Magnetic Resonance Imaging Effects of Interferon Beta-1b in the BENEFIT Study

Integrated 2-Year Results

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Background: In the Betaseron/Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) study, interferon beta-1b delayed conversion to multiple sclerosis in patients with a first clinical event and at least 2 clinically silent brain magnetic resonance imaging (MRI) lesions.

Objective: To examine detailed MRI findings from the first 2 years of this trial.

Design: Double-blind, placebo-controlled, randomized, parallel-group, multicenter, phase 3 study.

Setting: Ninety-eight centers worldwide.

Patients: A total of 404 individuals with a first demyelinating event suggestive of multiple sclerosis.

Interventions: Patients were randomized to receive interferon beta-1b, 250 µg subcutaneously every other day, or placebo. After 24 months of treatment or on conversion to clinically definite multiple sclerosis, open-label interferon beta-1b treatment was offered.

Main Outcome Measures: Reported MRI data from patients completing 2 years of follow-up.

Results: Data were analyzed from 248 patients taking interferon beta-1b and 156 taking placebo. Across 2 years the cumulative number of newly active lesions was lower in patients receiving interferon beta-1b vs placebo (median, 2.0 vs 5.0 [reduction of 60%]; $P<.001$). This corresponded to lower cumulative numbers of new T2 lesions (median, 1.0 vs 3.0 [reduction of 66%]; $P<.001$) and new gadolinium-enhancing lesions (median, 0.0 vs 1.0; $P<.001$) in patients receiving interferon beta-1b vs placebo. From screening to month 24, T2 lesion volume decreased and was more pronounced in patients receiving interferon beta-1b ($P=.02$).

Conclusions: Interferon beta-1b treatment had a robust effect on MRI measures, supporting its value as an early intervention in this patient group. This effect was maintained despite including patients who switched from placebo to interferon beta-1b in the active treatment group.

Trial Registration: clinicaltrials.gov Identifier: NCT00185211

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MULTIPLE SCLEROSIS (MS) has a natural history of progressive neurologic deterioration that can have profound effects on daily functioning and quality of life.[1,2] The presence and extent of magnetic resonance imaging (MRI) abnormalities at the time of the first clinical event suggestive of MS has a major impact on the probability of developing clinically definite MS (CDMS).[3] Magnetic resonance imaging also facilitates patient selection in clinical trials, provides information on the progression of subclinical disease, and is a sensitive technique for disease monitoring.[4,5]

Clinical studies in established MS have demonstrated the efficacy of interferon beta-1b in reducing the frequency and severity of relapses and the development of brain lesions assessed using MRI.[6-8] Moreover, once-weekly administration of interferon beta-1a, when initiated after the first clinical demyelinating event suggestive of MS, was shown to delay a subsequent diagnosis of CDMS and reduce MRI disease activity.[9,10] Such findings indicate that interferon beta treatment has a positive impact on the underlying pathophysiologic processes of MS, and this impact may be greatest when treatment is initiated early in the disease course.[11,12]

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The Betaseron/Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) trial has demonstrated the efficacy, safety, and tolerability of subcutaneous interferon beta-1b administered every other day in patients with a first clinical event and MRI evidence suggestive of MS.[13] Patients received interferon beta-1b or placebo for up to 24 months or until CDMS was reached. Most patients then chose to enter an ongoing preplanned open-label extension phase in which they were all offered active treatment. Kappos et al[13] reported the results of the double-blind phase of the study; treatment with interferon beta-1b markedly delayed the overall risk of conversion to CDMS within 2 years of observation, with a hazard ratio of 0.50 (95% confidence interval [CI], 0.3-0.70). Using the McDonald criteria for MS, which also take into account paraclinical findings, in particular from MRI, the conversion rate across 2 years in placebo-treated patients was much higher (85% vs 45% based on clinical findings only), but the hazard ratio of 0.54 (95% CI, 0.43-0.67) for the treatment effect was similar.[13]

Results of the double-blind phase of the BENEFIT study show that interferon beta-1b also had favorable effects on some MRI variables.[13] However, because double-blind treatment was terminated when a patient was diagnosed as having CDMS, the previous study did not cover an observation period of 24 months in many cases. Herein we report detailed MRI data obtained in the BENEFIT study across an observation period of 24 months for all patients, regardless of whether they completed this period in the double-blind period or the open-label extension period.

