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Quality of life, depression and fatigue in mildly disabled patients with relapsing–remitting multiple sclerosis receiving subcutaneous interferon beta-1a: 3-year results from the COGIMUS (COGNitive Impairment in MULTiple Sclerosis) study

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on behalf of the COGIMUS Study Group

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Abstract

Background: The precise relationships among quality of life, depression, fatigue and cognitive impairment in multiple sclerosis (MS) are complex and poorly understood.

Objective: To assess the effects of subcutaneous interferon beta-1a on quality of life, depression and fatigue over 3 years in the COGIMUS study, and to examine the relationship between these outcomes and baseline cognitive status.

Methods: COGIMUS was an observational 3-year trial assessing cognitive function in 459 patients with relapsing–remitting MS treated with subcutaneous interferon beta-1a.

Results: In total, 331 patients completed the study (168 received interferon beta-1a, 44 µg subcutaneously three times weekly, and 163 received interferon beta-1a, 22 µg subcutaneously three times weekly). Mean MS Quality of Life-54 (MSQoL-54) composite scores did not change over time. There were no significant differences between groups in MSQoL-54 composite scores when patients were grouped by treatment dose and baseline cognitive status. Mean (standard deviation) Hamilton Depression Rating Scale score decreased from 6.8 (4.9) at baseline to 5.8 (5.9) at year 3. Mean total Fatigue Impact Scale scores were low (<30) at all time points.

Conclusion: Quality of life, depression and fatigue remained largely stable over 3 years; no effects of treatment dose or baseline cognitive status were found.

Keywords

cognitive function, depression, fatigue, interferon beta-1a, longitudinal study, quality of life, relapsing–remitting multiple sclerosis

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Introduction

Multiple sclerosis (MS) has a significant and ongoing impact on patients' health-related quality of life (QoL).^{1,2} Neuropsychological symptoms, fatigue and declining social functioning are common and contribute to the burden of disease in MS,^{3,4} however, routine

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patient assessment tends to concentrate on physical disability, often leaving other symptoms and overall QoL overlooked. Furthermore, the degree to which patients perceive that their illness impacts on their daily lives has an important influence on their overall mental health.² Depression is a common complication of MS; the lifetime prevalence has been estimated to be as high as 50%, which is about three times that observed in the general population.^{1,5,6} In addition, fatigue is one of the most prevalent and disabling symptoms associated with MS, and has been reported in as many as 95–97% of patients.^{7,8} Depression and fatigue have been identified as major determinants of impaired QoL in MS, independent of physical disability.^{2,9–13} However, the precise relationships among QoL, depression and fatigue are likely to be complex and are still poorly understood. The involvement of moderating variables to explain diverse results has been suggested.^{8,14,15}

Cognitive impairment is also a common feature of MS, occurring in 20–70% of patients.^{1,16–18} It can occur in early-stage MS and even in patients with clinically isolated syndrome.¹⁹ Cognitive performance has been shown to have an association with QoL in early MS; however, interactions between cognitive status and depression or fatigue are deemed more complex.^{6,19–22}

The objective of the observational COGIMUS (COGnition Impairment in MULTiple Sclerosis patients) study was to assess the effects of subcutaneous (sc) interferon beta-1a (IFN β -1a) on cognitive function over 3 years in mildly disabled patients (Expanded Disability Status Scale [EDSS] score \leq 4.0) with relapsing–remitting MS (RRMS). At baseline, cognitive impairment was present in approximately 20% of patients, and was weakly but consistently correlated with MRI measures of disease.¹⁷ After 3 years on study, the results suggested that treatment with IFN β -1a may have cognitive benefits, with the higher dose (44 μ g sc three times weekly [tiw]) being more beneficial than the lower dose (22 μ g sc tiw).²³

The aim of the present analysis was to assess the effects of sc IFN β -1a treatment on QoL, depression and fatigue over 3 years in patients enrolled in the COGIMUS study, and to examine the relationship among longitudinal changes in QoL, depression and fatigue, and baseline cognitive status.

Patients and methods

COGIMUS was a prospective, multicentre, observational, 3-year cohort trial assessing cognitive function in Italian patients with RRMS treated with sc IFN β -1a. Methodological details have been described in detail elsewhere, and are summarized below only briefly.^{17,23}

Study population and treatment

Eligibility criteria have been described previously.¹⁷ In brief, patients were aged 18–50 years, with a diagnosis of RRMS (McDonald 2001 criteria) and an EDSS score of \leq 4.0, without severe psychiatric disorders, including major depressive disorder (DSM-IV criteria),²⁴ and were naïve to disease-modifying drug treatment. All patients gave written informed consent and all received IFN β treatment; the choice of IFN β formulation and dose were at the physician's discretion.²³ As the large majority of patients in the study (459/550; 83.5%) received IFN β -1a, 44 μ g sc tiw ($n=236$ [42.9%]) or 22 μ g sc tiw ($n=223$ [40.5%]), patients who received other IFN β treatments were excluded from this analysis.²³

Assessments

All patients underwent neuropsychological assessment at baseline and every 12 months for 3 years.²³ In the event of relapse at the time of scheduled neuropsychological assessments, cognitive testing was delayed until 30 days after the last steroid injection. Cognitive function was assessed using Rao's Brief Repeatable Battery (BRB) and the Stroop Colour-Word Task (ST) for cognitive domains. Patients were considered to be cognitively impaired if they showed impaired performance on at least three cognitive tests; for each cognitive test, impaired performance was defined as one standard deviation (SD) below the mean Italian normative values.²⁵ As the frequency of cognitive impairment was similar using this definition to that based on comparison with the fifth percentile (BRB) and the 95th percentile (ST),²³ the latter analysis was not considered necessary in the present paper.

