Real-Life Impact of Early Interferonβ Therapy in Relapsing Multiple Sclerosis

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Objective: Recent findings support greater efficacy of early vs. delayed interferon beta (IFNβ) treatment in patients with a first clinical event suggestive of multiple sclerosis (MS). We aimed to evaluate the effectiveness of early IFNβ treatment in definite relapsing-remitting MS (RRMS) and to assess the optimal time to initiate IFNβ treatment with regard to the greatest benefits on disability progression.

Methods: A cohort of 2,570 IFNβ-treated RRMS patients was prospectively followed for up to 7 years in 15 Italian MS Centers. A Cox proportional hazards regression model adjusted for propensity score (PS) quintiles was used to assess differences between groups of patients with early vs. delayed IFNβ treatment on risk of reaching a 1-point progression in the Expanded Disability Status Scale (EDSS) score, and the EDSS 4.0 and 6.0 milestones. A set of PS-adjusted Cox hazards regression models were calculated according to different times of treatment initiation (within 1 year up to within 5 years from disease onset). A sensitivity analysis was performed to assess the robustness of findings.

Results: The lowest hazard ratios (HRs) for the three PS quintiles–adjusted models were obtained by a cutoff of treatment initiation within 1 year from disease onset. Early treatment significantly reduced the risk of reaching a 1-point progression in EDSS score (HR = 0.63; 95% CI = 0.48–0.85; $p < 0.002$), and the EDSS 4.0 milestone (HR = 0.56; 95% CI = 0.36–0.90; $p = 0.015$). Sensitivity analysis showed the bound of significance for unmeasured confounders.

Interpretation: Greater benefits on disability progression may be obtained by an early IFNβ treatment in RRMS.

Ann Neurol 2009;66:513–520

The role of interferon beta (IFNβ) as a disease-modifying drug for the treatment of relapsing-remitting multiple sclerosis (RRMS) is now well established, and its efficacy has been demonstrated in randomized controlled trials (RCTs).[1–3] The long-term effectiveness of IFNβ on delaying irreversible clinical

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Potential conflicts of interest: M.T. received honoraria for consultancy or speaking from Sanofi-Aventis, Biogen, and Bayer Schering, and research grants from Merck Serono; F.P.[2] received honoraria for speaking from Biogen; I.L.S. received honoraria for speaking from Sanofi-Aventis and Biogen, and research grants from Sanofi-Aventis; F.P.[3] received honoraria for speaking from Sanofi-Aventis and Merck Serono; A.G. received honoraria for speaking from Bayer Schering, Merck Serono, and research grants from Sanofi-Aventis, Biogen Dompè, and Merck Serono; C.P. received honoraria for consultancy or speaking from Sanofi-Aventis, Biogen, Bayer Schering, and Novartis, and research grants from Merck Serono and Sanofi Aventis; A.L. received honoraria for speaking from Biogen and research grants from Sanofi-Aventis, Merck Serono, Biogen, and Bayer Schering; E.M. received honoraria for speaking from Bayer Schering and research grants from Merck Serono, Sanofi-Aventis, Biogen-Dompè, and Bayer Schering; C.A. received honoraria for consultancy or speaking from Sanofi-Aventis, Biogen-Dompè, Bayer Schering, and Merck Serono; M.C. received honoraria for speaking from Bayer Schering; P.L. received research grants from Sanofi-Aventis, Merck Serono, and Biogen; G.C. received honoraria for consultancy or speaking from Teva Neuroscience Plough Corporation and Merck Serono; M.P.A. received honoraria for speaking from Merck Serono and Biogen, and research grants from Sanofi-Aventis, Merck Serono, Biogen, and Bayer Schering. The other authors declare that they have no conflicts of interest.

Received Feb 20, 2009, and in revised form May 11. Accepted for publication May 18, 2009. Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.21757

worsening, which is the hallmark of the late phase of this disease, was also recently shown in a large-scale Italian observational study.[4] However, whether or not even greater benefits could have been obtained through a treatment initiated earlier in the course of the disease remains an open question.

