Comparative tolerance of IFN beta-1a regimens in patients with relapsing multiple sclerosis

The EVIDENCE study

M. Sandberg-Wollheim
C. Bever
J. Carter
M. Färkkilä
B. Hurwitz
Y. Lapierre
P. Chang
G. S. Francis
for the EVIDENCE Study Group

Abstract
The EVIDENCE study was a direct comparative study of two dose regimens of interferon (IFN) beta-1a used in the treatment of relapsing-remitting multiple sclerosis (RRMS): 30 mcg intramuscularly once weekly (qw; n = 338) and 44 mcg subcutaneously three times weekly (tiw; n = 339). The study continued for an average of 64 weeks. The safety population consisted of all patients receiving at least one dose of study drug. Clinical assessments occurred every 4 weeks for 24 weeks and then every 12 weeks. Blood tests for safety were taken at baseline and at weeks 4 and 12, and every 12 weeks thereafter. Overall adverse events were more common with the 44 mcg tiw regimen (p = 0.007), and were due predominantly to differences in injection-site reactions. The majority of adverse events were rated mild by investigators. Hepatic and haematological adverse events and asymptomatic laboratory abnormalities were more common with 44 mcg tiw (p < 0.001), with no difference seen for severe events. Flu-like symptoms were more common with 30 mcg qw (p = 0.031), were more severe and persisted for longer. Serious adverse events were comparable for both groups, as were drug discontinuations. In conclusion, although adverse events were more common with high-dose, high-frequency IFN therapy, differences were primarily for mild events and did not affect treatment adherence. Based on superior clinical and magnetic resonance imaging outcomes over an average of 64 weeks, coupled with modest safety differences, the risk-benefit ratio for IFN therapy in RRMS favours the 44 mcg tiw regimen over this period of time.

Key words multiple sclerosis · interferon beta-1a · adverse events · comparative study

Introduction
In the absence of a cure for multiple sclerosis (MS), interferon (IFN) beta has been shown to be beneficial in modifying the course of relapsing-remitting MS (RRMS) on both clinical and magnetic resonance imaging (MRI) measures [1–5]. Clinical studies suggest that the efficacy is dependent on both the dose and dosing frequency. Indeed, higher doses, either once weekly (qw)
or three times weekly (tiw), have been shown to be more efficacious than lower doses [1, 3, 5, 6], except for a single study with qw intramuscular (im) IFN beta-1a [7]. Furthermore, the measurement of classical IFN beta pharmacodynamic markers, such as neopterin and 2’-5’-oligoadenylate, indicates that IFN beta activity is greater as either the dose or frequency of injections is increased, when standardised doses are used [8–11].

Consistent with these data, the EVIDENCE study [12], a randomised, assessor-blinded study, showed significantly enhanced benefit on relapse measures (proportion of patients relapse-free, time to first relapse, relapse rate) and MRI outcomes (number of T2 active lesions, proportion of active scans per patient, proportion of patients with no active scans) for patients receiving IFN beta-1a (Rebif®), 44 mcg subcutaneously (sc) tiw, compared with patients receiving IFN beta-1a (Avonex®), 30 mcg im qw, for an average of 64 weeks [13].

IFN beta therapy is, however, associated with the occurrence of adverse events (AEs), particularly influenza (‘flu)-like symptoms (FLS) and injection-site disorders [1, 3, 5, 12], which, although generally mild, may affect treatment adherence in a proportion of patients. It is therefore important that the use of the more effective higher frequency, higher dose of IFN beta-1a does not compromise the benefit-to-risk ratio.

Here, we report the safety data from the EVIDENCE study for an average exposure of 64 weeks. This is the most comprehensive, comparative safety assessment of two IFN beta products, and evaluates the safety profiles of two treatment regimens indicated for relapsing MS, which differ in dose, frequency, and route of administration.

