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Post hoc analysis of PRISMS study: efficacy of interferon β-1a subcutaneously three times weekly according to baseline EDSS/duration, EDSS, and MSSS subgroups

R Berkovich,[1] H Zhang,[2] J Aldridge,[2] S Baver,[3,†] E Williamson[4]

[1]University of Southern California, Los Angeles, CA, USA; [2]EMD Serono, Inc.,* Billerica, MA, USA; [3]EMD Serono, Inc.,* Rockland, MA, USA; [4]University of Pennsylvania Penn Neuroscience Center, Philadelphia, PA, USA

INTRODUCTION

- The Expanded Disability Status Scale (EDSS) measures disability progression in patients with multiple sclerosis (MS).[1,2] The EDSS has been criticized for a lack of linearity and a lack of accounting for how long it took a patient to accumulate disability.[2]
- The Multiple Sclerosis Severity Scale (MSSS) was developed to adjust the EDSS for disease duration (a patient's MSSS score is the decile of the EDSS within the range of patients with the same disease duration).[2]
- In the 2-year, double-blind, placebo-controlled PRISMS (Prevention of Relapses and disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) study, interferon beta-1a (IFN β-1a) subcutaneously (SC) three times weekly (tiw) significantly reduced relapses and active T2 lesions, and prolonged time to confirmed disability progression, in patients with relapsing–remitting MS (RRMS). Disability worsening was significantly delayed by IFN β-1a 44 µg SC tiw in the overall population and in a prespecified subgroup with baseline EDSS score >3.5.[3]
- The 2-year extension of the PRISMS study enrolled 90 percent of the original PRISMS study cohort and provided the opportunity to evaluate the treatment effect over a longer term.[4]
- These analyses examine the efficacy results of IFN β-1a SC tiw in patients with RRMS across a range of severity levels, including effects of treatment in patients with slowly accumulating disability and in those who are rapidly losing physical function.

OBJECTIVE

- To determine the efficacy of IFN β-1a 44 µg SC tiw by baseline clinical disease severity characteristics in patients with RRMS from PRISMS.

METHODS

- Exploratory analyses were conducted on data from the PRISMS study, in which patients with RRMS were randomized to receive IFN β-1a 44 µg (n=184) or 22 µg SC tiw (n=189), or placebo (n=187), for 2 years. The primary endpoint was the number of relapses over 2 years.[3]
- Patients originally receiving IFN β-1a 44 µg (n=167) or 22 µg SC tiw (n=167) continued treatment in Years 3 and 4, while those originally receiving placebo (n=172) switched to IFN β-1a SC tiw in Years 3 and 4 (placebo/delayed treatment group) in the extension.[4]
- Eligible patients were 18–50 years of age, had a history of ⩾2 relapses in the previous 2 years, and had a baseline EDSS score of 0–5.0.[2] Diagnosis of clinically definite or laboratory-supported definite MS was based on the Poser criteria.[5]
- In the current analyses, patients were grouped into tertiles by EDSS (<2, ⩾2 to ⩽3, >3) and MSSS (⩽2.87, >2.87 to ⩽5.24, >5.24) scores. Tertiles were also determined for the ratio of EDSS/duration of disease (lowest tertile: ⩽0.27, middle: >0.27 to ⩽0.64, highest: >0.64) as a measure of the rate of accumulating disability. Effects of IFN β-1a 44 µg SC tiw compared with placebo/delayed treatment on annualized relapse rate (ARR) and EDSS progression (⩾1- or ⩾0.5-point increase from baseline EDSS score ⩽5.5 or ⩾6, respectively, sustained for ⩾3 months) were examined at Years 2 and 4.
- Differences in ARR were compared using a negative binomial model with number of relapses within 2 years prior, age, and treatment as independent variables. For differences in EDSS progression, hazard ratios and p values were based on Cox proportional hazards models with number of relapses within 2 years prior, age, and treatment as independent variables.

RESULTS

- **Table 1** shows the numbers of patients in each treatment group in each tertile. Baseline characteristics of the trial population are shown in **Table 2**.