Histopathological[5] and magnetic resonance imaging (MRI)[6] studies suggest that axonal loss occurs during the early inflammatory stages of MS and decreases over time. Natural-history studies have identified a relationship between clinical[7–9] and MRI[10,11] features during the early years and long-term disability. Multicenter RCTs[12–14] that have analyzed early IFNβ treatment in patients with a clinically isolated syndrome (CIS) suggestive of MS, report significant benefits in delaying further attacks at 2 years, and these benefits were sustained for up to 5 years.[15] More recently, the open-label follow-up phase[16] of the original BENEFIT study[14] demonstrated a higher effect of early vs. delayed IFNβ treatment on later accumulation of disability at 3 years. The conclusion from this clinical research is that the earlier treatment is initiated, the better the short-term outcome.

However, at present, a very important unresolved issue for practicing neurologists is to establish if early initiation of treatment with IFNβ is more efficacious than delayed treatment for preventing the development of long-term confirmed disability, which is ultimately the most important goal of treatment in MS. Another crucial question is how early should treatment be initiated in order to obtain the greatest benefit on long-term outcomes?

This work presents results from a prospective observational study that was conducted to evaluate the impact of early vs. delayed IFNβ treatment on long-term disability progression in a large cohort of 2,570 RRMS patients prospectively followed for up to 7 years in 15 Italian MS Centers. The main objective was to assess the optimal time to initiate IFNβ with regard to when the greatest beneficial effect on clinical outcomes was observed.

Patients and Methods

A cohort of 2,570 IFNβ-treated RRMS was prospectively followed for up to 7 years in 15 Italian MS Centers. The median follow-up time was 4.5 years. Clinical and therapeutic information was recorded according to a computerized and standardized protocol (iMED). A diagnosis of MS was established according to the Poser[18] and McDonald[19] online.

The dates of MS onset, first IFNβ administration, and assignment to irreversible 1-point progression in Expanded Disability Status Scale (EDSS)[20] score and EDSS 4.0 and 6.0 milestones were systematically assessed for each patient. The EDSS score was recorded at baseline and at least every 6 months thereafter. An EDSS score was defined as irreversible when it persisted for at least 6 months and all the subsequent scores assessed during the follow-up of the patient were either equal to or higher than that score. During the study period, four preparations of IFNβ were available: IFNβ-1b (Betaferon® 250μg subcutaneously [SC] every other day) and IFNβ-1a (Avonex® 30μg intramuscularly [IM] once weekly; Rebif® 22μg SC three times weekly; Rebif 44μg SC three times weekly). Periods of treatment with IFNβ were recorded for each patient, including the start and stop dates. The time spent receiving IFNβ therapy was calculated for each patient excluding transient discontinuations. The duration of time spent receiving transient combination therapy (eg, IFNβ and mitoxantrone or corticosteroids) was considered to be the same as administration of IFNβ alone. In this study, we assumed that different IFNβ products or transient combinations had equivalent impacts on EDSS progression.

Statistical Analysis

Baseline characteristics for the IFNβ early treatment and delayed treatment groups were reported as frequency (percentage), mean ± standard deviation (SD), and median (range), and compared with Pearson's χ^2 test and Mann-Whitney U test for categorical and continuous variables, respectively. Time (in years) from IFNβ treatment initiation and from date of birth to reaching an EDSS score of 4.0 or 6.0, and a 1-point progression in EDSS score were evaluated. For patients who did not reach the specified endpoint, time was censored at the last follow-up visit. Cox proportional hazards regression models adjusted for propensity score (PS) quintiles,[21] and for PS quintiles and disease duration were used to assess differences between early vs. delayed treatment groups. A set of PS-adjusted Cox models were calculated according to different early and delayed treatment cutoff points in terms of different duration from disease onset at treatment initiation (within 1 year up to within 5 years). Results are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs).

PS analysis was used to reduce bias in early and delayed treatment comparisons. Because there were three endpoints at issue, three separate PS logistic regression models were first built to predict the probability to be assigned to IFNβ early treatment. The models included the following covariates at treatment initiation: age, sex, number of relapses in the last year, EDSS score in quintiles, quadratic and cubic covariate terms, and a set of two-term and three-term interactions between the same predictors. Disease duration did not take part into the PS model building process since the definition of early treatment is based on disease duration itself, and adjustment for age at IFNβ should already account for any potential effect of this variable .

