⩾4 active T2 lesions at 6 months predicts future relapse/disability in patients with RMS on placebo but not IFN β-1a SC tiw: *post hoc* PRISMS analyses

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Introduction

- Magnetic resonance imaging (MRI) is an important component of diagnosing multiple sclerosis (MS),[1,2] as well as assessing the course of disease and efficacy of treatment.
- The ability to predict disease course in untreated patients, or future clinical response to treatment in those receiving disease-modifying drugs, would offer considerable advantage in clinical practice.
  - Multiple studies have examined the possible predictive value of early MRI lesions on future relapses and/or disease progression in patients with relapsing MS (RMS).[3-5]
  - A systematic review and meta-analytic approach concluded that the predictive value of early MRI for later clinical outcomes in patients with RMS increased with the number of new T2 lesions, and that the relationship between MRI lesions and longer-term outcomes was stronger for patients receiving interferon beta (IFN β) than those receiving placebo.[6]
  - However, studies are marked by heterogeneous designs, with variations including the MRI protocol, the length of follow-up, and the IFN agent being used.
  - In patients receiving IFN β-1a subcutaneously (SC) three times weekly (tiw), active T2 lesions at 1 year were associated with a 6% increase in the odds of disease progression over 2 years.[7] However, in an analysis of patients being treated with any IFN β formulation (including IFN β-1a 44 or 22 μg SC tiw as well as IFN β-1a 30 μg intramuscularly once weekly and IFN β-1b 250 μg every other day), those presenting new T2 lesions after 1 year of therapy had a 17-times greater risk of progression (hazard ratio 16.8, 95% confidence interval 7.6–37.1, p<0.001) over a mean 4.8 years of follow-up.[4]
  - The relevance of MRI lesion activity to future relapse and progression activity, and the effects of IFN β-1a 44 μg SC tiw on this relationship, thus remain incompletely understood.
- In the 2-year, double-blind, placebo-controlled PRISMS (Prevention of Relapses and disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) study, IFN β-1a SC tiw significantly reduced relapses and active T2 lesions, and prolonged time to confirmed disability progression, in patients with RMS.[8] Results in a cohort of patients undergoing monthly MRI scans for 9 months showed that IFN β-1a SC tiw significantly reduced active lesions compared with placebo as early as 2 months after the start of treatment.[9]
- The 2-year extension of the PRISMS study enrolled 90% of the original PRISMS study cohort and provided the opportunity to evaluate treatment effect over a longer term.[10]

Objective

- To examine relationships between increasing numbers of active T2 lesion numbers at 6 months and subsequent clinical events in patients receiving IFN β-1a SC tiw or placebo.

Methods

PRISMS study

- Exploratory analyses were conducted on data from the PRISMS study, in which patients with RMS were randomized to receive IFN β-1a 44 μg SC tiw (n=184) or 22 μg SC tiw (n=189) or placebo (n=187) for 2 years.[8] Patients originally receiving IFN β-1a 44 μg SC tiw (n=167) or 22 μg SC tiw (n=167) continued treatment for Years 3 and 4, while those originally receiving placebo (n=172) switched to IFN β-1a SC tiw for Years 3 and 4 (placebo/delayed treatment group) in the follow-up study.[10]
- Eligible patients were 18–50 years of age, had a history of ⩾2 relapses in the previous 2 years, and had an Expanded Disability Status Scale (EDSS) score of 0–5.0. Diagnosis of clinically definite or laboratory-supported definite MS was based on the Poser criteria.[11]
- The primary endpoint was the number of relapses over 2 years.
- All patients had T2 MRI scans every 6 months.
- *Post hoc* comparisons (in groups receiving IFN β-1a 44 μg SC tiw continuously or placebo/delayed treatment) of annualized relapse rate (ARR), according to the number of active (new or newly enlarging) T2 lesions on MRI scans at Month 6 (0 vs >0, ⩾2 vs 0–1, ⩾4 vs 0, and ⩾4 vs 0–1 lesions), were performed using a negative binomial model; relapses (yes/no) and disability progression were compared using logistic regression.
- Disability progression was defined as an increase of ⩾1 EDSS point if baseline EDSS score was ⩽5.5, or an increase of 0.5 points if baseline EDSS score was ⩾6, confirmed after 3 months.

Results

- Baseline characteristics are shown in **Table 1**.

Table 1. Demographic and disease characteristics at baseline.

	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 (75.4)	122 (66.3)
Race, white, n (%)	184 (98.4)	182 (98.9)
Time since MS onset, years, mean (SD)	6.1 (4.8)	7.8 (6.3)
Number of 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)
T2 burden of disease, mm², median (Q1, Q3)	2099 (763, 4430)	1903 (943, 4224)

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.

- Compared with placebo, fewer patients receiving IFN β-1a 44 μg SC tiw had active T2 lesions at 6 months (**Table 2**).