QoL was assessed by the MSQoL-54 questionnaire, depression by the Hamilton Depression Rating Scale (HDRS),²⁶ fatigue by the Fatigue Impact Scale (FIS),²⁷ social functioning by the Environmental Status Scale (ESS),²⁸ and intelligence quotient (IQ) using the Brief Intelligence Test.²⁹

Statistical analyses

Means, standard deviations, medians and ranges were calculated for all numerical variables at baseline and years 1, 2 and 3. Differences in baseline demographic and disease characteristics between patient groups were analysed using the Mann–Whitney test (quantitative variables) or the chi-squared test (qualitative variables). A Kruskal–Wallis test was performed to assess non-parametric four-group comparisons of k independent samples for IFN β -1a dose and presence or absence of cognitive impairment. Changes over time between

defined groups were analysed using analysis of variance (ANOVA) for repeated measures.

Baseline variables (e.g. age, and MSQoL-54, FIS and EDSS scores) were evaluated as potential confounding variables for a given endpoint measure or endpoint subcategory using analysis of covariance (ANCOVA). Multiple logistic regression (multivariate stepwise forward regression) was used to determine predictors of worsening score; a clinically relevant change in score was defined as a $\geq 0.5 - SD$ change from baseline to year 3 ($0.5 + SD$ for ESS and its subscales).³⁰ The significance level was set at 0.05. There was no imputation for missing data. All statistical analyses were performed using SAS 9 (SAS Institute Inc., Cary, NC, USA) and STATA 8.2 software (Stata Corp., College Station, TX, USA).

Results

Patients

Overall, 331/459 patients (72.1%) completed the 3-year study: 168 received IFN β -1a, 44 μ g sc tiw, and 163 received IFN β -1a, 22 μ g sc tiw. Dropout rates and reasons for discontinuation were similar in both dose groups and have been described previously.²³ There were no significant differences in baseline demographic and disease characteristics between patients who did and did not complete the study. Baseline demographic characteristics in patients who completed the study by assigned treatment dose and by baseline cognitive status are shown in Table 1.

Quality of life

At baseline, MSQoL-54 Physical Health Composite Score (PHCS) and Mental Health Composite Score (MHCS) did not differ between patients with and without cognitive impairment. Mean baseline scores were significantly higher (denoting better QoL) in cognitively impaired than cognitively preserved patients for two MSQoL-54 subscales: 'change in health' (mean [SD] score: 49.6 [25.4] vs 41.4 [2.7], $p=0.03$) and 'sexual function' (89.9 [22.0] vs 85.9 [21.9], $p=0.02$; Mann-Whitney test). No significant differences were seen in any other subscales.

In the group as a whole, PHCS and MHCS remained stable over the course of the study. The mean (SD) PHCS was 69.4 (15.8) at baseline and 69.7 (18.5) at year 3; MHCS was 66.1 (19.1) at baseline and 67.3 (20.0) at year 3. PHCS and MHCS were also similar in the two treatment groups at all time points. When PHCS or MHCS over time were analysed by treatment group (two-group analysis; ANOVA for repeated measures), no significant variation over time

was seen. Similarly, there were no between-group differences when analysed by treatment group and presence or absence of cognitive impairment at baseline (four-group analysis). Significant change over 3 years was seen in some MSQoL-54 subscales in both the two- and four-group analysis (ANOVA for repeated measures; Figure 1). There were no significant interactions between changes over time and group.

Depressive symptoms

Baseline HDRS was similar in patients with (mean [SD] score: 6.0 [4.4]) and without (7.0 [5.0]) cognitive impairment at baseline ($p=0.25$; Mann-Whitney test). Mean [SD] HDRS score in the whole population was reasonably stable over the course of the study (6.8 [4.9] at baseline and 5.8 [5.9] at year 3) and were similar in both treatment groups at all time points (data not shown).

The proportion of patients with depression (HDRS score > 10) decreased over time, from 82/319 (25.7%) at baseline to 52/319 (16.3%) at year 3 ($p=0.005$; ANOVA). This change was seen only in the subgroup of patients without cognitive impairment at baseline (baseline: 72/257 [28%] patients; year 3: 48/257 [18.7%] patients, $p=0.003$; ANOVA). HDRS score improved significantly over time when data were analysed by treatment group, from 6.8 at baseline to 6.3 at year 3 in patients receiving IFN β -1a, 44 μ g sc tiw, and from 6.7 to 5.5 in patients receiving IFN β -1a, 22 μ g sc tiw ($p=0.006$, ANOVA for repeated measures). There was no effect of treatment on this outcome ($p=0.48$). No significant effect of time or group was seen in the four-group analysis.

Fatigue

Overall, FIS scores increased slightly between baseline and year 3, although there was a large degree of variation in individual patient scores (Table 2). Mean total FIS scores throughout the study were low (< 30 at all time points) and similar in both treatment groups (Table 2). No significant differences over time or between groups were seen in either the two-group or four-group analysis (ANOVA for repeated measures). A trend towards worsening over time was seen in the FIS cognitive subscale in all four subgroups ($p=0.058$).

