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Predictive value of early MRI measures in patients with RRMS receiving interferon β–1a SC tiw or placebo: *post hoc* analyses of PRISMS data

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Introduction

- Magnetic resonance imaging (MRI) is an important component of diagnosis[1] and assessing the course of disease, as well as assessing the efficacy of treatment of patients with relapsing forms of multiple sclerosis (RMS). However, debate continues regarding which particular MRI measures are most relevant to clinical response.
- Early on-treatment prediction of which patients will show long-lasting clinical response to therapy would offer considerable advantage in clinical practice. Previous research has included evaluation of 6- or 12-month MRI results as predictors of response among groups of patients with RMS treated with interferon beta (IFN β).[2-4]
- PRISMS (Prevention of Relapses and disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) was a 2-year, double-blind, placebo-controlled study that demonstrated that IFN β-1a subcutaneously (SC) three times weekly (tiw) significantly reduced relapses and active T2 lesions, while significantly delaying disability progression in patients with active RMS.[5] Monthly MRI scans in the frequent-MRI cohort showed the rapid onset of radiologically measured treatment effect compared with placebo.
- The 2-year extension of the PRISMS study provides the opportunity to evaluate clinical effects over a long-term follow-up.

Objective

- To examine the predictive value of early MRI results on future clinical outcomes of patients with RMS receiving 4 years of treatment with IFN β-1a SC tiw or 2 years of treatment with placebo followed by 2 years of treatment with IFN β-1a SC tiw.

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.
  - In the 2-year extension phase, patients originally receiving placebo for 2 years in PRISMS were re-randomized to IFN β-1a 44 or 22 µg SC tiw (Years 3 and 4: delayed treatment group). Patients receiving IFN β-1a SC tiw continued at their original dosage in the extension phase (continuous treatment groups).[6]
- 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 0–5.0, were randomized and received treatment. Diagnosis of RMS was based on the Poser criteria.[7]
- The primary endpoint was the number of relapses over 2 years.
- All patients had proton density (PD)/T2-weighted scans twice yearly. A subgroup from PRISMS-2 had monthly PD/T2 and T1 gadolinium-enhancing (Gd+) scans before and during the first 9 months of treatment (frequent-MRI cohort).
- Exploratory analyses assessed monthly MRI lesions in the frequent-MRI cohort and the predictive value of active T2 lesions at 6 months on EDSS worsening (increase of ⩾1 point if baseline EDSS was ⩽5.5, or increase of 0.5 points if baseline EDSS was ⩾6), EDSS progression (worsening confirmed 3 months later), and relapses over 1, 2, 3, or 4 years in the entire cohort.
- For cumulative mean number of Gd+ or active T2 lesions per patient per scan from baseline to 9 months, negative binomial regression was conducted on the number of lesions while adjusting for number of corresponding lesions at baseline (natural log of the number of scans as the offset variable).
- Percentages of patients in each treatment group with or without 6-month active T2 lesions who had confirmed EDSS progression, had EDSS worsening, or had relapses at any point post treatment were compared at each year based on a logistic regression model. Independent variables included number of relapses within 2 years prior, age, baseline EDSS score, baseline burden of disease, and predictor.
- Additionally, percentages of patients with 0–1 or ⩾2 active T2 lesions at 6 months, who over 1, 2, 3, or 4 years had confirmed EDSS progression or had relapsed, were compared using a similar model.

