Randomised double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis

*PRISMS (Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) Study Group**

Summary

Background Previous trials of interferon β in multiple sclerosis (MS) have shown efficacy, but the degree of clinical benefit remains uncertain, and the optimum dose is not known. We undertook a double-blind, placebo-controlled study in relapsing/remitting MS to investigate the effects of subcutaneous interferon β-1a.

Methods 560 patients with Kurtzke expanded disability status scale (EDSS) scores of 0–5·0, from 22 centres in nine countries, were randomly assigned subcutaneous recombinant interferon β-1a 22 μg (n=189), or 44 μg (n=184), or placebo (n=187) three times a week for 2 years. Neurological examinations were done every 3 months. All patients had MRI twice yearly and 205 had monthly scans in the first 9 months of treatment. Analysis was by intention to treat.

Findings Clinical data on 533 (95%) patients were available at 2 years. The relapse rate was significantly lower at 1 and 2 years with both doses of interferon β-1a than with placebo (mean number per patient 1·82 for 22 μg group, 1·73 for 44 μg group *vs* 2·56 for placebo group: risk reductions 27% [95% CI 14–39] and 33 [21–44]). Time to first relapse was prolonged by 3 and 5 months in the 22 μg and 44 μg groups respectively, and the proportion of relapse-free patients was significantly increased ($p<0·05$). Interferon β-1a delayed progression in disability, and decreased accumulated disability during the study. The accumulation of burden of disease and number of active lesions on MRI was lower in both treatment groups than in the placebo group.

Interpretation Subcutaneous interferon β-1a is an effective treatment for relapsing/remitting MS in terms of relapse rate, defined disability, and all MRI outcome measures in a dose-related manner, and it is well tolerated. Longer-term benefits may become clearer with further follow-up and investigation.

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See Commentary

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Introduction

Therapeutic advances in multiple sclerosis (MS) have been slow to emerge, partly because of incomplete understanding of the pathogenesis of the disorder. For empirically based treatment the major obstacles to progress include the highly variable course of MS, the long-term nature of the most important outcome measures, and the lack of objective markers of treatment effect, particularly in the short term. Although the pathogenesis of MS remains uncertain, the natural history continues to be studied.[1–6] Objective outcome measures based on magnetic resonance imaging (MRI) have been developed[7–11] and many of the pitfalls of clinical trials are now known, which has led to improved trial methods and better interpretation of results.[12]

Two double-blind, placebo-controlled studies have shown interferon β to be active in relapsing/remitting MS at various doses and by different routes of administration, but evidence of efficacy has not been universally accepted.[13–18] The first of the studies used interferon β-1b, which is produced in *Escherichia coli* and which differs from natural interferon β by two aminoacids and by its lack of a glycosylated side-chain. At the high dose tested (8 million IU subcutaneously on alternate days), that study showed a 34% decrease in the relapse rate and a pronounced decrease in accumulation of disease burden as measured by the volume of T2-weighted lesions on MRI after 2 years. However, the effect of treatment on progression in disability was not significant[8,9,13] There was some concern over the high immunogenicity of interferon β-1b and the possible consequences for treatment efficacy.[13]

The second phase 3 study[14] used interferon β-1a, which is produced in mammalian cells, and which has the same aminoacid sequence and carbohydrate side-chain as the natural human cytokine. In that trial, patients with mild relapsing/remitting MS (scores on the Kurtzke expanded disability status scale [EDSS] of 1·0–3·5) were treated with weekly intramuscular injections of 30 μg for 1–2 years. The treatment had some effect on relapses (not significant at 1 year, 18% reduction at 2 years), and some effect on the MRI T2-weighted burden of disease.[14,19] There was a significant delay in 6-month confirmed progression by 1 point in the lower part of the EDSS, which measures impairment and not disability. However, the clinical significance of that result was unclear because of the small numbers of patients, the premature termination of the trial, the small and delayed effect on relapses, several analytical and methodological issues, and the disparity between the data on T2-weighted burden of disease and the data from the interferon β-1b trial.[16]

Our double-blind, randomised, placebo-controlled study with interferon β-1a addressed some of the questions raised by the other trials for the major outcome measures relapse rate, disability, and disease activity and burden of

