

Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study



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Summary

Background Several controlled studies provide evidence that treatment with interferon beta in patients with a first event suggestive of multiple sclerosis (MS) delays conversion to clinically definite MS (CDMS). Our aim was to determine whether early initiation of treatment with interferon beta prevents development of confirmed disability in MS.

Methods In the initial placebo-controlled phase of the double-blinded BENEFIT study, patients with a first event suggestive of MS and a minimum of two clinically silent lesions in MRI were randomised to receive either interferon beta-1b 250 µg (n=292) or placebo (n=176) subcutaneously every other day for 2 years, or until diagnosis of CDMS. Patients were then eligible to enter the follow-up phase with open-label interferon beta-1b. In the current prospectively planned analysis 3 years after randomisation, the effects of early interferon beta-1b treatment were compared with those of delayed treatment initiated after diagnosis of CDMS or after 2 years on the study. The primary outcomes of this ITT analysis were time to diagnosis of CDMS, time to confirmed expanded disability status scale (EDSS) progression, and score on a patient-reported functional assessment scale (FAMS-TOI). This trial is registered with ClinicalTrials.gov, number NCT00185211.

Findings Of the 468 patients originally randomised, 418 (89%) entered the follow-up phase; 392 (84%) completed 3 years' post-randomisation follow-up. After 3 years, 99 (37%) patients in the early group developed CDMS compared with 85 (51%) patients in the delayed treatment group. Early treatment reduced the risk of CDMS by 41% (hazard ratio 0·59, 95% CI 0·44–0·80; p=0·0011; absolute risk reduction 14%) compared with delayed treatment. Over 3 years, 42 (16%) patients in the early group and 40 (24%) in the delayed group had confirmed EDSS progression; early treatment reduced the risk for progression of disability by 40% compared with delayed treatment (0·60, 0·39–0·92; p=0·022; absolute risk reduction 8%). The FAMS-TOI score was high and stable in both groups over the 3-year period (p=0·31).

Interpretation Our data suggest that early initiation of treatment with interferon beta-1b prevents the development of confirmed disability, supporting its use after the first manifestation of relapsing-remitting MS.

Introduction

Three multicentre, placebo-controlled studies have shown that treatment of patients with a first episode of neurological symptoms (also called clinically isolated syndrome) highly suggestive of multiple sclerosis (MS) with interferon beta delays conversion to clinically definite MS (CDMS).^{1–4} Furthermore, neuropathological findings suggest the potential for immunomodulatory treatment of MS to have a greater effect early in the disease course, by early inhibition of the cascade of events that leads to irreversible axonal damage and disability.^{5–7} However, until now, there has been no controlled evidence showing that treatment with interferon beta initiated early after the first event has an effect on the development of confirmed disability as compared with delayed treatment. The Betaferon/Betaseron in Newly Emerging multiple sclerosis For Initial Treatment (BENEFIT) study, assessing interferon beta-1b in patients with a first event suggestive of MS, was designed to address this issue. Here, we present the results of the preplanned 3-year analysis of BENEFIT.

Methods

Patients and procedures

The BENEFIT study consisted of a placebo-controlled phase and a follow-up phase. The 2-year double-blinded, placebo-controlled phase, which was completed in 2005,³ assessed the safety, tolerability, and efficacy of interferon beta-1b 250 µg (8 MIU) subcutaneously every other day in patients with a first event suggestive of MS. Eligible patients had experienced a first neurological event suggestive of MS and had at least two clinically silent lesions on a T2-weighted brain magnetic resonance imaging (MRI) scan. Within 60 days of the onset of the first clinical event, and after providing written informed consent, patients were randomly assigned, in a 5:3 ratio, to interferon beta-1b 250 µg or placebo subcutaneously every other day. Patients completed the placebo-controlled phase when CDMS was diagnosed by use of modified Poser criteria,⁴ or after 2 years.

Patients who completed the placebo-controlled phase were eligible to enter the follow-up phase and, after

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renewing their written informed consent, were offered interferon beta-1b 250 µg subcutaneously every other day for up to 5 years from randomisation. Every effort was made to obtain full follow-up assessments of all patients, including those who did not opt for interferon beta-1b treatment. Patients and investigators were kept blinded to the original treatment allocation throughout the trial. Accordingly, at the beginning of the follow-up phase, interferon beta-1b was titrated in all patients, whether they had been on placebo or interferon beta-1b. However, 13 patients were unblinded: 12 placebo patients did not develop any clinical or MRI activity for 2 years and were informed accordingly after a recommendation from the study's independent advisory board; the treatment code of one further patient was unblinded by the investigator due to a serious adverse event.

