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Original Article

Prognostic factors for long-term outcomes in relapsing–remitting multiple sclerosis

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Abstract

Objective: The objective of this article is to investigate potential clinical and MRI predictors of long-term outcomes in multiple sclerosis (MS).

Methods: This was a post hoc analysis using data from all 382 patients in the PRISMS long-term follow-up (LTFU) study collected up to eight years after randomisation. An additional analysis was performed including only those patients originally randomised to receive early subcutaneous interferon (IFN) β-1a ($n = 259$). Baseline/prestudy variables, indicators of early clinical and MRI activity (baseline to month 24), and indicators of IFN β-1a treatment exposure (including medication possession ratio (MPR)) were investigated as candidate prognostic factors for outcomes measured from baseline and from month 24 to LTFU. Explanatory variables identified from univariate regression models ($p \leq 0.15$) were selected for inclusion in stepwise multiple regression models.

Results: Candidate prognostic factors selected by the univariate analysis ($p \leq 0.15$) included age, MS duration, baseline brain volume, EDSS score, and log(T2 burden of disease (BOD)). In most of the multivariate regression models applied, higher baseline brain volume and MPR predicted better long-term clinical outcomes, while higher baseline and greater early increase in EDSS score predicted worse outcomes.

Conclusion: Identification of markers that may be prognostic for long-term disability could help identify MS patients at higher risk of disability progression.

***Keywords*:** Disability, follow up, long-term outcomes, MRI, multiple sclerosis, prognosis

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Introduction

Multiple sclerosis (MS) is a chronic, lifelong disease that has a highly variable course which can cause severe disability over time in many patients. Therefore, early determination of clinical, magnetic resonance imaging (MRI), and/or biological markers that are prognostic for long-term outcomes would be valuable, to enable management strategies tailored to the needs of individual patients.[1] Currently, no baseline or short-term clinical or MRI measures have proven to be consistent prognostic factors.[2,3]

The Prevention of Relapses with Interferon beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) study demonstrated the efficacy of interferon (IFN) β-1a, 44 and 22 μg administered subcutaneously (sc) three times weekly (tiw), compared with placebo, in reducing relapses, MRI lesion activity and accumulation, and in preventing disability in patients with relapsing–remitting MS (RRMS).[4] This population was followed for up to eight years from randomisation,[5,6] with a 77% patient retention rate for sites that participated in the long-term follow-up (LTFU) visit, thus providing a useful cohort within which early clinical and MRI variables could be analysed as predictors for long-term disease status.

Long-term outcomes were determined seven to eight years after the start of the original randomised clinical trial. The objective of this post hoc analysis of the PRISMS LTFU data set was to determine whether prestudy and baseline characteristics,

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[a]At the time of the study.

indicators of early MRI and clinical activity, and indicators of treatment exposure could be identified as prognostic factors of long-term clinical and MRI outcomes in patients with RRMS.

Methods

Patients and study design

All patients ($N = 560$) who had undergone randomisation in the PRISMS study were eligible for enrolment into the LTFU study (protocol number 22930), regardless of when their participation in the original study had been terminated.

PRISMS was a randomised, double-blind trial that compared IFN β-1a (44 and 22 µg sc tiw) with placebo, for two years. The study was extended for two additional years (years 3–4), during which patients originally randomised to placebo were re-randomised to one of the two doses of sc IFN β-1a (Figure 1). Patients who completed the four-year study were then given the opportunity to continue on blinded or open-label treatment (44 or 22 µg sc tiw) for the following two years (i.e. up to year 6). Between withdrawal from, or completion of, six years on study, and up to and including the LTFU assessment, patients could take any or no disease-modifying drug (DMD) for MS. The trial finished at year 6 and the LTFU consisted of a single visit seven to eight years following original randomisation.[4–6]

Standard protocol approvals, registrations, and patient consents

Local ethical and health authority approval was required for participation at LTFU, and all patients gave written informed consent in accordance with the Declaration of Helsinki.