Results

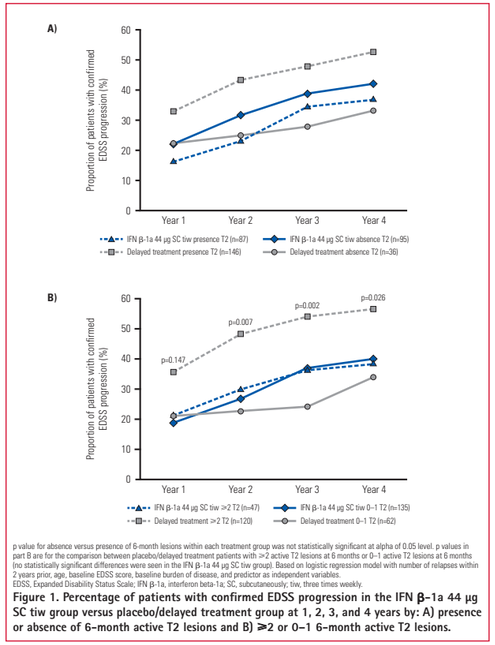
- 560 patients were recruited from 22 centers in nine countries. Demographic and baseline patient characteristics are shown in **Table 1**.

Table 1. Demographic and baseline patient characteristics.

	Placebo (n=187)	IFN β-1a 22 µg SC tiw (n=189)	IFN β-1a 44 µg SC tiw (n=184)
Age, years, mean (SD)	34.7 (7.5)	34.8 (7.0)	35.2 (7.9)
Sex, female, n (%)	141 (75)	126 (67)	122 (66)
Race, white, n (%)	184 (98)	188 (99)	182 (99)
Time since MS onset, years, mean (SD)	6.1 (4.8)	7.7 (6.1)	7.8 (6.3)
Number of relapses in past 2 years, mean (SD)	3.0 (1.3)	3.0 (1.1)	3.0 (1.1)
EDSS score, median	2.4	2.5	2.5

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

- In an analysis of frequent-MRI cohort data, IFN β-1a SC tiw (both doses) was associated with significantly fewer active T2 lesions per patient per scan versus placebo from 3 months onward. At Month 6, the mean number of active T2 lesions per patient per scan was 0.2 in the IFN β-1a 44 µg SC tiw group versus 0.8 in patients receiving placebo ($p<0.0001$). Similarly, beginning from 2 months onward, both IFN β-1a SC tiw doses were associated with significantly fewer Gd+ lesions per patient per scan versus placebo; at 6 months, mean Gd+ lesions per patient per scan were 0.3 and 1.5 in the IFN β-1a 44 µg SC tiw and placebo groups, respectively ($p<0.0001$).
- In the overall PRISMS cohort, 146/187 (78.1%) patients in the placebo/delayed treatment group had ⩾1 active T2 lesion at 6 months versus 87/184 (47.3%) and 100/189 (52.9%) patients in the IFN β-1a 44 and 22 µg SC tiw groups, respectively.
- In comparisons between patients with or without active T2 lesions at 6 months, no statistically significant differences in confirmed EDSS progression over 1, 2, 3, or 4 years were seen in the placebo/delayed treatment or IFN β-1a 44 µg SC tiw groups (**Figure 1A**). However, patients with active T2 lesions at 6 months in the placebo/delayed treatment group showed consistent trends toward higher percentages having progression (differences of 10–20% at each time point), while there was less of a difference between patients with or without 6-month active T2 lesions receiving IFN β-1a 44 µg SC tiw. In the IFN β-1a 22 µg SC tiw group, significantly more patients with active T2 lesions at 6 months (vs those without) had confirmed EDSS progression at 3 and 4 years (**Table 2**).
- When patients with 0–1 active T2 lesions at 6 months were compared with those with ⩾2 active T2 lesions at 6 months, statistically significant differences were seen in the placebo/delayed treatment group in terms of confirmed EDSS progression over 2, 3, and 4 years (**Figure 1B**). However, no significant differences were seen between patients with 0–1 or ⩾2 active T2 lesions at 6 months in the IFN β-1a 44 µg SC tiw group.
  - At Year 3 only, statistically significantly more patients in the IFN β-1a 22 µg SC tiw group with ⩾2 active T2 lesions at 6 months had confirmed EDSS progression versus those with 0–1 lesions (**Table 2**). At Year 4, this difference was marginally significant ($p=0.059$).
- The presence of 6-month active T2 lesions was predictive of EDSS worsening over 3 and 4 years in the placebo/delayed treatment group, but not in either of the IFN β-1a SC tiw groups (**Table 3**).



p value for absence versus presence of 6-month lesions within each treatment group was not statistically significant at alpha of 0.05 level. p values in part B are for the comparison between placebo/delayed treatment patients with ⩾2 active T2 lesions at 6 months or 0–1 active T2 lesions at 6 months (no statistically significant differences were seen in 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.