In the follow-up phase, regular visits were scheduled every 6 months. A specially trained physician, not involved in the patient's care and without access to their files, did standardised neurological assessments with the expanded disability status scale (EDSS). EDSS scores range from 0 to 10, with higher scores indicating more severe disease.⁸ Relapses were assessed and defined in accordance with established guidelines⁴ and the diagnosis of CDMS was confirmed by a central committee masked to treatment allocation. Additional assessments (all blinded) were: brain MRI scans every 12 months (assessed by the MRI Analysis Centre, Amsterdam) and the multiple sclerosis functional composite (MSFC) score⁹ every 6 months. Of note, MRI scans were more frequently obtained during the placebo-controlled phase of the trial (in total, there were up to seven scans post-screening for both study phases until year 3).³ Patient-reported outcomes were obtained every 12 months, by use of the functional assessment of MS (FAMS) instrument,¹⁰ the EuroQol-5 Dimensional Questionnaire (EQ-5D), and the visual analogue scale (VAS).¹¹ Neutralising antibodies were measured every 6 months with the MxA assay (cutoff value for neutralising activity was defined as 1:20).¹²

Statistical analysis

The statistical analysis plan was finalised before the database of the placebo-controlled phase was locked in June, 2005. The prespecified intention-to-treat (ITT) analysis set consisted of all randomised patients who received at least one dose of the study drug of the placebo-controlled phase after randomisation. The patient group initially randomised to interferon beta-1b (the early treatment group) was compared with the group initially randomised to placebo with the option of starting with interferon beta-1b after CDMS or after 2 years (the delayed treatment group).

After discussion with regulatory authorities, two analyses of the integrated data set after completion of years 3 and 5 were planned. A nominal two-sided significance level of 0.0253 (with Šidák's adjustment for

multiple comparisons) was assigned to the analyses of the primary endpoints at both time points, thus allowing for an overall type I error probability of 0.05.¹³ All data obtained up to the 3-year visit were used here for the 3-year analysis.

Three prespecified primary efficacy measures were tested in a sequential, conditional approach: time to CDMS was tested first, followed by time to confirmed EDSS progression (not previously tested in the placebo-controlled phase), and the FAMS-trial outcome index (FAMS-TOI) score (range of scores 0 [worst] to 148 [best]).

EDSS progression was defined as an increase in the EDSS score by 1.0 or more step compared with the lowest score obtained during the screening period (ie, at screening or at baseline visit); this progression had to be confirmed after 6 months. In the main analysis of this outcome, EDSS values obtained at unscheduled visits were not taken into account, since they largely represent relapse-associated changes in neurological symptoms, which do not necessarily imply permanent deficits. Sensitivity analyses were done, one that included unscheduled visits, two that both excluded unscheduled visits and, additionally, visits within 30 or 90 days after the onset of a relapse, one which took the EDSS obtained at the baseline visit (not the lowest of screening and baseline as in the main analysis) as the reference value, and one counting only EDSS progressions sustained until the last visit within the 3-year period. In a further sensitivity analysis, patient's who discontinued the study prematurely without confirmed progression were counted as having progressed, or as progression-free.

The effect of early versus delayed treatment on time to confirmed EDSS progression (main analysis) was also assessed post-hoc in subgroups of patients stratified by clinical presentation (monofocal *vs* multifocal) and MRI findings indicating subclinical disease dissemination (≥ 9 *vs* < 9 T2 lesions) or inflammatory activity (presence *vs* absence of gadolinium-enhanced lesions) at the time of the first event.

Prespecified secondary clinical outcome measures included: time to MS as defined by the McDonald criteria;¹⁴ annualised relapse rate; risk for recurrent relapses; neurological status as measured by MSFC score; and health-related quality of life as rated with EQ-5D and VAS. Secondary outcomes obtained by brain MRI included: cumulative number of newly active lesions (new T2 or new gadolinium-enhanced lesions); change in lesion burden (on T1-weighted and T2-weighted images); and change in brain volume as measured by a modified version of the Structural Image Evaluation using Normalisation of Atrophy (SIENA) program.¹⁵ p values for secondary outcomes were not corrected for multiple testing. In a post-hoc analysis, annualised relapse rates in the first, second, and third years were also calculated separately.

