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Long-Term Effects of Interferon Beta-1a Dose on Relapse Rate in Relapsing-Remitting Multiple Sclerosis: Results From a Post Hoc Analysis of PRISMS Study Data

Douglas Jeffery[1] and Victor Rivera[2]

[1]Wake Forest University School of Medicine, Winston-Salem, NC, USA; [2]Baylor College of Medicine, Houston, TX, USA

Abstract

Objective: To compare annualized relapse rates (ARRs) from patients participating in the PRISMS long-term follow-up (LTFU) study who received the minimal (lowest quartile, MIN) vs the maximal cumulative dose (highest quartile, MAX) of interferon beta (IFNβ)-1a subcutaneous (SC) over an 8-year study period

Background: The PRISMS LTFU study supports the efficacy of IFNβ-1a SC 3 times weekly in relapsing-remitting multiple sclerosis (RRMS) on relapses, disability, and magnetic resonance imaging outcomes.

Design/Methods: A post hoc exploratory analysis was performed on patients who participated in the LTFU study (n=382). Data were pooled from patients initially receiving either IFNβ-1a 22 or 44 µg SC or placebo. Total cumulative dose of IFNβ-1a SC over the 8-year period in mg/patient was estimated. ARR was assessed for the MIN and MAX dose groups for years 0–2, 2–4, and 4–8.

Results: Mean (SD) cumulative dose exposure was 10.79 (5.98) and 46.60 (4.56) mg/patient in the MIN and MAX groups, respectively. In the MIN dose group, the mean ARR was reduced by 48% between years 0–2 and 2–4 and by a further 20% in years 4–8. Patients in the MAX dose group experienced a 40% reduction in mean ARR between years 0–2 and 2–4 and by a further 37% in years 4–8. ARR was significantly lower in the highest cumulative dose group at years 0–2 and years 4–8.

Conclusions: Results from this exploratory analysis of the PRISMS LTFU study data demonstrate that, in RRMS, patients with the highest dose exposure to IFNβ-1a SC had a greater reduction in ARR than patients with lower dose exposure. These findings suggest a sustained and consistent effect on ARR for patients who maintain therapy with IFNβ-1a SC over an extended period of time, and this effect may be associated with a higher cumulative dose.

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) was effective at reducing relapses and delaying disability progression in patients with multiple sclerosis (MS).[1]
- The 2-year double-blind portion of PRISMS,[1] as well as its 4-year extension study,[2] suggested that, although both doses of IFNβ-1a SC were effective, patients who received the higher dose (44 µg 3 times weekly [TIW]) of IFNβ-1a SC may experience a greater benefit in relapse reduction compared with patients receiving the lower dose (22 µg TIW).
- Published data from the 8-year long-term follow-up (LTFU) of PRISMS[3] confirmed improved outcomes associated with long-term IFNβ-1a SC therapy, particularly at the higher dose; however, it has not been clarified how long-term reduction in relapses may be related to the cumulative dose of IFNβ-1a SC received by patients.

Objective

- The goal of this analysis was to examine data from the PRISMS LTFU study and to compare relapse rates of patients based on their received cumulative dose of IFNβ-1a SC.

Methods

Study Design

- This was a post hoc analysis of data obtained from patients with relapsing-remitting MS 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 were randomized to receive 22 or 44 µg IFNβ-1a SC TIW or placebo.[1]
  - Patients receiving placebo were randomized again to 1 of the 2 doses of IFNβ-1a SC for 2 additional years and, upon completion, were given the choice of continuing to receive blinded or open-label treatment for up to 6 years.[3]
  - 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 years on study and up to and including the LTFU assessment).[3]

Patient Selection

- Patients were eligible for enrollment in the LTFU study if they had been randomized in the original PRISMS study.[3]

LTFU Assessments

- Patients received a single LTFU assessment close to the 7th or 8th anniversary of their enrollment in PRISMS (hereafter referred to as LTFU).[3]
  - LTFU assessment included a neurologic evaluation, which involved documentation of relapses.[3]

Analyses and Statistics

- All patients included in the analysis, irrespective of initial randomization, were categorized into quartiles according to the estimated cumulative dose of IFNβ-1a SC received over the entire study period.
- Annualized relapse rate (ARR) was calculated for patients in the lowest and highest cumulative dose groups (1st and 4th quartiles, respectively) using the following formula:
  - ARR = 365.25 × (total number of relapses / total time on study in days)
- ARR was assessed for the entire time period from baseline to LTFU and separately for years 0–2 and 2–4 and year 4–LTFU assessment.

Results

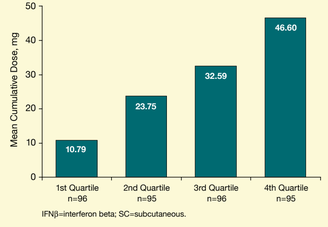
Patients

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

Cumulative Dose Analysis

- Mean cumulative-dose received by patients in the highest cumulative-dose (4th) quartile was >4-fold higher than that of the lowest cumulative-dose (1st) quartile (**Figure 1**).

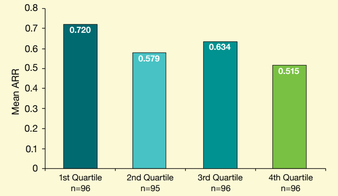
Figure 1. Mean Cumulative Dose of IFNβ-1a SC by Quartiles



IFNβ=interferon beta; SC=subcutaneous.

- For the entire time period up to LTFU, mean (SD) ARR was 0.720 (0.548) for patients in the 1st cumulative dose quartile and 0.515 (0.513) for patients in the 4th cumulative dose quartile (**Figure 2**).

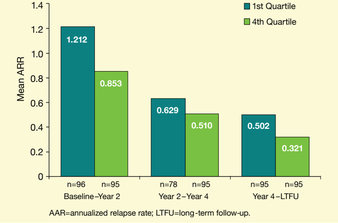
Figure 2. Effect of IFNβ-1a SC Cumulative Dose on ARR From Baseline to LTFU



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

- Patients in both the 1st and 4th cumulative dose quartiles experienced a decrease in ARR as a function of time (**Figure 3**).
  - Compared with years 0–2, patients in the 1st cumulative dose quartile had a 48.1% reduction in ARR in years 2–4, followed by an additional reduction of 20.2% during year 4–LTFU.
  - Compared with years 0–2, patients in the 4th cumulative dose quartile had a 40.2% reduction in ARR in years 2–4, followed by an additional reduction of 37.1% during year 4–LTFU.
- Overall, ARR was lower at years 0–2 and during year 4–LTFU among patients in the 4th cumulative dose quartile vs the 1st cumulative dose quartile, respectively (**Figure 3**).

Figure 3. Effect of Cumulative Dose in the First and Fourth Quartiles on ARR Over Time



AAR=annualized relapse rate; LTFU=long-term follow-up.

Study Limitations

- Data were derived from a retrospective, post hoc analysis.
- Assessment of absolute effect size in the PRISMS LTFU study was not possible without a placebo arm.
- Analyses did not account for patients who may have switched to other medications or discontinued treatment altogether.

Conclusions

- **This retrospective, post hoc analysis showed that MS patients exposed to the highest cumulative dose of IFNβ-1a SC experienced fewer relapses compared with patients exposed to a lower cumulative dose.**
- **The greater efficacy of higher dose IFNβ-1a SC exposure in reducing relapse rate persisted through the LTFU, 7–8 years after initial randomization to drug.**
- **These results suggest that patients could experience a sustained benefit of relapse reduction by maintaining long-term therapy with IFNβ-1a SC.**

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