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Effects of immunomodulatory treatment with subcutaneous interferon beta-1a oncognitive decline in mildly disabled patients with relapsing–remitting multiple sclerosis

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Abstract

The objective of this study was to assess the effects of subcutaneous (sc) interferon beta-1a (IFNβ-1a) on cognition in mildly disabled patients with relapsing–remitting multiple sclerosis (RRMS). Patients aged 18–50 years with RRMS (McDonald criteria; Expanded Disability Status Scale score ≤4.0) were assigned IFNβ therapy at the physician's discretion and underwent standardized magnetic resonance imaging, neurological examination and neuropsychological testing at the baseline and regular intervals for up to three years.

This analysis included 459 patients who received sc IFNβ-1a (44 mcg: $n = 236$; 22 mcg: $n = 223$; three-year follow up was available for 318 patients). The hazard ratio for cognitive impairment over three years (44 mcg versus 22 mcg) was 0.68 (95% confidence interval [CI]: 0.480–0.972), suggesting a 32% lower risk with the higher dose treatment. At year 3, the proportion of patients who were cognitively impaired increased slightly from 23.5% at the baseline to 24.8% in the IFNβ-1a 22 mcg treatment group, but remained stable at 15.2% in the IFNβ-1a 44 mcg treatment group. The proportion of patients with cognitive impairment at year 3 was significantly higher in the 22 mcg group than in the 44 mcg group ($P = 0.03$), although a trend was also seen at the baseline ($P = 0.058$). Multivariate logistic regression (corrected for baseline cognitive deficits) indicated that treatment with the higher dose of IFNβ-1a was predictive of lower cognitive impairment at three years (odds ratio: 0.51, 95% CI: 0.26–0.99) compared with the lower dose of IFNβ-1a.

These findings suggest that sc IFNβ-1a may have dose-dependent cognitive benefits in mildly disabled patients with RRMS, and may support early initiation of high-dose IFNβ-1a treatment.

Keywords

cognitive function, cognitive impairment, disability, disease progression, interferon beta-1a, multiple sclerosis

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Introduction

Cognitive impairment is a common symptom of multiple sclerosis (MS), occurring in approximately 40–65% of patients with MS.[1] Cognitive deficits may develop in all MS subtypes and at any disease stage,[2,3] including in patients without physical disability[4] or with clinically isolated syndrome.[5,6] Memory, learning, attention and information-processing activities are most commonly affected by MS, which may reflect damage to specific brain areas. Impaired cognitive function can cause considerable disability in MS, independent of physical symptoms, and contributes to a poor quality of life

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(QoL).[7] In addition, fatigue and depression are common comorbidities of cognitive impairment and can further increase disability levels.[8]

Although little is known about the natural history of cognitive impairment in MS, available data suggest that remission of cognitive symptoms is unlikely and that cognitive performance decreases with worsening disability.[9,10] Cognitive impairment may also predict physical disability or indicate progressive disease in the absence of worsening physical symptoms.[11]

Despite the high prevalence of cognitive impairment in MS, it is rarely assessed during routine patient management. Furthermore, treatment for cognitive impairment centres on symptomatic therapies, with few pharmacological options. The observation that some magnetic resonance imaging (MRI) disease measures, including lesion load and brain volume,[1] correlate with cognitive impairment, suggests that disease-modifying drugs (DMDs) that reduce lesion development may also prevent or delay cognitive decline. However, the potential cognitive benefits of DMDs in patients with MS are unconfirmed.[12,13]

The COGIMUS (COGnitive Impairment in MUltiple Sclerosis) study was performed to evaluate the progression of cognitive decline in patients with early relapsing–remitting MS (RRMS) receiving treatment with interferon beta-1a (IFNβ-1a), 22 or 44 mcg (Rebif®, Merck Serono S.A. – Geneva, Switzerland), administered subcutaneously (sc) three times weekly (tiw). Here, we report three-year cognition and clinical results from the study; two-year outcomes have been reported elsewhere.[14]

Methods

The COGIMUS study is a prospective, multicentre, observational, three-year cohort trial assessing cognitive function in Italian patients with RRMS treated with IFNβ. Study enrolment started in September 2003 at the University of Catania, and in January 2004 at the other participating centres, and was completed in March 2005.