Assessments

During the PRISMS study, neurological assessments were performed every three months over years 1 to 3, and then every six months over years 4 to 6. At the LTFU assessment, patients underwent a neurological evaluation to determine their current Expanded Disability Status Scale (EDSS) score and whether they had developed secondary progressive MS

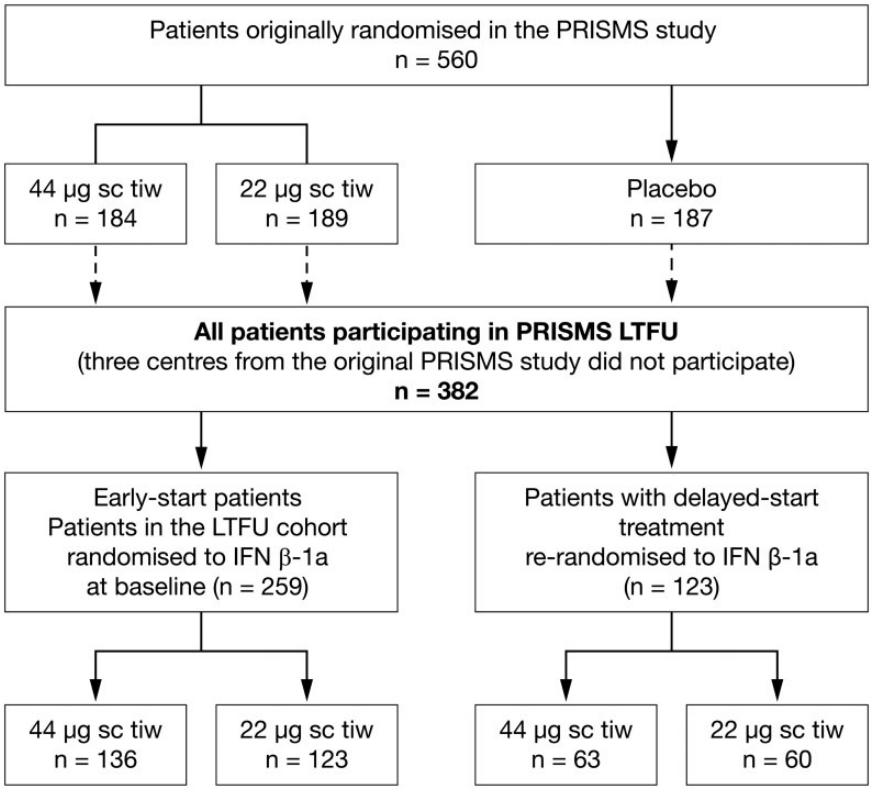

Figure 1. PRISMS study design and LTFU analysis sets.
Early-start patients received treatment from baseline of the current study. Patients with delayed-start treatment received IFN β-1a after a period of two years. IFN: interferon; LTFU: long-term follow-up; PRISMS: Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis; sc: subcutaneously; tiw: three times weekly.

(SPMS; defined as progressive deterioration of disability for ≥12 months and a deterioration in EDSS score of ≥1 point (or 0.5 points between EDSS scores 6.0 and 6.5) not associated with an exacerbation, following an initial relapsing–remitting course). A non-contrast proton-density/T2-weighted brain MRI scan was performed every six or 12 months during the original PRISMS study and extension study, respectively, and again at the LTFU visit using the same imaging protocol. New T2 activity was defined as new or enlarging T2 lesions compared with a previous MRI scan. T2 burden of disease (BOD) was defined as the summed cross-sectional area (in mm^2) of lesions on T2 scans. Brain volume was assessed using the brain parenchymal ratio, which was derived by subtracting cerebral spinal fluid (CSF) from intradural volume and normalising to the whole brain volume.

Post hoc analysis

This post hoc exploratory analysis was performed in all LTFU patients ($n = 382$) and in the subcohort originally randomised to sc IFN β-1a (early-start patients, $n = 259$) (Figure 1).

