Long-term follow-up of clinical trials of multiple sclerosis therapies
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ABSTRACT

Results from registry studies can provide valuable information about the prevalence and clinical course of different forms of multiple sclerosis (MS). Such studies can also help identify medical practice patterns in a real-world setting and important risk factors that may affect long-term outcomes in patients with MS. To date, however, these observational studies have provided less information than well-planned, randomized, controlled trials on the long-term treatment effects of disease-modifying therapies (DMTs). Short-term clinical trial results have indicated that currently available DMTs are effective in reducing disease activity, manifested by relapse or MRI change, and may slow disease progression. Because MS is a chronic disease that evolves over a period of 30 to 40 years, determining the long-term effects of treatment is of critical importance to both patients and providers. This article discusses long-term studies of DMTs in patients with MS. Exploratory data provided thus far support the hypothesis that early optimal treatment aimed at reducing disease activity can improve longer-term outcomes by delaying disease progression.

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RESULTS FROM SHORT-TERM STUDIES INDICATE THAT USE OF DISEASE-MODIFYING THERAPY (DMT) CAN REDUCE RELAPSES AND DELAY DISABILITY PROGRESSION IN PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS (RRMS).1 However, due to the slow progression of the disease, it is not known whether the short-term outcome measures used in such studies correlate with patient outcome many years later.1 When designing clinical trials that evaluate the effects of immunosuppressive agents, it is important to consider both the progressive nature of the disease as well as the relevant outcome measures. As such, long-term follow-up (LTFU) studies are valuable because they measure the progression of disease over a long period of time and reduce the variability associated with short-term studies.

There are little data available on the effects of using interferon-β (IFN-β) for more than 10 years. Because multiple sclerosis (MS) usually takes several decades to evolve (e.g., for RRMS, 30–40 years), there is a need for longer-term data on treatment outcomes. This article reviews key findings from 4 LTFU studies of DMTs. These studies include long-term treatment with IFN-β-1b (Betaseron®), IFN-β-1a (Rebif®), IFN-β-1a (Avonex®), and glatiramer acetate (GA) (Copaxone®). Approaches to improving long-term studies are discussed in the following article in this supplement.

THE 16-YEAR LTFU STUDY OF IFN-β-1b IFN-β-1b was approved for the treatment of relapsing forms of MS based on the results of a double-blind, placebo-controlled trial in which patients were randomized to receive placebo, IFN-β-1b 50 μg, or IFN-β-1b 250 μg SC every other day for up to 5 years.2-4 Patients with RRMS were included in the

Glossary

AE = adverse event; ARR = annualized relapse rate; ASSURANCE = Assessment of Drug Utilization, Early Treatment, and Clinical Outcomes; BOD = burden of disease; CHAMPIONS = Controlled High risk Avonex® MS Prevention study in Ongoing Neurological Surveillance; CHAMPS = Controlled High-risk Avonex® MS Prevention Study; COWAT = Controlled Oral Word Association Test; CVLT-II = California Verbal Learning Test–II; D-KEFS = Delis-Kaplan Executive Function System; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; IFN = interferon; LTFU = long-term follow-up; MS = multiple sclerosis; MSCRG = Multiple Sclerosis Collaborative Research Group; PRISMS = Prevention of Relapses and disability by Interferon β-1a Subcutaneously in Multiple Sclerosis; RRMS = relapsing-remitting multiple sclerosis; SDMT = Symbol Digit Modality Task; WTAR = Wechsler Test of Adult Reading ability.

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pivotal trial if they had Kurtzke Expanded Disability Status Scale (EDSS) scores of ≤5.5 and at least 2 acute exacerbations during the previous 2 years. Results showed IFNβ-1b to be effective, with a good safety and tolerability profile over the study period. In order to evaluate the long-term treatment effects of IFNβ-1b, the 16-year LTFU study, an open-label, observational study, was conducted.3

**Clinical outcomes.** A total of 328 of the original 372 patients in the pivotal study were identified.2,4 Efforts were made to contact all patients who participated in the pivotal trial to assess the impact of their IFNβ-1b therapy with regard to clinical disability, MRI, and cognitive outcomes.2,6 A total of 253 patients participated in the LTFU study. To maximize ascertainment of more disabled patients in the IFNβ-1b LTFU study, provision was made to facilitate travel to the study centers and, for those patients who declined to come to the study centers, home visits and telephone interviews were offered. When patients could not be found, attempts were made to locate them using local expertise and experience, as allowed by ethics approval. Death and other governmental and obituary records were searched when the investigators were unable to locate original trial participants. As a result of these efforts, the 16-year LTFU study of IFNβ-1b achieved nearly 90% ascertainment, the highest level among the long-term studies.2,6