Patients

Eligibility criteria have been described in detail elsewhere.[15] Briefly, patients aged 18–50 years with a diagnosis of RRMS, according to the McDonald criteria[16] and an Expanded Disability Status Scale (EDSS)[17] score of ≤4.0, who were naïve to DMD treatment and had not been taking corticosteroids in the prior 60 days, immunosuppressants in the prior six months, or other immunomodulators in the previous year, were eligible for the study. All patients at the 40 study centres who fulfilled the inclusion and exclusion criteria were invited to participate in the study. In accordance with Italian law, patients were not paid for participating in this study. Patients were not seeking neuropsychological (NPS) consultation for suspected cognitive problems, but were motivated to participate by the potential benefits of undergoing evaluations that would not be performed as part of routine clinical practice. All patients gave written informed consent prior to undergoing any tests not performed as part of their routine management.

Treatment

Patients were assigned IFNβ treatment (sc IFNβ-1a, 22 or 44 mcg tiw [Rebif®]; intramuscular [im] IFNβ-1a, 30 mcg once weekly [qw: Avonex®, Biogen Idec Inc, Cambridge, MA, USA]; or sc interferon beta-1a [IFNβ-1b], 250 mcg every other day [Betaferon®, Bayer Schering Pharma AG, Berlin, Germany]) at the discretion of the treating physician. A total of 550 patients were enrolled into the study. Of these patients, 459 (83.5%) received treatment with sc IFNβ-1a: 223 (40.5%) received 22 mcg tiw and 236 (42.9%) received 44 mcg tiw; 64 patients (11.6%) were treated with im IFNβ-1a and 27 patients (4.9%) with sc IFNβ-1b. At three years, only 13 patients receiving im IFNβ-1a and 19 patients receiving sc IFNβ-1b were available for follow up. As only a small proportion of patients in this observational study were assigned treatment with sc IFNβ-1b or im IFNβ-1a, and several dropped out over the three years, it was more appropriate to compare outcomes between the groups of patients receiving the two doses of sc IFNβ-1a than in all four study groups. The two groups of patients receiving sc IFNβ-1a were of a similar sample size and represented the majority of the study population (83.5%); therefore, the analyses focused on outcomes in these 459 patients.

Relapses were treated with corticosteroids and flu-like symptoms (FLS) were treated with non-steroidal anti-inflammatory drugs or paracetamol. Concomitant therapies were recorded on the case-report form. DMDs other than the study drug were not permitted.

Evaluation of disease status

Patients underwent a baseline neurological examination to determine physical disability (EDSS score), and clinical history was recorded. In two-thirds of the participating centres, conventional, standardized brain MRI (1.5 Tesla scanner) was performed at the baseline to determine T1 gadolinium-enhancing, T1 hypointense and T2 hyperintense lesion volumes, grey and white matter volumes and total brain volume. Baseline MRI

findings and correlations with cognitive impairment have been described elsewhere.[15] Clinical assessments (EDSS score and relapses) were repeated and safety data were collected every six months.

Neuropsychological evaluation

All patients underwent NPS evaluation at the baseline and every 12 months for three years. If patients were experiencing disease relapse at the time of scheduled NPS assessments, cognitive testing was delayed until 30 days after the last steroid injection. These assessments included Rao's Brief Repeatable Battery[10] and the Stroop Colour-Word Task (ST)[18] for cognitive domains (alternate, parallel versions of Rao's battery were used to minimize learning effects; alternate versions were administered in the order A, B, A, B to all patients), the Hamilton Depression Rating Scale,[19] the MSQoL-54 questionnaire[20] for QoL, the Fatigue Impact Scale[21] and the Environmental Status Scale[22] for social functioning. Patient intelligence quotient (IQ) was determined at the baseline by administering the Brief Intelligence Test,[23,24] as described previously.[15] Cognitive impairment was defined as 1 SD below the mean Italian normative values for each cognitive test, as described previously in a study of 200 healthy volunteers. This normative population had a mean (SD) age of 41.5 (9.8) years, a male:female ratio of 1:2, and had spent a mean (SD) of 12.3 (3.6) years in education.[25]