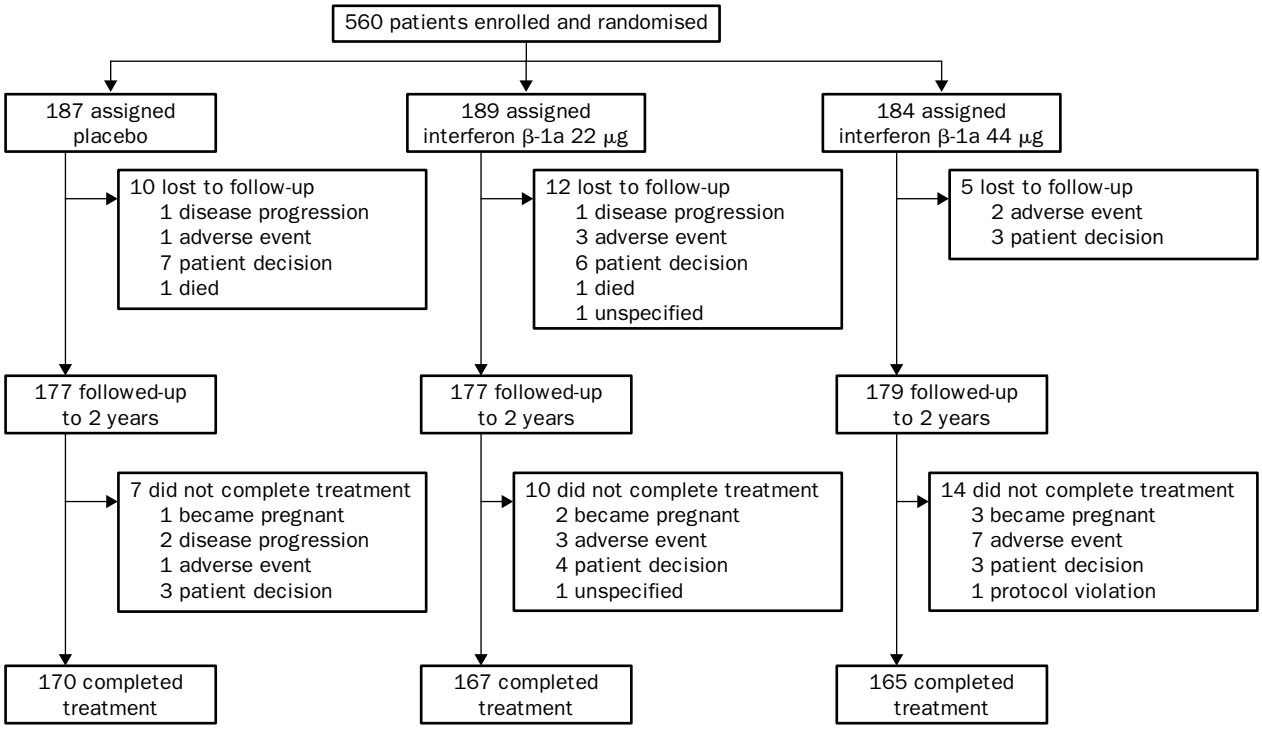


Figure 1: **Trial profile**

disease shown by MRI. The primary hypothesis was that interferon β-1a would lower the relapse rate. Earlier studies[13,20,21] suggested a dose effect, so we chose more intensive regimens of interferon β-1a for our study (66 and 132 μg per week). Since the bioavailability of the particular formulation of interferon β-1a that we used (Rebif, Ares-Serono) is comparable after subcutaneous and intramuscular injection,[22] the subcutaneous route was chosen because it is more convenient for the patient.

Methods

Patients

We studied 560 patients from 22 centres in nine countries, who had clinically definite or laboratory-supported definite MS[23] of at least 1 year's duration. Patients were recruited between May, 1994, and February, 1995.[24] Adults with relapsing/remitting MS were eligible for study if they had had at least two relapses in the preceding 2 years and had Kurtzke EDSS scores of 0–5·0.[25] Exclusion criteria included any previous systemic treatment with interferons, lymphoid irradiation, or cyclophospamide, or with other immunomodulatory or immunosuppressive treatments in the preceding 12 months. Only 3% of patients had received immunosuppressive therapy before that cut-off time. The study was approved by institutional review boards in the participating centres. All patients gave written informed consent. At the start of the study we established an Investigator Liaison Committee for liaison between the sponsor (Ares-Serono International SA) and ourselves. The Investigator Liaison Committee appointed an Independent Monitoring Committee that was responsible for review of safety information and for supervision of the study.

Design

Patients were randomly assigned interferon β-1a (Rebif, Ares-Serono) 22 μg (6 million IU), 44 μg (12 million IU), or placebo given three times weekly by subcutaneous injection. The randomisation list was computer-generated by Serono Biometrics and stratified by centre. The study drug was packed accordingly and delivered to the centres so that treatment allocation remained concealed. Equal allocation of the three treatment groups was used with a block size of six. Interferon β-1a, produced in Chinese hamster ovary cells, is glycosylated and identical to native human interferon β.[26] The total volume of the subcutaneously injected dose was 0·5 mL and study medication was usually self-administered. The dose was gradually increased over 4–8 weeks, with 20% of the dose given for 2–4 weeks and 50% for another 2–4 weeks before the full dose was given, to lessen expected side-effects. If WHO grade II or III toxic effects occurred, study medication was decreased to half dosage or temporarily discontinued. For WHO grade IV toxic effects and for protocol violations including non-compliance and unacceptable adverse events, patients were withdrawn from treatment. Paracetamol could be prescribed prophylactically for influenza-like side effects.

