Subcutaneous interferon beta-1a has a positive effect on cognitive performance in mildly disabled patients with relapsing–remitting multiple sclerosis: 2-year results from the COGIMUS study

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***Abstract*:** The effect of interferon (IFN) beta-1a (44 and 22 μg subcutaneously [sc] three times weekly [tiw]) on cognition in mildly disabled patients with relapsing–remitting multiple sclerosis (McDonald criteria; Expanded Disability Status Scale ≤4.0) was assessed by validated neuropsychological testing at baseline and at regular intervals for up to 2 years in this ongoing open-label, 3-year study. Year-2 data were available for 356 patients (22 μg, $n = 175$; 44 μg, $n = 181$). The proportion of patients with impaired cognitive function was stable during the study: 21.4% at baseline and 21.6% at 2 years. At 2 years, the proportion of patients with ≥3 impaired cognitive tests was significantly lower in the 44 μg treatment group (17.0%) compared with the 22 μg group (26.5%; $p = 0.034$), although there was already a trend towards a higher proportion of patients with cognitive impairment in the 22 μg group at baseline. Factors associated with impairment in ≥ three cognitive tests after 2 years were age (odds ratio [OR]: 1.05; 95% confidence interval [CI]: 1.00–1.09), verbal intelligence quotient (OR: 0.95; 95% CI: 0.92–0.98), and having ≥ three impaired cognitive tests at baseline (OR: 11.60; 95% CI: 5.94–22.64). These interim results show that IFN beta-1a sc tiw may have beneficial effects on cognitive function as early as 2 years after treatment initiation, but the final 3-year data of the study are required to confirm these results.

***Keywords*:** cognitive function, cognitive impairment, interferon beta-1a, relapsing–remitting multiple sclerosis

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Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, immune-mediated disease of the central nervous system (CNS) characterized by demyelination, the development of plaque lesions and episodes of neurological symptoms that often lead to progressive neurodegeneration. As MS lesions may form in various locations in the CNS, clinical presentations of the disease can be diverse.

It is now recognized that, in addition to causing physical symptoms, lesion formation in MS also affects patients' cognitive functions, with as many as 65% of patients experiencing some degree of cognitive impairment [Ghaffar and Feinstein, 2007; Amato *et al*. 2006c; Bagert *et al*. 2002]. Declining cognitive function may develop irrespective of disease subtype or stage [Gonzalez-Rosa *et al*. 2006; Huijbregts *et al*. 2006], including in patients with early-stage MS [Amato *et al*. 1995], without physical disability [Haase *et al*. 2003], and in those with clinically isolated syndrome [Feuillet *et al*. 2007; Glanz *et al*. 2007] or benign MS [Haase *et al*. 2004]. Although little is known about the natural history of cognitive impairment in MS, available data suggest that remission is unlikely and that, at least in patients with

existing cognitive impairment, cognitive performance decreases with worsening disability [Amato *et al*. 2006c; Lynch *et al*. 2005; Achiron *et al*. 2005; Bagert *et al*. 2002; Rao *et al*. 1991a]. Cognitive impairment has been shown to correlate positively with clinical and magnetic resonance imaging (MRI) measures of disease [Lazeron *et al*. 2006; Rovaris and Filippi, 2000; Patti *et al*. 1998] and may predict physical disability and the rate of disability progression [Lynch *et al*. 2005; Amato *et al*. 2001]. Furthermore, worsening cognitive function may indicate progressive disease in patients with stable physical symptoms [Lynch *et al*. 2005; Amato *et al*. 2001].

Despite the common occurrence of cognitive deficits in MS, cognitive function is rarely measured during routine patient assessment. In addition, cognitive symptoms are often missed partly due to heterogeneity between individual patients, although specific cognitive domains are particularly susceptible in MS. The most commonly affected cognitive domains are those involving memory, learning, attention, executive functions and information-processing activities, whereas those involving processing speed, recognition memory and sustained attention are affected to a lesser degree [Rogers and Panegyres, 2007; Bobholz and Rao, 2003].