Confounding factors

Confounding factors were identified using ANCOVA; results for global QoL, total FIS score and HDRS score at 3 years are shown in Table 3. As expected, there was some overlap between factors identified for global QoL

Table 1. Baseline demographic characteristics in patients who completed the study, by treatment group and presence or absence of baseline cognitive impairment

	IFN β -1a dose, sc tiw (cognitive status)	N	Mean	SD	p value ^a
Age (years)	44 μ g (not impaired)	143	32.5	7.9	0.006
	22 μ g (not impaired)	124	33.1	8.2	
	44 μ g (impaired)	26	33.8	6.7	
	22 μ g (impaired)	38	37.9	7.6	
Time in formal education (years)	44 μ g (not impaired)	143	12.7	3.4	0.794
	22 μ g (not impaired)	124	12.4	3.6	
	44 μ g (impaired)	26	12.6	3.3	
	22 μ g (impaired)	38	12.2	3.6	
Duration of disease (years)	44 μ g (not impaired)	143	3.4	4.2	0.608
	22 μ g (not impaired)	124	4.3	5.3	
	44 μ g (impaired)	26	3.5	3.5	
	22 μ g (impaired)	38	3.7	4.3	
Total IQ ^b	44 μ g (not impaired)	141	110.5	7.3	0.085
	22 μ g (not impaired)	121	109.8	8.2	
	44 μ g (impaired)	25	107.0	9.1	
	22 μ g (impaired)	34	106.1	10.7	
HDRS score	44 μ g (not impaired)	142	7.0	4.6	0.632
	22 μ g (not impaired)	124	7.0	5.5	
	44 μ g (impaired)	26	6.0	4.2	
	22 μ g (impaired)	38	6.1	4.6	
FIS total score	44 μ g (not impaired)	142	27.2	26.8	0.713
	22 μ g (not impaired)	124	25.4	26.6	
	44 μ g (impaired)	26	19.0	15.1	
	22 μ g (impaired)	38	25.7	23.6	
QoL total score	44 μ g (not impaired)	142	63.7	19.4	0.698
	22 μ g (not impaired)	124	65.6	15.5	
	44 μ g (impaired)	26	67.5	15.2	
	22 μ g (impaired)	38	65.6	15.7	
EDSS score	44 μ g (not impaired)	143	1.8	0.9	0.663
	22 μ g (not impaired)	124	1.8	0.9	
	44 μ g (impaired)	26	1.6	1.1	
	22 μ g (impaired)	38	1.8	1.0	

^aKruskal–Wallis.^bPopulation 'average' IQ score: 102.²⁹

EDSS, Expanded Disability Status Scale; FIS, Fatigue Impact Scale; HDRS, Hamilton Depression Rating Scale; IFN, interferon; IQ, intelligence quotient; QoL, quality of life; sc, subcutaneous; SD, standard deviation; tiw, three times weekly.

and for the MSQoL-54 MHCS and PHCS (i.e. baseline HDRS and age), and for those identified for FIS subscales and total score (data not shown). In addition, total IQ was a confounder for MHCS ($p=0.003$) and performance IQ for PHCS ($p=0.01$). Baseline HDRS score was a consistent confounding factor across all parameters assessed. Total FIS score at baseline was a confounder for global QoL, HDRS score and total FIS score at 3 years. Age was identified as a confounding factor for all FIS scores except the cognitive subscale,

for which verbal IQ was a confounding factor. Each baseline variable was also a confounding factor for that same variable at 3 years.

Predictors of clinically important changes over time

Variables predictive of clinically important worsening or improving scores for QoL, depression and fatigue are shown in Table 4. Total IQ was a predictor of better QoL outcomes, but was not a predictor of fatigue

