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Clinical and MRI efficacy of IFN β-1a SC tiw in MS patients with more advanced disease (EDSS 4.0–6.0)

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Introduction

- 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 interferon beta-1a (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 relapsing–remitting multiple sclerosis (RRMS). Time to disability progression was approximately doubled by IFN β-1a 44 µg SC tiw in the overall population and approximately tripled in the subgroup of patients with baseline Expanded Disability Status Scale (EDSS) scores >3.5.[1]
- In 3-year data from the double-blind, randomized, placebo-controlled SPECTRIMS (Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-beta-1a in MS) study, IFN β-1a SC tiw reduced relapses and active T2 lesions. A significant delay in disability progression was not seen in the overall secondary progressive MS (SPMS) population, although significantly fewer IFN β-1a SC tiw patients (44 and 22 µg combined) progressed in disability in a *post hoc* examination of those who had experienced relapses in the 2 years before the study.[2,3]
- Both the PRISMS and SPECTRIMS clinical trials included patients who at baseline had long duration of disease and high EDSS scores, representing an understudied MS population; however, a treatment effect was still observed in these studies.
- Understanding treatment effect in patients with more advanced disease (higher EDSS), particularly among those patients who are also actively relapsing, is of interest.

Objective

- To use combined PRISMS and SPECTRIMS data to further characterize IFN β-1a 44 µg SC tiw efficacy in patients with more advanced, but still active, disease.

Methods

- In PRISMS, 560 patients with RRMS (EDSS 0–5.0 and ⩾2 relapses in the past 2 years) were randomly assigned to IFN β-1a 44 or 22 µg SC tiw or placebo for 2 years.
- In SPECTRIMS, 618 patients with SPMS (EDSS increase of ⩾1 point over last 2 years [⩾0.5 points if baseline EDSS was 6.0–6.5]) and baseline EDSS 3.0–6.5 were randomly assigned to IFN β-1a 44 or 22 µg SC tiw or placebo for 3 years.
- These *post hoc* analyses of combined data from PRISMS and SPECTRIMS examined the treatment effect of IFN β-1a 44 µg SC tiw versus placebo in a subgroup of patients with EDSS 4.0–6.0 and in a subgroup of patients with EDSS 4.0–6.0 + activity at baseline. 'Plus activity' was defined as having either ⩾1 relapse within 2 years before baseline, or ⩾1 gadolinium-enhancing (Gd+) lesion at baseline. The following endpoints were investigated:
  - Annualized relapse rate (ARR) at Years 1 and 2
  - Time to relapse over 2 years
  - 3-month confirmed disability progression (EDSS increase of ⩾1 point [⩾0.5 points if baseline EDSS was ⩾6.0]) at 1 and 2 years
  - Burden of disease (total T2 lesion area) over 6 months and at 1 and 2 years
  - Mean number of active T2 lesions at 6 months and at 1 and 2 years.
- Additional endpoints included the treatment effect of IFN β-1a 44 µg SC tiw versus placebo on the risk of relapse and 6-month confirmed disability progression (EDSS increase of ⩾1 point [⩾0.5 points if baseline EDSS was ⩾6.0]) at 1 and 2 years in the subgroup of patients with EDSS 4.0–6.0 + activity at baseline.

Results

- Demographic and baseline characteristics are shown in **Table 1**.
  - Notably, both the EDSS 4.0–6.0 subgroup and the EDSS 4.0–6.0 + activity subgroup were characterized by long duration of disease at baseline in addition to high EDSS. Although both groups exhibited disease activity, subjects in the EDSS 4.0–6.0 + activity group had experienced a higher mean rate of relapses in the previous 2 years.

Table 1. Demographic and baseline characteristics.

