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Factors influencing long-term outcomes in relapsing–remitting multiple sclerosis: PRISMS-15

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ABSTRACT

Aim An exploratory study of the relationship between cumulative exposure to subcutaneous (sc) interferon (IFN) β-1a treatment and other possible prognostic factors with long-term clinical outcomes in relapsing–remitting multiple sclerosis (RRMS).

Methods Patients in the original PRISMS study were invited to a single follow-up visit 15 years after initial randomisation (PRISMS-15). Outcomes over 15 years were compared in the lowest and highest quartile of the cumulative sc IFN β-1a dose groups, and according to total time receiving sc IFN β-1a as a continuous variable per 5 years of treatment. Potential prognostic factors for outcomes were analysed.

Results Of 560 patients randomised in PRISMS, 291 returned for PRISMS-15 and 290 (51.8%) were analysed. Higher cumulative dose exposure and longer treatment time appeared to be associated with better outcomes on: annualised relapse rate, number of relapses, time to Expanded Disability Status Scale (EDSS) progression, change in EDSS, proportions of patients with EDSS ≥4 or ≥6, ≤5 relapses and EDSS <4 or <6, and time to conversion to secondary-progressive MS (SPMS). Higher dose exposure was associated with lower proportions of patients with EDSS progression and conversion to SPMS, and longer time on treatment with lower risk of first relapse. Change in EDSS from baseline to 24 months was a strong predictor of evaluated clinical outcomes over 15 years.

Conclusions These findings suggest that higher cumulative exposure to sc IFN β-1a may be associated with better clinical outcomes, and early change in EDSS score may have prognostic value, over many years, in RRMS.

INTRODUCTION

At diagnosis, more than 80% of patients with multiple sclerosis (MS) have the relapsing–remitting form of the disease (RRMS).[1] Most patients with RRMS (>80%) will develop secondary–progressive MS (SPMS) over 25 years,[2] with a median time to progression ranging from approximately 15–21 years after disease onset.[2 3] Owing to the lifelong course of MS, it is important to determine potential baseline or early prognostic factors for long-term outcomes.

One of the earliest MS therapy pivotal trials was the PRISMS (Prevention of Relapses and Disability by interferon (IFN) β-1a subcutaneously (sc) in MS) study. This 2-year controlled study was the first to establish the efficacy of IFN β-1a, 44 or 22 μg, administered sc three times weekly (tiw), versus placebo, on clinical and MRI measures in RRMS.[4] Results from an extension study[5] and long-term follow-up at 7–8 years[6] demonstrated benefits of early versus delayed sc IFN β-1a therapy, with these benefits most apparent at the 44 μg dose. Exploratory analyses at 7–8 years suggested that higher cumulative exposure to IFNβ-1a may be associated with better clinical outcomes,[7] and that baseline brain volume, early disability status and Medication Possession Ratio (MPR) may predict long-term outcomes.[8]

Patients were invited to a long-term follow-up visit at 15 years from randomisation (PRISMS-15). This offered the opportunity for exploratory analyses of the relationship of cumulative exposure to sc IFN β-1a and other potential prognostic factors with long-term clinical outcomes. The data were collected in accordance with Good Clinical Practice and quality assurance procedures.

METHODS

Study design

The design and conduct of the PRISMS study have been described previously.[4–6] In the initial double-blind phase, patients with RRMS were randomised to receive IFN β-1a 44 or 22 μg sc tiw, or placebo, for 2 years.[4] The study was extended for a further 2 years (years 3–4), during which patients continued the same blinded dose or, if originally randomised to placebo, were re-randomised to one of the two doses of sc IFN β-1a.[5] All patients were then given the opportunity to continue on blinded or open-label treatment for the following 2 years (years 5–6). After withdrawal or completion of 6 years on study, patients could continue on any or no treatment as per standard clinical practice. All originally randomised patients were invited to single-visit, long-term follow-up assessments at 7–8 years[6] and approximately 15 years after initial randomisation.