The onset of cognitive symptoms is a key determinant of quality of life (QoL) in patients with MS. Cognitive impairment may have a negative impact on patients' social relationships and overall QoL [Winkelmann *et al*. 2007; Benito-Leon *et al*. 2002; Amato *et al*. 2001], and is the major reason for disability and withdrawal from the workforce for persons with MS [Rao *et al*. 1991b]. Even mild impairment can interfere significantly with activities of daily life and can have profound social and economic consequences for both patients and their families [Rao *et al*. 1991b]. Furthermore, mood disorders such as depression may exist concurrently or arise as a consequence of socio-economic concerns and add to the complexity of symptoms [Ghaffar and Feinstein, 2007; Haase *et al*. 2003; Patten, 2005]. Fatigue is also a common symptom in MS [Bakshi, 2003], and can further impair cognitive performance [Barak and Achiron, 2006]. Patients often note a concurrent decline in their cognitive performance at times when they experience fatigue, due to limitation in their overall capacity to sustain mental activity.

Although cognitive impairment is highly prevalent in MS and has a strong functional impact, effective treatment strategies have not been established fully. Nonpharmacological measures such as occupational therapy, psychotherapy and cognitive rehabilitation can improve cognition, but may not prevent further decline [Pierson and Griffith, 2006]. The association between MRI lesions and cognitive decline [Amato *et al*. 2006c; Lazeron *et al*. 2006; Patti *et al*. 1998; Rovaris and Filippi, 2000] suggests that delaying disease progression may be a key aspect in the prevention of cognitive decline. Disease-modifying drugs (DMDs), such as interferon (IFN) beta, that inhibit pathological disease processes may prevent or delay cognitive impairment; however, the cognitive benefits of DMDs in MS remain unclear [Montalban and Rio, 2006; Bobholz and Rao, 2003].

The aim of the COGIMUS (COGnition Impairment in MUltiple Sclerosis patients) study was to evaluate the progression of cognitive decline in mildly disabled patients with relapsing–remitting MS (RRMS) receiving treatment with different regimens of IFN beta. Here, interim 2-year cognition and safety results from patients receiving subcutaneous (sc) IFN beta-1a in the 3-year, open-label COGIMUS study are reported.

Methods

The COGIMUS study was a prospective, multicentre, dose-controlled, observational, 3-year cohort trial comparing cognitive outcomes in Italian patients with RRMS treated with different regimens of IFN beta. An extension phase (up to 5 years) will also be conducted. Study enrolment started in January 2004 and was completed in March 2005. The ethics committees of all participating centres approved the study.

Patients

Patients aged 18–50 years with a diagnosis of RRMS according to the McDonald criteria [McDonald *et al*. 2001] and an Expanded Disability Status Scale (EDSS) [Kurtzke, 1983] score of $\leq$4.0 who were naïve to DMD treatment and had not been taking corticosteroids in the prior 60 days, immunosuppressants in the prior 6 months, or other immunomodulators in the previous year were eligible for the study. Patients were excluded from the study if they were pregnant or breastfeeding, or had a history of severe psychiatric disorders, alcohol abuse,

brain injury, severe depression, systemic endocrine or metabolic disorders, or severe disability that would interfere with cognitive test performance. All patients gave written informed consent prior to undergoing any pre-entry tests not performed during routine disease management.

Treatment

A total of 550 patients were enrolled into the study. Patients received IFN beta treatment (sc IFN beta-1a, 22 or 44 μg three times weekly [tiw] [Rebif®; Merck Serono International, S.A., Geneva]; intramuscular IFN beta-1a, 30 μg weekly [Avonex®; Biogen Idec Inc., Cambridge, MA]; or sc IFN beta-1b, 250 μg every other day [Betaferon®; Bayer Schering Pharma AG, Berlin]). Treatment was assigned at the physician's discretion.

Outcomes were analysed in only the patients receiving sc IFN beta-1a as these patients represented the majority (459/550, 83.5%) of the study population. Of these 459 patients, 223 (48.6%) received IFN beta-1a, 22 μg sc tiw, and 236 (51.4%) received IFN beta-1a, 44 μg sc tiw.

Relapses were treated with corticosteroids, and 'flu-like' symptoms (FLS) were treated with non-steroidal anti-inflammatory drugs or paracetamol. Any concomitant therapies were recorded on the case report form. No DMDs other than the study drug were permitted.

