DX14

Clinical and MRI benefits of IFN beta-1a 44 µg SC tiw treatment over 1 year in patients with RMS: subgroup analyses of the PRISMS study

M Cascione,[1] F Dangond,[2] J Fang,[2] A Miller[3]

[1]South Tampa Multiple Sclerosis Center, Tampa, FL, USA; [2]EMD Serono, Inc.,* Rockland, MA, USA; [3]Mount Sinai Hospital, New York, NY, USA

2015 Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC); May 27–30, 2015; Indianapolis, IN, USA

Introduction

- In general, clinical trials of disease-modifying drugs (DMDs) for relapsing forms of multiple sclerosis (RMS) assess the treatment effects on clinical and radiological endpoints over 2 years or longer, as the occurrence of relapses can be variable and infrequent, and the accumulation of physical disability is slow and gradual.[1,2]
- Evidence of rapid efficacy could further characterize the usefulness of DMDs if trials are able to illustrate clinical effects over shorter periods.
- In the 2-year 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 versus placebo, while significantly delaying disability progression in patients with active RMS.[3]
- The relationship between baseline and clinical characteristics and the treatment effect of IFN β-1a SC tiw at 1 year in patients with RMS remains to be characterized.

Objective

- The current *post hoc* analyses investigated the early treatment effect of IFN β-1a 44 µg SC tiw at 1 year in preselected subgroups of patients with RMS from the PRISMS study.

Methods

- Exploratory analyses were conducted on data from the PRISMS trial, in which patients with RMS were randomly assigned to IFN β-1a 44 or 22 µg SC tiw or placebo for 2 years.
- The trial included 560 patients with RMS between 18 and 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 to 5.0. The diagnosis of RMS was based on the Poser criteria.[4]
- The primary endpoint was the number of relapses over 2 years.
- Additional secondary endpoints included magnetic resonance imaging (MRI) measures of disease activity: all patients had proton density/T2-weighted scans twice yearly.
- The current *post hoc* subgroup analysis assessed the treatment effect of IFN β-1a 44 µg SC tiw versus placebo over 1 year in patient subgroups, stratified by the following prespecified baseline characteristics:
  - EDSS score ⩽ and >2.5 (median value)
  - Number of relapses in the prior 2 years (< and ⩾3)
  - Burden of disease (BOD; total T2 lesion area) of ⩽ and >1992.5 mm^2 (median value)
  - Age
  - Sex
  - Time since onset of MS.
- The between-treatment effects on clinical and MRI endpoints over 1 year were assessed for each subgroup. Endpoints included:
  - Relapses: annualized relapse rate (ARR), time to first relapse, and the proportion of patients relapse-free
  - Risk of 3-month confirmed disability progression (1-point increase in EDSS score if the baseline EDSS score was <6.0 or 0.5-point increase if the baseline EDSS score was ⩾6.0) and the proportion of patients free from confirmed disability progression
  - Mean number of active T2 (new or newly enlarging) lesions per patient per scan.
- Relative treatment effects of IFN β-1a 44 µg SC tiw versus placebo were examined using rate ratios, hazard ratios, and odds ratios, and their associated 95% confidence intervals (CIs).

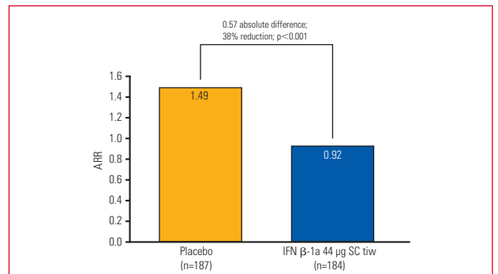
Results

- 560 patients were recruited from 22 centers in nine countries. Demographic and baseline characteristics are shown in **Table 1**.
- In the overall cohort, treatment with IFN β-1a 44 µg SC tiw was associated with significant reductions in clinical and MRI disease activity compared with placebo over 1 year, including: 38% reduction in ARR (p<0.001; **Figure 1**); 45% reduction in risk of relapse (p<0.001); 38% reduction in risk of 3-month confirmed disability progression (p=0.029); and 72% reduction in mean number of active T2 lesions per patient per scan (p<0.001).