	EDSS 4.0–6.0 subgroup		EDSS 4.0–6.0 + activity subgroup[a]	
	Placebo (n=164)	IFN β-1a 44 µg SC tiw (n=171)	Placebo (n=92)	IFN β-1a 44 µg SC tiw (n=103)
Age (years)				
n	164	171	92	103
Mean (SD)	41.5 (7.27)	41.2 (7.25)	40.0 (7.41)	39.4 (7.16)
Female sex, n (%)	108 (65.9)	107 (62.6)	62 (67.4)	66 (64.1)
Race, n (%)				
White	164 (100)	169 (98.8)	92 (100)	101 (98.1)
Other	0	2 (1.2)	0	2 (1.9)
Time since diagnosis (years)				
n	164	171	92	103
Mean (SD)	13.3 (7.28)	12.4 (7.00)	12.0 (7.53)	10.8 (6.40)
EDSS at baseline				
n	164	171	92	103
Mean (SD)	5.2 (0.81)	5.2 (0.80)	5.1 (0.81)	5.0 (0.78)
Relapses in previous 2 years				
n	163	170	92	103
Mean (SD)	1.3 (1.52)	1.3 (1.48)	2.2 (1.38)	2.1 (1.38)
Burden of disease, mm²				
n	164	171	92	103
Mean (SD)	4459.6 (3775.51)	4441.6 (4213.66)	4601.8 (4082.30)	4879.7 (4608.89)

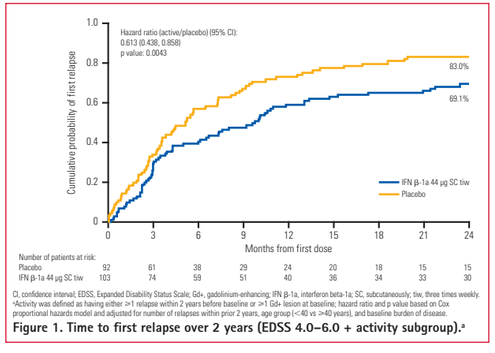
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta 1-a; MS, multiple sclerosis; PD, proton density; SC, subcutaneously; SD, standard deviation; tiw, three times weekly.
[a]Activity was defined as having either ⩾1 relapse within 2 years before baseline or ⩾1 Gd+ lesion at baseline. Burden of disease represented the total area of all MS lesions, outlined on the PD/T2 scan by a trained technician.

- In the EDSS 4.0–6.0 subgroup:
  - IFN β-1a 44 µg SC tiw reduced ARR versus placebo by 36.8% (rate ratio [RR] 0.632 [95% confidence interval (CI) 0.496–0.805]; p=0.0002) at 1 year and 36.2% (RR 0.638 [0.507–0.803]; p=0.0001) at 2 years.
  - IFN β-1a 44 µg SC tiw was associated with 30.4% less risk of first relapse over 2 years versus placebo (hazard ratio [HR] 0.696 [95% CI 0.525–0.923]; p=0.0119).
  - IFN β-1a 44 µg SC tiw was associated with 34.6% less risk of 3-month EDSS progression versus placebo over 1 year (HR 0.654 [95% CI 0.429–0.997]; p=0.0486), and similarly over 2 years, although this did not achieve statistical significance (HR 0.740 [0.530–1.035]; p=0.0785).
  - Numerically fewer patients treated with IFN β-1a 44 µg SC tiw versus placebo had 3-month EDSS progression (Year 1, 22.8% vs 31.1%; Year 2, 38.0% vs 46.3%).
- In the EDSS 4.0–6.0 + activity subgroup:
  - IFN β-1a 44 µg SC tiw significantly reduced the risk of relapse (Year 1, by 34.1%; p=0.0223; Year 2, by 38.7%; p=0.0043) and ARR (Year 1, by 39.4%; p=0.0003; Year 2, by 43.6%; p<0.0001) versus placebo (**Table 2**).
  - IFN β-1a 44 µg SC tiw was associated with 38.7% less risk of first relapse over 2 years versus placebo (p=0.0043; **Figure 1**).
  - No significant differences in time to first 3-month sustained EDSS progression over 2 years were seen for IFN β-1a 44 µg SC tiw versus placebo (**Figure 2**).
  - Numerically fewer patients treated with IFN β-1a 44 µg SC tiw versus placebo had 3-month EDSS progression (Year 1, 23.3% vs 29.3%; Year 2, 37.9% vs 47.8%).
  - There were no differences in the time to first 6-month sustained EDSS progression for patients treated with IFN β-1a 44 µg SC tiw compared with placebo over 1 year (HR 0.909 [95% CI 0.498–1.658]; p=0.7552) or over 2 years (HR 0.995 [95% CI 0.597–1.657]; p=0.9832).

