Effect of Interferon-β1b on Magnetic Resonance Imaging Outcomes in Secondary Progressive Multiple Sclerosis: Results of a European Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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A randomized placebo-controlled trial of interferon-β1b was performed on 718 patients with secondary progressive multiple sclerosis with follow-up of up to 3 years. In addition to clinical variables, serial magnetic resonance imaging (MRI) studies were performed to determine the effect of treatment on the pathological evolution of the disease. All patients eligible for MRI had annual proton density/T2-weighted brain scans from which total lesion volume was measured and the number of new and enlarging lesions noted. A subgroup of 125 patients also underwent monthly gadolinium-enhanced and proton density/T2-weighted brain MRI from months 0 to 6 and 18 to 24 to determine the effect of treatment on the frequency of new lesion activity, defined as new enhancing lesions and new/enlarging T2 lesions not enhancing with gadolinium. The difference in total lesion volume between treatment groups was highly significant. In the placebo group, there was an increase of 15% from baseline to last scan, whereas in the interferon-β1b group, a reduction of 2% was seen. Within the placebo group, there was a significant year-on-year increase in total lesion volume, with a mean increase of 16% at year 3 compared with baseline. In the treated group, there was a significant reduction at year 1 (4%) and year 2 (5%) compared with baseline; the 2% decrease at year 3 was not significant. The number of new or enlarging proton density/T2 lesions was also significantly reduced by treatment. In the frequent MRI subgroup, treatment was associated with a significant 65% reduction in new lesion activity between months 1 and 6, and 78% reduction from months 19 to 24. Interferon-β1b has a substantial and sustained effect on reducing the accumulation of new inflammatory disease foci in secondary progressive MS. This therapeutic mechanism may contribute to the positive clinical benefits of treatment on the progression of sustained neurological disability and relapse activity that were also identified in this trial.

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Recent randomized placebo-controlled trials have convincingly demonstrated a favorable effect of interferon-β (IFN-β) on clinical and magnetic resonance imaging (MRI) outcomes in ambulant patients with relapsing–remitting multiple sclerosis (RRMS).[1–6] Reductions in the relapse rate of about one-third have been consistently reported,[1,2,6] along with, in most[4–6] but not all[2,3] instances, an impressive reduction in MRI activity and change in brain total lesion volume (TLV). A trial of IFN-β1b in RRMS reported a median reduction of new lesions on T2-weighted imaging of about 80%, and whereas total T2 lesion load increased by about 5% to 10% per annum in the placebo group, there was no net change in lesion load in the treated group during a 4-year period.[4,5] The effect of IFN-β1b on monthly gadolinium enhancing lesions has not yet been evaluated in a placebo-controlled trial, although a study of a small cohort of relapsing–remitting patients,

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using a baseline crossover design, suggested that there might be a treatment-associated reduction in the number of enhancing lesions of about 80%.[7]

To date, there have been no published studies regarding the effect of IFN-β on MRI outcomes in patients with secondary progressive MS (SPMS). A recently completed European multicenter, placebo-controlled trial has reported clinical benefits in this patient subgroup, with a significant slowing in the sustained progression of disability being the main clinical result.[8] The present report concerns the MRI outcomes of this large trial.

Patients and Methods

Seven hundred eighteen patients with SPMS were recruited from 32 European centers into a randomized, double-blind, placebo-controlled trial of IFN-β1b planned for 3 years. The trial design and inclusion and exclusion criteria of the patients have been fully described elsewhere.[8,9] The study was performed according to ICH Harmonised Guidelines: Guidelines for Good Clinical Practice, and all patients provided informed written consent before treatment. SPMS was defined as having had a previous relapsing–remitting course, but subsequently entering a phase of gradual clinical progression, with or without superimposed relapses, for at least 6 months. Entry Expanded Disability Status Scale (EDSS) score was 3.0 to 6.5, inclusive, and patients were required to have had either two relapses or a 1-point increase in the EDSS during the 2 years before entering the study. All patients were randomized to treatment with either placebo or IFN-β1b (Betaseron), 8 million IU, subcutaneously on alternate days. The primary outcome was time to a 1-point increase in the EDSS (or a 0.5 increase if the baseline EDSS was 6 or 6.5) confirmed at two consecutive assessments at least 3 months apart. All the MRI studies performed at the individual centers were transferred to the MRI Analysis Centre (Institute of Neurology, University College London, Queen Square, London, UK), where analyses were performed by staff who were totally blinded to the clinical details.

MRI Acquisition Protocol

Two types of MRI assessment were planned to evaluate different aspects of the pathology and its modification by treatment. Protocols were developed accordingly.

