

Cognition and fatigue in patients with relapsing multiple sclerosis treated by subcutaneous interferon β -1a: an observational study SKORE

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Abstract

Background: Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system, which often causes progressive neurological disability. In addition to motor and sensory dysfunction, cognitive decline and fatigue are frequent manifestations of the disease. Fatigue is probably the most common symptom, with up to 90% of MS individuals reporting fatigue at some point. Cognitive impairment affects about 50% of patients and may be present at all MS stages. The aim of this observational study was to evaluate changes in cognition, fatigue, and disability status in 300 relapsing–remitting MS (RRMS) patients, treated with subcutaneous (sc) interferon (IFN) β -1a over 2 years.

Methods: The study was designed as an observational, multicentre, prospective, single-arm, phase IV study carried out in 13 MS centres in the Czech Republic. Cognition status was assessed using the Paced Auditory Serial Addition Task (PASAT), fatigue using the Fatigue Descriptive Scale (FDS), and disability using the Expanded Disability Status Scale (EDSS), at baseline, and after 6, 12 and 24 months. The percentage of patients with changed *versus* stable cognition, fatigue status and disability was calculated at each time point and the changes in these scores were evaluated.

Results: The proportion of patients with cognitive improvement was higher compared with those with a stable or decreased PASAT scores at all time points, and the average cognitive performance improved during the follow-up period. Also the proportion of patients with stable or improved fatigue and EDSS scores was higher compared with those in which FDS or EDSS scores declined, this was found at all time points of the analysed sample. However, the direct effect of IFN β -1a on cognition and fatigue cannot be concluded from this study.

Conclusions: The results of this observational study have demonstrated a stable or improved cognitive performance, fatigue status, and disability level in the majority of RRMS patients treated with sc IFN β -1a over a two-year follow-up period, in a real life setting, in the Czech Republic.

Keywords: cognitive impairment, fatigue, interferon β -1a, multiple sclerosis, treatment

Background

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) leading to demyelination and axonal damage, with subsequent degeneration, which causes progressive neurological disability [Hartung *et al.* 2004]. In addition to motor and sensory dysfunctions, progression of cognitive decline and fatigue are

frequent manifestations of the disease [Krupp *et al.* 2010; Lincoln *et al.* 2002].

Fatigue is probably the most common symptom of MS, with the majority of individuals (up to 90%) reporting fatigue at some point in their disease course [Krupp *et al.* 2010; Lerdal *et al.* 2007]. Fatigue is characterized by a lack of

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energy, feelings of exhaustion that are unaided by sleep, and the perception that one is unable to perform mental and physical activities [Harrington, 2012]; it is also frequently associated with anxiety and depression [Van Kessel and Moss-Morris, 2006].

One of the most characteristic features is the fluctuation of symptoms, which is usually exacerbated by exercise or an increased in body/ambient temperature (Uthoff symptom). Fatigue is often chronic and may occur with varying degrees of severity between mild and severely disabling [Fisk *et al.* 1994]. It is a significant symptom of MS that can negatively affect the patient's quality of life and socio-economic functions, including the ability to work, the effects of which are independent of the direct effects of disability [Bakshi *et al.* 2000; Lobentanz *et al.* 2004; Merkelbach *et al.* 2002]. Fatigue can be classified as physical or mental, with the mental part affecting working memory, processing speed, and other activities that require maintenance of mental effort [Ferreira, 2010]. The pathogenesis of chronic fatigue syndrome is unknown. Dobryakova and colleagues [Dobryakova *et al.* 2013] proposed that fatigue is caused by a dopamine imbalance within the CNS.

Cognitive impairment often occurs in patients with MS, affecting between 43% and 70% of patients [Rao, 1995] and may be present at stages ranging from clinically isolated syndrome (CIS) to relapsing or progressive forms of MS [Amato *et al.* 2006, 2010; Glanz *et al.* 2007; Langdon, 2011; Patti, 2009].

The pattern of cognitive impairment in MS is characterized by deficits in sustained attention, verbal and nonverbal memory, conceptual reasoning, and information processing speed, while language and intellectual functions are preserved [Amato *et al.* 2006; Rao, 1995]. The factors that have been shown to influence cognitive impairment in MS are disease course and duration [Amato *et al.* 2006], affective disturbance, and medication [Rogers and Panegyres, 2007]. It appears to be strongly related to brain magnetic resonance imaging (MRI) parameters, especially atrophy [Filippi *et al.* 2010], grey matter (GM) lesions and GM atrophy [Klaver *et al.* 2013], which are present from the earliest stages of the disease and increase with disease progression. Recent studies have demonstrated

significant GM demyelination and microglia activation [Klaver *et al.* 2013]. Candidate genetic risk factors, accelerated inflammatory processes [Benedict and Zivadinov, 2011] and dysregulated signalling pathways [Dutta *et al.* 2011] have been implicated as contributing factors. Rahn and colleagues [Rahn *et al.* 2012] found that right hippocampal NAAG/creatine (Cr) concentrations positively correlated with cognitive function in MS patients. Some studies have also described an association between cognitive impairment and fatigue [Andreasen *et al.* 2010; Cameron *et al.* 2014].

The most useful measurement of disability in MS patients is the Expanded Disability Status Scale (EDSS) [Kurtzke, 1983]. However, the scale provides only a rudimentary estimate of cognitive function [Marrie and Goldman, 2007; Meyer-Moock *et al.* 2014] and in many studies no correlations were found between cognitive deficits, fatigue, and disability when assessed using the EDSS [Bakshi *et al.* 2000; Polman and Rudick, 2010]. The reason is that the EDSS primarily evaluates motor functions and has low sensitivity relative to cognitive deficits.