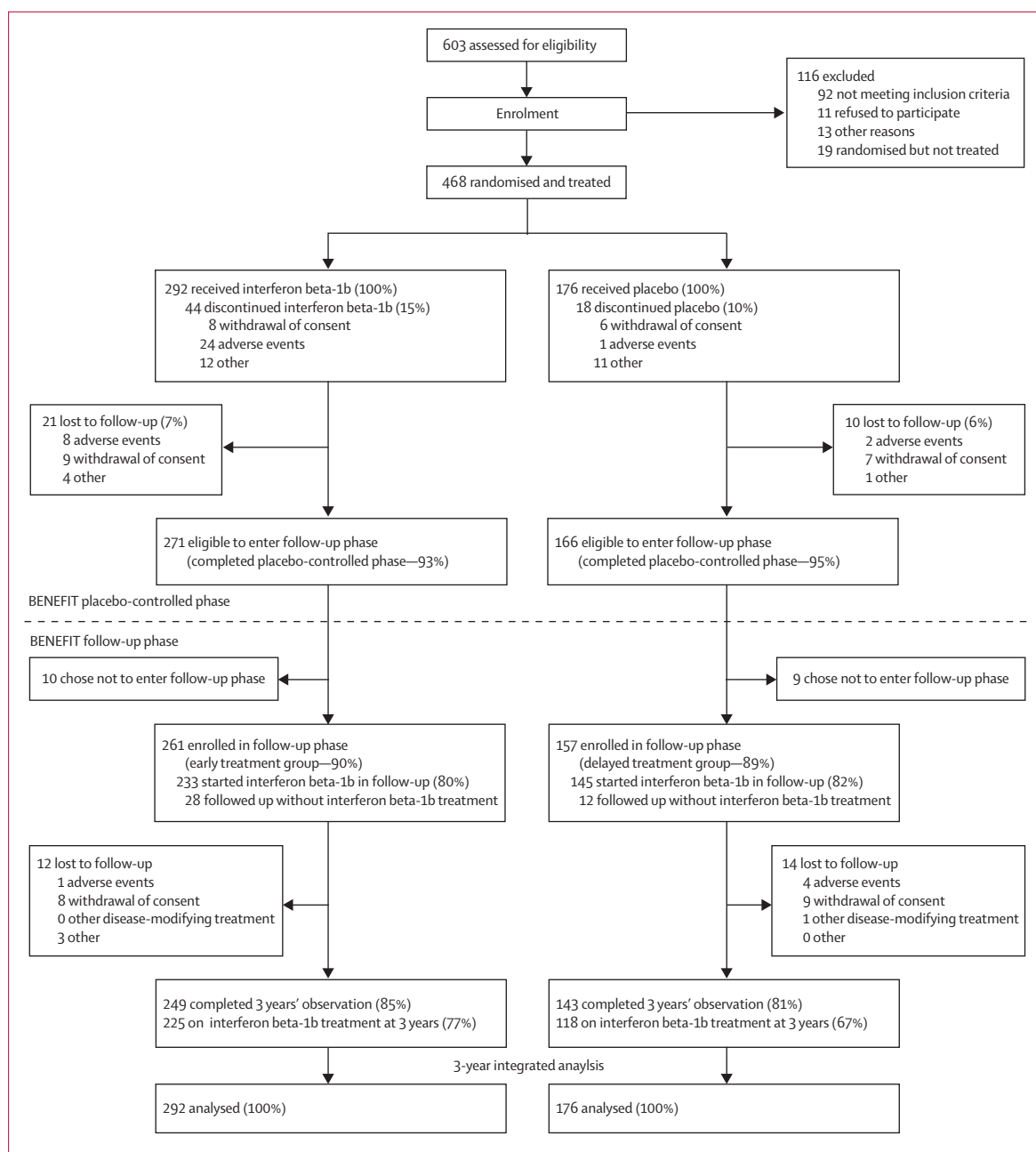


Figure 1: Trial profile

For time-to-event outcomes, differences between the early and delayed treatment groups were analysed by the log-rank test (primary analysis) and by adjusted Cox proportional hazards regression. As prespecified, covariates considered in Cox regressions for time to CDMS and time to McDonald MS were steroid use during the first clinical event, onset of disease (monofocal *vs* multifocal), age at screening, sex, and number of T2 lesions and gadolinium-enhanced lesions at screening; time to confirmed EDSS progression was adjusted (as preplanned) for T2-lesion volume at screening.

The treatment effect on the annualised relapse rate was assessed by a generalised linear Poisson regression model (covariates considered were steroids, onset of disease, and T2 lesions).