Table 1. Patient tertile categorization by EDSS, MSSS, and the ratio of EDSS to duration of disease

	Placebo/delayed treatment (n=187)	IFN β-1a 44 µg SC tiw (n=184)
EDSS, n (%)		
Lowest tertile (<2)	62 (33.2)	58 (31.5)
Middle tertile (⩾2 to ⩽3)	72 (38.5)	76 (41.3)
Highest tertile (>3)	53 (28.3)	50 (27.2)
MSSS,* n (%)		
Lowest tertile (⩽2.87)	55 (29.4)	66 (35.9)
Middle tertile (>2.87 to ⩽5.24)	59 (31.6)	65 (35.3)
Highest tertile (>5.24)	72 (38.5)	51 (27.7)
EDSS/duration, n (%)		
Lowest tertile (⩽0.27)	55 (29.4)	66 (35.9)
Middle tertile (>0.27 to ⩽0.64)	61 (32.6)	64 (34.8)
Highest tertile (>0.64)	71 (38.0)	54 (29.3)

EDSS, Expanded Disability Status Scale; **IFN β-1a**, interferon beta-1a; **MSSS**, Multiple Sclerosis Severity Scale; **SC**, subcutaneously; **tiw**, three times weekly.
*Three patients with MS duration less than 1 year were excluded for calculating MSSS.

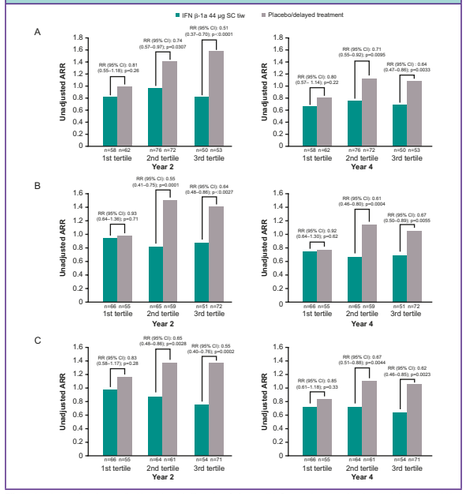
Table 2. Baseline demographic and clinical characteristics

Characteristic	PRISMS population (N=560)
Age, years	34.9 (7.5)
Sex, female, %	69.5
Time since disease onset, years	7.2 (5.8)
Relapses in previous 2 years	3.0 (1.2)
EDSS score at baseline	2.5 (1.2)

Values are expressed as mean (SD), unless otherwise stated.
EDSS, Expanded Disability Status Scale; **SD**, standard deviation.

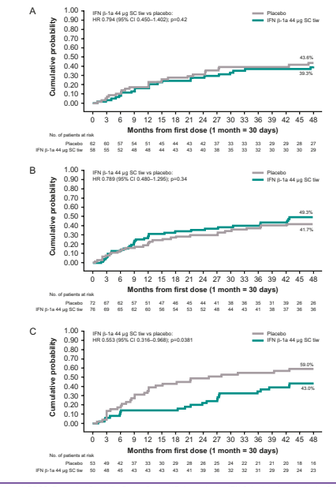
- At Year 2, ARR was significantly lower with IFN β-1a 44 µg SC tiw compared with placebo in the highest and middle tertiles of EDSS (rate ratio [RR] 0.51 [95% confidence interval (CI) 0.37–0.70], p<0.0001, and 0.74 [0.57–0.97], p=0.0307; **Figure 1A**). Similar results were seen in the highest and middle tertiles of MSSS (RR 0.64 [0.48–0.86], p=0.0027, and 0.55 [0.41–0.75], p=0.0001, respectively; **Figure 1B**), and in the highest and middle EDSS/duration tertiles (RR 0.55 [0.40–0.76], p=0.0002, and 0.65 [0.48–0.86], p=0.0028, respectively; **Figure 1C**).
  - Effects were maintained at Year 4.
  - Results in the lowest tertiles of severity trended towards lower ARR in the IFN β-1a 44 µg SC tiw group but were not statistically significant.
- Over 4 years, IFN β-1a 44 µg SC tiw significantly delayed EDSS progression compared with placebo/delayed treatment in the highest EDSS tertile (hazard ratio 0.55 [95% CI 0.32–0.97], p=0.0381; **Figure 2**).
  - This pattern was not reflected in the lowest and middle EDSS tertiles.
- Time to EDSS progression over 4 years among MSSS and EDSS/duration tertiles was longer with IFN β-1a 44 µg SC tiw compared with placebo/delayed treatment; however, a significant effect was only seen in the middle MSSS tertile (**Figure 3** and **Figure 4**).