Patients with RRMS who took IFNβ-1b almost continuously showed a sustained reduction in the annualized relapse rate (ARR) of up to 40% over 16 years when compared with those who had hardly ever or never taken IFNβ-1b.7 In addition, those who remained on long-term IFNβ-1b treatment had a slower disease progression compared with patients who did not remain on long-term treatment. Longer exposure to IFNβ-1b correlated with delayed progression to EDSS 6.0 (figure 1). Patients receiving long-term IFNβ-1b treatment reached EDSS 6.0 (i.e., needing a cane for walking) after a median time of 13 years from diagnosis, as compared with a median time of 7 years for patients receiving short-term treatment.7

A baseline EDSS ≥2.0 was found to be predictive of poorer long-term outcome (p < 0.001).8 The most powerful predictor of long-term EDSS was the change in EDSS from baseline to year 2 (r = 0.59, p < 0.0001), followed by the ARR during the pivotal trial (r = 0.57; p < 0.0001) and categorical change in EDSS of ≥1 point (r = 0.53, p = 0.0003). However, change in MRI disease burden was not such a valid predictor (r = 0.50; p > 0.5).8

**MRI outcomes.** During the pivotal study, results from yearly MRI examinations supported the clinical findings by demonstrating significant reduction in disease activity as measured by numbers of active scans (median 80% reduction, p = 0.0082), appearance of new lesions, and burden of disease (BOD) (p = 0.001).4,6 Although the long-term treatment effects on MRI parameters are of importance, technical changes in MRI capabilities during the intervening years have limited the ability to directly compare scans from the original study with those from the LTFU study. As such, new MRI data were obtained from patients in the original cohort for evaluation of current MRI status and for correlation with clinical disability.6 A single cranial and cervical cord MRI was performed using a standardized protocol in 192 of the 293 original patients (65.5%). The results demonstrated that patients with a higher EDSS score had a higher T2 BOD, higher T1 hypointense lesion (black hole) volumes, lower normalized brain volume, and a smaller cervical cord area.6 When patients were compared according to their current treatment status, more of the untreated (>90 days since discontinuation) patients had gadolinium-enhancing lesions compared with the IFNβ-1b-treated patients. Additional analyses of the MRI findings are ongoing.

**Cognition outcomes.** Cognitive dysfunction is estimated to affect about 40% to 65% of patients with MS and can be debilitating enough to affect quality of life.9 At the beginning of the 16-year LTFU study, a number of cognitive tests were chosen to determine patients’ working memory and attention, verbal memory function, and verbal fluency, an indicator of executive function. The tests included the Wechsler Test of Adult Reading ability (WTAR), Symbol Digit Modality Task (SDMT, oral version), PASAT3, California Verbal Learning Test–II (CVLT-II), Controlled Oral Word Association Test.
The 16-year long-term follow-up study of interferon (IFN)β-1b: Number of patients with multiple sclerosis, according to their original randomized study group, found alive, not found, or found to be deceased

![Figure 2](image-url)

Numbers within columns indicate the actual number of patients affected. Unidentified cases were equally distributed among the three treatment groups; deaths were more prevalent in the placebo group.


(COWAT), and Delis-Kaplan Executive Function System (D-KEFS). The level of performance on each cognitive task was obtained by computing the Z scores for each individual according to published norms. The results suggest that disease activity and progression in the early stages of MS are determinants of cognitive status 16 years later. Statistically independent predictors of cognitive performance index were premorbid IQ ($p < 0.0001$), EDSS scores at baseline ($p = 0.0001$), and MRI T2 BOD at baseline ($p < 0.0001$).

Safety and tolerability outcomes. The safety data supported the good long-term safety profile of IFNβ-1b, with no new safety issues being identified in the LTFU study compared with the original trial. Treatment side effects largely decreased with time when compared with incidence rates in the pivotal trial.