LESION EXTENT OR CHANGES IN BRAIN TLV. To evaluate this outcome, yearly proton density (PD) and T2-weighted conventional spin echo (SE) scans were acquired in all patients. The parameters were as follows: repetition time (TR) = 2 to 2.5 seconds; short echo time (TE) = 30 to 40 msec; long TE = 80 to 100 msec; 28 axial oblique, contiguous, interleaved, 5-mm-thick slices; matrix = 256 × 256; field of view = 25 cm; one or two excitations. The electronic data from each site were used to quantify TLV. Repositioning was achieved by using a protocol based on identification of standardized anatomical landmarks.[10]

LESION ACTIVITY. A subgroup of 125 patients from seven centers also underwent monthly gadolinium-DTPA (Gd)-enhanced T1-weighted SE (TR = 500–700 msec; TE = 5–25 msec; 256 × 256 matrix; slice thickness = 5 mm; 28 axial oblique, contiguous, interleaved slices) and PD/T2-weighted SE or fast SE imaging from months 0 to 6 and 18 to 24. Acquisition of the T1-weighted scan was begun 5 to 7 minutes after the Gd injection. The dose of Gd was 0.1 mmol/kg, although one site inadvertently used 0.05 mmol/kg for the first 6 months. The analyses were therefore performed with and without this site included (no differences in outcome were seen). At month 0, a T1-weighted SE sequence was also obtained before the administration of Gd. Hard copies of the annual scans in all 718 patients were also analyzed to count the number of new and enlarging lesions.

For both types of MRI assessments, images were not obtained within 1 week of corticosteroid use, to avoid bias between treatment groups.

MRI Analysis

TLV. All MRI scans at each site were archived onto hard copy film and electronic media and transported to the MRI analysis site. The hard copy was analyzed by a group of experienced clinical raters, working in pairs, who marked and roughly outlined on an overlaid transparency every lesion visible on the PD-weighted scan. First, lesions were identified and marked on the baseline scan. The month 12 study was then compared side by side with the baseline scan, and lesions were marked on the month 12 study. In parallel with this process, all new and enlarging lesions that had developed between these time points were identified and marked by consensus. This same approach was used to assess the month 24 against month 12 studies, and the month 36 against month 24 studies. Finally, a review of the entire scan series was performed to ensure a high standard of consistency in lesion delineation across the whole scan data set. This approach, therefore, identified all the lesions to be included in the TLV quantification and also documented the number of new and enlarging lesions seen on each annual follow-up scan.

The electronic data were received from the scanning sites on their usual archive media, and in their particular scanner's data format. They were first transferred to a "JukeBox" system, attached to a network of Sun Workstations (Sun Microsystems, Palo Alto, CA), and then converted to a single common format understood by all the subsequent display and analysis tools. The data were sorted by site, patient ID and scan date, and duplicate images (from scans repeated resulting from artifacts or patient motion, or because of multiple archiving, or other problems) were discarded. Throughout both the data conversion and sorting, the original hard copy (received from the site immediately after a scan was completed) was used to ensure that both the image data themselves, and the associated patient data (eg, initials, date of birth, and scan date) were correctly maintained.

A group of raters, previously trained to ensure a high level of reproducibility (see below), performed the TLV analysis as follows: (1) The hard copy with all lesions outlined was placed alongside the identical computer-generated image. (2) All lesions marked on the hard copy were outlined on the computer image, using the semiautomated local thresholding contour technique,[11–13] or, if the lesion could not be outlined satisfactorily with this approach, manual outlining was

performed. (3) After all lesions had been outlined, another observer checked the consistency of lesion identification from hard copy to computer image, and any lesions missed in the latter were outlined by the original rater. (4) A computer program then summed all the individual lesion volumes (calculated as the surface area of each lesion multiplied by the slice thickness [5 mm in all cases]) and a final TLV was generated and stored in a specially constructed database.

Before starting to analyze the computerized images from the trial patients, each rater underwent a period of comprehensive training in the use of the quantitative technique. Once a rater had developed a sufficient level of expertise in application of the technique, performance was evaluated by using a standardized MR data set, comprising the PD-weighted brain images of 16 MS patients with a representative range of lesion loads.[13] Each rater measured the brain lesion load on two separate occasions, separated by an interval of at least 1 week. The minimum acceptance criteria for passing this validation procedure was considered to be a median intrarater coefficient of variation of less than 5%. Only once this had been demonstrated was a rater allowed to start work on the trial data set.

LESION ACTIVITY. In the subgroup of those who also had monthly scans from months 0 to 6 and 18 to 24, all hard copy images were analyzed for lesion activity changes by two experienced observers working by consensus. The following outcomes were studied:

(1) The number of newly active lesions during months 1 to 6 (secondary efficacy end point of this study) and 19 to 24. A newly active lesion was defined as an area of new Gd enhancement or as a new or newly enlarging PD/T2 lesion that did not enhance.

(2) The number of persistently active lesions during months 1 to 6 and 19 to 24. These are lesions that had been newly enhancing on a previous scan, but continued to enhance on follow-up studies, or (very rarely) that continued to enlarge without enhancement, having been newly active on a previous scan.

(3) The number of active scans. These are scans that contained one or more newly active lesions, during months 1 to 6 and 19 to 24.

