BMC Neurology

RESEARCH ARTICLE Open Access

Comparative injection-site pain and tolerability of subcutaneous serum-free formulation of interferonβ-1a versus subcutaneous interferonβ-1b: results of the randomized, multicenter, Phase IIIb REFORMS study

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Abstract

Background: In patients with relapsing–remitting multiple sclerosis (RRMS), subcutaneous (sc) interferon (IFN)β-1a and IFNβ-1b have been shown to reduce relapse rates. A formulation of IFNβ-1a has been produced without fetal bovine serum and without human serum albumin as an excipient (not currently approved for use in the US). The objectives of this study were to evaluate tolerability, injection-site redness, subject-reported satisfaction with therapy, and clinical safety and efficacy of the serum-free formulation of IFNβ-1a versus IFNβ-1b in IFNβ-treatment-naïve patients with RRMS. The objectives of the extension phase were to evaluate long-term safety and tolerability of IFNβ-1a.

Methods: This randomized, parallel-group, open-label study was conducted at 27 clinical sites in the US. Eligible patients aged 18–60 years were randomized to receive either IFNβ-1a, titrated to 44 μg sc three times weekly (tiw) (n = 65), or IFNβ-1b, titrated to 250 μg sc every other day (n = 64) over 12 weeks. Following this, all patients received IFNβ-1a 44 μg tiw for 82–112 weeks. Primary endpoint was mean change in patient-reported pain, as assessed by visual analog scale (VAS) diary pain score (from 0 mm [no pain] to 100 mm [worst possible pain]) at the injection site, from pre-injection to 30 min post-injection over the first 21 full-dose injections. Secondary assessments included proportion of patients pain-free as recorded by VAS diary and the Short-Form McGill Pain questionnaire VAS.

Results: A total of 129 patients were included in the intent-to-treat analysis. Mean (standard deviation) change in VAS diary pain score was not significantly different between groups, although numerically lower with IFNβ-1a versus IFNβ-1b from pre-injection to immediately post-injection (1.46 [2.93] vs. 4.63 [10.57] mm), 10 min post-injection (0.70 [1.89] vs. 1.89 [5.75] mm), and 30 min post-injection (0.67 [2.32] vs. 1.14 [4.94] mm). Proportion of patients pain-free at all time periods post-injection was also not significantly different between groups. Adverse events were consistent with the known safety profiles of these treatments.

Conclusions: In IFNβ-treatment-naïve patients with RRMS, both the serum-free formulation of IFNβ-1a and IFNβ-1b treatments were generally accompanied by low-level injection-site pain and were well tolerated.

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Trial registration: ClinicalTrials.gov NCT00428584

Keywords: Randomized controlled trial, Interferonβ-1a, Interferonβ-1b, Relapsing–remitting multiple sclerosis, Subcutaneous injections, Injection-site pain, Pain measurement

Background

Clinical studies of subcutaneous (sc) interferon (IFN)β-1a and IFNβ-1b have shown that these disease-modifying drugs reduce relapse rates in patients with relapsing–remitting multiple sclerosis (RRMS) [1-4]. At the doses approved for the treatment of RRMS, both IFNβ-1a and IFNβ-1b have established long-term safety and tolerability profiles [5,6]. However, injections with these drugs are commonly associated with injection-site reactions (ISRs), injection-site pain, and flu-like symptoms (FLS), which can lead to poor adherence to treatment in some patients [7,8].

A formulation of IFNβ-1a has been developed without fetal bovine serum and without human serum albumin as an excipient, although this formulation is not currently approved for use within the US. In a 96-week study in patients with relapsing MS, the serum-free formulation of IFNβ-1a was associated with a lower prevalence of ISRs than had been seen in two earlier studies with the original IFNβ-1a formulation [9-11]. No randomized clinical study has yet compared the injection-site pain and tolerability profile of the serum-free formulation IFNβ-1a with that of another disease-modifying drug.

The primary objective of this study was to compare the tolerability of the serum-free formulation of IFNβ-1a, 44 μg sc three times weekly (tiw), with IFNβ-1b, 250 μg sc every other day (qod), as measured by the mean change in subject-reported injection-site pain from pre-injection to 30 min post-injection in IFNβ-treatment-naïve patients with RRMS during a 12-week period (comparative phase). During the extension phase, the primary objective was to evaluate long-term safety and tolerability of IFNβ-1a sc tiw.