A cognitive impairment index was constructed at the baseline and year 3 for each patient using the mean and SD from the normative sample of Rao's battery[25] in order to confirm that cognitive impairment was correctly detected. A grading system was applied to each patient's score on each cognitive test, dependent on the number of SDs below the normative mean as described previously.[15,26]

Study endpoints

The primary endpoint was the proportion of patients with cognitive impairment over three years in patients treated with different doses of sc IFNβ-1a. In the absence of widely accepted guidelines for the assessment of cognitive function, cognitive impairment was defined as impaired performance on at least three cognitive tests. This definition for cognitive impairment has previously been shown to be sensitive to changes in cognitive function over time in a study of Italian patients with early MS, in which cognitive decline was compared in patients and healthy volunteers over 10 years of follow up.[7] In this study population, we found that the proportion of patients identified as having cognitive impairment at the baseline was similar when using either this definition or a definition based on fifth and 95th percentiles for the Rao's battery and the ST, respectively.[15]

Additional endpoints were the change in cognitive impairment index score over three years and the assessment of factors predictive of cognitive impairment at three years. Other endpoints will be reported elsewhere. Discontinuations were recorded, and patients who discontinued treatment were followed up regularly in the clinical trial setting.

Statistical analyses

Descriptive analyses were performed at the baseline for the cohort of 459 patients treated with sc IFNβ-1a. For outcome measures at three years, only patients with three years of follow up were included in the analyses. No imputation of missing data was considered. The Cox proportional-hazards model was used to compare cognitive impairment over three years. A multivariate regression model was developed by sequentially adding variables that had a significant hazard ratio in the univariate analysis. To account for the fact that all patients were entered into the analysis, the hazard ratio was evaluated using 'more than one time option shared' (STATA software). Kaplan–Meier survival curves were constructed to evaluate longitudinal differences between treatments.

The following tests were also conducted, with a significance level of 0.05. Chi-squared tests were performed to compare proportions. The Mann–Whitney test was used for the comparison of two independent samples. The Kazis' effect was calculated to assess the variability of the cognitive tests over time, using the calculation: (mean score at year 3 – mean score at baseline)/SD at the baseline. A positive result indicated an improvement and a negative result indicated a worsening in cognitive function over three years of treatment. The effect sizes are defined as: small, 0.20–0.49; moderate, 0.50–0.79; and large, 0.80–1.00.[27] The Wilcoxon test for paired samples was performed to evaluate changes over time in the cognitive impairment index.

Risk factors for cognitive impairment at three years were identified using univariate and multivariate logistic regression. Univariate logistic regression was performed for the following variables: the baseline characteristics shown in Table 1; the presence or absence of cognitive impairment at the baseline; and treatment group (IFNβ-1a 22 or 44 mcg sc tiw). A multivariate regression model was then developed by sequentially adding variables with a significant odds ratio in the univariate analysis. Variables that remained significant were included in the final model.

Table 1. Baseline demographic characteristics in patients receiving sc IFNβ-1a, by treatment group