The 15-year visit included a neurological evaluation, and retrospective review of medical and treatment history collected since the final visit of the initial 4-year study period or the long-term follow-up assessment at 7–8 years.[6] Clinical evaluations throughout PRISMS included documentation of relapses and assessments using the Expanded Disability Status Scale (EDSS). At the 15-year visit, relapse counts were based on data prospectively

collected during the first 4 years plus retrospective data over subsequent years. EDSS progression at 15 years was defined as an increase in EDSS score of ≥1 points (≥0.5 points if the baseline score was ≥6) that was not associated with a relapse. For confirmation of EDSS progression, the increase had to be maintained for at least 3 months; progression at the time of PRISMS-15 was assumed to be confirmed as there was no subsequent follow-up visit. The 15-year visit had to be conducted at least 3 months after the onset of the last relapse to avoid EDSS assessment bias. Conversion to SPMS, which was defined as an endpoint and assessed at the long-term follow-up visits only, was defined as progressive worsening of disability for at least 12 months despite best symptomatic management and confirmed EDSS progression, following an initial relapsing–remitting disease course.[6 7]

PRISMS-15 was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation/Good Clinical Practice (GCP) Guidelines, and local regulations. The protocol was approved by health authorities and an independent ethics committee or institutional review board, according to country-specific laws. All patients gave written informed consent.

PRISMS-15 exploratory analyses

Impact of exposure to sc IFN β-1a on clinical outcomes

Clinical outcomes were investigated in subgroups of patients defined by cumulative treatment exposure to sc IFN β-1a from original randomisation over 15 years by cumulative dose or cumulative time on treatment. Categorisation of cumulative sc IFN β-1a dose exposure has been described;[7] briefly, patient data from the three original study arms (IFN β-1a 44 or 22 μg sc tiw, or placebo) were pooled and ranked from lowest to highest cumulative dose exposure to sc IFN β-1a over 15 years, calculated as (dose of IFN β-1a)×(frequency of application)×(period of application, in weeks). The minimum (lowest quartile, MIN) and maximum (highest quartile, MAX) cumulative dose exposure groups were compared with respect to the following clinical outcomes over 15 years: mean annualised relapse rate (ARR); mean number of relapses per patient; proportion of patients free from relapse; time to first relapse during the study; proportion of patients with 0–5, 6–10 and ≥11 relapses; proportion of patients with EDSS progression; time to first 3-month confirmed EDSS progression; change in EDSS score over 15 years; proportions of patients with EDSS score ≥4 or ≥6; proportions of patients with ≤5 relapses and EDSS score <4 or <6; proportion of patients converting to SPMS; and time to conversion to SPMS. SPMS was defined as a progressive deterioration of disability for a minimum of 6 months and an increase of EDSS of >1 point (or >0.5 point for EDSS > 6.0) not associated with an exacerbation). Total time receiving sc IFN β-1a (irrespective of dose) was examined as a continuous variable per 5 years of treatment for the clinical outcomes listed above, with the exceptions of mean number of relapses per patient and the proportions of patients remaining relapse free, with EDSS progression, and converting to SPMS.

Dichotomous variables were analysed using logistic regression. Time to event variables were analysed using a Cox proportional hazards model; if no event occurred, then the time was censored at the PRISMS-15 visit date. Change in EDSS score by cumulative time on sc IFN β-1a treatment was estimated using linear regression. ARR, defined as the total number of relapses divided by the length of the time in years, was analysed using Poisson regression. As these were *post hoc* exploratory analyses, p values were not calculated.

Prognostic factors for clinical outcomes

The following long-term outcome variables were assessed: change in EDSS score from baseline to 15 years (continuous variable), SPMS conversion status (yes/no) and 3-month confirmed EDSS progression over 15 years (yes/no). Baseline/prestudy characteristics, indicators of early clinical or MRI activity from baseline to 24 months and indicators of treatment exposure, were investigated as candidate prognostic factors for the long-term outcome variables. Baseline/prestudy characteristics were: age (years), female sex, time since MS onset (years), number of prior relapses, EDSS and log (T2 burden of disease (BOD)). Indicators of early clinical or MRI activity from baseline to 24 months were: change in EDSS, ARR, change in log (T2 BOD) and number of T2 active lesions (defined as new or enlarging T2 lesions) per scan. Indicators of treatment exposure were: early IFN β-1a (44 or 22 μg tiw) treatment and MPR (calculated as 100×time (days) on sc IFN β-1a treatment from baseline to the 15-year visit/time (days) from baseline to the 15-year visit).

