P05.133

A Post Hoc Analysis of Cumulative Dose Effects of Subcutaneous Interferon Beta-1a on Clinical and MRI Outcomes in Relapsing-Remitting Multiple Sclerosis: Results Over the Long Term

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Abstract

Objective: To examine long-term (≤8 y) clinical and magnetic resonance imaging (MRI) outcomes based on cumulative dose of subcutaneous (SC) interferon beta (IFNβ)–1a three times weekly (TIW) in relapsing-remitting MS (RRMS) in the PRISMS (Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis) long-term follow-up (LTFU) cohort

Background: The PRISMS LTFU study supported the beneficial effects of SC IFNβ-1a, TIW, in RRMS on clinical and MRI measures. The relation of cumulative dose exposure to IFNβ-1a on clinical and MRI outcomes is unknown.

Design/Methods: A post hoc exploratory analysis of the PRISMS LTFU study was performed. Patient data from the 3 original study arms (IFNβ-1a 22 µg [n=123], 44 µg [n=136], and placebo [n=123]) were pooled and ranked from lowest to highest cumulative dose exposure. Clinical and MRI outcomes were assessed in the minimal (lowest 25%) and maximal (highest 25%) cumulative dose groups.

Results: Mean (SD) cumulative dose exposure for the minimal and maximal cumulative dose groups was 10.79 mg (5.98) and 46.60 mg (4.56), respectively. The minimal cumulative dose group comprised mainly patients who were initially randomized to placebo and then converted to other treatment; the maximal cumulative dose group comprised predominantly patients initially receiving IFNβ-1a, 44 µg in the original PRISMS study. From baseline to LTFU, the highest cumulative dose group was associated with the lowest median (range) percentage change in T2 burden of disease, the greatest proportion of relapse-free patients, the lowest median (range) annualized relapse rate, and the lowest proportion of patients who had developed secondary-progressive MS compared with the minimal cumulative dose group.

Conclusions/Relevance: Results from this exploratory analysis of the PRISMS LTFU study data demonstrate that in RRMS patients, higher cumulative doses of SC IFNβ-1a yielded greater benefits on clinical and MRI outcomes than lower cumulative doses, over the long term.

Introduction

- The Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) study showed that interferon beta (IFNβ)–1a subcutaneous (SC) at doses of 22 or 44 µg 3 times weekly (TIW) reduced relapses, delayed disability progression, and reduced the number of active lesions on magnetic resonance imaging (MRI) in patients with relapsing-remitting multiple sclerosis (RRMS).[1]
- Data from the 4-year extension of the PRISMS study suggested that the higher dose of IFNβ-1a SC is associated with better outcomes on several clinical and MRI endpoints than the lower dose of IFNβ-1a SC.[2]
- Long-term clinical and MRI efficacy of IFNβ-1a SC was confirmed by the 8-year long-term follow-up (LTFU) of PRISMS,[3] which showed that patients originally randomized to the higher dose of the drug experienced the greatest therapeutic benefits.
- It has not been established whether the extent of clinical and MRI benefits of treating RRMS patients with IFNβ-1a SC is directly related to the cumulative dose of drug administered over the years.

Objective

- The goal of this analysis was to examine data from the PRISMS LTFU study and to evaluate the relationship of the cumulative administered dose of IFNβ-1a SC to long-term changes in annualized relapse rate (ARR), the proportion of patients remaining relapse-free, the proportion of patients progressing to secondary-progressive multiple sclerosis (SPMS), and the T2 burden of disease (BOD).

Methods

Study Design

- This was a post hoc analysis of data obtained from patients who participated in the PRISMS LTFU study. The PRISMS study consisted of the following 3 phases:
  - A 2-year double-blind trial, in which patients with RRMS were randomized to receive 22 or 44 µg IFNβ-1a SC TIW or placebo.[1]
  - Patients originally randomized to placebo were randomized again to 1 of the 2 doses of IFNβ-1a SC for 2 additional years, and on study completion, patients were given the choice of continuing to receive blinded or open-label treatment for up to 6 years.[2]
  - Patients were permitted to take any or no disease-modifying drugs (DMDs) during the open-label phase of the study (ie, between withdrawal from or completion of 6 y on study and up to and including the LTFU assessment).

Patient Selection

- All patients randomized in the original PRISMS study were eligible to participate in the LTFU study.[3]

Assessments From the PRISMS LTFU Study

- Patients received a single LTFU assessment close to the 7th or 8th anniversary of their enrollment in PRISMS (hereafter referred to as LTFU).[3]
- Complete neurologic assessment included documentation of relapses and determination of Kurtzke Expanded Disability Status Scale (EDSS) score.[3]
- Progression to SPMS was defined as progressive increase in disability over at least 1 year combined with a decrease of at least 1 point on the EDSS (0.5 points if baseline EDSS was ≥6) not associated with a relapse.[3]
- T2-weighted MRI scan was performed, using the same image acquisition parameters as those in the original PRISMS study.
  - BOD was defined as the summed cross-sectional area of T2 lesions.
  - Analysis of LTFU MRI data was blinded.[3]