	Treatment group (IFNβ-1a dose sc tiw)	*n*	Mean	SD	*P* value[a]
Age, years	22 mcg	223	33.8	8.4	0.259
	44 mcg	236	32.8	7.9	
Years in formal education	22 mcg	223	12.2	3.5	0.406
	44 mcg	236	12.5	3.4	
Duration of disease, years	22 mcg	223	4.0	4.7	0.374
	44 mcg	236	3.6	4.3	
Total IQ score[b]	22 mcg	213	108.8	8.8	0.422
	44 mcg	232	109.4	8.6	
Verbal IQ score	22 mcg	213	106.3	11.1	0.308
	44 mcg	232	106.8	9.1	
Performance IQ score	22 mcg	213	105.4	9.3	0.746
	44 mcg	232	106.0	8.9	
Physical Health Composite Score	22 mcg	223	69.6	16.8	0.313
	44 mcg	235	68.5	16.3	
Mental Health Composite Score	22 mcg	223	67.4	19.8	0.255
	44 mcg	235	65.9	19.1	
Fatigue Impact Scale, total score	22 mcg	223	25.1	25.5	0.224
	44 mcg	235	27.2	25.4	
Hamilton Depression Rating Scale, total score	22 mcg	223	6.7	5.2	0.496
	44 mcg	235	6.9	4.7	
Environmental Status Scale, total score	22 mcg	223	1.6	2.8	0.083
	44 mcg	235	1.6	2.3	
EDSS score	22 mcg	223	1.8	0.9	0.791
	44 mcg	236	1.8	1.0	
T2 hyperintense lesion volume, mm^3	22 mcg	118	5615.4	6484.4	0.724
	44 mcg	129	5909.4	6338.7	
T1 hypointense lesion volume (black holes), mm^3	22 mcg	116	1070.9	1794.1	0.651
	44 mcg	128	1001.2	1557.4	
Gd-enhancing T1 lesion volume, mm^3	22 mcg	112	35.2	115.8	0.172
	44 mcg	126	104.6	428.8	
Grey matter volume, mm^3	22 mcg	129	793,460.8	207,618.2	0.489
	44 mcg	144	801,810.1	178,519.7	
White matter volume, mm^3	22 mcg	129	770,537.2	277,669.3	0.551
	44 mcg	144	752,233.0	258,394.8	
Brain volume, mm^3	22 mcg	129	1,563,998.0	115614.9	0.533
	44 mcg	144	1,554,043.1	119,584.3	

Gd, gadolinium.
[a]Mann–Whitney test.
[b]Population 'average' IQ score: 99–109.

Results

Patients and baseline characteristics

Here we report baseline characteristics and three-year outcomes from the 459 patients treated with sc IFNβ-1a, of whom 223 (48.6%) received the 22 mcg dose and 236 (51.4%) received the 44 mcg dose. Descriptive data for the small subgroups of patients receiving im IFNβ-1a or sc IFNβ-1b are also provided.

Among the 459 patients receiving sc IFNβ-1a, the mean (SD) age was 33.3 (8.13) years, and the male:female ratio was 1:1.87. The mean (SD) duration of disease was 3.8 (4.47) years and the mean (SD) EDSS score was 1.8 (1.0). There were no significant differences

in the baseline demographics or general, clinical, NPS or MRI variables between the two treatment groups (Table 1).

Overall, 331 patients (72.1%) in the subgroup receiving sc IFNβ-1a completed the three-year study: 163 received IFNβ-1a, 22 mcg tiw, and 168 received IFNβ-1a, 44 mcg tiw. With the exception of verbal IQ, which was significantly higher in patients who stayed on treatment for the duration of the study than in those who did not ($P = 0.0465$), there were no significant differences in the baseline demographic, clinical, NPS and MRI characteristics, or in the assigned treatment between patients who were still under treatment at three years and those who dropped out of the study prematurely.

Dropout rates were similar in both treatment arms: 60 (26.9%) patients receiving IFNβ-1a 22 mcg and 68 (28.8%) patients receiving IFNβ-1a 44 mcg did not complete the study. Reasons for discontinuing were: adverse events (AEs), 13 (2.8%) patients; lost to follow up, 18 (3.9%) patients; protocol violation, 18 (3.9%) patients; lack of efficacy, 18 (3.9%) patients; pregnancy/planning to conceive, 16 (3.5%) patients; other, 45 (9.8%) patients. 'Other' reasons were predominantly subjective, such as 'patient decided not to continue'. There were no discontinuations due to injection-site reactions (ISRs).

Dropout rates for the subgroups of patients originally assigned to im IFNβ-1a or IFNβ-1b were as follows. A total of 51/64 patients (79.7%) receiving im IFNβ-1a did not complete the study. The reasons for study discontinuation were: lost to follow up ($n = 25$); pregnancy ($n = 4$); and switched to another DMD ($n = 22$). Of the 27 patients assigned sc IFNβ-1b treatment, 8 (29.6%) withdrew from the study. Of these, four were lost to follow up, one withdrew due to pregnancy and three switched to another therapy.