(4) The number of active patients. These are patients who had one or more newly active lesions, during months 1 to 6 and 19 to 24.

For the core annual protocol (all patients), the annual PD/T2-weighted scans were analyzed by experienced raters, working by consensus in pairs (see above), to determine the following: *(1) the number of active* (ie, new or enlarging) *lesions; (2) the number of active scans* (ie, that contained one or more active lesions); and *(3) the number of active patients* (ie, who displayed one or more active lesions at some stage during follow-up).

Statistical Analysis

The percentage change in TLV at end point (last scan available) and the number of newly active lesions during months 1 to 6 were secondary end points for this study; all other MRI end points were considered to be tertiary. Statistical analyses were based on the intention-to-treat population, including all data of all patients as randomized without any restrictive criteria. Data up to final termination of the study were evaluated (including data collected after the time of cutoff for the interim analysis, which lead to early termination of the study). At the time of interim cutoff, all patients had completed at least 24 months. Thus, the data set for the subgroup of patients who underwent monthly scans in months 1 to 6 and 19 to 24 was complete at month 24.

The initial rationale for sample size for the frequent MRI subgroup was based on the work of Nauta and colleagues.[14] Their results indicated that with a 6-monthly Gd-enhanced T1-weighted imaging, a sample size of approximately 54 patients per group would allow the detection of a 60% reduction in the total number of newly active lesions. Additional calculations were performed by Petkau,[15] based on substudy results from the trial of IFN-β1b in RRMS, which concludes that a sample size of about 60 per group should be a minimal requirement.

Baseline lesion volume and baseline number of enhancing lesions were compared between groups by using the Wilcoxon rank sum test. Nonparametric statistical methods[16,17] were used for the analysis of all MRI end points, and p values from two-sided statistical tests were provided.

CHANGE IN TLV ON ANNUAL MRI. Treatment groups were compared for percentage and absolute changes in lesion volume from baseline, using a nonparametric analysis of covariance with stratification adjustment for center and covariance adjustment for baseline lesion volume and center. Additional year-by-year analyses were performed post hoc. Only patients with a valid baseline scan and at least one valid on-study scan were included in the analyses. No correction was made for missing values.

LESION ACTIVITY ON FREQUENT MRI. The cumulative number of newly active lesions during months 1 to 6 and months 19 to 24 (month 18 considered as second baseline) were analyzed separately. Values were assigned to missing monthly MRI lesion counts by means of linear interpolation and extrapolation from available data. Patients with missing baseline scans were not used in the analyses. The treatment group comparison of the cumulative number of newly active lesions was done by using a nonparametric analysis of covariance with covariance adjustment for baseline number of lesions and stratification adjustment for center.

The above-specified statistical methods for the treatment comparison for cumulative numbers of newly active lesions were also applied to persistently active lesions during months 1 to 6, and months 19 to 24.

The proportion of scans that showed lesion activity and the proportion of active patients were compared between treatments for the two time periods separately, using the extended Mantel-Haenszel test with stratification adjustment for center.

Table 1. Annual MRI Analysis: Absolute and Percentage Change in TLV from Baseline

		Placebo	IFN-β1b	p^a
Baseline TLV	n	344	346	
	Mean (SD)	28.35 (22.46)	26.62 (21.17)	
	Median	23.82	21.6	0.4117
Absolute change in TLV from baseline (cm^3)				
Year 1	n	321	329	
	Mean (SD)	1.31 (4.82)	−1.22 (4.19)	
	Median	0.30	−0.77	<0.0001
	p^b	<0.0001	<0.0001	
Year 2	n	302	308	
	Mean (SD)	2.30 (7.58)	−1.53 (5.99)	
	Median	0.40	−1.06	<0.0001
	p^b	<0.0001	<0.0001	
Year 3	n	274	293	
	Mean (SD)	4.26 (8.97)	−0.61 (7.32)	
	Median	1.79	−0.73	<0.0001
	p^b	<0.0001	0.1530	
Last scan	n	330	334	
	Mean (SD)	4.16 (8.94)	−0.73 (6.99)	
	Median	1.70	−0.74	<0.0001
	p^b	<0.0001	0.0562	
Percentage change in TLV from baseline				
Year 1	Mean (SD)	3.60 (14.31)	−3.71 (17.12)	
	Median	1.64	−4.94	<0.0001
	p^b	<0.0001	0.0001	
Year 2	Mean (SD)	7.77 (23.31)	−4.77 (24.97)	
	Median	2.42	−6.92	<0.0001
	p^b	<0.0001	0.0009	
Year 3	Mean (SD)	16.01 (32.68)	−1.61 (25.75)	
	Median	10.98	−5.24	<0.0001
	p^b	<0.0001	0.2847	
Last scan[c]	Mean (SD)	15.37 (31.30)	−2.14 (24.57)	
	Median	9.67	−5.34	
	p^b	<0.0001	0.1125	<0.0001

[a]Nonparametric analysis of covariance with stratification adjustment for center and covariance adjustment for baseline TLV and center (except baseline comparison: Wilcoxon rank sum test).
[b]*t* test for significance of within-group change from baseline.
[c]Secondary efficacy end point of this study.