Post Hoc Analyses

- All patients included in the analysis were pooled irrespective of initial randomization.
- Patients were ranked according to the estimated cumulative dose of IFNβ-1a SC received over the entire study period and grouped into quartiles.
  - Patients with the lowest 25% of cumulative dose exposure composed quartile 1, and those with the highest 25% composed quartile 4.
- ARR was calculated using the following formula:
  - ARR = 365.25 × (total number of relapses / total time on study in days)

Results

Patients

- Of 560 patients originally randomized in the PRISMS study (IFNβ-1a SC 22 µg, n=189; IFNβ-1a SC 44 µg, n=184; placebo, n=187), 382 (68.2%) participated in the LTFU.
  - Of 382 participating patients, 123 had been originally randomized to 22 µg IFNβ-1a SC, 136 to 44 µg IFNβ-1a SC, and 123 to placebo.
- The median age, at screening, of patients who participated in the LTFU was 35.5 years.
- A higher proportion of women (71.2%) than men (61.4%) returned for the follow-up.[3]
- 275 (72.0%) of LTFU participants were receiving IFNβ-1a SC at the time of the visit, whereas 81 (21.2%) were not receiving any DMD.[3]

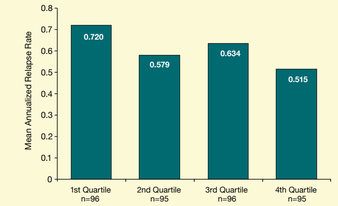
Cumulative Dose Distribution

- As shown in poster P05.126,[4] the mean (SD) cumulative dose received by patients in quartile 4 was 46.6 (4.56) mg, >4-fold higher than the dose of 10.79 (5.98) mg received by patients in quartile 1.
- Most patients in quartile 4 were initially randomized to receive IFNβ-1a SC 44 µg in the original PRISMS study, whereas most patients in quartile 1 were initially randomized to receive placebo and subsequently converted to therapy.

Clinical Outcomes

- Mean ARR for the entire study period from baseline to LTFU was substantially lower in patients who received the highest cumulative doses of IFNβ-1a SC (quartile 4) compared with those who received the lowest cumulative doses (quartile 1; **Figure 1**).

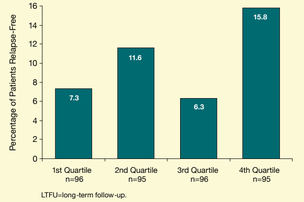
Figure 1. Effect of IFNβ-1a SC Cumulative Dose on Annualized Relapse Rate From Baseline to LTFU



IFNβ =interferon beta; LTFU=long-term follow-up; SC=subcutaneous.

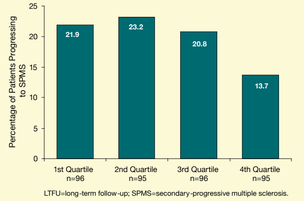
- The highest cumulative dose of IFNβ-1a SC had the greatest proportion of patients free from relapses throughout the entire study period (**Figure 2**).
- Patients appeared least likely to progress from RRMS to SPMS if they were in the group that received the highest cumulative dose of IFNβ-1a SC (**Figure 3**).

Figure 2. Frequency of Relapse-Free Patients From Baseline to LTFU by Total Cumulative Dose



LTFU=long-term follow-up.

Figure 3. Frequency of Patients Converting to SPMS From Baseline to LTFU by Total Cumulative Dose

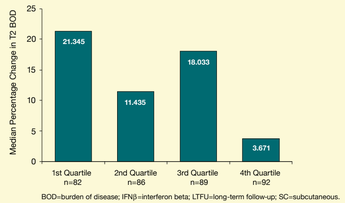


LTFU=long-term follow-up; SPMS=secondary-progressive multiple sclerosis.

MRI Outcome

- The highest cumulative dose of IFNβ-1a SC was associated with the lowest change in T2 BOD from baseline to LTFU (**Figure 4**).

Figure 4. Effect of IFNβ-1a SC Cumulative Dose on Percentage Change in T2 BOD From Baseline to LTFU



BOD=burden of disease; IFNβ=interferon beta; LTFU=long-term follow-up; SC=subcutaneous.

Study Limitations

- Data were derived from a retrospective, post hoc analysis.
- The LTFU portion of the PRISMS study did not have a placebo arm, thus, it was not possible to assess absolute effect sizes.
- Most patients in quartile 1 had been originally randomized to placebo and may have had a shorter exposure to therapy.
  - The present analysis did not differentiate the effects of cumulative dose from the effects of time on drug.
- Discontinuation of therapy and switching to alternative medications were not accounted for by the present analysis.

Conclusions

- **This retrospective analysis showed that RRMS patients exposed to the highest cumulative dose of IFNβ-1a SC experienced greater long-term benefits on clinical and MRI outcomes compared with patients exposed to a lower cumulative dose.**
- **Benefits of high-dose IFNβ-1a SC therapy appear to be sustained over a period of at least 8 years from baseline to LTFU.**

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