Treatment effects on patient-reported outcomes and MRI efficacy variables were analysed by non-parametric and on MSFC score by parametric analysis of covariance, with corresponding parameters from baseline (for patient-reported outcomes) or screening (for MRI) assessments as covariates. The frequencies of adverse events and the number of individuals above and below

	Placebo-controlled phase		Follow-up phase	
	Interferon beta-1b (n=292)	Placebo (n=176)	Early treatment (n=261)	Delayed treatment (n=157)
Sex (female)	207 (71%)	124 (71%)	186 (71%)	108 (69%)
Age (years)	30 (24.0–37.5)	30 (25.0–36.0)	30 (24.0–37.0)	30 (25.0–36.0)
Monofocal disease onset	153 (52%)	93 (53%)	134 (51%)	84 (54%)
Steroid use (yes)	209 (72%)	123 (70%)	180 (69%)	108 (69%)
Number of T2 lesions	18 (7.0–38.5)	17 (7.5–36.5)	18 (7.0–39.0)	17 (8.0–37.0)
Number of Gd-enhanced lesions	0 (0.0–1.0)	0 (0.0–1.0)	0 (0.0–1.0)	0 (0.0–1.0)
EDSS score at baseline	1.5 (1.0–2.0)	1.5 (1.0–2.0)	1.5 (1.0–2.0)	1.5 (1.0–2.0)

Data are median (IQR) or n (%).

Table 1: Screening characteristics of participants in the placebo-controlled and follow-up phases of BENEFIT

the threshold of neutralising antibody activity were analysed with descriptive statistics. Apart from the primary outcomes, all other statistical analyses were not adjusted for multiple testing.

Statistical analyses were done with SAS version 9.1.3. This trial is registered with ClinicalTrials.gov, number NCT00185211.

Role of the funding source

The members of the steering committee and the study sponsors designed the study. The authors had access to all the data, participated in the analysis and interpretation of data, and were members of the publication committee. LK, representing the study’s steering committee, had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 418 (89%) of the 468 patients who had started placebo-controlled treatment chose to enter the follow-up phase; 378 of these individuals opted for follow-up treatment with interferon beta-1b 250 µg subcutaneously every other day. 392 (84%) completed 3 years’ follow-up; 343 of those who had opted for further treatment were still on interferon beta-1b at this time. The median exposure time to interferon beta-1b over the 3-year period was 1080 days (IQR 854–1093) for the early treatment group and 364 days (175–679) for the delayed treatment group.

The two randomised groups of the double-blind study were much the same in terms of demographics and clinical and MRI characteristics (table 1). There were no substantial differences of key baseline characteristics and CDMS or McDonald MS conversion rates between patients of the two randomised groups who did not enter the follow-up study, suggesting that enrolment in the follow-up phase was not biased by selective dropouts (data not shown).

In the early treatment group, the risk of confirmed EDSS progression (main analysis; excluding unscheduled visits) was reduced by 40% over a 3-year period (figure 2 and table 2). The number needed to treat early to avoid one additional confirmed EDSS progression was 11.9. When unscheduled visits were included in the analysis, a similar reduction of the risk for confirmed EDSS progression was found in favour of early treatment (table 2). Sensitivity analyses of time to confirmed EDSS progression, which excluded visits within 30 or 90 days of the onset of a relapse, or only counting EDSS