Cognitive impairment at baseline

At study entry, 270 of 459 patients (58.8%) receiving sc IFNβ-1a had impaired performance on at least one cognitive test, 172 (37.5%) patients had impaired performance on at least two tests, and 98 (21.4%) patients had impaired performance on at least three tests. Hence, the prevalence of cognitive impairment in this population was 21.4%. The proportion of patients with cognitive impairment at the baseline was higher in the 22 mcg dose group (24.2%) than in the 44 mcg group (18.6%; $P = 0.145$). A similar trend was seen among the 318 patients for whom three-year cognitive data were available: at the baseline, 23.5% of these patients receiving IFNβ-1a, 22 mcg sc tiw, were cognitively impaired, compared with 15.2% of patients receiving IFNβ-1a, 44 mcg sc tiw ($P = 0.058$).

In the subgroups of patients assigned to im IFNβ-1a or sc IFNβ-1b, eight patients (12.5%) and five patients (18.5%), respectively, had impaired performance on at least three tests at the baseline.

Cognitive impairment at three years

Data on cognitive function at three years were available for 318 patients (22 mcg, $n = 153$; 44 mcg, $n = 165$). A Cox proportional-hazards survival analysis was performed for the development of cognitive impairment over three years (Figure 1), and showed a 32% risk reduction for treatment with IFNβ-1a 44 mcg versus 22 mcg. Kaplan–Meier survival curves confirmed the benefits of receiving the higher dose treatment over time ($P = 0.0109$; Figure 1).

At year 3, the proportion of patients who were cognitively impaired had increased slightly from the baseline value of 23.5% to 24.8% in the IFNβ-1a 22 mcg treatment group, and had remained stable at 15.2% in the IFNβ-1a 44 mcg treatment group. Hence, the proportion of patients with cognitive impairment was significantly higher in the lower dose treatment group than in the higher dose treatment group (15.2% versus 24.8%, respectively, $P = 0.030$), although the baseline trend for a difference between these two groups must be considered.

The cognitive impairment index was significantly lower at three years than at the baseline in both treatment groups (Table 2), indicating improved cognitive function over the course of the study, but there were no significant differences between the two treatment groups. The Kazis' effect for each cognitive test was calculated for each treatment group (Table 3). Similar effect sizes were seen for both treatments for all tests, with the exception of the Symbol Digit Modalities Test (SDMT; 22 mcg: –0.05, 44 mcg: 0.20).

In the subgroups of patients assigned to im IFNβ-1a or sc IFNβ-1b, the proportions of patients who were cognitively impaired at year 3 had increased from the baseline value in each group: from 12.5 to 23% in the im IFNβ-1a group and from 18.5 to 26% in the sc IFNβ-1b group. However, no further statistical analyses were performed due to the limited numbers of patients in these subgroups.

Predictors of cognitive impairment at three years

Variables that were significant in the univariate logistic regression were treatment, verbal IQ at the baseline and impaired cognitive function at the baseline, and these were included in the multivariate model. Multivariate logistic regression showed that, after correcting for baseline cognitive impairment, treatment with higher dose IFNβ-1a and higher verbal IQ at the baseline