Figure 1. ARR over 2 and 4 years by treatment: A) EDSS tertile,[a] B) MSSS tertile,[b] and C) EDSS/duration ratio tertile[c]



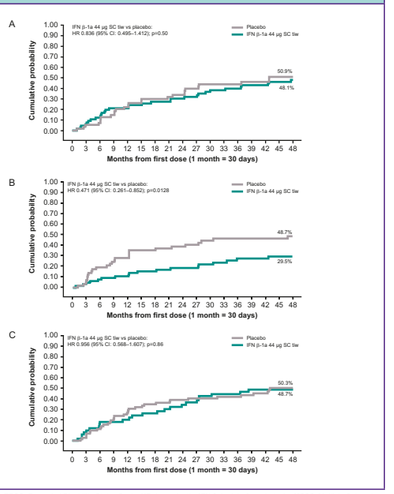
Effect and p value were based on negative binomial model with number of relapses within 2 years prior, age, and treatment as independent variables.
ARR, annualized relapse rate; **CI**, confidence interval; **EDSS**, Expanded Disability Status Scale; **IFN β-1a**, interferon beta-1a; **MSSS**, Multiple Sclerosis Severity Scale; **RR**, rate ratio; **SC**, subcutaneously; **tiw**, three times weekly.
[a]1st EDSS tertile: EDSS score <2; 2nd EDSS tertile: EDSS score ⩾2 to ⩽3; 3rd EDSS tertile: EDSS score >3.
[b]1st MSSS tertile: MSSS score ⩽2.87; 2nd MSSS tertile: MSSS score >2.87 to ⩽5.24; 3rd MSSS tertile: MSSS score >5.24.
[c]1st EDSS/duration ratio tertile: EDSS/duration ⩽0.27; 2nd EDSS/duration ratio tertile: EDSS/duration >0.27 to ⩽0.64; 3rd EDSS/duration ratio tertile: EDSS/duration >0.64.

Figure 2. Time to first sustained EDSS progression[a] over 4 years by treatment: A) 1st EDSS tertile,[b] B) 2nd EDSS tertile,[b] and C) 3rd EDSS tertile[b]



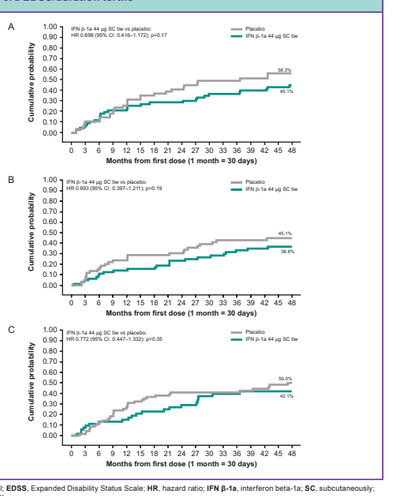
CI, confidence interval; **EDSS**, Expanded Disability Status Scale; **HR**, hazard ratio; **IFN β-1a**, interferon beta-1a; **SC**, subcutaneously; **tiw**, three times weekly.
*Sustained EDSS progression was defined as an increase, sustained for 3 months, of ⩾0.5 points from a baseline EDSS score ⩾6.0 or an increase of ⩾1.0 point from a baseline EDSS score <6.0. HRs and p values are based on Cox model with number of relapses within 2 years prior, age, and treatment as independent variables.
[a]1st EDSS tertile: EDSS score <2; 2nd EDSS tertile: EDSS score ⩾2 to ⩽3; 3rd EDSS tertile: EDSS score >3.

