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

- **PRIMS** (Prevention of Relapses and disability by Interferon β-1a) Subsequently in Multiple Sclerosis (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 tiw in the overall population and approximately tripled in the subgroup of patients with baseline Expanded Disability Status Scale (EDSS) scores <4.5.

- In a 3-year extension of PRIMS, patients who had been randomized to IFN-β-1a 44 µg SC tiw or placebo at baseline enrolled into a placebo-controlled extension study. Patients in the extension study were randomized to receive IFN-β-1a 44 µg SC tiw or placebo for 3 years.

- In this study, the PRIMS and SPECTRIMS (Secondary Progressive Efficacy Trial of Recombinant Interferon beta-1a in MS study) IFN-β-1a tiw has 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 tiw for patients 40 years and ≥50 continued to progress in disability in a post hoc examination of those who had experienced relapses in the 2 years prior to the study.

- Both the PRIMS and SPECTRIMS trials included patients who had baseline long duration of disease and high EDSS scores, representing an understudied MS population; however, a treatment effect was still observed in these bottles.

- Understanding treatment effects in patients with more advanced disease (higher EDSS), particularly among those patients who are also actively relapsing, is of interest.

Results

- **Deminographic 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.

- Additional endpoints included the treatment effect of IFN-β-1a 44 µg SC tiw versus placebo on the risk of relapse and Emron confirmed disability progression (EDSP) 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.

- If the EDSS 4.0–6.0 + activity subgroup:
  - IFN-β-1a 44 µg SC tiw significantly reduced the risk of relapse (Year 1, 7.4%, p=0.0333; Year 2, 5.7%, p=0.0025; and IFN-β-1a 1, by 39.4%, p<0.0001; Year 2, 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=0.0434; Figure 1).
  - No significant differences in time to first 3-month sustained EDSS progression from baseline 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, 27.0% vs 47.9%).
  - 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 0.999 [95% CI 0.986–1.011]), p=0.7531 or over 2 years (HR 0.990 [95% CI 0.973–1.007]), p=0.3630.

Table 1: Demographic and baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=185)</th>
<th>IFN-β-1a (n=186)</th>
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<tbody>
<tr>
<td>Time since diagnosis (years)</td>
<td>11.8±0.1</td>
<td>11.9±0.1</td>
</tr>
<tr>
<td>White</td>
<td>164 (88.5%)</td>
<td>164 (88.5%)</td>
</tr>
<tr>
<td>Black</td>
<td>8 (4.3%)</td>
<td>15 (8.1%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1.6%)</td>
<td>7 (3.8%)</td>
</tr>
<tr>
<td>Male</td>
<td>54 (29.2%)</td>
<td>57 (30.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>131 (70.8%)</td>
<td>129 (69.7%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.0±3.3</td>
<td>45.9±3.3</td>
</tr>
<tr>
<td>Baseline EDSS</td>
<td>5.0±1.3</td>
<td>5.0±1.3</td>
</tr>
<tr>
<td>Baseline T2 lesions</td>
<td>460±180</td>
<td>459±180</td>
</tr>
<tr>
<td>Baseline EDSS progression</td>
<td>0.5±0.5</td>
<td>0.5±0.5</td>
</tr>
<tr>
<td>Baseline relapse rate</td>
<td>2.7±1.0</td>
<td>2.7±1.0</td>
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</tbody>
</table>

Table 2: Significant reductions in risk of relapse and EDSS progression over 6, 12, and 24 months (EDSS 4.0–6.0 + activity subgroup).

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard ratio vs placebo (95% CI)</th>
<th>p value</th>
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<tr>
<td>Relapse</td>
<td>0.571 (0.429–0.997)</td>
<td>0.0486</td>
</tr>
<tr>
<td>3-month relapse</td>
<td>0.696 (0.525–0.923)</td>
<td>0.0119</td>
</tr>
</tbody>
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- **In the EDSS 4.0–6.0 subgroup:**
  - IFN-β-1a 44 µg SC tiw significantly reduced ARR versus placebo by 36.8% (1.36 [0.79–2.34]; p=0.0333) in the EDSS 4.0–6.0 + activity subgroup.
  - IFN-β-1a 44 µg SC tiw reduced ARR versus placebo by 34.6% (1.44 [0.84–2.49]; p=0.0181) in the EDSS 4.0–6.0 subgroup.
  - IFN-β-1a 44 µg SC tiw significantly reduced mean numbers of active T2 lesions at 6 months and at 1 and 2 years.
  - Mean number of active T2 lesions at 6 months: 41.5 (7.27) vs 36.0 (7.25), p=0.0434.
  - Mean number of active T2 lesions at 1 year: 44 (42.7) vs 39.1 (41.2), p=0.0434.
  - Mean number of active T2 lesions at 2 years: 40 (39.5) vs 35.2 (38.5), p=0.0434.

- **Conclusions**
  - **In post hoc analyses of combined data from PRIMS 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 fewer 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 almost shows 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 cohort. Therefore, some of the numerically greater effects might have reached statistical significance that the studies had 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, time to 1 relapse, 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


Disclosures

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4.0–6.0 subgroup and EDSS 4.0–6.0 + activity subgroup.**

**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).**