PS logistic models were selected in a step-wise fashion, and model-building stopped when adequate balance of covariates was achieved.[22] Residual imbalances of covariates in PS quintiles were assessed at each step with a two-way analysis of variance (ANOVA) where each confounder was considered as an outcome and PS quintiles and treatment as factors. Overlapping of PS between treatment and control groups was also checked, and nonoverlapping subjects were excluded from the analyses. Finally, PS quintiles derived from the definitive logistic models were introduced in the Cox models to allow unbiased treatment comparisons. In addition to further eliminate any concerns related to the po-

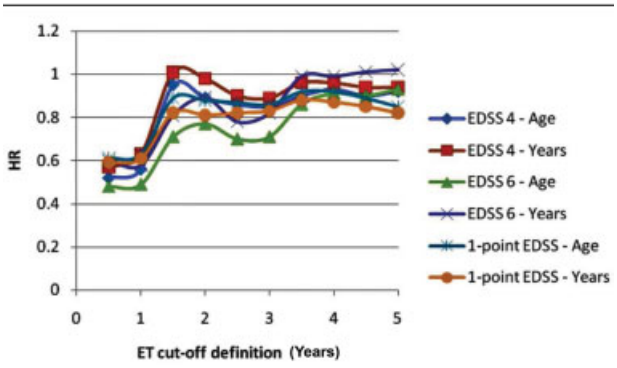

Fig 1. Graphical trends of the propensity score quintiles–adjusted hazard ratios (HRs) according to different early treatment (ET) cutoff points (within 1 year up to within 5 years from disease onset) and to both survival times (years from IFNβ assignment to endpoint and age at endpoint) for the risk of EDSS 4.0, EDSS 6.0, and 1-point progression in EDSS score. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]

tential role of differential disease duration in early and late treatment groups, PS-adjusted Cox models were also adjusted for disease duration as a linear covariate. The adjustment for duration as a linear covariate was chosen after exploring, on the same endpoints, different forms of adjustment in terms of goodness-of-fit (namely, Akaike's information criterion) in a cohort of untreated patients previously analyzed.[4]

The proportional hazards assumption was checked by graphical inspection of log (−log [survival]) plot and assessing the consistency of the HRs in the PS-adjusted Cox models censored to shorter follow-up time frames (from 6 years back to only 3 years of follow-up). This analysis also allowed for the exclusion of the differences in the dropout mechanism between early treatment and delayed treatment patients. Further, since PS methodology only addresses imbalances due to measured confounders, we also performed a sensitivity analysis[23] on positive findings to account for potential residual confounding due to an unmeasured confounder.

p-Values <0.05 were considered significant. All the analyses were performed using the Statistical Analysis System (SAS) Package, Release 9.1 (SAS Institute, Cary, NC).

Results

A plot of the PS quintiles adjusted HRs according to different early treatment cutoff points (within 1 year from disease onset to within 5 years from disease onset) for the risk of reaching EDSS 4.0 and 6.0 milestones and a 1-point progression in EDSS score with both survival times is shown in Fig 1. The lowest HRs for the three PS quintiles–adjusted models were observed with a cutoff of ≤1 year. HRs for times from IFNβ treatment initiation and from date of birth to reaching an EDSS score of 4.0 were 0.63 and 0.56; to reaching an EDSS score of 6.0 were 0.58 and 0.49; and to reaching a 1-point EDSS score progression were 0.61 and 0.63, respectively. Based on these results, for subsequent analyses, early treatment was defined as ≤1 year from disease onset and delayed treatment was defined as >1 year from disease onset.

Fifteen percent (n = 47) and 85% (n = 263) of patients in the early treatment group (n = 310), and 12% (n = 271) and 88% (n = 1,989) of those in the delayed treatment group (n = 2,260) had a diagnosis of definite MS according to the McDonald et al.[19] and Poser et al.[18] criteria, respectively. Forty percent (n = 124), 37% (n = 114), 16% (n = 50), and 7% (n = 22) of 310 patients in the early-treatment group and 36% (n = 814), 38% (n = 859), 18% (n = 407), and 8% (n =181) of 2,260 patients in the delayed-treatment group received, at their first prescription, Avonex, Rebif 22μg, Rebif 44μg, and Betaferon, respectively. Only 2.5% (n = 8) of the 310 patients in the early-treatment group and 3.4% (n = 77) of the 2,260 patients in the delayed-treatment group were, also, treated with mitoxantrone (median length of exposure = 0.6 years; range = 0.15–1.0).