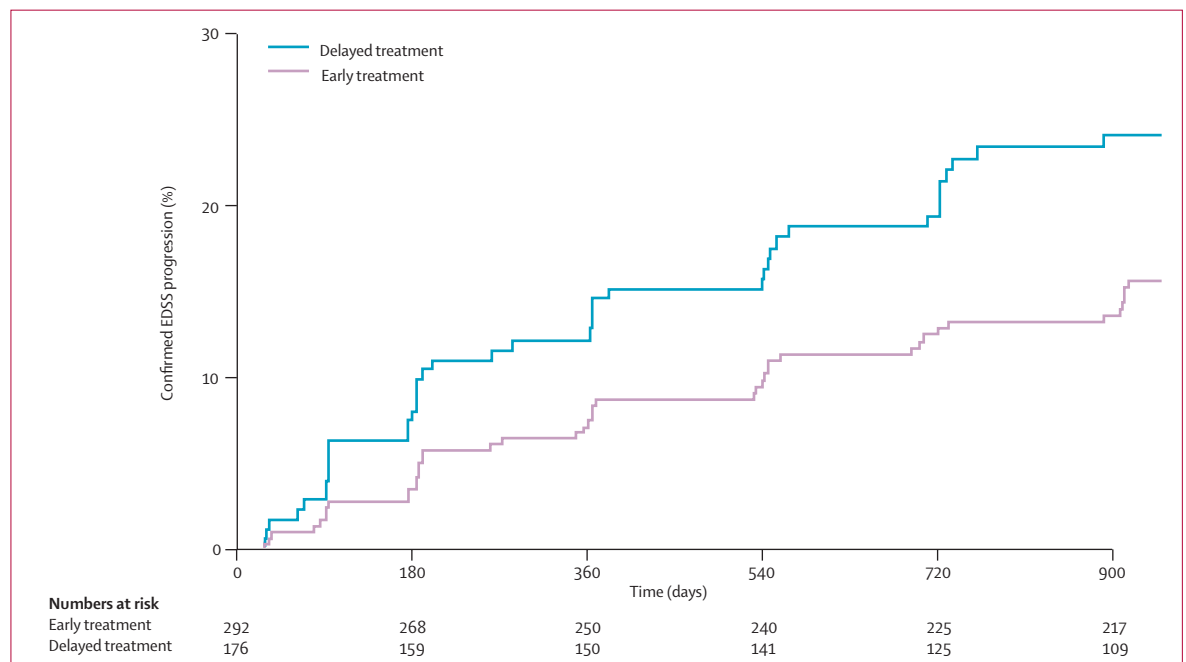


Figure 2: Kaplan-Meier estimates for the probability of progression on the expanded disability status scale (EDSS) confirmed after 6 months within the 3-year period
The cumulative probability of EDSS progression was lower in the early treatment group (p=0.022, log-rank test).

	Number of patients with event (up to day 1080)		Risk (Kaplan-Meier estimates up to day 1080)		Hazard ratio (95% CI)	p value (log-rank test)	Absolute risk reduction (day 1080)
	Early treatment (n=292)	Delayed treatment (n=176)	Early treatment (n=292)	Delayed treatment (n=176)			
CDMS	99 (34%)	85 (48%)	37%	51%	0.59 (0.44–0.80)	0.0011	14%
McDonald MS	205 (70%)	146 (83%)	74%	85%	0.54 (0.44–0.68)	≤0.0001	11%
EDSS progression							
Excluding unscheduled visits (main analysis)*	42 (14%)	40 (23%)	16%	24%	0.60 (0.39–0.92)	0.022	8%
Including unscheduled visits*	45 (15%)	42 (24%)	17%	25%	0.61 (0.40–0.93)	0.024	9%
Sensitivity analyses							
Unscheduled visits and visits 30 days after relapse excluded*	41 (14%)	38 (22%)	15%	23%	0.61 (0.39–0.95)	0.032	7%
Unscheduled visits and visits 90 days after relapse excluded*	38 (13%)	36 (20%)	14%	22%	0.60 (0.38–0.95)	0.030	7%
Unscheduled visits excluded, baseline EDSS as reference†	36 (12%)	37 (21%)	14%	22%	0.54 (0.32–0.91)	0.010	9%
Unscheduled visits excluded, sustained up to last clinical visit within 3 years*	28 (10%)	27 (15%)	10%	16%	0.61 (0.36–1.03)	0.063	6%

*Defined as an increase in the EDSS score by ≥1.0 step compared with the lowest score obtained during the screening period (ie, at the screening or at the baseline visit). †EDSS progression was defined as an increase in the EDSS score by ≥1.0 step compared with the baseline visit.

Table 2: Effect of early vs delayed interferon beta-1b on occurrence of clinically definite MS, MS according to the McDonald criteria, and confirmed EDSS progression

progression if sustained until month 36 further support the results of the main analysis (table 2).

When a patient's premature study discontinuation was counted as progression, the log-rank test for time to confirmed EDSS progression yielded a p value of 0.1011 (HR 0.72, 95% CI 0.51–1.02; p=0.07). If these patients were counted as progression free the log-rank test yielded a p value of 0.0172 (0.59, 0.38–0.91; p=0.017). The number of confirmed EDSS progressions up to year 3 was low compared with the number of patients who were lost to follow-up without confirmed EDSS progression (68 patients).

Analysis of unconfirmed EDSS scores by visits showed that somewhat fewer patients in the early treatment group had an increase in EDSS score from their first event to the last clinical visit within the 3-year period than did those in the delayed group (change of EDSS scores by 0.5 step or less: 233 [80%] patients in the early group vs 137 [78%] in the delayed group; EDSS increase by 1.0–2.0 steps: 42 [14%] vs 27 [15%]; EDSS increase by >2.0 steps: 10 [3%] vs 11 [6%]). At the year 3 visit, most patients were still in the low-to-medium range of the EDSS scale (median 1.5, range 0.0–7.5). Mean EDSS scores tended to increase over time in the delayed treatment group (mean score 1.43 [SD 0.86] at first event vs 1.58 [1.11] at year 3) while remaining stable or better in the early treatment group (1.52 [0.85] vs 1.41 [1.24]). The difference in the mean EDSS score at year 3 was lower in the early group than in the delayed group (p=0.0475). The distribution of changes across functional systems related to confirmed EDSS progressions was much the same in the early and delayed treatment groups (table 3).

Post-hoc analysis of the treatment effect in subgroups defined by disease characteristics at the time of the first event suggestive of MS showed that early treatment with interferon beta-1b reduced the risk for confirmed EDSS progression in each of the groups (table 4). Treatment effects seemed to be lower, and were not significant, in patients with less clinical or MRI disease dissemination. The magnitude of the treatment effect was largely comparable in patients with or without gadolinium-enhanced lesions in the screening MRI.