Secondary efficacy endpoints included: the mean difference in injection-site pain from pre-injection to immediately post-injection and to 10 min post-injection, the proportion of pain-free patients, number and severity of relapses, assessments of the treatment of side effects, patient-rated treatment satisfaction, and rater-blinded assessment of injection-site redness.

Safety endpoints included analysis of adverse events (AEs), laboratory tests, physical examinations, vital signs, and concomitant medications.

Methods

Study design and patients

The Rebif New Formulation Versus Betaseron Tolerability Study (REFORMS) (ClinicalTrials.gov identifier: NCT00428584) was a randomized, multicenter, 2-arm, Phase IIIb study conducted at 27 clinical sites in the US. The study consisted of a 12-week randomized comparative phase, which was followed by a safety-extension phase of up to 112 weeks (range 82–112 weeks). The study was open-label, except for blinded assessments of ISRs. The initial central Institutional Review Board (IRB) submission was approved by Coast IRB, Colorado Springs, Colorado and, later, Schulman Associates IRB, Cincinnati, Ohio. For those sites that were not permitted to use a central IRB for study approval, submissions were made to the local IRB. This study was performed in accordance with the study protocol, the Declaration of Helsinki, the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP), and all applicable regulatory requirements. Patients provided written informed consent for participation in the study.

Eligible patients were 18–60 years of age, had a primary diagnosis of RRMS as defined by the Poser or 2005 revised McDonald criteria [12,13], and had not previously received IFNβ treatment. Patients were not eligible if they had used any other approved disease-modifying treatment for MS (e.g. glatiramer acetate) or any cytokine or anti-cytokine treatment within 3 months before study initiation, used any immunomodulatory or immunosuppressive treatment within 12 months before study initiation, used any investigational drug or experimental procedure within 12 weeks before screening, received oral or systemic corticosteroids or adrenocorticotropic hormone within 30 days of study initiation, or used other injectable medications on a regular basis during the week before screening. Other exclusion criteria included having an alternative diagnosis to RRMS and being pregnant or breastfeeding. Women of childbearing potential were required to use appropriate contraception. All patients provided written informed consent.

Treatments

Patients were randomized 1:1 to receive either the serum-free formulation of IFNβ-1a 44 μg sc tiw or IFNβ-1b 250 μg sc qod for the 12 weeks of the comparative phase. Treatments were allocated using a computer-generated randomization code. The doses of IFNβ-1a and IFNβ-1b were up-titrated at the beginning of the study according to the US prescribing information for each drug (Figure 1) [14,15]. Following the 12-week

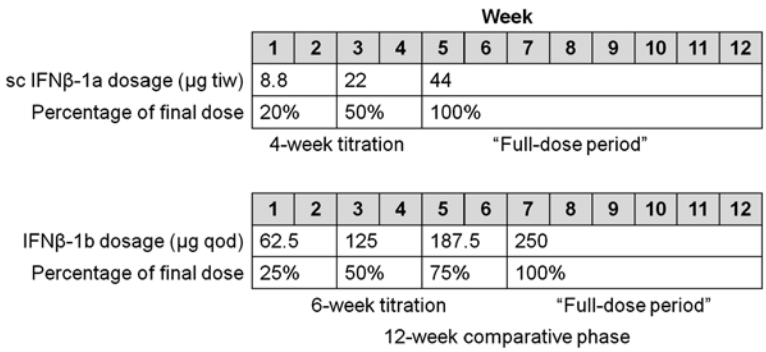

Figure 1 Titration schedules for subcutaneous IFNβ-1a and IFNβ-1b. The first 21 injections of full-dose IFNβ-1a and IFNβ-1b treatment were termed the "full-dose period". IFN, interferon; qod, every other day; tiw, three times weekly.

comparative phase, all patients received the serum-free formulation of IFNβ-1a 44 μg sc tiw during the safety-extension phase. Patients who transitioned from IFNβ-1b to IFNβ-1a could be up-titrated to the full dose of IFNβ-1a at the discretion of the investigator. Patients who did not wish to transition from IFNβ-1b to IFNβ-1a were withdrawn from the study. The length of the extension phase varied between 82 and 112 weeks, depending on the patient's date of enrollment. The extension phase ended within 14 days of when the last enrolled patient completed the last visit at Week 94.

