Articles

Interferons in relapsing remitting multiple sclerosis: a systematic review

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Summary

Background Recombinant interferons have been approved by many national regulatory agencies for treatment of relapsing remitting multiple sclerosis, but widespread discussion continues about their true effectiveness, benefits, side-effects, and costs.

Methods With the Cochrane Collaboration methodology, we reviewed all published, randomised, placebo-controlled trials of recombinant interferons undertaken in patients with relapsing remitting multiple sclerosis between 1993 and 2002. Our primary aim was to find out whether recombinant interferons reduced the number of patients who had clinical exacerbations and disease progression, compared with placebo.

Findings The seven trials that met our criteria included 1215 randomised patients: data from 667 (55%) were available for analysis at 1 year's and from 919 (76%) at 2 years' follow-up. Interferon seemed to reduce the number of patients who had exacerbations during the first year of treatment (relative risk 0·73, 95% CI 0·54–0·99), but results at 2 years' follow-up were not robust and were difficult to interpret because of the many dropouts. Although the number of patients who had exacerbations (0·81, 0·74–0·89) or progressed (0·70, 0·55–0·88) during the first 2 years fell significantly in the protocol analysis, results were inconclusive after sensitivity analyses for exacerbations (1·11, 0·73–1·68) and disease progression (1·31, 0·60–2·89). Data were insufficient to establish whether steroid use and admissions to hospital were reduced in the interferon group. Similarly, MRI outcome data could not be analysed quantitatively. Side-effects were common, and acute toxic effects adversely affected quality of life.

Interpretation Recombinant interferons slightly reduce the number of patients who have exacerbations during first year of treatment. Their clinical effect beyond 1 year is uncertain and new trials are needed to assess their long-term effectiveness and side-effects.

Lancet 2003; **361:** 545–52

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Introduction

Use of interferons in multiple sclerosis has been studied for more than 20 years. Interferons exert effects of potential relevance to multiple sclerosis: their antiviral action, and their pleiotropic effects on the immune system and blood-brain barrier, could benefit patients with multiple sclerosis.[1]

Results of some early pilot trials showed fewer exacerbations in multiple sclerosis patients given human interferon than in those on placebo.[2,3] Recombinant interferons were approved by many national regulatory agencies for the treatment of relapsing remitting multiple sclerosis, after clinical trials established that interferon beta preparations reduced disease activity.[4-8] Interferon beta-1b is now also licensed for secondary progressive multiple sclerosis[9] and interferon beta-1a for the treatment of patients who have had a sole demyelinating event.[10] Interferons have been used for the treatment of multiple sclerosis for almost a decade, and are available for this use free of charge from many national health services. However, doubts remain as to their effectiveness, in particular whether they can really prevent progression of the disease and whether the effect is sustained over time.[11] Furthermore, the beneficial effects might be small or non-existent in relation to untoward side-effects and high cost.[12]

We therefore undertook an assessment of the methodological quality of interferon trials, and did a meta-analysis of the results. Our primary question was: are recombinant interferons more effective than placebo in reduction of the number of patients with relapsing remitting multiple sclerosis who have clinical exacerbations and disease progression? Our secondary objectives were to assess the effectiveness of recombinant interferons in reduction of the need for treatment with corticosteroids and hospital admission, the incidence and severity of side-effects, and the effect of interferons on cerebral lesions as measured by serial MRI.

Methods

For our systematic review we applied the Cochrane Collaboration methodology (www.cochrane.org) and followed our predefined protocol.[13] We assessed only randomised, double-blind, placebo-controlled trials that compared alfa or beta recombinant interferons with placebo in patients diagnosed with relapsing remitting multiple sclerosis according to accepted criteria.[14] Trials in which the comparisons of interest were confounded by other treatments, such as immunosuppressive drugs, were excluded.

We searched for trials in the Cochrane controlled trials register, MEDLINE (1966–2002), and EMBASE (1988–2002), and hand-searched references in identified trials and symposia reports (1990–2002) from the major neurological and multiple sclerosis associations. Contacts with investigators and sponsor companies (Biogen, Ares Serono International SA, Schering AG, and Berlex Laboratories) did not identify any unpublished trials. Four of the authors scrutinised all articles found by the searches;

all decided independently whether a trial met the criteria for inclusion in the review. Any disagreement about trial status was resolved by discussion among the authors.