All personnel involved in the study were unaware of treatment allocation. Patients were assessed by two physicians. A "treating" neurologist was responsible for overall medical management of the patient, including treatment of any side-effects, and an "assessing" neurologist was responsible for neurological assessments and follow-up of relapses. All injection sites were covered up at neurological examinations to ensure that masking was not compromised because of local reactions. Relapses could be treated with a standard regimen of 1·0 g intravenous methylprednisolone for 3 consecutive days.

All patients had a neurological assessment every 3 months. Additional assessments were done during relapses and within 48 h of all MRI scans. All patients had proton density T2-weighted scans twice yearly, and a subgroup of 205 patients had monthly proton density T2 and T1 gadolinium-enhanced scans before and during the first 9 months of the trial. Scans were analysed centrally by the University of British Columbia MS/MRI Analysis Research Group (Vancouver, Canada) and treatment allocation was concealed from these researchers.

Patients had haematology and biochemical tests, including liver-function tests, every 2 weeks for the first 8 weeks, and then every 3 months. Thyroid-function tests were done every 6 months. Serum samples were tested for antibodies to interferon β every 6 months by SCL Bioscience Services (Cambridge, UK). Positive samples were tested for interferon β neutralising antibody (NAB) activity by RBM (Ivrea, Italy). NAB positivity was defined as a titre of 20 neutralising units or more per mL.

The primary outcome measure was the relapse count over the course of the study. Relapse, as defined by Schumacher and colleagues,[27] required the appearance of a new symptom or worsening of an old symptom over at least 24 h that could be