Therefore, other scales for the assessment of fatigue and cognitive functions have been developed and recommended. A widely used test is the Paced Auditory Serial Addition Task (PASAT). The PASAT is a measure of cognitive function that specifically assesses auditory information processing speed and flexibility, as well as calculation ability. It was initially developed by Gronwall [Gronwall, 1977] to monitor recovery of patients who had sustained mild head injuries. It was adapted for use in MS patients [Rao *et al.* 1991] and has been widely used in MS studies during the last decade. This test has been used to monitor therapeutic efficacy of disease-modifying drugs (DMDs) on cognition [Fischer *et al.* 1999; Kappos *et al.* 2009].

Several scales have been developed to measure fatigue. One of them, the Fatigue Descriptive Scale (FDS) was developed by Krupp and colleagues [Krupp *et al.* 1989] and has been tested in patients with MS and systemic lupus erythematosus. The FDS evaluates and measures the severity of MS related fatigue, which is defined by some of its characteristics, and provides information regarding the impact of fatigue on daily living [Iriarte *et al.* 1999]. The FDS has been validated.

Table 1. Summary of reasons for early termination of sc IFN β -1a treatment during the observational period, by subgroups.

Reason for the early termination	Subgroup by sc IFN β -1a dosage			Total
	22 μ g thrice in week	44 μ g thrice in week	Dose escalation	
Disease progression	5	3	4	12
Liver tests elevation	2	-	-	2
Pregnancy	3	-	-	3
Leukopenia	1	-	-	1
Tolerability issue: injection site reaction	2	2	1	5
Patient's decision	1	1	-	2
Participation in a clinical trial	1	-	-	1
Change of location	1	-	-	1
Out of reimbursement criteria	1	-	-	1
Sum	17	6	5	28

Material and methods

Study purpose and design

The purpose of this study was to evaluate cognition, fatigue, and neurological disability in relapsing–remitting MS (RRMS) patients treated with sc IFN β -1a (Rebif[®]) over two years. The study was designed as an observational, multicentre, single-arm, phase IV study carried out in 13 MS centres in the Czech Republic between March 2009 and June 2013.

Patient characteristics

The baseline group consisted of 300 White patients fulfilling the McDonald [McDonald *et al.* 2001] criteria for MS with a mean (standard deviation [SD]) age of 36.33 (10.04) years, of whom 198 (66.6%) were females. The mean (SD) duration of the disease was 61.6 (5.63) months, the mean annualized relapse rate (SD) was 1.15 (0.91) during the 2 years prior to baseline. Two patients discontinued prior to month 6, seven by month 12, and 19 by month 24. Overall, 272 (90.7%) patients completed a 2-year follow-up period, and represent the analysed population. The reasons for early termination of Rebif treatment are summarized in Table 1. The frequency of the early discontinuation did not differ between the subgroups ($p=0.3592$).

Patients were eligible for enrolment in the study if they fulfilled the following criteria: diagnosis of RRMS; 18–65 years of age; EDSS score < 4 and treatment with sc IFN β -1a starting no more than

3 months prior to their baseline visit. Enrolment of patients and follow-up visits were performed during routine neurological visits to MS centres.

All patients were treated with subcutaneous IFN β -1a (Rebif[®]). Therapy was initiated with a titration pack, 8.8 mcg, followed by 22 or 44 mcg 3x/week (tiw) thereafter.

The study was approved by the Ethics Committee of the local Association of Innovative Pharmaceutical Industry (AIFP), and the regulatory authority; the State Institution for Drug Control was also notified of the study. All persons gave their informed consent prior to enrolment in the study.

Primary objective and endpoint

The primary objective was to assess cognition and its changes. The cognition status was assessed using the PASAT at defined time points (baseline, months 6, 12 and 24) in all patients. The percentage of patients with either decreased, increased or stable cognition status was calculated for each time point. The PASAT score and its changes were also expressed in terms of descriptive statistics (mean, standard deviation) at each time point.

The PASAT was presented on an audiocassette tape or compact disc to control the rate of stimulus presentation. Single digits were presented every 3 seconds, and the patient was tasked with adding each new digit to the one immediately

preceding it. The test score was the total number of correct responses and ranged from 0 to 60 on each trial.

In order to minimize the learning effect, two PASAT forms (A and B) were used alternatively on subsequent visits. Thus, the interval between testing with same form was 12 months for each patient. As a result, each form was never used more than twice per patient during the study period.

Secondary objective and endpoint

The secondary objective was to assess fatigue and its changes. We also assessed correlations between cognition, fatigue and disability status. In addition, we assessed differences in the cognition, fatigue, and disability in patients with different sc IFN β -1a dosages.

Fatigue level and disability were assessed using the FDS and EDSS, respectively, at the defined time points (baseline, months 6, 12 and 24) in all patients. The percentage of patients with either decreased, increased, or stable fatigue levels and disability status was evaluated for each time point. FDS and EDSS scores and changes in scores were assessed at baseline as well as months 6, 12 and 24. Results are presented using descriptive statistics for each time point as well as trend changes over the 2-year study period, relative to each time point.

Fatigue was evaluated using the FDS. The FDS was designed specifically to measure the severity, and to define the characteristics of MS fatigue. The questionnaire contained 12 items and assesses four domains. It included information regarding the modality of fatigue: spontaneity in the narration of the symptoms, severity, frequency and Uhthoff's phenomenon. Uhthoff's phenomenon is a transient worsening of neurological symptoms in MS when the body gets overheated. Each of the 12 items was scored on a 4-point scale, except for the Uhthoff domain items, which was scored as either 'yes' or 'no' answers. The range of the scale was from 0–17 points. Zero points means that fatigue was not present with higher scores indicating progressively greater levels of fatigue.

