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Survival in MS
A randomized cohort study 21 years after the start of the pivotal IFNβ-1b trial

D.S. Goodin, MD*
A.T. Reder, MD*
G.C. Ebers, MD
G. Cutter, PhD
M. Kremenchutzky, MD
J. Oger, MD
D. Langdon, PhD
M. Rametta, DO
K. Beckmann, MSc
T.M. DeSimone, PhD
V. Knappertz, MD

ABSTRACT

Objective: To examine the effects of interferon beta (IFNβ)-1b on all-cause mortality over 21 years in the cohort of 372 patients who participated in the pivotal randomized clinical trial (RCT), retaining (in the analysis) the original randomized treatment-assignments.

Methods: For this randomized long-term cohort study, the primary outcome, defined before data collection, was the comparison of all-cause mortality between the IFNβ-1b 250 μg and placebo groups from the time of randomization through the entire 21-year follow-up interval (intention-to-treat, log-rank test for Kaplan-Meier survival curves). All other survival outcomes were secondary.

Results: After a median of 21.1 years from RCT enrollment, 98.4% (366 of 372) of patients were identified, and, of these, 81 deaths were recorded (22.1% [81 of 366]). Patients originally randomly assigned to IFNβ-1b 250 μg showed a significant reduction in all-cause mortality over the 21-year period compared with placebo (p = 0.0173), with a hazard ratio of 0.532 (95% confidence interval 0.314–0.902). The hazard rate of death at long-term follow-up by Kaplan-Meier estimates was reduced by 46.8% among IFNβ-1b 250 μg–treated patients (46.0% among IFNβ-1b 50 μg–treated patients) compared with placebo. Baseline variables did not influence the observed treatment effect.

Conclusions: There was a significant survival advantage in this cohort of patients receiving early IFNβ-1b treatment at either dose compared with placebo. Near-complete ascertainment, together with confirmatory findings from both active treatment groups, strengthens the evidence for an IFNβ-1b benefit on all-cause mortality.

Classification of Evidence: This study provides Class III evidence that early treatment with IFNβ-1b is associated with prolonged survival in initially treatment-naive patients with relapsing-remitting multiple sclerosis. Neurology® 2012;78:1315–1322

GLOSSARY

16Y-LTF = 16-Year Long-Term Follow-Up; 21Y-LTF = 21-Year Long-Term Follow-Up; BOD = burden of disease; CI = confidence interval; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; HR = hazard ratio; IFNβ-1b = interferon β-1b; MS = multiple sclerosis; RCT = randomized clinical trial.

Multiple sclerosis (MS) is a chronic, inflammatory disease of the CNS with a lifelong course, necessitating outcome assessments over both the short term and long term.1 However, randomized clinical trials (RCTs) have typically focused only on short-term outcomes such as clinical measures of relapse and physical disability, as well as MRI measures of disease activity and severity.2–8 Although survival is the ultimate long-term outcome, to date mortality in patients with MS treated with disease-modifying therapy (DMT) has not been well-studied, largely because of the length and completeness of observation needed.9

*These authors contributed equally to this work.

From the Department of Neurology (D.S.G.), University of California, San Francisco; Department of Neurology (A.T.R.), University of Chicago, IL; University Department of Clinical Neurology (G.C.E.), John Radcliffe Hospital, Oxford, UK; Department of Biostatistics (G.C.), University of Alabama School of Public Health, Birmingham; London Health Sciences Center (M.K.), London, Canada; Neuroimmunology Laboratories and Multiple Sclerosis Clinic (J.O.), University of British Columbia, Vancouver, Canada; Department of Psychology (D.L.), Royal Holloway, University of London, Surrey, UK; Bayer HealthCare Pharmaceuticals (M.R.), Wayne, NJ; Bayer HealthCare Pharmaceuticals (K.B.), Berlin, Germany; PAREXEL (T.M.D.), Hennensack, NJ; Bayer HealthCare Pharmaceuticals (V.K.), Monstein, NJ; and Heinrich-Heine-Universitat (V.K.), Dusseldorf, Germany.

