Poster No. DX14

Post hoc analyses of PRISMS study: clinical efficacy of interferon β-1a subcutaneously three times weekly according to baseline radiological activity

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INTRODUCTION

- The presence of radiological measures of disease activity (eg, lesion load) early in the multiple sclerosis (MS) disease course is predictive of disease progression and carries a poor prognosis.[1]
- Furthermore, some evidence suggests that baseline radiological activity is predictive of worse long-term outcomes in patients receiving interferon beta-1a (IFN β-1a)[2]; however, the predictive effect of inflammatory lesions in relation to disease duration has not been established.
- PRISMS (Prevention of Relapses and disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) was a 2-year, double-blind, placebo-controlled study in patients with relapsing–remitting MS (RRMS). Treatment with IFN β-1a 44 µg or 22 µg subcutaneously (SC) three times weekly (tiw) significantly reduced relapse rate, prolonged time to first relapse, and delayed disability progression, compared with placebo.[3]
- The effect of IFN β-1a on clinical outcomes in patients enrolled in PRISMS, stratified by baseline radiological characteristics, has not been previously investigated.

OBJECTIVE

- To evaluate clinical efficacy, as indicated by annualized relapse rate (ARR), time to first relapse, and disability progression, of IFN β-1a according to baseline radiological activity and disease duration in patients with RRMS from the PRISMS study.

METHODS

PRISMS study

- PRISMS was a 2-year, double-blind, placebo-controlled study in which 560 patients with RRMS aged 18–50 years of age, with a history of ⩾2 relapses in the previous 2 years and an Expanded Disability Status Scale (EDSS) score of 0–5.0, were randomized to receive IFN β-1a 44 µg (n=184) or 22 µg SC tiw (n=189), or placebo (n=187).[3] Diagnosis of clinically definite or laboratory-supported definite MS was based on the Poser criteria.[4]
- In the 2-year extension phase, patients originally receiving placebo were re-randomized to either IFN β-1a 44 µg or 22 µg SC tiw (placebo/delayed treatment); patients originally receiving active treatment continued treatment at their original dosage.[5]
- All patients received T2-weighted magnetic resonance imaging (MRI) scans twice yearly. A subgroup of patients (frequent-MRI cohort, n=205) received monthly T2 and T1 gadolinium-enhancing (Gd+) scans at baseline and during the first 9 months of treatment.[3,6]
- The primary outcome measure was ARR over 2 years.[3]

Post hoc analyses

- We examined the effects of IFN β-1a on ARR, time to first relapse, and EDSS progression at Year 2 and Year 4 in patients from the frequent-MRI cohort stratified by baseline radiological activity and baseline disease duration (DD).
- Patients were categorized into tertiles of baseline radiological activity (ratio of T2 or Gd+ lesions to DD [T2/DD and Gd/DD, respectively]) (**Table 1**).
- Cutoffs based on tertiles were defined for the ratio of lesion number to DD, allowing for even distribution across the population (approximately 67 observations per tertile). However, due to a high number of '0' values for T2 and Gd+ lesions, the data are not distributed evenly and most subjects are categorized in the lowest tertile. Due to low patient numbers in the middle tertile, the analysis focuses on patients in the highest tertile. Between-treatment differences in ARR were analyzed using a negative binomial model with number of relapses within 2 years prior, age, and treatment as independent variables and with log of time on study as an offset.

Table 1. Patient tertile categorization[a] by ratio of baseline radiological activity and disease duration

	Placebo/delayed treatment (n=69)	IFN β-1a 44 µg SC tiw (n=68)	IFN β-1a 22 µg SC tiw (n=64)
T2/DD,[b,c] n (%)			
Lowest tertile	37 (53.6)	36 (52.9)	41 (64.1)
Middle tertile	8 (11.6)	8 (11.8)	5 (7.8)
Highest tertile	24 (34.8)	24 (35.3)	18 (28.1)
Gd/DD,[c,d] n (%)			
Lowest tertile	31 (44.9)	39 (57.4)	31 (48.4)
Middle tertile	11 (15.9)	9 (13.2)	14 (21.9)
Highest tertile	27 (39.1)	20 (29.4)	19 (29.7)

