group 1993; The MSCRG 1996; The PRISMS 1998; The OWIMS 1999) involving 1117 (86%) participants included in this review. These symptoms were experienced by 48% of participants receiving interferon and 28% of those receiving placebo: the relative risk was 1.70, 95% CI 1.23 to 2.37, p = 0.001) using a random effects model. All authors reported that flu-like symptoms diminished after three months of treatment. One author (Durelli 1994) reported that these symptoms were experienced by "several participants" receiving interferon, but usually disappeared the following morning after injection. Another author (Myhr 1999) did not give the frequency of this side effect but reported that

one participant in the higher dose interferon group discontinued treatment because of "flu-like" symptoms and an exacerbation.

Fever and myalgias or arthralgias were described as isolated symptoms in six of the studies (IFNB MS Group 1993; Durelli 1994; The MSCRG 1996; The PRISMS 1998; Myhr 1999; The OWIMS 1999) that included 1199 (92%) participants considered in this review. Fever occurred in 28% of participants receiving interferon and in 14% receiving placebo; myalgias or arthralgias in 26% of treated and 13% of placebo participants. The risks for fever (relative risk 2.01, 95% CI 1.60 to 2.52, p < 0.001) and myalgias or arthralgias (relative risk 1.92, 95% CI 1.52 to 2.43, p < 0.00001) were increased in the treated group.

Fatigue was reported in five of the studies (Durelli 1994; The MSCRG 1996; The PRISMS 1998; Myhr 1999; The OWIMS 1999), involving 952 (73%) participants included in this review. Fatigue occurred in 17% of participants treated with interferon and 12% treated with placebo. The risk for fatigue was 1.37 (95% CI 1.01 to 1.88, p = 0.05). In one study (IFNB MS Group 1993) fatigue was the cause for the withdrawal of three participants receiving interferon.

Information on the frequency of nausea and vomiting was available in two studies (The MSCRG 1996; Myhr 1999) involving 363 (28%) participants included in this review. Participants receiving interferon were at increased risk for this side effect compared to controls (relative risk 1.59, 95% CI 1.11 to 2.28, p = 0.01) using a fixed effect model.

Headache was reported as an isolated symptom in five studies (Durelli 1994; The MSCRG 1996; The PRISMS 1998; Myhr 1999; The OWIMS 1999) involving 952 (73%) participants. Headache was experienced by 50% of participants taking interferon and 42% taking placebo, and was the reason for one participant withdrawing from one study (IFNB MS Group 1993). The relative risk was 1.16, 95% CI 1.02 to 1.33, p = 0.02, using a fixed effect model.

Injection site reactions: in five studies, interferon was given by the subcutaneous route and in four of these (IFNB MS Group 1993; The PRISMS 1998; Myhr 1999; The OWIMS 1999) the proportion of participants with injection site reactions was reported: 62% in the participants receiving interferon and 14% in those receiving placebo. There was significant heterogeneity between these studies (chi2 = 17.75, df = 2, p < 0.0001). This is probably due to the different definitions of injection site reaction and the clinical ascertainment of cutaneous reactions to interferon injection. The relative risk of such reactions, estimated by random effects model, was greater in treated participants (5.57, 95% CI 2.33 to 13.29, p < 0.0001). The severity of skin reactions was not specified in any of the included trials. Only in two studies which reported them, were there comments on the presence or absence of skin necrosis at the site of injection. This occurred in "1 to 3% of participants" (IFNB MS Group 1993) or not at all (The OWIMS 1999). In two studies, interferon was given intramuscularly (The MSCRG 1996; Durelli 1994). In the first of these, skin reactions were reported in 10 to 15% of participants in both treated and control groups and in the second study in none of the participants. The possibility of inadvertent subcutaneous injection was not mentioned.

Hair loss was only described in two studies (Durelli 1994; Myhr 1999) and occurred in 36% of participants in the interferon group and 2% in the placebo group: an increased risk of 9.78, 95% CI 1.98 to

48.27, p = 0.005). In the Myhr study, this symptom affected 40% of interferon participants over the first six months of treatment.

Dysesthesias, paresthesias and weakness: in one study (Myhr 1999) one participant (1/32) in the control group experienced dysesthesias or paresthesias and six participants (4/30 in the interferon group and 2/32 in the placebo group) had weakness.

Depression was assessed and reported in six trials (IFNB MS Group 1993; Durelli 1994; The MSCRG 1996; The PRISMS 1998; Myhr 1999; The OWIMS 1999) and 1199 participants representing 92% of those included in this review. Depression was reported in 16% of participants and did not differ between the interferon and control groups. Suicide or attempted suicide was reported by three studies (IFNB MS Group 1993; The MSCRG 1996; The PRISMS 1998) and occurred in seven participants. These events did not differ between the interferon and placebo participants. Only two studies reported data on anorexia (Durelli 1994; Myhr 1999) which was present in three participants.

Muscle hypertonia was reported in one small study (Knobler 1993) and was present at the same frequency in treated and control groups.

Hypertension requiring drug treatment was not reported in any trials included in this review.

(b) PARTICIPANTS WHO HAD ABNORMAL VALUES DURING TREATMENT

Lowered hemoglobin levels values were reported in three studies (Durelli 1994; The MSCRG 1996; Myhr 1999) and 383 (29%) participants included in this review. This event occurred more frequently in participants receiving interferon than controls (3.5% versus 1%) but the increased risk was not statistically significant.

Leukopenia was reported in five studies (IFNB MS Group 1993; Durelli 1994; The MSCRG 1996; The PRISMS 1998; Myhr 1999) and 1004 (77%) participants. It was found in 6% of participants in the interferon group and 0.6% in the control group, with a significantly increased risk for treated participants (relative risk 6.47, 95% CI 2.43 to 17.20, p < 0.001).

Lymphopenia was reported in two studies (IFNB MS Group 1993; The PRISMS 1998) and 618 (48%) participants included in this review. It occurred in 27% of participants receiving interferon and 14% receiving placebo, a significantly increased risk for treated participants (relative risk 2.16, 95% CI 1.01 to 4.64, p = 0.05, using a random effects model.

Thrombocytopenia was described in three studies (Durelli 1994; The MSCRG 1996; Myhr 1999) and 383 (29%) participants. The risk for this side effect was greater in treated participants in only one of these studies (Myhr 1999). Myhr reported that the proportion of participants experiencing thrombocytopenia was 23% in the interferon group and 3% in the placebo group.

The values of two hepatic enzymes in blood were reported. Aspartate aminotransferase (AST) was reported in three studies (IFNB MS Group 1993; The MSCRG 1996; The PRISMS 1998) and 919 (71%) participants, and alanine aminotransferase (ALT) in four studies (IFNB MS Group 1993; The MSCRG 1996; The PRISMS 1998; Myhr 1999) and 981 (75%) participants. Increased AST and ALT occurred more frequently in participants who received interferon

(4% and 9%) than controls (1% and 3%). Participants treated with interferon had a higher risk both for increased AST (relative risk 2.83, 95% CI 1.14 to 7.06, p = 0.03) and ALT (relative risk 3.57, 95% CI 1.98 to 6.43, p < 0.0001, using a fixed effect model).

Neutralizing antibodies (NAB) against interferon developed in approximately 20% (83/421) of the treated participants in whom this parameter was assessed (IFNB MS Group 1993; Knobler 1993; The MSCRG 1996; The PRISMS 1998; The OWIMS 1999; Myhr 1999). The nature of the biological assays was different and the definitions of positive titres were variable between the studies. When assays were performed the timing and sample sizes were often not reported. Antibodies developed most commonly in the first treatment year. Neutralizing antibodies were only rarely reported in placebo-treated participants.

(6) MAGNETIC RESONANCE IMAGING (MRI)

There was a significant evolution in the application of MRI technology in the decade in which these trials were conducted and it was not possible to make comparisons across the trials from published data. Different measures of MRI were used and reported in the included trials, often on small samples of randomised participants and at different times of follow-up. For these reasons, we therefore present a qualitative summary of MRI findings (Table 4). In each trial, lesion activity was measured somewhat differently, commonly without reported measures of variance. An analysis of changes in T2 burden was possible only for the trials of interferon beta 1b (IFNB MS Group 1993) and the PRISMS (The PRISMS 1998).

Unpublished data (mean change in T2 burden, standard deviation) were provided by the sponsor of these two trials who reported a significant reduction in T2 burden aggregating both studies (weighted mean difference -24.67, 95% CI -33.84 to -15.50, p < 0.001). Numerical data on this aspect were not available for the MSCRG study, in which a significant effect on the change in T2 burden was not found at the end of the second year of the study (The MSCRG 1996).

Data on gadolinium enhancing lesions were available from two studies (The MSCRG 1996; Myhr 1999) after one year of treatment and from one study after two years of treatment on a small sample of randomised participants (The MSCRG 1996). A reduction in gadolinium enhancement was evident at one year but not at two years. In individual studies, treatment with recombinant interferon was associated with reductions in other MRI measures, such as the number of new T2 or enlarging lesions.

No significant differences in new active lesions were observed between the oral interferon-1a and control groups (Polman 2003).

NUMBERS NEEDED TO TREAT

The estimates of numbers needed to treat to prevent one patient having at least one exacerbation at 1 year in relation to the baseline risks are shown in Table 5. This figure shows, for example, that nine patients needed to be treated to prevent one patient having at least one exacerbation at 1 year when the risk of recurrence was 40% in the multiple sclerosis population.

DISCUSSION

The results support a modest protective effect of interferon against recurrence of exacerbations during the first two years of treatment

Treatment of patients with interferon was associated with a 20% reduction in the relative risk of having attacks. Sensitivity analysis indicates that this value is likely true, considering the intermediate between the "best" and the "worst" case scenario. Interferon administered by the oral route is not effective for prevention of relapses.

We chose the proportion of participants who continued to experience exacerbations as the principal outcome rather than the more commonly reported "annualised exacerbation rate". The principal reason for this was that these annualised rates were not reported with a measure of the variance of the observation. Also, the reporting of annualised exacerbation rates could overestimate the extent of a treatment effect. Unusually high rates of exacerbations in individuals who were treated with placebo could embellish the "annualised rate" for the group (The MSCRG 1996). Reporting the absolute numbers of participants who continued to experience exacerbations, despite treatment, is a more meaningful estimation of the shouldering of the treatment effect in a treated population.

The need for steroid treatment did not decrease for participants treated with interferon during the first or the second year after randomisation. In the interferon beta 1b trial, a claim was made that steroid treatments were reduced but the authors did not report the data. Disconcertingly, these data were missing in the other trials, given the strength of the claims that interferon suppressed clinical attacks.

Hospitalisation was not significantly reduced in two trials that reported on this aspect; however this could have been to some extent related to the major shift to outpatient management of exacerbations that occurred in the decade of these trials.

Interferon treatment was associated with a reduction in the number of participants whose MS condition progressed. This effect was identified in three trials (IFNB MS Group 1993; The MSCRG 1996; The PRISMS 1998). To calculate the effect, we tallied the number of participants who fulfilled the definition for progression at the end of two years. The effect was significant (relative risk 0.69, 95% CI 0.55 to 0.87, p = 0.002). However, this effect of interferon on the prevention of disease progression could clearly be influenced by inappropriate consideration of dropouts. If all dropouts in the treated group were assumed to have progressed, the significance of the effect disappeared (relative risk 1.31, 95% CI 0.60 to 2.89, p = 0.5). Only in the interferon beta 1b study was the disability status of dropouts mentioned in any detail: the participants who dropped out of that trial experienced higher exacerbation rates, a greater accumulation of disability, and more disease activity on the magnetic resonance imaging. There was a very modest support for an effect on disability by examination of the mean change in disability scores between randomisation and the end of the second year.

In this review, it was not possible to ascertain if the decreased number of participants whose condition progressed was independent from the effect of interferon on exacerbations. Two issues regarding this should be considered. First, is possible that interferon reducing the MS exacerbation could contribute to a perception that treatment prevented unremitting disability (Rice 1998). The probability of not progressing in disability over time was evaluated by survival analysis (Kaplan-Meier curves) in the trials which included this outcome (IFNB MS Group 1993; The

MSCRG 1996; The PRISMS 1998). Once participants worsen and have a subsequent confirmation of disease worsening (generally after three to six months, depending on the study) they do not contribute any further information to a survival analysis. Later improvement would suggest that patients were experiencing severe exacerbations with slow recovery, rather than unremitting disease progression. The extent to which this might have occurred in these trials is unknown. In the MSCRG study, 50% of interferon-treated patients who worsened in the first year of the study, actually improved in the second year (Rice 1998). The MSCRG study investigators made a substantial claim that interferon treatment prevented disability, when the reported effect might have been actually the effect on exacerbations. The error rates in application of "confirmed disability" definitions is substantial (Liu 2000). Another weakness of the disability claims should be identified. Most participants in these randomised trials had low disability scores at entry. The lower range of the disability scale (Expanded Disability Status Scale) is derived from a composite of the neurological examination and scoring in the lower echelons is fraught with high inter- and intra-rater variability (Goodkin 1992). Missing from all the trials was a sense of how often worsening was based on a subscale that is convincingly associated with disability, such as sustained worsening on a pyramidal or cerebellar subscale.

It was anticipated that the effect of interferon on exacerbations and disability in patients with relapsing remitting MS would produce a similar effect on these outcomes in the clinical trials of progressive MS patients. However, this does not appear to be the case. Large clinical trials of interferons in progressive MS have reported modest (European Group 1998; Cohen 2001) or no effect (Goodkin 2000; Hughes 2000) on disability outcomes. The failure of interferons to convincingly prevent disease progression in progressive MS, despite slight effects on exacerbations, has focused attention on the relevance of exacerbations to disease progression. It has been suggested that a high frequency of exacerbations in the early years of the illness is associated with a more severe disease course in the long term (Weinshenker 1989) whereas others have suggested that the disease progression is not influenced by superimposed attacks during the course of the disease (Confavreux 2000).