Mortality. Figure 2 summarizes the patient disposition by original treatment group. After 16 years, 95% of the identified patients originally assigned to IFNβ-1b 250 μg were still alive compared with 92% of those assigned to IFNβ-1b 50 μg, and 82% of patients assigned to receive placebo. A total of 35 patients were deceased at the LTFU. Of note, these deaths occurred at a much lower age than in the general population, with a peak death rate at 46–50 years. The cause of death was established in only 8 patients. Most deaths occurred after more than 10 years of follow-up and, therefore, would not have been observed in a shorter study. Thus, LTFU is essential if hard endpoints like all-cause mortality are to be used to assess treatment effects in MS.

Study limitations. Limitations of the 16-year LTFU study of IFNβ-1b largely matched those expected of any LTFU of this nature. Retrospectively collected relapse data may not be accurate and could be affected by recall bias. Because not all of the patients could be interviewed directly, information was also gathered through self-administered questionnaires. In-person evaluations, which generally gather more complete data than questionnaires, were utilized in the 16-year follow-up for the majority of patients. Moreover, obtaining information on deceased patients is challenging for a variety of reasons, as there may be legal implications, the next-of-kin may be unknown or unreachable, there could be a possible delay in the registration of death, or the most recent treating physician may not be known. As such, there was incomplete ascertainment for endpoints such as disability status prior to death and time of progression to SPMS. Another limitation to this study is that, despite clearly defined criteria, the transition from RRMS to SPMS remained a subjective and imprecise event. Finally, because patients were treated according to clinical need by their physicians after trial completion, a number of different treatments were used. Thus, demonstrating a relationship between a particular therapy and clinical outcomes is difficult.

THE PRISMS LTFU STUDY OF IFNβ-1a The original Prevention of Relapses and disability by Interferon β-1a Subcutaneously in Multiple Sclerosis (PRISMS) study was a double-blind, placebo-controlled trial designed to investigate the effects of IFNβ-1a (Rebif®) in patients with RRMS. Eligible patients had at least 2 relapses within the preceding 2 years, and EDSS scores of 0–5.0. After 2 years of treatment, patients who were randomly assigned to receive IFNβ-1a 22 μg or 44 μg 3 times weekly by SC injection showed significant clinical and MRI benefits compared with placebo-treated patients.

The PRISMS-4 study, a 2-year extension of the original study, was designed to obtain information about the duration of the effect of treatment with IFNβ-1a. An important goal of this study was to compare the long-term effects of early vs delayed initiation of IFNβ-1a treatment. Patients who received active medication in the original study continued to receive the same blinded dose, whereas placebo-treated patients were re-randomized, in a blinded fashion, to one of the two doses of IFNβ-1a (22 μg or 44 μg). Patients who completed the 4-year study were provided with an opportunity to continue blinded or open-label treatment with IFNβ-1a for the following 2 years (up to year 6).
Data for the LTFU study were obtained from prospectively collected information (for the earliest enrolled patients who were waiting for the others to complete the study) or retrospectively for those who declined to enter the post-4-year extension from patient records.12-14 The LTFU assessment consisted of one predefined visit from 1 to 2 years after the 6-year safety visit (i.e., years 7–8 after the original start of PRISMS). A total of 382 of the 560 (68.2%) patients randomized originally in PRISMS returned for the LTFU assessment. All patients were eligible to participate in the LTFU regardless of when they discontinued treatment. The final LTFU visit therefore included a mixture of patients: those remaining on IFNβ-1a since enrollment in the original PRISMS study (initial treatment), those whose treatment was delayed for 2 years (the original placebo patients), and those who chose to either stop IFNβ-1a or switch to another treatment.14 After 4 years, patients received either open-label treatment (in countries approving either the low or high dose of treatment) or were switched from low to high dose after an analysis of the data suggested that the latter produced a greater effect. As such, patients at the LTFU visit had been exposed to the high dose of IFNβ-1a for variable periods of time. Long-term analysis therefore focused on the original blinded and placebo-controlled 2- to 4-year vs the long-term outcome.14

Clinical outcomes. Patients treated with IFNβ-1a from the beginning of the original PRISMS study accumulated disability more slowly than patients who delayed treatment by taking a placebo for the first 2 years.14 A longer time to 1-point, 2-point, and EDSS 6.0 progression was observed with initial IFNβ-1a therapy compared with later treatment (figure 3). In addition, time to first 2-point-confirmed EDSS progression was delayed with the 44 μg dose compared with the 22 μg dose or late treatment (table 1). Overall, 31% of patients in the original PRISMS cohort progressed by 2 EDSS points.14 For the 25th percentile, this translated into a gain of 2.8 years in time to progression between the original 44 μg dose group and those receiving late treatment.