DD, disease duration; **Gd+**, gadolinium-enhancing; **IFN β-1a**, interferon beta-1a; **SC**, subcutaneously; **tiw**, three times weekly.
[a]Cutoffs based on tertiles were determined to allow for even distribution across tertiles (approximately 67 patients per tertile); however, a high number of '0' values for T2 and Gd+ lesions were recorded. Therefore, most patients were categorized in the lowest tertile and, as a result, remaining patients in the middle and highest tertiles were unevenly distributed.
[b]1st tertile: 0; 2nd tertile: >0 to ≤0.13; 3rd tertile: >0.13.
[c]1st tertile: 0; 2nd tertile: >0 to ≤0.22; 3rd tertile: >0.22.
[d]Percentages do not total 100% due to rounding.

- Cumulative incidence of time to relapse and time to EDSS progression were graphed using Kaplan-Meier methods, and IFN β-1a was compared with placebo using Cox models with number of relapses within 2 years prior, age, and treatment as independent variables.
  - Disability progression was defined as an increase of ⩾1 point if baseline EDSS score was <6.0, or an increase of ⩾0.5 points if baseline EDSS score was ⩾6, confirmed after 3 months.

RESULTS

- Of the 205 patients in the original frequent-MRI cohort, four patients refused to undergo monthly scans.[3,6] Therefore, a total of 201 patients who received T2 and Gd+ scans at baseline were included in the current analysis (placebo, n=69; IFN β-1a 44 µg SC tiw, n=68; IFN β-1a 22 µg SC tiw, n=64).
- Baseline demographic and clinical characteristics were similar between patient cohorts (**Table 2**).

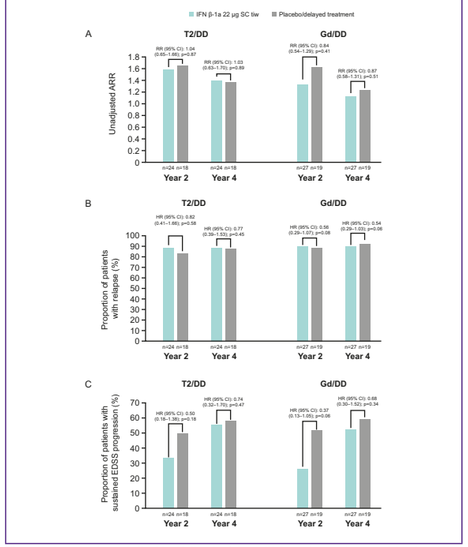
Table 2. Baseline demographic and clinical characteristics

Characteristic[a]	Full cohort (N=560)	Frequent-MRI cohort (n=205)[b]
Age, years	34.9 (7.5)	35.3 (7.4)
Sex, female, %	69.5	69.8
Time since disease onset, years	7.2 (5.8)	7.5 (5.8)
Relapses in previous 2 years	3.0 (1.2)	3.1 (1.1)
EDSS score at baseline	2.5 (1.2)	2.4 (1.2)

EDSS, Expanded Disability Status Scale; **MRI**, magnetic resonance imaging; **SD**, standard deviation.
[a]Values are mean (SD), unless otherwise stated.
[b]Four patients of the original frequent-MRI cohort (n=205) refused to undergo monthly MRI scans and were excluded from the current analysis (n=201).