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Go to Neurology.org for full disclosures. Disclosures deemed relevant by the authors, if any, are provided at the end of this article.
Despite these challenges, several independent studies have demonstrated that the standardized mortality ratio is 2–3 times higher for patients with MS than for control subjects without MS in the general population,\textsuperscript{10–15} with differences emerging as early as 2–10 years after MS diagnosis.\textsuperscript{15} Although MS seems to cause a significant survival disadvantage, the impact of DMTs on longevity is unknown. As a reflection of the underlying safety and efficacy of treatment regimens, survival can be considered an integrated measure of long-term outcome, one that could potentially be influenced by early treatment. The long-term follow-up study was therefore undertaken to investigate the impact of early treatment with interferon β-1b (IFNβ-1b) on survival up to 21.4 years after patient enrollment in the pivotal IFNβ-1b trial.

**METHODS Patients.** From October 1, 2009, to December 15, 2010, we sought to identify each of the 372 patients from the 11 North American trial centers who participated in the pivotal, randomized placebo-controlled RCT of IFNβ-1b in relapsing-remitting MS.\textsuperscript{2,16,17} Cohort randomization at the time of the original treatment assignment was maintained for the entire 21-year period and, as shown in table e-1 on the Neurology® Web site at www.neurology.org, treatment allocation cohorts were well-balanced for all baseline demographic variables.\textsuperscript{2,16,17} All randomly assigned patients who were enrolled (for any amount of time) in the pivotal IFNβ-1b trial were eligible to participate. The inclusion criteria for the original RCT have been published previously.\textsuperscript{2} In brief, treatment-naive patients aged 18–50 years with an Expanded Disability Status Scale (EDSS) score ≤5.5 and with 2 or more clinical exacerbations within the previous 2 years, were randomly assigned to receive IFNβ-1b 50 μg (n = 125), IFNβ-1b 250 μg (n = 124), or placebo (n = 123) every other day. During the RCT, patients were treated and prospectively followed for a period of up to 5.1 years, with a median of 3.8 years (range 0.1–5.1 years) and a mean of 3.3 ± 1.4 years on assigned treatment. At the end of the pivotal RCT in 1993, subsequent use of DMTs was at the discretion of patients and their physicians. Only IFNβ-1b was available initially; after 1996, use of alternative DMTs was possible.\textsuperscript{18}

Standard protocol approvals, registrations, and patient consents. The preplanned 21-Year Long-Term Follow-Up (21Y-LTF) study (ClinicalTrials.gov Identifier: NCT01031459) was conducted in accordance with good clinical practice guidelines. Appropriate written informed consent was obtained. The steering committee, consisting of 6 neurologists, 1 internal medicine specialist, 1 neuropsychologist, and 2 biostatisticians, developed the study protocol. This protocol was approved by the institutional review board or independent ethics committee at each center.

Study procedures. Mortality status was determined by linkage of patients to the National Death Index in the United States and other public domain databases. To achieve the most complete ascertainment possible, investigators also reviewed patient charts, conducted in-person interviews, and initiated telephone contact with patients or their proxies.

**Study endpoints.** The primary endpoint of the 21Y-LTF was survival/mortality (all-cause mortality), comparing the IFNβ-1b 250 μg group with the placebo group (by original treatment randomization using an intention-to-treat analysis), approximately 21 years after RCT enrollment. As a secondary outcome, we compared all-cause mortality between the IFNβ-1b 50 μg group and the placebo group.

Statistical analysis. Data were analyzed in accordance with a predefined statistical plan. Survival outcome was analyzed by original treatment assignment during the RCT, using intention-to-treat principles, the Kaplan-Meier method of time to death from randomization, and a log-rank test using SAS (version 9.1). Six patients whose vital status could not be identified were censored at their last observation. The predictive value of baseline characteristics was assessed by unadjusted and adjusted Cox proportional hazard regression models. Adjusted models included both individual covariates and interactions with treatment. Baseline clinical variables included gender, age at disease onset, duration of disease, EDSS score, and relapse rate. Baseline MRI variables included T2 burden of disease (BOD), defined as the area (cm$^2$ per slice) of hyperintense lesions seen on T2-weighted images, and third ventricular width (mm). Continuous variables were dichotomized according to the variable’s median value. As a sensitivity analysis, we also analyzed the data using continuous variables.