Table 1. Demographic and baseline characteristics.

	Placebo (n=187)	IFN β-1a 44 µg SC tiw (n=184)
Age, years, mean (SD)	34.7 (7.5)	35.2 (7.9)
Sex, female, n (%)	141 (75)	122 (66)
Race, white, n (%)	184 (98)	182 (99)
Time since MS onset, years, mean (SD)	6.1 (4.8)	7.8 (6.3)
Relapses in past 2 years, mean (SD)	3.0 (1.3)	3.0 (1.1)
EDSS score, median (Q1, Q3)	2.5 (1.5, 3.5)	2.5 (1.5, 3.5)
BOD (mm^2), median (Q1, Q3)	2099 (763.0, 4430.0)	1903 (943.0, 4223.5)

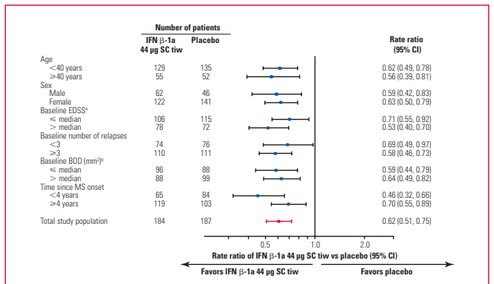
BOD, burden of disease; EDSS, Expanded Disability Status Scale; IFN β-1a, interferon beta 1-a; MS, multiple sclerosis; Q, quartile; SC, subcutaneously; SD, standard deviation; tiw, three times weekly.



Based on negative binomial model with baseline EDSS (⩽3.5 vs >3.5) and age (<40 vs ⩾40 years) as fixed factors, number of relapses 2 years prior to screening and baseline BOD (total area [mm^2] of all MS lesions outlined on the PD/T2 scan) as covariates, and log time on study up to 1 year as offset variable. ARR, annualized relapse rate; BOD, burden of disease; EDSS, Expanded Disability Status Scale; IFN β-1a, interferon beta-1a; MS, multiple sclerosis; PD, proton density; SC, subcutaneously; tiw, three times weekly.

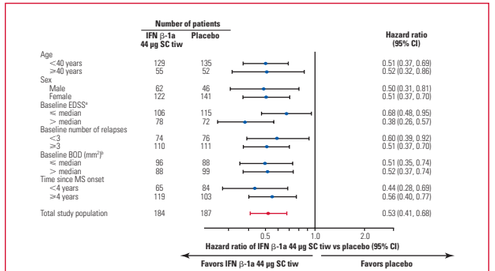
Figure 1. Annualized relapse rate at Year 1.

- The results of the subgroup analyses were consistent with the efficacy results seen in the overall population over 1 year. In all subgroups, point estimates and 95% CIs indicated treatment benefits in favor of IFN β-1a 44 µg SC tiw versus placebo on:
  - ARR (**Figure 2**)
  - Time to first relapse (**Figure 3**)
  - Proportion of patients relapse free (with the exception of patients aged ⩾40 years; **Figure 4**)
  - Number of active T2 lesions (**Figure 5**).
- There was a **significant effect** favoring IFN β-1a 44 µg SC tiw versus placebo on risk of 3-month confirmed **disability progression** in **females** (p=0.029) and in **patients with BOD above the median** (p=0.015); there was also a consistent trend for estimates of relative treatment effects to favor IFN β-1a 44 µg SC tiw versus placebo across all other patient subgroups (**Figure 6**). Similar treatment benefits were seen in favor of IFN β-1a 44 µg SC tiw versus placebo on proportion of patients free from 3-month confirmed disability progression (**Figure 7**).