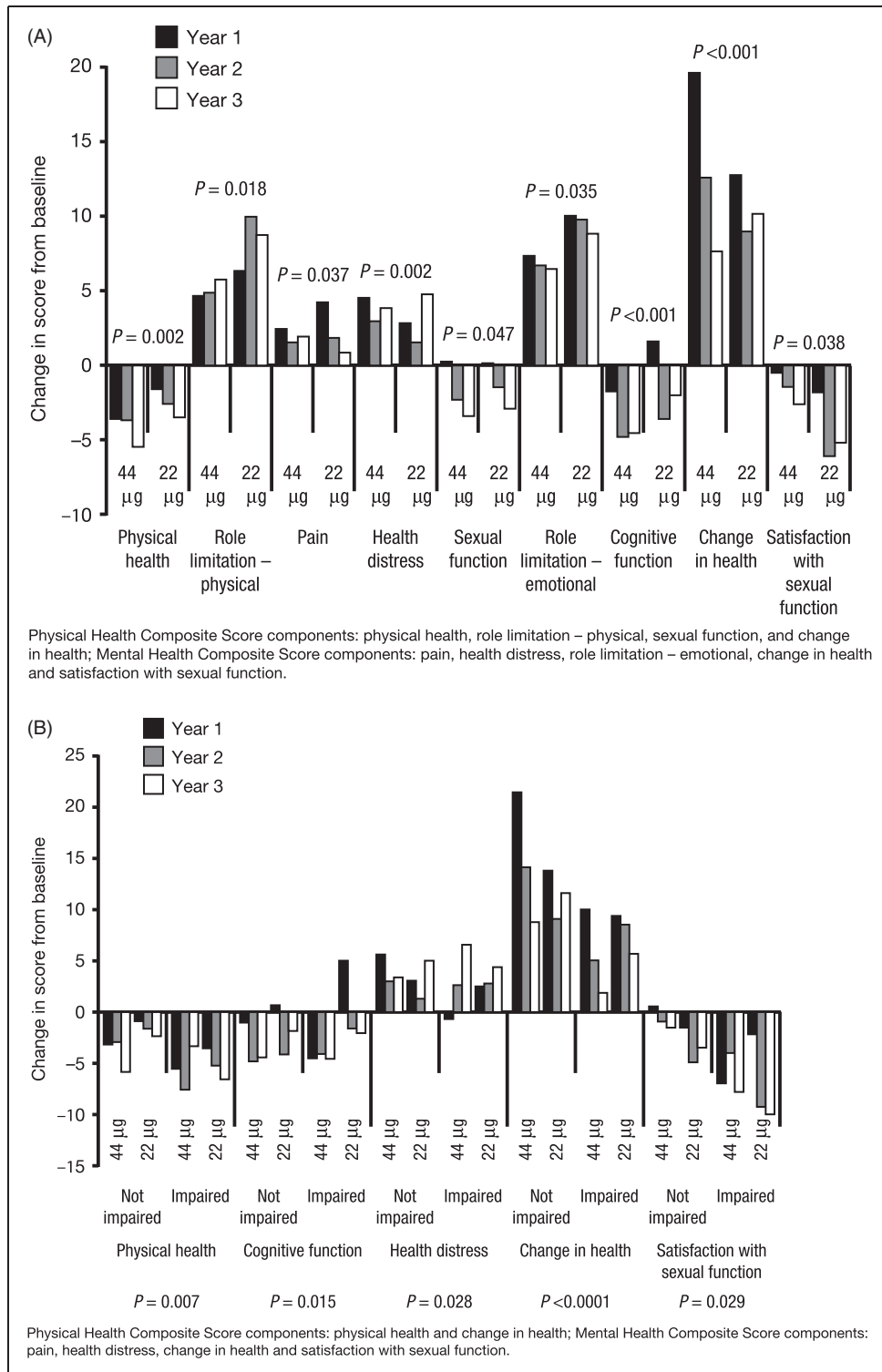


Figure 1. Significant changes over time in Multiple Sclerosis Quality of Life (MSQoL)-54 subscale scores by (A) treatment group (two-group analysis), and (B) treatment group and presence/absence of cognitive impairment at baseline (four-group analysis), analysed by analysis of variance for repeated measures. Increasing scores indicate improved quality of life.

Table 2. Fatigue Impact Scale (FIS) scores over time

FIS score		Year 1			Year 2			Year 3				
		N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)		
FIS cognitive subscale score												
All patients	330	5.5 (7.1)	3 (0-36)	322	5.6 (6.6)	4 (0-36)	317	6.0 (7.0)	3.0 (0-39)	318	6.2 (7.3)	3 (0-35)
IFN β -1a, 44 μ g sc tiw	168	5.6 (7.4)	2.5 (0-36)	168	5.8 (6.5)	4 (0-32)	163	6.4 (7.2)	4 (0-36)	165	6.5 (7.5)	4 (0-35)
IFN β -1a, 22 μ g sc tiw	162	5.5 (6.8)	3 (0-27)	154	5.4 (6.8)	3 (0-36)	154	5.5 (6.8)	3 (0-39)	153	5.9 (7.0)	3 (0-29)
FIS physical subscale score												
All patients	330	8.2 (7.8)	6 (0-39)	322	8.1 (7.6)	6 (0-36)	317	8.5 (8.3)	6 (0-35)	318	8.6 (8.3)	6 (0-35)
IFN β -1a, 44 μ g sc tiw	168	8.4 (7.8)	7 (0-39)	168	8.3 (7.5)	6 (0-32)	163	9.1 (8.8)	6 (0-32)	165	9.2 (8.3)	7 (0-35)
IFN β -1a, 22 μ g sc tiw	162	8.1 (7.9)	5.5 (0-34)	154	7.8 (7.7)	6 (0-35)	154	7.8 (7.6)	6 (0-35)	153	7.9 (8.3)	5 (0-35)
FIS social subscale score												
All patients	330	12.0 (12.3)	9 (0-59)	322	11.7 (12.0)	8 (0-70)	317	12.3 (12.6)	8 (0-56)	316	12.7 (13.6)	8 (0-60)
IFN β -1a, 44 μ g sc tiw	168	12.0 (12.2)	9 (0-59)	168	12.1 (11.4)	9 (0-45)	163	13.2 (12.6)	9 (0-56)	163	13.4 (13.7)	9 (0-58)
IFN β -1a, 22 μ g sc tiw	162	11.9 (12.4)	8 (0-56)	154	11.4 (12.6)	8 (0-70)	154	11.4 (12.4)	7 (0-56)	153	11.9 (13.5)	6 (0-60)
Total FIS score												
All patients	330	25.7 (25.6)	18.0 (0-134)	322	25.4 (24.8)	17.5 (0-132)	317	26.7 (26.4)	17.0 (0-129)	316	27.3 (27.5)	17.0 (0-119)
IFN β -1a, 44 μ g sc tiw	168	25.9 (25.4)	17.5 (0-134)	168	26.1 (23.7)	17.5 (0-90)	163	28.6 (27.0)	19 (0-122)	163	28.7 (27.6)	20 (0-119)
IFN β -1a, 22 μ g sc tiw	162	25.5 (25.8)	18 (0-115)	154	24.6 (25.9)	17.5 (0-132)	154	24.7 (25.6)	16 (0-129)	153	25.8 (27.5)	16 (0-119)

IFN, interferon; sc, subcutaneous; SD, standard deviation; tiw, three times weekly.

or depression. Baseline total FIS score predicted for worse QoL and fatigue, but better depressive outcomes at study end. Higher EDSS score predicted worse QoL, in terms of both MSQoL-54 PHCS and MHCS.