**Materials and methods**

The design of the EVIDENCE study has been published previously [12, 13]. Briefly, the EVIDENCE study was designed as a 48-week, randomised, controlled, multicentre trial with blinded assessors of clinical and MRI outcomes, comparing two IFN beta-1a treatment profiles in 677 IFN-naïve patients with RRMS. All patients gave their informed consent prior to study inclusion. Following randomisation, patients received either IFN beta-1a (Rebif®), 44 mcg sc tiw, or IFN beta-1a (Avonex®), 30 mcg im qw, ongoing until the final enrolled patient had completed 48 weeks of treatment, resulting in a mean total follow-up of 64 weeks of direct comparative data. Patients could use, prophylactically or as needed, non-steroidal anti-inflammatory medications or acetaminophen.

The primary outcome of the study was the proportion of patients who remained relapse-free. Relapse rate and MRI measures were secondary endpoints. Safety was assessed by monitoring AEs throughout the study and by physical examination by the unblinded treating physician. Routine haematology, clinical chemistry, urinalysis (pre-study, at weeks 4 and 12, and every 12 weeks thereafter), and thyroid function tests (pre-study, and every 24 weeks thereafter) were also performed. The number of AEs and the number of patients reporting AEs were summarised by body system and preferred term for each treatment group. Additionally, the severity of an AE was assessed, according to the WHO common toxicity criteria, as 'mild', 'moderate', 'severe', or 'life-threatening', and the relationship of the AE to study treatment was classified as 'unlikely', 'possible', or 'probable'. The proportion of patients experiencing AEs was compared using Fisher’s exact test. Deviations from laboratory test baselines were also reported for each treatment group and compared using Fisher’s exact test. Treatment discontinuations were summarised by primary reason for each treatment group.

All patients who had received at least one injection of IFN beta-1a were included in the safety analyses.

To compare the risk with benefit, calculations of the number needed to treat for harm (NNH) were performed using the formula, NNH = 1/ARI, where ARI is the absolute risk increase of having an adverse occurrence during therapy. These values were examined in relation to the number needed to treat for benefit (NNT), as reported elsewhere [12, 13].

**Results**

The comparative phase of the EVIDENCE study was completed by 299/339 (88%) patients receiving IFN beta-1a, 44 mcg sc tiw, and by 306/338 (91%) patients given IFN beta-1a, 30 mcg im qw (p = 0.38). The time on study and time on treatment were similar for both treatment groups (Table 1).

Overall, AEs were approximately 15% more common with the 44 mcg tiw regimen (9.1 AEs/patient) than with the 30 mcg qw regimen (7.9 AEs/patient; p = 0.007). Most of this difference reflects the different routes of injection, with the greatest number of AEs being related to injection-site disorders, the vast majority (> 85%) of which were graded as mild. Excluding injection-site disorders from both groups, AE rates were 7.9 AEs/patient and 7.5 AEs/patient for 44 mcg tiw and 30 mcg qw, respectively (p = 0.57). The overall rate of severe AEs was similar (0.33 and 0.34 AEs/patient, respectively), although some individual AE differences were noted (Fig.1). Considering AEs related to IFN (‘flu-like symptoms, fatigue, headache, fever, myalgia, arthralgia, rigors, liver or WBC dysfunction), 10.5% of patients receiving 44 mcg tiw experienced a severe event, compared with 14.4% of those receiving 30 mcg qw (p = 0.08).

Influenza-like symptoms (FLS) were significantly more common in patients treated with 30 mcg qw than those receiving 44 mcg tiw (53% versus 45%, respectively; p = 0.031). The symptoms were generally graded as mild in severity, but a higher proportion of FLS was considered moderate and severe in patients receiving 30 mcg qw. The number of events was also greater with 30 mcg qw, although clinicians did not necessarily count each single event, but could label events as ‘ongoing’ or ‘intermittent’. With the exception of rigors, which showed a trend towards a higher incidence in patients treated with 30 mcg qw, the occurrence of other components of FLS, such as fever, myalgia, and fatigue, were similar between groups. Persisting FLS were more common in patients receiving 30 mcg qw (Fig. 2).