METHODS

STUDY DESIGN, PATIENTS, AND PROCEDURES

The design and main outcomes of the double-blind treatment phase of the BENEFIT trial have been reported elsewhere.[13] Briefly, BENEFIT was a double-blind, placebo-controlled, randomized, parallel-group, multicenter (N=98), phase 3 study that evaluated the safety, tolerability, and efficacy of interferon beta-1b (Betaseron; Bayer HealthCare Pharmaceuticals Inc, Montville, New Jersey), 250 µg subcutaneously every other day, in patients with a first demyelinating event suggestive of MS. Eligible patients (aged 18-45 years) had a monofocal or multifocal presentation of the disease and were required to have presented with a first neurologic event suggestive of MS that lasted for at least 24 hours and to have at least 2 clinically silent lesions on a T2-weighted brain MRI with a minimum size of 3 mm, of which at least 1 was ovoid, periventricular, or infratentorial. The baseline Expanded Disability Status Scale score was 0.0 to 5.0. Patients with signs and symptoms that could be explained by a disease other than MS, a previous demyelinating event, complete transverse myelitis or bilateral optic neuritis, or previous immunosuppressive therapy were excluded. Study treatment was initiated within 60 days after establishment of the first clinical event. Patients were randomized in a 5:3 ratio to receive interferon beta-1b, 250 µg, or placebo subcutaneously every other day for up to 24 months or until CDMS was diagnosed according to the modified Poser criteria.[13,14] During this double-blind phase, visits were scheduled for collection of Expanded Disability Status Scale, MRI, and other efficacy data and for safety data at months 3, 6, 9, 12, 18, and 24.

All the patients who completed the double-blind treatment phase as planned (converting to CDMS or completing 24 months of double-blind treatment) were offered enrollment into a single-arm follow-up study involving treatment with open-label interferon beta-1b, 250 µg subcutaneously every other day, for at least 3 years. This extension study was prospectively designed to evaluate the long-term impact of early vs delayed intervention with interferon beta-1b on the progression of neurologic disability and brain MRI findings across 5 years. When patients entered the extension phase, further assessments, including MRI, were scheduled at yearly intervals with respect to the baseline visit.

All the MRIs were performed at 0.5 to 1.5 T and included transaxial contiguous 3-mm dual-echo T2-weighted images and T1-weighted images after injection of 0.1 mmol/kg of gadolinium (Gd)-diethylenetriamine pentaacetic acid. Whenever possible, MRI was performed before corticosteroids were administered for the clinically isolated syndrome (CIS) or a relapse. All of an individual patient's MRI was performed using the same machine. Assessment of the MRIs was performed centrally at the Image Analysis Centre at the Vrije Universiteit Medical Center. The quality assessment included a trial-specific standard operating procedure, training specifications (including a dummy-run procedure for site selection), and internal quality control procedures. During the trial each MRI was subjected to a routine quality control procedure, and additional MRIs were obtained when quality standards were not met.

The numbers and volumes of hyperintense lesions on T2-weighted images (T2 lesions) and Gd-enhancing (Gd lesions) and hypointense lesions on T1-weighted images (T1-hypointense lesions) were determined by evaluators who were blinded to treatment allocation but not to MRI order. Because all the MRIs were performed after Gd administration, T1-hypointense lesions were defined as the subset of new or enlarging lesions on T2-weighted images that were isointense to hypointense relative to gray matter on T1-weighted images. Lesions were identified by trained (adjunct) radiologists who marked the MS lesions on hard copy[15,16]; their volumes were subsequently determined electronically by trained technicians using in-house–developed software (Show_Images version 3.6.3) based on local thresholding.

STATISTICAL ANALYSES

Analyses were performed using data from all the patients who received treatment at least once and had MRIs up to 24 months (at least at months 12 and 24) in the double-blind or the follow-up study (integrated data set of the double-blind and follow-up study). Treatment effects were evaluated with respect to the original treatment allocation regardless of a change in treatment (mostly from placebo to interferon beta-1b) after conversion to CDMS. Efficacy analyses were performed for cumulative counts of new lesions occurring at subsequent visits using the number of enhancing lesions at screening as a covariate and for the change in lesion volumes from the screening MRI to the month 24 visit.