In the early treatment group, the risk for CDMS was reduced by 41% over a 3-year period (table 2). The number needed to treat early to avoid one additional conversion to CDMS was 7.1. Differences in favour of early interferon beta-1b treatment were also found for time to McDonald MS (table 2) and annualised relapse rate over

	Early treatment (n=42)	Delayed treatment (n=40)
Visual functions	8 (19%)	12 (30%)
Brainstem functions	11 (26%)	7 (18%)
Pyramidal functions	21 (50%)	14 (35%)
Cerebellar functions	13 (31%)	12 (30%)
Sensory functions	24 (57%)	17 (43%)
Bladder and bowel functions	9 (21%)	10 (25%)
Cerebral functions	17 (40%)	16 (40%)

Data are n (%) of patients with increase in functional system(s) from lowest score obtained during the screening period to first score relevant for EDSS confirmation. *An increase in EDSS score by ≥1.0 step compared with the lowest score obtained during the screening period (ie, at the screening or the baseline visit).

Table 3: Change in functional system scores in patients with confirmed EDSS progression (up to day 1080)

	Number of patients with event (up to day 1080)		Risk (Kaplan-Meier estimates up to day 1080)		Hazard ratio (95% CI)	p value
	Early treatment	Delayed treatment	Early treatment	Delayed treatment		
Monofocal* at first event suggestive of MS (n=246)	26	21	19%	24%	0.75 (0.42-1.34)	0.330
Multifocal† at first event suggestive of MS (n=222)	16	19	12%	24%	0.47 (0.24-0.90)	0.024
<9 T2 lesions at screening MRI (n=138)	13	10	17%	20%	0.78 (0.34-1.78)	0.553
≥9 T2 lesions at screening MRI (n=330)	29	30	15%	26%	0.55 (0.33-0.91)	0.020
No gadolinium-enhanced lesion at screening MRI (n=266)	19	21	13%	21%	0.55 (0.30-1.03)	0.063
≥1 gadolinium-enhanced lesion at screening MRI (n=198)	19	23	19%	29%	0.63 (0.34-1.16)	0.139

*Signs and symptoms at the first event indicate one lesion in the CNS. †Signs and symptoms at the first event indicate at least two anatomically separate lesions in the CNS. ‡Unscheduled visits excluded.

Table 4: Treatment effect of early vs delayed interferon beta-1b on confirmed EDSS progression in subgroups of patients with different clinical/MRI characteristics at the time of the first event‡

3 years (figure 3). Post-hoc analyses of the annualised relapse rates within the first, second, and third year after the first event showed the most marked differences between the early and delayed treatment groups in the first year (figure 3).

Throughout the 3 years of observation, most patients in both groups had high and stable scores on the FAMS-TOI (p=0.31 for group difference at 3 years; data not shown). Scores on the EQ-5D rating scale decreased in the delayed group, and improved in the early group (p=0.016 at 3 years; data not shown). The compound MSFC score improved over the 3 years in most patients

and no significant difference was found between treatment groups (p=0.408; data not shown). In the cognitive subtest of MSFC (the paced auditory serial addition test), patients in the early treatment group had better results than did those in the delayed group (p=0.011 at 3 years). In the subtests of upper (nine-hole peg test, p=0.118) and lower (25-foot walk, p=0.792) extremity function, results did not differ significantly between treatment groups.

Fewer newly active lesions developed in the early treatment group over 3 years than in the delayed treatment group (p<0.0001; data not shown). T2-lesion volume in both groups decreased from screening to year 3 in most patients. This decrease was more pronounced in the early treatment group; however, the difference between the groups was not statistically significant (p=0.070; data not shown). There were only minor changes over time and there were no differences between groups when the volume of T1-hypointense lesions (p=0.89) and the brain volume (p=0.15) at 3 years were compared with those of the screening MRI (data not shown).

The frequency of adverse events was within the known safety and tolerability profile of interferon beta-1b, and did not differ from those reported at the end of the placebo-controlled phase.³ The most common adverse events in the study period were flu-like symptoms (391 events in 49% of all patients; 144 [49%] patients in the early group and 86 [49%] patients in the delayed group) and injection site reaction (286 adverse events in 47% of all patients; 158 [54%] patients in the early group and 68 [39%] patients in the delayed group). The most frequent abnormal laboratory findings were leucopenia (65 [22%] patients in the early group vs 22 [13%] in the delayed group) and raised alanine aminotransferase concentrations (46 [16%] patients in the early group vs 12 [7%] in the delayed group). During the follow-up phase more patients in the delayed treatment group prematurely stopped interferon beta-1b due to adverse events (18 [12%] in the delayed group vs six [2%] in the early group).