Figure 3. Time to first sustained EDSS progression[a] over 4 years by treatment: A) 1st MSSS tertile,[b] B) 2nd MSSS tertile,[b] and C) 3rd MSSS tertile[b]



CI, confidence interval; **EDSS**, Expanded Disability Status Scale; **HR**, hazard ratio; **IFN β-1a**, interferon beta-1a; **MSSS**, Multiple Sclerosis Severity Scale; **SC**, subcutaneously; **tiw**, three times weekly.
*Sustained EDSS progression was defined as an increase, sustained for 3 months, of ⩾0.5 points from a baseline EDSS score ⩾6.0 or an increase of ⩾1.0 point from a baseline EDSS score <6.0. HRs and p values are based on Cox model with number of relapses within 2 years prior, age, and treatment as independent variables.
[b]1st MSSS tertile: MSSS score ⩽2.87; 2nd MSSS tertile: MSSS score >2.87 to ⩽5.24; 3rd MSSS tertile: MSSS score >5.24.

Figure 4. Time to first sustained EDSS progression[a] over 4 years by treatment: A) 1st EDSS/duration ratio tertile,[b] B) 2nd EDSS/duration ratio tertile,[b] and C) 3rd EDSS/duration tertile[b]



CI, confidence interval; **EDSS**, Expanded Disability Status Scale; **HR**, hazard ratio; **IFN β-1a**, interferon beta-1a; **SC**, subcutaneously; **tiw**, three times weekly.
*Sustained EDSS progression was defined as an increase, sustained for 3 months, of ⩾0.5 points from a baseline EDSS score ⩾6.0 or an increase of ⩾1.0 point from a baseline EDSS score <6.0. HRs and p values are based on Cox model with number of relapses within 2 years prior, age, and treatment as independent variables.
[b]1st EDSS/duration ratio tertile: EDSS/duration ⩽0.27; 2nd EDSS/duration ratio tertile: EDSS/duration >0.27 to ⩽0.64; 3rd EDSS/duration ratio tertile: EDSS/duration >0.64.

CONCLUSIONS

- **Early IFN β-1a 44 µg SC tiw treatment demonstrated clinical benefits compared with placebo/delayed treatment in patients with RRMS with high or moderate baseline EDSS score, MSSS score, and EDSS/duration ratio.**
  - **Patients in the second and third tertiles showed significant reductions in ARR with IFN β-1a 44 µg SC tiw compared with placebo.**
- **IFN β-1a 44 µg SC tiw significantly delayed EDSS progression compared with placebo/delayed treatment in the highest EDSS tertile. This is consistent with the original PRISMS results showing IFN β-1a 44 µg SC tiw delayed progression in the subgroup with EDSS scores >3.5.**
  - **Attempts to draw conclusions regarding treatment effects in time to EDSS progression over 4 years in the MSSS and EDSS/duration tertiles are complicated by the *post hoc* nature of these analyses.**
  - **Additionally, at 4 years of study, patients originally randomized to placebo had been receiving active treatment for 2 years.**
- **Effects of early IFN β-1a 44 µg SC tiw in subgroups stratified by baseline disease characteristics were generally consistent with the overall results of PRISMS.**

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DISCLOSURES

RB acted as a consultant for Acorda, Avanir, Bayer, Biogen, Genzyme, Novartis, and Teva.

HZ and **JA** are employees of EMD Serono, Inc.,* Billerica, MA, USA.

SB was an employee of EMD Serono, Inc.,* Rockland, MA, USA at the time the research was conducted.

EW acted as a consultant for Novartis, EMD Serono, Inc.,* and Teva Neuroscience, and is Principal Investigator on a clinical trial sponsored by Alexion Pharmaceuticals.

*A business of Merck KGaA, Darmstadt, Germany.
†Affiliation at the time the research was conducted.

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