Neurological disability was assessed using the EDSS score [Kurtzke, 1983]. The EDSS score assesses 8 functional systems with each system

scored on a 0 (normal) to 10 (maximal impairment) scale. The EDSS (complete) is measured in half points on a 0.0 (normal neurologic exam) to 10.0 (death due to MS) scale.

Statistical analysis

Statistical analysis was performed using SAS software (SAS Institute Inc., Cary, NC, USA) and Statistica Software (StatSoft, Inc., Tulsa, OK, USA). Statistical analyses were performed on all available data ($N=300$), and separately on those patients who completed the whole study period ($n=272$), i.e. baseline, months 6, 12 and 24. The latter sample results are presented here.

For the primary endpoint analysis, changes in the PASAT score from baseline to months 6, 12 and 24 were calculated, along with the percentage of patients with decreased, increased or stable cognitive status. The PASAT score was also expressed in terms of descriptive statistics (mean, standard deviation) at each time point. Descriptive statistics [all data were evaluated descriptively by number (n), mean, SD for continuous variables, and by counts and percentages for categorical variables].

For the secondary endpoint analyses, the changes in FDS and EDSS scores from baseline to months 6, 12 and 24 were calculated, along with the percentage of patients with decreased, increased or stable fatigue or disability levels. The FDS and EDSS scores were also expressed using descriptive statistics (mean, SD) at each time point.

The relationship between the PASAT, FDS and EDSS scores was assessed using Spearman's correlation coefficient at the given time points.

Differences from baseline to follow-up measurement points (months 6, 12 and 24) were evaluated using the paired Wilcoxon test. The development of PASAT, FDS and EDSS scores across all four time points was tested separately using the Friedman analysis of variance (ANOVA; one p value for each score) in all samples, and for each subgroup separately. The parametric repeated ANOVA was used for testing the interactions, that is, differences from baseline to each time point for each score separately in all samples, and for each subgroup separately.

For evaluation of differences relative to sc IFN β -1a dosage, the sample was divided into three

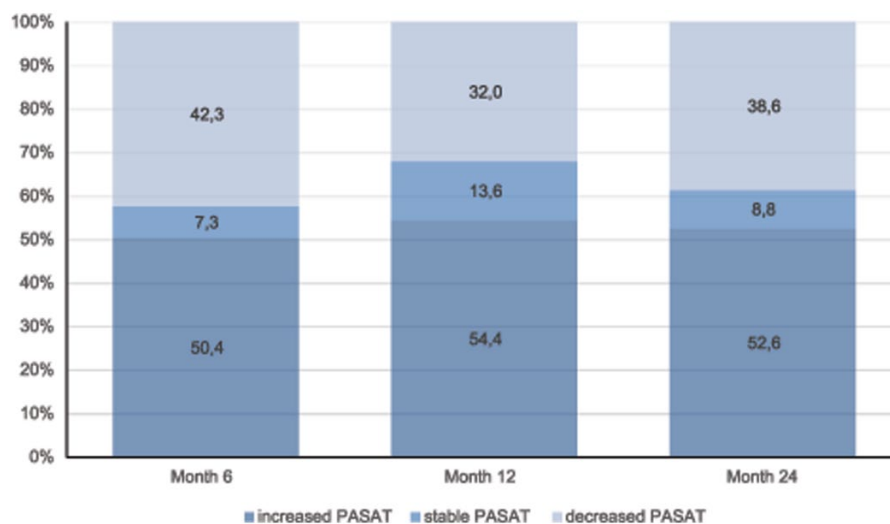


Figure 1. Overall proportion of patients with increased, stable or decreased Paced Auditory Serial Addition Task (PASAT) scores *versus* baseline for each time point.

subgroups: (1) low-dose, those treated with 22 µg tiw; (2) high-dose, 44 µg tiw during the whole follow-up period; and (3) dose-escalation, those who experienced dose escalation from 22 to 44 µg tiw. In each subgroup the following numbers were calculated at the defined time points:

- proportion of patients with increased, stable, or decreased PASAT scores;
- proportion of patients with decreased, stable, or increased FDS scores;
- proportion of patients with improved, stable, or worsened EDSS scores;
- descriptive statistics for the PASAT, FDS and EDSS, and comparison of its development and changes;
- correlation among the PASAT, FDS and EDSS in all samples and in all three subgroups.

Differences between subgroups with regard to Rebif dosage were analysed nonparametrically using a nonparametric ANOVA (Kruskal–Wallis test, Wilcoxon Two-Sample Test) for numerically continuous variables, and the chi-square test for categorical ordinal variables. Values of $p \leq 0.05$ were considered statistically significant.

A correlation among PASAT, FDS and EDSS scores was calculated in total, and for each subgroup separately at each time point using Spearman's correlation coefficient with the correlation size defined as follows: 0.90–1.00 very

high; 0.70–0.89 high; 0.50–0.69 moderate; 0.30–0.49 low; and 0.00–0.29 little if any.

Results

Cognition

Overall, the proportion of patients with an increased or stable PASAT score was higher compared with those with decreased PASAT scores at all time points, and the average cognitive performance improved over the 2-year follow-up period.

In the analysed population ($n = 272$), the proportion of patients with an increased or stable PASAT score vs baseline was 57.7% at 6 months, 68.0% at 12 months and 61.4% at 24 months (the end of the 2-year follow-up period). Additional information regarding patients with an increased, stable or decreased PASAT scores at each time point is shown in Figure 1. The mean (SD) PASAT score increased from a baseline value of 48.42 (9.09) to 49.98 (8.00) at month 24. The mean PASAT score by time points is detailed in Figure 2. The increase in the mean PASAT score was statistically significant throughout the follow-up period ($p = 0.00026$), and the pair test demonstrated a statistically significant increase in the PASAT score compared to the baseline at each time point, that is, at 6 months ($p = 0.006$), 12 months ($p = 0.001$) and 24 months ($p = 0.004$).