Characteristic	Total (n=560)	Placebo (n=187)	Interferon β-1a 22 μg (n=189)	Interferon β-1a 44 μg (n=184)
Age				
Median (IQR)	34·9 (29·1–40·4)	34·6 (28·8–40·4)	34·8 (29·3–39·8)	35·6 (28·4–41·0)
Australia (n=50)	34·4 (30·2–40·1)	33·6 (30·2–39·5)	35·7 (29·6–40·3)	34·4 (32·3–38·1)
Belgium (n=70)	34·9 (29·9–41·0)	33·6 (28·4–39·4)	34·9 (29·9–42·5)	36·7 (30·2–41·1)
Canada (n=109)	36·7 (31·3–41·4)	37·0 (33·0–43·4)	36·3 (32·0–41·2)	36·0 (26·9–43·5)
Finland (n=54)	35·5 (29·2–40·4)	37·2 (29·1–45·6)	35·5 (31·4–41·6)	33·7 (24·5–37·3)
Germany (n=30)	32·9 (27·2–37·2)	30·7 (25·7–35·4)	34·8 (31·3–39·1)	33·8 (27·2–37·2)
Netherlands (n=70)	32·9 (26·4–37·6)	30·7 (26·2–37·1)	33·1 (27·4–36·3)	33·0 (26·4–37·9)
Sweden (n=30)	36·5 (28·9–41·1)	36·6 (23·1–42·1)	31·1 (28·9–36·5)	39·9 (30·3–43·8)
Switzerland (n=40)	33·1 (26·6–41·4)	30·3 (24·7–41·1)	34·5 (26·6–41·8)	34·9 (30·7–41·0)
UK (n=107)	34·7 (30·0–40·5)	34·5 (32·0–38·8)	34·5 (28·4–39·1)	37·4 (31·0–44·6)
Sex				
M/F(%)	31/69	25/75	33/67	34/66
Australia (n=50)	30/70	35/65	19/81	35/65
Belgium (n=70)	36/64	21/79	43/57	43/57
Canada (n=109)	28/72	17/83	37/63	31/69
Finland (n=54)	26/74	33/67	22/78	22/78
Germany (n=30)	30/70	20/80	40/60	30/70
Netherlands (n=70)	31/69	29/71	29/71	36/64
Sweden (n=30)	40/60	30/70	60/40	30/70
Switzerland (n=40)	25/75	8/92	33/67	31/69
UK (n=107)	31/69	28/72	29/71	36/64
History of MS				
Duration (years)	5·3 (2·8–10·0)	4·3 (2·4–8·4)	5·4 (3·0–11·2)	6·4 (2·9–10·3)
Australia (n=50)	4·3 (3·0–7·9)	3·3 (1·9–7·1)	4·5 (3·7–7·7)	6·2 (3·1–9·2)
Belgium (n=70)	5·9 (2·4–8·9)	6·3 (2·8–7·9)	4·9 (2·3–7·5)	6·9 (2·0–9·9)
Canada (n=109)	5·7 (2·4–11·8)	4·2 (2·1–11·5)	8·0 (2·8–12·6)	6·1 (2·2–11·5)
Finland (n=54)	6·4 (3·3–11·3)	4·6 (2·7–11·0)	7·6 (4·3–15·3)	5·4 (3·3–9·3)
Germany (n=30)	4·1 (2·9–7·2)	3·6 (2·9–4·2)	5·0 (2·6–13·2)	5·8 (3·4–8·2)
Netherlands (n=70)	4·4 (2·8–8·3)	3·6 (2·6–7·6)	4·8 (2·6–8·5)	4·7 (2·9–8·2)
Sweden (n=30)	6·7 (2·6–9·8)	3·2 (2·6–5·6)	7·1 (6·2–9·2)	10·6 (2·4–15·2)
Switzerland (n=40)	5·5 (3·0–12·1)	3·3 (1·8–6·4)	4·5 (3·4–14·5)	11·3 (6·4–15·4)
UK (n=107)	5·8 (2·9–11·4)	5·6 (3·2–11·2)	4·1 (2·1–11·4)	7·2 (3·2–13·3)
Relapses in previous 2 years*				
Number of relapses	3·0 (1·2)	3·0 (1·3)	3·0 (1·1)	3·0 (1·1)
% of patients with				
2 relapses	41	41	43	40
3 relapses	33	36	29	34
⩾4 relapses	26	23	28	26
Australia (n=50)	2·9 (0·8)	2·8 (0·9)	3·1 (1·1)	2·8 (0·6)
Belgium (n=70)	2·7 (0·9)	2·6 (0·8)	2·7 (0·9)	3·0 (1·1)
Canada (n=109)	2·8 (1·1)	2·8 (1·2)	2·8 (1·1)	2·9 (1·0)
Finland (n=54)	3·2 (1·4)	2·9 (1·3)	3·6 (1·5)	3·1 (1·4)
Germany (n=30)	3·3 (1·3)	3·1 (0·9)	2·8 (0·8)	4·0 (1·8)
Netherlands (n=70)	2·9 (1·0)	3·0 (1·1)	2·8 (0·9)	2·8 (1·1)
Sweden (n=30)	3·5 (1·4)	3·7 (1·8)	3·7 (1·2)	3·1 (1·0)
Switzerland (n=40)	3·0 (1·2)	3·2 (1·7)	2·7 (1·0)	3·2 (1·0)
UK (n=107)	3·2 (1·2)	3·5 (1·4)	3·1 (1·1)	3·0 (1·1)
EDSS at baseline				
Score*	2·5 (1·2)	2·4 (1·2)	2·5 (1·2)	2·5 (1·3)
% of patients with score				
⩽1·5	32	33	30	31
2·0–2·5	27	28	27	26
3·0–3·5	24	24	24	26
⩾4·0	17	15	19	17
Australia (n=50)	2·5 (1·2)	2·1 (1·1)	2·6 (1·21)	2·9 (1·1)
Belgium (n=70)	2·6 (1·1)	2·4 (1·2)	2·8 (1·1)	2·5 (1·1)
Canada (n=109)	2·3 (1·3)	2·3 (1·3)	2·5 (1·4)	2·0 (1·1)
Finland (n=54)	2·8 (1·2)	2·6 (1·1)	3·0 (1·2)	2·8 (1·3)
Germany (n=30)	2·6 (1·1)	2·8 (1·0)	2·5 (1·2)	2·5 (1·1)
Netherlands (n=70)	2·5 (1·2)	2·7 (1·4)	2·3 (1·1)	2·5 (1·1)
Sweden (n=30)	2·3 (0·9)	2·3 (0·8)	2·1 (1·0)	2·5 (1·1)
Switzerland (n=40)	2·5 (1·1)	2·0 (1·0)	2·5 (1·1)	2·8 (1·1)
UK (n=107)	2·5 (1·4)	2·5 (1·3)	2·5 (1·3)	2·4 (1·7)

Data are median (IQR) or *mean (SD).

Table 1: **Baseline characteristics**

attributed to MS activity and was preceded by stability or improvement for at least 30 days. We requested a visit to the study centre within 7 days of relapse for confirmation and assessment of severity by the assessing neurologist. Severity of relapses was measured by the Scripps neurological rating scale (mild: decrease of 0–7 points; moderate: 8–14 points; severe: 15 points or more) or the activities of daily living scale (mild: no effect; moderate: significant effect; severe: hospital admission).

Other efficacy measures were times to first and second relapse, proportion of relapse-free patients, progression in disability, defined as an increase in EDSS of at least 1 point sustained over at least 3 months, ambulation index,[28] arm-function index,[29] need for steroid therapy and hospital admission, and disease activity under MRI and burden of disease. In our initial analysis we added the integrated disability status scale (IDSS),[30] a summary measure derived from the time/EDSS plot. The IDSS is defined as the area under a time/EDSS curve, with the use of a trapezoidal rule and adjustment for baseline EDSS.[30] The more disabled patients who had a baseline EDSS of more than 3·5 were assessed as a separate group.