Table 3. ANCOVA analysis showing significant confounding variables for global MSQoL-54 score, total Fatigue Impact Scale (FIS) score and Hamilton Depression Rating Scale (HDRS) score at 3 years

Variable	Estimate	p value
Global MSQoL-54 score		
Intercept	57.37	<0.0001
Age	-0.40	<0.0001
Baseline HDRS score	-0.50	0.007
Baseline QoL	0.38	<0.0001
Baseline FIS total score	-0.09	0.02
Total FIS score		
Intercept	-10.92	0.0423
Age	0.42	0.005
Baseline HDRS score	0.95	0.0007
Baseline EDSS score	2.37	0.0577
Baseline FIS total score	0.55	<0.0001
HDRS score		
Intercept	9.58	0.0079
Baseline HDRS score	0.52	<0.0001
Baseline EDSS score	0.65	0.0187
Baseline FIS total score	0.06	<0.0001
Total IQ score	-0.09	0.005

ANCOVA, analysis of covariance; EDSS, Expanded Disability Status Scale; IQ, intelligence quotient; MSQoL, Multiple Sclerosis Quality of Life; QoL, quality of life.

Discussion

Complex interrelationships exist among cognition, QoL, fatigue and depression in MS,^{13-15,19,21} to which both physical and psychological components may contribute. In the present study of patients with mild physical disability, QoL, depression and fatigue all remained relatively stable and outcomes were similar in both treatment groups. Overall, patients had high QoL scores, mild depressive symptoms, high cognitive reserve (high IQ scores) and a high level of education. In addition, cognitive performance at baseline did not influence these measures: only the 'sexual function' and 'change in health' subscales of the MSQoL-54 differed significantly between patients with and without cognitive impairment. While this finding may seem unexpected, it may be because QoL was a subjective assessment (patient-reported MSQoL-54) whereas cognitive function was assessed objectively by a neuropsychologist. It is possible that cognitively impaired patients were not aware of disease-related deficits that were detected by neuropsychological tests, and so those with cognitive impairment actually reported a better QoL than those without.

The lack of change in QoL composite scores over 3 years is noteworthy, and probably results from significant improvement or deterioration in individual subscales. Comparable QoL has been reported in mildly disabled patients and in control subjects,³¹ suggesting that changes in QoL may be difficult to detect in patients with mild MS. Nonetheless, in a recent study of patients with mild disability, worse QoL after 2 years was found in those who discontinued treatment.³²

Table 4. Variables predictive of clinically relevant changes over time in quality of life (QoL), fatigue and depression, determined by multivariate logistic regression models

Parameter	Baseline variable	OR	95% CI	Change
QoL	Age	1.05	(1.01-1.09)	Worsened
	QoL	1.07	(1.04-1.10)	Worsened
	FIS total score	1.02	(1.01-1.04)	Worsened
	Total IQ score	0.96	(0.93-0.99)	Improved
PHCS	EDSS score	1.44	(1.04-1.99)	Worsened
	Total IQ score	0.96	(0.93-0.99)	Improved
MHCS	EDSS score	1.62	(1.14-2.30)	Worsened
	MHCS	1.02	(1.00-1.04)	Worsened
	Total IQ score	0.93	(0.89-0.96)	Improved
FIS total score	FIS total score	1.05	(1.03-1.07)	Worsened
	Time in formal education	1.22	(1.06-1.40)	Worsened
HDRS score	HDRS score	1.36	(1.25-1.47)	Worsened
	FIS total score	0.98	(0.97-0.99)	Improved

CI, confidence interval; EDSS, Expanded Disability Status Scale; FIS, Fatigue Impact Scale; HDRS, Hamilton Depression Rating Scale; IQ, intelligence quotient; MHCS, Mental Health Composite Score; OR, odds ratio; PHCS, Physical Health Composite Score.

In addition, historical data indicate that QoL deteriorates over 2 years in untreated patients with RRMS,³⁰ suggesting that our results may possibly reflect a protective effect of sc IFN β -1a on QoL. Similarly, little change in QoL over 1 year has been reported in patients treated with intramuscular IFN β -1a.³³ However, the effect of IFN β on QoL in MS is currently unclear; most previous studies found that IFN β treatment improved QoL,^{31,32,34,35} but in one small study worsened QoL was seen.¹²

Patients in the present analysis had high cognitive reserves (IQ score >102), which may have protected against cognitive decline, as previously reported.^{23,36} Indeed, baseline total IQ score predicted for better QoL, possibly reflecting better coping strategies or greater employability among patients with a higher IQ, both of which likely impact on perceived QoL.³⁷ As higher cognitive reserves can reduce the effects of brain disease on cognition,³⁶ this, together with any protective effects of treatment, could have helped to preserve QoL.