Table 1 presents the baseline characteristics according to treatment group (early-treatment vs. delayed-treatment) for the overall sample. Patients in the early-treatment group were significantly ($p < 0.0001$) younger (28.8 ± 8.3; mean ± SD), had a higher number of relapses in the last year (1.8 ± 0.9) and a lower EDSS score (1.8 ± 0.9) than those in the delayed group (27.0 ± 8.6, 1.2 ± 0.9, and 2.3 ± 1.0, respectively). The percentage of females was greater ($p < 0.0026$) in the early (76.5%) than in the delayed (68.0%) group. These significant differences justified the use of PS-adjusted comparisons for all the analyses. Due to nonoverlapping propensity score, from 1% to 3% of patients were excluded from the analyses. The final sample sizes were 2,277 patients for the EDSS 4.0, 2,570 for the EDSS 6.0, and 2,396 patients for the 1-point EDSS progression outcome.

PS quintiles–adjusted Cox models results are shown in detail for the ≤1 year early treatment cutoff (Table 2). Early treatment significantly reduced, by approximately 40%, the risk of reaching the EDSS 4.0 ($p = 0.015$, $p = 0.053$) and 1-point EDSS progression ($p < 0.002$) compared with delayed treatment; there was a trend ($p = 0.09$) to reduce the risk of reaching EDSS 6.0 with early treatment vs. delayed treatment.

Further adjustment for disease duration of PS quintiles–adjusted Cox models did not materially change our findings. HRs for times from IFNβ treatment initiation and from date of birth to reaching an EDSS score of 4.0 were 0.49 and 0.70 (95% CI = 0.30–0.78 and 0.43–1.12; $p = 0.0028$ and 0.13, respectively); to reaching an EDSS score of 6.0 were 0.43 and 0.63 (95% CI = 0.19–1.01 and 0.27–1.47; $p = 0.052$ and 0.28, respectively); and to reaching a 1-point progression in EDSS score were 0.52 and 0.66 (95%

Table 1. **Baseline Characteristics of MS Groups According to Early and Delayed IFNβ Treatment Initiation***

Variable	Early (n = 310)	Delayed (n = 2,260)	All (n = 2,570)	*p*-Value
Age at treatment initiation (years)				
Mean ± SD	28.8 ± 8.3	34.2 ± 9.1	33.5 ± 9.2	
Median (range)	27.4 (6.3–59.2)	33.4 (4.4–61.4)	32.8 (4.4–61.4)	<0.0001
Age at onset (years)				
Mean ± SD	28.2 ± 8.3	27.0 ± 8.6	27.1 ± 8.6	
Median (range)	26.8 (5.9–58.9)	25.7 (1.4–57.7)	26.0 (1.4—58.9)	0.0094
Disease duration (years)				
Mean ± SD	0.6 ± 0.3	7.1 ± 5.8	6.3 ± 5.8	
Median (range)	0.6 (0.1–1.0)	5.4 (1.0–42.2)	4.6 (0.0-42.2)	0.0001
EDSS score				
Mean ± SD	1.8 ± 0.9	2.3 ± 1.0	2.16 ± 1.0	
Median (range)	1.5 (1.0–5.5)	2.0 (1.0–5.5)	2.0 (1.0–5.5)	<0.0001
Number of bouts in the last year				
Mean ± SD	1.8 ± 0.9	1.2 ± 0.9	1.3 ± 0.9	
Median (range)	2.0 (0.0–6.0)	1.0 (0.0–6.0)	1.0 (0.0–6.0)	<0.0001
Sex, female, n (%)	237 (76.5)	1537 (68.0)	1774 (69.0)	0.0026

*Data are reported as number (percentage), mean ± SD, and median (range); *p*-values refer to Pearson's χ^2 test and Mann-Whitney U test for categorical and continuous variables, respectively.
MS = multiple sclerosis; early = ≤1 year from disease onset; delayed = >1 year from disease onset; SD = standard deviation; EDSS = Expanded Disability Status Scale.

CI = 0.39–0.70 and 0.49–0.89; $p = 0.0001$ and 0.0068, respectively).

PS-adjusted estimated survival curves, which graphically translated risk reductions expressed by HRs, showed that early treatment slowed the time to reach an EDSS of 4.0 and a 1-point progression in EDSS progression (Fig 2). The estimated percentage of patients that would reach EDSS 4.0 after a median follow-up of 4.5 years was 33.5% for the delayed treatment group vs. 23.2% for early treatment. The 23.2% threshold was reached with a delay of 19.5 months (84 months for the early-treatment group and 64.5 months for the delayed-treatment group). About 60% of delayed treatment patients compared with 42.6% of the early treated group would reach a 1-point EDSS progression after 4.5 years. The 42.6% threshold was reached with a delay of 14 months (84 months for the early-treatment group and 70 months for the delayed-treatment group).