All patients self-administered IFNβ using the Rebiject II® autoinjector (EMD Serono, Inc., Rockland, MA, USA) with a 29-gauge needle for IFNβ-1a or Betaject® (with a 27-gauge needle), Betaject Lite® (with a 30-gauge needle), or Betaject® 3 (with a 27-gauge needle) (Bayer HealthCare Pharmaceuticals Inc., Montville, NJ, USA). Acetaminophen was given prophylactically at the discretion of the treating physician and dosed as needed to ameliorate constitutional symptoms (e.g. fever, myalgia, and FLS). Nonsteroidal anti-inflammatory drugs were given and dosed as needed at the discretion of the treating physician if acetaminophen failed to alleviate or prevent constitutional symptoms or if patients were allergic to, or unable to tolerate, acetaminophen.

Assessments

Patient-reported pain was evaluated in a visual analog scale (VAS) diary and the Short-Form McGill Pain Questionnaire (SF-MPQ) [16]. Patients used the VAS diary to record the level of pain on a scale from 0 mm (no pain) to 100 mm (worst possible pain), immediately before, immediately after, 10 min after, and 30 min after the injection. The SF-MPQ also included a VAS for patients to record the level of the maximum amount of pain experienced during the 60 min after injection, from 0 mm (no pain) to 100 mm (worst possible pain). In addition, patients were requested to describe the types of pain that they experienced during the 60 min after injection. Patients completed the VAS diary and the SF-MPQ after every injection during the comparative phase and for the first 4 weeks of the safety-extension phase.

The Multiple Sclerosis Treatment Satisfaction Questionnaire (MSTSQ) adapted from Cramer *et al.* [17] included patient assessments of mood, treatment satisfaction, FLS, and ISRs. The MSTSQ was issued to patients at Weeks 2, 4, 6, 8, 12, 16, 24, 36, and 48. Mean values are reported for each treatment phase.

ISRs were assessed at each visit during the first 48 weeks by a healthcare professional who was blinded to treatment assignment. ISR measures included the diameter of injection-site redness, injection-site swelling, bruising, and consideration of patient-reported itching, within 72 h of the most recent injection.

Compliance was recorded throughout the study and was defined as the actual number of injections divided by the expected number of injections, expressed as a percentage. Safety assessments included AEs (coded to system organ class and preferred term using the MedDRA dictionary [Version 9.1] and summarized by severity and relationship), vital signs, hematology, and serum chemistry. Analgesic use among patients with and without AEs related to FLS was summarized by treatment group during the comparative phase and by treatment group and overall population during the extension phase.

The primary endpoint was the mean change in the VAS diary pain score from pre-injection to 30 min post-injection over the first 21 injections of full-dose IFNβ-1a and IFNβ-1b treatment ("full-dose period"). Due to the different titration schedules and dose frequencies of each treatment, the first 21 full-dose injections were administered during Weeks 5–11 in the IFNβ-1a group and during Weeks 7–12 in the IFNβ-1b group (Figure 1). Secondary endpoints included mean changes in the VAS diary pain score from pre-injection to immediately post-injection and 10 min post-injection; MSTSQ assessments; rater-blinded assessment of the mean diameter of

injection-site redness; and SF-MPQ assessments, including the proportion of patients pain-free as recorded on the SF-MPQ VAS. Types of pain and severity experienced by the patient were also recorded on the SF-MPQ. The number of relapses and severity were secondary efficacy endpoints. Relapses were patient-reported and not objectively assessed; the number and severity of relapses were observational clinical assessments.

Statistical analysis

The primary analysis population was the intent-to-treat population (all patients randomized to treatment). The safety population consisted of all patients who received at least one injection of study drug. The safety-extension population consisted of all patients who received at least one injection of study drug and had available extension phase data. Baseline characteristics of the two treatment groups were compared using analysis of variance (ANOVA) with effects for treatment group and pooled site for continuous variables and the Cochran–Mantel–Haenszel general association test, adjusted for pooled site, for categorical variables.