Evaluation of disease status

At the baseline visit, patents underwent a complete neurological examination to determine EDSS score and clinical history was recorded. Clinical assessments were repeated and safety data collected every 6 months.

Neuropsychological evaluation

Neuropsychological evaluation was performed at baseline and every 12 months over 2 years for all patients. Cognitive function was assessed by administering the Rao's Battery and the Stroop Color-Word Task for cognitive domains (alternate, parallel versions of the Rao's Battery were used to minimize learning effects: alternate versions were administered in the order A, B, A, B to all patients) [Rao *et al.* 1991a]. Cognitive impairment was defined as one standard deviation (SD) below the mean normative values for each cognitive test of the Rao's Battery, as described in a study of 200 healthy Italian volunteers [Amato *et al.* 2006a]. Patients demonstrating impaired cognitive function on at least three tests were considered cognitively impaired [Amato *et al.* 2001]. The cognitive impairment index for each patient with 2 years of follow-up was constructed at baseline and year 2. A grading system was applied to the patient's score on each cognitive test, dependent on the number of SDs that fell below the mean value described for a normative Italian population [Amato *et al.* 2006a]. Patients' scores were graded as follows: 0, at or above normative mean; 1, ≤1 SD below normative mean; 2, >1 SD but ≤2 SD below normative mean; 3, >2 SD but ≤3 SD below normative mean; and so on. The sum of these grades was calculated across all variables to produce a single overall value indicating the degree of cognitive impairment for each patient [Camp *et al.* 1999].

Additional neuropsychological tests were the Hamilton Depression Rating Scale (depression) [Hamilton, 1967], the MSQoL-54 questionnaire (QoL) [Vickrey *et al.* 1995], the Fatigue Impact Scale (fatigue) [Fisk *et al.* 1994] and the Environmental Status Scale (ESS; social functioning) [Rao *et al.* 1991b]. Cognitive testing was delayed until 30 days after the last steroid injection in the event that a patient was in relapse when cognitive assessments were scheduled. Intelligence quotient (IQ) was determined at baseline by administering the Brief Intelligence Test [Kaufman and Wang, 1992], which evaluates general intelligence by exploring verbal, nonverbal and IQ components of intelligence.

Study endpoints

The primary endpoint of the COGIMUS study was the proportion of patients with cognitive impairment at year 3 in patients treated with different sc IFN beta regimens, and will be reported separately (manuscript in preparation). The results of an interim analysis looking at the effect of treatment with sc IFN beta-1a on cognitive impairment over 2 years are reported here.

Sample size

Study sample size was estimated based on two-way analysis of variance with a fixed factor (IFN beta-1a regimen) and one recall (initial cognitive assessment *versus* final assessment). The α value was 0.05 and power was set at 0.8. To detect a difference in functional performance z-score of 0.5 points (corresponding to a relative increase in mean scores on the Rao's Battery subscales of 8.4–14.0%) between the two defined groups, the required sample size was calculated to be

254 patients (127 patients per treatment group). Based on the assumption of a possible dropout rate of 20% over the 3 years of the study, the target sample size was 304 patients (152 per treatment group).

Statistical analyses

At baseline, descriptive analyses were performed for the population of 459 patients treated with sc IFN beta-1a. For outcome measures at 2 years, analyses included only patients with 2 years of follow up. No imputation of missing data was performed. The analysis at 2 years was exploratory, with no adjustment for multiplicity. The following tests were conducted, using a significance level of 0.05: the Chi-squared test was performed for the comparison of proportions and the Mann–Whitney test for comparison of independent samples. Kazis' effect was calculated as follows: (mean score at year 2 – mean score at baseline)/SD. This score gives an estimate of the variability of cognitive tests over time, with a positive result representing an improvement and a negative result representing a worsening in cognitive function over 2 years of treatment. An effect size of 0.20 is considered to be small, 0.50 to be moderate and 0.80 to be large [Kazis *et al*. 1989]. To identify risk factors for cognitive impairment at 2 years, univariate and multivariate logistic regression were performed. All variables were tested by univariate logistic regression. Variables that had a significant odds ratio in the univariate analysis were sequentially added to develop a multivariate model of regression. Variables that were still significant remained in the final model.