The treatment effect on all MRI efficacy variables defined below was assessed by means of univariate nonparametric analysis of covariance[17] using corresponding MRI variables from the screening MRI as covariates. The nonparametric Wilcoxon-Mann-Whitney rank sum test was used to compare baseline MRI findings between treatment groups. Spearman rank correlation coefficients were calculated to investigate any association between MRI variables.

Two secondary MRI efficacy variables were predefined[13]: the cumulative number of newly active lesions (NALs), defined as new Gd lesions or, if nonenhancing on T1-weighted images,

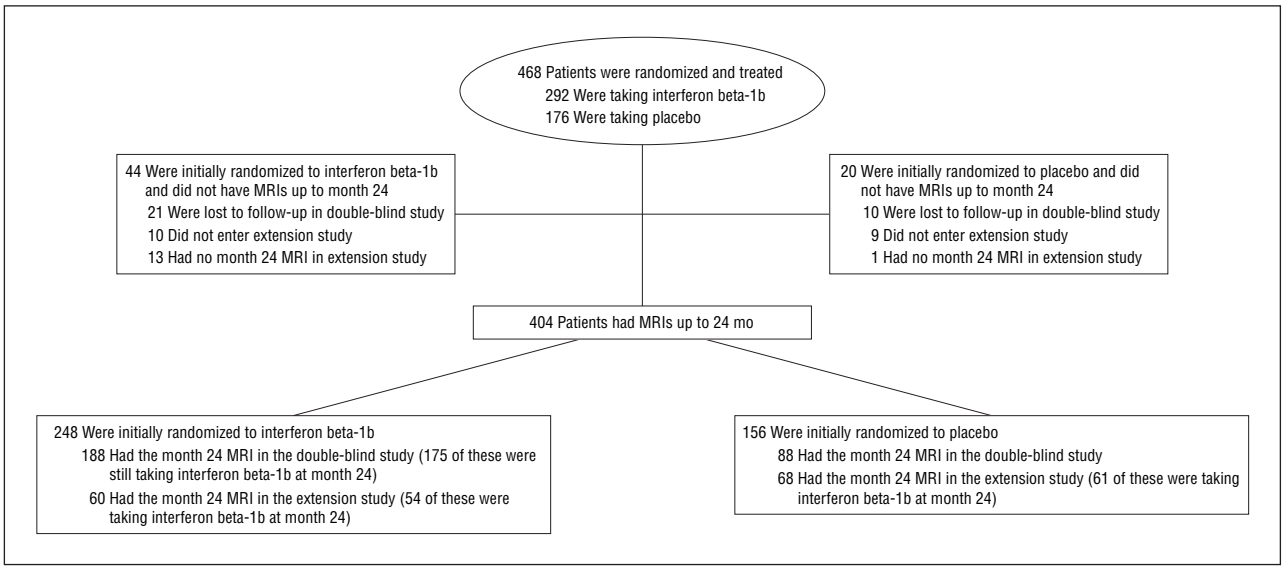

Figure. Trial flowchart for month 24 data. MRI indicates magnetic resonance imaging.

new or enlarging T2 lesions, and change in T2 lesion volume from baseline. Whether a treatment effect depends on inflammatory activity at screening was investigated in a post hoc manner by analyzing patients with and without Gd lesions on the screening MRI separately and comparing the results.

The MRI variables related to the evolution of T2 and Gd lesions were predefined as supportive secondary efficacy variables: the cumulative number of new T2 and Gd lesions and the cumulative volume of Gd lesions. To account for the different numbers of MRIs in patients who entered the follow-up study before 24 months (less frequent MRIs were obtained in the follow-up study), the cumulative number and volume of Gd lesions were also divided by the individual number of MRIs to give a mean value per MRI (assuming that Gd lesions are transient and, therefore, are unlikely to appear twice on MRIs separated by a minimum of 3 months). The T2 lesion counts were not corrected for the number of MRIs considering that most T2 lesions persist across time.[18] The MRI variables related to the evolution of T1-hypointense lesions were predefined as tertiary efficacy variables: the cumulative number of new T1-hypointense lesions and the change in the volume of T1-hypointense lesions from baseline.