Events influencing patient perception of different aspects of QoL will differ for different subscales. It is interesting that the 'cognitive function' subscale of MSQoL-54 deteriorated when an improvement in neuropsychologist-assessed cognitive function in the same study has been reported.²³ As discussed above, this discrepancy may reflect differences in patient-perceived cognitive impairment, measured subjectively using MSQoL-54, and cognitive performance measured objectively by a neuropsychologist. A patient's perception of cognitive performance and QoL may be influenced by many external factors, including general feeling of wellness and support networks, in addition to the actual disease status. Furthermore, treatment effects on physical symptoms such as relapses could explain the improvement in the 'role limitation – physical' subscale and a perceived or expected benefit of treatment may have positively affected the 'role limitation – emotional' subscale, which is influenced partly by depression. Indeed, HDRS scores were low throughout the study, and it is possible that the opportunity to start treatment and participate in a trial provided some reassurance and hope for disease control, promoting positive emotions. Consistent with this suggestion, we found that the proportion of patients with depression decreased over 3 years; furthermore, improving access to disease-modifying drugs has been identified as a means of enhancing QoL in patients with MS.³⁸ Thus, our results might reflect a beneficial effect of treatment on emotions in patients with MS.

Overall, our findings suggest that this patient group did not experience significant levels of fatigue, which may be due to the mild nature of their physical

disability. As with QoL, fatigue in MS is a complex issue. It has been reported that fatigue correlates with depression but not cognitive capacity.³⁹ In contrast, a correlation between information processing speed and fatigue has been reported,²⁰ while another study found that adjusting for depression revealed such a correlation.²¹ Impaired attention, information processing speed and working memory could worsen cognitive fatigue, which may explain the trend towards worsening cognitive fatigue over time reported here.

Several confounding factors and predictors of outcomes were identified. Depression was a confounding factor for QoL and fatigue. Fatigue was predictive of itself and of depression over time. Others have also observed a relationship between fatigue and depressive symptoms.^{7,8} These findings are unsurprising, as a subjective measure such as QoL will inevitably be influenced by factors such as the patient's mood and energy levels. The relationships among QoL, depression and fatigue outcomes suggest that treatment of MS-associated depression may also improve fatigue and QoL.⁷ In addition, as MS-related depression is believed to result from brain lesions in specific loci,^{1,40} treatment with disease-modifying drugs, such as IFN β , which reduce the development of MS brain lesions, could potentially have positive effects on depression, fatigue and QoL.

Interestingly, cognitive performance at baseline had little impact on other outcomes over 3 years. Other studies have also found QoL to be more strongly determined by psychological factors, including mood, than by cognitive function,⁴¹ and have failed to find a correlation between QoL and cognitive function in a similar patient population.²¹ It is possible that the exclusion of patients with significant depression influenced our findings; this has previously been associated with a null correlation between cognition and depression.^{14,42}

The present study design has a number of limitations, as discussed in detail previously.²³ This was an observational study with patients assigned to treatment at the physician's discretion, so there was potential for selection bias. Only patients with mild RRMS were included in the study, so any findings are restricted to this MS population. A major limitation was the lack of an untreated control group, so treatment effects can only be speculated and not confirmed. QoL, depression or fatigue data at 3 years were also missing for a number of patients. In addition, compared with objective assessments, the subjective patient-reported assessments used here could have increased the likelihood of associations being found among depression, fatigue and QoL. There was much variation in individual scores for all outcomes, and analyses were not exhaustive as several other factors, such as social support and

coping, may also influence depression, cognitive function and fatigue in MS.¹⁴

In summary, QoL, depression and fatigue remained largely stable over 3 years in this study of patients receiving sc IFN β -1a, which could possibly reflect a protective effect of treatment, although this cannot be demonstrated due to the lack of an untreated control group. The potential benefits of sc IFN β -1a on these outcomes warrant further investigation. Treatment dose and baseline cognitive function did not affect outcomes over 3 years. Interactions were identified among QoL, depression and fatigue, but further studies are needed to unravel the complex relationships between these outcomes. Our findings support the expansion of the definition of clinical efficacy beyond relapse rate and disability to include QoL and its constituent factors, such as fatigue, depression and cognition,³ whereby improvement is optimal but preservation without worsening is still desirable.

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Conflict of interest statement

F Patti has received honoraria for consultancy or speaking from Biogen, sanofi-aventis, Merck Serono, Bayer Schering and Novartis. MP Amato has received honoraria for consultancy or speaking from Biogen, sanofi-aventis, Merck Serono, Bayer Schering and Novartis. M Trojano received honoraria for consultancy or speaking from Biogen, sanofi-aventis, Merck Serono, Bayer Schering and Novartis, and research grants from Merck Serono and Biogen. S Cilia has received honoraria for consultancy from the Cesare Serono Foundation. S Cottone has received personal compensation from CIC International for serving as a member of an editorial advisory board; and financial support for research activities from Biogen-Dompè. D Centonze has declared having served on scientific advisory boards for Teva Pharmaceutical Industries and Novartis; having received speaker honoraria and funding for travel from sanofi-aventis, Merck Serono, Serono Symposia International Foundation, Bayer Schering, and Biogen-Dompè; and having received research support from sanofi-aventis, Bayer Schering, Merck Serono, Novartis, and Teva Pharmaceutical Industries. C Gasperini has served as a consultant for Merck Serono and Biogen Idec; and has received speaker honoraria from Teva Pharmaceutical Industries, Merck Serono, Bayer Schering and Biogen Idec. S Bastianello, MR Tola, O Picconi and S Cottone have no conflicts of interest to declare.