MRI = magnetic resonance imaging; TLV = total lesion volume; IFN-β1b = interferon-β1b.

Table 2. Annual MRI Analysis: Change in Absolute TLV from Previous Year (cm^3)

		Placebo	IFN-β1b	p^a
Year 0–1	n	321	329	
	Mean (SD)	1.31 (4.82)	−1.22 (4.19)	
	Median	0.30	−0.77	<0.0001
	p^b	<0.0001	<0.0001	
Year 1–2	n	306	318	
	Mean (SD)	1.04 (5.20)	−0.23 (3.50)	
	Median	0.15	−0.20	0.0012
	p^b	0.0005	0.2464	
Year 2–3	n	272	296	
	Mean (SD)	2.32 (5.51)	0.88 (3.75)	
	Median	1.04	0.37	0.0002
	p^b	<0.0001	0.0001	

In Table 2, changes were evaluated compared with previous year including all patients with available data at two successive years. Only patients with a valid baseline scan and at least one valid on-study scan were included in the analyses. No correction for missing values was made. In contrast, Table 1 is a display of absolute and percentage changes for each year compared with baseline where only patients with available data at baseline and the year of interest were included.

[a]Nonparametric analysis of covariance with stratification adjustment for center and covariance adjustment for baseline TLV and center.
[b]*t* test for significance of within-group change from previous year.

MRI = magnetic resonance imaging; TLV = total lesion volume; IFN-β1b = interferon-β1b.

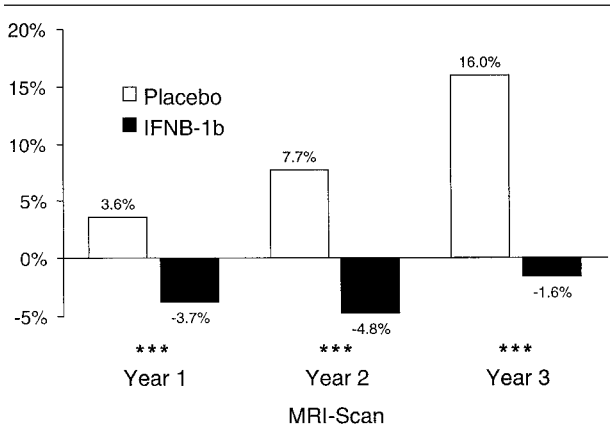

*Fig 1. Annual magnetic resonance imaging (MRI) analysis. Percentage change in total lesion volume (TLV) (mean) seen in the study cohort during years 1 to 3. Baseline = MRI scan at study entry. ***p < 0.0001, difference between treatment groups. IFNB-1b = interferon-β1b.*

LESION ACTIVITY ON ANNUAL MRI. For the number of new or enlarging lesions detected on annual MRI, treatment groups were compared by using the extended Mantel-Haenszel test, stratified for center. The proportion of active scans per patient and the proportion of active patients were also compared between treatment groups, using the extended Mantel-Haenszel test with stratification adjustment for center.

Results

Annual MRI Analysis

The placebo and IFN-β1b groups were well matched with respect to their baseline TLV (Table 1); median TLV was 23.8 cm^3 in the placebo and 21.6 cm^3 in the IFN-β1b group ($p = 0.41$, two-sided Wilcoxon rank sum test).

A highly significant treatment effect on the change in TLV was demonstrated ($p < 0.0001$), with an increase of 15% from baseline to last scan in the placebo group, whereas in the IFN-β1b group a reduction of 2% was seen (see Table 1).

In the placebo group, there was a significant increase in TLV at each yearly time point when compared with baseline TLV, and also when compared with the previous year's TLV (Table 2, see Table 1). The absolute and percentage increases in TLV were somewhat larger in the third than in the preceding 2 years. At year 3, the mean and median percentage increases in TLV compared with baseline were 16% and 11%, respectively, in the placebo group (see Table 1).

In the IFN-β1b group, there was a significant decrease in TLV at year 1 compared with baseline, with mean and median decrease of 4% and 5%, respectively (see Table 1). There was no significant change in TLV between years 1 and 2 ($p = 0.24$), but there was a significant increase in TLV during the third year ($p = 0.0001$), although to a lesser degree than that seen in the placebo group (see Table 2). The net effect of these changes was a nonsignificant reduction in TLV of 2% over the 3-year period.

When the placebo and IFN-β1b groups were compared, there was a highly significant difference in the TLV change, in favor of IFN-β1b at all three annual follow-ups compared with baseline (see Table 1; Fig 1), and also during each yearly interval, including year 2 versus year 1, and year 3 versus year 2 (see Table 2).