The primary outcome measures of the meta-analysis were the proportions of patients who had one or more exacerbations during the treatment and follow-up periods (1 and 2 years, respectively), and disease progression after 1 year and 2 years. Exacerbations were defined as newly developed or recently worsened symptoms of neurological dysfunction that lasted more than 24 h, with or without objective confirmation, and that stabilised or resolved either partly or completely. The definition of progression was taken from the original articles. Most investigators used the expanded disability status scale (EDSS)[15] and defined progression as a sustained (3 or 6 months') increase in EDSS of at least one point recorded in a period when the patient had no exacerbation. EDSS is the most widely used disability measure in clinical trials of multiple sclerosis. It is based on the results of a neurological examination and the patient's ability to walk. Scores range from 0 (no neurological abnormality) to 10 (death from multiple sclerosis). We also assessed mean change in disability, measured by the EDSS at the end of follow-up. Secondary outcome measures were need for steroid treatment, hospital admission during the trial and follow-up, and side-effects or adverse events. We grouped the data we extracted as clinical or haematological side-effects and combined data across trials in the analysis. We also assessed the effect of treatment on cerebral MRI findings, a widely accepted surrogate outcome measure in multiple sclerosis.

The four reviewers independently extracted trial data onto a standard form that focused on four recognised aspects of methodological quality in randomised controlled trials: (1) concealment of treatment allocation (defined as adequate, unclear, or inadequate according to Cochrane criteria[16]); (2) type of blinding in outcome assessment (double, single, or not reported); (3) whether data were analysed according to an intention-to-treat analysis (yes, no, or not reported); and (4) number of patients lost to follow-up or excluded after randomisation. If necessary, additional information was sought from the trial investigators or trial sponsors.

The meta-analysis was done with the aid of Review Manager software (version 4.1). For trials in which treatment effects were reported for more than one dose of interferon, we restricted the analysis to the higher dose, which was the most frequently used in clinical practice.

Study; country (number of centres)	Accrual period (years)	Length of follow-up (months)	Interventions	Number of patients	Patients' characteristics	Interferon
IFNB;[4-6] USA, Canada (11)	1988–90	24	1·6 MIU interferon beta-1b 8·0 MIU interferon beta-1b Placebo	125 124 123	Age: 18–50 years; clinical or laboratory-supported definite RRMS; EDSS ⩽5·5; disease duration >1 year; at least two relapses in the 2 years before randomisation; no exacerbations for at least 1 month before randomisation	Interferon beta-1b 1·6 or 8·0 MIU subcutaneously every other day for 24 months
MSCRG;[7,8,38] USA (4)	1990–93	24	6·0 MIU interferon beta-1a Placebo	158 143	Age: 18–55 years; definite RRMS; EDSS 1–3·5; disease duration ⩾1 year; at least two relapses in the 3 years before randomisation; no exacerbations for at least 2 months before randomisation	Interferon beta-1a 6·0 MIU intramuscularly weekly for 104 weeks
Knobler;[36] USA (3)	1986	6	0·8 MIU interferon beta-1b 4·0 MIU interferon beta-1b 8·0 MIU interferon beta-1b 16·0 MIU interferon beta-1b Placebo	6 6 6 6 7	Age: 18—50 years; clinical definite RRMS; EDSS ⩽5·5; disease duration ⩾1 and ⩽15 years; at least two relapses in the 2 years before randomisation; in remission at randomisation	Interferon beta-1b 0·8 or 4·0 or 8·0 or 16·0 MIU subcutaneously three times weekly for 36 months
Durelli;[37] Italy (1)	NS	6	9·0 MIU interferon alpha-2a Placebo	12 8	Age: 18–57 years; clinical definite RRMS; EDSS ⩽6·0; disease duration >3 years; at least two relapses in the 2 years before randomisation; no exacerbations for at least 3 months before randomisation	Interferon alfa-2a 9·0 MIU intramuscularly every other day for 6 months
PRISMS;[39,40] Canada, Germany, Netherlands, Australia, Sweden, Finland, Belgium, UK, Switzerland, (22)	1994–95	24	6·0 MIU interferon beta-1a 12·0 MIU interferon beta-1a Placebo	189 184 187	Age: not reported; clinical or laboratory-supported definite RRMS; EDSS 0–5·0; disease duration ⩾1 year; at least two relapses in the 2 years before randomisation	Interferon beta-1a 6·0 or 12·0 MIU subcutaneously three times weekly for 24 months
OWIMS;[41] Canada, Netherlands, Italy, Israel, France (11)	1995	12	6·0 MIU interferon beta-1a 12·0 MIU interferon beta-1a Placebo	95 98 100	Age: 18–50 years; clinical or laboratory-supported definite RRMS; EDSS 0–5·0; disease duration ⩾1 year; at least one relapse in the 2 years before randomisation; no exacerbations for at least 2 months before randomisation	Interferon beta-1a 6·0 or 12·0 MIU subcutaneously weekly for 24 weeks
Myhr;[42-44] Norway (8)	NS	12	4·5 MIU interferon alpha-2a 9·0 MIU interferon alpha-2a Placebo	32 32 33	Age: 18–50 years; clinical or laboratory-supported definite RRMS; EDSS ⩽5·5; at least two relapses in the 2 years before randomisation	Interferon alfa-2a 4·5 or 9·0 MIU subcutaneously three times weekly for 6 months

RRMS=relapsing remitting MS; MIU=million international units. NS=not specified.