In subgroup analyses of the 24 months visit, a stable or improved PASAT score was reported in

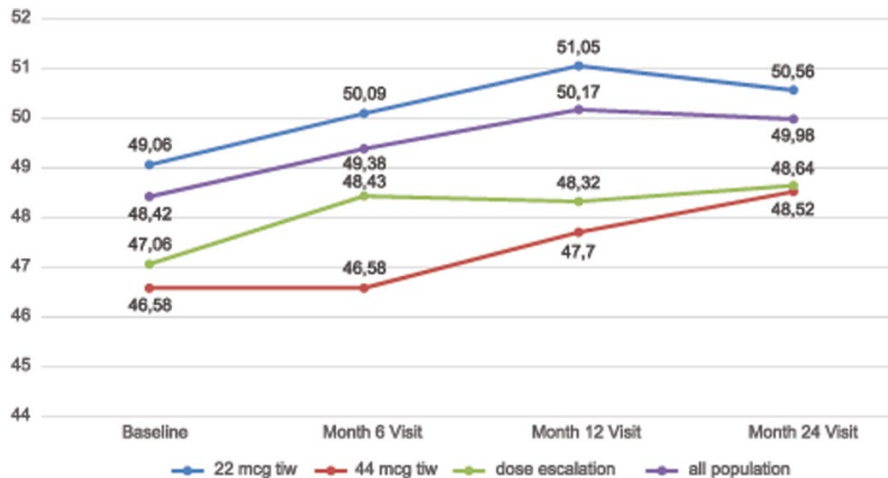


Figure 2. Total mean Paced Auditory Serial Addition Task (PASAT) scores and for subgroups for all time points.

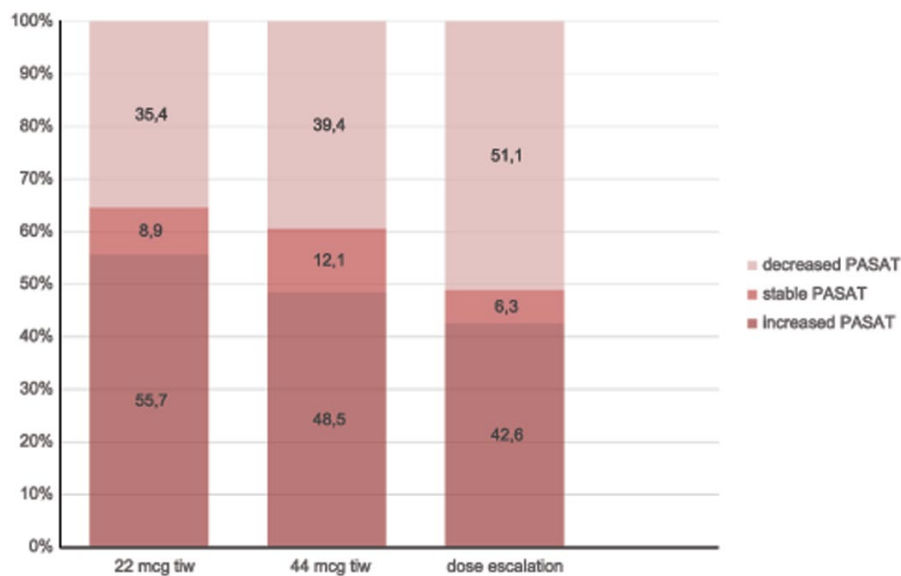


Figure 3. Proportion of patients with increased, stable or decreased Paced Auditory Serial Addition Task (PASAT) scores at 24 months versus baseline, by subgroups.

64.6%, 60.6% and 48.9% of patients in the low-dose, high-dose and dose-escalation subgroups, respectively. The proportion of patients with an increased, stable or decreased PASAT score in each subgroup at the month 24 visit is detailed in Figure 3. The mean PASAT score at each time point in each subgroup is detailed in Figure 2. The increase in the mean PASAT score throughout the defined time points reached statistical significance in the low-dose subgroup ($p=0.0004$), and was not significant in the high-dose ($p=0.293$) and dose escalation ($p=0.798$) subgroups. Comparisons of the mean PASAT scores at each time point showed an increase in all subgroups

($p=0.0001$) with no difference in mean values ($p=0.06$) or the change, over time, among subgroups ($p=0.52$).

Furthermore, comparisons of PASAT score differences from baseline among subgroups showed no statistical significance at month 6 ($p=0.40$), month 12 ($p=0.53$) or month 24 ($p=0.75$).