There was also a highly significant reduction in the number of new or enlarging lesions in the IFN-β1b group at all annual time points compared with baseline, apparent even at year 1 (Table 3; Fig 2). The mean and median reductions compared with placebo were 57% and 70%, respectively, during the 3 years of follow-up. In the placebo group, 70% of patients had activity on half or more of the follow-up scans, com-

Table 3. Annual MRI Analysis: Lesion Activity

		Placebo (n = 345)	IFN-β1b (n = 350)	p^a
Cumulative number of new or enlarging lesions calculated from baseline				
Year 1	Mean (SD)	3.76 (5.37)	1.48 (3.04)	
	Median	2.00	0	<0.0001
Year 2	Mean (SD)	6.67 (8.42)	2.65 (5.70)	
	Median	4.00	1.00	<0.0001
Year 3	Mean (SD)	8.82 (11.3)	3.77 (7.47)	
	Median	5.00	1.50	<0.0001
Proportion of active patients	n (%)	289 (83.8%)	225 (64.3%)	<0.0001
Proportion of active scans per patient				
0	n (%)	56 (16.2%)	125 (35.7%)	
<50%	n (%)	51 (14.8%)	91 (26.0%)	
≥50%	n (%)	238 (70.0%)	134 (38.3%)	<0.0001

[a]Extended Mantel-Haenszel test with stratification adjustment for center.

MRI = magnetic resonance imaging; IFN-β1b = interferon-β1b.

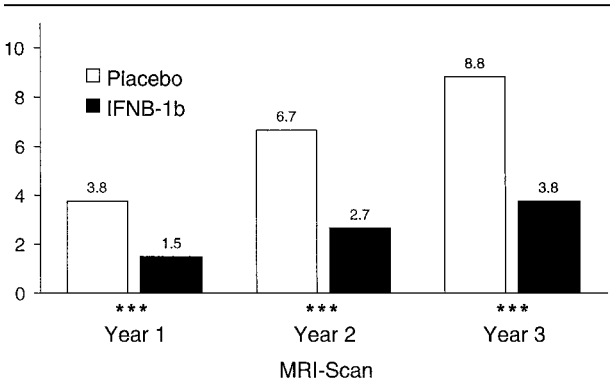

*Fig 2. Annual magnetic resonance imaging (MRI) analysis. Cumulative number of active lesions (mean) seen in the study cohort during years 1 to 3. Baseline = MRI scan at study entry. ***p < 0.0001, difference between treatment groups. IFNB-1b = interferon-β1b.*

pared with only 38% of the IFN-β1b patients ($p < 0.0001$). No active lesions were seen in 16% of placebo and 36% of IFN-β1b patients during the study period ($p < 0.0001$) (see Table 3).

Monthly MRI Activity Subgroup

At baseline, enhancing lesions were seen in 29 of 61 (47%) patients randomized to placebo and 31 of 64 (48%) patients randomized to IFN-β1b. There was no difference between the two groups in terms of the numbers of enhancing lesions at baseline (Table 4) (mean 2.21 in the placebo and 2.95 in the IFN-β1b group; $p = 0.87$, two-sided Wilcoxon rank sum test).

During the first 6 months of follow-up, there was a significant reduction in the cumulative numbers of new (65% mean decrease) and persistently (67% mean decrease) active lesions in the IFN-β1b versus placebo group (see Table 4); the difference in favor of treatment was apparent at every monthly time point and was already significant at the first month of follow-up ($p = 0.001$, for newly active lesions at month 1; $p < 0.001$, for persistent activity at month 1) (Figs 3 and 4). During the first 6 months of follow-up, 31% of placebo patients and 52% of IFN-β1b patients had no new active lesions ($p = 0.07$); 51% of placebo and 16% of treated patients had new active lesions on 50% or more of their MRI examinations during the same MRI period ($p = 0.0008$) (see Table 4).

At month 18, which served as a "second baseline" for scans in months 19 to 24, there was a mean of 2.43 enhancing lesions in the placebo group and 1.00 in the IFN-β1b group ($p = 0.0613$). During months 19 to 24 (Table 5), there were significantly fewer new (78% mean decrease) and persistently (88% mean decrease) active lesions in the IFN-β1b than in the placebo group. The difference in favor of treatment was apparent at every time point and was significant from month 19 onwards; 38% of placebo and 68% of IFN-β1b patients had no new active lesions during months 19 to 24 of follow-up ($p = 0.0046$); 40% of placebo and 13% of IFN-β1b patients had exhibited new active lesions on 50% or more of the follow-up scans during the same period ($p = 0.0009$) (see Table 5).