Table 1: **Characteristics of included trials**

Study	Allocation concealment	Type of blinding	Intention-to-treat analysis	Number lost to follow-up	
				Treatment	Placebo
IFNB[5]	Unclear	Double-blind	Yes	25 (20%)	23 (19%)
MSCRG[8]	Unclear	Double-blind	Yes	73 (46%)	56 (39%)
Knobler[36]	Unclear	Double-blind	Not reported	2 (33%)	3 (43%)
Durelli[37]	Adequate	Double-blind	Yes	0	0
PRISMS[39]	Adequate	Double-blind	Yes	19 (10%)	17 (9%)
OWIMS[41]	Adequate	Double-blind	Yes	13 (13%)	3 (3%)
Myhr[42]	Unclear	Double-blind	Yes	5 (16%)	1 (3%)

Table 2: **Assessment of quality of trials**

Binary outcomes were assessed by calculation of relative risks (RRs) and 95% CIs for each trial. Continuous outcomes were assessed as differences between the means of the intervention and control groups. We also calculated a weighted overall estimate of the RRs with 95% CI for binary outcomes, and weighted averages of differences between means for continuous outcomes. We used a random effects model to combine the study findings.[17]

We did a sensitivity analysis to assess the effect of patient withdrawal or loss to follow-up on primary outcomes: in the best-case scenario (with regards to treatment) we assumed that none of the interferon-group patients but all controls who dropped out had a primary outcome. The worst-case scenario was the opposite: namely, that all dropouts from the treatment group but no controls had a primary outcome. In the likely scenario, we assumed that active and placebo dropouts both worsened.

We estimated the number of patients that needed to be treated (NNT) to prevent one patient from having one or more exacerbations using: NNT=1/[BR(1–RR)] where BR (baseline risk) is the risk of having one or more exacerbations in the control group and RR is the weighted relative risk estimated by our meta-analysis. We estimated NNT by variation of the values of the baseline risk.[18]

Role of the funding source

The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the review.

Results

We identified 227 abstracts (144 in MEDLINE, 23 in EMBASE, 46 by hand-searching, and 14 in the Cochrane controlled trials register). 24 studies were identified as potentially fulfilling inclusion criteria. We excluded 17 studies after reading the full published papers: a randomised controlled trial of ingested interferon alfa-2a;[19] two controlled clinical trials;[20,21] two open-label trials;[22,23] four studies of natural interferon alfa;[24–27] two in which only immunological, not clinical, outcomes had been reported;[28,29] a dose-comparison trial of interferon beta-1a without a placebo group;[30] two studies with both relapsing-remitting and secondary progressive multiple sclerosis patients, and only amalgamated results;[31,32] one with only placebo group data;[33] one in which patients had been treated after a first exacerbation, before definite diagnosis of multiple sclerosis;[34] and one because neither blinding criteria nor clinical outcomes were clearly described.[35] Thus, seven trials (table 1) were eligible, in which 1674 patients had been randomised.[4–8,36–44] Data from only 1215 patients were available: 614 in the higher-dose interferon groups and 601 controls. All patients had been recruited during a stable phase of a relapsing remitting course.

The methodological quality of the included studies is summarised in table 2. Concealment of treatment allocation had been adequate in three trials[37,39,41] and unclear in the other four.[5,8,36,42] The well documented side-effects of interferon injection,[1,11] mainly injection-site reactions and influenza-like symptoms, make it likely that patients could become unblinded during trials. Analysis of blinding in two studies[5,8] identified a strong tendency for treated patients to become unblinded. Specifically, 80% of patients in the 8 million IU interferon beta-1b group, 51% in the 1·6 million IU interferon beta-1b group, and 30% in the placebo group had correctly guessed their treatment at the end of follow-up.[5] 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.