The null hypothesis was that there would be no difference in mean change in VAS pain score at 30 min post-injection from pre-injection across the treatments at full dose. The primary endpoint was evaluated with a two-way ANOVA model on signed ranked data, including treatment group and pooled site as main effects. The same method was also used to analyze treatment comparisons of the mean changes in the VAS diary pain score from pre-injection to immediately post-injection and 10 min post-injection, as well as mean SF-MPQ pain score at 60 min post-injection. An ANOVA model was used for between-group comparisons; for MSTQ scores, treatment group and pooled site were main effects; for injection-site redness, treatment group and site were main effects. The proportion of patients pain-free on SF-MPQ VAS was analyzed using the Cochran–Mantel–Haenszel general association test, adjusted for site, or Fisher's exact test, if appropriate. Injection-site swelling, bruising, and itching were compared between groups using a Cochran–Armitage trend test. In the comparative phase, all statistical tests were two-sided and used a significance level of $\alpha = 0.05$. No adjustment was made for multiple comparisons.

Patient-reported relapses during the comparative phase were compared using a Poisson regression model with the total number of relapses as the dependent variable and treatment group and pooled site as independent variables.

Determination of sample size

A total of 100 patients (50 per arm) was calculated to provide at least 90% power to detect the difference between treatment groups for the primary objective, when the expected treatment effect size (the difference between the treatment groups divided by the standard deviation [SD]) was at least 0.735. The effect size was based on a difference between the treatment groups of 0.025 mm and an SD value of 0.034 mm. The difference between the treatment groups was based on a mean change of 0.1 mm in the IFNβ-1a group and 0.125 mm in the IFNβ-1b group, and assumed that the mean VAS diary pain scores at pre-injection in the two treatment groups were similar. The calculation also assumed a two-sided Wilcoxon rank sum test, a common SD of the change of ≤0.034 mm, and a Type I error rate of 5%.

Results

Patient disposition and baseline characteristics

Between May 2006 and July 2009, a total of 129 patients were enrolled: 65 were randomized to IFNβ-1a and 64 to IFNβ-1b (Figure 2). Patient baseline characteristics (Table 1) did not differ significantly between groups. Fifty-six patients in the IFNβ-1a group completed the comparative phase and entered the safety-extension phase, and these were termed the "Always IFNβ-1a" group (Figure 2). Of the 63 patients in the IFNβ-1b group who completed the comparative phase, 60 entered the extension phase and were termed the "Delayed IFNβ-1a" group. During the extension phase, the mean (SD) duration of treatment with IFNβ-1a was longer in the Always IFNβ-1a group (436 [251] days) than in the Delayed IFNβ-1a group (338 [260] days).

Tolerability

Comparative phase

During the full-dose period, the VAS diary pain score was very low across both treatments. Mean changes in pain scores from pre-injection to immediately, 10 min, and 30 min after injection were all <5 mm with both treatments (Figure 3). The mean (SD) pre-injection VAS diary pain score was 0.43 (2.06) mm in the IFNβ-1a group and 0.40 (1.64) mm in the IFNβ-1b group. The primary endpoint of mean change in the VAS diary pain score from pre-injection to 30 min post-injection during the full-dose period was not statistically different between IFNβ-1a and IFNβ-1b (mean [SD] 0.67 [2.32] mm vs. 1.14 [4.94] mm, respectively, $p = 0.524$; Figure 3) but was numerically lower with IFNβ-1a than with IFNβ-1b. Mean changes in the VAS diary pain score from pre-injection to immediately and 10 min post-injection during the full-dose period were also not statistically different across groups (Figure 3).

The proportions of patients who were pain-free on the VAS diary during the full-dose period (score of 0 mm for all full-dose injections) immediately, 10 min, and 30 min after injection were not statistically different