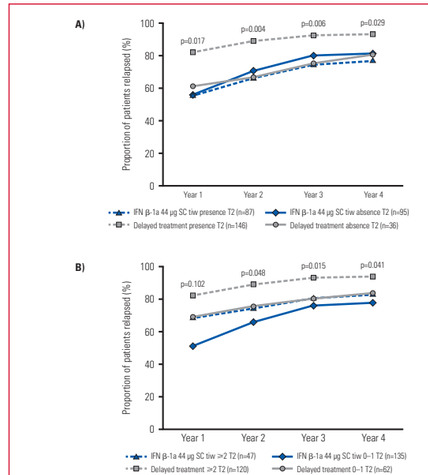
Figure 1. Percentage of patients with confirmed EDSS progression in the IFN β–1a 44 µg SC tiw group versus placebo/delayed treatment group at 1, 2, 3, and 4 years by: A) presence or absence of 6–month active T2 lesions and B) ⩾2 or 0–1 6–month active T2 lesions.

Table 3. Percentages of patients in each treatment group having EDSS worsening,[a] by active T2 lesions at 6 months (presence vs absence and 0–1 vs ⩾2).

	Active T2 lesions at 6 months	Year 1, % with EDSS worsening	p value (between lesion subgroups)	Year 2, % with EDSS worsening	p value (between lesion subgroups)	Year 3, % with EDSS worsening	p value (between lesion subgroups)	Year 4, % with EDSS worsening	p value (between lesion subgroups)
Placebo/delayed treatment	Absence (n=36)	47.2	0.453	55.6	0.086	58.3	0.019	58.3	0.006
	Presence (n=146)	60.3		74.0		81.5		83.6	
IFN β-1a 22 µg SC tiw	Absence (n=83)	42.2	0.598	53.0	0.401	57.8	0.189	62.7	0.157
	Presence (n=100)	47.0		59.0		68.0		74.0	
IFN β-1a 44 µg SC tiw	Absence (n=95)	41.1	0.476	53.7	0.311	60.0	0.636	63.2	0.388
	Presence (n=87)	41.4		50.6		59.8		59.8	
Placebo/delayed treatment	0–1 (n=62)	48.4	0.317	59.7	0.102	62.9	0.013	66.1	0.025
	⩾2 (n=120)	62.5		75.8		84.2		85.0	
IFN β-1a 22 µg SC tiw	0–1 (n=117)	45.3	0.764	55.6	0.722	61.5	0.523	65.0	0.183
	⩾2 (n=66)	43.9		57.6		66.7		75.8	
IFN β-1a 44 µg SC tiw	0–1 (n=135)	40.0	0.898	52.6	0.424	62.2	0.093	64.4	0.060
	⩾2 (n=47)	44.7		51.1		53.2		53.2	

EDSS, Expanded Disability Status Scale; IFN β-1a, interferon beta 1-a; SC, subcutaneously; tiw, three times weekly.
[a]EDSS worsening was defined as an increase of ⩾1 point if baseline EDSS was ⩽5.5, or increase of 0.5 point if baseline EDSS was ⩾6. Based on logistic regression model with number of relapses within 2 years prior, age, baseline EDSS, baseline burden of disease, and predictor as independent variables.