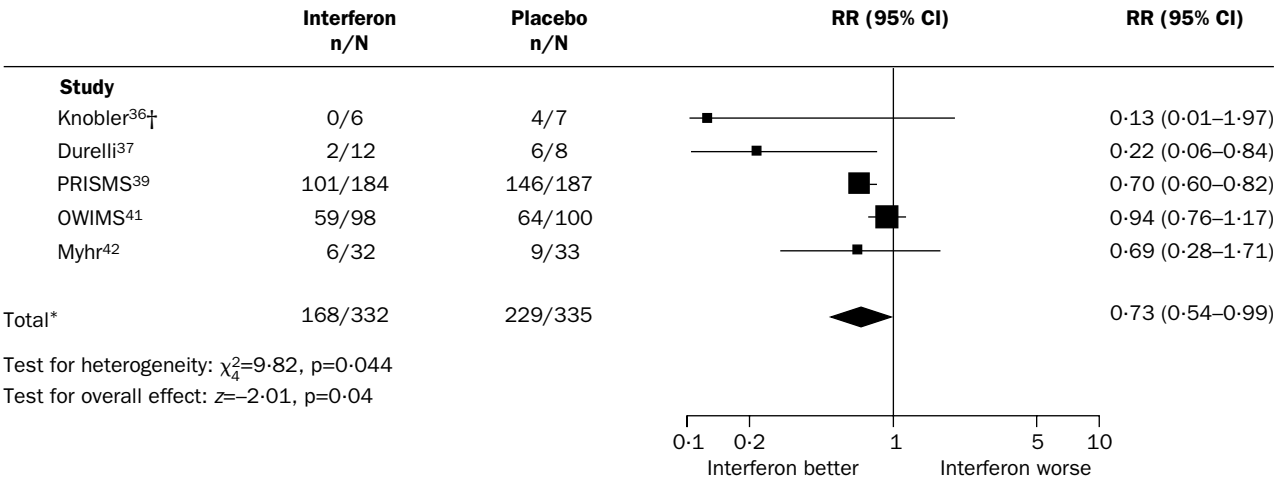

Figure 1: **Patients who had at least one exacerbation during the first year of treatment**

n/N=number of patients who had exacerbations/number of patients randomised. To estimate RR, 0·5 was added to each cell of the 2×2 table for the trial. *Random effects model.[17] †No patients with exacerbations in the interferon group.

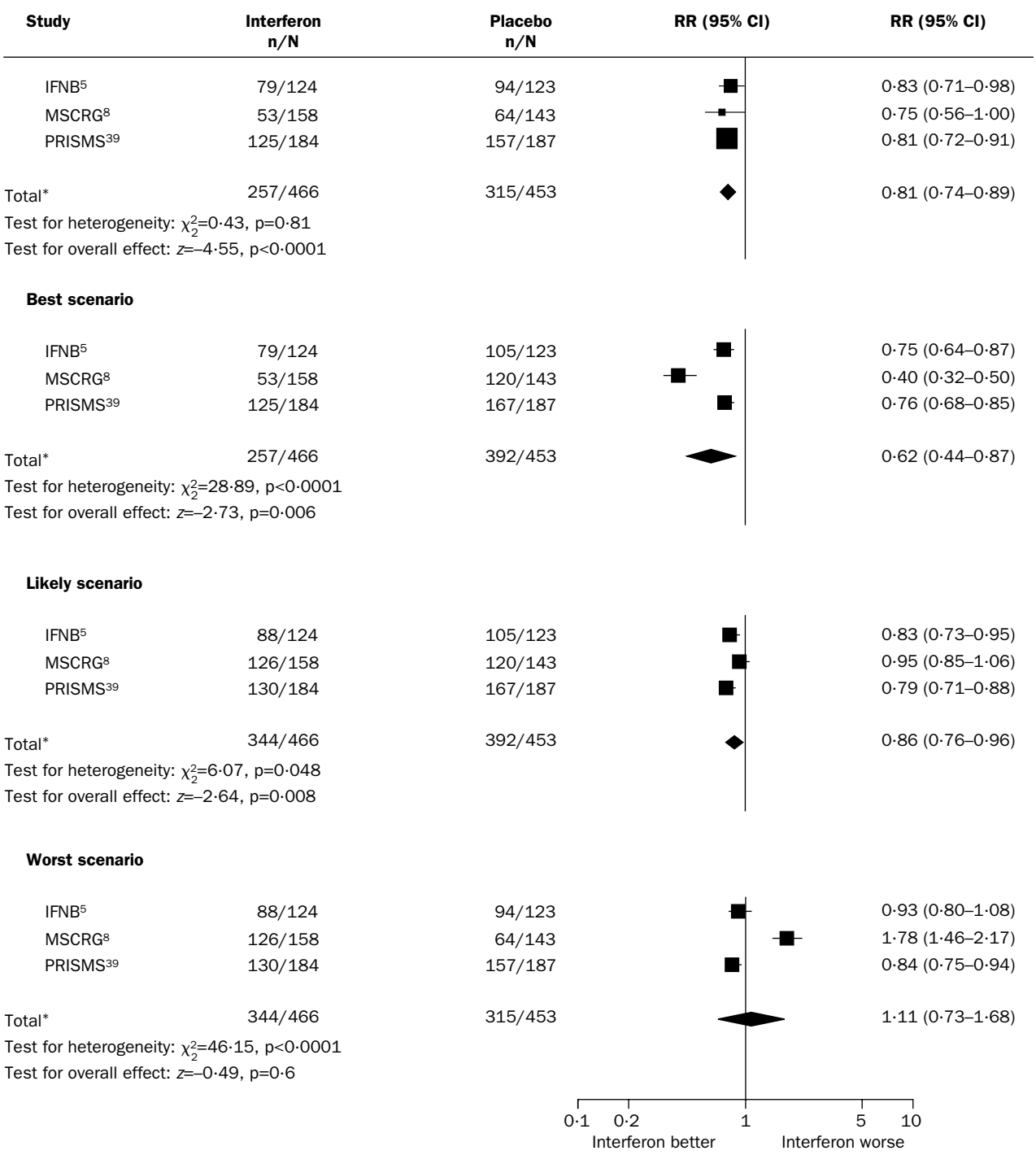

Figure 2: **Patients who had at least one exacerbation during the first 2 years of treatment**
n/N=number of patients who had exacerbations/number of patients randomised. *Random effects model.[17]