Initially, the prognostic factors were tested in univariate models using linear regression for change in EDSS score from baseline to 15 years, and logistic regression for SPMS conversion and 3-month confirmed EDSS progression over 15 years. Factors significant in univariate models ($p \leq 0.10$) were entered into forward selection, stepwise multivariate analyses, in which only factors with $p \leq 0.10$ remained in the final models. The final predictive models for each outcome were summarised by parameter estimates per prognostic factor; positive regression coefficients indicate that a positive/increasing value in the prognostic factor leads to an increase in the outcome, while negative regression coefficients indicate that a positive/increasing value in the prognostic factor leads to a decrease in the outcome.

RESULTS

Patients

Of the 560 patients originally randomised in the PRISMS study, 291 (52.0%) returned for PRISMS-15. Four of the original 22 centres did not participate in PRISMS-15; when the 89 patients from these non-participating centres were excluded, 61.8% (291/471) of eligible patients attended the 15-year visit. One patient who returned at 15 years was excluded because of a revised diagnosis (neuromyelitis optica). Of the 290 patients analysed in PRISMS-15, 234 (80.7%) had participated in the long-term follow-up at 7–8 years and 56 (19.3%) attended PRISMS-15 only. At the year 15 visit, of the 290 patients included in the analysis, 118 patients were recorded as still receiving any IFN β-1a treatment and 168 as still receiving any DMD.

There were no differences in baseline demographics and disease characteristics between patients who did and did not attend PRISMS-15 (see online supplementary table S1). Similar proportions of patients returned for the 15-year visit from each of the original randomisation groups. Demographic and disease characteristics, and treatment exposure, are presented for the PRISMS-15 cohort by original randomisation group (table 1), and for the MIN and MAX cumulative dose groups (table 2). The lower mean time on sc IFN β-1a treatment for patients originally randomised to placebo is consistent with the 2 years of delay prior to receiving active treatment.[4]

Treatment responses and safety data after the first 2 years of the PRISMS study in patients who did and did not attend PRISMS-15 are presented in table 3. Differences in efficacy outcomes favouring the group that participated at PRISMS-15 were observed regarding T2 lesion change and ARR. Adverse events

Table 1 Demographic and disease characteristics and time on treatment in the PRISMS-15 cohort, by original randomisation group (see also online supplementary tables S4 and S5 for characteristics at 24 and 48 months after randomisation)

	Original randomisation group			
	IFN β-1a, 44 μg sc tiw (n=95)	IFN β-1a, 22 μg sc tiw (n=95)	Placebo (n=100)	Overall (N=290)
Female, n (%)	63 (66.3)	65 (68.4)	76 (76.0)	204 (70.3)
White, n (%)	94 (98.9)	94 (98.9)	99 (99.0)	287 (99.0)
At baseline				
Median (range) time from MS onset, years	7.0 (0.6–34.4)	5.9 (1.0–22.8)	4.6 (1.2–18.8)	5.6 (0.6–34.4)
Mean (SD) number of relapses in prior 2 years	3.0 (1.1)	3.0 (1.1)	3.1 (1.3)	3.0 (1.2)
Mean (SD) EDSS score	2.5 (1.2)	2.4 (1.2)	2.2 (1.2)	2.4 (1.2)
At PRISMS-15				
Median (range) age, years	52.3 (35.4–66.4)	50.3 (36.9–66.1)	51.1 (36.2–64.6)	51.2 (35.4–66.4)
Mean (SD) time on sc IFN β-1a treatment, years	10.6 (5.0)	10.6 (4.9)	8.8 (5.1)	10.0 (5.0)

EDSS, Expanded Disability Status Scale; IFN, interferon; MS, multiple sclerosis; sc, subcutaneous(ly); tiw, three times weekly.