To examine differences in the interferon beta-1b treatment effect on MRI variables across time, further analyses were performed post hoc to evaluate the impact of active treatment on the change in the T2- and T1-hypointense lesion volumes during the first and second years of the study. The *P* values and the results of the statistical tests performed on the MRI variables should be interpreted in an exploratory sense. Accordingly, no adjustment of the *P* values for multiple testing was performed.

RESULTS

A total of 468 patients were randomized, of which 404 had MRIs up to and including month 24, either in the double-blind study (n=276) or after entering the follow-up period in patients who had developed CDMS (n=128). Of the 404 patients, 248 were initially randomized to receive interferon beta-1b and 156 to receive placebo. At the month 24 visit, 290 of the 404 patients received interferon beta-1b, of which 229 had interferon beta-1b from the start of treatment and 61 had switched from placebo after CDMS. The **Figure** shows details of the patient disposition.

Patients randomized to receive interferon beta-1b or placebo were well-matched in terms of demographic, clinical, and MRI variables (**Table 1**). The baseline characteristics of these 404 patients were similar to those of the 468 patients who received treatment at least once.[13] The distribution of scanner types across treatment groups was similar. Of the 404 patients (156 receiving placebo and 248 receiving interferon beta-1b) included in the MRI analysis, 337 (128 receiving placebo and 209 receiving interferon beta-1b) were imaged using 1.5-T scanners, 60 (26 receiving placebo and 34 receiving interferon beta-1b) using 1.0-T scanners, 6 (1 receiving placebo and 5 receiving interferon beta-1b) using 0.5-T scanners, and 1 (receiving placebo) using a 2.0-T scanner.

There were significant differences between the interferon beta-1b and placebo groups in all predefined secondary and supportive secondary MRI efficacy variables (**Table 2**). After 24 months of treatment, the cumulative number of NALs was lower in patients initially randomized to receive interferon beta-1b compared with those randomized to receive placebo, with a median value of 2.0 in the interferon beta-1b group and 5.0 in the placebo group (60% reduction) ($P<.001$). The median cumulative number of new T2 lesions (1.0 in interferon beta-1b–treated patients vs 3.0 in placebo-treated patients [66% reduction]; $P<.001$) and of new Gd-enhancing lesions (1.0 in placebo-treated patients vs 0.0 in interferon beta-1b–treated patients; $P<.001$) showed similar treatment effects. Treatment with interferon beta-1b also had an effect on the development of new T1-hypointense lesions (13.3% in the interferon beta-1b arm vs 21.2% in the placebo arm; $P<.001$).

The cumulative volume of Gd lesions was also decreased in interferon beta-1b–treated patients compared with placebo-treated patients ($P<.001$). Despite the development of new T2 lesions across time, the T2

Table 1. Baseline Characteristics of Patients With MRIs Up to 24 Months[a]