Since the incidence of depression among MS patients is high, and since a previous study showed that depression might be exacerbated by interferon β treatment,[13] we assessed the psychological status of 267 patients enrolled in English-speaking centres by means of the Beck's hopelessness scale, the Centre for Epidemiologic Studies' depression mood scale, and the general

	Placebo (n=187)	Interferon β-1a 22 μg (n=189)	Interferon- β-1a 44 μg (n=184)
Relapses per patient			
Mean	2·56	1·82*	1·73*
% reduction vs placebo	..	29	32
% reduction vs placebo (95% CI) by GLM log link	..	27 (14–39)	33 (21–44)
% relapse-free over 1 year	22	37*	45*
% relapse-free over 2 years	16	27†	32*
% with 1–2 relapses	39	45	40
% with ⩾3 relapses	45	28	28
Odds ratio, none *vs* any relapses (95% CI)	1·00	2·01 (1·21–3·35)†	2·57 (1·56–4·25)*
Moderate or severe relapses			
Mean	0·99	0·71*	0·62*
% with 0 relapses	42	61	62
% with 1–2 relapses	47	32	32
% with ⩾3 relapses	11	7	6
Odds ratio, none *vs* any (95% CI)	1·00	2·13 (1·41–3·21)*	2·32 (1·47–3·37)*
Steroid courses			
Mean	1·39	0·97†	0·75*
% with 0 courses	44%	58%	61&
% with 1–2 courses	36%	27%	30%
% with ⩾3 courses	20%	15%	9%
Odds ratio (95% CI)	1·00	1·71 (1·14–2·57)†	1·99 (1·32–3·02)*
Hospital admission for MS			
Mean	0·48	0·38	0·25*
% with 0 admissions	75	77	82
% with 1–2 admissions	20	20	16
% with ⩾3 admissions	5	3	2
Odds ratio (95% CI)	1·00	1·11 (0·69–1·77)	1·54 (0·93–2·54)
Changes in EDSS			
Mean (SD)	0·48 (1·3)	0·23 (1·3)†	0·24 (1·1)†
Difference from placebo (95% CI)	..	–0·25 (–0·50 to 0)†	–0·25 (–0·50 to 0)†
Ambulation index			
2-step increase sustained for 3 months (%)	13	12	7†

*p<0·005 compared with placebo. †p⩽0·05 compared with placebo.

Table 2: **Clinical endpoints**

health questionnaire.

Statistical analysis

Analysis was by intention to treat. All outcome data were included. The data from the few patients who withdrew from the study early were retained in the statistical analyses, if relevant, by use of a censoring mechanism, an offset for the time spent in the study, or calculation of a rate that was standardised for the time spent in the study. The study had a power of 80% to detect a mean difference of 0·64 in the mean number of relapses between the 44 μg group and the placebo group. With an effect size of 0·4 (mean 0·64, SD 1·62), a two-sample two-sided *t* test at p=0·05 needed a minimum sample size of 100 patients per group. For each endpoint, a global model was fitted that took account of centre and treatment, but their interaction was not significant in any of the models and was thus removed. A generalised linear model (GLM) with a log link and variance proportional to the mean was used to analyse relapse count. We used Cox proportional hazards models for time to event endpoints, logistic regression for binary outcomes, ANOVA on rank data for other continuous endpoints, and χ^2 tests for counts of patients with particular categories of adverse event. In our protocol, the main comparison of interest was that between the high-dose (44 μg) and placebo groups, but no trend test was done for the three groups. The analysis of more disabled patients with baseline EDSS of more than 3·5 used a model that controlled for treatment, centre, baseline EDSS cohort, and treatment by baseline EDSS cohort.

	Placebo (n=187)	Interferon β-1a 22 μg (n=189)	Interferon β-1a 44 μg (n=184)
All patients			
First quartile time to progression (months)	11·9	18·5*	21·3*
Risk ratio (95% CI)	1·00	0·68 (0·48–0·98)*	0·62 (0·43–0·91)*
Group with high baseline EDSS (>3·5)			
First quartile time to progression (months)	7·3	7·5	21·3*
Risk ratio (95% CI)	1·00	0·75 (0·35–1·56)	0·42 (0·18–0·99)

Progression=1 or more steps in the EDSS, sustained for at least 3 months.
*p<0·05 compared with placebo.