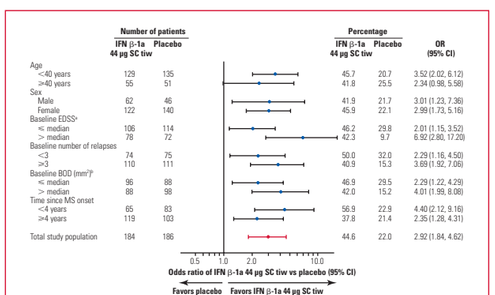
Based on Poisson model with treatment as factor; age, number of pre-study relapses, baseline EDSS, and baseline BOD as covariates; and log time on study at 1 year as offset variable. (Age, number of pre-study relapses, baseline EDSS, and baseline BOD were not covariates used in analysis of the subgroups determined by each of these respective characteristics).
BOD, burden of disease; CI, confidence interval; EDSS, Expanded Disability Status Scale; IFN β-1a, interferon beta-1a; MS, multiple sclerosis; SC, subcutaneously; tiw, three times weekly.
*Median baseline EDSS score: 2.5.
†Median baseline BOD: 1992.5 mm².

Figure 2. Forest plot of ARR at Year 1.



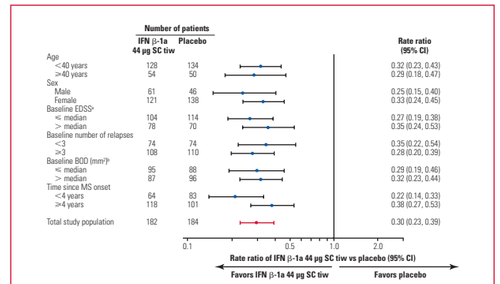
Based on Cox's proportional hazard model with treatment as factor, and age, number of pre-study relapses, baseline EDSS, and baseline BOD as covariates. (Age, number of pre-study relapses, baseline EDSS, and baseline BOD were not covariates used in analysis of the subgroups determined by each of these respective characteristics).
BOD, burden of disease; CI, confidence interval; EDSS, Expanded Disability Status Scale; IFN β-1a, interferon beta-1a; MS, multiple sclerosis; SC, subcutaneously; tiw, three times weekly.
*Median baseline EDSS score: 2.5.
†Median baseline BOD: 1992.5 mm².

Figure 3. Forest plot of time to first relapse over Year 1.



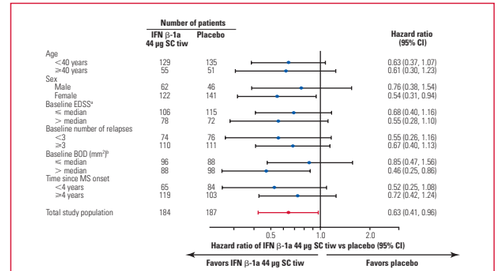
Based on logistic model with treatment as factor, and age, number of pre-study relapses, baseline EDSS, and baseline BOD as covariates. (Age, number of pre-study relapses, baseline EDSS, and baseline BOD were not covariates used in analysis of the subgroups determined by each of these respective characteristics.)
BOD, burden of disease; CI, confidence interval; EDSS, Expanded Disability Status Scale; IFN β-1a, interferon beta-1a; MS, multiple sclerosis; OR, odds ratio; SC, subcutaneously; tiw, three times weekly.
*Median baseline EDSS score: 2.5.
†Median baseline BOD: 1992.5 mm².

Figure 4. Forest plot of proportion of patients relapse free at Year 1.



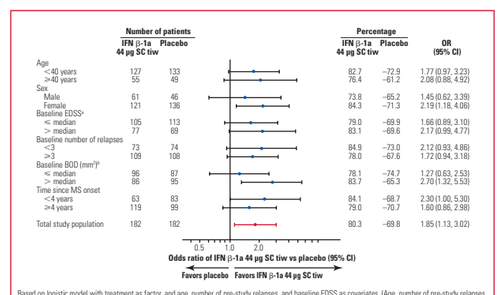
Based on negative binomial model with treatment as factor, baseline BOD as covariate, and log number of scans up to Year 1 as offset variable. Baseline BOD was not a covariate used in analysis of the baseline BOD subgroups. Active T2 lesions up to 1 year included those lesions detected at the 6-month or 1-year MRI assessments.
BOD, burden of disease; CI, confidence interval; EDSS, Expanded Disability Status Scale; IFN β-1a, interferon beta-1a; MRI, magnetic resonance imaging; MS, multiple sclerosis; SC, subcutaneously; tiw, three times weekly.
*Median baseline EDSS score: 2.5.
†Median baseline BOD: 1992.5 mm².