Results

Patients and baseline characteristics

The baseline characteristics of the study population included in this 2-year interim analysis are shown in Table 1. The mean (SD) age of patients was 33 (8.1) years and the mean (SD) duration of disease was 4 (4.5) years. The female-to-male ratio was 1.9:1. There were no significant differences between the two treatment groups in any of the general, clinical, neuropsychological or MRI variables at baseline. Full baseline characteristics, including baseline MRI variables for these populations, and the relation between baseline disease and cognitive impairment, will be reported elsewhere (manuscript in preparation).

At baseline, of the 459 patients treated with sc IFN beta-1a, 270 patients (58.8%) had cognitive impairment on at least one neuropsychological test, 172 (37.5%) had cognitive impairment on at least two tests and 98 patients (21.4%) had cognitive impairment on at least three tests. There was a trend for a higher proportion of patients in the 22 μg dose group to show cognitive impairment on at least three neuropsychological tests (24.2%) than in the 44 μg group (18.6%; $p = 0.145$).

Cognitive impairment at 2 years

Follow-up data at year 2 were available for 356 (77.6%) patients, of whom 175 received IFN beta-1a, 22 μg sc tiw, and 181 received IFN beta-1a, 44 μg sc tiw. Year-2 cognitive data were available for 342 patients (166 receiving IFN beta-1a 22 μg and 176 receiving IFN beta-1a 44 μg). There were no significant differences in baseline demographic, clinical, neuropsychological and MRI characteristics, or in assigned treatment, between the patients who stayed on treatment ($n = 356$) and those who prematurely dropped out of the study ($n = 103$; data not shown).

At 2 years of follow up, a significantly lower proportion of patients receiving IFN beta-1a, 44 μg sc tiw, had impairment in at least three cognitive tests than those receiving IFN beta-1a, 22 μg sc tiw (17.0% *versus* 26.5%, respectively; $p = 0.034$; Figure 1), although there was already a nonsignificant trend towards this difference at baseline. The cognitive impairment index decreased slightly, but not significantly, between baseline and year 2 in both treatment groups (Figure 2). There were no significant differences in the cognitive impairment index between the two treatment groups at either time point.

Most individual cognitive tests were similar between treatment groups, but the Selective Reminding Test–Consistent Long-Term Retrieval (SRT–CLTR) was significantly higher for the IFN beta-1a 44 μg group than for the IFN beta-1a 22 μg group (Table 2).

Other neuropsychological tests were similar between treatment groups, but the ESS at 2 years was significantly higher for patients receiving IFN beta-1a 44 μg compared with those receiving IFN beta-1a 22 μg (Table 2). Scores for both depression and QoL were numerically lower at 2 years than at baseline; fatigue scores remained stable over 2 years (Tables 1 and 2).

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

	Treatment group (IFN beta-1a dose sc tiw)	Number of patients	Mean	SD	*p* value*
Age, years	22 µg	223	33.8	8.4	0.259
	44 µg	236	32.8	7.9	
Years in formal education	22 µg	223	12.2	3.5	0.406
	44 µg	236	12.5	3.4	
Duration of disease, years	22 µg	223	4.0	4.7	0.374
	44 µg	236	3.6	4.3	
Total IQ score†	22 µg	213	108.8	8.8	0.422
	44 µg	232	109.4	8.6	
Verbal IQ score	22 µg	213	106.3	11.1	0.308
	44 µg	232	106.8	9.1	
Performance IQ score	22 µg	213	105.4	9.3	0.746
	44 µg	232	106.0	8.9	
EDSS score	22 µg	223	1.8	0.9	0.791
	44 µg	236	1.8	1.0	
QoL score	22 µg	223	65.6	16.7	0.724
	44 µg	235	64.4	19.3	
Physical Health Composite Score	22 µg	223	69.6	16.8	0.313
	44 µg	235	68.5	16.3	
Mental Health Composite Score	22 µg	223	67.4	19.8	0.255
	44 µg	235	65.9	19.1	
Fatigue Impact Scale, total score	22 µg	223	25.1	25.5	0.224
	44 µg	235	27.2	25.4	
Hamilton Depression Rating Scale, total score	22 µg	223	6.7	5.2	0.496
	44 µg	235	6.9	4.7	
Environmental Status Scale, total score	22 µg	223	1.6	2.8	0.083
	44 µg	235	1.6	2.3	

EDSS, Expanded Disability Status Scale; Gd, gadolinium; IFN, interferon; IQ, intelligence quotient; QoL, quality of life; sc, subcutaneous; SD, standard deviation; tiw, three times weekly.
*Chi squared test. †Population 'average' IQ score: 99–109.