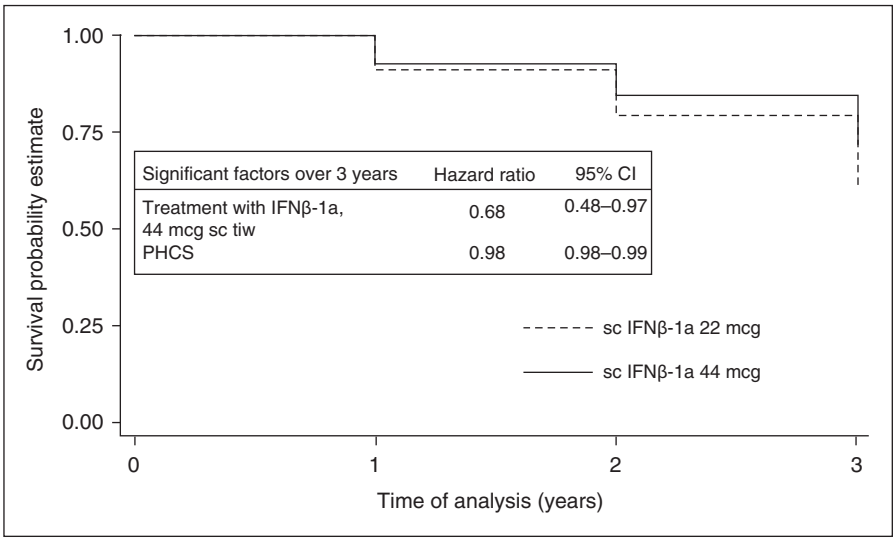

Figure 1. Kaplan–Meier survival curves for the proportion of patients with ≥3 impaired cognitive tests during the three-year study, by treatment. The Cox proportional-hazards model showed that treatment and Physical Health Composite Scores (PHCS) were significant factors over three years. The hazard ratio (95% confidence interval) for sc IFNβ-1a, 22 mcg tiw, versus 44 mcg sc tiw was 0.68 (0.480–0.972; $P = 0.0109$) and for PHCS was 0.98 (0.98–0.99; not shown).

Table 2. Improvement in cognitive impairment index over three years in patients treated with IFNβ-1a, 22 mcg or 44 mcg sc tiw

Treatment group	Timepoint	*n*	Cognitive impairment index		*P* value[a]
			Mean	SD	
IFNβ-1a, 22 mcg sc tiw	Baseline	153	9.27	5.948	<0.001
	Year 3	153	7.75	5.618	
IFNβ-1a, 44 mcg sc tiw	Baseline	165	8.22	4.858	<0.001
	Year 3	165	6.75	4.880	

[a]Wilcoxon test.

Table 3. Effect size (Kazis' effect) for individual cognitive tests in patients treated with IFNβ-1a, 22 or 44 mcg sc tiw, for three years. Positive numbers indicate improved test performance; effect sizes of 0.20 or above indicate a small effect

Cognitive test	Treatment group	
	IFNβ-1a 22 mcg sc tiw ($n = 153$)	IFNβ-1a 44 mcg sc tiw ($n = 165$)
SRT–LTS	0.36	0.39
SRT–CLTR	0.18	0.25
SPART	0.26	0.34
SDMT	–0.05	0.20
PASAT-30	0.20	0.29
PASAT-20	0.18	0.20
SRT-D	0.27	0.21
SPART-D	0.29	0.14
WLG	–0.26	–0.23

PASAT-20, 20-second Paced Auditory Serial Addition Test; PASAT-30, 30-second PASAT; SDMT, Symbol Digit Modalities Test; SPART, Spatial Recall Test; SPART-D, SPART-Delayed; SRT–CLTR, Selective Reminding Test–Consistent Long-Term Retrieval; SRT-D, SRT-Delayed; SRT–LTS, SRT–Long-Term Storage; WLG, Word-List Generation.

were associated with a lower risk of cognitive impairment at year 3 (Table 4). In addition, the model showed that impaired cognitive function at the baseline was a risk factor for cognitive impairment at year 3 (Table 4).

Clinical outcomes

At year 3, complete clinical data were available for 331 patients. Sustained EDSS progression occurred in 55 of 331 (16.6%) patients. Relapse data were available for 428 (93.2%) patients at year 1, 394 (85.8%) patients at year 2, and 376 (81.9%) patients at year 3. Over the three-year study period, the mean relapse rate was 0.23 relapses per patient, and 62% of patients remained free from relapse. No significant differences were found between the two treatment groups (data not shown).

Safety

The most common AEs reported over the three-year study were consistent with the known safety profile of

Table 4. Multivariate logistic regression analyses for the proportion of patients with ≥3 impaired cognitive tests during the three-year study. Baseline predictors for cognitive impairment at three years, corrected for baseline cognitive impairment, are shown

Logistic regression: significant predictors at baseline		
	Odds ratio	95% CI
Treatment with IFN beta-1a, 44 mcg sc tiw	0.51	0.26–0.99
Verbal IQ	0.97	0.93–0.99
≥3 impaired cognitive tests	11.23	5.66–22.28

CI, confidence interval; IFN, interferon; IQ, intelligence quotient; sc, subcutaneously; tiw, three times weekly.