Outcome and explanatory prognostic variables

The long-term outcome variables for which prognostic factors were sought were: change in EDSS score, EDSS progression, time to first EDSS progression, EDSS score ≥6, time to EDSS score ≥6, conversion to SPMS, time to conversion to SPMS (calculated as the number of days between study day 1 of the original PRISMS study and the date on which SPMS conversion was observed), negative disability outcome (NDO; EDSS score ≥ 6 and/or SPMS), time to negative disability outcome, change in log(T2 BOD), and percentage change in brain volume (change in brain volume was measured from baseline to LTFU only).

The baseline/prestudy explanatory variables investigated as candidate prognostic factors were: age, sex, duration of MS, prestudy annualised relapse rate (ARR; during the two years prior to baseline), EDSS score, log(T2 BOD), and brain volume.

Explanatory variables were investigated as candidate prognostic factors for outcomes measured from baseline to LTFU and from month 24 to LTFU. Some potential predictors might have changed within the first 24 months of the PRISMS study. Thus, the month 24 to LTFU analysis was conducted to account for potential cases of an outcome occurring before a predictor.

The indicators of early clinical or MRI activity from baseline to month 24 that were investigated as candidate prognostic factors were: ARR, EDSS progression, number of EDSS progressions, change in EDSS score, number of new or enlarging T2 lesions, number of active T2 scans (showing at least one new or enlarging T2 lesion), change in log(T2 BOD), and T2 composite score (measured at months 12 and 24; missing values were imputed by the last observation carried forward (LOCF) approach; details on the T2 composite score are given below).

EDSS progression was defined as an increase in EDSS score by ≥1 point if the score was <6 at baseline or the last visit, or otherwise by ≥0.5 points, confirmed after three months. Long-term clinical outcome variables also included a combined negative disability outcome, which was defined as an EDSS score ≥6 and/or SPMS. Outcome variables and explanatory variables that were related to T2 BOD used the logarithm of T2 BOD to normalise this measurement, which tends to be skewed.

A T2 composite score was created to combine and categorise the two T2 lesion-related variables: active T2 lesion number and T2 BOD change. The score is the sum of a three-point score for the number of active T2 lesions between baseline and months 12 or 24 (0 points: ≤6 lesions; 1 point: 7–20 lesions; 2 points: >20 lesions), and a 3-point score for T2 BOD change from baseline to months 12 or 24 (0 points: change $\leq -700\,mm^2$; 1 point: change > -700 and $\leq +300\,mm^2$; 2 points: change $> +300\,mm^2$), yielding a composite score of 0–4 points.

Indicators of IFN β-1a treatment exposure that were investigated as candidate prognostic factors were: medication possession ratio (MPR; calculated as 100 × time (days) on sc IFN β-1a treatment from baseline to LTFU visit/time (days) from baseline to LTFU visit); IFN β-1a early or delayed start status (all-patients analysis only); and IFN β-1a high (44 μg) or low (22 μg) dose (early-start IFN β-1a patients analysis only).

Regression analyses

Stage 1 of the post hoc analysis used univariate regression models to identify explanatory variables ($p > 0.15$) for further evaluation using multivariate regression analysis (Stage 2). This conservative cutoff ($p > 0.15$) was selected to ensure that potential prognostic factors were not prematurely discarded. Correlation analysis of explanatory

variables was also carried out; if a pair of explanatory variables had a Spearman rank correlation coefficient (r) ≥ 0.7 or ≤ -0.7, only one of the two variables was selected to avoid problems with multicollinearity.

At Stage 2, the selected explanatory variables were fitted in final stepwise multivariate regression models using multiple linear regression for continuous or ordinal outcomes, logistic regression for binary outcomes, and Cox proportional hazards model for time-to-event outcomes.

Results

Patients

A total of 382 patients participated in the LTFU visit (Figure 1), representing 77% (382/493) of patients originally randomised in the PRISMS study at sites which participated in the LTFU visit (of the original participating centres, three did not participate in the LTFU study for administrative reasons not related to the outcomes). Of the returning patients, 72% (275/382) were still receiving sc IFN β-1a at LTFU (160 receiving 44 μg tiw and 115 receiving 22 μg tiw).