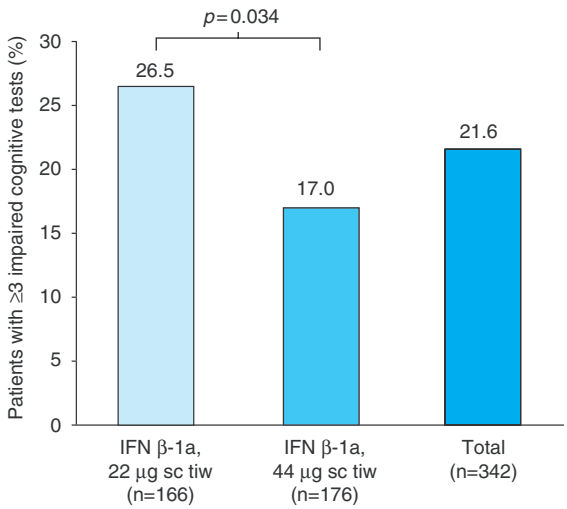

Figure 1. Proportion of patients in each treatment group, and in both groups combined, with at least three impaired cognitive tests at 2 years ($p=0.034$ for the difference between treatment groups). IFN, interferon; sc, subcutaneous; tiw, three times weekly.

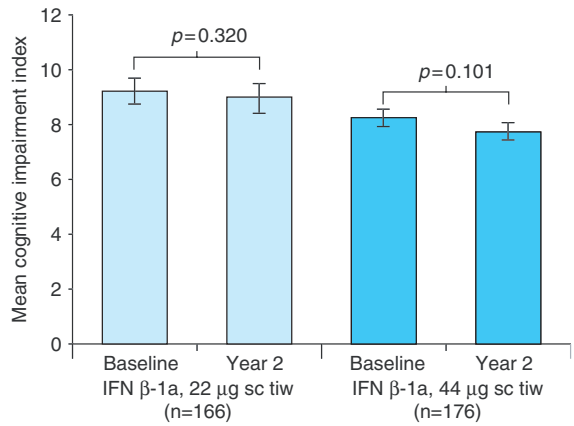

Figure 2. Cognitive impairment index at baseline and year 2 in patients receiving one of two doses of sc IFN beta-1a with 2 years of follow up. IFN, interferon; sc, subcutaneous; SD, standard deviation; tiw, three times weekly.

Table 2. Year-2 follow-up data for patients receiving sc IFN beta-1a, by treatment group.

	Treatment group (IFN beta-1a dose sc tiw)	Number of patients	Mean	SD	*p* value*
EDSS score	22 µg	174	1.8	1.2	0.631
	44 µg	181	1.8	1.1	
QoL score	22 µg	168	64.3	17.4	0.395
	44 µg	177	63.2	16.9	
Physical Health Composite Score	22 µg	166	70.9	17.3	0.341
	44 µg	177	68.7	18.4	
Mental Health Composite Score	22 µg	168	68.2	20.1	0.418
	44 µg	177	66.6	20.1	
Fatigue Impact Scale, total score	22 µg	168	25.1	25.2	0.262
	44 µg	177	28.7	27.0	
Hamilton Depression Rating Scale, total score	22 µg	168	5.7	5.9	0.367
	44 µg	176	6.0	5.3	
Environmental Status Scale, total score	22 µg	168	1.6	3.1	0.043
	44 µg	177	1.8	2.8	
SRT–LTS	22 µg	163	44.0	15.0	0.076
	44 µg	171	47.2	12.8	
SRT–CLTR	22 µg	163	33.1	15.7	0.039
	44 µg	171	36.9	14.6	
SPART	22 µg	166	21.4	5.4	0.631
	44 µg	176	21.9	4.7	
SDMT	22 µg	166	46.3	14.0	0.140
	44 µg	176	48.4	12.8	
PASAT-30	22 µg	164	40.1	15.5	0.169
	44 µg	169	43.3	12.3	
PASAT-20	22 µg	164	30.7	13.6	0.919
	44 µg	169	31.0	12.9	
SRT-D	22 µg	166	8.4	2.4	0.457
	44 µg	176	8.6	2.6	
SPART-D	22 µg	166	7.4	2.1	0.777
	44 µg	176	7.5	2.1	
WLG	22 µg	166	29.0	10.7	0.941
	44 µg	176	28.8	9.7	