IFNβ-1a,[28,29] and included ISRs, FLS, headache, depression and laboratory abnormalities.

Discussion

In this study, the proportion of patients with impaired cognitive function over the three years remained stable, suggesting that treatment with IFNβ-1a, 22 or 44 mcg sc tiw may prevent cognitive decline. Despite the fact that this study did not include an untreated control group, making it impossible to determine to what extent IFNβ-1a prevented cognitive decline, cognitive deterioration over time has been reported in patients with MS, particularly those with existing cognitive impairment.[7]

Longitudinal studies of cognitive impairment in MS are rare. In addition, differences in study design, patient populations and definitions of cognitive impairment, and the inclusion of patients receiving active treatment,[1] make it difficult to describe the natural history of MS-related cognitive decline. The findings of three studies (which included healthy volunteers as a control group) indicate that declining cognitive function can be detected over 2–5 years in both cognitively preserved and cognitively impaired patients.[30–32] In contrast, one study reported minimal cognitive decline over four years.[33]

Published data suggest that the remission of cognitive symptoms is unlikely,[1,9] but we found significant improvement in the cognitive impairment index from baseline to year 3 with sc IFNβ-1a, suggesting DMD treatment may improve cognitive function, at least in patients with mild physical disability. When effect-size data are considered for individual cognitive tests, positive effects of both sc IFNβ-1a doses were seen at year 3 for all tests, with the exception of Word-List Generation and SDMT. Although all effects were small (the greatest Kazis' effect size was 0.39), these equated to a significant improvement in the global cognitive impairment index over the course of the study. Thus, small improvements in the function of individual cognitive domains could result in a measurable improvement in overall cognitive performance for the patient.

The Cox regression model analyses temporal trends in outcome variables. Therefore, in this study it enabled us to show that the effects of high-dose treatment started earlier than those of the lower dose, and that the size of this effect increased over time. Indeed, the effects of sc IFNβ-1a on cognitive function may be more pronounced with the high-dose treatment: the risk of cognitive impairment over three years was reduced by 32% with the 44 mcg dose compared with the 22 mcg dose. This finding was confirmed by the results of the multivariate logistic regression analysis and the significantly lower proportion of cognitively impaired patients at three years with higher, rather than lower, dose treatment. Importantly, considering the trend towards a higher proportion of patients with cognitive impairment at the baseline in the lower dose group, both the regression analyses controlled for the baseline differences between treatment groups. In addition, most Kazis' effect sizes were numerically greater in the IFNβ-1a 44 mcg group than in the 22 mcg group. However, the small differences between treatment groups detected here may not be clinically relevant to the individual patient.

As with all longitudinal cognition studies, the possible influence of learning effects[34] must be considered. To minimize learning effects in our study, cognitive function was measured using the parallel, equivalent, versions of Rao's battery for serial assessments, although this may not entirely eliminate learning effects. In the absence of an untreated control group, the presumed dose effect may provide supportive evidence that IFNβ-1a might stabilize cognitive function. The more pronounced effect of the higher IFNβ-1a dose on cognitive decline might be taken into account by neurologists when starting DMD treatment to delay physical and cognitive worsening in patients with RRMS.

The results presented must be considered after taking into account the limitations of this study. This was an observational study in which patients were not randomized to treatment, but treatment was assigned at the physician's discretion. The study was designed and performed in accordance with the Guidelines for Good Clinical Practice in randomized, controlled trials, and it has been shown that observational studies performed in this way do not overestimate the magnitude of effects for study outcomes.[35,36] Indeed, in the MS setting, observational studies may provide similar evidence to that obtained from Phase III trials.[36]

While observational studies are more reflective of the clinical setting, there is the potential for selection bias

towards treatment groups. Although treatment groups were well balanced at the baseline, a non-significant difference in baseline cognitive function was seen between groups. However, baseline cognitive performance was not an influential factor in the treatment decision-making process due to the lack of data regarding the cognitive effects of DMD treatment in patients with MS at the start of the study. We used the Cox proportional-hazards model to control for such differences, but other baseline differences that were not assessed could exist between the two groups. In addition, with the exception of the verbal IQ score, baseline patient demographics and disease and NPS characteristics did not differ between those patients who continued treatment for three years and those who discontinued treatment early. This difference in the baseline verbal IQ score was not responsible for the difference in cognitive performance at three years between the two treatment groups and did not influence the overall results of the study.