Characteristic	Initially Randomized to Interferon Beta-1b (n = 248)	Initially Randomized to Placebo (n = 156)
Clinical and demographic factors		
Female sex	175 (70.6)	109 (69.9)
Age, y		
Mean ± SD	31.0 ± 7.7	30.5 ± 7.1
Median (Q1-Q3)	30.0 (24.0-38.0)	30.0 (25.0-36.0)
White race	242 (97.6)	154 (98.7)
Corticosteroid treatment of first event	172 (69.4)	113 (72.4)
Clinical presentation of first event		
Monofocal onset	128 (51.6)	83 (53.2)
Multifocal onset	120 (48.4)	73 (46.8)
EDSS score at baseline		
Mean ± SD	1.6 ± 0.9	1.5 ± 0.9
Median (Q1-Q3)	1.5 (0.0-2.0)	1.5 (0.0-2.0)
CSF sample taken at first event	169 (68.1)	103 (66.0)
Of these, CSF typical for MS	143 (84.6)	86 (83.4)
MRI variables		
T2 lesions, No.		
Mean ± SD	28.2 ± 29.6	28.8 ± 32.8
Median (Q1-Q3)	18.0 (7.0-39.0)	17.0 (8.0-36.5)
Patients with T2 lesions		
2-4 Lesions	36 (14.5)	20 (12.8)
5-8 Lesions	37 (14.9)	24 (15.4)
≥9 Lesions	175 (70.6)	112 (71.8)
Volume of T2 lesions, cm^3[b]		
Mean ± SD	3.9 ± 6.1	3.1 ± 3.8
Median (Q1-Q3)	1.9 (0.6-5.0)	1.9 (0.8-3.5)
Gd lesions, No.[c]		
Mean ± SD	1.5 ± 3.4	1.2 ± 2.5
Median (Q1-Q3)	0.0 (0.0-1.0)	0.0 (0.0-1.0)
Patients with Gd lesions		
0 Lesions	136 (54.8)	90 (57.7)
1 Lesion	53 (21.4)	28 (17.9)
2 Lesions	20 (8.1)	16 (10.3)
≥3 Lesions	37 (14.9)	21 (13.5)
Volume of Gd lesions, cm^3[c]		
Mean ± SD	0.3 ± 0.8	0.2 ± 0.4
Median (Q1-Q3)	0.0 (0.0-0.2)	0.0 (0.0-0.2)
T1-hypointense lesions, No.[d]		
Mean ± SD	4.3 ± 5.8	3.2 ± 4.8
Median (Q1-Q3)	2.0 (0.0-5.0)	1.0 (0.0-4.0)
Patients with T1-hypointense lesions		
0 Lesions	73 (29.4)	54 (34.6)
≥1 Lesions	174 (70.2)	102 (65.4)
Volume of T1-hypointense lesions, cm^3[b]		
Mean ± SD	0.5 ± 0.9	0.4 ± 0.9
Median (Q1-Q3)	0.1 (0.0-0.6)	0.1 (0.0-0.3)

Abbreviations: CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; Gd, gadolinium; MRI, magnetic resonance imaging; MS, multiple sclerosis; Q1-Q3, first to third quartile.

[a] Data are given as number (percentage) except where otherwise indicated. There were no statistically significant differences between the 2 groups in clinical baseline data.

[b] T1-hypointense and T2 lesion volumes could not be assessed in 1 placebo-treated and 2 interferon beta-1b–treated patients at screening for technical reasons.

[c] Gadolinium was not administered to 1 placebo-treated and 2 interferon beta-1b–treated patients at screening.

[d] T1-hypointense MRIs were not obtained in 1 interferon beta-1b–treated patient at screening.

Table 2. Treatment Effect on MRI Efficacy Variables

Variable	Initially Randomized to Interferon Beta-1b (n = 248)	Initially Randomized to Placebo (n = 156)	*P* Value
Lesion counts			
Newly active lesions, cumulative No.			<.001
Mean ± SD	5.7 ± 10.0	10.3 ± 12.9	
Median (Q1-Q3)	2.0 (0.0 to 6.5)	5.0 (1.0 to 14.5)	
New T2 lesions, cumulative No.			<.001
Mean ± SD	3.2 ± 5.0	5.3 ± 6.5	
Median (Q1-Q3)	1.0 (0.0 to 4.0)	3.0 (1.0 to 7.5)	
New Gd lesions, cumulative No.			<.001
Mean ± SD	2.2 ± 5.5	4.6 ± 7.6	
Median (Q1-Q3)	0.0 (0.0 to 2.0)	1.0 (0.0 to 6.0)	
New Gd lesions per MRI, No.			<.001
Mean ± SD	0.4 ± 1.1	1.0 ± 1.8	
Median (Q1-Q3)	0.0 (0.0 to 0.3)	0.3 (0.0 to 1.0)	
New T1-hypointense lesions, cumulative No.			<.001
Mean ± SD	0.2 ± 0.6	0.3 ± 1.4	
Median (Q1-Q3)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	
Lesion volumes, cm^3[a]			
Change in volume of T2 lesions from screening to month 24			.02
Mean ± SD	−1.0 ± 3.2	−0.3 ± 2.0	
Median (Q1-Q3)	−0.2 (−1.0 to 0.1)	−0.1 (−0.7 to 0.3)	
Change in volume of T1-hypointense lesions from screening to month 24			.29
Mean ± SD	−0.0 ± 0.6	0.1 ± 0.7	
Median (Q1-Q3)	0.0 (−0.1 to 0.1)	0.0 (−0.1 to 0.1)	
Cumulative volume of Gd lesions			<.001
Mean ± SD	0.2 ± 0.6	0.5 ± 0.8	
Median (Q1-Q3)	0 (0.0 to 0.2)	0.1 (0.0 to 0.6)	
Volume of Gd lesions per MRI			<.001
Mean ± SD	0.1 ± 0.1	0.1 ± 0.2	
Median (Q1-Q3)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.1)	