Table 3: **Time in months to confirmed progression in disability**

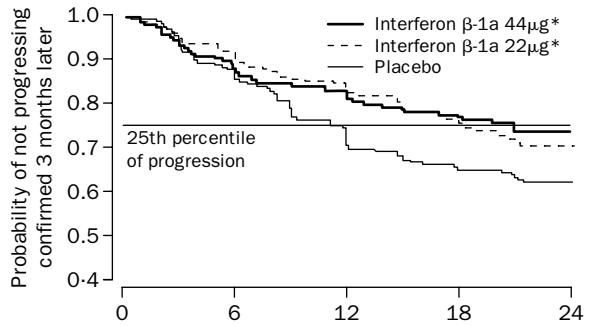
Results

Patients

Of the 560 patients randomised, 533 (95%) completed 1 year of treatment and 502 (90%) completed 2 years of treatment. 2 years of data were available for 533 (95%) patients, including follow-up for most patients who stopped treatment prematurely, to give a total of 1094 patient-years of observation (figure 1). 58 patients discontinued treatment prematurely; 17 had an adverse event, 26 patients decided to stop treatment, six became pregnant, four had disease progression, two died of unrelated causes, one violated protocol, and two discontinued for unspecified reasons. Baseline characteristics were similar among the three treatment groups (table 1). The median age and the male-to-female ratio were characteristic of patients with relapsing/remitting MS.

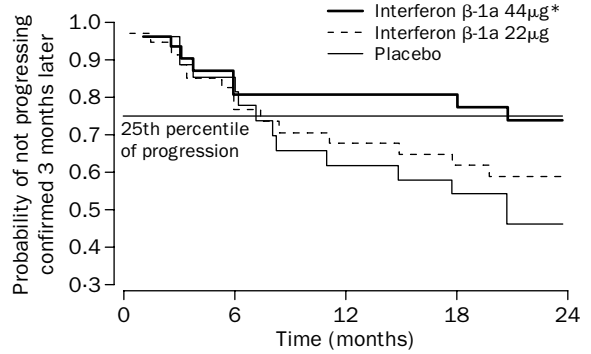
Relapses

The mean number of relapses during the 2 years of the



Patients at risk (n)

Placebo	161	126	117	110
Interferon β-1a 22μg	171	151	137	125
Interferon β-1a 44μg	161	147	139	130



Patients at risk (n)

Placebo	22	18	14	11
Interferon β-1a 22μg	28	23	21	20
Interferon β-1a 44μg	26	25	25	22

Figure 2: **Time to confirmed progression in disability in whole study group (top) and in patients with baseline EDSS >3·5**
*p<0·05 compared with placebo.

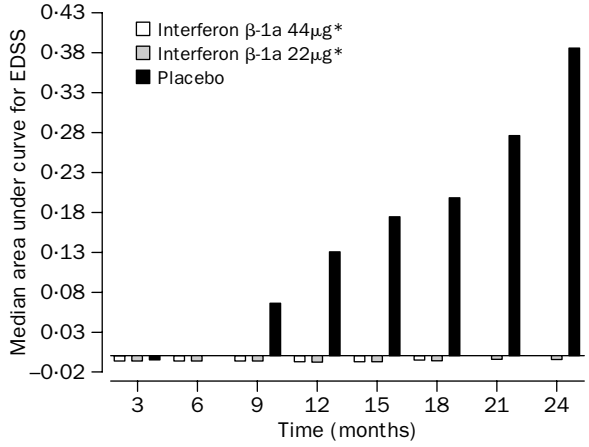


Figure 3: **Evolution of median IDSS**
*p<0·05 compared with placebo.

study was lower in both interferon β-1a groups than in the placebo group (table 2; p<0·005). The percentage reduction for the 22 μg dose against placebo was 27% (95% CI 14–39%), and that for the 44 μg dose against placebo was 33% (21–44). The mean number of moderate and severe relapses during the 2-year follow-up period was also lower in both interferon β-1a groups than in the placebo group (p<0·005). Moreover, median time to first relapse was delayed by 3 and 5 months in the 22 μg and 44 μg groups respectively. Similar results were observed after the first year of treatment (33% and 37% lower relapse rates for 22 μg and 44 μg doses respectively *vs* placebo, p<0·0001).

Other efficacy measures

Time to sustained progression was significantly longer (p<0·05) in both interferon β-1a treatment groups than in the placebo group (table 3, figure 2). The IDSS (area under EDSS curve) showed that recipients of interferon β-1a therapy did not increase their score during the study (median IDSS stayed at 0), but that the placebo group showed a gradual increase of 0·4 IDSS steps per year (figure 3). In the group with high baseline EDSS (>3·5) the time to sustained progression was significantly longer than in the placebo group only in the 44 μg group (table 3, figure 2). The treatment benefits were similar if scores from unplanned visits, generally for acute relapses, were excluded from the IDSS analysis.