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preparation of this manuscript. The manuscript has been reviewed by Merck Serono for the limited purpose of providing complete and balanced medical/scientific information and to ensure that the publication is objective and scientifically/medically accurate. The views and opinions described herein do not necessarily reflect those of Merck Serono. The COGIMUS Study Group consisted of the following investigators: Catania: F Patti, S Lo Fermo, D Maimone, S Messina, E D'Amico, V Cimino; Rome: C Gasperini, S Galgani; Naples: V Orefice, V Brescia Morra, C Florio; Florence: MP Amato, B Goretti, E Portaccio, V Zipoli; Orbassano: A Bertolotto; Messina: P Bramanti, E Sessa; Rome Tor Vergata: D Centonze; Palermo: S Cottone, G Salemi; Prato: M Falcini; Padova: P Gallo, P Perini; Udine: GL Gigli; Macerata: G Giuliani, S Pucci; Cefalù: LM Grimaldi; Pisa: L Murri; Chieti: A Lugaresi; Novara: F Monaco; Fidenza: E Montanari; Reggio Emilia: L Motti; Terni: S Neri; Potenza: M Paciello; Ancona: L Provinciali; Ascoli Piceno: M Ragno; Sassari: G Rosati; Pozzilli: S Ruggieri, P Bell'antonio; Ferrara: MR Tola, L Caniatti; Roma Gemelli: P Tonali, AP Batocchi; Bari: M Trojano, E Di Monte, MF De Caro; Gallarate: A Ghezzi, M Zaffaroni; Arezzo: P Zolo; Trieste: M Zorzon; Fermo: M Signorino; Milan: E Scarpini; Torino: L Durelli; L'Aquila: A Carolei, M Todaro, R Todaro; Avellino: D Spitaleri; La Spezia: A Tartaglione.

References

1. Ghaffar O and Feinstein A. The neuropsychiatry of multiple sclerosis: a review of recent developments. *Curr Opin Psychiatry* 2007; 20: 278–285.
2. Turpin KV, Carroll LJ, Cassidy JD and Hader WJ. Deterioration in the health-related quality of life of persons with multiple sclerosis: the possible warning signs. *Mult Scler* 2007; 13: 1038–1345.
3. Foley JF and Brandes DW. Redefining functionality and treatment efficacy in multiple sclerosis. *Neurology* 2009; 72(Suppl.): S1–S11.
4. Rothwell PM, McDowell Z, Wong CK and Dorman PJ. Doctors and patients don't agree: cross sectional study of patients' and doctors' perceptions and assessments of disability in multiple sclerosis. *BMJ* 1997; 314: 1580–1583.
5. Arnett PA, Higginson CI, Voss WD, Bender WI, Wurst JM and Tippin JM. Depression in multiple sclerosis: relationship to working memory capacity. *Neuropsychology* 1999; 13: 546–556.
6. Lester K, Stepleman L and Hughes M. The association of illness severity, self-reported cognitive impairment, and perceived illness management with depression and anxiety in a multiple sclerosis clinic population. *J Behav Med* 2007; 30: 177–186.
7. Patrick E, Christodoulou C and Krupp LB. Longitudinal correlates of fatigue in multiple sclerosis. *Mult Scler* 2009; 15: 258–261.
8. Penner IK, Bechtel N, Raselli C, Stocklin M, Opwis K, Kappos L, et al. Fatigue in multiple sclerosis: relation to depression, physical impairment, personality and action control. *Mult Scler* 2007; 13: 1161–1167.
9. Amato MP, Ponziani G, Rossi F, Liedl CL, Stefanile C and Rossi L. Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. *Mult Scler* 2001; 7: 340–344.