Abbreviations: Gd, gadolinium; MRI, magnetic resonance imaging; Q1-Q3, first to third quartile.

[a] Differences in T1-hypointense and T2 lesion volumes from screening to month 24 could not be assessed in 6 placebo-treated and 6 interferon beta-1b–treated patients for technical reasons.

lesion volume decreased from screening to month 24 in the interferon beta-1b and placebo groups. The decrease in T2 lesion volume was more pronounced in the interferon beta-1b–treated patients ($P<.05$). No difference was observed for the change in T1-hypointense lesion volume from screening to month 24 between the interferon beta-1b and placebo groups.

There was a treatment effect in favor of interferon beta-1b on the development of NALs in patients with and without Gd lesions at the screening MRI (**Table 3**). Patients with Gd lesions at baseline tended to develop more disease activity than those without, regardless of treatment. The change in T2 lesion volume from screening

Table 3. Treatment Effect on Secondary MRI End Points in Patients With and Without Gd-Enhancing Lesions at Screening

	Initially Randomized to Interferon Beta-1b	Initially Randomized to Placebo	*P* Value
Newly active lesions, cumulative No.[a]			
Without initial Gd lesions	n = 136	n = 90	<.001
Mean ± SD	3.0 ± 4.4	7.9 ± 11.0	
Median (Q1-Q3)	1.0 (0.0 to 4.0)	4.0 (1.0 to 11.0)	
With initial Gd lesions	n = 110	n = 65	<.001
Mean ± SD	8.8 ± 13.5	13.7 ± 14.6	
Median (Q1-Q3)	4.0 (1.0 to 11.0)	7.0 (3.0 to 21.0)	
Change in volume of T2-hyperintense lesions from screening to month 24, cm^3[b]			
Without initial Gd lesions	n = 134	n = 87	.06
Mean ± SD	–0.5 ± 2.4	–0.0 ± 1.3	
Median (Q1-Q3)	–0.1 (–0.5 to 0.1)	–0.0 (–0.3 to 0.3)	
With initial Gd lesions	n = 106	n = 62	.10
Mean ± SD	–1.4 ± 3.8	–0.8 ± 2.7	
Median (Q1-Q3)	–0.5 (–1.8 to 0.1)	–0.3 (–1.1 to 0.2)	

Abbreviations: Gd, gadolinium; MRI, magnetic resonance imaging; Q1-Q3, first to third quartile.

[a] Gadolinium was not administered in 1 placebo-treated and 2 interferon beta-1b–treated patients at screening.

[b] Differences in T1-hypointense and T2 lesion volumes from screening to month 24 could not be assessed in 6 placebo-treated and 6 interferon beta-1b–treated patients for technical reasons.

to the month 24 MRI (integrated data) tended to decrease in patients with signs of inflammation at the screening MRI (Table 3): the change in the T2 lesion volume up to month 24 was negatively correlated with the volume of Gd lesions at screening (Spearman rank correlation coefficients, –0.34 in interferon beta-1b–treated patients and –0.18 in placebo-treated patients). The treatment effect on T2 lesion volume development seemed to be less pronounced in patients with Gd enhancement, but the limited size of the subgroups precluded any formal statistical testing to show an interaction.