Overall, 240 (20%) patients had been excluded after randomisation or were lost to follow-up: 137 interferon patients and 103 controls. In one study,[8] 73 (46%) of 158 patients in the treatment group and 56 (39%) of 143 controls had not completed the scheduled 2 years of follow-up because the study had ended prematurely; the frequency of acute exacerbations and disease progression had not been reported at 1 year; at 2 years these primary outcomes were available for only 57% of randomised patients. In another trial,[5] withdrawals and losses to follow-up were difficult to find, and different data were given in different articles about the same trial. Specifically, 2 years after randomisation, withdrawals plus losses to follow-up in the treated group were described as either 18[4] or 20[5] in the 1·6 million IU interferon group and as 24[4] or 25[5] in the 8 million IU group. Although an intention-to-treat analysis was mentioned in six trials,[5,8,37,39,41,42] in most cases patients who were withdrawn and lost to follow-up had been excluded from the analyses.

Information on clinical side-effects and haematological toxic effects was reported for all trials. However, neither the definitions nor methods of quantification were specified for most of these studies. The scales used to assess depression were reported in three trials,[8,37,39] and

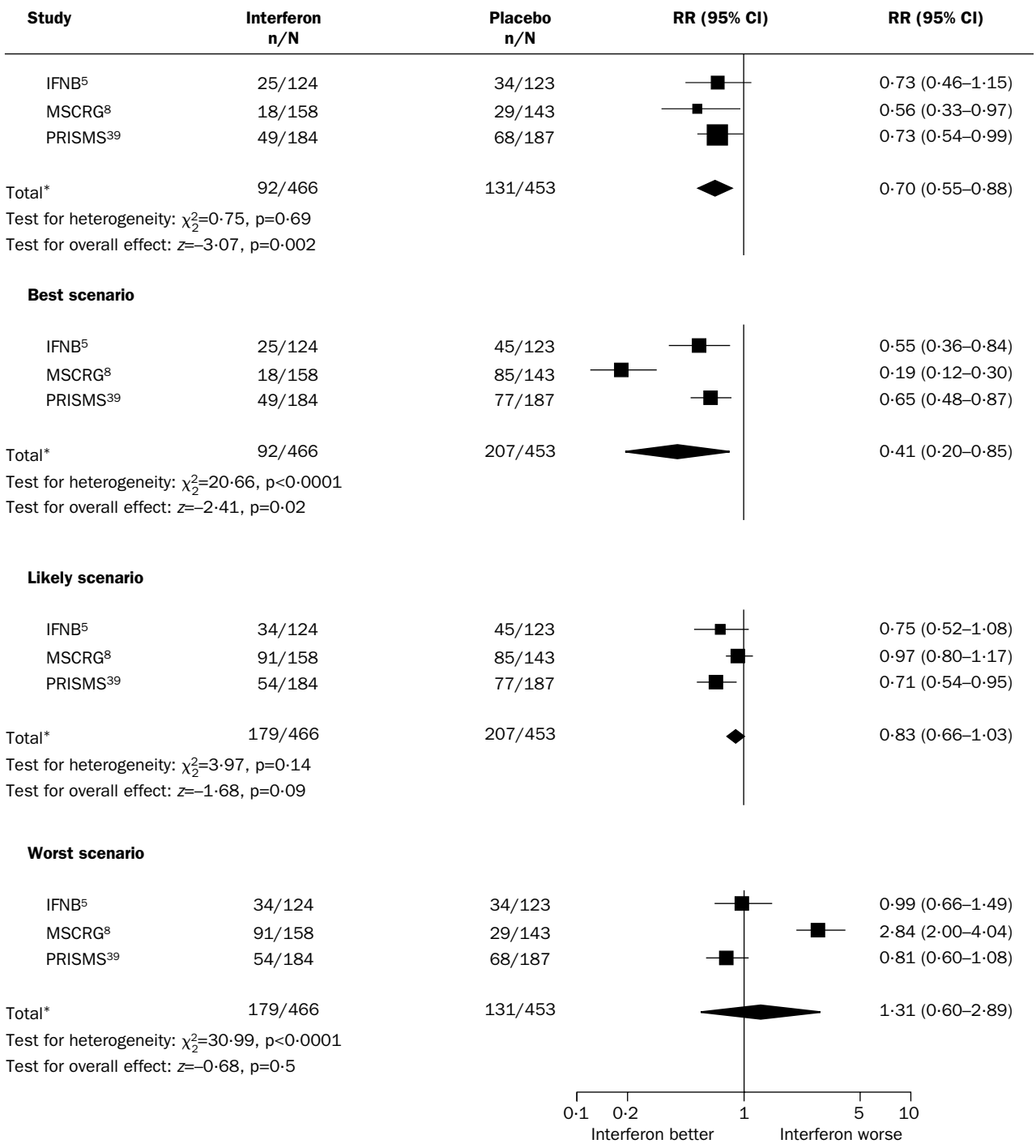

Figure 3: **Patients who progressed during the first 2 years of treatment**
n/N=number of patients who progressed/number of patients randomised. *Random effects model.[17]

criteria for haematological measurements were reported in two trials.[8,39] In one trial, information on clinical and haematological side-effects at each interferon dose was not presented; only the amalgamated results for both doses were given.[36]

