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 (3 y) clinical and magnetic resonance imaging (MRI) outcomes based on cumulative dose of subcutaneous (SC) interferon beta-1a (IFN-β1a) from 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 (PRISMS) long-term follow-up (LTFU) cohort.

Background: The PRISMS LTFU study supported the beneficial effects on clinical MRI outcomes than lower cumulative doses of SC IFN-β1a. The relation of cumulative dose exposure to clinical MRI outcomes has not been established.

Design/Methods: A post hoc exploratory analysis of the PRISMS LTFU study was performed. Patient data from the original study arms (β1a SC, n=123; β1a SC, n=136, and placebo; n=132) were pooled and ranked from lowest to highest cumulative dose exposures. Clinical and MRI outcomes were assessed in the minimal (25%) and maximal (25%) cumulative dose groups.

Results: Mean (SD) cumulative dose exposure for the minimal (25%) and maximal (25%) cumulative dose groups was 10.79 mg (5.98) and 213.54 mg (103.98), respectively. The minimal cumulative dose group comprised mainly patients who were initially randomized to placebo and converted to other treatments. A maximal cumulative dose group comprised predominantly patients initially receiving IFN-β1a SC and patients with the greatest proportion of patients free from relapses throughout the entire study period (36.1% vs 25.4% in the minimal cumulative dose group). The highest cumulative dose group was comprised primarily of patients who received IFN-β1a SC for 6 years. It has not been established whether the extent of clinical and MRI benefits of treating RRMS patients with IFN-β1a SC reflect the direct and indirect 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 determine the relationship of the cumulative administered dose of IFN-β1a 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 bulbar percentage of disease (BOD2).

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 3-y double-blind trial, in which patients with RRMS were randomized to receive 22 or 44 µg IFN-β1a SC TIW or placebo.

• Patients originally randomized to placebo were randomized again to 1 of the 3 doses of IFN-β1a SC for 2.1 y, and on study completion, patients were given the choice of continuing to receive blinded or open-label study medication.

• Patients were permitted to take any other medications as long as these medications were not accounted for by the present analysis. The mean (SD) cumulative dose exposure for the minimal (25%) and maximal (25%) cumulative dose groups was 10.79 mg (5.98) and 213.54 mg (103.98), respectively.

Results

Patient Selection

• All patients randomized in the original PRISMS study were eligible to participate in the LTFU study.

• Assessments From the PRISMS LTFU Study

• Patients received a single LTFU assessment close to the 7th or 8th anniversary of enrollment in the PRISMS trial mentioned above.

• Complete neurologic assessment included documentation of mental status, cognitive function, and Karnofsky Performance Status

• Progression of SPMS was defined as progressive increase in disability in at least 1 y combined with a decrease of at least 1 point on the EDSS (3.5 points if baseline EDSS was <4.0) associated with a relapse.

• T2-weighted MRI scan was performed, using the same imaging acquisition parameters as those in the original PRISMS study.

• BOD2 was calculated as the summed cross-sectional area of T2 lesions.

• Analysis of LTFU MRI data was blinded.

Post Hoc Analyses

• All analyses were performed irrespective of incomplete randomization.

• Patients were ranked according to the estimated cumulative dose of IFN-β1a SC received over the entire study period and grouped into quartiles.

• Patients with the lowest 25% of cumulative dose exposure comprised quartile 1, and those with the highest 25% comprised quartile 4.

• ARR was calculated using the following formula:

• (A-R) / T × 100

• where A is the number of relapses, R is patients at risk, and T is time on study in days.

MRI Outcome

• The highest cumulative dose of IFN-β1a SC was associated with the least change in T2 BOD from baseline to LTFU.

Conclusions

• The retropective analysis showed that RRMS patients exposed to the highest cumulative dose of IFN-β1a SC experienced greater long-term clinical and MRI outcomes compared with patients exposed to a lower cumulative dose.

• Benefits of high-dose IFN-β1a SC therapy appear to be sustained over a period of at least 8 years from baseline to LTFU.

References