Additional sensitivity analyses were performed to assess the robustness of the results. First, we analyzed the time from onset of clinical symptoms to death (rather than from RCT onset), using the Kaplan-Meier log-rank test. Second, we analyzed the joint influence of baseline variables and treatment on survival using a multivariate Cox regression, with $p = 0.5$ required to enter the model and $p \leq 0.1$ needed to remain in the model; because of the question being addressed in this study, treatment assignment during the RCT was forced into these models.\textsuperscript{19} Third, we reanalyzed the data, assuming that all nonidentified patients in the IFNβ-1b–treated groups had died at the time of their last observation and that all placebo-treated patients were alive at the end of the 21Y-LTF. Fourth, we sequentially excluded all patients from the 2 sites with the highest mortality rates and subsequently reanalyzed the data using these smaller datasets.

**RESULTS** Patient identification and baseline characteristics. Of the 372 patients enrolled in the pivotal IFNβ-1b trial, only 6 patients (2 per group) were lost to follow-up, such that 366 (98.4%) were included in the 21Y-LTF study (figure 1). Of the 6 patients who could not be identified, 3 withdrew from the pivotal study within 3 months of RCT onset and are therefore unlikely to have been influenced by treatment assignment. The remaining 3 patients terminated their participation after 1.2, 2.9, and 4.2 years. Patient identification rates among the 11 study centers ranged from 89.3% to 100%. Of these 366 patients, 81 (22.1%) had died and 285 (77.9%) were alive. Between the 16-Year Long-Term Follow-Up (16Y-LTF) and 21Y-LTF studies, an additional 38 patients were identified, 7 of whom were found to be deceased at the time of the 16Y-LTF trial. Deceased
patients therefore represented 18.4% (7 of 38) of those unidentified patients in the 16Y-LTF cohort, a higher proportion than the 10.7% (35 of 328) originally reported. The median time from pivotal trial randomization to 21Y-LTF was 21.1 years. There were no notable differences in baseline characteristics among the groups at the start of the RCT for the 366 patients identified at 21Y-LTF (table e-1).

Survival outcomes. Original randomization to IFNβ-1b 250 μg was associated with a significant reduction in all-cause mortality over the 21Y-LTF period compared with randomization to placebo (figure 2A), with a hazard ratio (HR) of IFNβ-1b 250 μg compared with that for placebo of 0.532 (95% confidence interval [CI] 0.314–0.902; \( p = 0.0173 \)). This represents a reduction in the hazard rate of dying by 46.8% (figure 2A). A similar result was observed for the IFNβ-1b 50 μg treatment arm, with an HR of 0.540 (95% CI 0.317–0.910; \( p = 0.0202 \)), representing a reduction in the hazard rate of dying of 46.0% (figure 2B).

Predictive markers in the 21Y-LTF. Certain baseline parameters were associated with longer survival, using univariate Cox models with dichotomized variables. These included assignment to IFNβ-1b 250 μg (HR 0.533, 95% CI 0.314–0.904; \( p = 0.0195 \)), assignment to IFNβ-1b 50 μg (HR 0.537, 95% CI 0.317–0.910; \( p = 0.0209 \)), lower EDSS score (HR 0.628, 95% CI 0.399–0.989; \( p = 0.0449 \)), lower T2 BOD (HR 0.424, 95% CI 0.264–0.682; \( p = 0.0004 \)), and smaller MRI ventricle size (HR 0.576, 95% CI 0.353–0.940; \( p = 0.0272 \)).

Bivariate regression models (using dichotomized variables), which included treatment together with each individual baseline variable, showed that gender, T2 BOD, and MRI ventricle size, in addition to treatment, influenced the risk of dying (table e-2). In these models, the HR for the treatment effect on mortality remained quite stable, ranging from 0.506 to 0.608 (table e-2). Thus, the treatment-related HR was unchanged by the inclusion of baseline variables, even when these variables were themselves associated with an increased likelihood of mortality (table e-2). Moreover, no significant or important interactions were noted when baseline variables such as age were analyzed continuously or dichotomized by median values (data not shown). Thus, the association of early IFNβ-1b therapy with mortality/survival was independent of demographic and baseline clinical and MRI disease parameters. The presence of neutralizing antibodies against IFNβ-1b during the RCT did not affect survival.

Sensitivity analyses. Analyzing the data from the onset of clinical symptoms (rather than from RCT onset) again showed that original randomization to either IFNβ-1b 250 μg or IFNβ-1b 50 μg was associated with a significant reduction in all-cause mortality over the 21Y-LTF period compared with that for placebo (figure 2, C and D). For the IFNβ-1b 250 μg group, the HR compared with placebo was
0.495 (95% CI 0.289–0.847; \( p = 0.0089 \)). For the IFN-\( \beta \)-1b 50 \( \mu \)g group, the HR compared with placebo was 0.545 (95% CI 0.321–0.924; \( p = 0.0223 \)).