MRI criteria that had been used and reported as surrogate endpoints differed between trials; the timing of the scans also varied. Furthermore, MRI technology developed substantially during the decade in which the trials were done. For all these reasons it was not possible to compare MRI outcomes adequately across the trials from the published results. We therefore undertook only a qualitative analysis of the MRI findings.

Sufficient data were available from five trials[36,37,39,41,42] (667 patients; 55% of those included in this review) to estimate the RR of recurrence of exacerbations during the first year of treatment (figure 1). The RR was 0·73 (95% CI 0·54–0·99, p=0·04)—a 27% reduction in the number of patients who had had exacerbations.

Data from three trials [5,8,39] with 919 patients (76%) were available to calculate the number of patients who continued to have exacerbations during the first 2 years of treatment (figure 2). The overall results (0·81, 0·74–0·89, p<0·0001) indicated a benefit for interferon. However, patients randomised but excluded from analyses (withdrawn or lost to follow-up) had important effects on

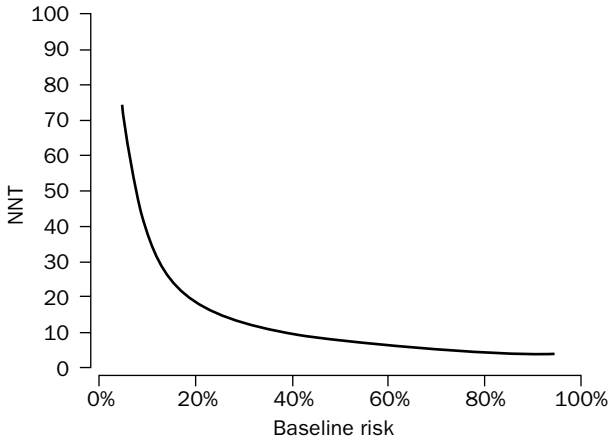

Figure 4: **NNT to prevent one patient having at least one exacerbation at 1 year in relation to baseline risks**

these results. The sensitivity analysis (worst-case scenario) showed no treatment effect (1·11, 0·73–1·68, p=0·6). This result was mostly accounted for by the study by the Multiple Sclerosis Collaborative Research Group, which presented results only at 2 years: only 57% of the patients randomised were analysed.[8]

The number of patients who had progressed at 2 years was available for three trials[5,8,39] and 919 (76%) patients (figure 3): 92 (20%) patients in the interferon groups and 131 (29%) controls. From these data we calculated an RR of 0·70 (0·55–0·88, p=0·002). However, the worst-case scenario in the sensitivity analysis showed complete disappearance of the treatment effect (1·31, 0·60–2·89, p=0·5), mostly because of the results of the Multiple Sclerosis Collaborative Research Group's study.[8]

The estimates of NNT to prevent one patient having at least one exacerbation at 1 year in relation to the baseline risks are shown in figure 4. 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.

Mean change in disability, measured by EDSS at 2 years, was available from only two trials,[5,39] (618 [51%] patients). The treatment effect was significant (weighted mean difference –0·25, 95% CI –0·05 to –0·46, p=0·01).

The number of patients who received steroids for exacerbations was not significantly reduced during the first year of interferon treatment compared with controls (RR 0·52, 95% CI 0·04–7·31, p=0·6). However, this result was based on only two small trials[37,42] (85 [7%] patients). The first of these[37] showed a non-significant reduction in the use of steroids in patients receiving interferon, but the second did not.[42] Data on steroid use for exacerbations over the 2 years from randomisation were available from one trial (371 [30%] patients);[39] steroid treatment was administrated less often in the interferon group (0·70, 0·56–0·87, p=0·001) than in controls.

