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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

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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 (IEN B-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.
- 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 B-1a 44 ug SC tiw at 1 year in preselected subgroups of patients with RMS from the PRISMS study.

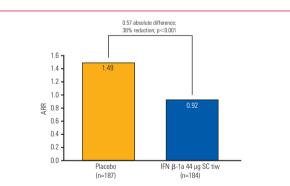
Methods

- 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 μ g 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 \geq 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 vear in patient subgroups. stratified by the following prespecified baseline characteristics:
- EDSS score \leq 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 mm² (median value)
- Aae
- 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 ABB (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).

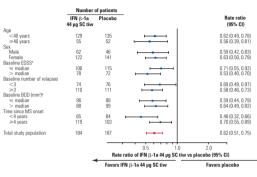
| | Placebo (n=187) | IFN β-1a 44 μg SC tiw (n= |
|---|----------------------|---------------------------|
| Age, years, mean (SD) | 34.7 (7.5) | 35.2 (7.9) |
| Sex, female, n (%) | 141 (75) | 122 (66) |
| Race, white, n (%) | 184 (98) | 182 (99) |
| Time since MS onset, years, mean (SD) | 6.1 (4.8) | 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) |



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 and baseline BOD (butal area (amm)² of all MS) lesions outlined on the PV/I2 scan) as covariante, and log time on study up to 1 year as offset variable. Indicated relapse rent BOD, burtlen of disease: EDSS, Epanded Disability Status Scale: INR J PL a internet heat-a NK, Smulphe sclemasis;

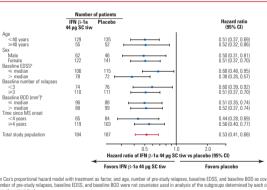
Figure 1. Annualized relapse rate at Year 1.

- 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 $\beta\text{-1a}$ 44 μg SC tiw versus placebo on proportion of patients free from 3-month confirmed disability progression (Figure 7).



warev un voson mean munutament as racur, agu, number of pris-tuny relapses, baseline USS, and baseline BDD as covarietes, ar ulty at 1 years as obstavitable. (Age, number of pris-tuny relapses, baseline USS, and baseline BDD were not covarietes are ubgroups determined by each of these respective danacteristics). Ob, budre of disease, Cl, confidence intervale; USS, Expanded Disability Status Scale: IFN B-1a. Interferen hata-1a: MS, ma^kinia e-lar istics). ded Disability Status Scale; IFN β -1a, interferon beta-1a; MS, multiple sclerosis isly; tiw, three times weel

Figure 2. Forest plot of ARR at Year 1.

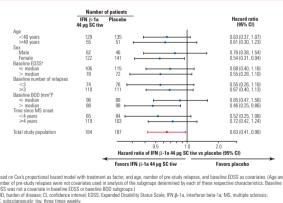


| Baseline EDSS ^a | | | | |
|---|--|-------------------------------|---|------------|
| ≪ median | 104 | 114 | — | |
| > median | 78 | 70 | H | |
| Baseline number of relapse | | | | |
| <3 | 74 | 74 | | |
| ≥3 | 108 | 110 | H | |
| Baseline BOD (mm ²) ^b | | | | |
| ≪ median | 95 | 88 | F | |
| > median | 87 | 96 | — | |
| Time since MS onset | | | | |
| <4 years | 64 | 83 F | | |
| ≫4 years | 118 | 101 | H | |
| Total study population | 182 | 184 | — | |
| | | | | |
| | | 0.1 | 0.5 | 1.0 |
| | | | Rate ratio of IFN β -1a 44 μ | g SC tiw |
| | | | Favors IFN β-1a 44 μg SC | tiw |
| line BOD was not a covariate us i-month or 1-year MRI assessme | ed in analysis ents. ce interval; ED | of the baseli SS, Expanded | eline BOD as covariate, and log nu ne BOD subgroups. Active T2 lesior Disability Status Scale; IFN β-1a, i akly. | ns up to 1 |
| | | | | |

IFN β-1a Placebo

128 54 134 50

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



| | | of patients Placebo | | Perce IFN β-1a | | OR |
|---|--------------|------------------------|---|--------------------|--------------|------------------|
| | 44 μg SC tiv | | | 44 μg SC tiv | | (95% CI) |
| Age | | | 1 | | | |
| <40 years | 129 | 135 | | 45.7 | 20.7 | 3.52 (2.02, 6.1 |
| ≫40 years Sex | 55 | 51 | | 41.8 | 25.5 | 2.34 (0.98, 5.5 |
| Sex Male | 62 | 46 | | 41.9 | 21.7 | 3.01 (1.23. 7.3 |
| Female | 122 | 140 | | 41.5 | 22.1 | 2.99 (1.73, 5.1 |
| Baseline EDSS* | 122 | 140 | | 40.0 | 22.1 | 2.33 (1.73, 3.1 |
| ≤ median | 106 | 114 | | 46.2 | 29.8 | 2.01 (1.15.3.5 |
| > median | 78 | 72 | · · · · · | 42.3 | 9.7 | 6.92 (2.80, 17.) |
| Baseline number of relap | | | | | | |
| <3 | 74 | 75 | | 50.0 | 32.0 | 2.29 (1.16, 4.5 |
| ≥3 | 110 | 111 | | 40.9 | 15.3 | 3.69 (1.92, 7.0 |
| Baseline BOD (mm ²) ^b ≤ median | 96 | 88 | | 46.9 | 29.5 | 2.29 (1.22, 4.2 |
| < median | 88 | 98 | | 40.5 | 15.2 | 4.01 (1.99, 8.0 |
| Time since MS onset | 00 | 30 | | 42.0 | 13.2 | 4.01 (1.33, 0.0 |
| <4 years | 65 | 83 | | 56.9 | 22.9 | 4.40 (2.12.9.1 |
| ≫4 years | 119 | 103 | | 37.8 | 21.4 | 2.35 (1.28, 4.3 |
| Total study population | 184 | 186 | — | 44.6 | 22.0 | 2.92 (1.84, 4.6 |
| | | _ | | | | |
| | | 0.11- | | 0.0 | | |
| | | Udds | of IFN β-1a 44 μg SC tiw vs plac | (95% UI) | | |
| | | Favo | cebo Favors IFN β-1a 44 μg SC | tiw | | |
| | | | | | | |
| | | | of pre-study relapses, baseline EDSS, | | | |
| | | | ed in analysis of the subgroups detern | | | |
| . burden of disease; CI, co idds ratio: SC. subcutanec | | | d Disability Status Scale; IFN β -1a, | interreron peta-1a | ; ws, multip | IE SCIEIOŠIŠ; |