In the multivariate Cox regression analysis, the treatment effect on mortality was maintained for IFN-\( \beta \)-1b (table 1), and the HR remained stable for the IFN-\( \beta \)-1b 250 \( \mu \)g (0.533) and IFN-\( \beta \)-1b 50 \( \mu \)g (0.659) doses. In the IFN-\( \beta \)-1b 250 \( \mu \)g group analysis, gender and baseline T2 BOD were retained as concomitant predictors of mortality, whereas in the IFN-\( \beta \)-1b 50 \( \mu \)g group analysis, baseline T2 disease burden and age at disease-onset were retained (table 1). The same multivariate stepwise Cox regression analyses using continuous variables (i.e., without dichotomization) showed that both IFN-\( \beta \)-1b 250 \( \mu \)g and IFN-\( \beta \)-1b 50 \( \mu \)g had significant effects on mortality (data not shown).

Analysis assuming that all nonidentified patients in the IFN-\( \beta \)-1b–treated groups had died at the time of their last observation and that all placebo-treated patients were alive at the end of the 21Y-LTF showed no significant impact on the findings in either of the treated groups or the placebo group. A reanalysis of a smaller dataset in which all patients at the 2 study sites with the highest mortality rates were excluded sequentially did not alter the findings.

**DISCUSSION** The clinical course of MS can evolve over a period of 30 years or more,\(^{20,21}\) so that long-term follow-up studies are necessary to define disease progression and survival. To date, however, only natural history populations have been investigated in studies of sufficient duration.\(^{11-13}\) Questions about the impact of any DMTs on long-term outcomes
was required to stay in the model. For the regression analysis, entry into the model required a Treatment forced into the model. Continuous variables were dichotomized according to the variable’s median value at baseline. HRs are presented as the hazard in the first dichotomized group divided by that in the second. Thus, for example, for T2 burden of disease (≤15.0 cm²), the HR is the hazard in the (≤15.0) group divided by that in the (>15.0) group. For the regression analysis, entry into the model required p < 0.5; p < 0.1 was required to stay in the model.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Multivariate elimination Cox regression analysis of baseline variables on time from randomized controlled trial randomization to death</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>IFNβ-1b</td>
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<tr>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>p Value</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.533 (0.310–0.917)</td>
</tr>
<tr>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Baseline T2 burden of disease (≤15.0 vs &gt;15.0 cm²)</td>
<td></td>
</tr>
<tr>
<td>0.435 (0.246–0.770)</td>
<td></td>
</tr>
<tr>
<td>p &lt; 0.05</td>
<td></td>
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<tr>
<td>Gender (female vs male)</td>
<td></td>
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<tr>
<td>0.531 (0.312–0.906)</td>
<td></td>
</tr>
<tr>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>50 µg group</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>0.659 (0.383–1.135)</td>
</tr>
<tr>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Baseline T2 burden of disease (≤15.0 vs &gt;15.0 cm²)</td>
<td></td>
</tr>
<tr>
<td>0.330 (0.183–0.596)</td>
<td></td>
</tr>
<tr>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Disease onset age (≥27.0 vs &gt;27.0 y)</td>
<td></td>
</tr>
<tr>
<td>0.618 (0.358–1.065)</td>
<td></td>
</tr>
<tr>
<td>p &lt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; HR = hazard ratio.

* Treatment forced into the model. Continuous variables were dichotomized according to the variable’s median value at baseline. HRs are presented as the hazard in the first dichotomized group divided by that in the second. Thus, for example, for T2 burden of disease (≤15.0 vs >15.0 cm²), the HR is the hazard in the (≤15.0) group divided by that in the (>15.0) group. For the regression analysis, entry into the model required p < 0.5; p < 0.1 was required to stay in the model.

remain unanswered. To provide data for the impact of therapy on survival, we analyzed survival in patients 21 years after their enrollment into the original IFNβ-1b RCT.