Information on the frequency of admission to hospital over 2 years was available from two trials, (391 [32%] patients)[37,39] Hospital admissions were not reduced in patients on interferon compared with placebo (0·44, 0·08–2·36, p=0·3). Another study provided data only at 3 years; however, patients' participation in the third year had been optional.[5]

Clinical side-effects are shown in table 3. 48% of interferon patients and 28% of controls had influenza-like symptoms. Fever, myalgia, fatigue, and headache were recorded more frequently in interferon groups than in controls; the difference in frequency would have been larger if we had included duration of symptoms in the calculation. Injection-site reactions were also more common in treatment than control groups (62% *vs* 14%); the severity of skin reactions was not specified in any of the trials. Presence or absence of skin necrosis at the site of injection was recorded in two trials: this problem arose in 1–3% of patients[5] or not at all.[41] Hair loss was described in two studies[37,42] and affected 36% of patients on interferon and 2·5% on placebo. In one of these studies, this symptom was reported in 53% of patients on interferon during the first 6 months of treatment.[43]

Depression was reported in 16% of patients and did not differ between treated and control groups. Suicide or attempted suicide was reported in three studies, and affected seven patients (five of 466 treated and two of 453 controls).[5,8,39] Haematological toxic effects were recorded more often (table 3) in interferon-treated patients than in controls (haemoglobin reduction, 3·5% *vs* 1%; leucopenia, 6% *vs* 0·6%; lymphocytopenia, 27% *vs* 14%; thrombocytopenia, 3·5% *vs* 0·5%; increased aspartate aminotransferase, 4% *vs* 1%; increased alanine aminotransferase, 9% *vs* 3%). No information about any side-effects or adverse events was available beyond 2 years.

In one trial of interferon alfa-2a, quality of life was assessed with the eight scales of the SF-36 health survey, and was measured at baseline and 3, 6, and 12 months. Most domains of SF-36 tended to fall in the treatment groups at 3 and 6 months compared with placebo. The presence of fatigue, myalgia, headache, and weakness

	Number of trials	Treatment (events/patients)	Placebo (events/patients)	Relative risk (95% CI)	p
Influenza-like symptoms	4[5,8,39,41]	269/564	157/553	1·70 (1·23–2·37)	0·001
Fever	6[5,8,37,39,41,42]	168/606	81/593	2·01 (1·60–2·52)	<0·0001
Myalgias/arthralgias	6[5,8,37,39,41,42]	157/606	79/593	1·93 (1·51–2·45)	<0·0001
Fatigue	5[8,37,39,41,42]	82/482	57/470	1·37 (1·01–1·88)	0·05
Nausea and vomiting	2[8,42]	60/188	35/175	1·59 (1·11–2·28)	0·01
Headache	5[8,37,39,41,42]	241/482	200/470	1·16 (1·02–1·33)	0·02
Injection-site reactions	4[5,39,41,42]	268/436	60/442	5·57 (2·33–13·29)	0·0001
Hair loss	2[37,42]	15/42	1/40	9·78 (1·98–48·27)	0·005
Major psychiatric disorders	6[8,37,39,41,42]	96/606	97/593	0·98 (0·76–1·26)	0·8
Committed or attempted suicide	3[5,8,39]	5/466	2/453	1·95 (0·50–7·66)	0·3
Haemoglobin reduction	3[8,37,42]	7/200	2/183	2·84 (0·69–11·59)	0·15
Leucopenia	5[5,8,37,39,42]	29/510	3/494	6·47 (2·43–17·20)	0·0002
Lymphocytopenia	2[5,39]	82/308	43/310	2·16 (1·01–4·64)	0·05
Thrombocytopenia	3[8,37,42]	7/200	1/183	7·47 (0·98–57·15)	0·05
Increased AST	3[5,8,39]	17/466	6/453	2·83 (1·14–7·06)	0·03
Increased ALT	4[5,8,39,42]	46/496	13/485	3·43 (1·90–6·19)	<0·0001

AST=aspartate aminotransferase. ALT=alanine aminotransferase.

Table 3: **Results for clinical and haematological side-effects**

correlated inversely with most of the SF-36 domains at 3 and 6 months. These effects disappeared between 12 months after the start of treatment and 6 months after treatment ended.[43,44]

Additional unpublished information about MRI findings was provided by the sponsors of two trials:[6,40] in both there was a significant reduction in the total burden of MRI lesions in the interferon group compared with the control group at 1 and 2 years. Detailed MRI data were not available from a trial in which no significant difference was noted between the interferon patients and controls in total lesion burden from baseline to the second year of follow-up.[8] Data on gadolinium-enhancing lesions were available from 2 studies[8,42] after 1 year of treatment and from one study after 2 years for a sample of participants.[8] Fewer gadolinium-enhanced lesions had occurred in the interferon group than in controls at 1 year but not at 2 years. In six studies, treatment with recombinant interferon was associated with favourable changes in other MRI variables, such as the number of new lesions or number of enlarging lesions.[6,8,37,40-42]

Discussion

Our results show a modest protective effect of interferon against recurrence of exacerbations during the first year of treatment. This effect could not be confirmed during the second year since the results were highly dependent on what happened to the dropouts. We analysed all the randomised controlled trials undertaken so far on the use of interferon in patients with the relapsing-remitting form of multiple sclerosis. Most trials had major weaknesses. The commonest flaws were high dropout rates after randomisation, combined with failure to do an intention-to-treat analysis—even though most trialists specifically declared their intention to do such an analysis. Although 1215 patients were included in our review, only 919 (76%) contributed to the analysis of primary outcomes.