Discussion

This is the first placebo-controlled trial to evaluate the effect of IFN-β on the evolving pathological process in SPMS. It is also, by far, the largest study, to date, in MS in which MRI analysis has been performed. It reveals that IFN-β1b has a substantial effect on the pathological evolution of disease in patients with SPMS, and that the effect was sustained for the dura-

Table 4. Frequent MRI Subgroup Analyses: Lesion Activity During Months 1 to 6

Months 1–6		Placebo (n = 61)	IFN-β1b (n = 64)	*p*
Number of patients with enhancing lesions at baseline	n (%)	29 (47.5%)	31 (48.4%)	
Number of enhancing lesions at baseline	Mean (SD)	2.21 (3.83)	2.95 (6.56)	0.8686[a]
	Median	0	0	
Number of newly active lesions[b]	Mean (SD)	10.24 (14.14)	3.57 (10.24)	<0.0001[c]
	Median	5.00	0	
Number of persistently active lesions	Mean (SD)	3.10 (6.03)	1.02 (2.37)	0.0009[c]
	Median	1.00	0	
Proportion of active patients	n (%)	42 (68.9%)	31 (48.4%)	0.0634[d]
Proportion of active scans per patient				0.0008[d]
0	n (%)	19 (31.1%)	33 (51.6%)	
<50%	n (%)	11 (18.0%)	21 (32.8%)	
≥50%	n (%)	31 (50.8%)	10 (15.8%)	

[a]Wilcoxon rank sum test.
[b]Secondary efficacy end point of this study.
[c]Nonparametric analysis of covariance with stratification adjustment for center and covariance adjustment for baseline lesion number.
[d]Extended Mantel-Haenszel test with stratification adjustment for center.

MRI = magnetic resonance imaging; IFN-β1b = interferon-β1b.

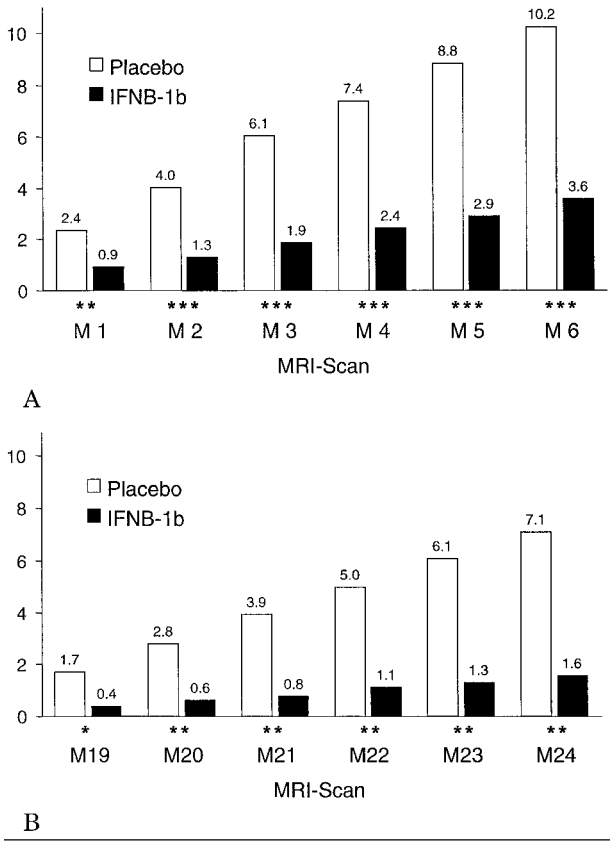

*Fig 3. Frequent magnetic resonance imaging (MRI) subgroup analysis. Cumulative number of newly active lesions (mean) seen in patients of the frequent MRI subgroup. (A) Lesion activity during months 1 to 6 (M1–M6). Baseline = MRI scan at study entry. (B) Lesion activity during months 19 to 24 (M19–M24). Baseline = MRI scan at month 18. *p < 0.01; **p < 0.001; ***p < 0.0001, difference between treatment groups. IFNB-1b = interferon-β1b.*