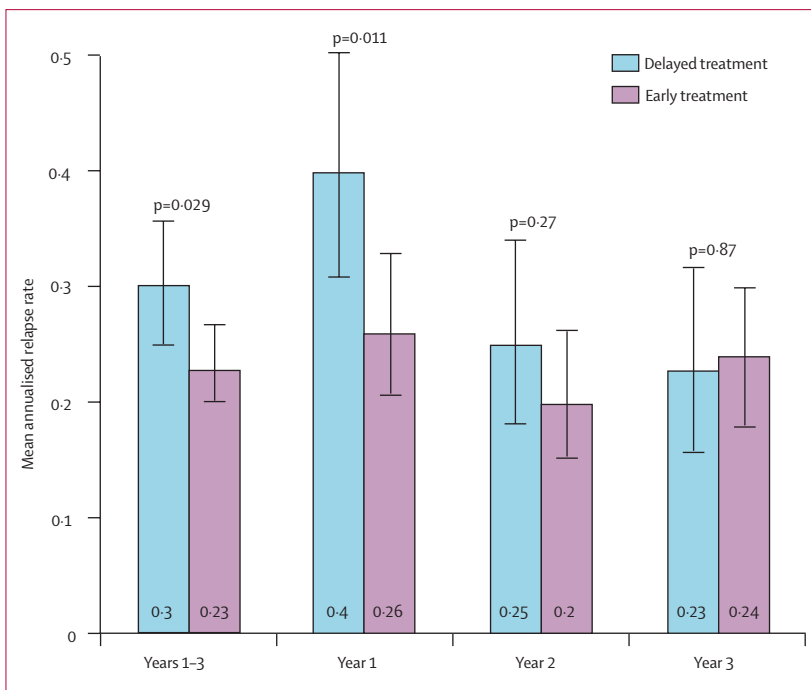


Figure 3: Annualised relapse rate estimates over the 3-year follow-up period
 Error bars are 95% CI. p values refer to Poisson regression analysis. The proportion of patients exposed to interferon beta-1b in subsequent years of the study was as follows (early/delayed treatment group): first year 100%/28%, second year 94%/48%, third year 87%/88%.

Neutralising activity (defined as a titre ≥ 20 NU/mL) was detected at least once in 88 of 277 (32%) patients in the early treatment group and in 34 of 173 (20%) patients in the delayed treatment group; of these, 41 (47%) patients in the early group and eight (24%) of those in the delayed treatment group had converted to negative status by 36 months. Neutralising activity had no effect on either relapse-related or disability-related outcomes (data not shown).

Discussion

We found a beneficial effect of early treatment with interferon beta-1b (250 μ g, every other day, subcutaneously) on 6-month confirmed EDSS progression 3 years after the first event suggestive of MS, indicating that a delay of such treatment by, essentially, just one event, even at this early stage of the disease, has an effect on later accumulation of disability. Even though most patients in both groups remained at a low level of disability 3 years after the initial event, the delay in accumulation of disability with early treatment seen here is clinically relevant.

Relapsing-remitting MS presents with a first neurological attack and most patients recover fully from their initial symptoms within a short period of time. Recent evidence, however, suggests that subclinical damage persists and is frequently progressive, although its functional consequences are still being compensated by existing redundant connections and reorganisation of neuronal networks.^{16,17} Over time, most patients with a first event suggestive of MS and additional clinically silent MRI lesions develop relapsing-remitting MS and have a substantial risk for progressive disease and severe disability later on. An effective immunomodulatory treatment initiated early after the presenting symptoms of MS would be expected not only to delay a second demyelinating event but also to prevent or delay permanent disability.^{7,18}

The need for methodologically sound follow-up studies of placebo-controlled trials in a chronic disease such as MS has been emphasised repeatedly. Previous studies have shown a beneficial effect of early treatment on the risk of conversion to CDMS, but they were too brief and not prospectively designed to capture any effect on disability.^{1,2} For example, in an open-label, investigator-initiated 5-year follow-up of one of these studies, nearly 50% of the original population was lost to follow-up and no effect of early versus delayed treatment with interferon beta-1a (30 μ g, once weekly intramuscularly) on confirmed progression was found.¹⁹ Therefore, we made major efforts to address these issues by strictly applying the ITT principle, keeping the original treatment allocations masked, retaining the same standards of assessments, and by prospective planning of the statistical analysis. The value of EDSS as an outcome measure was supported by a study by Rio and colleagues,²⁰ which provided evidence that a confirmed increase by one

step on the EDSS is an important negative predictor of permanent and severe disability 5 years later.