A total of 75 of the 381 patients (20%) assessed at LTFU had progressed from RRMS to SPMS since baseline assessment (13 years from onset of RRMS).14 A higher proportion of patients reaching SPMS might have been expected based on some older,15-17 but not more recent natural history studies.18 In PRISMS, initial treatment with IFNβ-1a also decreased overall relapse rates compared with later treatment. Compared with later treatment, ARR was significantly lower for patients receiving initial treatment with IFNβ-1a 44 μg (0.78 vs 0.6, p = 0.014) or 22 μg (0.78 vs 0.63, p < 0.001), even though patients in the late treatment group were on IFNβ-1a therapy for >75% of the time, and most exposed for at least some time on the higher dose. The median time to onset of progressive disability in patients randomized originally to the 44 μg dose was delayed by about 3 years compared with the late treatment. Progression to EDSS 4.0 and EDSS 6.0 was also slower among patients originally randomized to IFNβ-1a 44 μg when compared to late treatment.14

MRI outcomes. With regard to MRI parameters, patients treated with IFNβ-1a 44 μg from the start of the original PRISMS study had a significantly smaller percentage change from baseline to LTFU in terms of total T2 BOD than the late-treated patients (p = 0.002).14 The largest effects were observed in the first 2 years of the study.14

Safety and tolerability outcomes. No new safety issues were defined during the LTFU study and most adverse events (AEs) were mild in severity (65%, 198/304).14 Injection site reactions were the most
commonly reported AE (44%, 128/291) and flu-like symptoms occurred in 12% (34/291) of patients. Three patient deaths were reported during PRISMS, and 5 between the 6-year safety follow-up (PRISMS-6) and LTFU. The deaths included 2 patients originally randomized to placebo who did not receive active treatment during PRISMS, 5 patients randomized to IFNβ-1a 22 μg, and 1 patient randomized to IFNβ-1a 44 μg. Thus, there were too few of these events to identify any difference between the initial randomization groups.14

Study limitations. An important limitation of this study is that the frequency and timing of assessments were not consistent over time. As such, patients enrolled during the initial part of the study were seen at 3-month intervals, while those seen at follow-up had a single exit visit. Long intervals during which patients were not assessed could have resulted in a reduced rate of reporting relapses and AEs. In addition, high and transient variability in EDSS scores can lead to false positives in determining disability progression without a second confirmatory visit. Another limitation to this study is the fact that a large proportion of patients randomized in the original study did not participate in the extension study. Both patients and evaluators were unblinded, which might have influenced the results. Patients returning for LTFU assessment might represent a subgroup of patients who responded differently to treatment than the nonreturning patients.

Long-term data on IFNβ-1a. IFNβ-1a (Avonex®) was approved based on the results from a randomized, placebo-controlled, phase III clinical trial by the Multiple Sclerosis Collaborative Research Group (MSCRG).19 In this study, the safety and efficacy of IFNβ-1a 30 μg by weekly IM injection was demonstrated for up to 2 years in patients with RRMS who had baseline EDSS scores of 1.0–3.5, at least 2 documented exacerbations in the prior 3 years, and no exacerbations for at least 2 months prior to study entry.19 This LTFU trial, an open-label extension of the original study, was conducted to determine the long-term safety of IFNβ-1a IM over 6 years of follow-up.20 The clinical efficacy and MRI data have been reported in LTFU over an 8-year period,21 and correlation between EDSS progression in the pivotal trial and disability at 8-year LTFU has also been assessed.22 In addition, the Assessment of Drug Utilization, Early Treatment, and Clinical Outcomes (ASSURANCE) study, a 15-year, open-label, safety extension of the original 2-year trial, was conducted to determine the impact of early vs delayed initiation of treatment on the long-term physical status.23 Data from ASSURANCE were collected by questionnaires completed by self-reporting patients.