Descriptive statistics

Prestudy and baseline characteristics were similar in the two LTFU analysis sets (all patients and early-start IFN β-1a patients), except for slightly longer mean (SD) disease duration in the early-start patients: 7.97 (6.14) years, compared with 7.35 (5.81) years in all patients. The median time to EDSS progression was also longer in early-start patients compared with all patients (6.54 vs 5.80 years). In keeping with the beneficial therapeutic effect, indicators of clinical and MRI activity from baseline to month 24 were also more favourable in early-start patients compared with the all-patients group: a smaller percentage of patients with EDSS progression (27.8% vs 31.7%), a smaller increase in log(T2 BOD) (mean (SD) change + 0.01 (0.46) vs + 0.05 (0.44)), and fewer new or enlarging lesions at month 24 (mean (SD) 1.30 (2.73) vs 1.91 (3.15)). Prestudy and baseline characteristics are shown in Table 1; indicators of early disease activity for these two patient groups are available in Table e-1.

Univariate explanatory variables for LTFU outcomes

All patients. Age, duration of MS, baseline EDSS score, baseline log(T2 BOD), and baseline brain volume were variables with $p \leq 0.15$ for most long-term outcomes, both for outcomes measured from baseline to LTFU (Table e-2) and outcomes measured from month 24 to LTFU (data not shown). Sex did not reach a $p \leq 0.15$ for any long-term outcome and was therefore not selected for the multivariate analysis. Explanatory variables which fulfilled the $p \leq 0.15$ criterion included only three outcomes (change in EDSS score, time to EDSS progression, change in brain volume) measured from baseline to LTFU (Table e-2), and for only one outcome (time to EDSS progression) measured from month 24 to LTFU.

EDSS progression, number of EDSS progressions, and change in EDSS from baseline to month 24 were associated with all clinical outcomes measured from baseline to LTFU (Table e-3) and for the majority of outcomes from month 24 to LTFU (data not shown). ARR during the first two years was associated with change only in log(T2 BOD) measured from month 24 to LTFU.

T2 composite scores at months 12, 24, and 24 LOCF were associated with the largest number of long-term clinical and MRI outcomes measured from baseline to LTFU (Table e-3) and from month 24 to LTFU. Early MRI activity fulfilled the cutoff criterion both for change in log(T2 BOD) and change in brain volume from baseline to LTFU but not for clinical outcomes (Table e-3).

Mean (SD) MPR was 78.0% (26.7%) and MPR was associated with the majority of long-term clinical and MRI outcomes measured from baseline to LTFU (Table e-3).

Simple Pearson correlation coefficients for explanatory variables with $p \leq 0.15$ varied depending on the final clinical or MRI outcome, and generally ranged from 0.1 to 0.5. Medium strength baseline explanatory variables for later clinical outcomes were EDSS score ($r = 0.51$ for EDSS ≥ 6; $r = 0.39$ for SPMS). Further explanatory variables were duration of MS ($r = 0.15$ for EDSS ≥ 6; $r = 0.14$ for NDO); baseline log(T2 BOD) ($r = 0.16$–0.22), and baseline brain volume ($r = 0.21$–0.33). At month 12, the T2 composite score showed correlations with change in EDSS ($r = 0.20$) and EDSS score ≥ 6 ($r = 0.13$). Other explanatory variables at month 24 were ARR ($r = 0.16$ for change in EDSS to LTFU; $r = 0.14$ for EDSS progression) and change in EDSS score from baseline to month 24, which gave r values between 0.33 and 0.55 for all clinical outcomes.

Early-start patients. Results similar to those found in the all-patients cohort were seen when univariate

Table 1. Baseline characteristics and long-term outcomes in all patients and in early-start IFN β-1a patients.