- The presence of 6-month active T2 lesions was associated with a statistically significantly higher percentage of patients who had relapses over 1, 2, 3, and 4 years in the placebo/delayed treatment group only; in the IFN β-1a 44 µg SC tiw group, the percentages of patients with relapses were similar regardless of presence or absence of active T2 lesions at 6 months, and were similar to the percentage of patients in the placebo/delayed treated group without active T2 lesions at 6 months (**Figure 2A**). When patients were categorized by number of T2 lesions at 6 months (having ⩾2 vs 0–1 active T2 lesions), significantly more patients in the placebo/delayed treatment group with ⩾2 active T2 lesions at 6 months (vs those with 0–1 active T2 lesions) had relapsed at Years 2, 3, and 4 (**Figure 2B**); no significant differences were seen in the IFN β-1a 44 µg SC tiw group regardless of whether patients had 0–1 or ⩾2 active T2 lesions at 6 months.
  - No significant differences in percentages of patients who relapsed were seen in the IFN β-1a 22 µg SC tiw group when comparing those with presence or absence of active T2 lesions at 6 months, or those with 0–1 versus 2 active T2 lesions at 6 months (data not shown).



p value indicates differences according to 6-month lesions within the placebo/delayed treatment group (no statistically significant differences were seen in 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.

Figure 2. Percentage of patients relapsed in the IFN β–1a 44 µg SC tiw versus placebo/delayed treatment groups over Years 1, 2, 3, and 4 by: A) presence or absence of 6–month active T2 lesions and B) ⩾2 or 0–1 6–month active T2 lesions.

Table 2. Percentages of patients having sustained EDSS progression[a] in the IFN β–1a 22 µg SC tiw group, by T2 lesions at 6 months (presence vs absence and 0–1 vs ⩾2).

	Active T2 lesions at 6 months	Year 1, % with sustained EDSS progression	p value (between lesion subgroups)	Year 2, % with sustained EDSS progression	p value (between lesion subgroups)	Year 3, % with sustained EDSS progression	p value (between lesion subgroups)	Year 4, % with sustained EDSS progression	p value (between lesion subgroups)
IFN β-1a 22 µg SC tiw	Absence (n=83)	14.5	0.127	26.5	0.102	31.3	0.008	37.3	0.020
	Presence (n=100)	22.0		37.0		51.0		54.0	
	0–1 (n=117)	16.2	0.162	29.1	0.165	36.8	0.043	41.9	0.059
	⩾2 (n=66)	22.7		37.9		51.5		54.5	

EDSS, Expanded Disability Status Scale; IFN β-1a, interferon beta 1-a; SC, subcutaneously; tiw, three times weekly.
[a]Sustained EDSS progression was defined as an increase of ⩾1 point if baseline EDSS was ⩽5.5, or increase of 0.5 point if baseline EDSS was ⩾6, confirmed 3 months later.

Conclusions

- Patients receiving IFN β-1a 44 µg SC tiw benefited from treatment regardless of presence/absence of active T2 lesions at 6 months; these patients relapsed at rates similar to patients in the placebo/delayed treatment group without 6-month T2 lesions, who may be considered to have a relatively benign level of disease activity.
- Presence versus absence of active T2 lesions at 6 months showed no statistically significant difference in future confirmed EDSS progression in either the placebo/delayed treatment or IFN β-1a 44 µg SC tiw group, although there was a clear trend toward difference between patients with presence versus absence of active T2 lesions in the placebo/delayed treatment group only.
  - However, when groups with 0–1 versus ⩾2 active T2 lesions at 6 months were examined, placebo/delayed treatment patients with ⩾2 active T2 lesions showed significantly greater likelihood of progression than those with 0–1 lesion.
- Additional research is still needed to clarify the amount of lesion activity that can be shown to predict future EDSS progression.

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

AT has acted as a consultant for Biogen, Chugai, Genzyme, MedImmune, Novartis, Roche, Serono, and Teva Innovation, and is Principal Investigator on clinical trials with Genzyme and Roche.

GZ and **YC** have nothing to disclose.

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

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