(AEs) and serious AEs were reported at similar frequencies in each group. Compared with patients who attended PRISMS-15, a slightly higher proportion of patients who did not attend had at least one AE leading to treatment discontinuation.

Overall, 36/290 (12.4%) patients had received IFN β-1a 44 and/or 22 μg sc tiw continuously from randomisation to PRISMS-15 (some patients having switched dose over the course of the 15-year period).

Impact of exposure to IFN β-1a on clinical outcomes

Relapse outcomes

The MAX cumulative dose group had a lower mean ARR and number of relapses over 15 years compared with the MIN group (table 4). No difference was observed between the MAX and MIN groups regarding the proportion of patients remaining relapse free (table 4), and the time to first relapse (HR 0.73; 95% CI 0.52 to 1.03). Compared with the MIN group, a lower proportion of patients had ≥11 relapses but a higher proportion had 0–5 relapses in the MAX group (table 5).

For each cycle of 5 years of sc IFN β-1a treatment, there was a reduction in the mean ARR by 14% (parameter estimate (SE) −0.15 (0.02); 95% CI −0.19 to −0.10) and risk of first relapse by 13% (HR 0.87; 95% CI 0.77 to 0.99). Time on treatment tended to be longer in patients with fewer relapses (table 5).

For relapse-related outcomes, similar benefits with higher dose exposure were observed in the subgroup of patients who did not have SPMS at PRISMS-15 (n=179; data not shown).

Table 2 Demographic and disease characteristics, original randomisation groups, and treatment exposure in the lowest (MIN) and highest (MAX) quartiles of cumulative total dose of sc IFN β-1a (see also online supplementary tables S4 and S5 for characteristics at 24 and 48 months after randomisation)

	Cumulative dose of sc IFN β-1a (quartiles)	
	MIN (n=73)	MAX (n=72)
Median (range) age,* years	33.6 (20.4–50.3)	36.6 (20.6–49.4)
Female, n (%)	53 (72.6)	46 (63.9)
White, n (%)	72 (98.6)	70 (97.2)
Median (range) time from MS onset,* years	6.2 (1.0–24.2)	5.2 (1.1–34.4)
Mean (SD) number of relapses in prior 2 years*	3.1 (1.3)	3.0 (1.0)
Mean (SD) EDSS score*	2.5 (1.2)	2.2 (1.0)
Original randomisation group, n (%)		
IFN β-1a 44 μg	14 (19.2)	35 (48.6)
IFN β-1a 22 μg	27 (37.0)	14 (19.4)
Placebo	32 (43.8)	23 (31.9)
Mean (SD) time on sc IFN β-1a treatment,† years	2.9 (1.9)	14.7 (1.3)
Mean (SD) cumulative total dose of sc IFN β-1a,† mg	12.3 (7.4)	94.9 (10.4)
Use of other first-line DMDs,† n (%)	38 (52.1)	2 (2.8)

*At baseline.
†At PRISMS-15.
DMD, disease-modifying drug; EDSS, Expanded Disability Status Scale; IFN, interferon; sc, subcutaneous.

Disability and composite outcomes

Compared with the MIN cumulative dose group, the MAX group had a lower proportion of patients with 3-month confirmed EDSS progression, a smaller mean increase in EDSS score, lower proportions of patients with EDSS scores ≥4 or ≥6, and higher proportions of patients with ≤5 relapses and EDDS scores <4 or <6 (table 4). Time to first 3-month confirmed EDSS progression was delayed in the MAX versus MIN group (HR 0.64; 95% CI 0.42 to 0.98).

The risk of 3-month confirmed EDSS progression was reduced by 14% with each cycle of 5 years of sc IFN β-1a treatment (HR 0.86; 95% CI 0.74 to 0.98). A reduction of approximately 0.5 points on the EDSS was associated with each cycle of 5 years of sc IFN β-1a treatment (parameter estimate (SE) −0.43 (0.11); 95% CI −0.65 to −0.20). With each cycle of 5 years of sc IFN β-1a treatment, the risk of reaching an EDSS score of ≥4 or ≥6 was reduced and the likelihood of having ≤5 relapses and an EDSS score <4 or <6 was increased (table 4).