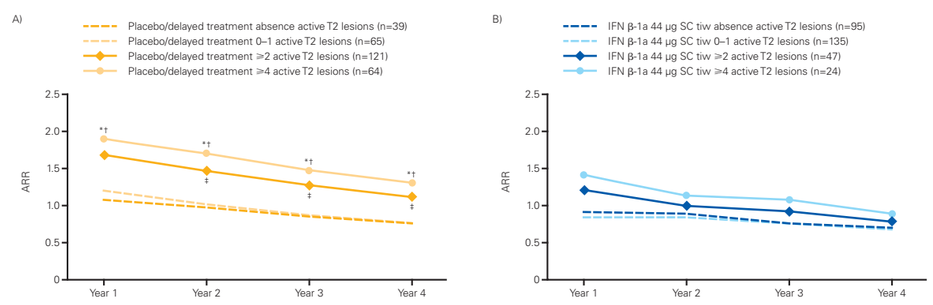
Table 2. Number of patients with various numbers of active T2 lesions at 6 months.

	Placebo (n=186)[a]	IFN β-1a 44 μg SC tiw (n=182)[a]
Absence, n (%)	39 (21.0)	95 (52.2)
Presence, n (%)	147 (79.0)	87 (47.8)
0–1, n (%)	65 (34.9)	135 (74.2)
⩾2, n (%)	121 (65.1)	47 (25.8)
⩾4, n (%)	64 (34.4)	24 (13.2)

IFN β-1a, interferon beta 1-a; SC, subcutaneously; tiw, three times weekly.
[a]Indicates the number with data available for this analysis.

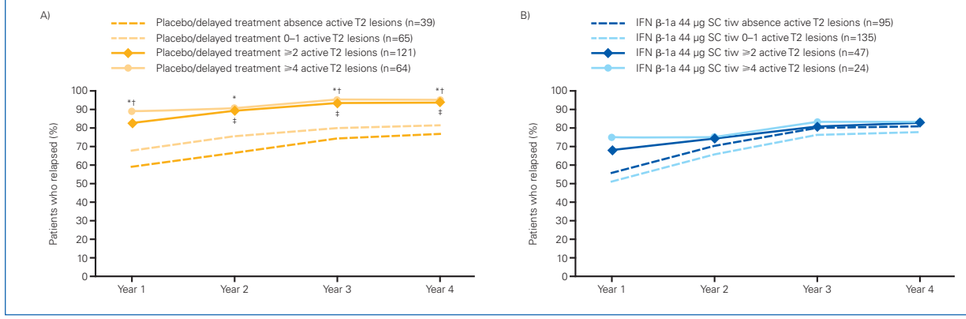
- In the placebo/delayed treatment group, there was a trend, although not significant, for a higher ARR for those who had any active T2 lesions at Month 6 versus those without (1.055 vs 0.780, respectively, over 4 years; p=0.0807). As shown in **Figure 1A**, ARR was significantly higher over Years 1, 2, 3, and 4 among patients with ⩾4 active T2 lesions at 6 months versus those with 0 or 0–1 lesions, and those with ⩾2 active T2 lesions at 6 months had significantly higher ARR over Years 2, 3, and 4 versus those with 0–1 active T2 lesions.
  - Higher lesion count was not associated with significantly higher ARR in the IFN β-1a 44 μg SC tiw group (**Figure 1B**).
  - The ARR over 4 years among patients in the IFN β-1a 44 μg SC tiw group with ⩾2 active T2 lesions at 6 months (0.781) was similar to the ARR in the placebo/delayed treatment group among those with 0 active T2 lesions at 6 months (0.780).
- In the placebo/delayed treatment group, the presence of ⩾4 active T2 lesions at 6 months was associated with a statistically significantly higher percentage of patients who had relapses over 1, 2, 3, and 4 years, versus patients with 0 lesions, and over Years 1, 3, and 4 versus patients with 0–1 lesions (**Figure 2A**). Patients with ⩾2 active T2 lesions at 6 months were more likely to have relapsed over 2, 3, and 4 years versus those with 0–1 active T2 lesions. Additionally, the presence of any active T2 lesions at 6 months was associated with a significantly higher percentage of patients who relapsed over 1, 2, 3, and 4 years versus the absence of active T2 lesions (over 4 years, 93.2% and 76.9% relapsed; p=0.0067).
- However, in the IFN β-1a 44 μg SC tiw group, relapses over 1, 2, 3, or 4 years were not predicted by any of the lesion counts studied (**Figure 2B**).
- For the endpoint of confirmed EDSS progression in the placebo/delayed treatment group, the presence of any active T2 lesions was not associated with a greater risk of progression versus the absence of lesions. However, the presence of ⩾2 active T2 lesions at 6 months was associated with a significantly higher percentage of patients with progression over Years 2, 3, and 4 versus those with 0–1 lesions; the presence of ⩾4 active T2 lesions was associated with a higher percentage of patients with progression over Years 2 and 3 versus those with 0–1 lesions (**Figure 3A**).
- In the IFN β-1a 44 μg SC tiw group, percentages of patients with progression were not significantly different whether patients had ⩾4 versus 0 or 0–1 lesions, or between patients with presence versus absence or ⩾2 versus 0–1 active T2 lesions (**Figure 3B**).

Figure 1. ARR over Years 1, 2, 3, and 4 by 6-month active T2 lesions for A) the placebo/delayed treatment group and B) the IFN β-1a 44 μg SC tiw group.