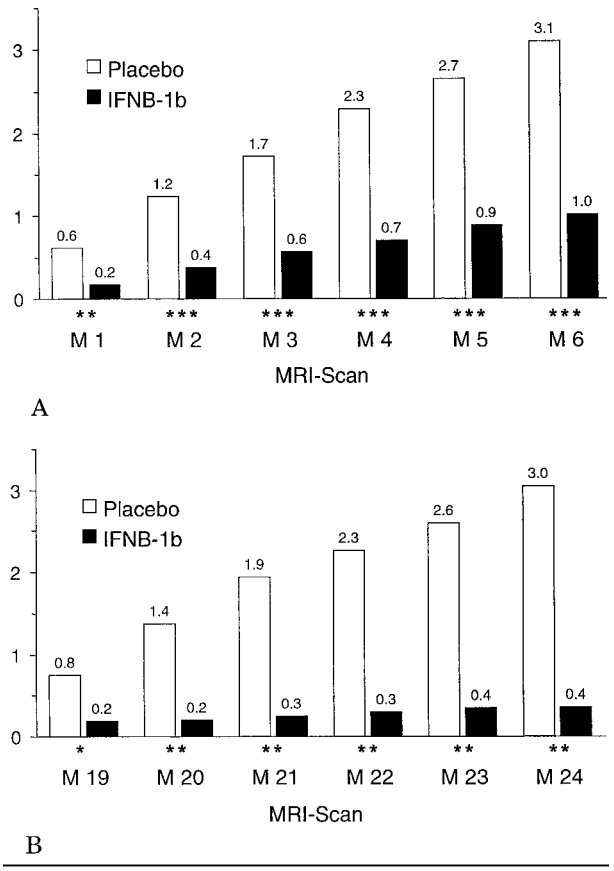

*Fig 4. Frequent magnetic resonance imaging (MRI) subgroup analysis. Cumulative number of persistently active lesions (mean) seen in patients of the frequent MRI subgroup. (A) Lesion activity during months 1 to 6 (M1–M6). Baseline = MRI scan at study entry. (B) Lesion activity during months 19 to 24 (M19–M24). Baseline = MRI scan at month 18. *p < 0.01; **p < 0.001; ***p < 0.0001, difference between treatment groups. IFNB-1b = interferon-β1b.*

tion of the trial (up to 3 years). The treatment effect was readily apparent for both the total volume of brain abnormality visible on T2-weighted images and the numbers of new, enlarging or contrast-enhancing lesions that appeared during the study period. The data strongly support the clinical evidence for efficacy demonstrated in this trial,[8] and the results are now discussed in more detail.

The baseline TLV was similar and generally large in both treatment arms of the study; mean and median TLV values were approximately twice those reported in previous trials involving cohorts of patients with relapsing–remitting disease. This is consistent with the results of previous studies of untreated cohorts.[18,19]

In the placebo-treated group, median TLV increased significantly year after year. The overall percentage increases from baseline (1.6%, 2.4%, and 10%, at 1, 2, and 3 years, respectively) are somewhat lower than those reported in previous relapsing–remitting placebo cohorts (~5–10% per annum); this largely reflects the much higher baseline TLV in the secondary progressive cohort, and the absolute increase in TLV is similar to that found in early relapsing–remitting cohorts. One might have anticipated a linear increase in TLV from year to year, but a greater increase was seen in the third year. Between years 2 and 3, several sites changed their scanner, with an increase in field strength and a noticeable improvement in image quality. Such changes can have an important impact on measured TLV,[20] and this may explain the year 2 to 3 result. However, any such effect would apply equally to both treatment arms (because of the randomization schedule treatments were balanced within centers), and the difference in outcome between the treatment groups was still clearly evident. Thus, during year 3, the median change in TLV was +1.05 cm^3 in the placebo group and +0.37 cm^3 in the IFN-β1b group ($p = 0.0002$).

In the treated group, there was a significant and sub-

Table 5. Frequent MRI Subgroup Analyses: Lesion Activity During Months 19 to 24

Months 19–24		Placebo (n = 53)	IFN-β1b (n = 56)	*p*
Number of patients with enhancing lesions at baseline (month 18)	n (%)	32 (57.1%)	24 (42.9%)	
Number of enhancing lesions at baseline (month 18)	Mean (SD)	2.43 (6.75)	1.00 (2.79)	0.0613[a]
	Median	0	0	
Number of newly active lesions (relative to month 18)	Mean (SD)	7.08 (11.05)	1.55 (5.19)	0.0008[b]
	Median	2.00	0	
Number of persistently active lesions (relative to month 18)	Mean (SD)	3.04 (6.30)	0.36 (0.52)	0.0004[b]
	Median	0	0	
Proportion of active patients	n (%)	33 (62.3%)	18 (32.1%)	0.0046[c]
Proportion of active scans per patient				0.0009[c]
0	n (%)	20 (37.7%)	38 (67.9%)	
<50%	n (%)	12 (22.6%)	11 (19.6%)	
≥50%	n (%)	21 (39.6%)	7 (12.5%)	

[a]Wilcoxon rank sum test.
[b]Nonparametric analysis of covariance with stratification adjustment for center and covariance adjustment for baseline (month 18) lesion number.
[c]Extended Mantel-Haenszel test with stratification adjustment for center.

MRI = magnetic resonance imaging; IFN-β1b = interferon-β1b.

stantial reduction in TLV evident at the first follow-up. The same phenomenon has been reported in two previous studies in RRMS.[4,6] This is likely to reflect both (1) the striking spontaneous resolution on T2-weighted images often seen in inflammatory/edematous lesions of recent origin even without therapeutic intervention, and (2) the effect of treatment on inhibiting new lesion development. It is also possible that IFN-β1b treatment facilitates a more rapid and complete resolution of preexisting active lesions by suppressing inflammation and creating a more favorable environment for effective repair to take place. This hypothesis is supported by the fact that enhancement persisted in significantly fewer baseline lesions at month 1 in the treated group, implying an effect on the duration of enhancement as well as its frequency. In the IFN-β1b group during the first year of follow-up, the effect of resolution of existing inflammatory/edematous lesions clearly outweighed the increase in TLV because of the small number of new lesions identified despite treatment. Further reduction in TLV was not seen beyond the first annual follow-up.