Variable	All patients ($n = 382$)	Early-start IFN β-1a patients ($n = 259$)
Baseline and prestudy characteristics		
Age (years) at baseline, mean (SD)	35.35 (7.46)	35.30 (7.34)
Women, %	72.5	69.9
Duration (years) of MS at baseline, mean (SD)	7.35 (5.81)	7.97 (6.14)
24-month prestudy ARR, mean (SD)	1.44 (0.52)	1.42 (0.49)
EDSS score at baseline, mean (SD)	2.43 (1.21)	2.43 (1.22)
log(T2 BOD) at baseline, mean (SD)	7.03 (1.30)	7.01 (1.31)
Brain volume (mm^3) at baseline, mean (SD)	79.35 (3.94)	79.21 (3.98)
Clinical outcomes at LTFU		
Change in EDSS score, mean (SD)	+1.07 (1.67)	+1.08 (1.65)
EDSS progression, %	60.7	60.2
Time (years) to EDSS progression, median[a]	5.80	6.54
EDSS score ≥ 6, %	22.8	23.9
Time (years) to EDSS score ≥ 6, median[a]	NA[b]	NA[b]
Conversion to SPMS, %	19.9	20.1
Time (years) to SPMS, median[a]	NA[b]	NA[b]
NDO, %	26.4	27.0
Time (years) to NDO, median[a]	NA[b]	NA[b]
MRI outcomes at LTFU		
Change in log(T2 BOD), mean (SD)	+0.23 (0.52)	+0.21 (0.53)
Change (%) in brain volume, mean (SD)	−4.39 (3.01)	−4.31 (2.98)
Indicators of treatment exposure		
Medication possession ratio (%), mean (SD)	77.97 (26.65)	87.25 (23.12)
Medication possession ratio (%), median	85.61	99.42

ARR: annualised relapse rate; BOD: burden of disease; EDSS: Expanded Disability Status Scale; IFN: interferon; LTFU: long-term follow-up; MS: multiple sclerosis; NA: not applicable; NDO: negative disability outcome; SPMS: secondary progressive multiple sclerosis.
[a]Kaplan-Meier estimates.
[b]Median not reached, therefore not applicable because of censoring rate of >50%.

regression analyses were performed on the cohort of early-start IFN β-1a patients (data not shown). Original randomised IFN β-1a dose (44 or 22 µg sc tiw) was not associated with any long-term clinical outcome measured from baseline and/or month 24 to LTFU.

Multivariate predictors for LTFU outcomes

When variables reaching $p \leq 0.15$ in univariate analyses were included in multivariate models, the predictive value for LTFU outcomes varied (Table 2). A consistent association with six or more of the clinical disability outcomes measured from baseline to LTFU (Table 2) and from month 24 to LTFU (Table 3) was found for: EDSS score at baseline, change in EDSS score from baseline to month 24, baseline brain volume, and MPR. Higher brain volume at baseline and greater MPR were associated with better long-term clinical outcomes (including less likelihood of conversion to SPMS), while higher baseline EDSS score and greater increase in EDSS score during the first 24 months were associated with worse long-term clinical outcomes. Associated with some (≥2), but not all, disability outcomes measured from baseline to LTFU were: T2 composite score at month 12, ARR during the first 24 months, and EDSS progression in the first 24 months.

In the multivariate models, baseline EDSS score, EDSS progression in the first 24 months, T2 composite score at month 24 LOCF, and baseline log(T2 BOD) were associated with percentage change in brain volume from baseline to LTFU in the all-patients cohort. Baseline EDSS score and T2 composite score at month 24 LOCF were also associated

Table 2. Coefficients for explanatory variables that were found to be prognostic factors ($p \leq 0.15$) in the final predictive multivariate regression models for long-term clinical outcomes: baseline to LTFU, all patients.