10. Janardhan V and Bakshi R. Quality of life in patients with multiple sclerosis: the impact of fatigue and depression. *J Neurol Sci* 2002; 205: 51–58.
11. Patti F, Cacopardo M, Palermo F, Ciancio MR, Lopes R, Restivo D, et al. Health-related quality of life and depression in an Italian sample of multiple sclerosis patients. *J Neurol Sci* 2003; 211: 55–62.
12. Simone IL, Ceccarelli A, Tortorella C, Bellacosa A, Pellegrini F, Plasmati I, et al. Influence of interferon beta treatment on quality of life in multiple sclerosis patients. *Health Qual Life Outcomes* 2006; 4: 96.
13. Ziemssen T. Multiple sclerosis beyond EDSS: depression and fatigue. *J Neurol Sci* 2009; 277(Suppl. 1): S37–S41.
14. Arnett PA, Barwick FH and Beeney JE. Depression in multiple sclerosis: review and theoretical proposal. *J Int Neuropsychol Soc* 2008; 14: 691–724.
15. Pittion-Vouyovitch S, Debouverie M, Guillemin F, Vandenberghe N, Anxionnat R and Vespignani H. Fatigue in multiple sclerosis is related to disability, depression and quality of life. *J Neurol Sci* 2006; 243: 39–45.
16. Amato MP, Zipoli V and Portaccio E. Multiple sclerosis-related cognitive changes: a review of cross-sectional and longitudinal studies. *J Neurol Sci* 2006; 245: 41–46.
17. Patti F, Amato M, Trojano M, Bastianello S, Tola M, Goretti B, et al. Cognitive impairment and its relation with disease measures in mildly disabled patients with relapsing–remitting multiple sclerosis: baseline results from the Cognitive Impairment in Multiple Sclerosis (COGIMUS) study. *Mult Scler* 2009; 15: 779–788.
18. Patti F. Cognitive impairment in multiple sclerosis. *Mult Scler* 2009; 15: 2–8.
19. Simioni S, Ruffieux C, Bruggimann L, Annoni JM and Schlupe M. Cognition, mood and fatigue in patients in the early stage of multiple sclerosis. *Swiss Med Wkly* 2007; 137: 496–501.
20. Andreasen AK, Spliid PE, Andersen H and Jakobsen J. Fatigue and processing speed are related in multiple sclerosis. *Eur J Neurol* 2010; 17: 212–218.
21. Glanz BI, Healy BC, Rintell DJ, Jaffin SK, Bakshi R and Weiner HL. The association between cognitive impairment and quality of life in patients with early multiple sclerosis. *J Neurol Sci* 2010; 290: 75–79.
22. Winkelmann A, Engel C, Apel A and Zettl UK. Cognitive impairment in multiple sclerosis. *J Neurol* 2007; 254(Suppl. 2): II35–II42.
23. Patti F, Amato MP, Bastianello S, Caniatti L, Di Monte E, Ferrazza P, et al. Effects of immunomodulatory treatment with subcutaneous interferon beta-1a on cognitive decline in mildly disabled patients with relapsing–remitting multiple sclerosis. *Mult Scler* 2010; 16: 68–77.
24. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR*, 4th edn. Washington, DC: American Psychiatric Publishing, 1994.
25. Amato MP, Portaccio E, Goretti B, Zipoli V, Ricchiuti L, De Caro MF, et al. The Rao's Brief Repeatable Battery and Stroop Test: normative values with age, education and gender corrections in an Italian population. *Mult Scler* 2006; 12: 787–793.
26. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1967; 6: 278–296.
27. Fisk JD, Ritvo PG, Ross L, Haase DA, Marris TJ and Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis* 1994; 18(Suppl. 1): S79–S83.
28. Møllerup E, Fog T, Raun N, Colville P, De Rham B, Hannah B, et al. The socio-economic scale. *Acta Neurol Scand* 1981; 64: 130–138.
29. Colombo L, Sartori G and Brivio C. La stima del quoziente intellettuale tramite l'applicazione del TIB (Test di Intelligenza Breve). *G Ital Psicol* 2002; 3: 613–637.
30. Rudick RA, Miller D, Hass S, Hutchinson M, Calabresi PA, Confavreux C, et al. Health-related quality of life in multiple sclerosis: effects of natalizumab. *Ann Neurol* 2007; 62: 335–346.
31. Jongen PJ, Sindic C, Carton H, Zwanikken C, Lemmens W and Borm G. Improvement of health-related quality of life in relapsing remitting multiple sclerosis patients after 2 years of treatment with intramuscular interferon-beta-1a. *J Neurol* 2010; 257: 584–589.
32. Wu N, Minden SL, Hoaglin DC, Hadden L and Frankel D. Quality of life in people with multiple sclerosis: data from the Sonya Slifka Longitudinal Multiple Sclerosis Study. *J Health Hum Serv Adm* 2007; 30: 233–267.
33. Zivadinov R, Zorzon M, Tommasi MA, Nasuelli D, Bernardi M, Monti-Bragadin L, et al. A longitudinal study of quality of life and side effects in patients with multiple sclerosis treated with interferon beta-1a. *J Neurol Sci* 2003; 216: 113–118.
34. Lobentanz IS, Asenbaum S, Vass K, Sauter C, Klosch G, Kollegger H, et al. Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. *Acta Neurol Scand* 2004; 110: 6–13.
35. Putzki N, Fischer J, Gottwald K, Reifschneider G, Ries S, Siever A, et al. Quality of life in 1000 patients with early relapsing–remitting multiple sclerosis. *Eur J Neurol* 2009; 16: 713–720.
36. Sumowski JF, Wylie GR, Chiaravalloti N and DeLuca J. Intellectual enrichment lessens the effect of brain atrophy on learning and memory in multiple sclerosis. *Neurology* 2010; 74: 1942–1945.
37. Patti F, Pozzilli C, Montanari E, Pappalardo A, Piazza L, Levi A, et al. Effects of education level and employment status on HRQoL in early relapsing–remitting multiple sclerosis. *Mult Scler* 2007; 13: 783–791.
38. Hopman WM, Coo H, Pavlov A, Day AG, Edgar CM, McBride EV, et al. Multiple sclerosis: change in health-related quality of life over two years. *Can J Neurol Sci* 2009; 36: 554–561.
39. Morrow SA, Weinstock-Guttman B, Munschauer FE, Hojnacki D and Benedict RH. Subjective fatigue is not associated with cognitive impairment in multiple sclerosis: cross-sectional and longitudinal analysis. *Mult Scler* 2009; 15: 998–1005.
40. Bakshi R, Czarnecki D, Shaikh ZA, Priore RL, Janardhan V, Kaliszky Z, et al. Brain MRI lesions and atrophy are related to depression in multiple sclerosis. *Neuroreport* 2000; 11: 1153–1158.

41. Benedict RH, Wahlig E, Bakshi R, Fishman I, Munschauer F, Zivadinov R, et al. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *J Neurol Sci* 2005; 231: 29–34.
42. Good K, Clark CM, Oger J, Paty D and Klonoff H. Cognitive impairment and depression in mild multiple sclerosis. *J Nerv Ment Dis* 1992; 180: 730–732.