Conversion to SPMS

A lower proportion of patients converted to SPMS in the MAX versus MIN group (table 4). Time to SPMS was delayed in the MAX versus MIN group (HR 0.31; 95% CI 0.17 to 0.56). With each cycle of 5 years of sc IFN β-1a treatment, the risk of SPMS was reduced by 28% (HR 0.72; 95% CI 0.60 to 0.86).

Prognostic factors for clinical outcomes

In univariate models, change in EDSS score from baseline to 24 months and MPR over 15 years were both predictors

Table 3 Efficacy and safety outcomes over the first 2 years of the PRISMS study in patients who did and did not return for PRISMS-15

Outcomes at 2 years	Patients attending PRISMS-15 (n=290)	Patients not attending PRISMS-15 (n=270)	p Value for between-group comparison
Mean (SD) number of relapses	1.9 (1.7)	2.2 (2.0)	0.290
Mean (SD) ARR	0.98 (0.92)	1.15 (1.09)	0.104
Mean (SD) change from baseline in EDDS score	0.23 (1.08)*	0.36 (1.27)†	0.516
3-month confirmed EDSS progression, n (%)	84 (29.2)‡	87 (34.4)§	0.193
Mean (SD) % change from baseline in T2 BOD	7.36 (45.91)¶	21.96 (120.97)**|	0.006
Mean (SD) mean number of T2 active lesions per scan	2.05 (3.02)‡	2.26 (3.64)††	0.679
≥1 AE, n (%)	290 (100)	269 (99.6)	0.300
≥1 SAE, n (%)	28 (9.7)	33 (12.2)	0.330
≥1 AE possibly or probably related to treatment, n (%)	272 (93.8)	258 (95.6)	0.355
≥1 AE leading to treatment discontinuation, n (%)	8 (2.8)	19 (7.0)	0.018

*n=285.
†n=248.
‡n=288.
§n=253.
¶n=277.
**n=237.
††n=263.
p Values for efficacy outcomes were estimated using a non-parametric analysis of variance model on ranked data (except 3-month confirmed EDDS progression where the p value was calculated using a χ^2 test); p values for safety outcomes were calculated using a χ^2 test.
AE, adverse event; ARR, annualised relapse rate; BOD, burden of disease; EDSS, Expanded Disability Status Scale; SAE, serious adverse event.

(p≤0.10) for SPMS conversion, change in EDSS score and confirmed EDSS progression over 15 years (see online supplementary table S2). Regression coefficients for prognostic factors that were predictive in multivariate models are shown in table 6. An increase in EDSS score from baseline to 24 months was associated with an increase in EDSS score and likelihood of confirmed EDSS progression as well as SPMS conversion over 15 years. Associations were also observed between a higher MPR over 15 years and a lower increase in EDSS score over 15 years and lower risk of SPMS.

Prognostic factors were examined separately in the original randomisation groups. In patients who had initially been randomised to placebo for 2 years, baseline log (T2 BOD) and change in log (T2 BOD) to 24 months were identified as predictive factors for SPMS conversion that were not present in the overall analysis (see online supplementary table S3).

DISCUSSION

The main strength of the PRISMS-15 study is the inclusion of a well-characterised group of patients with RRMS who were comprehensively assessed during the core study and reassessed after 15 years according to GCP standards. This provided an opportunity to assess long-term clinical outcomes at 15 years in patients with varying exposure to sc IFN β-1a treatment. Overall,

Table 4 Measures of clinical disease activity from baseline to PRISMS-15 in the lowest (MIN) and highest (MAX) quartiles, by cumulative total dose of sc IFN β-1a and by time receiving sc IFN β-1a per 5 years