An influenza-like reaction was very common in treated patients, and injection site reactions were common in those who received interferon subcutaneously. Patients treated with interferon had leukopenia, lymphopenia, thrombocytopenia and increased plasma hepatic enzymes. Both clinical and laboratory side effects were more frequent in patients treated with interferon than in controls.

Depression and depressive symptoms did not appear to be a major problem in the first two years of treatment with interferon across the trials in which this information was available. This potential side effect may have been minimised by greater sensitivity concerning it subsequent to the reporting of the trial of interferon beta 1b (IFNB MS Group 1993).

The impact of these side effects and adverse events on the quality of life of the participants was not reported in any of the trials included in this review.

In order to assess the impact of interferon in clinical practice, the number of participants who need to be treated to prevent one unfavourable outcome (NNT) has also been determined. This measure is generally calculated as the reciprocal of absolute risk

differences. However, weighted absolute risk differences estimated from meta-analysis are applicable only to patients who are at the risk level corresponding to the average risk of the trial participants, and this may not be relevant to individual clinical situations (Smeeth 1999). Therefore we chose to show a full range of possible NNT according to different values of patient baseline risk for the principal outcomes.

Neutralizing antibodies against interferon developed in 83 of the 421 participants treated with interferon in whom this parameter was assessed. As there were differences between the studies with regard to the type of antibody assay, and definitions of antibody positive titers, it was impossible to perform a quantitative analysis on this aspect. Similarly, because of inconsistent reporting of an effect of these antibodies on clinical outcomes, it was not possible to evaluate a deleterious effect on the major outcomes. Since neutralizing antibodies tend to appear in the first year of treatment, an effect would not be expected until the second or third year of study. Most trials have not been adequately powered in the second and third year of study to show this effect.

AUTHORS' CONCLUSIONS

Implications for practice

We found a modest effect in patients with relapsing remitting MS, treated with interferon, in reducing exacerbations and disability. Information on the frequency and severity of side effects and adverse events was limited to a follow-up period of two years.

Implications for research

Due to inconsistent data reporting among these trials, it was impossible to conduct all of the intended analyses. More randomised clinical trials are needed to answer the following questions:

- Is there a convincing effect from interferon on disability in patients with MS?
- Does treatment with interferon improve the quality of life of the patient?
- How durable are the effects on clinical outcome?
- How long should patients be treated?
- What is the optimum dose and type of interferon?
- Are there long term side effects and adverse events?
- Are neutralising antibodies relevant to drug efficacy?

Given the substantial expense of these drugs, these are important questions of immense clinical relevance.

Finally, there is an urgent need to develop a general consensus regarding the quality of reporting of trial results in the MS literature.

REFERENCES

References to studies included in this review

Durelli 1994 *{published data only}*

Bongioanni MR, Durelli L, Ferrero B, Imperiale D, Oggero A, Verdun E, et al. Systemic high-dose recombinant-alpha-2a-interferon therapy modulates lymphokine production in multiple sclerosis. *Journal of the Neurological Sciences* 1996;**143**(1-2):91-9. [MEDLINE: 97135767; EMBASE-1996367643]

* Durelli L, Bongioanni MR, Cavallo R, Ferrero B, Ferri R, Ferrio MF, et al. Chronic systemic high-dose recombinant interferon alfa-2a reduces exacerbation rate, MRI signs of disease activity, and lymphocyte interferon gamma production in relapsing-remitting multiple sclerosis. *Neurology* 1994;**44**(3 Pt 1):406-13. [MEDLINE: 94195489; EMBASE-94096622]

Durelli L, Bongioanni MR, Ferrero B, Ferri R, Imperiale D, Bradac GB, et al. Interferon alpha-2a treatment of relapsing-remitting multiple sclerosis: disease activity resumes after stopping treatment. *Neurology* 1996;**47**(1):123-9. [MEDLINE: 96291029; EMBASE-1996221919]

Durelli L, Bongioanni MR, Ferri R, Cavallo R, Aimo G, Ferrero B, et al. Interferon (IFN)-Alpha 2a treatment of relapsing-remitting (R/R) multiple sclerosis (MS): disease activity resumes after stopping treatment [Abstract]. *Neurology* 1994;**44 Suppl (2)**:A358.

IFNB MS Group 1993 *{published data only}*

Arnason BGW. Interferon beta in multiple sclerosis [Editorial]. *Neurology* 1993;**43**(4 Pt 1):641-3. [EMBASE-1993121948]

Broderick JP, Samaha FJ. Interferon beta treatment of multiple sclerosis [Letter]. *Neurology* 1994;**44**(1):186. [MEDLINE: 94119382; EMBASE-1994036622]

Ebers GC, Lublin F, Paty D, Reder A. Treatment of multiple sclerosis with interferon beta-1b [Letter]. *Neurology* 1997;**49**:641-2.

Klapper JA. Interferon beta treatment of multiple sclerosis [Letter]. *Neurology* 1994;**44**(1):188. [MEDLINE: 94119389; EMBASE-1994036622]

Longstreth WT Jr, Franklin GM. Interferon beta treatment of multiple sclerosis [Letter]. *Neurology* 1994;**44**(1):187. [MEDLINE: 94119387; EMBASE-1994036622]

Metz L, Bell R, Zochodne D. Interferon beta treatment of multiple sclerosis [Letter]. *Neurology* 1994;**44**(1):187-8. [MEDLINE: 94119388; EMBASE-1994036622]

Pachner AR. Anticytokine antibodies in beta-interferon-treated patients [Letter]. *Neurology* 1998;**50**(6):1931-2. [MEDLINE: 98295536; EMBASE-1998205394]

Pachner AR. Interferon beta treatment of multiple sclerosis [Letter]. *Neurology* 1994;**44**(1):188. [MEDLINE: 94119390; EMBASE-1994036622]

Packner AR. Anticytokine antibodies in beta interferon-treated patients and the need for testing: plight of the practicing neurologist. *Neurology* 1997;**49**(3):647-50. [MEDLINE: 97450328]

Paty DW, Li DKB, the UBC MS/MRI Study Group, the IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI Study Group and the IFNB Multiple Sclerosis Study Group. *Neurology* 1993;**43**(4):662-7. [MEDLINE: 93226095; EMBASE-93121952]

Petkau J, White R. Neutralizing antibodies and the efficacy of interferon beta-1b in relapsing remitting multiple sclerosis. *Multiple Sclerosis* 1997;**3**(6):402. [MEDLINE: 98152637; EMBASE-1998027511]

Rice GPA, Paszner B, Oger J, Lesaux J, Paty D, Ebers G. The evolution of neutralizing antibodies in multiple sclerosis patients treated with interferon beta-1b. *Neurology* 1999;**52**:1277-9.

Sibley W, Paty D, Rice GPA, Masuoka LK. Anticytokine antibodies in beta-interferon-treated patients [Letter]. *Neurology* 1998;**50**(6):1930-2. [MEDLINE: 98295535; EMBASE-1998205394]

Sibley WA, Ebers G, Panitch HS, Reder AT. Interferon beta treatment of multiple sclerosis [Letter]. *Neurology* 1994;**44**(1):188-90. [MEDLINE: 94119393; EMBASE-1994036622]

* The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993;**43**(4):655-61. [MEDLINE: 93226094; EMBASE-93226094]

The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. *Neurology* 1995;**45**(7):1277-85. [MEDLINE: 95342398; EMBASE-95224550]

The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Neutralizing antibodies during treatment of multiple sclerosis with interferon beta-1b: experience during the first three years. *Neurology* 1996;**47**(4):889-94. [MEDLINE: 97010681; EMBASE-1996330779]

Knobler 1993 *{published data only}*

Knobler RL, Greenstein JI, Johnson KP, Lublin FD, Panitch HS, Conway K, et al. Systemic recombinant human interferon-beta treatment of relapsing-remitting multiple sclerosis: pilot study analysis and six-year follow-up. *Journal of Interferon Research* 1993;**13**(5):333-40. [MEDLINE: 94132656; EMBASE-94358097]

Myhr 1999 *{published data only}*

Myhr KM, Riise T, Green Lilleas FE, Beiske TG, Celius EG, Edland A, et al. Interferon-alpha2a reduces MRI disease activity in relapsing-remitting multiple sclerosis. Norwegian Study

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Group on Interferon-alpha in Multiple Sclerosis. *Neurology* 1999;**52**(5):1049-56. [MEDLINE: 99200550; EMBASE-1999124033]

Polman 2003 *{published data only}*

Polman C, Barkhof F, Kappos L, Pozzilli C, Sandbrink R, Dahlke F, et al. Oral interferon beta-Ia in relapsing-remitting multiple sclerosis: a double-blind randomized study. *Multiple Sclerosis* 2003;**9**:342-48.

The MSCRG 1996 *{published data only}*

Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, et al. A phase III trial of intramuscular recombinant interferon beta as treatment for exacerbating-remitting multiple sclerosis: design and conduct of study and baseline characteristics of patients. Multiple Sclerosis Collaborative Research Group (MSCRG). *Multiple Sclerosis* 1995;**1**(2):118-35. [MEDLINE: 98005322]

* Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Annals of Neurology* 1996;**39**(3):285-94. [MEDLINE: 96180905; EMBASE-1996105672]

Rudick RA, Fisher E, Lee JC, Simon J, Jacobs L, Munschauer III FE, et al. Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting MS. Multiple Sclerosis Collaborative Research Group. *Neurology* 1999;**53**(8):1698-704. [MEDLINE: 20025139; EMBASE-1999394535]

Rudick RA, Goodkin DE, Jacobs LD, Cookfair DL, Herndon RM, Richert JR, et al. Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Neurology* 1997;**49**(2):358-63. [MEDLINE: 97416612; EMBASE-97265436]

Simon JH, Jacobs LD, Campion M, Wende K, Simonian N, Cookfair DL, et al. Magnetic resonance studies of intramuscular interferon beta-1a for relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group. *Annals of Neurology* 1998;**43**(1):79-87. [MEDLINE: 98111247; EMBASE-1998090133]

Simon JH, Jacobs LD, Campion MK, Rudick RA, Cookfair DL, Herndon RM, et al. A longitudinal study of brain atrophy in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Neurology* 1999;**53**(1):139-48. [MEDLINE: 99335035; EMBASE-1999247274]

The OWIMS 1999 *{published data only}*

The Once Weekly Interferon for MS Study Group (OWIMS). Evidence of interferon beta-1a dose response in relapsing-remitting MS. The OWIMS Study. *Neurology* 1999;**53**(4):679-86. [MEDLINE: 99417151; EMBASE-1999332822]

The PRISMS 1998 *{published data only}*

Ebers GC. Interferon beta treatment for multiple sclerosis [Letter]. *Lancet* 1999;**353**(9151):497. [MEDLINE: 99142850; EMBASE-1999051720]

Li DKB, Paty DW, the UBC MS/MRI Analysis Research Group, the PRISMS Study Group. Magnetic resonance imaging results of the PRISMS trial: a randomized, double-blind, placebo-controlled study of interferon-beta1a in relapsing-remitting multiple sclerosis. Prevention of Relapses and Disability by Interferon-beta1a Subcutaneously in Multiple Sclerosis. *Annals of Neurology* 1999;**46**(2):197-206. [MEDLINE: 99371485; EMBASE-1999285158]

* The PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet* 1998;**352**(9139):1498-504. [MEDLINE: 99036183; EMBASE-1998379966]

References to studies excluded from this review

AUSTIMS 1989 *{published data only}*

The AUSTIMS Research Group. Interferon-alpha and transfer factor in the treatment of multiple sclerosis: a double-blind, placebo-controlled trial. AUSTIMS Research Group. *Journal of Neurology, Neurosurgery & Psychiatry* 1989;**52**(5):566-74. [MEDLINE: 89279360; EMBASE-1989151752]

Granger 2003 *{published data only}*

Granger CV, Wende K, Brownscheidler CM. Use of the FIM instrument in a trial of intramuscular interferon beta-Ia for disease progression in relapsing-remitting multiple sclerosis. *American Journal of Phisical Medicine & Rehabilitation* 2003;**82**(6):427-36.

Herndon 1999 *{published data only}*

Herndon RM, Jacobs LD, Coats ME, Goodkin DE, Mass MK, Richert JR, et al. Results of an ongoing, open-label, safety-extension study of interferon beta-1a (Avonex) treatment in multiple sclerosis. *International Journal of MS Care* 1999;**1**(2):1-6.

Hirsch 1986 *{published data only}*

Hirsch RL, Johnson KP. The effects of long-term administration of recombinant alfa-2 interferon on lymphpcyte substes, proliferation, and suppressor cell function in multiple sclerosis. *Journal of Interferon Research* 1986;**6**(2):171-7. [MEDLINE: 86252599]

Jacobs 2000 *{published data only}*

Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. *New England Journal of Medicine* 2000;**343**(13):898-904.

Knobler 1984 *{published data only}*

Knobler RL, Panitch HS, Braheny SL, Sipe JC, Rice GP, Huddlestone JR, et al. Clinical trial of natural alpha interferon in multiple sclerosis. *Annals of the New York Academy of Sciences* 1984;**436**:382-8.

Milanese 1990 *{published data only}*

Milanese C, Salmaggi A, La Mantia L, Campi A, Eoli M, Savoiardo M, et al. Double blind study of intrathecal beta-interferon in multiple sclerosis: clinical and laboratory

results. *Journal of Neurology, Neurosurgery & Psychiatry* 1990;**53**(7):554-7. [MEDLINE: 90362109; EMBASE-90245871]

Pozzilli 1997 *{published data only}*

Koudriavtseva T, Pozzilli C, Fiorelli M, Gasperini C, Bagnato F, Galgani S, et al. Determinants of Gd-enhanced MRI response to IFN-beta-1a treatment in relapsing-remitting multiple sclerosis. *Multiple Sclerosis* 1998;**4**(5):403-7. [MEDLINE: 99056678; EMBASE-1998381761]

Paolillo A, Bastianello S, Frontoni M, Gasperini C, Giugni E, Ciccarelli O, et al. Magnetic resonance imaging outcome of new enhancing lesions in relapsing-remitting multiple sclerosis patients treated with interferon beta-1a. *Journal of Neurology* 1999;**246**(6):443-8. [MEDLINE: 99358715; EMBASE-1999244760]

* Pozzilli C, Bastianello S, Koudriatseva T, Gasperini C, Mainero C, Giugni E, et al. An open randomised trial with two different doses of recombinant interferon beta-1a in relapsing-remitting multiple sclerosis: clinical and MRI results at 24 months [Abstract]. *Journal of Neurology* 1997;**244**:S25.