In the RCT, both doses of IFNβ-1b had significant benefits relative to those of placebo, as determined by both clinical and MRI outcomes.2,17 These benefits were most conspicuous for the subsequently licensed IFNβ-1b 250 µg dose.2,17 Nevertheless, the fact that both doses of IFNβ-1b had a clear therapeutic benefit becomes important when the possible manner in which the original randomization scheme has been imprinted on mortality outcomes was considered.

In the 21Y-LTF study, 81 deaths were recorded; the greatest number of which were observed among individuals assigned to placebo. Thus, relative to that for placebo, the hazard rate of death at 21Y-LTF was reduced by 46.8% in the IFNβ-1b 250 µg group and by 46.0% in the IFNβ-1b 50 µg group. The virtually identical effect sizes, together with the therapeutic benefits of both doses on short-term outcomes,2,17 lend support to our observations. If these survival outcomes were due to chance (i.e., from a type I error), it could reflect an unusually high mortality rate in the placebo arm or use of other treatments during long-term follow-up. However, counter to this possibility, the observed survival rate in our placebo arm is consistent with reports from natural history studies.10,12–15 For example, as shown in figure e-1, the survival rate 29 years after disease onset (~70%) observed by others10 was essentially identical to that in our placebo group (70.4%). Furthermore, the medications taken after the end of the pivotal study did not differ systemically.18 Taken together, these observations support the notion that there is a survival advantage after early exposure to IFNβ-1b.

Despite several baseline variables being significantly associated with earlier mortality in our univariate regression models, the inclusion of these variables in bivariate models did not alter the observed HR for the treatment effect (table e-2). In addition, although T2 disease burden, as well as some other baseline covariates, proved predictive of mortality, their effect was additive to the predictive power of the treatment effect (table 1). Finally, further sensitivity analyses did not alter our results. Each of these observations supports an observed survival benefit associated with therapy.

Importantly, the baseline variables (T2 BOD and MRI ventricle size) associated with increased mortality are themselves markers of MS severity, suggesting that these patients were dying due to advancing MS. This notion is further supported by our observations in the 21Y-LTF study: 78.3% (54 of 69) of patients were determined to have died of MS-related causes, as expected for deaths that occur at ages when other causes of mortality are uncommon. Moreover, all excess deaths were in the MS-related category and, in particular, were the result of pulmonary infections.

There are several key features regarding our trial, which are critical to any evaluation of the validity of the reported findings. These include the facts that we had a very long follow-up period (>21 years), that our treatment allocation cohorts were randomized at baseline, and that we achieved near-complete ascertainment (98.4%) of the RCT cohort.2,17 In contrast to this, previous long-term studies in MS have had much shorter periods of follow-up (8–15 years) and much less complete ascertainment of the original RCT population (39.8%–68.2%).24–26 Reports based on relatively short periods of follow-up or low patient ascertainment rates have a high probability of bias. A high ascertainment rate is critically important for a rare event such as mortality, especially when we consider that unidentified patient cohorts are likely to be enriched with deceased individuals relative to identified patient cohorts.2,17 We observed this in our own work: the death rate in the unidentified patient cohort in the 16Y-LTF study (18.4% [7 of 38]) was higher than that observed in the identified cohort (10.7% [35 of 328]).18 Moreover, the 5 years between the 16Y-LTF and 21Y-LTF studies resulted in a doubling of the number of observed deaths (35 vs 81 deaths), increasing the precision of the estimates. The results of the 21Y-LTF study extend the treatment benefits first suggested in the 16Y-LTF study. We also conclude that datasets examining survival are less informative with greater numbers of “miss-
Table 2  Treatment exposure according to original treatment assignment in the 21Y-LTF and the 16Y-LTF populations