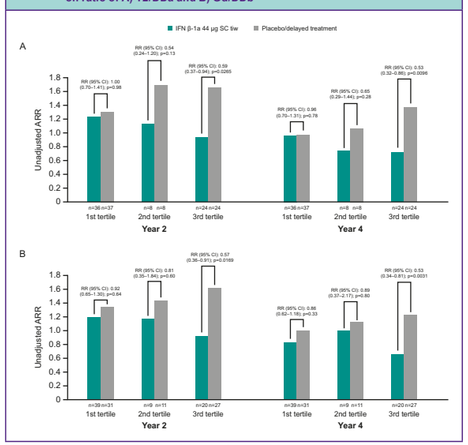
- IFN β-1a 22 µg SC tiw treatment had no statistically significant effects on ARR, time to relapse, and time to sustained EDSS progression in patients categorized in the highest tertiles of baseline radiological activity (T2/DD >0.13 and Gd/DD >0.22), compared with placebo/delayed treatment at Year 4 (**Figure 1**).
  - Differences in time to sustained EDSS progression were observed at Year 2, but these were not statistically significant.
- IFN β-1a 44 µg SC tiw reduced ARR in patients categorized in the highest baseline radiological activity tertiles, compared with placebo/delayed treatment (**Figure 2**).
  - At Year 2, IFN β-1a 44 µg SC tiw treatment was associated with a significant reduction in ARR in patients in the highest tertiles of T2/DD and Gd/DD (T2/DD: rate ratio [RR] 0.59 [95% confidence interval (CI): 0.37–0.94], p=0.0265; Gd/DD: RR 0.57 [0.36–0.91], p=0.0169).
    - IFN β-1a 44 µg SC tiw treatment had a greater effect on patients in the middle and highest tertiles of T2/DD, compared with patients in the lowest tertile of T2/DD (as indicated by lower RRs).
  - At Year 4, the effects of IFN β-1a 44 µg SC tiw treatment on ARR were maintained (T2/DD: RR 0.53 [95% CI: 0.32–0.86], p=0.0096; Gd/DD: RR 0.53 [0.34–0.81], p=0.0031).
  - No significant between-treatment differences were observed in the middle or lowest T2/DD and Gd/DD tertiles.

Figure 1. Effect of IFN β-1a 22 µg SC tiw treatment on A) ARR, B) time to relapse, and C) time to sustained EDSS progression over 4 years in patient tertiles of baseline radiological activity based on ratio of T2/DD[a] and Gd/DD[b]



Effects and p values are 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; **DD**, disease duration; **EDSS**, Expanded Disability Status Scale; **Gd**, gadolinium; **HR**, hazard ratio; **IFN β-1a**, interferon beta-1a; **RR**, rate ratio; **SC**, subcutaneously; **tiw**, three times weekly.
[a]3rd tertile: >0.13.
[b]3rd tertile: >0.22.

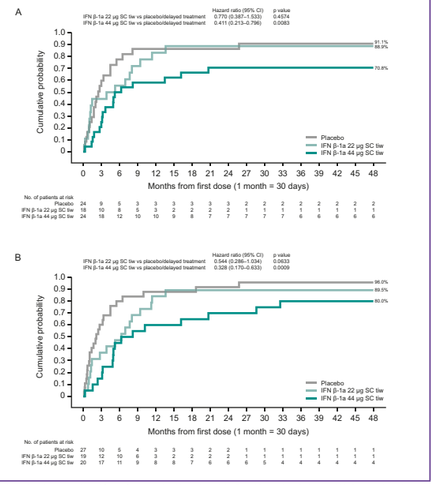
Figure 2. ARRs over 4 years in patient tertiles of baseline radiological activity based on ratio of A) T2/DDa and B) Gd/DDb



Effects and p values are 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; **DD**, disease duration; **Gd**, gadolinium; **IFN β-1a**, interferon beta-1a; **RR**, rate ratio; **SC**, subcutaneously; **tiw**, three times weekly.
[a]1st tertile: 0; 2nd tertile: >0 to ≤0.13; 3rd tertile: >0.13.
[b]1st tertile: 0; 2nd tertile: >0 to ≤0.22; 3rd tertile: >0.22.

- Time to relapse was significantly longer among patients receiving IFN β-1a 44 µg SC tiw in the highest baseline radiological activity tertiles over 4 years, compared with patients in the placebo/delayed treatment group (**Figure 3**).
  - In patients in the highest T2/DD tertile, IFN β-1a 44 µg SC tiw treatment significantly reduced the likelihood of relapse by Year 4 (HR 0.41 [95% CI: 0.21–0.80], p=0.0083).
  - A similar effect was observed up to Year 4 in patients in the highest Gd/DD tertile (HR 0.33 [0.17–0.63], p=0.0009).
  - No significant between-treatment differences were observed in the other tertiles of baseline radiological activity.
- No significant differences in time to EDSS progression were observed in patients receiving IFN β-1a 44 µg SC tiw over 4 years in the highest T2/DD (HR 0.55 [95% CI: 0.25–1.22], p=0.14) and Gd/DD tertiles (HR 0.71 [0.32–1.58], p=0.40) (graphs not shown).