Pozzilli C, Bastianello S, Koudriavtseva T, Gasperini C, Bozzao A, Millefiorini E, et al. Magnetic resonance imaging changes with recombinant human interferon-beta-1a: a short term study in relapsing-remitting multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry* 1996;**61**(3):251-8. [MEDLINE: 96388194; EMBASE-1996271523]

Rudge 1995 *{published data only}*

Rudge P, Miller D, Crimlisk H, Thorpe J. Does interferon beta cause initial exacerbation of multiple sclerosis? [Letter]. *Lancet* 1995;**345**(8949):580. [MEDLINE: 95295442; EMBASE-1995077181]

Rudick 1998 *{published data only}*

Rudick RA, Simonian NA, Alam JA, Campion M, Scaramucci JO, Jones W, et al. Incidence and significance of neutralizing antibodies to interferon beta-1a in multiple sclerosis. Multiple Sclerosis Collaborative Research Group (MSCRG). *Neurology* 1998;**50**(5):1266-72. [MEDLINE: 98255412; EMBASE-1998175405]

Schwartz 1997 *{published data only}*

Schwartz CE, Coulthard-Morris L, Cole B, Vollmer T. The quality-of-life effects of interferon beta-1b in multiple sclerosis. An extended Q-TWIST analysis. *Archives of Neurology* 1997;**54**(12):1475-80. [MEDLINE: 98062884; EMBASE-1997379054]

Simon 1999 *{published data only}*

Simon JH, Jacobs LD, Campion MK, Rudick RA, Cookfair DL, Herndon RM, et al. A longitudinal study of brain atrophy in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Neurology* 1999;**53**(1):139-48. [MEDLINE: 99335035; EMBASE-1999247274]

References to studies awaiting assessment

Abdul-Ahad 1997 *{published data only}*

Abdul-Ahad AK, Galazka AR, Revel M, Biffoni M, Borden ED. Incidence of antibodies to interferon-beta in patients treated with recombinant human interferon-beta1a from mammalian

cells. *Cytokines Cellular & Molecular Therapy* 1997;**3**(1):27-32. [MEDLINE: 97432414; EMBASE-1997288646]

Camenga 1986 *{published data only}*

Camenga DL, Johnson KP, Alter M, Engelhardt CD, Fishman PS, Greenstein JI, et al. Systemic recombinant alfa-2 interferon therapy in relapsing multiple sclerosis. *Archives of Neurology* 1986;**43**(12):1239-46. [MEDLINE: 87048244]

Edwards 1998 *{published data only}*

Edwars S, Zvartau M, Clarke H, Irving W, Blumhardt LD. Clinical relapses and disease activity on magnetic resonance imaging associated with viral upper respiratory tract infections in multiple sclerosis. *Journal of Neurology Neurosurgery & Psychiatry* 1998;**64**(4):736-41. [MEDLINE: 98309516; EMBASE-1998198807]

Additional references

Barnes 1997

Barnes D, Hughes RA, Morris RW, Wade-Jones O, Brown P, Britton T, et al. Randomised trial of oral and intravenous methylprednisolone in acute relapses of multiple sclerosis. *Lancet* 1997;**349**(9056):902-6. [MEDLINE: 97247116; EMBASE-1997097394]

Clarke 2000

Clarke M, Oxman AD, editors. Cochrane Reviewers' Handbook [updated July 1999]; Section 6.3. In: The Cochrane Library [database on CDROM]. The Cochrane Collaboration. Oxford: Update Software; 2000.

Cohen 2001

Cohen JA, Cutter GR, Fischer JS, Goodman AD, Heidenreich FR, Jak AJ, et al. Use of the multiple sclerosis functional composite as an outcome measure in a phase 3 clinical trial. *Archives of Neurology* 2001;**58**(6):961-7. [MEDLINE: 11405811]

Confavreux 2000

Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and Progression of Disability in Multiple Sclerosis. *New England Journal of Medicine* 2000;**343**(20):1430-8.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**:177-88.

European Group 1998

European Study Group on Interferon beta-1b in Secondary Progressive MS. Placebo-controlled multicentre randomized trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. *Lancet* 1998;**52**:491-7.

Goodkin 1992

Goodkin DE, Cookfair D, Wende K, Bourdette D, Pullicino P, Scherokman B, et al. Inter- and intrarater scoring agreement using grades 1.0 to 3.5 of the Kurtzke Expanded Disability Status Scale (EDSS). Multiple Sclerosis Collaborative Research Group. *Neurology* 42;**4**:859-63. [MEDLINE: 92228182]

Goodkin 2000

Goodkin DE and the North American Study Group on Interferon beta-1b in Secondary Progressive MS. Interferon beta-1b in secondary progressive MS: clinical and MRI results of a 3-year randomized controlled trial [Abstract]. American Academy of Neurology 2000.

Hauser 1983

Hauser SL, Dawson DM, Lehrich JR, Beal MF, Kevy SV, Propper RD, et al. Intensive immunosuppression in progressive multiple sclerosis. A randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. *New England Journal of Medicine* 1983;**308**(4):173-80. [MEDLINE: 83088812]

Hohlfeld 1997

Hohlfeld R. Biotechnological agents for the immunotherapy of multiple sclerosis. Principles, problems and perspectives [Review]. *Brain* 1997;**120**(Pt 5):865-916. [MEDLINE: 97326435; EMBASE-1997157798]

Hughes 2000

Hughes RAC and the SPECTRIMS group. Relapsing versus nonrelapsing SPMS: different prognosis and response to interferon therapy in the SPECTRIMS study. *Neurology* 2000;**54 Suppl (3)**:A233.

Jacobs 1981

Jacobs L, O'Malley J, Freeman A, Ekes R. Intrathecal interferon reduces exacerbations of multiple sclerosis. *Science* 1981;**214**(4524):1026-8. [MEDLINE: 82061836]

Knobler 1984a

Knobler RL, Panitch HS, Braheny SL, Sipe JC, Rice GP, Huddlestone JR, et al. Systemic alpha-interferon therapy of multiple sclerosis. *Neurology* 1984;**34**(10):1273-9. [MEDLINE: 85013159]

Kurtzke 1961

Kurtzke JF. On the evaluation of disability in multiple sclerosis. *Neurology* 1961;**11**:686-94.

Kurtzke 1983

Kurtzke JF. Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;**33**(11):1444-52. [MEDLINE: 84040263]

Liu 2000

Liu C, Blumhardt LD. Disability outcome measures in therapeutic trials of relapsing-remitting multiple sclerosis: effects of heterogeneity of disease course in placebo cohorts. *Journal of Neurology, Neurosurgery & Psychiatry* 2000;**68**(4):450-7. [MEDLINE: 20193717; EMBASE-2000163002 EMBASE-2000163002]

Noseworthy 1999

Noseworthy JH. Progress in determining the causes and treatment of multiple sclerosis [Review]. *Nature* 1999;**399**(6738 Suppl):40-7. [MEDLINE: 99319750; EMBASE-1999223163]

Poser 1983

Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology* 1983;**13**(3):227-31. [MEDLINE: 83202737]

Rice 1998

Rice G, Ebers G. Interferons in the treatment of multiple sclerosis: do they prevent the progression of the disease?. *Archives of Neurology* 1998;**55**(12):1578-80. [MEDLINE: 99081403]

Schumacher 1968

Schumacher GA, Beebe G, Kilber RF, et al. Problems of experimental trials of therapy in MS: report of the panel on evaluation of experimental trials in MS. *Annals of the New York Academy of Sciences* 1968;**122**:552-68.

Smeeth 1999

Smeeth L, Haines A, Ebrahim S. Numbers needed to treat derived from meta-analyses- sometimes informative, usually misleading. *British Medical Journal* 1999;**318**:1548-51.

vanBoxel-Dezaire2000

van Boxel-Dezaire AH, van Trigt-Hoff SC, Killestein J, Schrijver HM, van Houwelingen JC, Polman CH, et al. Contrasting responses to interferon beta-1b treatment in relapsing-remitting multiple sclerosis: does baseline interleukin-12p35 messenger RNA predict the efficacy of treatment ?. *Annals of Neurology* 2000;**48**(3):313-22. [MEDLINE: 20431149; EMBASE-2000315459]

Weinshenker 1989

Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J, et al. The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. *Brain* 1989;**112 (Pt 6)**:1419-28. [MEDLINE: 90090007; EMBASE-1990024556]

Yusuf 1985

Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomised trials. *Progress in Cardiovascular Diseases* 1985;**27**(5):335-71. [MEDLINE: 85141015]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Durelli 1994

Methods	Randomised controlled trial. Centrally randomization performed at Roche S.p.A., Milan, Italy Intention to treat. Double-blind; however, the occurence of side effects, mainly injection site reactions, raises doubts about blindness of patients. Treatment period 6 months. Follow-up 6 months. Withdrawn criteria: not reported. Withdrawals 0. Lost to follow-up 0
Participants	20 patients: 9.0 MIU IFNA-2a 12, placebo 8. Italy 1 Centre. Sex: both. Age: 18-57 years. Included: clinical definite relapsing-remitting MS (Poser 1983) of duration > 3 years; at least 2 exacerbations in the 2 years before study entry, no exacerbations for 3 months before entry; EDSS = 6.0 or less; normal blood, liver, and renal function. Excluded: other severe illness; pregnancy; prior interferon or cytostatic drugs; corticotropin or corticosteroids in 3 months before entry. Baseline characteristics: 55% female mean age (range): IFNA-2a 33 years (18-46), placebo 38 years (29-57) mean EDSS (range): IFNA-2a 3.4 (1-6), placebo 2.8 (1.5-5) mean disease duration (range): IFNA-2a 8.9 years (3-19), placebo 6.4 years (3-10).
Interventions	Rx: 9.0 MIU IFNA-2a (Roferon) Placebo: human albumin and sodium chloride IFNB or placebo self-admin. i.m. every other day for 6 months. All patients received paracetamol 2 h. before and 2 and 8 h. after treatment. Co-intervention: intravenous methylprednisolone tapered over 15 days, followed by oral prednisone tapered over 15 days to treat exacerbations.
Outcomes	Primary outcomes: number of patients who continued to experience exacerbations and exacerbation rate during the first 6 months of treatment; exacerbation severity measured by the Neurological Rating Scale (NRS), median time to first exacerbation. Other clinical outcomes: mean (without standard deviation) Expanded Disability Status Scale (EDSS) and NRS at 6 months. Exacerbation defined as "acute or subacute objective deterioration of neurologic status attributable to MS, lasting at least 24 h. in absence of fever and followed by complete or partial resolution (Poser, 1983). Severity of exacerbation was defined as "change in the NRS (0 to 7 = mild; 8 to 14 = moderate; > 14 = severe)". Magnetic Resonance Imaging (MRI): number of patients who had active lesions at 6th month, mean number of active lesions per patient at 6th month, total number of enlarging lesions and new lesions at 6th month. Active lesion: defined. Side effects and adverse events: described (method of data collection not reported). Neutralizing antibodies: not mentioned.
Notes	Recruitment period not reported. Sponsored in part by Roche S.p.A., Milan, Italy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

IFNB MS Group 1993

Methods	Randomised controlled trial. Central randomisation. Intention to treat mentioned. Double-blind; however, the occurrence of side effects, mainly injection site reactions, raises doubt as to real blindness of patients. Treatment 2 years. Follow-up 2 years. After 2nd year all patients still in study given choice of continuing treatment, extending the treatment period to 5 years for some patients. Therefore after 2nd year the study was not blind. For this reason this review considers only 2 years of follow-up. Withdrawal: steady worsening of EDSS (> 1 point) for 6 months; > 3 courses of ACTH or steroid in 1-year period; non-compliance > 2 consecutive weeks; moderate or severe drug toxicity re-occurring on rechallenge. Withdrawals and losses at 2 years = 68 patients: 1.6 MIU IFNB-1b = 20 patients (5 adverse events, 3 worsening, 2 prohibited drugs, 2 non-compliance or losses to follow-up, 1 entry violation, 7 other reasons), 8.0 MIU IFNB-1b = 25 patients (10 adverse events, 9 worsening, 1 prohibited drugs, 2 non-compliance or losses to follow-up, 1 entry violation, 2 other reasons), placebo =23 patients (1adverse events, 5 worsening, 9 prohibited drugs, 2 non-compliance or losses to follow-up, 1 entry violation, 5 other reasons).
Participants	372 patients: 1.6 MIU IFNB-1b = 125, 8.0 MIU IFNB-1b = 124, placebo = 123. US and Canada 11 Centres. Sex: both. Age: 18-50 years. Included: clinically or laboratory-supported definite relapsing-remitting MS (Poser, 1983) of more than 1 year duration; at least 2 exacerbations in the 2 years before study entry; free of exacerbations for at least 1 month before entry; EDSS = 5.5 or less. Excluded: use of ACTH or prednisone in the month before entry; prior treatment with azathioprine or cyclophosphamide. Baseline characteristics: 70% female mean age: IFNB 1.6 MIU 35.3 years, IFNB 8 MIU 35.2 years, placebo 36.0 years mean EDSS: IFNB 1.6 MIU 2.9, IFNB 8 MIU 3.0, placebo 2.8 mean disease duration: IFNB 1.6 MIU 4.7 years, IFNB 8 MIU 4.7 years, placebo 3.9 years.
Interventions	Rx 1: 1.6 MIU IFNB-1b (Betaseron or Betaferon) Rx 2: 8.0 MIU IFNB-1b Placebo: human albumin and dextrose IFNB or placebo self-administered subcutaneously every other day for 2 years Co-intervention: ACTH or prednisone for exacerbation
Outcomes	Primary outcomes: annual exacerbation rate and proportion of exacerbation-free patients over the 2 years. Secondary clinical outcomes: number of patients who progressed at 2 years, median time to first exacerbation, exacerbation duration and severity, mean (and standard deviation) annual change in EDSS, median time to progression. Exacerbation defined as "a new symptom or worsening of old symptom accompanied by new neurologic abnormality, lasting at least 24 h. in absence of fever and preceded by stability or improvement for at least 30 days" (Schumacher, 1968). Severity of exacerbation defined as change in the NRS (0 to 7 = mild; 8 to 14 = moderate; > 14 = severe). Disease progression defined as "increase in EDSS of at least 1.0 point sustained over at least 3 months". MRI: annual mean and median % change in total lesion area from baseline. Proportion of active scans/patient and annual rate of active lesions/patient in a subgroup (14%) who had scans every 6 weeks. Active scan and new or enlarging lesion: defined. Adverse events: criteria for monitoring and recording were not specified.