<table>
<thead>
<tr>
<th>Treatment exposure according to original treatment assignment</th>
<th>Placebo</th>
<th>IFNβ-1b 50 µg</th>
<th>IFNβ-1b 250 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>21Y-LTF populationa</td>
<td>121</td>
<td>123</td>
<td>122</td>
</tr>
<tr>
<td>Total duration of original treatment exposure during the RCT</td>
<td>Mean (SD), y 3.3 (1.4)</td>
<td>3.3 (1.3)</td>
<td>3.3 (1.5)</td>
</tr>
<tr>
<td>Total duration of IFNβ-1b exposure (50 µg or 250 µg) after the RCT</td>
<td>Mean (SD), y 6.6 (4.7)</td>
<td>7.8 (4.8)</td>
<td>7.1 (4.4)</td>
</tr>
<tr>
<td>Total duration of IFNβ-1b exposure (250 µg only)</td>
<td>Mean (SD), y 6.9 (0-12.5)</td>
<td>10.6 (0-12.6)</td>
<td>7.7 (0-12.5)</td>
</tr>
<tr>
<td>16Y-LTF populationb</td>
<td>79</td>
<td>85</td>
<td>96</td>
</tr>
<tr>
<td>Total duration of IFNβ-1b exposure (50 µg or 250 µg)</td>
<td>Mean (SD), y 5.1 (4.5)</td>
<td>6.4 (5.0)</td>
<td>9.2 (4.9)</td>
</tr>
<tr>
<td>Total duration of IFNβ-1b exposure (50 µg or 250 µg)</td>
<td>Mean (SD), y 5.0 (0-12.5)</td>
<td>5.9 (0-12.5)</td>
<td>8.9 (0-1.17.1)</td>
</tr>
<tr>
<td>Total duration of IFNβ-1b exposure (50 µg or 250 µg)</td>
<td>Mean (SD), y 6.6 (4.7)</td>
<td>11.1 (5.6)</td>
<td>10.7 (5.0)</td>
</tr>
<tr>
<td>Total duration of IFNβ-1b exposure (50 µg or 250 µg)</td>
<td>Mean (SD), y 6.9 (0-12.5)</td>
<td>13.6 (0.2-16.7)</td>
<td>12.0 (0.1-17.1)</td>
</tr>
</tbody>
</table>

Abbreviations: 16Y-LTF = 16-year long-term follow-up; 21Y-LTF = 21-year long-term follow-up; RCT = randomized controlled trial.

a n = 366 patients identified at 21Y-LTF

b n = 260 patients participating in the 16Y-LTF study. Last available drug usage data were collected during the 16Y-LTF study.

It is conceivable that the survival advantage conferred by IFNβ-1b may be mediated through its antioxidative properties. Regardless of this theoretical possibility, however, considerably more work will be necessary to understand fully the biologic basis for these findings.

The total duration of original treatment exposure during the RCT in the 21Y-LTF cohort is summarized in table 2. After the RCT, the use of DMTs was both optional and unmasked. Although the choice, type, and duration of therapy among patients were variable, until 1996, the only DMT available in the United States and Canada was IFNβ-1b. After this time, the type of treatment received could have varied. Despite this possibility, at the time of the 16Y-LTF (when data on treatment use were collected), the median medication use in this cohort was largely restricted to IFNβ-1b (either 250 or 50 µg): 6.9 years for the original placebo group, 13.6 years for the original IFNβ-1b 50 µg group, and 12.0 years for the original IFNβ-1b 250 µg group (table 2). Thus, patients originally randomly assigned to placebo had less cumulative exposure to IFNβ-1b than those originally assigned to either IFNβ-1b 50 µg or IFNβ-1b 250 µg during the pivotal RCT (table 2). Consequently, we cannot distinguish between the possibility that the observed survival benefit was due to an effect of early treatment and the possibility that the benefit was due to a longer duration of IFNβ-1b exposure.

Theoretically, varying treatments and drug holidays during the uncontrolled phase of the 21Y-LTF should lessen any survival differences because these variations are expected to blur the distinction between groups. This variance should therefore bias the result toward the null hypothesis. Despite this theoretical possibility, we detected a large and clinically important survival benefit associated with randomization to IFNβ-1b treatment (either dose) vs placebo. With near-complete patient ascertainment (98.4%), randomized cohorts, the longest period of follow-up for a treatment-exposed MS population, and similar results from 2 parallel groups of IFNβ-1b–treated patients, these data support the notion that early use of IFNβ-1b improves survival in patients with MS.

AUTHOR CONTRIBUTIONS

Dr. Goodin has contributed to the design/conceptualization of the study, analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content. Dr. Reder has contributed to the analysis/interpretation of the data and drafting/revising the manuscript for intellectual content. Dr. Ebers has contributed to the analysis/interpretation of the data, and drafting/revising the manuscript for intellectual content. Dr. Reder has contributed to the analysis/interpretation of the data, statistical analysis, and drafting/revising the manuscript for intellectual content. Dr. Kremenchutzky has contributed...
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DISCLOSURE

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REFERENCES