Table 2. Significant reductions in risk of relapse and ARR versus placebo over 1 and 2 years (EDSS 4.0–6.0 + activity subgroup).[a]

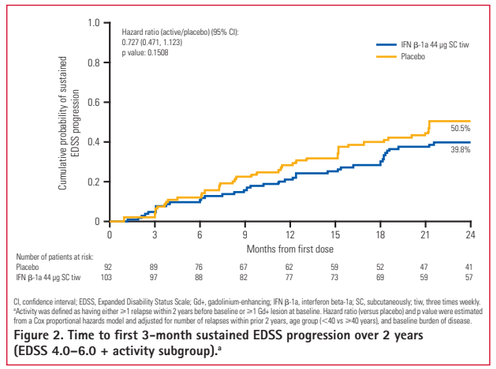
	Placebo (n=92)	IFN β-1a 44 µg SC tiw (n=103)
Year 1		
Risk of relapse vs placebo[b]		
Patients with relapse, n (%)	66 (71.7)	59 (57.3)
Patients without relapse, n (%)	26 (28.3)	44 (42.7)
Hazard ratio vs placebo (95% CI)	–	0.659 (0.461–0.942)
p value		0.0223
ARR[c]		
Adjusted relapse rate (95% CI)	1.413 (1.185–1.685)	0.856 (0.693–1.058)
Relative reduction vs placebo (%)		39.4
Rate ratio vs placebo (95% CI)		0.606 (0.463–0.793)
p value		0.0003
Year 2		
Risk of relapse vs placebo[b]		
Patients with relapse, n (%)	76 (82.6)	69 (67.0)
Patients without relapse, n (%)	16 (17.4)	34 (33.0)
Hazard ratio vs placebo (95% CI)	–	0.613 (0.438–0.858)
p value		0.0043
ARR[c]		
Adjusted relapse rate (95% CI)	1.222 (1.046–1.428)	0.690 (0.574–0.829)
Relative reduction vs placebo (%)		43.6
Rate ratio vs placebo (95% CI)		0.564 (0.444–0.716)
p value		<0.0001

ARR, annualized relapse rate; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta-1a; SC, subcutaneously; tiw, three times weekly.
[a]Activity was defined as having either ⩾1 relapse within 2 years before baseline or ⩾1 Gd+ lesion at baseline.
[b]Hazard ratio and p value based on Cox proportional hazards model and adjusted for number of relapses within prior 2 years, age group (<40 vs ⩾40 years), and baseline burden of disease.
[c]p values based on negative binomial regression and adjusted for number of relapses within prior 2 years, age group (<40 vs ⩾40 years), and baseline burden of disease.



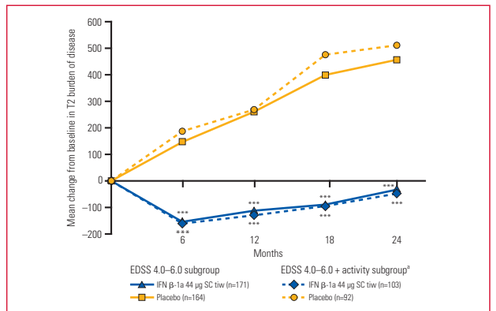
CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta-1a; SC, subcutaneously; tiw, three times weekly.
[a]Activity was defined as having either ⩾1 relapse within 2 years before baseline or ⩾1 Gd+ lesion at baseline; hazard ratio and p value based on Cox proportional hazards model and adjusted for number of relapses within prior 2 years, age group (<40 vs ⩾40 years), and baseline burden of disease.