IFNB MS Group 1993 *(Continued)*

Neutralizing antibodies: reported.

Notes	Recruitment period: June 1988-May 1990.
	Sponsored by Triton Biosciences, Inc., Alameda, CA and Berlex Laboratories Inc.
	Withdrawals and losses to follow-up: conflicting figures in the articles and letters reporting trial.
	Blindness: 80% patients in 8 MIU IFNB-1b arm, 51% in 1.6 MIU IFNB-1b arm and 30% placebo correctly guessed treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Knobler 1993

Methods	Randomised controlled trial, 30 initially randomised; one more patient randomised to substitute one withdrawn at 14th day.
	Allocation concealment: not reported.
	Intention to treat not mentioned.
	Double-blind; however, occurrence of side effects and crossing to different IFNB-1b dose after 6 months raise doubt as to true blindness of patients.
	After 24 weeks all patients initially randomised to IFNB-1b crossed to 8.0 MIU.
	Treatment 3 years.
	Follow-up 3 years
	After the 3rd year all patients still in the study given choice of continuing open label treatment, extending the treatment period to 6 years. Therefore after 3rd year the study was not randomised. Therefore this review considered 3 years of follow-up.
	Withdrawals: steady worsening of EDSS (> 1 point) for 6 months; > 3 courses of ACTH or steroid over 1-year; non-compliance > 2 consecutive weeks; persistence or recurrence of moderate or severe drug toxicity after rechallenge with half dose.
	Withdrawals = 6 patients: 0.8 MIU IFNB-1b = 1 prohibited treatment, 4.0 MIU IFNB-1b = 2 (1 prohibited treatment, 1 non-compliance), 8.0 MIU IFNB-1b = 1 prohibited treatment, 16.0 MIU IFNB-1b = 0, placebo = 1 prohibited treatment. Unknown treatment for 1 for accidental un-blinding.
	Losses to follow-up = 7 patients (all self-terminated):
	0.8 MIU IFNB-1b = 1
	4.0 MIU IFNB-1b = 1
	8.0 MIU IFNB-1b = 1
	16 MIU IFNB-1b = 2
	placebo = 2
Participants	31 patients: 6 patients to each IFNB-1b arm and 7 to placebo.
	US 3 Centres.
	Sex: both.
	Age: 18-50 years.
	Included: clinically definite relapsing-remitting MS (Poser, 1983) of at least 1 year duration and not more than 15 years; at least 2 exacerbations in the 2 years before study entry; in remission at entry.
	EDSS = 5.5 or less.
	Exclusion criteria: not reported.
	Baseline characteristics:
	48,4% female
	mean age: IFNB-1b 0.8 MIU 34.3 years; IFNB-1b 4.0 MIU 38.4 years; IFNB-1b 8.0 MIU 35.4 years; IFNB-1b 16.0 MIU 35.7 years; placebo 34.5 years
	mean EDSS: IFNB-1b 0.8 MIU 2.8; IFNB-1b 4.0 MIU 4.0; IFNB-1b 8.0 MIU 2.7; IFNB-1b 16.0 MIU 2.9; placebo 3.1
	mean disease duration: IFNB-1b 0.8 MIU 6.2 years; IFNB-1b 4.0 MIU 8.2 years; IFNB-1b 8.0 MIU 4.2 years; IFNB-1b 16.0 MIU 7.3 years; placebo 7.0 years.

Knobler 1993 *(Continued)*

Interventions	Rx 1: 0.8 MIU IFNB-1b (Betaseron or Betaferon) Rx 2: 4.0 MIU IFNB-1b Rx 3: 8.0 MIU IFNB-1b Rx 4: 16.0 MIU IFNB-1b Placebo: human albumin. IFNB or placebo self-administered subcutaneously 3 times weekly for 3 years. Co-intervention: intravenous ACTH, methylprednisolone, or oral prednisone for exacerbations.
Outcomes	Primary outcomes: number of patients who contimued to experience exacerbations during the first 24 weeks, annual exacerbation rate, median time to first exacerbation and proportion of exacerbation-free patients at 3 years. Exacerbation was defined as "new symptom or worsening of an old symptom in absence of fever, associated with a new abnormality of at least 24 h. duration, which followed clinical stability or improvement of at least 30 days duration" (Schumacher, 1968). Adverse events: reported. Neutralizing antibodies: reported.
Notes	Recruitment period: June-October 1986. Sponsored by Triton Biosciences, Inc., Alameda, CA and Berlex Laboratories Inc. Poor description of results.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Myhr 1999

Methods	Randomised controlled trial. Allocation concealment: not reported. Intention to treat mentioned. Double-blind; however, occurrence of side effects, mainly injection site reactions, raises doubts as true blindness of patients. Treatment = 6 months. Follow-up = 12 months. Reason for withdrawal: worsening of EDSS; > 2 courses with corticosteroids; non-compliance > 3 consecutive doses or total of 15 doses during study; persistent moderate to severe side effects of IFNA-2a. Withdrawals = 6 patients: 4.5 MIU IFNA-2a = 3 (adverse effects), 9.0 MIU IFNA-2a = 3 (1 non-compliance; 2 adverse effects) and placebo = 0. Losses to follow-up = 4 patients: 4.5 IFNA-2a = 1 (exacerbation), 9.0 MIU IFNA-2a = 2 (exacerbation) and placebo = 1 (patient decision).
Participants	97 patients: 32 in each IFNA-2a arm and 33 in placebo. Norway 8 Centres. Sex: both. Age: 18-50 years. Included: clinically or laboratory-supported definite relapsing-remitting MS (Poser, 1983), at least two exacerbations during the 2 years before entry into the study, stable at inclusion; EDSS = 5.5 or less Exclusion: pregnant or lactating; unwilling to use contraception during study; therapy with IFN or immunosuppressants during the previous year, steroids during the month before inclusion; chronic progressive course of MS, liver or renal disease or other serious concomitant disease. Baseline characteristics: 71% female mean age (range): 4.5 MIU = 33.9 years (23-47), 9.0 MIU = 32.8 years (21-44), placebo = 36.7 years (25-48) mean EDSS (range): 4.5 MIU = 3.11 (1.0-5.0), 9.0 MIU = 2.69 (0.0-5.5), placebo = 2.73 (0.0-5.5)

Myhr 1999 *(Continued)*

mean disease duration (range): 4.5 MIU = 7.6 years (1-25), 9.0 MIU = 7.5 years (1-18), placebo = 5.5 years (1-19).

Interventions	Rx 1: 4.5 MIU IFNA-2a (Roferon) Rx 2: 9.0 MIU IFNA-2a Placebo: constituents not reported. IFNA or placebo administered by study physician subcutaneously 3 times weekly for 6 months. Co-intervention: methylprednisolone intravenous for 3 days followed by prednisolone tapered over 14 days for exacerbations.
Outcomes	Primary MRI outcomes: mean (without standard deviation) and median of new lesions per patient at 6 months and 1 year. Number of patients who had new active lesions. Mean and median of total number of lesions per patient. New lesion: not defined. Secondary clinical outcomes: annual exacerbation rate, exacerbation-free patients, mean (without standard deviation) and median change in EDSS, quality of life (SF-36 Health Survey and General Health Questionnaire 20). All outcomes were at 6 months and 1 year. Exacerbation was defined as "new symptom or worsening of an old symptom in absence of fever, asso-ciated with new abnormality of at least 24 h. duration, which followed clinical stability or improvement of at least 30 days duration" (Schumacher, 1968). Severity of exacerbation defined as change in the NRS (0 to 7 = mild; 8 to 14 = moderate; >14 = severe). Adverse events: criteria for monitoring and recording were reported (WHO criteria for reporting results of cancer treatment). Neutralizing antibodies: reported.
Notes	When recruited: not specified. Sponsored by Roche Norge and Nycomed Imaging, Oslo, Norway.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Polman 2003

Methods	Randomised, double-blind controlled trial. Allocation concealment: not reported. Intention to treat mentioned. Treatment = 6 months. Fllow up: not specified. Treatment prematurely discontinued: 0.06 MIU =2 (adverse events); 6 MIU =3 (1 withdrawal of consent, 1 adverse events, 1 other); placebo =3 (1 withdrawal of consent, 1 adverse events, 1 other)
Participants	173 pts: 44 to 0.06 and 6 IFNB-1a arm, 43 to 0.6 arm and 42 to placebo. 15 European centers. Sex: both. Age: 18-55 years. Included: clinically definite relapsing-remitting MS (Poser, 1983); at least 2 relapses within 24 months prior to entry in conjunction with 7 lesions on the screening T2 scan or at least 1 documented relapse within 24 month prior to study entry in conjunction with at least 1 gadolinium-enhancing lesion and at least another 3 T2 lesions on the screening MRI. EDSS = score of 1 - 5.5. Exclusion criteria: any previous parenteral IFN treatment stopped for inefficacy. Baseline characteristics: 72,8% female mean age: 0.06 MIU 34 years; 0.6 MIU 35.8 years; 6 MIU 36.8 years; placebo 35.4 years

Polman 2003 *(Continued)*

	years since onset of MS (median): 0.06 MIU 5 years; 0.6 MIU 5 years; 6 MIU 5 years; placebo 5.5 years
Interventions	Rx 1: 0.06 MIU IFNB-1a Rx 2: 0.6 MIU IFNB-1a Rx 2: 6 MIU IFNB-1a Placebo IFNB or placebo self-administered every day via oral route. Pts were instructed to ingest the drug in a fasting state 30 min before breakfast. They were to retain the solution in the mouth for 2 min before swallowing.
Outcomes	Primary: cumulative number of newly active lesions over 6 months as seen on monthly brain MRI scan. Newly active lesions display one of the following features: new gadolinium enhancement on T1-weighted images, new on T2-weighted images but non-enhancing on T1-weighted images, new enlargement on T2-weighted images but non-enhancing on T1-weighted images. Secondary: cumulative number of newly active lesions over 1, 2, 3, 4 and 5 months of treatment; cumulative number of newly active lesions on monthly scans over months 4 to 6; number of newly active lesions at each individual monthly time point; volume of gadolinium-enhancing lesions at each individual monthly time point; volume of hypertense lesions seen on T2-weighted scans after 3 and 6 months of treatment; scan activity at each monthly visit (ie. the proportion of active scans per pts); patients activity (ie. the proportion of pts with at least 1 post-baseline active scan).
Notes	When recruited: not specified. Sponsored by Schering AG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

The MSCRG 1996

Methods	Randomised controlled trial. Randomisation at statistical centre of Buffalo General Hospital, one of the participating centres (biased coin). Allocation concealment: schedule sent to each clinical centre, included patients were sequentially assigned the next ID number from the schedule. Intention to treat mentioned. Double-blind; however, occurrence of side effects, mainly injection site reactions, raises doubts as true blindness of patients. Treatment = 104 weeks. Follow-up = 2 years. Reasons for withdrawal : pregnancy, encephalopathy, increased levels of hepatic enzymes and creatinine, white blood count < 2300, platelet count < 80.000, heart failure, adverse events, non-compliance, protocol violation. Withdrawals = 23 patients: IFNB-1a = 14 (non-compliance), placebo = 9 (non-compliance). Losses to follow-up: 5 patients (reasons and treatment group not reported). 129 patients did not reach 2 years of follow-up because study ended prematurely.
Participants	301 patients: IFNB-1a = 158, placebo = 143. United States 4 Centres. Sex: both. Age: 18-55 years. Included: definite relapsing-remitting MS (Poser, 1983) of at least 1-year duration; at least 2 exacerbations in the 3 years before study entry (patients with disease duration less than 3 years must have had at least one exacerbation per years prior to entry); free of exacerbations for at least 2 months before entry; EDSS = 1-3.5.

The MSCRG 1996 *(Continued)*

Exclusion: prior therapy with immunosuppressants or interferon; ACTH or corticosteroids in 2 months before entry; concurrent infection or other serious disease; chronic progressive MS; pregnant or lactating; unwilling to use contraception during study.

Baseline characteristics:

73,5% female

mean age (range): IFNB-1a = 36.7 years (18-55), placebo = 36.9 years (16-54)

mean EDSS (range): IFNB-1a = 2.4 (1.0-3.5), placebo = 2.3 (1.0-3.5)

mean disease duration (range): IFNB-1a = 6.6 years (1.0-30.7), placebo = 6.4 years (1.0-31.0).