EDSS, Expanded Disability Status Scale; IFN, interferon; PASAT-20, 20-second Paced Auditory Serial Addition Test; PASAT-30, 30-second PASAT; QoL, quality of life; sc, subcutaneous; SD, standard deviation; 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; tiw, three times weekly; WLG, Word List Generation.
*Chi squared test.

For each individual cognitive test, the Kazis' effect was determined for the two treatment groups (Table 3). Effects were similar between groups for all tests except the Symbol Digit Modalities Test and the SRT–CLTR.

Factors predictive of cognitive impairment at 2 years

According to the results of multivariate logistic regression, the factors associated with a higher risk of impairment in at least three cognitive tests at 2 years were increased age (odds ratio [OR]: 1.05, 95% confidence interval [CI]: 1.00–1.09), lower baseline verbal IQ (OR: 0.95, 95% CI: 0.92–0.98), and cognitive impairment at baseline (OR: 11.60, 95% CI: 5.94–22.64). Although not significant in the multivariate model, higher-dose IFN beta-1a (44 µg) was associated with a lower risk of cognitive impairment at 2 years in the univariate model (OR: 0.57, 95% CI: 0.34–0.96); however, this finding should be interpreted cautiously because of the trend towards an imbalance in the proportion of patients with cognitive impairment at baseline.

Clinical outcomes at 2 years

Clinical data at year 2 were available for 356 patients. The mean (SD) EDSS score was 1.8 (1.2) for the IFN beta-1a 22 µg group and 1.8 (1.1) for the IFN beta-1a 44 µg group.

Table 3. Effect size (Kazis' effect) for individual cognitive tests in patients treated with IFN beta-1a, 22 or 44 μg sc tiw, for 2 years. Positive numbers represent improved test performance; effect sizes of 0.20–0.49 indicate a small effect.

Cognition test	Treatment group	
	IFN beta-1a, 22 μg sc tiw ($n=153$)	IFN beta-1a, 44 μg sc tiw ($n=165$)
SRT–LTS	0.34	0.48
SRT–CLTR	0.22	0.41
SPART	0.23	0.19
SDMT	−0.04	0.24
PASAT-30	0.23	0.29
PASAT-20	0.20	0.09
SRT-D	0.24	0.19
SPART-D	0.29	0.14
WLG	−0.09	−0.07

IFN, interferon; PASAT-20, 20-second Paced Auditory Serial Addition Test; PASAT-30, 30-second PASAT; sc, subcutaneous; 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; tiw, three times weekly; WLG, Word List Generation.

Relapse data were available for 394 patients. Over the 2-year study period, 72.1% of patients for whom relapse data were available remained relapse-free. There were no significant differences between the two treatment groups (data not shown). Progression data were available for 355 patients, 85.1% of whom were free from progression at 2 years.

Safety

The safety profile of IFN beta-1a reported in this study was consistent with previous reports [Gold *et al.* 2005; PRISMS Study Group and University of British Columbia MS/MRI Analysis Group, 2001]. Adverse events (AEs) included injection-site reactions (ISRs), headache, FLS, depression and laboratory abnormalities. The most common ISR, inflammation, occurred slightly more frequently with IFN beta-1a 44 μg (141/236, 59.7%) than with the 22 μg dose (118/223, 52.3%). No skin necrosis was reported. More than one-third of patients reported FLS, predominantly during the first 6 months of treatment, but the incidence declined with time on study (from 45% at month 6 to 29% at 2 years' follow up). Approximately 5% of treated patients were reported to have asymptomatic laboratory abnormalities, with lymphopenia and increased liver transaminase levels being the most common; the majority of these were World Health Organization grade 1 or 2. Both of these symptoms occurred slightly more frequently with IFN beta-1a 44 μg than with IFN beta-1a 22 μg (8% *versus* 5%), but the differences were not statistically significant. Thyroid autoimmunity was rare (<1% of patients). No deaths occurred during the study.