Significant treatment effects were noted over 2 years for mean EDSS change (p<0·05), for number of steroid courses (p≤0·05), and, at the higher dose, for mean number of times a patient was admitted to hospital and for progression in the ambulation index (table 2, p<0·05). The arm-function index did not change significantly in any group. Few patients (17% overall) deteriorated according to this assessment; thus there was not adequate sensitivity to treatment effect. the relative insensitivity of this measure has been shown by Barnes and colleagues.[29]

The burden of disease measured with proton density T2 MRI showed a progressive median increase of 10·9% in placebo-treated patients, whereas the 22 μg group showed a median decrease of 1·2% and the 44 μg group a median decrease of 3·8% (p<0·0001 compared with placebo for both doses). The number of T2 active lesions on the biannual scans was also significantly lower (difference 67% and 78%) in the low-dose and high-dose groups than in the placebo group (p<0·0001), and there

	Placebo (n=187)	Difference from placebo (95% CI)	
		Interferon β-1a 22 μg (n=189)	Interferon β-1a 44 μg (n=184)
Symptoms and signs			
Headache	43·9	3·2 (–6·8 to 13·3)	1·3 (–8·9 to 11·4)
Influenza-like symptoms	24·1	0·8 (–7·9 to 9·5)	3·1 (–5·8 to 12·0)
Injection-site reactions	21·9	38·9 (29·8 to 48·1)*	40·0 (30·9 to 49·2)*
Fatigue	15·5	–1·2 (–8·4 to 6·0)	3·0 (–4·7 to 10·6)
Myalgia	8·0	4·7 (–1·50 to 10·8)	5·6 (–0·7 to 11·9)
Fever	6·4	6·8 (–0·1 to 14·8)	5·5 (–1·7 to 13·1)
Laboratory measurement			
Lymphopenia	3·7	1·0 (–4·4 to 7·3)	9·3 (2·4 to 16·7)*
Increased alanine aminotransferase	1·1	3·7 (–0·8 to 9·5)	5·4 (0·2 to 11·4)*
Leucopenia	1·6	2·6 (–2·0 to 8·4)	6·5 (0·9 to 12·9)*
Increased aspartate aminotransferase	1·1	1·0 (–3·0 to 6·1)	2·2 (–2·5 to 7·3)
Granulocytopenia	1·1	2·6 (–1·7 to 8·2)	7·1 (1·6 to 13·4)*

*p≤0·05 compared with placebo.

Table 4: **Adverse events (% of patients) in first 3 months of therapy**

was a dose-effect in favour of the 44 μg dose over the 22 μg dose (p=0·0003).

Safety and tolerability

In general, interferon β-1a was tolerated well. Adverse events previously shown with interferon β were common. These events (eg, influenza-like symptoms) are common in the general population and their frequency in the placebo group was high, probably because of the long duration of the study. Therefore, analysis of the first 3 months of treatment was more discriminating (table 4). Injection-site reactions did not differ between the lower and higher doses of interferon β-1a, although they were more common in both than in the placebo group. Significant asymptomatic decreases in white cells, neutrophils, and lymphocytes, and raised aminotransferase values were seen with interferon β-1a compared with placebo (table 4, p≤0·05). These effects were more pronounced in patients receiving the higher dose, and generally lessened during the second year of treatment. There were 17 (3%) adverse events that resulted in dropout from the study: two in the placebo group, six in the 22 μg group, and nine in the 44 μg group. The reasons for discontinuation of treatment were depression (five) asymptomatic rises in aminotransferase (two), injection-site reactions (two), influenza-like symptoms (two), and lymphopenia, anaphylactoid reaction, colon cancer, palpitation, psychological disturbance, or septicaemia (one each).

There were no significant differences among these three groups in any of the measures of psychological status at any time during the study. Depression was reported by 52 (28%) placebo-treated patients, by 39 (21%) patients receiving interferon β-1a 22 μg, and by 44 (24%) patients receiving 44 μg interferon β-1a. One placebo-treated patient committed suicide during the study, and three patients in each group attempted suicide or reported suicidal thoughts.

At baseline, only one patient was positive for neutralising antibodies to interferon β. At the end of treatment, 23·8% of patients receiving 22 μg and 12·5% of patients receiving 44 μg had neutralising antibodies. The presence of neutralising antibodies did not affect the mean relapse count (22 μg group 1·80 *vs* 1·77 in patients without neutralising antibodies; 44 μg group 1·75 *vs* 1·74).

Discussion

Our study showed that for all major outcome measures—

relapse, sustained progression in functional impairment and disability, and MRI lesion change including lesion burden and "activity" measures—there were significant benefits from subcutaneous treatment with interferon β-1a at either of two doses. The reduction in relapse rate from that with placebo (27–33%) is similar to that shown in the interferon β-1b study[9] and to that shown with copolymer 1,[31] and greater than that previously reported for interferon β-1a in a study that used weekly intramuscular injections and a substantially lower dose (18%).[14]

In a large population-based natural history study, Weinshenker and colleagues[2] showed that a high relapse frequency early in MS correlated with 10-year disability outcome, and a 25-year follow-up of the patients from that study showed that the relation becomes stronger with time.[32] Whether treatment-related decrease in relapses actually leads to a decrease in long-term disability remains to be shown.