Figure 5. Forest plot of number of active T2 lesions per patient per scan up to Year 1.



Based on Cox's proportional hazard model with treatment as factor, and age, number of pre-study relapses, and baseline EDSS as covariates. (Age and number of pre-study relapses were not covariates used in analysis of the subgroups determined by each of these respective characteristics. Baseline EDSS was not a covariate in baseline EDSS or baseline BOD subgroups.)
BOD, burden of disease; CI, confidence interval; EDSS, Expanded Disability Status Scale; IFN β-1a, interferon beta-1a; MS, multiple sclerosis; SC, subcutaneously; tiw, three times weekly.
*Median baseline EDSS score: 2.5.
†Median baseline BOD: 1992.5 mm².

Figure 6. Forest plot of time to 3-month confirmed disability progression over Year 1.



Based on logistic model with treatment as factor, and age, number of pre-study relapses, and baseline EDSS as covariates. (Age, number of pre-study relapses, and baseline EDSS were not covariates used in analysis of the subgroups determined by each of these respective characteristics.)
BOD, burden of disease; CI, confidence interval; EDSS, Expanded Disability Status Scale; IFN β-1a, interferon beta-1a; MS, multiple sclerosis; OR, odds ratio; SC, subcutaneously; tiw, three times weekly.
*Median baseline EDSS score: 2.5.
†Median baseline BOD: 1992.5 mm².

Figure 7. Forest plot of proportion of patients free of 3-month confirmed disability progression at Year 1.

Conclusions

- Subgroup analyses were consistent with findings in the overall population, demonstrating the treatment benefit of IFN β-1a 44 µg SC tiw versus placebo on relapse and MRI endpoints at 1 year in patients with RMS, including:
  - Significant benefits on ARR across all subgroups
  - A robust, consistent benefit on MRI disease activity
  - Consistent benefit on 3-month confirmed disability progression, with significant effects in females and patients with baseline BOD above the median. It should be noted that significant treatment benefits on disability outcomes may have been difficult to ascertain within 1 year due to the relatively slow development of disability progression within this short time frame.
- In conclusion, these subgroup analyses were consistent with findings in the overall population, demonstrating the early treatment benefit of IFN β-1a 44 µg SC tiw in key patient subgroups, including those with higher levels of disease activity at baseline.

References

1. Uitdehaag B, *et al. Curr Med Res Opin* 2011;27:1529–37.

2. Bevan CJ, Cree BA. *JAMA Neurol* 2014;71:269–70.

3. PRISMS Study Group. *Lancet* 1998;352:1498–504.

4. Poser CM, *et al. Ann Neurol* 1983;13:227–31.

Acknowledgments

The authors thank Stephen Craig, PhD, of Caudex, Oxford, UK (supported by EMD Serono, Inc.,* Rockland, MA, USA and Pfizer Inc, New York, NY, USA) for editorial assistance in drafting the poster, collating the comments of authors, and assembling tables and figures.

Study supported by EMD Serono, Inc.,* Rockland, MA, USA and Pfizer Inc, New York, NY, USA.

Disclosures

MC has received funding/honoraria for research, consultation, and/or speakers bureau participation from Acorda, Bayer HealthCare, Biogen, EMD Serono, Inc.,* Genentech, Sanofi-Genzyme, Novartis, Pfizer, Roche, and Teva Pharmaceuticals.

FD and **JF** are employees of EMD Serono, Inc.,* Rockland, MA, USA.

AM has received consulting fees from Acorda, Biogen, CVS Caremark, EMD Serono, Inc.,* Sanofi-Genzyme, GlaxoSmithKline, Novartis, Nuron Biotech Inc., ONO, and Questcor; has received fees for advisory board participation from Acorda, Biogen, CVS Caremark, EMD Serono, Inc.,* Sanofi-Genzyme, GlaxoSmithKline, Novartis, Nuron Biotech Inc., ONO, and Questcor; and has received grant/research support from Acorda, Biogen, Genentech, Sanofi-Genzyme, Questcor, and Roche.

To view the ePoster, scan the QR code or go to http://medpub-poster.merckgroup.com/CMSC2015_DX14.pdf

*A subsidiary of Merck KGaA, Darmstadt, Germany.