Dropout rates were similar in both treatment arms: 48 (21.5%) patients receiving IFN beta-1a 22 μg and 53 (22.5%) patients receiving IFN beta-1a 44 μg did not complete the study. There were no discontinuations due to ISRs. Reasons for discontinuing were as follows: AEs, 10 (2.2%) patients; lost to follow up, 13 (2.8%); protocol violation, 16 (3.5%); lack of efficacy, 14 (3.1%); pregnancy/planning to conceive, 11 (2.4%); other, 37 (8.1%). Reasons included in the 'Other' category were mostly subjective; for example, 'patient decided not to continue'.

Discussion

The results from this interim analysis of the observational, open-label COGIMUS study indicate that, after 2 years, treatment with IFN beta-1a has a positive effect on cognitive function in mildly disabled patients with RRMS.

Treatment with IFN beta-1a, 22 μg or 44 μg sc tiw, was associated with stable cognitive performance over 2 years in this study population. Overall, the proportion of patients with impaired cognitive function was stable during the 2-year period of treatment (21.4% at baseline *versus* 21.6% at 2 years) and the cognitive impairment index showed a trend towards improvement from baseline. Of note, the proportion of patients with cognitive impairment decreased in the 44 μg group from 18.6% at baseline to 17.0% at 2 years. At this time point, significantly fewer patients who received the higher 44 μg dose of IFN beta-1a had at least three impaired cognitive tests compared with the lower-dose group. This suggests that the benefit of IFN beta-1a on cognition may be dose dependent, although the data need confirming as there was a trend towards a higher proportion of patients with baseline cognitive impairment in the lower-dose group and there was no placebo-treated group for comparison. The possibility of a dose effect is supported by the results from analyses of individual cognitive tests, with the higher-dose group recording significantly higher SRT–CLTR scores than the

lower-dose group. The higher-dose group also recorded higher scores on the ESS, suggesting that there may be other neuropsychological benefits of IFN beta-1a relating to social function. However, it should be noted that cognitive benefits of higher-dose IFN beta-1a were not different to lower-dose IFN beta-1a according to multivariate regression analysis, which accounted for differences at baseline. While data concerning a dose-dependent effect are not conclusive in this 2-year analysis, previous results obtained using a less stringent definition of cognitive impairment ($\geq$ two impaired tests compared with $\geq$ three impaired tests used here) support a possible dose effect after 2 years of follow up [Patti *et al*. 2007; Gold *et al*. 2005]. Taken together, these preliminary results further support the clinical benefit of initiating IFN beta-1a treatment as soon as possible after diagnosis of MS is made. In this open-label study, the dose of sc IFN beta-1a was selected at the discretion of the treating physician, and therefore patients receiving low-dose IFN beta-1a were not switched to the higher dose during the study period as there was no rationale for doing so.

Results from other studies investigating the effects of IFN beta on cognitive function in patients with MS have generally been promising [Flechter *et al*. 2007; Fischer *et al*. 2000; Pliskin *et al*. 1996]. The mechanism by which IFN beta may act on cognitive function is not clear. MRI studies have revealed small but consistent correlations between the progression of cognitive impairment and increasing brain lesion load and brain atrophy [Amato *et al*. 2006c]. Thus, the ability of DMDs to reduce lesion development may also prevent or delay cognitive decline. Alternatively, IFN treatment may increase production of neurotrophic factors that protect against damage, such as brain-derived neurotrophic factor or nerve growth factor [Caggiula *et al*. 2006].

Previous studies have shown that cognitive impairment often occurs in the early stages of MS [Feuillet *et al*. 2007; Glanz *et al*. 2007]. The high incidence of cognitive impairment in at least one test at baseline (more than half of the patients had impaired performance in at least one test) in our study confirms that cognitive impairment is a significant problem even in patients with only mild physical disability (baseline mean EDSS score was 1.8 in both treatment groups).