Fatigue

In the analysed sample ($n=272$), the proportion of patients with stable or improved fatigue status

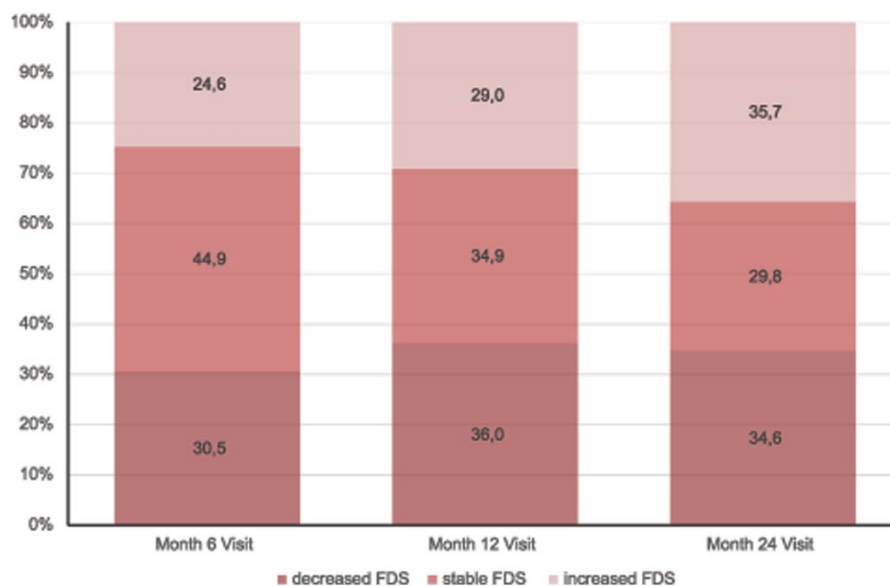


Figure 4. Overall proportion of patients with increased, stable or decreased Fatigue Descriptive Scale (FDS) score *versus* baseline for each time point.

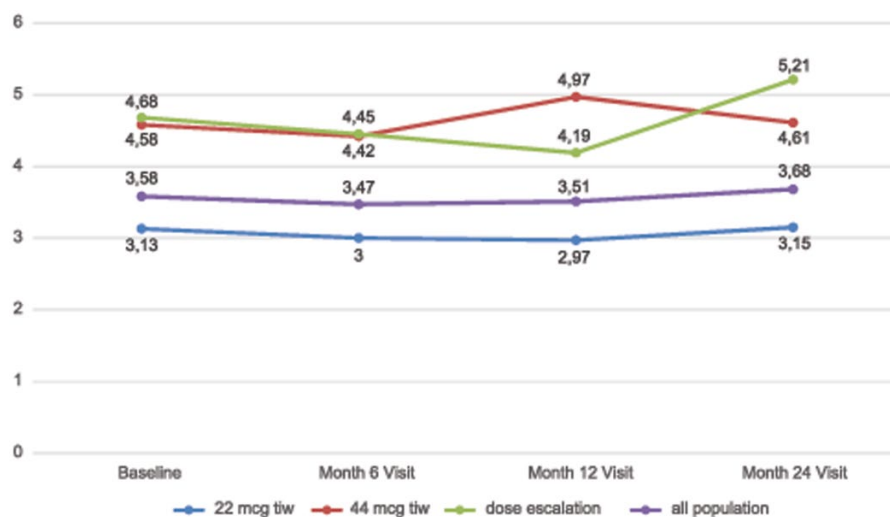


Figure 5. Total mean Fatigue Descriptive Scale (FDS) scores and for subgroups for all time points.

was higher compared with those with an increased FDS score at all time points.

The proportion of patients with a decreased or stable FDS score *versus* baseline was 75.4% at 6 months, 71.0% at 12 months and 64.3% at 24 months. Additional information regarding patients with a decreased or stable or increased FDS score at each time point is shown in Figure 4.

The mean (SD) FDS score was 3.58 (3.66) at baseline and 3.68 (3.83) at 24 months (Figure 5). There was no statistically significant change

during follow-up ($p=0.39036$). No statistically significant change in the FDS score at baseline, compared with each time point, month 6 ($p=0.6609$), month 12 ($p=0.6797$) and month 24 ($p=0.2794$) was observed.

Subgroup analysis at month 24 *versus* baseline showed stable or improved FDS scores at the 2-year follow up in 68.2%, 51.5% and 57.4% of patients in the low-dose, high-dose and dose-escalation subgroups, respectively. Additional information regarding proportions of patients with decreased, stable, or increased FDS scores

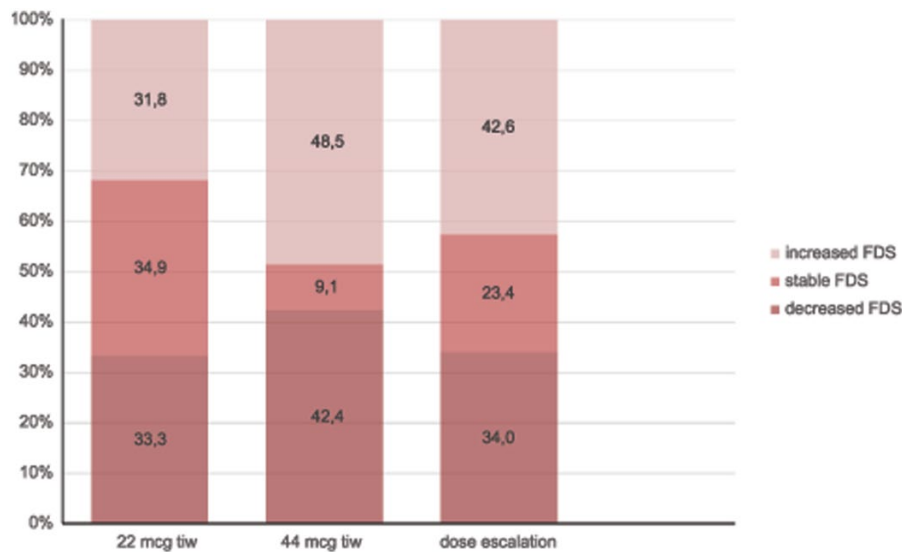


Figure 6. Proportion of patients with increased, stable or decreased Fatigue Descriptive Scale (FDS) scores at 24 months versus baseline, by subgroups.

in each subgroup at 2 years are shown in Figure 6. The mean FDS score in subgroups at each time point is shown in Figure 5. No changes in mean FDS scores, over time, was seen in the three subgroups. There was a significant difference among the subgroups with a lower mean FDS in the low-dose subgroup at all time points ($p=0.0008$), however, there was no difference in the time changes of mean FDS scores among the subgroups ($p=0.53$). Comparison of FDS score differences from baseline among subgroups showed no statistical significance at month 6 ($p=0.65$), month 12 ($p=0.20$) or month 24 ($p=0.60$). Thus, there was significantly lower fatigue in the low-dose subgroup from baseline through to the end of the study (24 months), however there were no differences in fatigue status changes among all three subgroups.