The sample size may affect the study outcomes, as the three-year results in this report are from a subcohort of patients recruited to the study. As no imputation method was used for missing data, it is not known how the lack of these data affected the study results. Although high discontinuation rates can be a problem for observational studies, the proportion of patients who completed this study (72%) is comparable with data from other clinical trials. In the Phase III PRISMS (Prevention of Relapses and disability by IFNβ-1a Subcutaneously in Multiple Sclerosis) study, the total study-completion rate for patients receiving sc IFNβ-1a was 81% (302/373) over four years.[28] In addition, patients receiving sc IFNβ-1b or im IFNβ-1a were excluded from the study due to the small patient numbers in these treatment groups. The dropout rate was particularly high (79.7%) among patients receiving im IFNβ-1a. Considering that over 50% of patients in this treatment group experienced relapses in the first 6–12 months of the study (data not shown), it is possible to speculate that perceived lack of efficacy and the general belief that higher and more frequent IFNβ therapies are more effective than lower-dose, less-frequent treatment regimens may have contributed to this observation.

Additional limitations to this study are common to cognition studies in MS. The assessment and definition of cognitive function in patients with MS has yet to be standardized. Here, we used a validated assessment tool and a conservative definition of 'cognitive impairment', based on impairment in at least three cognitive tests,[7] with impairment on tests defined as 1 SD below normative Italian values. Furthermore, it has been suggested that cognitive changes occur too slowly to be a useful endpoint in studies of DMDs,[37] although our results do not support this view.

Few studies have investigated the effects of DMDs on cognitive function in patients with MS, and results are inconclusive. In a prospective, placebo-controlled trial, im IFNβ-1a, 30 mcg qw, was shown to have protective effects on the cognitive domains most commonly affected in MS over two years of treatment; however, learning effects were reported.[34] The cognitive benefits of high dose sc IFNβ-1b have also been reported following two and four years of treatment,[38] and after one year, independent of effects on clinical disease measures.[39] Glatiramer acetate has not been shown to have cognitive benefits.[40]

How IFNβ-1a may protect against cognitive decline is unclear. Small but consistent correlations between cognitive function and MRI disease measures have been reported,[1,15] suggesting that inhibition of inflammation and lesion development may also preserve cognitive function. Another possibility is that IFNβ may increase the production of neurotrophic factors that protect against damage due to disease processes; the IFNβ-induced production of brain-derived neurotrophic factor[41] and nerve growth factor have been demonstrated.[42]

The results of our study confirm that cognitive impairment is a substantial problem, even in patients with only mild physical disability: over half of all patients had impaired performance on at least one cognitive test, despite the fact that this patient cohort included only patients with 'mild' physical disability. The high incidence of cognitive impairment at the baseline, and the confirmation that this is a risk factor for ongoing cognitive impairment in later years,[31] demonstrates the importance of cognitive assessment in patients with early MS. Identifying patients with, or at risk of, cognitive decline could enable therapeutic intervention, but treatment options are currently limited to symptomatic therapies[9,43] and acetylcholinesterase inhibitors,[44] although the clinical benefits of these are yet to be confirmed.

The results reported here indicate that treatment with sc IFNβ-1a may have dose-dependent cognitive benefits in mildly disabled patients with RRMS. In addition, sc IFNβ-1a was shown to achieve good disease control and was well tolerated in this cohort of patients. Several studies have demonstrated the beneficial effects of early treatment on clinical disease parameters[45–47] and brain atrophy.[48] Our results further support the clinical benefit of initiating higher dose sc IFNβ-1a treatment, even in patients with mild physical disability.

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