	Prognostic factor for long-term clinical outcome								
Variable	Change in EDSS score	EDSS prog.	Time to EDSS prog.	EDSS score ≥ 6	Time to EDSS score ≥6	SPMS	Time to SPMS	NDO	Time to NDO
Baseline/prestudy variables									
Prestudy ARR	–	–	+0.2358	–	–	–	–	–	–
EDSS score at baseline	–	–	–	+1.4125	+1.2795	+0.8694	+0.6304	+1.2814	+1.0979
Brain volume at baseline	−0.0552	−0.1245	−0.0514	−0.1326	−0.0970	−0.0833	−0.0614	−0.0871	−0.0742
Indicators of early clinical activity									
ARR from baseline to month 24	–	+0.2640	–	–	–	–	–	–	–
EDSS progression in first 24 months	+0.3550	–	–	–	+0.5027	–	–	+1.1660	+0.7262
Change in EDSS score from baseline to month 24	+0.6600	+1.4095	+0.7770	+1.0363	+0.8996	+0.6781	+0.5986	+0.5906	+0.7181
Indicators of early MRI activity									
T2 composite score at month 12	+0.2011	–	–	+0.3360	–	–	–	–	–
Indicators of IFN β-1a treatment exposure									
MPR	–	–	–	–	−0.0078	−0.0093	−0.0073	–	−0.0065

ARR: annualized relapse rate; EDSS: Expanded Disability Status Scale; IFN: interferon; LTFU: long-term follow-up; MPR: medication possession ratio; MRI: magnetic resonance imaging; NDO: negative disability outcome; prog.: progression; SPMS: secondary progressive multiple sclerosis.

Table 3. Coefficients for explanatory variables that were found to be prognostic factors ($p \leq 0.15$) in the final predictive multivariate regression models for long-term clinical outcomes: month 24 to LTFU, all patients.

	Prognostic factor for long-term clinical outcome								
Variable	Change in EDSS score	EDSS prog.	Time to EDSS prog.	EDSS score ≥ 6	Time to EDSS score ≥6	SPMS	Time to SPMS	NDO	Time to NDO
Baseline/prestudy variables									
Age	–	+0.0231	+0.0153	–	–	–	–	–	–
EDSS score at baseline	–	–	–	+1.1775	+1.0862	+0.8634	+0.6477	+1.0564	+0.9218
Brain volume at baseline	−0.0541	−0.1073	−0.0612	−0.1228	−0.1068	−0.0779	−0.0602	−0.0726	−0.0758
Indicators of early clinical activity									
Change in EDSS score from baseline to month 24	−0.2386	−0.1073	−0.1723	+0.7916	+0.7080	+0.6615	+0.5997	+0.6465	+0.6068
Indicators of early MRI activity									
T2 composite score at month 12	+0.2328	–	–	–	–	–	–	–	–
Indicators of IFN β-1a treatment exposure									
IFN β-1a start status: delayed start	−0.2317	–	–	−1.0409	−0.8929	–	–	−0.7221	−0.6745

EDSS: Expanded Disability Status Scale; IFN: interferon; LTFU: long-term follow-up; MPR: medication possession ratio; NDO: negative disability outcome; prog.: progression; SPMS: secondary progressive multiple sclerosis.

with this MRI outcome in early-start patients, as was prestudy ARR.

The R^2 coefficient of determination for the final model predicting change in EDSS score from baseline to LTFU was 0.35 for all patients and 0.31 for the early-start cohort.

Discussion

Disease course, MRI findings, and treatment response are highly heterogeneous among patients with MS, especially over time. Identifying factors that are prognostic for long-term disability outcomes could therefore be useful in identifying patients at high risk of disability progression, and help determine appropriate long-term treatment. Due to the heterogeneity of MS, large and robust long-term data sets are required to identify factors that may be prognostic. The PRISMS LTFU population provides one of the most complete data sets of its type, with data available up to eight years after study initiation. Participating centres had a high average retention rate (77%) and 72% of patients returning for the LTFU visit were still receiving sc IFN β-1a. In addition, assessment and MRI protocols for the LTFU visit were consistent with those used throughout the study.

Patients enrolled in the PRISMS study represented a relatively homogeneous population (83% had an EDSS score $\leq$3.5) and whilst this may have limited generalisability to other clinical settings it may have helped to minimise confounding of the analysis of prognostic variables. After eight years, the levels of disability and disability progression were much more heterogeneous, making this a valuable cohort in which to explore early predictors of relatively long-term clinical outcomes. There is a possibility of selection bias among the patients who returned for the LTFU visit, as patients with better disease outcomes at seven to eight years may have been more willing or able to participate.