Figure 1. Time to first relapse over 2 years (EDSS 4.0–6.0 + activity subgroup).[a]



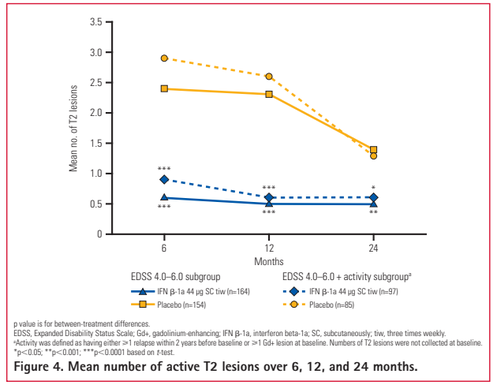
CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta-1a; SC, subcutaneously; tiw, three times weekly.
[a]Activity was defined as having either ⩾1 relapse within 2 years before baseline or ⩾1 Gd+ lesion at baseline. Hazard ratio (versus placebo) and p value were estimated from a Cox proportional hazards model and adjusted for number of relapses within prior 2 years, age group (<40 vs ⩾40 years), and baseline burden of disease.

Figure 2. Time to first 3-month sustained EDSS progression over 2 years (EDSS 4.0–6.0 + activity subgroup).[a]



ANCOVA, analysis of covariance; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta-1a; SC, subcutaneously; tiw, three times weekly.
p value is for between-treatment differences in change from baseline.
[a]Activity defined as having either ⩾1 relapse within 2 years before baseline or ⩾1 Gd+ lesion at baseline.
***p<0.0001 based on ranked ANCOVA adjusting for number of relapses within prior 2 years, age group (<40 vs ⩾40 years), baseline EDSS, and baseline burden of disease, and by Wilcoxon rank-sum test.

Figure 3. T2 burden of disease at 6, 12, and 24 months.



p value is for between-treatment differences.
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN β-1a, interferon beta-1a; SC, subcutaneously; tiw, three times weekly.
[a]Activity was defined as having either ⩾1 relapse within 2 years before baseline or ⩾1 Gd+ lesion at baseline. Numbers of T2 lesions were not collected at baseline.
*p<0.05; **p<0.001; ***p<0.0001 based on *t*-test.

Figure 4. Mean number of active T2 lesions over 6, 12, and 24 months.

- IFN β-1a 44 µg SC tiw reduced the T2 burden of disease from baseline significantly more than placebo through Month 24 in both the EDSS 4.0–6.0 subgroup and EDSS 4.0–6.0 + activity subgroup (**Figure 3**).
- IFN β-1a 44 µg SC tiw significantly reduced mean numbers of active T2 lesions versus placebo at Months 6, 12, and 24 in both the EDSS 4.0–6.0 subgroup and the EDSS 4.0–6.0 + activity subgroup (**Figure 4**).

Conclusions

- In these *post hoc* analyses of combined data from PRISMS and SPECTRIMS, IFN β-1a 44 µg SC tiw was associated with significant benefits (versus placebo) with regard to relapses, time to first relapse, T2 lesions, and burden of disease in both the EDSS 4.0–6.0 subgroup and in the EDSS 4.0–6.0 + activity subgroup.
- Neither the EDSS 4.0–6.0 subgroup nor the EDSS 4.0–6.0 + activity subgroup showed significant differences between treatment groups with regard to time to sustained 3-month progression over 2 years; however, numerically lower proportions of patients treated with IFN β-1a 44 µg SC tiw had 3-month EDSS progression compared with placebo.
  - It is important to note that these analyses included data from a trial that did not show a significant effect of IFN β-1a 44 µg SC tiw on EDSS progression in patients with SPMS (SPECTRIMS).
  - In addition, these were *post hoc* analyses performed on the studies that individually or collectively were not powered to determine efficacy in the investigated cohorts. Therefore, some of the numerically greater effects might have reached statistical significance had the studies been powered appropriately.
- In general, the *post hoc* analyses indicate that the effect of IFN β-1a 44 µg SC tiw on reduction in relapse, burden of disease, T2 lesions, and delay of EDSS progression is preserved in a subgroup of patients with advanced but active MS, despite the inclusion of patients with SPMS in the pooled dataset.

References

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