	Cumulative dose of sc IFN β-1a			
Outcomes at year 15	MIN (n=73)	MAX (n=72)	OR* (95% CI) MAX vs MIN	Odds ratio† (95% CI) per 5 years of sc IFN β-1a treatment
Mean (95% CI) annualised relapse rate‡	0.50 (0.46 to 0.54)	0.37 (0.33 to 0.40)	–	–
Mean (SD) number of relapses	7.8 (5.8)	5.8 (4.8)	–	–
Relapse-free, n (%)	5 (6.8)	5 (6.9)	–	–
3-month confirmed EDSS progression, n (%)	50 (68.5)	38 (52.8)	–	–
Mean (SD) change in EDSS score	2.53 (2.01)	1.15 (1.52)	–	–
EDSS ≥4, n (%)	37 (60.7)§	21 (31.8)¶	0.30 (0.15 to 0.63)	0.75 (0.58 to 0.96)
EDSS ≥6, n (%)	38 (52.1)	10 (13.9)	0.15 (0.07 to 0.33)	0.60 (0.47 to 0.77)
≤5 relapses and EDSS <4,** n (%)	11 (16.9)††	25 (35.7)‡‡	2.73 (1.21 to 6.14)	1.39 (1.05 to 1.83)
≤5 relapses and EDSS <6,§§ n (%)	12 (16.4)	34 (47.2)	4.55 (2.10 to 9.85)	1.68 (1.29 to 2.18)
Converted to SPMS, n (%)	38 (52.1)	15 (20.8)	–	–

*MIN quartile as a reference category; logistic regression model.
†Logistic regression model.
‡Poisson regression model with factors for quartile of cumulative dose of sc IFN β-1a. The log of total observation time in years from PRISMS baseline to PRISMS-15 was used as the offset variable.
§n=61.
¶n=66.
**Patients with baseline EDSS ≥4 are counted as missing on the EDSS component of the variable.
††n=65.
‡‡n=70.
§§Patients with baseline EDSS ≥6 are counted as missing on the EDSS component of the variable.
EDSS, Expanded Disability Status Scale; IFN, interferon; sc, subcutaneous; SPMS, secondary progressive multiple sclerosis.

Table 5 Categorised relapse outcomes from baseline to PRISMS-15 in the lowest (MIN) and highest (MAX) quartiles by cumulative total dose of sc IFN β-1a, and by time receiving sc IFN β-1a

	Number of relapses		
	0–5	6–10	≥11
Cumulative dose of sc IFN β-1a			
MIN (n=73), n (%)	29 (39.7)	25 (34.2)	19 (26.0)
MAX (n=72), n (%)	41 (56.9)	20 (27.8)	11 (15.3)
Mean (SD) time on sc IFNβ-1a treatment,*years	10.70 (4.73)	9.45 (5.27)	8.44 (5.23)

*n=156 in the 0–5 relapses group; n=85 in the 6–10 relapses group; n=49 in the ≥11 relapses group.
IFN, interferon; sc, subcutaneous.

61.8% of eligible patients from participating centres returned for the 15-year visit, which compares well with the proportions of patients returning for similar long-term studies.[9–11] Nonetheless, the substantial proportion of patients lost to long-term follow-up remains an important limitation to this type of study. Equal proportions of patients returned from each original randomisation group, suggesting that there was no systematic bias as related to initial randomised treatment. The higher proportion of females and slightly shorter time since MS onset in the original placebo group, compared with the active treatment groups in the PRISMS-15 cohort, reflected the characteristics of the three arms at randomisation in the PRISMS study.[4]

However, the results of this *post hoc* exploratory analysis should also be considered in the context of the study limitations. A greater proportion of patients in the MIN versus MAX group switched to other treatments, and disease progression may have been a reason for switching therapy. Moreover, patients with worse outcomes may have been more likely to discontinue treatment. Other issues include different timings and frequencies of assessments, retrospective collection of relapse data that may be affected by recall bias, difficulties confirming EDSS progression (if not from existing medical records), unblinded assessment of patients who may no longer be receiving study medication, and treatment interruptions and conversions to non-study medications.[6] Differences between returning and non-returning patients may have introduced selection bias. Patients with better disease outcomes may have tended to continue on treatment and/or have been more willing or able to participate, leading to under-representation of patients with worse outcomes. However, the returning and non-returning groups appeared similar in terms of baseline characteristics, with some differences in outcomes at 2 years, which suggests that the findings of this study were not driven by selection bias.