We identified several baseline risk factors that were predictive of cognitive impairment at 2 years in this cohort of mildly disabled patients. In addition to cognitive impairment at baseline, increased age and lower verbal IQ were also found to be associated with increased risk of developing cognitive impairment at 2 years, although these two factors only just reached significance. Age >40 years has been identified previously as being associated with cognitive decline in a small controlled study [Sartori and Edan, 2006]. Increasing age was found to correlate positively with the severity of cognitive decline after 10 years in a longitudinal study of patients with MS [Amato *et al*. 2001]. Age has also been shown to significantly affect the rate of disability progression in patients with MS [Trojano *et al*. 2002], although this study did not assess cognitive performance. Routine assessment of patients at diagnosis could enable early intervention to preserve cognitive function. However, as cognitive assessments can be costly and difficult to administer, identification of factors predictive of cognitive impairment may be important so that at-risk patients can be selected and monitored. The patients in this study population had very mild disability, and therefore might not be considered in the clinic as being at particular risk of cognitive impairment. Thus, more knowledge of factors influencing cognitive function would be beneficial.

Limitations of these results must be considered. The data represent a 2-year interim analysis from the open-label COGIMUS study, and full 3-year data are required to assess the impact of IFN beta-1a treatment in these patients. No firm conclusions about treatment effects can be made until results are confirmed by the primary endpoint analysis at 3 years. The possibility that the beneficial effects on cognition we observed in this study are accountable to a learning effect of repetitive neuropsychological testing cannot be excluded, although alternate versions were used to minimize these effects and tests were only repeated at 12-month intervals. Furthermore, while observational studies are a valuable representation of the real-life situation in clinical practice, there is an inherent potential for selection bias in treatment groups. Such bias could have contributed to the differences in baseline cognitive impairment in at least three tests that we observed between the dose groups.

Physical disability has been the focus of research and clinical attention in MS for many years, but more recently the impact of cognitive dysfunction on patients' daily lives has gained awareness. Cognitive impairment can have a profound negative impact on many aspects of daily life, such as working, driving and personal relationships, which contributes greatly to poor overall QoL [Amato *et al*. 2001; Benito-Leon *et al*. 2002; Schultheis *et al*. 2001; Rao *et al*. 1991b]. Furthermore, cognitive decline can occur in the absence of worsening physical disability and therefore may be an important predictor of disease progression, particularly in the early stages.

Very little is known about effective strategies for managing cognitive impairment in MS [Amato *et al*. 2006b]. Currently, symptomatic therapies, including cognitive behavioural therapy, psychotherapy and occupational therapy, form the basis of treatment for neuropsychological symptoms of MS and can help to limit the impact of cognitive dysfunction [Amato *et al*. 2006b; Bagert *et al*. 2002]. Acetylcholinesterase inhibitors, which are used in the treatment of Alzheimer's disease, may improve cognitive function in patients with MS [Christodoulou *et al*. 2006]. In addition, pharmacological treatment of depression and fatigue may reduce some symptoms of cognitive dysfunction, but there are currently no approved pharmacological therapies for cognitive dysfunction in MS, since the cognitive benefits of such agents require confirmation [Montalban and Rio, 2006; Patten, 2005]. Hence, treatment of cognitive dysfunction in patients with MS remains inadequate.

The interim results from the open-label COGIMUS study reported here indicate that the beneficial effects of IFN beta-1a sc tiw on cognitive function can be detected after 2 years of treatment, subject to confirmation by final 3-year data from the study. Furthermore, our data suggest that the cognitive benefits of IFN beta may be more pronounced at higher doses, although this observation requires confirmation. These findings further support the clinical benefit of initiating IFN beta-1a treatment as early as possible in the course of MS disease management.

Conflict of interest statement

FP has received financial support for research activities from the University of Catania and has also received fees from Merck Serono International S.A. (an affiliate of Merck KGaA, Darmstadt, Germany) and Sanofi Aventis. MPA has received grants for research, speaking and participating in scientific congresses from Merck Serono International S.A. and Biogen Dompè. MT has received fees for speaking and consulting activities with Biogen Dompè, Bayer Schering, Merck Serono International S.A. and Sanofi Aventis. SB, BG, FL, LC, EDiM, OP, MRT and SM have nothing to declare.

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