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

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

| | Number IFN β-1a 44 μg SC ti | | | Perce IFN β-1a 44 μg SC tiv | | OR (95% CI) |
|---|-----------------------------------|-----------|--|-----------------------------------|----------------|--|
| Age <40 years ≫40 years Sex | 127 55 | 133 49 | | 82.7 76.4 | -72.9 -61.2 | 1.77 (0.97, 3.23) 2.08 (0.88, 4.92) |
| Male Female Baseline EDSS* | 61 121 | 46 136 | | 73.8 84.3 | -65.2 -71.3 | 1.45 (0.62, 3.39) 2.19 (1.18, 4.06) |
| ≤ median > median | 105 77 | 113 69 | | 79.0 83.1 | -69.9 -69.6 | 1.66 (0.89, 3.10) 2.17 (0.99, 4.77) |
| Baseline number of relaps <3 ≥3 ≥3 | es 73 109 | 74 108 | | 84.9 78.0 | -73.0 -67.6 | 2.12 (0.93, 4.86) 1.72 (0.94, 3.18) |
| Baseline BOD (mm²) ^b ≤ median > median | 96 86 | 87 95 | | 78.1 83.7 | -74.7 -65.3 | 1.27 (0.63, 2.53) 2.70 (1.32, 5.53) |
| Time since MS onset <4 years ≥4 years | 63 119 | 83 99 | | 84.1 79.0 | -68.7 -70.7 | 2.30 (1.00, 5.30) 1.60 (0.86, 2.98) |
| Total study population | 182 | 182 | — | 80.3 | -69.8 | 1.85 (1.13, 3.02) |
| | | | 0.5 1.0 2.0 tio of IFN β-1a 44 μg SC tiw vs pla prs placebo Favors IFN β-1a 44 μg SC | ≻ | | |

Status Scale: IFN R-1a, interferon heta-1a: MS, multiple scienceis: OR, odds ratio

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

| | Hazard ratio of IFN B-18 44 µg Sc | mazard ratio of IFN p-1a 44 µg SC tiw vs placebo (55% Cl) | | |
|---------------------------|---|---|--|--|
| | Favors IFN β-1a 44 μg SC tiw | Favors placebo | | |
| | Based on Cox's proportional hazard model with treatment as factor, and age, number of pre-study relag (Age, number of pre-study relapses, baseline EDSS, and baseline BDD were not covariates used in an respective characteristical. BOD, burden of disease; UL, confidence interval; EDSS, Expanded Disability Status Scale; IFN β-1a, in SC, subcataneous; Ivit, three terms week)r. Median baseline EDSS score 25. | alysis of the subgroups determined by ea | | |
| | Figure 3. Forest plot of time to first relapse over Year | 1. | | |
| releases 2 years prior to | | | | |

| Rate ratio (95% Cl) | | | | |
|--|--|--|--|--|
| 0.32 (0.23, 0.43) 0.29 (0.18, 0.47) | | | | |
| 0.25 (0.15, 0.40) 0.33 (0.24, 0.45) | | | | |
| 0.27 (0.19, 0.38) 0.35 (0.24, 0.53) | | | | |
| 0.35 (0.22, 0.54) 0.28 (0.20, 0.39) | | | | |
| 0.29 (0.19, 0.46) 0.32 (0.23, 0.44) | | | | |
| 0.22 (0.14, 0.33) 0.38 (0.27, 0.53) | | | | |
| 0.30 (0.23, 0.39) | | | | |
| 2.0 s placebo (95% Cl) | | | | |
| Favors placebo | | | | |
| ns up to Year 1 as offset variable. ar included those lesions detected at | | | | |
| ata-1a; MRI, magnetic resonance imaging; | | | | |
| | | | | |

| | | Hazard ratio (95% Cl) |
|---|-----|--|
| | | 0.63 (0.37, 1.07) 0.61 (0.30, 1.23) |
| - | | 0.76 (0.38, 1.54) 0.54 (0.31, 0.94) |
| | | 0.68 (0.40, 1.16) 0.55 (0.28, 1.10) |
| | | 0.55 (0.26, 1.16) 0.67 (0.40, 1.13) |
| - | | 0.85 (0.47, 1.56) 0.46 (0.25, 0.86) |
| | | 0.52 (0.25, 1.08) 0.72 (0.42, 1.24) |
| | | 0.63 (0.41, 0.96) |
| | 2.0 | |

Conclusions

- Subgroup analyses were consistent with findings in the overall population, demonstrating the treatment benefit of IFN B-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

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