Disability

In total, the proportion of patients with stable or improved EDSS compared to baseline was higher than those with an EDSS that worsened at each time point: 77.2% after 6 months, 69.8% after 12 months and 63.2% after 24 months. Detailed proportions of patients with improved, stable or worsened EDSS scores at each time point are shown in Figure 7.

The mean EDSS (SD) score is detailed in Figure 8. For the analysed population ($n=272$), it was 2.85 (1.10) at baseline, and 2.98 (1.40) at

24 months, without significant development over time ($p=0.085$); the paired test demonstrated no statistically significant change in mean EDSS scores compared with baseline and at month 6 ($p=0.73$), month 12 ($p=0.56$) and month 24 ($p=0.06$), respectively.

In subgroup analyses, stable or improved EDSS scores at 24 months was reported in 69.8%, 57.6% and 40.4% of patients in the low-dose, high-dose and dose-escalation subgroups, respectively. Additional information regarding mean EDSS scores at all time points in each subgroup, and the proportion of patients with improved, stable or worsening EDSS scores at 24 months are shown in Figures 8 and 9, respectively. The changes in mean EDSS scores over time were insignificant in the low-dose ($p=0.317$) and high-dose ($p=0.356$) subgroups, while there was a significant increase in mean EDSS scores in the dose-escalation subgroup ($p=0.00029$). Comparison of mean EDSS at all time points in subgroups revealed a significant increase over time in the dose-escalation subgroup ($p=0.00063$) due to the difference between baseline and month 24 values; and there was a significant difference in the mean EDSS ($p=0.00016$) among all subgroups at all time points. A significant difference in EDSS scores from baseline was found at month 6 ($p=0.0247$), month 12 ($p=0.0331$) and month 24 ($p=0.0017$) between the dose-escalation and stable-dosage subgroups. So, there was a significantly higher but stable mean EDSS in the high-dose subgroup,

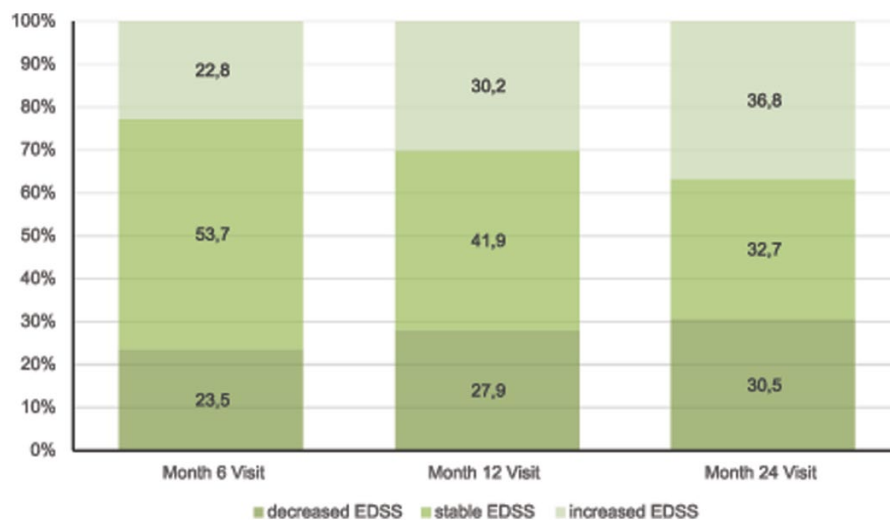


Figure 7. Overall proportion of patients with increased, stable or decreased Expanded Disability Status Scale (EDSS) scores versus baseline for each time point.

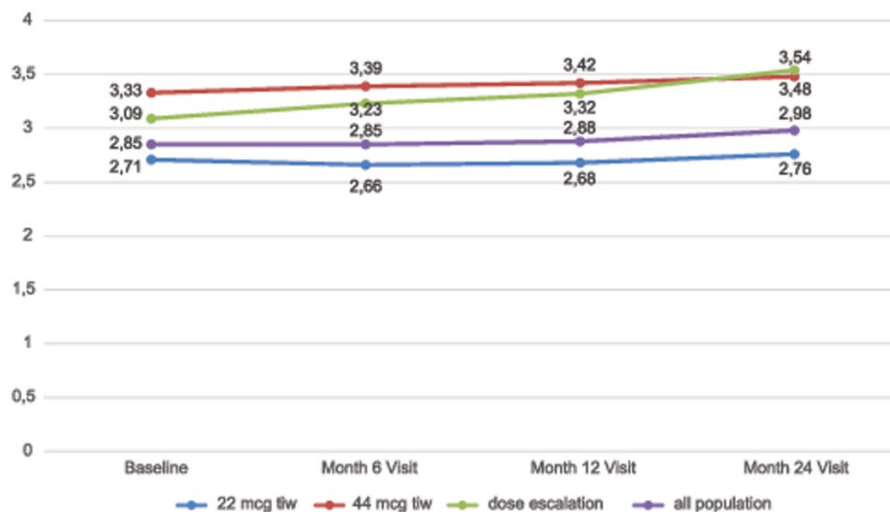


Figure 8. Total mean Expanded Disability Status Scale (EDSS) scores and for subgroups for all time points.

and a higher mean EDSS with more pronounced EDSS worsening in the dose escalation subgroup over the 2-year follow up. These findings are discussed in the following.