A sensitivity analysis (Table 3) was performed for the two significant endpoints to assess the robustness of our findings. For the risk of reaching an EDSS milestone of 4.0, the significant effect of early treatment might be altered by an unmeasured confounder with

Table 2. **PS Quintiles Adjusted Cox Models for Time from IFNβ Assignment and from Date of Birth (Age at Endpoint) To Reach the Three Endpoints by Early Treatment Within 1 Year of Disease Onset**

Endpoint	Survival Time (years)	PS Quintiles		
		HR[a]	95% HR CI	*p*
EDSS 4	Age at endpoint	0.56	0.36–0.90	0.0150
	Years from IFNβ to endpoint	0.63	0.40–1.01	0.0529
EDSS 6	Age at endpoint	0.49	0.22–1.13	0.0936
	Years from IFNβ to endpoint	0.58	0.25–1.33	0.1979
EDSS 1-point progression	Age at endpoint	0.63	0.48–0.85	0.0019
	Years from IFNβ to endpoint	0.61	0.46–0.82	0.0009

[a]HR < 1 favors early treatment.
PS = propensity score; HR = hazard ratio; IFN = interferon; EDSS = Expanded Disability Status Scale; CI = confidence interval.

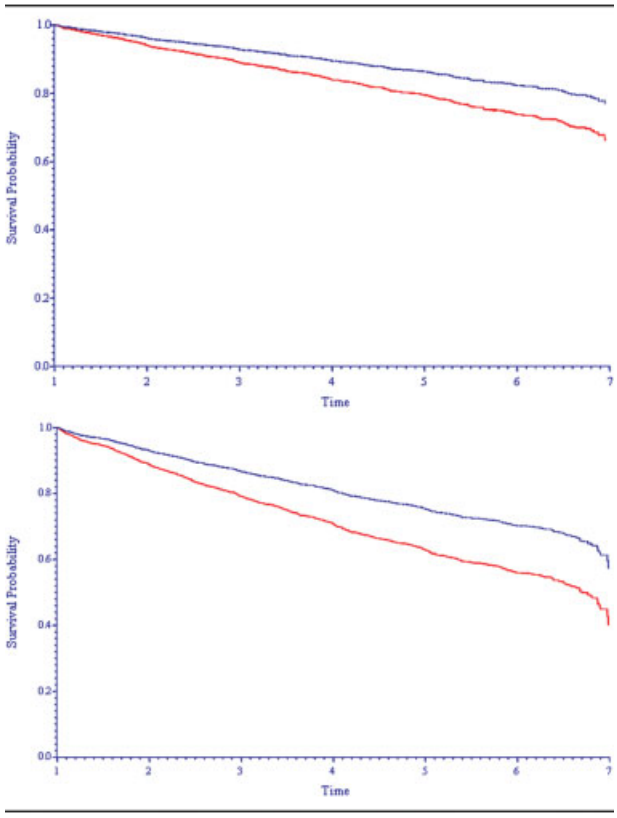

Fig 2. Propensity score–adjusted survival curves for time from treatment initiation to reach (A) confirmed EDSS 4.0 score, and (B) a 1-point progression in EDSS score. Survival probability represents the estimated proportion of patients who did not reach the endpoint. Continuous line = delayed treatment group; dotted line = early treatment group. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

an HR = 1.5 and a prevalence imbalance between the early-treatment group and the delayed-treatment group ($P_0 - P_1$) of at least 30% or with a prevalence imbalance of 20% but an HR = 2.0 or with a prevalence imbalance of at least 10% but an HR = 2.5. For the risk of a 1-point progression in EDSS score, an unmeasured confounder with an HR = 1.5 and a 50% prevalence imbalance or with a prevalence imbalance of at least 30% but an HR = 2.0 or with a prevalence imbalance of at least 20% but an HR = 2.5 would be sufficient to alter the significant effect of early treatment.

Discussion and Conclusions

In this exploratory analysis we assessed whether longer-term disability of RRMS patients would benefit from earlier initiation of treatment with IFNβ. The availability of a large sample of patients, followed for up to 7 years by 15 experienced Italian MS centers, allowed us to prospectively evaluate the impact of early vs. delayed IFNβ treatment on the natural course of MS.