Figure 3. Time to first relapse over 4 years in highest patient tertile of baseline radiological activity based on ratio of A) T2/DD[a] and B) Gd/DD[b]



Hazard ratios and p values are estimated from a Cox proportional hazards model, adjusted for number of relapses within 2 years prior and age. **CI**, confidence interval; **DD**, disease duration; **Gd**, gadolinium; **IFN β-1a**, interferon beta-1a; **SC**, subcutaneously; **tiw**, three times weekly.
[a]1st tertile: 0; 2nd tertile: >0 to ≤0.13; 3rd tertile: >0.13.
[b]1st tertile: 0; 2nd tertile: >0 to ≤0.22; 3rd tertile: >0.22.

CONCLUSIONS

- **The clinical efficacy of IFN β-1a treatment in patients stratified by tertiles of baseline radiological activity was assessed in the current analysis.**
  - **The upper T2/DD and Gd/DD tertiles (the most active tertiles) are equivalent to approximately 1 T2 lesion per 8 years' disease duration and 1 Gd+ lesion per 4–5 years' disease duration, respectively.**
  - **Patients in the upper T2/DD and Gd/DD tertiles had relatively high levels of inflammatory lesion activity despite long disease duration, compared with patients in the middle and lowest tertiles.**
- **Early IFN β-1a 44 µg SC tiw treatment significantly improved clinical outcomes, ARR, and relapse in patients in the highest tertile of baseline radiological activity.**
  - **There was a significant reduction in ARR at Years 2 and 4 in patients treated with IFN β-1a 44 µg SC tiw versus placebo/delayed treatment.**
  - **Over 4 years, IFN β-1a 44 µg SC tiw significantly delayed time to relapse compared with placebo/delayed treatment.**
  - **Results suggest that the greatest reductions in relapse activity occurred in patients in the highest tertile of baseline radiological activity (ie, patients with the highest ratio of lesion number to disease duration).**
- **In the current analysis, we did not individually assess the predictive value of baseline MRI activity and disease duration on clinical outcomes. Further investigation of this relationship is warranted.**

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ACKNOWLEDGMENTS

The trial was sponsored by EMD Serono, Inc.,* Rockland, MA, USA. The authors would like to thank patients, investigators, co-investigators, and the study teams at each of the participating centers. Medical writing assistance was provided by Derek Lavery, Caudex, New York, NY, USA and funded by EMD Serono, Inc.,* Rockland, MA, USA.

DISCLOSURES

ATR has received consulting fees from Acorda, Bayer, Biogen, EMD Serono, Inc.,* Genentech, Genzyme, Mallinckrodt (formerly known as Questcor), Novartis, Pfizer, Sanofi, and Teva Pharmaceuticals.

GC has participated on data and safety monitoring committees for AMO Pharma, Apotek, Gilead Pharmaceuticals, Horizon Pharmaceuticals, Merck, Merck/Pfizer, ModigeneTech/Prolor, Neuren, NHLBI (Protocol Review Committee), NICHD (OPRU oversight committee), OPKO Biologics, Reata Pharmaceuticals, Receptos/Celgene, Sanofi-Aventis, and Teva Pharmaceuticals; has received consulting, speaker, and advisory board fees from CereSpir Inc, Consortium of Multiple Sclerosis Centers (grant), Genentech, Genzyme, Innate Therapeutics, Janssen Pharmaceuticals, Klein-Buendel Incorporated, MedDay, Medimmune, Nivalis, Novartis, Opexa Therapeutics, Roche, Savara Inc., Somahlution, Teva Pharmaceuticals, TG Therapeutics, and Transparency Life Sciences; is employed by the University of Alabama at Birmingham; is President of Pythagoras, Inc., a private consulting company located in Birmingham, AL, USA; and is a statistical reviewer for *JASN*.

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FN has received consulting or speaker fees from Acorda, Bayer HealthCare, the Consortium of Multiple Sclerosis Centers, Genentech, the National MS Society, and Sanofi-Genzyme; and has received research support from Alkermes, the National MS Society, and Novartis.

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Presented at the 31st Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC); May 24–27, 2017; New Orleans, LA, USA