Correlation of cognition, fatigue and disability

Generally, none of the correlations among EDSS, PASAT and FDS scores reached the size of very high or high at any time point in the whole sample, or in any of the subgroups.

There was a low negative correlation between the PASAT and FDS scores at baseline [correlation coefficient (r) = -0.32148] and month 6

(r = -0.30236), that is, there was a higher probability of low fatigue in patients with better cognition and *vice versa*, p < 0.0001; there was also little, if any, negative correlation between PASAT and EDSS scores at baseline (r = -0.26292) and month 6 (r = -0.28649), that is, patients with higher disability had a higher probability of lower cognitive performance, p < 0.0001. There was a small positive correlation between EDSS and FDS scores at baseline (r = 0.44018) and month 6 (r = 0.43800), that is, a higher probability of more pronounced fatigue with more severe disability, p < 0.0001.

At months 12 and 24, there was a low negative correlation between PASAT and FDS scores

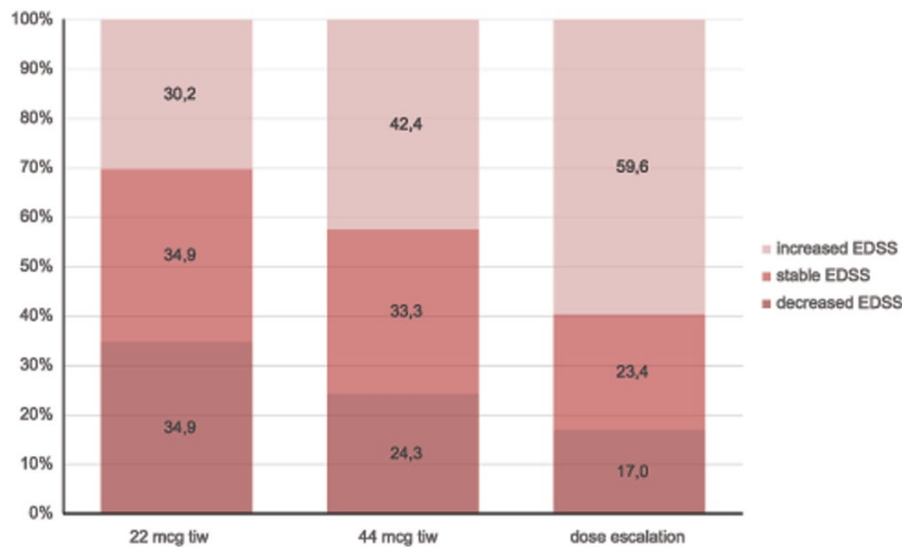


Figure 9. Proportion of patients with total mean Fatigue Descriptive Scale (FDS) scores and for subgroups for all time points with improved, stable or worsened Expanded Disability Status Scale (EDSS) scores at 24 months versus baseline, by subgroups.

($r = -0.38837$ and $r = -0.35189$, respectively, $p < 0.0001$), a low negative correlation between PASAT and EDSS scores ($r = -0.37947$ and $r = -0.41383$, respectively, $p < 0.0001$), and a small positive correlation between EDSS and FDS scores ($r = 0.49890$ and $r = 0.48975$, respectively, $p < 0.0001$).

Only four patients (1.3%) experienced adverse reactions leading to early discontinuation of IFN β -1a treatment during the observational period. None of the reported adverse reactions were evaluated as serious, and no deaths were reported in this study.

Discussion

We have observed stable or improved cognitive performance in the majority of patients treated with sc IFN β -1a. In comparison, a significant decline in cognitive functions has been previously observed in the natural course of the disease. A longitudinal observation showed that the proportion of patients with cognitive impairment increased dramatically from 29% at baseline to 54% during the 5 years following a CIS, and it was partly predicted by the baseline T2 lesion load [Reuter *et al.* 2011]. Another prospective study showed a significant proportion of MS patients had a decline in verbal memory performance from the beginning of the disease through the 2 years of follow up; the decline

was independent of other parameters of disease activity [Duque *et al.* 2008]. Compared with these observations, our findings could indicate that sc IFN β -1a may protect against cognitive decline in patients with MS.

Our results are in accordance with findings that show IFN β treatment influences cognitive maintenance in MS patients [Patti *et al.* 2010]. In addition, a significant benefit has been shown for 44 μ g doses over 22 μ g doses; higher-dose treatments have been predictive of better cognitive outcomes over 3- and 5-year periods [Bastianello *et al.* 2011; Patti *et al.* 2013]. It has also been found that IFN β -1a may have a dose-dependent influence on cognitive maintenance in mildly disabled patients with RRMS. These findings support the point of view that early initiation treatment with high-dose IFN β -1a treatment is more beneficial [Patti *et al.* 2010].

Other factors, such as cognitive and brain reserve capacity [Modica *et al.* 2016; Pinter *et al.* 2014], employment, social status and support [Baughman *et al.* 2015], or sleep disturbance [Braley *et al.* 2016] are possible influencing factors that contribute to the level of cognitive impairment in MS. It has been shown that patients with greater education are protected against disease-related cognitive inefficiency and memory problems [Modica *et al.* 2016; Pinter *et al.* 2014; Sumowski, 2015]. Benefits of leisure

activities (e.g. reading, hobbies, etc.) have also been shown to be protective against cognitive impairment in MS [Schwartz *et al.* 2013; Sumowski *et al.* 2016]. Separate from the cognitive reserve hypothesis, the theory of brain reserve capacity proposes that cognitive impairment emerges when brain volume falls below a critical threshold [MacLulich *et al.* 2002]. Also sleep disturbances are significantly associated with diminished visual and verbal memory, executive function, attention, processing speed and working memory in patients with MS [Braley *et al.* 2016].