The results show that patients treated early respond better than those who initiated the treatment later. Early IFNβ treatment was associated with a significant reduction in the risk of reaching an EDSS milestone of 4.0 and the risk of a 1-point progression in EDSS score, and with a trend suggestive of reduction in risk of reaching an EDSS milestone of 6.0 (likely not statistically significant due to a low number of events during the follow-up) when compared with delayed treatment. More interestingly, we found that the greatest difference in treatment benefit was observed between patients who received IFNβ within the first year from disease onset in comparison with those who received the treatment after this time.

Our data followed by a median of 4.5 years are consistent with the 3-year results of the open-label follow-up phase[16] of the original BENEFIT study,[14] which showed a slower disease progression in patients treated continuously with IFNβ-1b vs. those treated with placebo for the first 1 or 2 years, and with the 4-year results of the PRISMS study[24] showing time to EDSS progression was longer in those patients who had been initially randomized to IFNβ-1a than in those in the crossover group who had received placebo during years 1–2. It is noteworthy that in the former study[16] the early treatment at 3 years reduced the risk for the progression of 1 point in the EDSS score, confirmed at 6 months, compared with delayed treatment, by the same rate (40%) of reduction that we found at 4.5 years. Moreover, in the latter study[24] the delay (11–18 months) to first confirmed EDSS progression observed in the earlier IFNβ-1a-22μg/44μg-treated groups in comparison with in the placebo/22–44μg-treated crossover groups was similar to that we found (14 months) between early- and delayed-treatment patients. In addition, in our study, the extremely larger sample size (n = 2,570 RRMS patients) and the longer follow-up in comparison with those in the BENEFIT[16] and PRISM-4[24] trials, and the adjustment for selection bias, by using propensity score, add considerable value to this particular analysis. Although RCT is undoubtedly the ideal way for providing evidence on drug efficacy, results derived from open-label extensions of RCTs are not necessarily better than those obtained by long-term observational studies with rigorous study design or statistical analysis.[25] Indeed, the methodological rigor (randomization) of the initial RCTs is often eroded during the extension phase[26] because the number of patients often decreases dramatically and the data might be collected unblinded. Moreover, observational clinical data have the advantage to be more representative of the MS population than RCT study samples. Finally, the most important finding is that we were able to perform a cutoff analysis to assess the optimal time to initiate IFNβ treatment with regard to the greatest benefits on long-term disability progres-

Table 3. **Representative Results of Sensitivity Analysis on Significant Findings of Table 2: How the Magnitude of an Unmeasured Binary Confounder Might Affect the Propensity Score–Adjusted Hazard Ratios***

Endpoint	HR[a]	$P_1 - P_0$[b]	HR	95% CI
EDSS 4.0	1.5	0.3	0.64	0.41–1.03
	2	0.2	0.66	0.43–1.06
	2.5	0.1	0.63	0.41–1.02
EDSS 1-point progression	1.5	0.5	0.76	0.57–1.02
	2	0.3	0.78	0.59–1.04
	2.5	0.2	0.77	0.58–1.03

*This analysis assumes that (1) the unmeasured confounder is binary, (2) the unmeasured confounder is independent of measured confounders, and (3) no interaction occurs between the unmeasured confounder and exposure.
[a]Hypothetical HR of the unmeasured confounder on time to endpoints.
[b]Differences in prevalence of the unmeasured confounder between early vs. delayed treatment groups.
HR = hazard ratio; EDSS = Expanded Disability Status Scale; CI = confidence interval.

sion. This kind of analysis is easily obtained with an observational design, but would be infeasible and unethical within a clinical trial setting. That is, no patients could be forced to any treatment arm with a prespecified delay time.