The analysis was performed in all patients who had returned for the LTFU visit and also in patients from the early-start sc IFN β-1a cohort only. Separate analysis of the early-start cohort patients allowed evaluation of whether earlier initiation of treatment impacts the predictive value of early variables, especially those referring to changes in MRI and relapse rate during the first two years.

IFN β-1a start status (early or delayed) was not a significant univariate predictor for any clinical outcomes measured during the eight-year follow-up. However, in such an intention-to-treat analysis, not all early-start patients had a longer duration of active treatment over the follow-up period. MPR, a measure of time on therapy during the eight-year follow-up, was identified as a predictor of clinical outcome in the final multivariate regression models, favouring patients with the highest MPR. Notably, the coefficients calculated for MPR were very small. This is consistent with the high adherence rates observed (mean MPR overall, 78%; for early-starters, 87%). Previous data suggest a potential worsening of relapse rates at lower adherence rates, with relapse rates tending to remain low in patients with higher adherence (objective adherence up to 75% or MPR up to 70%).[7,8] A recent 15-year follow-up of patients with RRMS indicating that higher levels of cumulative dose exposure and longer time on sc IFN β-1a treatment were associated with better clinical outcomes, further highlights the potential benefits of a longer duration of MS therapy.[9]

Multivariate analysis identified the following variables to be predictors of long-term disability: age, EDSS score and brain volume at baseline, early change in EDSS and MPR. Markers of inflammatory activity from baseline to month 24 included ARR and the T2 composite score. Analysis of the early-start cohort patients provided similar results to the analysis of all patients. Baseline brain volume, baseline EDSS and early change in EDSS were the most frequently identified predictors of the various long-term disability outcomes. Assessing a patient's baseline brain volume and early disability status may therefore be important in therapeutic decision making.

The prognostic value of EDSS observed in the current study is supported by a number of other studies that previously identified baseline EDSS or early change in EDSS as predictive of long-term disability or cognitive outcomes in MS patients.[10–12] MRI at baseline, in terms of brain volume and lesion burden, have also been found to correlate with disability outcomes.[11,13] Other prognostic factors previously identified include age older than 25 years at onset, clinical course during the first two years of disease, and involvement of the pyramidal system at onset.[10] In a long-term trial of patients on IFNβ-1b, measurements at baseline were observed to have a greater prognostic value than on-study measurements, which were found to contribute little to the variance in long-term outcomes.[11]

In the current study, all identified predictors taken together accounted for only approximately one-third

of the variability in long-term disability outcome, suggesting that other unidentified factors must play important roles. Similarly, models developed previously accounted for approximately half of the variance in long-term outcomes.[11] In addition, it is possible that the predictive value of the EDSS-related explanatory variables could have been affected by the known low sensitivity and low inter-rater reliability of the EDSS.[14,15]

Although it is widely considered that poor adherence to treatment can adversely affect disease outcomes in patients with MS,[8,16–18] to date few studies have examined this association. Post hoc analyses (separate to the current analysis) of clinical and MRI outcomes in the PRISMS LTFU cohort according to exposure to IFN β-1a treatment (cumulative dose of IFN β-1a, cumulative time on treatment, and continuous vs non-continuous treatment) have also suggested that better adherence leads to better outcomes.[15]

In summary, in clinical practice we are still in need of more accurate factors that can predict a successful or poor outcome at up to eight years after starting therapy. In this post hoc analysis of the PRISMS LTFU cohort, higher baseline brain volume predicted better long-term clinical outcomes, while larger increases in EDSS score during the first 24 months predicted worse outcomes. A measure of time on therapy, MPR, was also identified as a predictor for many long-term clinical outcomes, with a longer duration of IFN β-1a treatment associated with better outcomes. Relapse rate and changes in MRI disease measures in the first two years of treatment were also predictors of long-term outcomes, but not as consistently so as change in EDSS score over a similar interval.

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Declaration of conflicting interests

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