Interventions	Rx: 6.0 MIU IFNB-1a (Avonex) Placebo: human albumin. IFNB-1a or placebo intramuscular given weekly for 104 weeks by study nurses or local health professionals under supervision of study personnel. Co-intervention: intramuscular ACTH or intravenous methylprednisolone followed by tapered oral prednisone for exacerbations.
Outcomes	Primary outcome: mean time to disability progression (EDSS-measured). Other clinical outcomes: median time to first exacerbation, proportion of exacerbation-free patients at 2 years, number of relapses per patient at 1 and 2 years, annual exacerbation rate, mean (without standard deviation) change in EDSS. Sustained worsening in disability defined as "deterioration from baseline 1.0 points on EDSS persisting at least 6 months". Exacerbation defined as "new symptom or worsening of an old symptom of at least 48 h., which followed clinical stability or improvement of at least 30 days duration" (Jacobs, 1995). MRI: number of patients who had active lesions at 1st and 2nd years. Mean (standard error) number and volume of active lesions per patient. Median % change of total lesion volume from baseline. New lesion: defined. Other clinical outcomes: time to first worsening in visual function and time to beginning of sustained visual function progression (EDSS-measured); time to beginning of sustained progression of disability in upper and lower extremity function (EDSS-measured). Other measures: neuropsychological (MSCRG battery), emotional status (defined), functional assessment (defined), quality of life (Sickness Impact Profile). Adverse events: criteria for monitoring and recording clearly described (according to Food and Drug Administration, HHS 21 CFR, Chapters 1,312.32, part c, 4/1/90). Neutralizing antibodies: reported.
Notes	Recruitment period: November 1990 - early 1993 Supported by National Institutes of Health, National Institute of Neurological Disorders and Stroke (NINDS) and Biogen, Inc, Cambridge, MA Withdrawals and losses to follow-up: poorly described.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

The OWIMS 1999

Methods	Randomised controlled trial. Randomisation performed at Corporate Biometrics Department of Ares-Serono (computer-generated list). Allocation concealment : code sent to each centre in sealed envelopes. Intention to treat mentioned. Double-blind; however, occurence of side effects, mainly injection site reactions, raises doubts as true blindness of patients. Treatment = 24 weeks.

Interferon in relapsing-remitting multiple sclerosis (Review)

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The PRISMS 1998 *(Continued)*

	Intention to treat mentioned. Double-blind; however, occurence of side effects, mainly injection site reactions, raises doubts as to true blindness of patients. Treatment period = 2 years. Follow-up = 2 years. Reason for withdrawal: WHO grade IV toxic effects; protocol violations; non-compliance. Withdrawals = 32 patients: 6.0 MIU = 12 (1 worsening, 1 death, 6 adverse events, 2 unknown, 2 pregnant), 12.0 MIU = 13 (9 adverse events, 3 pregnant, 1 protocol violation), placebo = 7 (3 worsening, 2 adverse events, 1 death, 1 pregnant). Losses to follow-up = 26 patients: 6.0 MIU = 10; 12.0 MIU = 6; placebo = 10.
Participants	560 patients: 6.0 MIU = 189, 12.0 MIU = 184, placebo = 187. Canada, Germany, Netherlands, Australia, Sweden, Finland, Belgium, United Kingdom and Switzerland 22 Centres. Sex: both. Included: clinically or laboratory-supported definite relapsing-remitting MS (Poser, 1983) of at least 1 year duration; at least 2 exacerbations in the 2 years before entry; EDSS = 0-5.0. Exclusion: prior interferon, lymphoid irradiation, cyclophosphamide, immunomodulatory or immunosuppressive treatment in the preceding 12 months. Baseline characteristics: 69% female median age: IFNB-1a 6 MIU = 34.8 years, IFNB-1a 12 MIU = 35.6, placebo 34.6 mean EDSS: IFNB-1a 6 MIU = 2.5, IFNB-1a 12 MIU = 2.5, placebo = 2.4 median disease duration: IFNB-1a 6 MIU = 5.4 years, IFNB-1a 12 MIU = 6.4 years , placebo = 4.3 years.
Interventions	Rx 1: 6.0 MIU IFNB-1a (Rebif) Rx 2: 12.0 MIU IFNB-1a Placebo: constituents not reported. IFNB or placebo administered subcutaneously 3 times weekly for two years, by treating study physician. Co-intervention: paracetamol for influenza-like side effects and intravenous methylprednisolone for 3 consecutive days for exacerbations.
Outcomes	Primary outcomes: number of exacerbations/patient, exacerbation severity (NRS or the activities of daily living scale-measured). Other outcomes: number of patients who progressed at 2 years, median times to first and second exacerbation, proportion of exacerbation-free patients, first quartile time to progression, mean (and standard deviation) change of EDSS from baseline. Exacerbation defined according to Schumacher (1968). Progression in disability defined as "increase in EDSS of at least 1.0 point sustained over at least 3 months, ambulation index (Hauser 1983), arm-function index (Barnes 1997), need for steroid therapy and hospital admission". Severity of exacerbations defined as "change in NRS (0 to 7 = mild; 8 to 14 = moderate; > 14 = severe) or the activities of daily living scale (mild: no effect; moderate: significant effect; severe: hospital admission)". MRI: annual change of total lesion area. Total lesion area: not defined. Adverse events: reported. Neutralizing antibodies: reported.
Notes	Recruited: May 1994-February 1995 Supported by: Ares-Serono International SA, Geneva, Switzerland.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

EDSS: Expanded Disability Status Scale
IFNA-2a: interferon alfa-2a
IFNB-1a: interferon beta- 1a
IFNB-1b: interferon beta- 1b
Interferon beta- 1b (Betaseron, Betaferon) [Drug company: Berlex Laboratories in North America, Schering AG in Europe and other countries of the world]
Interferon beta- 1a (Avonex) [Drug company: Biogen, Inc.]
Interferon beta- 1a (Rebif) [Drug company: Ares Serono International SA]
Interferon alfa- 2a (Roferon) [Drug company: F. Hoffmann-La Roche Ltd.]
MIU: million international units
MRI: magnetic resonance imaging
Rx: treatment

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
AUSTIMS 1989	The patients were treated with natural interferon-alfa
Granger 2003	Secondary analysis of the MSCRG 1996
Herndon 1999	Open-label study (safety extension study)
Hirsch 1986	Immunological outcomes only
Jacobs 2000	Patients were included during a first exacerbation, prior to a definite diagnosis of multiple sclerosis
Knobler 1984	The patients were treated with natural interferon-alfa
Milanese 1990	The patients were treated with natural interferon-alfa
Pozzilli 1997	A dose comparison study of interferon beta-1a without a placebo group
Rudge 1995	This study included progressive patients and only 2 patients with relapsing-remitting multiple sclerosis
Rudick 1998	Open-label study (safety extension study)
Schwartz 1997	Neither blinding criteria nor clinical outcomes were described
Simon 1999	The authors reported data only relating to the placebo group of a study on interferon beta-1a

DATA AND ANALYSES

Comparison 1. interferon versus placebo: primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients with at least one exacerbation until 1 yr	5	667	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.55, 0.97]

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
2 Patients with at least one exacerbation until 1 year: subgroup analysis	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 duration of treatment: 6 months	3	283	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.33, 1.29]
2.2 duration of treatment: 12 months	2	384	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.14, 1.92]
3 Patients with at least one exacerbation at 2 yrs	3	919	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.73, 0.88]
4 Patients with at least one exacerbation at 2 yrs (best scenario)	3	919	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.44, 0.87]
5 Patients with at least one exacerbation at 2 yrs (worst scenario)	3	919	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.73, 1.68]
6 Patients who progressed at 2 yrs	3	919	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.55, 0.87]
7 Patients who progressed at 2 yrs (best scenario)	3	919	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.35, 0.53]
8 Patients who progressed at 2 yrs (worst scenario)	3	919	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.60, 2.89]
9 Mean change in disability (EDSS) at 2 yrs	2	618	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.46, -0.05]

Analysis 1.1. Comparison 1 interferon versus placebo: primary outcomes, Outcome 1 Patients with at least one exacerbation until 1 yr.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
The OWIMS 1999	57/98	64/100		40.17%	0.91[0.73,1.14]
Durelli 1994	2/12	6/8		4.19%	0.22[0.06,0.84]
Myhr 1999	6/32	9/33		8.16%	0.69[0.28,1.71]
The PRISMS 1998	101/184	146/187		46.44%	0.7[0.6,0.82]
Knobler 1993	0/6	4/7		1.04%	0.13[0.01,1.97]
Total (95% CI)	**332**	**335**		**100%**	**0.73[0.55,0.97]**

Total events: 166 (Treatment), 229 (Control)

Heterogeneity: Tau²=0.04; Chi²=8.54, df=4(P=0.07); I²=53.18%

Test for overall effect: Z=2.2(P=0.03)

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

Analysis 1.2. Comparison 1 interferon versus placebo: primary outcomes, Outcome 2 Patients with at least one exacerbation until 1 year: subgroup analysis.

Study or subgroup	Case n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 duration of treatment: 6 months					
Durelli 1994	2/12	6/8		7.97%	0.22[0.06,0.84]
Myhr 1999	6/32	9/33		15.54%	0.69[0.28,1.71]
The OWIMS 1999	57/98	64/100		76.48%	0.91[0.73,1.14]
Subtotal (95% CI)	**142**	**141**		**100%**	**0.65[0.33,1.29]**
Total events: 65 (Case), 79 (Control)					
Heterogeneity: Tau²=0.21; Chi²=4.66, df=2(P=0.1); I²=57.08%					
Test for overall effect: Z=1.23(P=0.22)					
1.2.2 duration of treatment: 12 months					
Knobler 1993	0/6	4/7		2.2%	0.13[0.01,1.97]
The PRISMS 1998	101/184	146/187		97.8%	0.7[0.6,0.82]
Subtotal (95% CI)	**190**	**194**		**100%**	**0.52[0.14,1.92]**
Total events: 101 (Case), 150 (Control)					
Heterogeneity: Tau²=0.54; Chi²=1.55, df=1(P=0.21); I²=35.46%					
Test for overall effect: Z=0.99(P=0.32)					

Favours treatment 0.2 0.5 1 2 5 Favours control

Analysis 1.3. Comparison 1 interferon versus placebo: primary outcomes, Outcome 3 Patients with at least one exacerbation at 2 yrs.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
IFNB MS Group 1993	79/124	94/123		29.74%	0.83[0.71,0.98]
The MSCRG 1996	53/158	64/143		21.18%	0.75[0.56,1]
The PRISMS 1998	125/184	157/187		49.08%	0.81[0.72,0.91]
Total (95% CI)	**466**	**453**		**100%**	**0.8[0.73,0.88]**
Total events: 257 (Treatment), 315 (Control)					
Heterogeneity: Tau²=0; Chi²=0.43, df=2(P=0.81); I²=0%					
Test for overall effect: Z=4.45(P<0.0001)					

Favours treatment 0.001 0.1 1 10 1000 Favours control
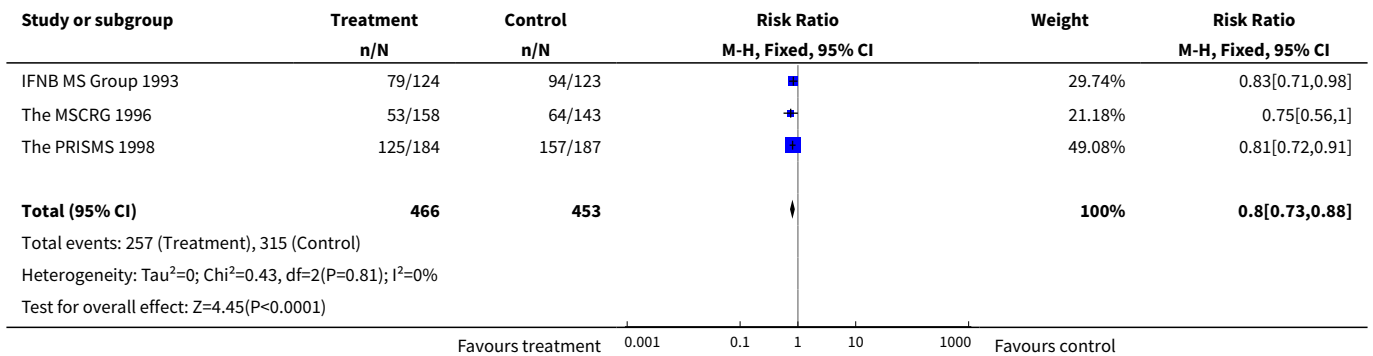
Analysis 1.4. Comparison 1 interferon versus placebo: primary outcomes, Outcome 4 Patients with at least one exacerbation at 2 yrs (best scenario).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
IFNB MS Group 1993	79/124	105/123		33.88%	0.75[0.64,0.87]
The MSCRG 1996	53/158	120/143		31.19%	0.4[0.32,0.5]
The PRISMS 1998	125/184	167/187		34.94%	0.76[0.68,0.85]
Total (95% CI)	**466**	**453**		**100%**	**0.62[0.44,0.87]**
Total events: 257 (Treatment), 392 (Control)					

Favours treatment 0.001 0.1 1 10 1000 Favours control

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Study or subgroup	Treatment	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Heterogeneity: Tau²=0.09; Chi²=28.89, df=2(P<0.0001); I²=93.08%					
Test for overall effect: Z=2.73(P=0.01)					

Favours treatment 0.001 0.1 1 10 1000 Favours control

Analysis 1.5. Comparison 1 interferon versus placebo: primary outcomes, Outcome 5 Patients with at least one exacerbation at 2 yrs (worst scenario).

Study or subgroup	Treatment	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
IFNB MS Group 1993	88/124	94/123		33.48%	0.93[0.8,1.08]
The MSCRG 1996	126/158	64/143		32.4%	1.78[1.46,2.17]
The PRISMS 1998	130/184	157/187		34.12%	0.84[0.75,0.94]
Total (95% CI)	466	453		100%	1.11[0.73,1.68]
Total events: 344 (Treatment), 315 (Control)					
Heterogeneity: Tau²=0.13; Chi²=46.15, df=2(P<0.0001); I²=95.67%					
Test for overall effect: Z=0.49(P=0.62)					

Favours treatment 0.001 0.1 1 10 1000 Favours control

Analysis 1.6. Comparison 1 interferon versus placebo: primary outcomes, Outcome 6 Patients who progressed at 2 yrs.