Clinical outcomes. Findings from 160 of 172 patients (93%) enrolled for at least 2 years in the pivotal trial were used as baseline data.21 In general, during the time between baseline and the 8-year follow-up, the group worsened in terms of disability. The mean EDSS increased from 2.35 at baseline to 4.38 at the 8-year follow-up, and 35% of patients had progressed to EDSS ≥6.0.21 In addition, patients from the original pivotal trial were re-examined after 8 years to assess correlation between EDSS progression over 2 years and future, clinically significant disability.22 Post hoc analysis of the data demonstrated that patients with baseline EDSS ≥2.0 were significantly more likely than those with baseline EDSS ≤2.0 to reach the milestone EDSS scores ≥4.0, 5.0, 6.0, or 7.0 at 8 years (p < 0.001). Although IFNβ-1a-treated patients were significantly less likely than placebo-treated patients to progress to EDSS ≥4.0 or 5.0 at 8 years (p = 0.007 and 0.01, respectively), multivariate regression analysis of disability progression did not show a significant difference between the IFNβ-1a and placebo groups.22

The ASSURANCE study represents the LTFU of patients who participated in the MSCRG.23 A total of 136 of 172 eligible patients enrolled in the ASSURANCE study. Of these, 46% were taking IFNβ-1a for a median duration of 13.3 years. Those not taking IFNβ-1a were treated with a number of other DMTs. Preliminary results have demonstrated a significantly lower EDSS score among longer-term users compared with patients not receiving IFNβ-1a therapy (2.3 vs 3.3, respectively; p = 0.011). In addition, patients receiving IFNβ-1a had lower disability progression to EDSS 4.0 (64% vs 83%, p = 0.06), EDSS 6.0 (32% vs 62%, p = 0.007), and EDSS 7.0 (9% vs 33%, p = 0.008) compared with those not receiving therapy.

MRI outcomes. To examine the relationship between brain atrophy and subsequent disability, a subgroup of 138 patients with at least 2 MRI scans during the original trial, and EDSS measurement at 8-year follow-up, was used.21 Percent change in brain atrophy from baseline to year 2 was correlated with EDSS at the 8-year LTFU (r = −0.27; p = 0.001). Patients with the least amount of brain atrophy in the pivotal trial were less likely to reach EDSS 6.0 at the 8-year LTFU compared with patients with the most amount of atrophy.21 The progression of brain atrophy during the 8-year follow-up study was determined using a subgroup of 106 patients who had analyzable MRI scans at baseline, years 1 and 2 of the original trial, and the 8-year follow-up.21
treatment, the severity of brain atrophy worsened significantly between baseline and the 8-year LTFU. Although the pivotal MSCRG trial demonstrated that brain atrophy progressed at a significantly slower rate in the second year in the IFNβ-1a group, the 8-year follow-up demonstrated a numerical, albeit nonsignificant, difference between groups (mean percent change in brain parenchymal fraction) (2.5%, initial IFNβ-1a vs −3.0, initial placebo; p = 0.18).

Safety and tolerability outcomes. Patients who participated in the original phase III trial were eligible for enrollment in the safety study, as were patients who had not participated in the pivotal trial. All patients in the safety study received weekly IFNβ-1a 30 μg IM for a treatment duration of up to 8 years. Among those enrolled in the safety extension, 218 of the 382 patients had participated in the original study. However, in the time between the end of the pivotal study and the start of the safety extension study, some patients switched to IFNβ-1b. An additional 164 patients not in the original trial enrolled in the safety extension study. Both the incidence and types of AEs observed in the extension study were similar to those observed in the pivotal trial. Flu-like symptoms were the most common AE (74%) and were more frequently reported in IFNβ-naïve patients (96%) compared with other groups. Other common AEs included headache (58%) and muscle aches (48%). Overall, the treatment was well-tolerated for up to 8 years and only 2% of patients discontinued due to AEs.

Study limitations. A number of study limitations might affect interpretation of the LTFU data. First, because a highly select group of patients was included in the post hoc analysis, the results, including p values, should be interpreted within this context. In addition, treatment between the end of the pivotal trial and the LTFU was variable, and it is not clear how many patients received other preparations of IFNβ and for what time period. Finally, a large proportion of patients not enrolled in the pivotal trial were enrolled in the safety extension.