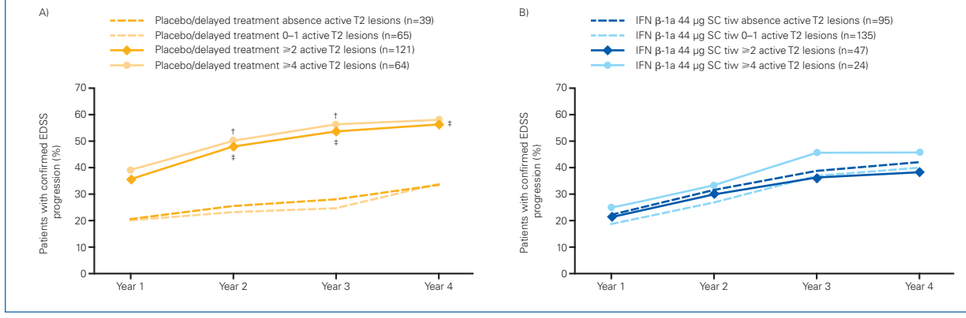
Based on logistic regression model with number of relapses within 2 years prior, age, baseline EDSS score, baseline burden of disease, and predictor as independent variables.
ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; IFN β-1a, interferon beta-1a; SC, subcutaneously; tiw, three times weekly.
*p<0.05 for the ⩾4 versus the 0 lesion group; †p<0.05 for the ⩾4 versus the 0–1 lesion group; ‡p<0.05 for the ⩾2 versus the 0–1 lesion group. Other comparisons were not significant.

Figure 2. Percentage of patients with relapse at Years 1, 2, 3, and 4 by 6-month active T2 lesions for A) the placebo/delayed treatment group and B) the IFN β-1a 44 μg SC tiw group.



Based on logistic regression model adjusting for number of relapses within 2 years prior, age, baseline EDSS score, and baseline burden of disease.
EDSS, Expanded Disability Status Scale; IFN β-1a, interferon beta-1a; SC, subcutaneously; tiw, three times weekly.
*p<0.05 for the ⩾4 versus the 0 lesion group; †p<0.05 for the ⩾4 versus the 0–1 lesion group; ‡p<0.05 for the ⩾2 versus the 0–1 lesion group. Other comparisons were not significant.

Figure 3. Percentage of patients with confirmed EDSS progression at Years 1, 2, 3, and 4 by 6-month active T2 lesions for A) the placebo/delayed treatment group and B) the IFN β-1a 44 μg SC tiw group.



Based on logistic regression model with number of relapses within 2 years prior, age, baseline EDSS score, baseline burden of disease, and predictor as independent variables.
EDSS, Expanded Disability Status Scale; IFN β-1a, interferon beta-1a; SC, subcutaneously; tiw, three times weekly.
†p<0.05 for the ⩾4 versus the 0–1 lesion group; ‡p<0.05 for the ⩾2 versus the 0–1 lesion group. Other comparisons were not significant.

Conclusions

- **Compared with patients in the placebo/delayed treatment group, fewer patients receiving IFN β-1a 44 μg SC tiw had active T2 lesions at 6 months, and notably fewer had ⩾4 active T2 lesions.**
- **Greater T2 lesion activity was not associated with worsened clinical results in patients with RMS receiving IFN β-1a 44 μg SC tiw, but was associated with poorer outcomes in those receiving placebo/delayed treatment.**
  - **This contrasts with previous results that suggested a greater relevance of early T2 lesions in patients receiving any IFN β therapy to future clinical effects than in patients receiving placebo, and of a greater predictive value for increasing numbers of T2 lesions in patients receiving IFN β.**
- **The observation that in other research early T2 lesions were associated with subsequent clinical decline when including any IFN β therapy, but not in these results among patients receiving only IFN β-1a 44 μg SC tiw, suggests possible relevance of the dose of IFN β-1a to the predictive effect of early lesions. The long-term effects of T2 lesions at 6 months in patients receiving placebo, even after being switched to active treatment at 2 years, highlights the importance of early treatment in patients with RMS.**

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Disclosures

AT has acted as a consultant for Biogen, Genzyme, Roche, and Teva, and is Principal Investigator on clinical trials with Biogen, Chugai, Genzyme, and Roche. **RB** has acted as a consultant for Acorda, Avanir, Bayer, Biogen, Genzyme, Novartis, and Teva. **HZ** is an employee of EMD Serono, Inc.,* Rockland, MA, USA. **FD** is an employee of EMD Serono, Inc.,* Billerica, MA, USA. **DL** is the director of the UBC MS/MRI Research Group, which has been contracted to perform central analysis of MRI scans for therapeutic trials with Genzyme, Hoffmann-La Roche, Merck Serono, Nuron, Perspectives, and Sanofi-Aventis. He has acted as a consultant to Vertex Pharmaceuticals; has served on scientific advisory boards for Novartis, Nuron, and Roche; has served on a data and safety advisory board for Opexa; and has received research funding from the Canadian Institute of Health Research and Multiple Sclerosis Society of Canada.

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