Study or subgroup	Treatment	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
IFNB MS Group 1993	25/124	34/123		25.86%	0.73[0.46,1.15]
The MSCRG 1996	18/158	29/143		23.06%	0.56[0.33,0.97]
The PRISMS 1998	49/184	68/187		51.09%	0.73[0.54,0.99]
Total (95% CI)	466	453		100%	0.69[0.55,0.87]
Total events: 92 (Treatment), 131 (Control)					
Heterogeneity: Tau²=0; Chi²=0.75, df=2(P=0.69); I²=0%					
Test for overall effect: Z=3.13(P=0)					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

Analysis 1.7. Comparison 1 interferon versus placebo: primary outcomes, Outcome 7 Patients who progressed at 2 yrs (best scenario).

Study or subgroup	Case	Control	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
IFNB MS Group 1993	25/124	45/123		21.43%	0.55[0.36,0.84]
The MSCRG 1996	18/158	85/143		42.33%	0.19[0.12,0.3]
The PRISMS 1998	49/184	77/187		36.23%	0.65[0.48,0.87]
Total (95% CI)	466	453		100%	0.43[0.35,0.53]

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

Study or subgroup	Case n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 92 (Case), 207 (Control)					
Heterogeneity: Tau²=0; Chi²=20.66, df=2(P<0.0001); I²=90.32%					
Test for overall effect: Z=7.83(P<0.0001)					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

Analysis 1.8. Comparison 1 interferon versus placebo: primary outcomes, Outcome 8 Patients who progressed at 2 yrs (worst scenario).

Study or subgroup	Case n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
IFNB MS Group 1993	34/124	34/123		32.64%	0.99[0.66,1.49]
The MSCRG 1996	91/158	29/143		33.34%	2.84[2,4.04]
The PRISMS 1998	54/184	68/187		34.02%	0.81[0.6,1.08]
Total (95% CI)	**466**	**453**		**100%**	**1.31[0.6,2.89]**
Total events: 179 (Case), 131 (Control)					
Heterogeneity: Tau²=0.45; Chi²=30.99, df=2(P<0.0001); I²=93.55%					
Test for overall effect: Z=0.68(P=0.5)					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

Analysis 1.9. Comparison 1 interferon versus placebo: primary outcomes, Outcome 9 Mean change in disability (EDSS) at 2 yrs.

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
The PRISMS 1998	184	0.2 (1.1)	187	0.5 (1.3)		68.9%	-0.24[-0.48,0]
IFNB MS Group 1993	124	-0.1 (1.4)	123	0.2 (1.5)		31.1%	-0.28[-0.64,0.08]
Total ***	**308**		**310**			**100%**	**-0.25[-0.46,-0.05]**
Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.86); I²=0%							
Test for overall effect: Z=2.43(P=0.01)							

Favours treatment -10 -5 0 5 10 Favours control

Comparison 2. Interferon versus placebo: secondary outcomes

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Patients who required steroid treatment until first year	2	85	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.04, 7.31]
2 Patients who required steroid treatment until 2 years	1	371	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.56, 0.87]

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
3 Patients with at least one hospital admission until 2 years	2	391	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.08, 2.36]

Analysis 2.1.   Comparison 2 Interferon versus placebo: secondary outcomes, Outcome 1 Patients who required steroid treatment until first year.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Durelli 1994	0/12	3/8		38.24%	0.1[0.01,1.69]
Myhr 1999	7/32	5/33		61.76%	1.44[0.51,4.08]
Total (95% CI)	**44**	**41**		**100%**	**0.52[0.04,7.31]**
Total events: 7 (Treatment), 8 (Control)					
Heterogeneity: Tau²=2.67; Chi²=3.25, df=1(P=0.07); I²=69.21%					
Test for overall effect: Z=0.49(P=0.63)					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control
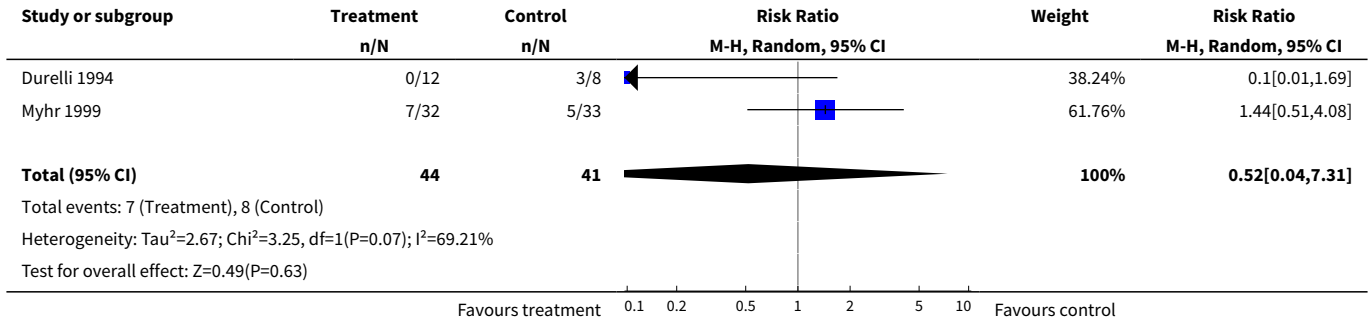
Analysis 2.2.   Comparison 2 Interferon versus placebo: secondary outcomes, Outcome 2 Patients who required steroid treatment until 2 years.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
The PRISMS 1998	72/184	105/187		100%	0.7[0.56,0.87]
Total (95% CI)	**184**	**187**		**100%**	**0.7[0.56,0.87]**
Total events: 72 (Treatment), 105 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.21(P=0)					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control
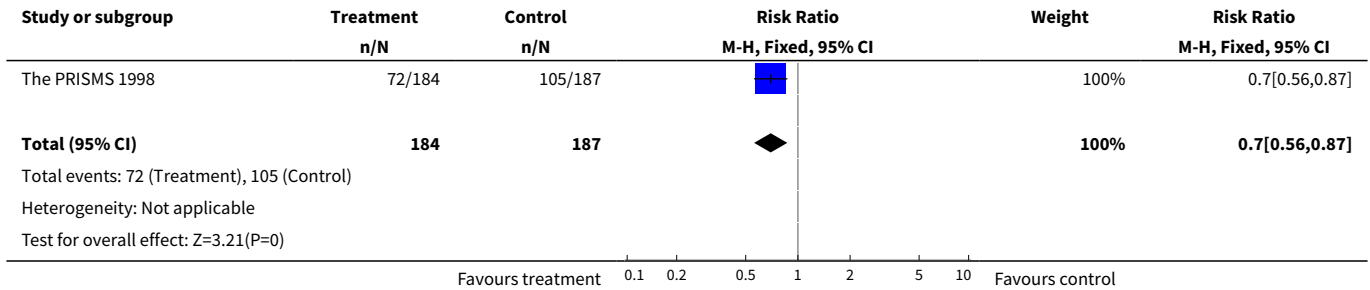
Analysis 2.3.   Comparison 2 Interferon versus placebo: secondary outcomes, Outcome 3 Patients with at least one hospital admission until 2 years.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Durelli 1994	0/12	3/8		24.1%	0.1[0.01,1.69]
The PRISMS 1998	33/184	47/187		75.9%	0.71[0.48,1.06]
Total (95% CI)	**196**	**195**		**100%**	**0.44[0.08,2.36]**
Total events: 33 (Treatment), 50 (Control)					
Heterogeneity: Tau²=0.92; Chi²=1.86, df=1(P=0.17); I²=46.15%					
Test for overall effect: Z=0.95(P=0.34)					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control
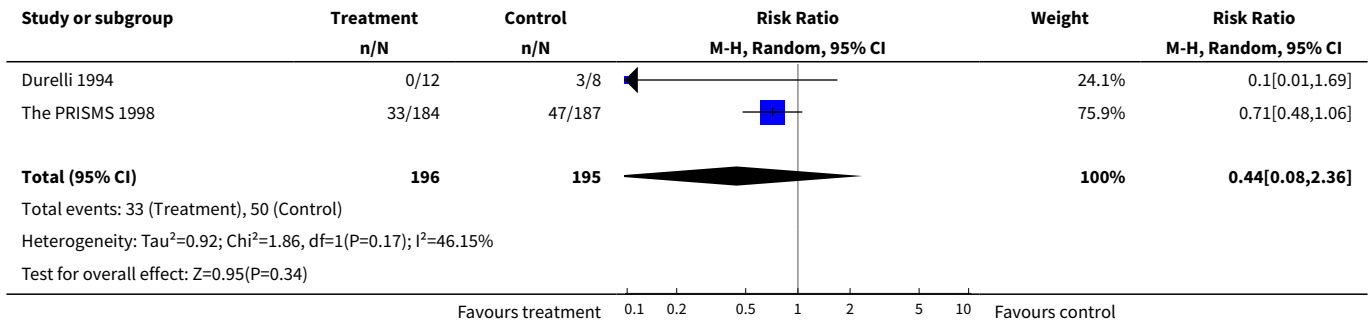
Comparison 3.   interferon versus placebo: adverse events

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Patients who had clinical adverse events during treatment	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Flu-like symptoms	4	1117	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.23, 2.37]
1.2 Fever	6	1199	Risk Ratio (M-H, Random, 95% CI)	1.92 [1.52, 2.43]
1.3 Myalgias/arthralgias	6	1199	Risk Ratio (M-H, Random, 95% CI)	1.90 [1.50, 2.42]
1.4 Fatigue	5	952	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.01, 1.88]
1.5 Nausea and vomiting	2	363	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.75, 5.31]
1.6 Headache	5	952	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.03, 1.33]
1.7 Injection site-reactions by subcutaneous route	4	878	Risk Ratio (M-H, Random, 95% CI)	5.57 [2.33, 13.29]
1.8 Hair loss	2	82	Risk Ratio (M-H, Random, 95% CI)	9.32 [1.84, 47.23]
1.9 Major psichic disorders	6	1199	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.75, 1.24]
1.10 Committed or attempted suicide	3	919	Risk Ratio (M-H, Random, 95% CI)	1.98 [0.41, 9.56]
2 Patients who had abnormal laboratory values during treatment	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Decreased hemoglobin values	3	383	Risk Ratio (M-H, Fixed, 95% CI)	2.84 [0.69, 11.59]
2.2 Leukopenia	5	1004	Risk Ratio (M-H, Fixed, 95% CI)	6.47 [2.43, 17.20]
2.3 Lymphopenia	2	618	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [1.39, 2.60]
2.4 Thrombocytopenia	3	383	Risk Ratio (M-H, Fixed, 95% CI)	7.47 [0.98, 57.15]
2.5 Increased aspartate aminotransferase	3	919	Risk Ratio (M-H, Fixed, 95% CI)	2.83 [1.14, 7.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.6 Increased alanine aminotransferase	4	981	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [1.98, 6.43]

Analysis 3.1. Comparison 3 interferon versus placebo: adverse events, Outcome 1 Patients who had clinical adverse events during treatment.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Flu-like symptoms					
IFNB MS Group 1993	64/124	22/123		23.07%	2.89[1.91,4.37]
The MSCRG 1996	96/158	57/143		27.02%	1.52[1.2,1.93]
The OWIMS 1999	59/98	33/100		25.24%	1.82[1.32,2.52]
The PRISMS 1998	50/184	45/187		24.67%	1.13[0.8,1.6]
Subtotal (95% CI)	**564**	**553**		**100%**	**1.7[1.23,2.37]**
Total events: 269 (Treatment), 157 (Control)					
Heterogeneity: Tau²=0.08; Chi²=12.37, df=3(P=0.01); I²=75.75%					
Test for overall effect: Z=3.18(P=0)					
3.1.2 Fever					
Durelli 1994	8/12	1/8		5.12%	5.33[0.82,34.83]
IFNB MS Group 1993	72/124	42/123		30.1%	1.7[1.28,2.27]
Myhr 1999	5/30	1/32		4.26%	5.33[0.66,43.05]
The MSCRG 1996	37/158	18/143		23.88%	1.86[1.11,3.12]
The OWIMS 1999	24/98	7/100		16.92%	3.5[1.58,7.74]
The PRISMS 1998	22/184	12/187		19.72%	1.86[0.95,3.65]
Subtotal (95% CI)	**606**	**593**		**100%**	**1.92[1.52,2.43]**
Total events: 168 (Treatment), 81 (Control)					
Heterogeneity: Tau²=0; Chi²=5.18, df=5(P=0.39); I²=3.42%					
Test for overall effect: Z=5.44(P<0.0001)					
3.1.3 Myalgias/arthralgias					
Durelli 1994	1/12	0/8		2.01%	2.08[0.09,45.45]
IFNB MS Group 1993	51/124	30/123		26.73%	1.69[1.16,2.46]
Myhr 1999	7/30	2/32		7.18%	3.73[0.84,16.57]
The MSCRG 1996	53/158	21/143		24.69%	2.28[1.45,3.59]
The OWIMS 1999	20/98	11/100		18.79%	1.86[0.94,3.67]
The PRISMS 1998	25/184	15/187		20.6%	1.69[0.92,3.11]
Subtotal (95% CI)	**606**	**593**		**100%**	**1.9[1.5,2.42]**
Total events: 157 (Treatment), 79 (Control)					
Heterogeneity: Tau²=0; Chi²=1.97, df=5(P=0.85); I²=0%					
Test for overall effect: Z=5.25(P<0.0001)					
3.1.4 Fatigue					
Durelli 1994	6/12	2/8		11.65%	2[0.53,7.54]
Myhr 1999	4/30	3/32		10.61%	1.42[0.35,5.83]
The MSCRG 1996	33/158	18/143		30.81%	1.66[0.98,2.81]
The OWIMS 1999	5/98	5/100		13.34%	1.02[0.3,3.41]