In these exploratory analyses at 15 years, higher levels of cumulative dose exposure and longer time on treatment appeared to be associated with better clinical outcomes. This is consistent with findings from similar *post hoc* analyses from the previous long-term follow-up of PRISMS at 7–8 years after initial randomisation,[7] and data from other IFN β and glatiramer acetate studies supporting long-term disease-modifying drug (DMD) therapy in MS.[6 9–11] The association of higher exposure to sc IFN β-1a treatment with better relapse-related outcomes was similar in the overall population and the subgroup of patients who had not converted to SPMS over 15 years, suggesting that this did not reflect the development of relapse-independent continuous progression. In the MAX cumulative dose group, only 20.8% of patients had converted to SPMS over 15 years, compared with 52.1% in the MIN dose group. Although a direct comparison cannot be made, natural history data in patients with RRMS at disease onset who were not exposed to DMDs have indicated a median time to SPMS ranging from approximately 15–21 years.[2 3] The use of other DMDs was not controlled for in PRISMS-15; about half of patients in the MIN dose group received other first-line DMDs after discontinuing sc IFN β-1a, but this group had poorer outcomes despite the high proportion of patients switching to other treatments. Less than 3% of patients in the MAX dose group received other first-line DMDs.

Owing to the methods for calculating cumulative dose and time on treatment, it is not possible to definitively state cut-off points when a certain dose exposure resulted in a particular outcome, but these totals can be considered to provide an indication of adherence to sc IFN β-1a treatment over 15 years. The positive association of higher treatment exposure with more favourable outcomes suggests that starting treatment early and maintaining adherence over the long term may be important for optimal clinical outcomes. However, as this was an observational study without a randomised control group, it is impossible to determine whether better clinical outcomes are a consequence or cause of adherence to therapy.[6 7]

Identification of prognostic factors that can predict a successful or poor long-term outcome after starting therapy is required to assist therapeutic decision-making in clinical practice. Even after 15 years, a greater increase in EDSS score from baseline to 24 months appeared to be a strong predictor of worse outcomes in final multivariate models, consistent with results from a similar analysis after 7–8 years of follow-up.[8] An association between higher MPR and a lower increase in EDSS score and risk of SPMS conversion over 15 years was also observed, which supports the importance of treatment adherence. In the

Table 6 Regression coefficients for prognostic factors in the final predictive multivariate regression models for selected clinical outcomes at 15 years

	Clinical outcomes at 15 years*		
Variable	SPMS conversion	Change in EDSS	EDSS 3-month confirmed progression
Female sex	−0.5176; p=0.0864	–	–
Baseline EDSS score	+0.6587; p<0.0001	–	–
Change in EDSS score at 24 months	+0.5963; p<0.0001	+0.7087; p<0.0001	+1.3607; p<0.0001
Change in log(T2 BOD) at 24 months	–	+0.8351; p=0.0268	–
Medication Possession Ratio	−0.0099; p=0.0261	−0.0078; p=0.0238	–

*Data calculated using forward selection, stepwise multivariate analysis.
BOD, burden of disease; EDSS, Expanded Disability Status Scale; SPMS, secondary progressive multiple sclerosis.

univariate analysis, female sex, baseline log (T2 BOD), ARR at 24 months and the number of T2 active lesions per scan at 24 months predicted change in EDSS score over 15 years; and age at baseline, number of prior relapses, baseline log (T2 BOD) and ARR at 24 months predicted SPMS conversion; however, these variables were not confirmed as independent predictors in the multivariate analysis. Although this indicates that these putative prognostic factors have lower predictive value, the limitations of the statistical approach must be taken into account. The final multivariate models for the prognostic factor analyses were dependent on the particular combination of variables chosen for inclusion in the original candidate set of predictors. Predictors that were only marginally less powerful may have been forced out of the models by slightly more powerful predictors. It should also be noted that, in general, the R^2 values of the predictive models were low.

Despite the limitations inherent in long-term follow-up studies, the findings of these *post hoc* exploratory analyses suggest that higher dose exposure to IFN β-1a and longer time on treatment may be associated with better outcomes over many years in patients with RRMS. Change in EDSS score from baseline to 24 months and MPR also appeared predictive of long-term outcomes.

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