In our study, the time to sustained progression in disability showed a significant increase at either dose. The IDSS, a summary measure of disability, allowed us to quantify both temporary and unremitting disability during the study period—it therefore has several advantages over the standard measure of time to confirmed progression. The IDSS showed significant treatment effects at both doses. Although this result is encouraging, further research is needed to assess the IDSS as a surrogate marker for longer-term outcomes. The issue of accumulating disability in trials of relapsing/remitting MS has been debated, particularly in terms of what constitutes progression in a short-term trial using the standard Kurtzke EDSS.[16] Small changes (1 point) at the lower end of the scale in the short term have not been validated as surrogates for longer-term outcomes, and are less stable than changes at the higher end of the scale.[33] Confirmed 1-point progression, which was suggested by a previous study as a suitable outcome measure in patients with MS, is acceptable in the context of treatment trials for progressive MS.[34] We acknowledge that disability related to relapse may affect the disability scores, although we reduced this bias by requiring confirmation after 3 months. This requirement was not met in the trials of intravenous immunoglobulin[35] and copolymer I.[31] If the disability scores measured within 6 weeks of a relapse were excluded from our data on the high-dose group, the treatment effect on progression remained significant.

The MRI findings of this study support the clinical findings on relapse rates and delay in disease progression. The results also showed a significant dose effect, in favour of the 44 μg dose. This dose effect is stronger than that for interferon β-1a given by intramuscular injection at a lower dose,[14] and confirms the effect on lesion burden shown with interferon β-1b.[8,9]

Our choice of medication doses was informed by previous reports of a dose effect, and findings that a dose three times weekly gave a more sustained improvement in interferon β-1a concentrations and biological markers than a once-weekly dose.[13,20,21,36] Both treatment groups showed significant benefit over placebo. Dose effects were shown for most clinical outcome measures including relapse rates and severity, and were stronger for MRI outcomes. In the subgroup of patients likely in the short term to develop progressive MS (baseline EDSS >3·5), the 44 μg dose delayed progression of disability significantly better than either 22 μg or placebo (table 3). In addition, neutralising antibodies were significantly less frequent in the 44 μg group than in the low-dose group.

Assessment of treatment effects on long-term disability in MS in the context of a prospective study is difficult. Double-blind controlled studies in MS are difficult to run for longer than 2 or 3 years, and high dropout rates have confounded analysis. Accordingly, to gauge the effects of interferons on long-term outcomes, researchers have had to extrapolate these results to show what might happen over many years. By contrast, our study had a low dropout rate. We have also extended our study, with placebo patients randomly assigned two doses of interferon β-1a in an attempt to obtain definitive results to compare the efficacy of the two doses in the longer term.

The safety profile in the doses used in our trial was reassuring. Although comparison of safety profiles between trials is difficult, our findings were similar to previous findings on interferon β-1a,[14] which seems to have a better profile than interferon β-1b particularly in terms of local injection-site reactions, neutralising antibodies, and influenza-like symptoms. In this study, neutralising antibodies seemed to have no negative effect. However, given the results of other studies[37] more detailed analysis is underway. Serum antibody concentrations generally wane with time.[38] Mild injection-site reactions were common, but there were only eight episodes of skin necrosis out of a total of more than 150 000 injections during the study. Skin necrosis never occurred more than once in the same patient, and may have been caused by inadvertent intracutaneous injection. No patient discontinued injections because of necrosis. Treatment allocation may have been revealed because adverse events were listed on the consent form, and because these event occurred frequently in the active treatment groups. However, events characteristic of type-1 interferons occurred frequently in the placebo group. Furthermore, a revealed treatment allocation would not have affected the MRI results, the relapses confirmed by objective neurological assessments, or the consistent trend in favour of the 44 μg dose. Although we identified asymptomatic lymphopenia, granulocytopenia, and thrombocytopenia, and slightly raised liver aminotransferase values, no serious toxic effects were shown in this trial through laboratory monitoring. The explanation for our finding of a lower proportion of patients with neutralising antibodies to interferon in the higher-dose than in the lower-dose group could be the induction of high-zone tolerance[39] in patients treated with the 44 μg dose. An effect of antibody is plausible and is supported by studies of MS and other disorders treated by interferon.

This study shows that subcutaneous interferon β-1a has a good safety profile and offers clinical benefits to patients by reducing exacerbations and delaying progression of disability over 2 years. Follow-up of patients from this study will define more clearly whether the profound effects observed on MRI translate into longer-term clinical benefits.

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