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
The PRISMS 1998	34/184	29/187		33.59%	1.19[0.76,1.87]
Subtotal (95% CI)	**482**	**470**		**100%**	**1.37[1.01,1.88]**
Total events: 82 (Treatment), 57 (Control)					
Heterogeneity: Tau²=0; Chi²=1.42, df=4(P=0.84); I²=0%					
Test for overall effect: Z=2(P=0.05)					
3.1.5 Nausea and vomiting					
Myhr 1999	11/30	3/32		27.75%	3.91[1.21,12.67]
The MSCRG 1996	49/158	32/143		72.25%	1.39[0.94,2.03]
Subtotal (95% CI)	**188**	**175**		**100%**	**2[0.75,5.31]**
Total events: 60 (Treatment), 35 (Control)					
Heterogeneity: Tau²=0.35; Chi²=2.74, df=1(P=0.1); I²=63.51%					
Test for overall effect: Z=1.39(P=0.17)					
3.1.6 Headache					
Durelli 1994	2/12	1/8		3.68%	1.33[0.14,12.37]
Myhr 1999	2/30	5/32		6.71%	0.43[0.09,2.04]
The MSCRG 1996	106/158	82/143		31.4%	1.17[0.98,1.4]
The OWIMS 1999	48/98	34/100		27.85%	1.44[1.03,2.02]
The PRISMS 1998	83/184	78/187		30.37%	1.08[0.86,1.36]
Subtotal (95% CI)	**482**	**470**		**100%**	**1.17[1.03,1.33]**
Total events: 241 (Treatment), 200 (Control)					
Heterogeneity: Tau²=0; Chi²=3.5, df=4(P=0.48); I²=0%					
Test for overall effect: Z=2.36(P=0.02)					
3.1.7 Injection site-reactions by subcutaneous route					
IFNB MS Group 1993	86/124	7/123		25.77%	12.19[5.88,25.26]
Myhr 1999	0/30	0/32			Not estimable
The OWIMS 1999	68/98	12/100		32.26%	5.78[3.35,9.99]
The PRISMS 1998	114/184	41/187		41.97%	2.83[2.11,3.79]
Subtotal (95% CI)	**436**	**442**		**100%**	**5.57[2.33,13.29]**
Total events: 268 (Treatment), 60 (Control)					
Heterogeneity: Tau²=0.52; Chi²=17.75, df=2(P=0); I²=88.73%					
Test for overall effect: Z=3.87(P=0)					
3.1.8 Hair loss					
Durelli 1994	3/12	0/8		34.32%	4.85[0.28,82.84]
Myhr 1999	12/30	1/32		65.68%	12.8[1.77,92.55]
Subtotal (95% CI)	**42**	**40**		**100%**	**9.32[1.84,47.23]**
Total events: 15 (Treatment), 1 (Control)					
Heterogeneity: Tau²=0; Chi²=0.31, df=1(P=0.58); I²=0%					
Test for overall effect: Z=2.7(P=0.01)					
3.1.9 Major psichic disorders					
Durelli 1994	1/12	0/8		2.27%	2.08[0.09,45.45]
IFNB MS Group 1993	21/124	18/123		24.07%	1.16[0.65,2.06]
Myhr 1999	2/30	1/32		3.75%	2.13[0.2,22.33]
The MSCRG 1996	20/158	18/143		23.58%	1.01[0.55,1.82]
The OWIMS 1999	8/98	8/100		15.3%	1.02[0.4,2.61]
The PRISMS 1998	44/184	52/187		31.03%	0.86[0.61,1.22]
Subtotal (95% CI)	**606**	**593**		**100%**	**0.96[0.75,1.24]**
Total events: 96 (Treatment), 97 (Control)					

0.1 0.2 0.5 1 2 5 10

Favours treatment   Favours control

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=1.52, df=5(P=0.91); I²=0%					
Test for overall effect: Z=0.28(P=0.78)					
3.1.10 Committed or attempted suicide					
IFNB MS Group 1993	2/124	0/123		27.63%	4.96[0.24,102.27]
The MSCRG 1996	0/158	1/143		24.99%	0.3[0.01,7.35]
The PRISMS 1998	3/184	1/187		47.38%	3.05[0.32,29.04]
Subtotal (95% CI)	**466**	**453**		**100%**	**1.98[0.41,9.56]**
Total events: 5 (Treatment), 2 (Control)					
Heterogeneity: Tau²=0; Chi²=1.83, df=2(P=0.4); I²=0%					
Test for overall effect: Z=0.85(P=0.39)					

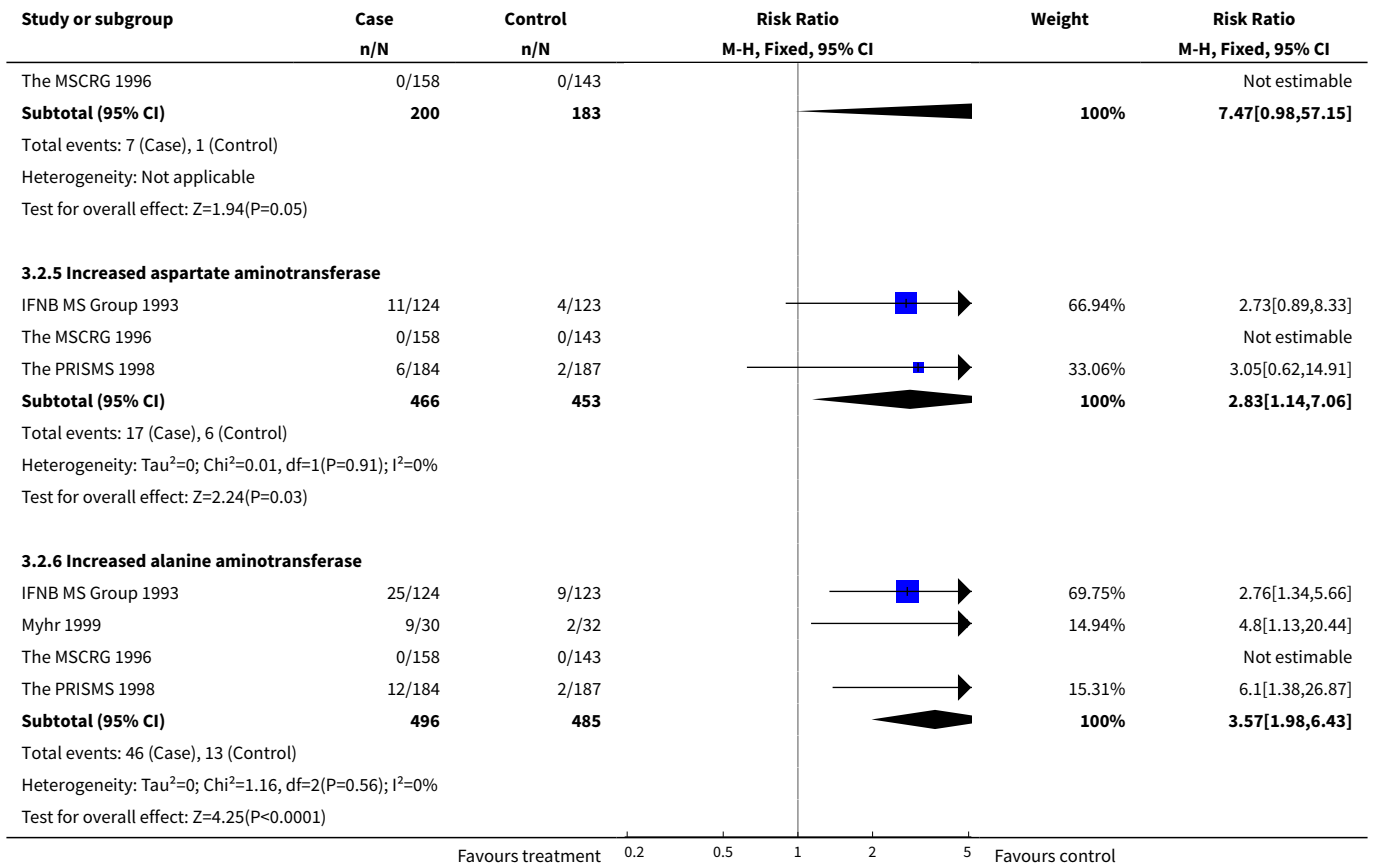Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

Analysis 3.2. Comparison 3 interferon versus placebo: adverse events, Outcome 2 Patients who had abnormal laboratory values during treatment.

Study or subgroup	Case n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Decreased hemoglobin values					
Durelli 1994	0/12	0/8			Not estimable
Myhr 1999	2/30	0/32		18.74%	5.32[0.27,106.54]
The MSCRG 1996	5/158	2/143		81.26%	2.26[0.45,11.48]
Subtotal (95% CI)	**200**	**183**		**100%**	**2.84[0.69,11.59]**
Total events: 7 (Case), 2 (Control)					
Heterogeneity: Tau²=0; Chi²=0.24, df=1(P=0.62); I²=0%					
Test for overall effect: Z=1.45(P=0.15)					
3.2.2 Leukopenia					
Durelli 1994	6/12	0/8		12.96%	9[0.58,140.5]
IFNB MS Group 1993	4/124	0/123		11.01%	8.93[0.49,164.08]
Myhr 1999	4/32	0/33		10.8%	9.27[0.52,165.55]
The MSCRG 1996	0/158	0/143			Not estimable
The PRISMS 1998	15/184	3/187		65.24%	5.08[1.5,17.26]
Subtotal (95% CI)	**510**	**494**		**100%**	**6.47[2.43,17.2]**
Total events: 29 (Case), 3 (Control)					
Heterogeneity: Tau²=0; Chi²=0.31, df=3(P=0.96); I²=0%					
Test for overall effect: Z=3.74(P=0)					
3.2.3 Lymphopenia					
IFNB MS Group 1993	58/124	36/123		83.89%	1.6[1.15,2.23]
The PRISMS 1998	24/184	7/187		16.11%	3.48[1.54,7.89]
Subtotal (95% CI)	**308**	**310**		**100%**	**1.9[1.39,2.6]**
Total events: 82 (Case), 43 (Control)					
Heterogeneity: Tau²=0; Chi²=3.16, df=1(P=0.08); I²=68.37%					
Test for overall effect: Z=4.04(P<0.0001)					
3.2.4 Thrombocytopenia					
Durelli 1994	0/12	0/8			Not estimable
Myhr 1999	7/30	1/32		100%	7.47[0.98,57.15]

Favours treatment 0.2 0.5 1 2 5 Favours control

Study or subgroup	Case n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
The MSCRG 1996	0/158	0/143			Not estimable
Subtotal (95% CI)	**200**	**183**		**100%**	**7.47[0.98,57.15]**
Total events: 7 (Case), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.94(P=0.05)					
3.2.5 Increased aspartate aminotransferase					
IFNB MS Group 1993	11/124	4/123		66.94%	2.73[0.89,8.33]
The MSCRG 1996	0/158	0/143			Not estimable
The PRISMS 1998	6/184	2/187		33.06%	3.05[0.62,14.91]
Subtotal (95% CI)	**466**	**453**		**100%**	**2.83[1.14,7.06]**
Total events: 17 (Case), 6 (Control)					
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.91); I²=0%					
Test for overall effect: Z=2.24(P=0.03)					
3.2.6 Increased alanine aminotransferase					
IFNB MS Group 1993	25/124	9/123		69.75%	2.76[1.34,5.66]
Myhr 1999	9/30	2/32		14.94%	4.8[1.13,20.44]
The MSCRG 1996	0/158	0/143			Not estimable
The PRISMS 1998	12/184	2/187		15.31%	6.1[1.38,26.87]
Subtotal (95% CI)	**496**	**485**		**100%**	**3.57[1.98,6.43]**
Total events: 46 (Case), 13 (Control)					
Heterogeneity: Tau²=0; Chi²=1.16, df=2(P=0.56); I²=0%					
Test for overall effect: Z=4.25(P<0.0001)					

Favours treatment 0.2 0.5 1 2 5 Favours control

ADDITIONAL TABLES

Table 1.   Kurtzke Expanded Disability Status Scale (EDSS)

Score
0-Normal neurologic examination
1.0-No disability, minimal signs on one Functional System (FS)*
1.5-No disability, minimal signs on >1 FS
2.0-Minimal disability in 1 FS
2.5-Minimal disability in 2 FS
3.0-Moderate disability in 1 FS; or mild disability in 3-4 FS, though fully ambulatory
3.5-Fully ambulatory but with moderate disability in 3-4 FS
4.0-Fully ambulatory without aid, up and about 12hrs./day despite relatively severe disability. Able to walk without aid 500meters
4.5-Fully ambulatory without aid, up and about much of day, able to work a full day, may otherwise have some limitations of full activity or require minimal assistance. Relatively severe disability. Able to walk without aid 300meters

Table 1.   Kurtzke Expanded Disability Status Scale (EDSS) *(Continued)*

5.0-Ambulatory without aid for about 200m. Disability impairs full daily activities
5.5-Ambulatory for 100m, disability precludes full daily activities
6.0-Intermittent or unilateral constant assistance required to walk 100m with or without resting
6.5-Constant bilateral support required to walk 20m. without resting
7.0-Unable to walk beyond 5m even with aid, essentially restricted to wheelchair, wheels self, transfers alone
7.5-Unable to take more than a few steps, restricted to wheelchair, any need aid in transfer, wheels self but may require motorized chair for full day's activities
8.0-Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed much of day, retains self care functions, generally effective use of arms
8.5-Essentially restricted to bed much of day,some effective use of arms, some self care functions
8.5-Essentially restricted to bed much of day,some effective use of arms, some self care functions
9.0-Helpless bed patient, can communicate and eat
9.5-Unable to communicate effectively or eat/swallow
10.0-Death
* Functional Systems are eight scales representing different functions of the Central Nervous System (Kurtzke 1961). Each system is rated on a five-point (three systems) or six-point (four systems) response scale except 'Other Functions' which is rated dichotomously (0 = none, 1 = any other neurological findings attributed to multiple sclerosis)