The effects of interferon beta-1b treatment on the development of T1-hypointense vs T2 lesion volumes in the first and the second years of the study separately were assessed post hoc to analyze whether the decrease in T2 lesion volume was initially more prominent after the first event and whether a delayed effect on the progression of lesion volumes could be detected (**Table 4**). Distribution of the T2 lesion volume change in the first year was skewed toward a decrease that was more pronounced in the interferon beta-1b group ($P=.03$). In the second year the distribution of T2 volume changes was minimal in the interferon beta-1b and placebo groups. In contrast, the distribution of the T1-hypointense lesion volume change in the first study year was minimal in both groups. However, in contrast to T2 lesion volume, in the second year of the study the distribution of the change in the T1-hypointense lesion volume was skewed toward a decrease in patients treated with interferon beta-1b and toward an increase in patients initially receiving placebo ($P=.02$).

COMMENT

In the BENEFIT study, treatment with interferon beta-1b was shown to delay time to CDMS and time to McDonald MS; the incorporation of MRI criteria in the latter[19] allowed the detection of a significant treatment effect as early as 6 months after the start of therapy.[13] The objective of the present study was to present more detailed MRI findings from the BENEFIT study. Moreover, to overcome the effect of data censoring inherent to a time-to-event type of analysis that limits interpretation from the double-blind phase of the trial, data from the preplanned open-label extension study of BENEFIT were included across 24 months of observation.

Extending previously reported MRI findings,[13] early treatment with interferon beta-1b compared with placebo had beneficial effects on the cumulative number of NALs and on the change in volume of T2-hyperintense lesions during an observation period of 24 months. This robust treatment effect occurred despite active patients from the placebo arm opting for open-label interferon beta-1b treatment after developing CDMS and thus gaining the subsequent benefits of active drug during the follow-up study (68 of the 156 placebo-treated patients had CDMS during the 24-month observation period, 61 of whom were treated with interferon beta-1b at the month 24 visit). Consequently, the treatment effects of interferon beta-1b on the reported MRI outcomes are likely to be underestimated.

Early interferon beta-1b treatment also had significantly favorable effects compared with placebo on the supportive MRI efficacy variables, such as number of T2, Gd, and T1-hypointense lesions and Gd lesion volume. The results further corroborate previously reported MRI results.[13]

Use of interferon beta-1b reduced the cumulative number of NALs by 60% up to month 24. Accordingly, the favorable effect of interferon beta-1b on the development of new T2 and new Gd lesions found in patients with relapsing-remitting MS[8] and secondary progressive MS[20] was confirmed in patients with a CIS. Despite the methodological bias that worked against the interferon beta-1b group, this potentially underestimated treatment effect clearly supports the primary efficacy analysis of the trial as reported by Kappos et al.[13] Further supporting the efficacy of interferon beta in patients with a CIS, significant effects of once-weekly administered interferon beta-1a preparations on the development of T2 and Gd lesions have also been shown in previous treatment trials in patients with a monofocal CIS[9] and in patients who were either monosymptomatic or polysymptomatic at the time of the CIS.[10]

In contrast to other treatment trials in patients with relapsing-remitting and secondary progressive MS that usually avoid recruitment of patients during or shortly after a relapse, the BENEFIT study enrolled patients during or shortly after the CIS. Consequently, the frequent occurrence (in 44% of 404 patients) of active inflammation on the screening MRI affected the efficacy analyses. When patients in the BENEFIT trial were stratified according to the presence of active lesions on the initial MRI, patients with Gd lesions developed considerably more

Table 4. Change in T2 and T1-Hypointense Lesion Volume in the First and Second Study Years

	Change From Screening to Month 12			Change From Month 12 to Month 24		
	Initially Randomized to Interferon Beta-1b (n = 263)[a]	Initially Randomized to Placebo (n = 163)[a]	*P* Value	Initially Randomized to Interferon Beta-1b (n = 240)[b]	Initially Randomized to Placebo (n = 149)[b]	*P* Value
T2 lesion volume, cm^3			.03			.10
Mean ± SD	–1.0 ± 3.5	–0.4 ± 2.2		0.0 ± 0.8	0.1 ± 1.0	
Median (Q1-Q3)	–0.2 (–1.1 to 0.1)	–0.2 (–0.6 to 0.1)		–0.0 (–0.2 to 0.2)	–0.0 (–0.2 to 0.2)	
T1-hypointense lesion volume, cm^3			.91			.02
Mean ± SD	0.0 ± 0.6	0.0 ± 0.6		–0.0 ± 0.5	0.1 ± 0.4	
Median (Q1-Q3)	0.0 (–0.1 to 0.1)	0.0 (–0.1 to 0.1)		0.0 (–0.1 to 0.0)	0.0 (–0.0 to 0.0)	