The delay in accumulation of disability with early treatment, seen in this study, is in line with neuropathological, clinical, and MRI findings[5–11,27,28] showing that processes which lead to irreversible disability actually begin very early in the course of the disease. Such damage, primary or secondary to inflammation, may be irreversible, and there is strong evidence to suggest that efficacy lost as a consequence of delay in the onset of treatment cannot be regained.[29] Moreover, the extent of the benefits that can be obtained from a treatment with IFNβ decreases in patients with secondary progressive MS.[30,31] Furthermore, natural history studies demonstrated that the early course of disease can influence long-term outcome. The frequency of relapse and the interval between relapses during the first 2 years,[7] incomplete recovery from relapses during the first 5 years,[9] and the degree of disability after 5 years have been associated with the development of disability up to 25 years later.[8] Moreover, the number and volume changes in MRI lesions seen in the first 2 to 5 years of disease course correlate with the degree of disability in the longer-term.[10,11] It therefore seems logical that effective treatment should be initiated early in the disease course to early inhibit the cascade of events that leads to irreversible axonal damage and disability. Our results strongly support this hypothesis.

In this study, we estimated the effect of IFNβ also by age at endpoints because recent reports suggested that the accumulation of irreversible disability in MS appear to be, at least in part, an age-dependent process[32] and survival techniques accounting for the assessment of ages at reaching irreversible disability end points may provide more accurate target outcomes for therapeutic trials.[33]

However, the limitations of this observational study merit discussion. As with all observational studies, the major issue of was the lack of randomization and therefore potential selection bias.[34–36] The treatment groups were imbalanced for all of the baseline covariates. Particularly, the early-treatment group included MS patients with a more active course and a faster disability progression (median number of relapses = 2 and median EDSS score = 1.5 in a median disease duration of less than 1 year) than the delayed group (median number of relapses in the last year = 1 and median EDSS score = 2 in a median disease duration of 5.4 years). This meant that it was necessary to use statistical methods to adjust the comparisons. Therefore, we used the most common approach to overcome this issue in treatment comparisons in observational studies; ie, a PS-adjusted analysis.[21,22] This technique has already been used to test drug effects in other therapeutic areas[37,38] and also in MS.[4] PS analysis, taking into consideration parameters of interest (age, sex, EDSS score, and number of relapses in the last year prior to the start of treatment) that would likely affect the outcome, allowed us to obtain two balanced groups of patients who have similar likelihoods of receiving an early therapy, and resembling randomized cohorts of patients. Moreover, although we checked externally on the untreated cohort of a previously analyzed dataset[4] that age at IFNβ already takes into account any potential effect of disease duration (ie, for duration defined as $\leq$1 year vs. $>$1 year, the HRs for time to reaching EDSS 4 were 0.76 [unadjusted], 1.23 [age-adjusted], and 1.82 [duration-adjusted]) a clearer assessment of early treatment unconfounded by disease duration was also reported, showing that the consistency of results was retained.

An important limitation of the PS approach is that it cannot adjust for variables that are not measured in a study (such as MRI variables in this study); therefore, we conducted a sensitivity analysis[23] to evaluate their

possible impact on the study outcome. The results of this analysis showed that the positive effect of early IFNβ treatment for the endpoints 1-point EDSS progression and risk of reaching an EDSS of 4.0 appeared sensitive to small bias, but their HRs were still suggestive of a slower disease progression in comparison with a delayed treatment. In our study, hidden bias might reflect the inability to account for factors related to physicians. Absence of blinding, for instance, might affect EDSS assessment at each visit. However, even though findings that could be sensitive to small unmeasured confounders should be interpreted with caution in a disproof approach, sensitivity to small biases is not a sufficient reason to dismiss such findings.

Moreover, once overt and hidden bias are taken into account, any attempt to assess treatment effectiveness in "real-world" settings within the framework of properly conducted observational studies should not be dismissed a priori. An enhanced quality of observational studies may provide the opportunity for a less expensive evaluation of therapies in clinical medicine.

The key findings from this study, already demonstrated in clinical trials with shorter follow-up,[16,24] are that patients who begin treatment later do not reap the same long-term benefits as those who begin treatment earlier during the disease course and that the first year from disease onset seems to represent the time frame when we could expect that initiation of an effective treatment would allow subsequent accumulation of disability to be minimized.

Since patients had some clinical heterogeneity, it could be useful for clinical practice to further analyze the long-term benefit of early-stage IFNβ treatment in different patient subgroups.

Italian Multiple Sclerosis Database Network (MSDN) Group

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This work was supported by annual research grants from the Italian University and Research Ministry (MIUR) (COFIN 2005–2006 M.T. Proselto Stzetegieo Regiolle Puque "Nurobío tech" PS 124, M.T., V.L.).

We thank all patients who participated in this study and the Fondazione Internazionale Cesare Serono for providing the iMED software to the Italian MS centers.

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