Table 2.   Withdrawals and losses to follow-up in the included studies

Study	Withdrawals	Losses to follow-up	Total	% of patients
MSCRG (1996)	23 (included in analysis)	129 (premature study termination)	129	43
Myhr (1999)	3	3	6	9
Durelli (1994)	0	0	0	0
Knobler (1993)	1	4	5	38
OWIMS (1999)	8	8	16	8
PRISMS (1998)	20	16	36	10
IFNB MS Group (1993)	unreported	unreported	48	19
Polman (2003)	2	4	6	7

Table 3. Side effects or adverse events: definitions as reported in the original articles

Study	Data in the articles
IFNB MS Study Group (1993)	Abnormal laboratory values: 1) Increased aspartate aminotransferase (AST) = above upper limit of normal; 2) Increased alanine aminotransferase (ALT) = above upper limit of normal; 3) Leukopenia = white blood cells < 2,999 per mm3; 4) Lymphopenia = lymphocytes < 1,499 per mm3; 5) Decreased haemoglobin values = no definition; 6) Thrombocytopenia = no definition. Clinical side effects = no definition. Neutralizing antibodies against interferon (NAB) = neutralizing titres were expressed relative to the National Institute of Health (NIH) standard, with the limit of detection at 20 neutralizing units per milliliter
Knobler (1993)	Abnormal laboratory values: 1) Increased AST = no definition; 2) Increased ALT = no definition; 3) Leukopenia = no definition; 4) Lymphopenia = lymphocytes < 1,000 per mm3; 5) Decreased haemoglobin values = no definition; 6) Thrombocytopenia = no definition. Clinical side effects = no definition. NAB = neutralizing titres were expressed relative to the NIH standard, with the limit of detection at 20 neutralizing units per milliliter
Durelli (1994)	Abnormal laboratory values: 1) Increased AST = mild elevation: 2 x normal value and moderate elevation: 3 x normal value; 2) Increased AST and ALT = mild elevation: 2 x normal value and moderate elevation: 3 x normal value; 3) Neutropenia = cell number between 1,000 and 2,000 per mm3; 4) Lymphopenia = no definition; 5) Decreased haemoglobin values = no definition; 6) Thrombocytopenia = no definition. Depression = tested with the Hamilton Depression Scale; Flu-like syndrome = contemporary presence of fever, headache, arthralgias and myalgias; Other clinical outcomes = no definition. NAB = neutralizing titres were not defined
The MSCRG (1995)	Abnormal laboratory values: 1) Increased AST; 2) Increased ALT; 3) Leukopenia; 4) Lymphopenia; 5) Decreased haemoglobin values; 6) Thrombocytopenia. The Authors reported "Adverse events and current laboratory data were monitored and recorded according to the Food and Drug Administration (FDA) phase III requirements". Moreover, they reported "FDA, HHS 21 CFR, Chapt. 1, 312.32, part c, 4/1/90". Depression = tested with the Beck Depression Inventory and Functional Assessment: using several scales = The MS Functional Disability Assessment, The Functional Indipendence Measure, The Barthel Index, The Incapacity Status Scale, and The Brief Symptom Inventory. NAB = neutralizing titres were expressed relative to the NIH standard, with the limit of detection at 20 neutralizing units per milliliter
The PRISMS (1998)	Abnormal laboratory values: 1) Increased AST = no definition; 2) Increased ALT = no definition; 3) Leukopenia = no definition; 4) Lymphopenia = lymphocytes < 1,000 per mm3; 5) Decreased haemoglobin values = no definition; 6) Thrombocytopenia = no definition. Depression = tested with the Beck Depression Inventory, The Centre for Epidemiologic Studies' Depression Mood Scale, and the General Health Questionnaire. Other clinical outcomes = no definition. NAB = neutralizing titres were expressed relative to the NIH standard, with the limit of detection at 20 neutralizing units per milliliter. The Authors used the four grades of the World Health Organization about toxic effects
Myhr (1999)	Abnormal laboratory values: 1) Increased AST = no definition; 2) Increased ALT = no definition; 3) Leukopenia = no definition; 4) Lymphopenia = no definition; 5) Decreased haemoglobin values = no definition; 6) Thrombocytopenia = no definition. Clinical side effects = no definition. NAB = the Authors reported that "they were analyzed by F. Hoffmann-La Roche according to standardized protocols"
The OWIMS (1999)	Abnormal laboratory values: 1) Increased AST = no definition; 2) Increased ALT = no definition; 3) Leukopenia = no definition; 4) Lymphopenia = no definition; 5) Decreased haemoglobin values = no definition; 6) Thrombocytopenia = no definition. Clinical side effects = no definition. NAB: no definition

Table 4. Magnetic Resonance Imaging (MRI) as reported in the original articles

Study	MRI	Year(s) of follow-up	Control group	Treated group
IFNB (1993)	Mean [standard error (SE)] and median annual % change of total lesion area.	1 and 2 years from randomisation	At 1st year: mean 110.6; median 6.7 (SE 96.3). At 2nd year: mean 43.8; median 11.9 (SE 14.0). N. of patients 72	At 1st year: mean 5.4; median -4.9 (5.1). Number of patients 77. At 2nd year: mean 9.4; median - 5.6 (SE 8.5). Number of patients 73
Knobler (1993)	No MRI outcome			
Durelli (1994)	Number of patients who had active lesions. Total number of enlarging lesions and new lesions in the two groups. Mean (SE) number of active lesions per patient	6 months from randomisation.	Number of patients with active scans: 6 of 8 patients (enlarging lesions: 12 of 6; new lesions: 15 of 6). Mean number of active lesions per patient 3.37 (1.03)	Number with active scans: 1 of 12 patients (enlarging lesions: 1; new lesions: 0). Mean number of active lesions per patient 0.08 (0.08)
MSCRG (1995)	Number of patients who had active lesions. Mean (SE) number and volume of active lesions per patient. Median % change of total lesion volume (mm3).	1 and 2 years from randomisation	At 1st year: number of patients with active scans: 52 of 123 patients. Mean number of active lesions per patient 1.59 (0.31). Mean volume per patient 96.5 (21.2) mm3. Median change -3.3%. At 2nd year: number of patients with active scans: 35 of 82 patients. Mean number of active lesions per patient 1.65 (0.48). Mean volume per patient 122.4 (48.5) mm3. Median change -6.5%.	At 1st year: number of patients with active scans: 40 of 134 patients. Mean number of active lesions per patient 1.04 (0.28). Mean volume per patient 70.0 (24.9) mm3. Median change -13.1%. At 2nd year: number of patients with active scans: 24 of 83 patients. Mean number of active lesions per patient 0.80 (0.22). Mean volume per patient 74.1 (38.3) mm3. Median change -13.2%.
PRISMS (1998)	Median % change of total lesion burden (area or volume?). Difference (%) of the number of active lesions between treated and control groups.	2 years from randomisation	Median 10.9 (N. 187 patients).	Median -3.8 (N. 184). Difference of active lesions - 78% than placebo group
Myhr (1999)	Mean (no SE) and median of new active lesions per patient. Number of patients with new active lesions. Mean (no SE) and median of total number of lesions per patient (number of T1-weighted active lesions plus unactive T2-weighted lesions)	6 months and 1 year from randomisation	At 6th month: mean 7.3 and median 2.5 new active lesions per patient ; 24 of 32 patients with new active lesions; mean 1.6 and median 1.0 total number of lesions per patient. At 1st year: mean 1.6 and median 0.0 total number of lesions per patient. (N. 32 patients)	At 6th month: mean 1.4 and median 0.0 new active lesions per patient; 9 of 28 patients with new active lesions; mean 0.3 and median 0.0 total number of lesions per patient. At 1st year: mean 0.7 and median 0.0 total number of lesions per patient (N. 28 patients)
OWIMS (1999)	Mean [standard deviation (SD)] and median number of active lesions (measured by different MRI techniques). The	24 and 48 weeks from ran-	At 24th week: mean and median number of combined unique active lesions 1.7 (2.7) and 0.7 per patient; median number of proton density/T2 unique active le-	At 24th week: mean and median number of combined unique active lesions 0.8 (1.1) and 0.3 per

Table 4. Magnetic Resonance Imaging (MRI) as reported in the original articles *(Continued)*

	proportion of scans showing active lesions. Mean (no SE) and median % change of total lesion area.	domisa-tion	sions 0.3 per patient; median number of T1-Gadolinium unique active lesions 0.7 per patient; 50% of scans with combined active lesions. At 48th week: mean 15.5 % and median 5.9% change of total lesion area (N. of patients at 24th and 48th week = unknown).	patient; median number of proton density/T2 unique active lesions 0.2 per pa-tient; median number of T1-Gadolinium unique active lesions 0.3 per pa-tient; 33% of scans with combined active lesions. At 48th week: mean 0.8% and median -1.4% change of total lesion area (N. of patients at 24th and 48th week = unknown).
Polman (2003)	Cumulative number of newly active lesions over 6 months.	6 months from ran-domisa-tion.	Median and quartiles (Q1; Q3): 4.0 (2.7; 10.0)	Median and quartiles (Q1; Q3): 9.0 (1.0; 16.0)

Outcomes	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Patients who continued to experience exacerbations during the first year	37 (22:333)	19 (11:177)	12 (7:111)	9 (6:83)	7 (4:67)	6 (4:56)	5 (3:48)	5 (3:42)	4 (2:37)
Patients who continued to experience exacerbations during the first 2 years	50 (37:83)	25 (19:42)	17 (12:28)	13 (9:21)	10 (7:17)	8 (6:14)	7 (5:12)	6 (5:10)	6 (4:9)
Patients who continued to experience exacerbations during the first 2 yrs (base case) Patients who continued to experience exacerbations during the first 2 yrs (base case)									
Patients who progressed during the first 2 years	32 (22:77)	16 (11:38)	11 (7:26)	8 (6:19)	6 (4:15)	5 (4:13)	5 (3:11)	4 (3:10)	4 (2:9)

APPENDICES

Appendix 1. MEDLINE (PubMed) search strategy

((((("Multiple Sclerosis"[mh]) OR ("Myelitis, Transverse"[mh:noexp]) OR ("Demyelinating Diseases"[mh:noexp]) OR ("Encephalomyelitis, Acute Disseminated"[mh:noexp]) OR ("Optic Neuritis"[mh])) OR ((("multiple sclerosis") OR ("neuromyelitis optica") OR ("transverse myelitis") OR (encephalomyelitis) OR (devic) OR ("optic neuritis")) OR ("demyelinating disease*") OR ("acute disseminated encephalomyelitis"))) AND (((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT ((animals[mh]) NOT ((animals[mh]) AND (human[mh]))))) AND (("Interferon-beta"[Mesh]) OR (rebif OR "interferon beta" OR "beta interferon" OR betaseron OR avonex))

Appendix 2. EMBASE (EMBASE.com) search strategy

((((('encephalomyelitis'/exp) OR ('demyelinating disease'/exp) OR ('multiple sclerosis'/exp) OR ('myelooptic neuropathy'/exp) OR ('multiple sclerosis':ti,ab) OR ('neuromyelitis optica':ab,ti) OR (encephalomyelitis:ab,ti) OR (devic:ti,ab)) AND (('crossover procedure'/exp) OR ('double blind procedure'/exp) OR ('single blind procedure'/exp) OR ('randomized controlled trial'/exp) OR (random*:ab,ti) OR (factorial*:ab,ti) OR (crossover:ab,ti) OR (cross:ab,ti AND over:ab,ti) OR (placebo:ab,ti) OR ('double blind':ab,ti) OR ('single blind':ab,ti) OR (assign*:ab,ti) OR (allocat*:ab,ti) OR (volunteer*:ab,ti)))) AND (('beta interferon'/exp) OR ('interferon'/de) OR ('interferon beta':ab,ti AND rebif:ab,ti) OR (betaseron:ab,ti) OR ('beta interferon') OR (avonex:ab,ti)) AND [humans]/lim AND [embase]/lim

WHAT'S NEW

Date	Event	Description
11 April 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2000
Review first published: Issue 4, 2001

Date	Event	Description
29 July 2007	Amended	No changes to conclusion, added a review author
29 April 2007	New search has been performed	Run searches for new studies

CONTRIBUTIONS OF AUTHORS

Prof G PA Rice and Dr G Filippini conceived the idea and development of the project, posed the questions of the research project, designed the protocol, appraised the relevance and the validity of the papers and co-ordinated the review. G Rice abstracted data and wrote to sponsors of trials for additional information. They both analyzed the results and wrote the text of the review.
Dr B Incorvaia and Dr L Munari: They both were involved in the search strategy, abstracted data and helped in the analysis of the results and writing of the test of the review. Dr B Incorvaia organized retrieval of papers.
Prof Chris Polman: Assisted in the design of the protocol, abstracted data, assisted in data interpretation and reviewed the manuscript drafts.
Dr R D'Amico assisted in statistical analysis and writing of the test of the review.
Prof George Ebers: Assisted in the design of the protocol, data interpretation and reviewed the manuscript drafts.
Dr E Parmelli collaborated to the update of the review.

DECLARATIONS OF INTEREST

The review was assembled, analysed and reported independent from any pharmaceutical company input.
Prof Rice has participated in clinical trials sponsored by SCHERING, SERONO, BERLEX, BIOGEN, and TEVA. He has received honoraria from these companies.

SOURCES OF SUPPORT

Internal sources

External sources

INDEX TERMS

Medical Subject Headings (MeSH)

Interferon Type I [*therapeutic use]; Multiple Sclerosis, Relapsing-Remitting [*drug therapy]; Randomized Controlled Trials as Topic; Recombinant Proteins

MeSH check words

Humans