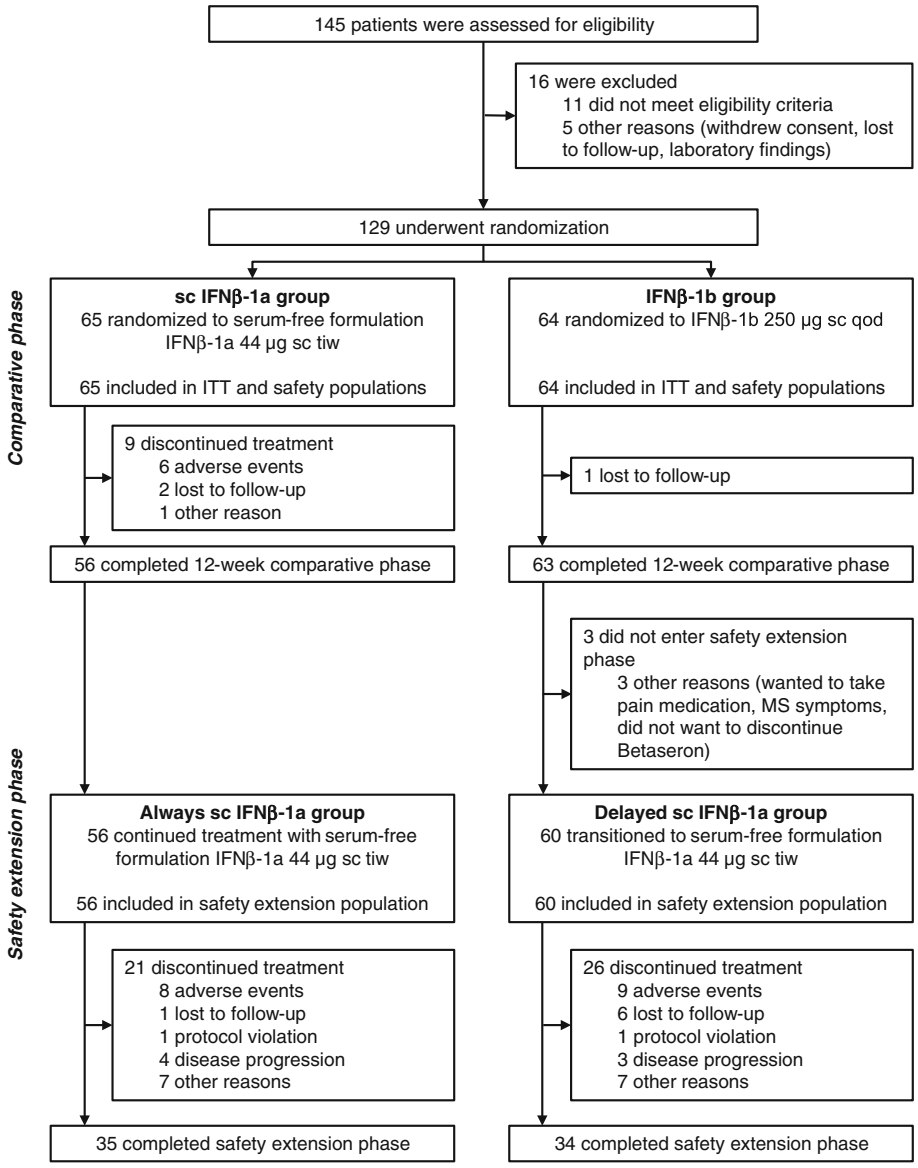

Figure 2 Patient enrollment and disposition. IFN, interferon; ITT, intent-to-treat; qod, every other day; sc, subcutaneous; tiw, three times weekly.

across groups, but scores were numerically higher with IFNβ-1a than with IFNβ-1b (Figure 4). The mean SF-MPQ VAS pain scores were similar between the two groups, as were the proportions of patients who were pain-free on the SF-MPQ VAS (Table 2). During the full-dose period, the most common types of pain experienced during the 60 min after injection (incidence of ≥20% in either group) were hot-burning (reported by 40.0% of patients in the IFNβ-1a group vs. 53.1% of patients in the IFNβ-1b group), aching (29.2% vs. 45.3%), sharp (35.4% vs. 42.2%), tender (33.8% vs. 35.9%), shooting (26.2% vs. 34.4%), stabbing (29.2% vs. 32.8%), throbbing (27.7% vs. 32.8%), and heavy (9.2% vs. 23.4%).

The proportion of patients who reported any occurrence of FLS during the entire 12-week comparative phase on the MSTSQ was 84.6% with IFNβ-1a and 93.8% for IFNβ-1b; for the titration period, the occurrence of FLS was 75.4% and 87.5% with IFNβ-1a and IFNβ-1b, respectively. For the full-dose period, the FLS score was 84.6% and 76.6% with IFNβ-1a versus IFNβ-1b, respectively. The difference in frequency of FLS between IFNβ-1a (mean 3.55; SD 1.45) and IFNβ-1b (mean 2.78; SD 1.4) was significant (p = 0.003). The ratio of the percentage of patients reporting ISRs on the MSTQ during the full-dose period was similar to that of the FLS score. The difference in frequency of ISRs between

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