Our results also demonstrated stable or improved fatigue status in the majority of patients. There has been only one study evaluating fatigue and cognitive deficits in patients with RRMS receiving IFN β treatment [Melanson *et al.* 2010]. The outcome of the Melanson study suggests that IFN β may reduce fatigue and cognitive deficits in patients with RRMS which correlates with our results. The aetiology of fatigue remains unclear. Dobryakova and colleagues proposed that fatigue is caused by an imbalance of the modulatory neurotransmitter, dopamine, in both the CNS and the immune system, and that fatigue depends on the levels of dopamine in the CNS. This is supported by neuroimaging studies in clinical populations with fatigue that have shown the structural and functional impairments in regions innervated by dopaminergic neurons, namely the striatum and mesocorticolimbic pathway [Dobryakova *et al.* 2013]. It has been shown that proliferated CD4+ T cells in MS express the D3 receptor that contributes to the destruction of dopamine neurons in the substantia nigra and leads to the production of IFN γ , a compound that exacerbates inflammation and prevents dopamine synthesis [Cosentino *et al.* 2005, 2012; González *et al.* 2013; Pacheco *et al.* 2014]. IFN β increases dopamine synthesis in the brain [Cosentino *et al.* 2005, 2012; Zaffaroni *et al.* 2008], and it is possible that MS patients treated with the IFN β might benefit from its dopaminergic effect.

Both, cognition and fatigue could be influenced by comorbidities such as depression or endocrinological conditions [Langdon, 2011; Niino *et al.* 2014]. In our sample, the reported baseline frequency of psychological and/or psychiatric comorbidities was 6.9% and endocrinological conditions was 13.8%. However, the frequency of depression and endocrinological conditions were

low and are unlikely to have affected cognition or fatigue functions.

We have also observed that about two-thirds of the patients treated using sc IFN β -1a experienced no progression in disability during the 2-year follow-up period. This is in agreement with many clinical studies that have demonstrated that IFN β significantly prevented relapses and disability progression [Comi *et al.* 1995, 2001; Durelli *et al.* 2002; Edan *et al.* 2014; Filippini *et al.* 2013; Freedman *et al.* 2003; Goodin *et al.* 2012; Jacobs *et al.* 2000; Kappos *et al.* 2007, 2009; Panitch *et al.* 2002]. Nevertheless, due to the fact that disability progresses gradually in most patients with RRMS, the relatively short 2-year observational period, and a lack of a control group in our study, we cannot conclude that the lack of disability progression was a treatment effect. We observed higher levels of disability in the 44 μ g tiw subgroup and a more pronounced accumulation of disabilities in the dose escalation subgroup. These findings reflect the facts that: (a) based on the previous Czech national DMD reimbursement criteria, Rebif 22 μ g tiw was used as a treatment for patients with less active disease, (b) Rebif 44 μ g tiw was reimbursed in more active diseases and (c) a dose-escalation from 22 to 44 μ g tiw was used in patients with suboptimal disease control (relapses or disability progression). Therapy optimization as first-line treatment is also supported by recent results coming from the CARE-MS II study in RRMS patients with suboptimal responses to IFN β or glatiramer acetate. Switching to sc IFN β -1a (44 μ g tiw) resulted in only 21.13% of them having sustained accumulation of disability during the subsequent 2 years of follow up [Coles *et al.* 2012]. A similar treatment algorithm and significant disease stabilization after optimization of first-line DMD treatment to sc IFN- β -1a (44 μ g tiw) has also been reported in a German observational study [Masri *et al.* 2010]. Furthermore, CIS and RRMS trials have shown a more pronounced benefit in prevention of disability progression in cases where sc IFN β -1a was started early using a high-dose, high-frequency regimen [Comi *et al.* 2011; Kappos *et al.* 2015; Cohen and Rivera, 2010]. Thus, our explanation for the observed difference in disability among subgroups relative to dose is that the higher level of disability and its progression had led to treatment with a higher dose of IFN β -1a as well as dose escalation. In other words, the higher dose and dose escalation was a response to and not the cause of disability progression.

The limitations of our study include a relatively short observation period of 24 months and the lack of control group, thus no conclusions regarding causality can be drawn from our results. Additional controlled, prospective studies using large RRMS populations with longer observation periods need to be performed to fully demonstrate the effect of sc IFN- β -1a on cognitive performance, disease progression and fatigue status.

Conclusion

The results of this observational, prospective, multicentre study in patients with RRMS, have demonstrated stable or improved cognitive performance and fatigue status in the majority of those treated with sc IFN- β -1a over the 2-year follow-up period, in a real-life setting, in the Czech Republic. Almost two-thirds of patients experienced improvement in their cognitive performance, and there was a significant increase in average cognitive performance; almost two thirds reported “stable or” improved fatigue levels with a stable average fatigue level, however, direct effects of IFN β -1a on cognition and fatigue cannot be concluded from this observational study. In addition, almost two thirds of the study group maintained stable disability levels or saw improvements in their disability status, but with no significant change in the mean EDSS score. The stable or improved disability levels observed in the majority of patients was in accordance with the proven efficacy of sc IFN β -1a in preventing disability progression.

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Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Yvonne Benešová has nothing to disclose. Aleš Tvaroh is an employee of Merck spol. s r. o., Prague, Czech Republic, an affiliate of Merck KGaA, Darmstadt, Germany.

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