The number of patients who continued to have exacerbations was the only measure common to all trials and available for comparison between them. A quantitative analysis of rate and severity of relapse was not possible because of substantial differences between trials in assessment and reporting of methods.

Information on steroid use and hospital admissions was available in only three trials. Unless affected by blinding, we would expect such data to provide important corroboration of the supposed effect of interferon on clinical exacerbations. The available evidence does not indicate that patients treated with interferon require fewer hospital admissions and courses of steroids than untreated controls. We note, however, that in the years (1993–99) in which the seven trials were undertaken, there was a major shift to outpatient management of exacerbations, which might have masked any effect of treatment on hospital admissions.

Investigators in three trials reported that fewer patients progressed during 2 years of interferon treatment than controls.[5,8,39] The sensitivity analysis showed the fragility of this claim. The status of dropouts was clearly described for only one trial, in which they had a higher exacerbation rate, accumulated more disability, and had more active disease than patients who continued to be followed up.[5]

All studies included in our review defined progression as a sustained (3-month or 6-month) increase in EDSS score by at least one point recorded out of exacerbation. This definition meant that patients with exacerbations that lasted more than 3 months, who recovered slowly, could have been regarded as having unremitting disease progression. The extent of this misclassification of outcome in the three trials[5,8,39] in which progression was an outcome measure is unknown. In one of these trials,[8] half the patients on interferon who worsened in the first year, actually improved in the second.[45] The trial investigators claimed that interferon treatment prevented disease progression, but did not exclude the possibility that the findings showed that progression results had been biased by the attacks that were yet to remit. Furthermore, there was little support for an effect of interferons on disability.

Our estimate of NNT was possible only for the outcome at 1 year, since the results of the sensitivity analysis showed it was inappropriate to provide an estimate at 2 years. NNTs estimated by meta-analyses are applicable only to patients who are at the average risk level of trial participants.[46] Since patients with relapsing remitting multiple sclerosis have differing clinical courses, the expected clinical benefit of treatment should be related to the underlying risk of exacerbation.

Clinical and haematological toxic effects were greater in the interferon group than placebo group in all the trials, and acute toxic effects adversely affected quality of life.[43] Unfortunately, no data were given for the course and severity of the adverse events. 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 higher frequencies of leucopenia, lymphocytopenia, thrombocytopenia, and raised liver enzymes in blood than controls. Depression and depressive symptoms did not seem to be a major problem in the first 2 years of treatment with interferon in the six trials in which this factor was investigated.[5,8,37,39,41,42] This potential side-effect may have been reduced by the exclusion of patients prone to depression in subsequent trials after results of the first trial showed raised frequency of psychiatric symptoms in interferon-treated patients.[5]

We conclude from our meta-analysis that there is evidence for a modest effect of interferon in the first year of treatment in reduction of the number of patients with relapsing remitting multiple sclerosis having exacerbations. However, although interferon is widely used in clinical practice and patients are treated for long periods, its clinical effect beyond 1 year is not clear, and should be assessed.

Contributors

G Filippini and G P A Rice conceived the idea and development of the project, designed the protocol, appraised the relevance and validity of the papers, coordinated the review, analysed the results, and wrote the text of the review. G P A Rice abstracted data and wrote to sponsors of trials for additional information. B Incorvaia and L Munari took part in the search strategy, abstracted data, and helped in the analysis of the results and the writing of the text of the review. C Polman assisted in the design of the protocol, abstracted data, assisted in data interpretation, and reviewed the manuscript drafts. R D'Amico assisted in statistical analysis and writing of the text of the review. G C Ebers assisted in the design of the protocol, data interpretation, and reviewed the manuscript drafts.

Conflict of interest statement

The review was assembled, analysed, and reported independently of any pharmaceutical company. G Filippini received travel expenses from Farmades pharmaceutical company for participating at neurological conferences. G P A Rice participated in clinical trials sponsored by Schering, Serono, Berlex, Biogen, and Teva. He received honoraria from these companies. G Ebers received honoraria for lectures found to be sponsored by relevant companies and was an investigator for several clinical trials in multiple sclerosis including three interferon studies involving funding from Schering and Serono. He does not feel his opinions are affected by these associations. C Polman received honoraria for lecturing and consultancy from companies producing interferon beta, and participated in clinical trials sponsored by Schering and Biogen. L Munari, R D'Amico, and B Incorvaia had no conflict of interest.

Acknowledgments

We thank Jon Deeks, Alessandro Liberati, Bernard MJ Uitdehaag, Silvio Garattini, John Cornell, Walter Torri, Alan Thompson, Silvana Simi, Daniela Lupo, and Lorenzo Brait for useful comments during the preparation of the manuscript, and Don C Ward for help with the English. G Filippini and the study were funded by a grant from the Fondazione Italiana Sclerosi Multipla.

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