The treatment effect on the annual assessment of lesion activity on T2-weighted images was significant and sustained throughout the study; thus, treatment was associated with a 57% reduction in the mean and a 70% reduction in the median number of new or enlarging lesions. A similar magnitude of treatment effect was apparent in each of the 3 years of the study.

In the frequent MRI subgroup, a significant and sustained reduction in the number of new and persistently active lesions was found. In particular, there was no reduction of efficacy in the second period of frequent imaging. Indeed, a slight increase in treatment effect (vs placebo) was apparent; thus, in the first period, there was a 65% and 68% reduction in new and persistently active lesions, respectively; in the second period, the reduction was 78% for new and 88% for persistently active lesions. The overall levels of activity were about 30% lower in the second than the first period of follow-up. This could reflect either (1) regression to the mean, a well-recognized feature of some clinical disease activity measures (eg, relapse rate) in patients with MS recruited into treatment trials or natural history studies, or (2) patients who were particularly active during the first phase being lost to the trial. Furthermore, the results from the first month after starting treatment suggest a significant effect on the duration of enhancement in addition to the number of enhancing lesions per se. Although the pathological mechanisms underlying this effect are as yet unclear, possibilities include a more rapid repair of the blood–brain barrier on treatment and restriction of the inflammatory process of established lesions.

Gadolinium-enhancing lesions have been correlated in biopsy and postmortem studies with signs of active inflammation.[21–23] This observation, together with the moderate correlations recently reported between lesion volume on T2-weighted images and gadolinium enhancement,[19,24] suggests that IFN-β1b has a marked impact on the evolution of MRI markers of disease progression related to new inflammatory lesion formation. Such a therapeutic mechanism may underlie the beneficial clinical effects of IFN-β1b in reducing relapse rate and slowing the accumulation of disability.

The MRI outcomes do not quantify other patholog-

ical features found in MS lesions, in particular, demyelination and axonal loss, the substrates of permanent disability. Several other MRI markers that may be more specific to these processes (T1 low-signal lesion volume, brain and spinal cord atrophy, and lesion magnetization–transfer ratios) have also been acquired in the present trial, and the effect of IFN-β1b on these outcomes will be the subject of future reports.

In conclusion, the present study demonstrated that IFN-β1b has a substantial and sustained effect on reducing the accumulation of new inflammatory disease foci in SPMS. This therapeutic mechanism may contribute to the clinical benefits of treatment on the progression of sustained neurological disability and relapse activity that were the main clinical effects identified in this trial.

Appendix

MRI Investigators: Annual and Frequent Scans: Amsterdam: C. Polman,* J. Valk, F. Barkhof, J. H. van Waesberghe, T. Schweigmann; Helsinki: J. Wikström,* O. Salonen; London: D. Miller (members of MRI Central Evaluation Unit listed below); Milan: G. Comi,* M. Filippi, M. Rovaris; Munich: R. Hohlfeld,* T. A. Yousry, C. Becker, F. Stadie, P. Eppmann; Rennes: G. Edan,* M. Carsin, Y. Rolland; Würzburg: R. Gold,* H.-P. Hartung,* D. Hahn, W. Kenn, T. Pabst.

MRI Investigators: Annual Scans: Aberdeen: R. Knight,* J. E. C. Hern,* O. J. Robb; Barcelona: J. Montalbán,* A. Rovira, S. Pedraza; Basel: L. Kappos,* E. W. Radü; Belfast: S. Hawkins,* K. E. Bell,* C. S. McKinstry*; Berlin: H. Altenkirch, K. Baum, K. M. Einhäupl, P. Marx, R. Lehmann; Birmingham: D. Francis,* E. B. Rolfe; Bordeaux: B. Brochet,* V. Dousset; Cardiff: C. M. Wiles,* S. F. S. Halpin, M. D. Hourihan; Dublin: M. Hutchinson,* D. McErlaine; Düsseldorf: G. Stoll,* T. Kahn; Erfurt: H. W. Kölmel,* R. Kachel; Florence: L. Amaducci* (died 1998), L. Massacesi,* C. Fonda; Göttingen: S. Poser,* A. Riegel, B. Welskop; Groningen: J. Minderhoud,* J. De Keyser,* H. van Woerden, T. de Jong; Huddinge: S. Fredrikson,* B. Isberg; Leuven: G. Wilms, P. Demaerel; Lyon: C. Confavreux,* J.-C. Froment; Masku: M. Panelius,* P. Sonninen, H. Oivanen, J. Ruutiainen; Melsbroek: M. D'Hooghe*; Newcastle: N. Cartlidge,* A. Coulthard, P. English; Osnabrück: P. Haller,* A. W. Frank; Paris: O. Lyon-Caen,* E. Cabanis, M.-T. Iba-Zizen; Rome: C. Fieschi,* S. Bastianello, E. Giugni; Sheffield: S. J. L. Howell,* T. J. Hodgson, C. A. J. Romanowski; Toulouse: M. Clanet,* I. Berry, D. Ibarrolla, O. Martin; Vienna: H. Kollegger,* L. Deecke,* S. Trattnig.

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