LTFU OF THE CHAMPIONS TRIAL The Controlled High-risk Avonex\textsuperscript{40} MS Prevention Study (CHAMPS) demonstrated that IFNβ-1a 30 μg administered IM significantly slows the rate of development of CDMS over 2 years in high-risk patients with a first demyelinating event.\textsuperscript{24} To determine whether these benefits are sustained for 5 years, the Controlled High risk Avonex\textsuperscript{40} MS Prevention study in Ongoing Neurological Surveillance (CHAMPIONS), an open-label extension study, was undertaken,\textsuperscript{25} results of which have been described previously in this supplement (see article entitled: Treatment effects of immunomodulatory therapies at different stages of MS in short-term trials). The 10-year LTFU study is ongoing. When evaluating study data, the following limitations need to be considered: only 53% of the CHAMPS patients enrolled in the extension study, which could introduce ascertainment bias and influence the long-term results.\textsuperscript{25} Interruptions in treatment and their potential influence on the results will also need to be considered.

THE LONG-TERM US GLATIRAMER ACETATE TRIAL The US Glatiramer Acetate Trial was a phase III study that compared the daily use of GA, 20 mg SC, and placebo in patients with RRMS.\textsuperscript{26} The original trial began in 1991 and, after double-blind treatment for a mean of 30 months, all patients were offered the opportunity to participate in an ongoing, open-label, prospective study and receive active treatment.\textsuperscript{27} The primary aim of the study was to assess the long-term effects of GA in patients with RRMS over a 10-year period. The study also gathered information on the disease course of patients who had withdrawn from the study. Only 50 of the 124 withdrawn patients returned for the LTFU visit. Adherence to any set treatment regimen was variable and 38 of these patients took a variety of agents after withdrawal, often in combination and for varying lengths of time. A unique aspect of this study was that EDSS was prospectively evaluated in the clinic every 6 months.

Clinical outcomes. The mean exposure to GA therapy in the ongoing cohort was 10.12 years compared with 4.26 years for all patients who had withdrawn.\textsuperscript{27} Relapse rates remained low among patients who had received GA from the outset (initial randomization).\textsuperscript{25} Yearly relapse rates declined from a mean of 1.18 from 2 years before the start of GA therapy to less than 0.5 from year 2 through year 12 of follow-up. Relapse rates were reduced by >80% from rates at the start of treatment to approximately one relapse every 5 years. Among 108 GA-treated ongoing patients, 62% had clinically stable/improved EDSS scores compared with only 55% in the withdrawn cohort. In addition, 58% of the GA-treated patients maintained stable/improved EDSS scores from the start of treatment and their last on-treatment EDSS assessment. Patients who withdrew from the study had an EDSS change almost 4.5 times that of the continuously treated patients.\textsuperscript{27} There were also significant differences between groups in the proportions of patients reaching EDSS thresholds of 4.0, 6.0, and 8.0. More continuously treated patients who remained in the study had clinically stable/improved EDSS scores between the start of treatment and the 10-year LTFU visit compared with the withdrawn patients returning for a LTFU assessment.
The importance of long-term treatment with DMT has been demonstrated in patients with MS. Collectively, results of these exploratory studies suggest that exposure to DMT over a long period of time improves outcomes by delaying the time to significant disease progression. In the IFNβ-1b 16-year LTFU study of patients with RRMS, for example, longer exposure to IFNβ-1b correlated with delayed progression to EDSS 6.0 and longer time to onset of SPMS. In addition, results of these studies suggest that delaying therapy, even by 2 years, in patients with established RRMS (PRISMS) yields poorer long-term outcomes compared with initiating treatment earlier. Patients who started and continued treatment with IFNβ-1a 44 μg in PRISMS accumulated less disability over time and did so more slowly than those delaying treatment. The 8-year follow-up of IFNβ-1a 30 μg (IM) therapy showed that patients who delayed therapy were more likely to progress to EDSS 4.0. Long-term treatments were generated with a favorable safety and tolerability profile. The most common AEs associated with GA were local injection site reactions and postinjection reaction symptoms, although these declined over time. Twenty-three patients withdrew due to AEs. The 15-year analysis of this study has recently been published. The 100 GA-treated ongoing cohort (patients who continued in the study from February 2008) showed a decline in ARR from 1.12 ± 0.82 at baseline to 0.25 ± 0.34 per year, while 57% had stable or improved EDSS scores (change ≤0.5 points). The change in mean EDSS scores from start of treatment to the last observation while on GA was 0.6 ± 2.0 (table 2). These improvements are greater than those seen in the withdrawn cohort. The safety and tolerability profile of GA therapy was similar to that observed at 10 years.