Our findings are in line with those of an extension of a pivotal study for interferon beta-1a.²¹ In this study, patients with established relapsing-remitting MS initially randomised to placebo were offered active treatment with interferon beta-1a (22 or 44 μ g subcutaneously, three times a week) after completing 24 months on study. In a post-hoc analysis 4 years after the start, time to EDSS progression (confirmed after 3 months) was longer in those patients who had been initially randomised to the 44 μ g dose than in those in the crossover group ($p=0.047$).²²

Changes in the EDSS scores in a relapsing-remitting MS population, even if confirmed after 6 months, could reflect continuing relapse-associated temporary changes, rather than permanent disability. The annualised relapse rates in the early and delayed treatment groups were very similar in the second year and nearly identical in the third, most probably due to the increasing exposure to interferon beta-1b in the delayed group. This finding suggests that the differential effect of early treatment on disability seen in the third year after the initial event is not due to a direct effect of relapses at the time of the last assessments. In support of this argument, sensitivity analyses excluding EDSS values obtained at visits up to 90 days after a relapse confirmed the robustness of the effect of early interferon beta-1b treatment on time to confirmed EDSS progression.

To better define patients who might benefit more or less from early treatment initiation, we did analyses in subgroups with different levels of disease activity at first presentation. The smaller sample size in each of the dichotomised groups and the low rate of confirmed EDSS progressions limit the interpretation of this approach. Interestingly, the effect of early versus delayed interferon beta-1b treatment is different from that previously reported on time to CDMS as described in the analysis of the placebo-controlled phase of the BENEFIT study.³ Here, multifocal initial presentation and higher lesion load seem to define subgroups of patients who benefit more from early treatment initiation (while occurrence of contrast-enhanced lesions had no effect); by contrast, in the earlier analysis, the treatment effect of interferon beta-1b on the risk of CDMS seemed to be more pronounced in patients with monofocal disease or lower T2-lesion counts at baseline. The longer observation period provided by the planned 5-year analysis of this trial, should allow for more events of confirmed disability progression to occur, and could provide more informative evidence on prognostic indicators of treatment response.

The MSFC score did not detect any relevant deterioration of neurological function in either of the treatment groups during the observation period. This occurrence is somewhat surprising, since the aim of

MSFC was to improve on sensitivity to change as compared with EDSS and other pre-existing measures of neurological deficits. Nevertheless, a low sensitivity for change has also been described by others,²² and could indicate that this measure is not equally suitable for all MS subpopulations. Specifically, the MSFC score was developed with data from patients with established MS and not clinically isolated syndrome.²³ As a composite instrument, MSFC captures three domains of neurological function, which are affected in nearly all patients in later stages of MS (ambulation, dexterity of upper extremities, and attention/short-term memory) but are less frequently affected in patients with earlier-stage disease, where symptoms such as visual or sensory deficits are frequently found in isolation. These symptoms are not at all captured by MSFC, but do affect EDSS scores. Of note, improvements in the cognitive subtest of MSFC after 3 years were more pronounced in patients receiving early treatment. Given the exploratory nature of these analyses of a single component of MSFC, the relevance of this finding needs further confirmation.

In patients with relapsing-remitting MS, interferon beta-1b has previously been shown to have a profound effect on the development of new inflammatory lesions as shown by cerebral MRI.²⁴ For patients with a first event suggestive of MS, this effect was confirmed in the placebo-controlled part of the BENEFIT study³ and preserved over 3 years, despite increasing exposure to interferon beta-1b in the initial placebo group. Since patients had to enter our study soon after the onset of neurological symptoms of the first event, pretreatment MRI frequently depicted active inflammation that is subject to spontaneous remission. Only a few of our patients had an increase in overall T2-lesion or T1-lesion volumes during the 3 years of observation, and overall changes in brain volume seemed to be low compared with findings reported for established MS.

Contributors

LK was responsible for the central CDMS confirmation during the study. CHP and FB were responsible for the central eligibility assessment during the study. LK, MSF, CHP, GE, HPH, DHM, XM, FB, LB, SD, CP, and RS, were actively involved in drafting and amending the study protocol, reviewed the statistical analysis, and actively contributed to the writing and reviewing of the submitted manuscript. FB was responsible for the central MRI analysis (apart from brain volume analysis) of the study. EWR was responsible for the central MRI brain volume analysis of the study. SD and VL were responsible for biometric analyses in the study, created the statistical analysis plan, and actively contributed to writing and reviewing of the submitted manuscript. LB, CP, and RS were actively involved in amending the statistical analysis plan. All authors saw and approved the final version of the manuscript.

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Conflict of interest statement

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