Abbreviation: Q1-Q3, first to third quartile.
[a] For evaluation of the difference in T1-hypointense and T2 lesion volumes in the first year of the study, measurements in 426 patients were available (obtained at screening vs month 12 in the double-blind or follow-up study).
[b] For evaluation of the difference in T1-hypointense and T2 lesion volumes in the second year of the study, measurements in 389 patients were available (obtained at month 12 vs month 24 in the double-blind or follow-up study).

NALs than those without. This finding supports the observation that the presence of Gd lesions is correlated with subsequent lesion activity.[21,22] In contrast, we showed that the favorable treatment effect of interferon beta-1b on subsequent lesion development per se was largely independent of the presence of active lesions at the time of the CIS (Table 3). This is in line with the fact that the treatment effect of interferon beta-1b on the conversion to CDMS was robust throughout the BENEFIT study population and numerically even more pronounced in patients without Gd enhancement on the initial MRI.[13]

The selection of active patients with inflammatory lesions present on the initial MRI affected the change in T2 lesion volume. Despite the development of new T2 lesions, mean T2 lesion volume decreased in both groups. Because this decrease was negatively correlated with the volume of Gd lesions on the initial MRI, it seems that resolving inflammatory lesions (and associated edema) beyond baseline have a confounding effect on the measure of T2 lesion volume. A decrease in the mean T2 lesion volume has also been observed in most patients in the Early Treatment of Multiple Sclerosis (ETOMS) trial,[10] whereas the T2 lesion volume increased in most patients in the CHAMPS (Controlled High-risk Subjects Avonex Multiple Sclerosis Prevention Study).[9] This difference between the 3 large CIS studies may be explained by the higher MRI activity at the time of the initial MRI observed in the patient populations enrolled in the ETOMS and BENEFIT trials. The overall proportion of patients with at least 1 enhancing lesion at the initial MRI was higher in the BENEFIT (44%) and ETOMS (60%) studies compared with the CHAMPS (30%)[9,10]; in the latter study, intravenous corticosteroid therapy was mandatory for the treatment of the CIS before the screening MRI was performed.[9]

The use of interferon beta-1b also had an impact on the cumulative number of new T1-hypointense lesions, although only a few patients developed such lesions during the study. As expected, the change in the T1-hypointense lesion volume was much less profound than the T2 lesion volume change in both arms, and not significantly different. These findings may be explained by increased baseline noise for volumetric assessments caused by the presence of temporary hypointense lesions that are included in the T1-hypointense lesion volume.[23] The more interesting persistent T1-hypointense lesions ("black holes"), which are more destructive in terms of histopathologic features,[24,25] are observed infrequently in patients with a CIS, and it would require a very large patient sample to observe a treatment effect in this phase of the disease. There was a statistically significant difference in favor of interferon beta-1b in reducing the T1-hypointense lesion volume from the month 12 to the month 24 MRI, whereas no such difference could be observed in the first year of the study. We speculate that this observation might indicate a favorable effect of early interferon beta-1b treatment on subsequent central nervous system tissue damage. Analyses of the full 5-year follow-up data are needed to fully understand the long-term benefits of early intervention with interferon beta-1b in MS, which might also be shown by MRI measures of tissue destruction, such as brain atrophy.

In summary, the findings from the present analyses corroborate and extend the earlier observations of the BENEFIT study.[13] Treatment with interferon beta-1b had a beneficial impact on all MRI efficacy measures regarding lesion activity and Gd and T2 lesion volumes. Beneficial treatment effects were maintained for 2 years despite the fact that active patients from the placebo group were treated with open-label interferon beta-1b, potentially minimizing the detection of any differences between the 2 groups. The continued follow-up of those patients remains an important objective of the BENEFIT study that will hopefully allow us to examine whether clinical disability and MRI measures will be impacted positively in the long-term by early interferon beta-1b treatment.

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