**Study limitations.** One of the limitations of this study that may influence the interpretation of the data is the potential selection bias. That is, for the most part, only patients who responded to and remained on GA treatment were included in the study. Although such patients may have appeared to do well, it is possible that they may have done well without therapy. Lack of information on a substantial number of patients who dropped out as well as ignoring missing data are limitations of this study. It is possible, for example, that patient withdrawal was influenced by the availability or introduction of other DMTs. Finally, there are important differences between patients who continued and those who discontinued treatment. The most important difference is that patients choosing not to continue overall did worse then those who remained on treatment, which may have resulted in a selection bias.

**DISCUSSION**

The long-term treatment with GA was associated with a favorable safety and tolerability profile. The most common AEs associated with GA were local injection site reactions and postinjection reaction symptoms, although these declined over time. Twenty-three patients withdrew due to AEs. The 15-year analysis of this study has recently been published. The 100 GA-treated ongoing cohort (patients who continued in the study from February 2008) showed a decline in ARR from 1.12 ± 0.82 at baseline to 0.25 ± 0.34 per year, while 57% had stable or improved EDSS scores (change ≤0.5 points). The change in mean EDSS scores from start of treatment to the last observation while on GA was 0.6 ± 2.0 (table 2). These improvements are greater than those seen in the withdrawn cohort. The safety and tolerability profile of GA therapy was similar to that observed at 10 years.

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**DISCUSSION**

The importance of long-term treatment with DMT has been demonstrated in patients with MS. Collectively, results of these exploratory studies suggest that exposure to DMT over a long period of time improves outcomes by delaying the time to significant disease progression. In the IFNβ-1b 16-year LTFU study of patients with RRMS, for example, longer exposure to IFNβ-1b correlated with delayed progression to EDSS 6.0 and longer time to onset of SPMS. In addition, results of these studies suggest that delaying therapy, even by 2 years, in patients with established RRMS (PRISMS) yields poorer long-term outcomes compared with initiating treatment earlier. Patients who started and continued treatment with IFNβ-1a 44 μg in PRISMS accumulated less disability over time and did so more slowly than those delaying treatment. The 8-year follow-up of IFNβ-1a 30 μg (IM) therapy showed that patients who delayed therapy were more likely to progress to EDSS 4.0. Long-term treatments were gen-

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<th>Table 2</th>
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<td>EDSS measure</td>
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<td>Withdrawed cohort, n = 131</td>
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<td>Time from GA start to last observation, y</td>
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<tr>
<td>Average EDSS change per year</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>Median</td>
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<tr>
<td></td>
<td>Range</td>
</tr>
</tbody>
</table>

Abbreviations: EDSS = Expanded Disability Status Scale; GA = glatiramer acetate.
erally well-tolerated and the favorable safety profiles that were reported in short-term studies were maintained. In addition, no new safety concerns were identified in the follow-up studies.

There are important challenges in analyzing these studies to control for obvious as well as unknown bias. In general, due to the lack of a blinded, long-term, placebo-controlled group, it is difficult to determine whether a given treatment affects the natural history of that cohort. While it would be ideal for a long-term clinical trial to be randomized, blinded, and controlled via a matched, untreated group, this setup is impractical. As such, there are a number of limitations that must be considered when interpreting data from long-term, open-label, follow-up studies. For all LTFU studies, completeness of patient ascertainment is a critical factor for success. Although the patient ascertainment in these studies was quite high, none had 100%. Enrollment of pivotal trial patients was 67.4% for the ASSURANCE trial, 68.1% for the GA LTFU, 68.2% for the PRISMS trial, and 69.9% in the IFNβ-1b LTFU. With regards to LTFU findings, it is important to note that the analyses were exploratory because some of the data were collected retrospectively and the studies were not designed to make specific comparisons a priori. Therefore, all analyses and p values should be interpreted within this context. Methods have been developed that help compensate for these limitations and reduce bias in the correlation of treatment to clinical outcomes, such as propensity scoring, matching, stratification, partitioning, adjustment, and restriction.

Despite these limitations, results to date suggest that long-term treatment has an impact on patient outcomes and that those who start treatment earlier do better than those who delay treatment. It is hoped that results from future studies will continue to define strategies that optimize the long-term treatment of patients with MS.

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