Original Research

The STAR Study: A Real-World, International, Observational Study of the Safety and Tolerability of, and Adherence to, Serum-Free Subcutaneous Interferon β-1a in Patients With Relapsing Multiple Sclerosis

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ABSTRACT

Background: Adverse reactions, particularly injection site reactions (ISRs), are common reasons for nonadherence to injectable multiple sclerosis (MS) treatments. Adherence to MS treatment is important to ensure good treatment outcomes.

Objective: The aim of this study was to assess the local tolerability of subcutaneous (SC) serum-free interferon (IFN) β-1a in patients with relapsing MS over 1 year in a real-life, international setting. The study also assessed safety, disease activity, and adherence.

Methods: This was a prospective, international, multicenter, observational study of 251 patients with relapsing-remitting MS treated with SC serum-free IFN β-1a 44 μg or 22 μg 3 times weekly for 12 months or until early discontinuation. The primary end point was the proportion of patients with ISRs. Secondary end points included proportion of patients with adverse events (AEs); annualized relapse rate (ARR); proportion of patients remaining relapse-free; and adherence to treatment.

Results: During the observation period, 27.5% (69 of 251) of patients experienced nonserious ISRs, which was consistent with the incidence reported in clinical studies. Five patients discontinued treatment and 2 patients suspended treatment because of ISRs. Mean age was 35.8 years; patients were predominantly white (94.8%), and two thirds (66.1%) were female. The overall incidence of AEs was 63.7% (160 of 251), and overall safety and tolerability were assessed as excellent, very good, or good in >85% of patients. More than 70% of patients remained relapse-free, and the mean ARR was 0.4. More than 90% of patients had very good or good adherence to treatment; a significantly greater proportion of these were relapse-free at 12 months compared with those with fair or poor adherence (77.6% vs 50.0%; $P = 0.0107$), and their ARR was significantly lower (0.3 vs 0.9; $P = 0.0055$). Patients with fair or poor adherence had 4.6 times higher odds of experiencing a relapse than those with very good or good adherence.

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Conclusions: The incidence of ISRs and the overall safety profile in this observational study, in an international population in a real-life setting, confirm the good local tolerability of SC serum-free IFN β-1a reported in clinical studies. The association between good adherence and a lower ARR underlines the importance of good adherence. The good local and general tolerability of SC IFN β-1a may help ensure a high level of adherence, which is associated with better clinical outcomes. ClinicalTrials.gov identifier: NCT01080027. (*Clin Ther*. 2014;36:1946–1957)

Key words: adherence, injection site reactions, injection subcutaneous, interferon β-1a.

INTRODUCTION

Multiple sclerosis (MS) is a heterogeneous, immune-mediated, demyelinating, neurodegenerative disease and is the most common cause of neurologic disability in young adults. It is a chronic and, as yet, incurable disease that in its most common clinical form has a relapsing-remitting course that necessitates lifelong treatment. The chronic nature of MS makes treatment adherence challenging, particularly in patients with long-lasting disease.[1] Nonadherence to MS treatments has been well documented,[2–4] with studies reporting adherence rates between 28% and 87% among patients taking disease-modifying drugs.[5] Several studies have demonstrated that patients with MS who have gaps in their treatment have a higher risk of relapse than those with better adherence,[6–9] indicating that adherence to prescribed therapy is important to ensure clinical efficacy.

The established first-line immunomodulatory disease-modifying drugs, namely interferon (IFN) β and glatiramer acetate, have been shown to modify the course of MS and have established benefit-to-risk profiles that make them suitable for long-term use from the initial diagnosis of the disease.[10–16] IFN β preparations and glatiramer acetate are administered by subcutaneous (SC) or intramuscular injection, and some studies have reported that factors related to self-injection can have a negative effect on patients' quality of life and on their adherence to medication.[17,18] Skin reactions and pain at the injection site are commonly cited reasons for nonadherence to injectable MS therapies.[1,3,19] In 1 study, 12% of patients who interrupted IFN β treatment for >1 month cited injection-site reactions (ISRs) as the reason.[4] In a survey of 2648 patients treated with injectable MS therapies, injection-related adverse effects (including pain at the injection site, injection anxiety, and fatigue with the injection process) were the second most common reasons for nonadherence (32% of nonadherent patients) after forgetting to administer the injection (50.2%).[20]

The efficacy and safety of serum-free SC IFN β-1a have been demonstrated in closely monitored patient populations in clinical trials.[21,22] However, in daily clinical practice, the patient population is more heterogeneous and patients have less intensive monitoring by health care professionals. The objectives of the present study were therefore to evaluate the local tolerability, general safety, and efficacy of serum-free SC IFN β-1a in patients with relapsing-remitting MS (RRMS) and to assess patients' adherence to treatment over a 12-month period in an international population in a real-life setting.

PATIENTS AND METHODS

Study Design

The STAR (Safety, Tolerability and Adherence with Rebif® New Formulation in Real Life Settings) study was a prospective, international, multicenter, observational study conducted in 47 centers in Finland, Greece, the Netherlands, Norway, Portugal, and Sweden between October 2008 and September 2011. The study was performed in accordance with the Declaration of Helsinki (Edinburgh 2000 version, with the clarifications of Washington 2002 and Tokyo 2004) and applicable national regulatory requirements. It was approved by local ethics committees for the participating centers.

Participants

Patients diagnosed with RRMS according to the 2005 McDonald criteria[23] were eligible for enrollment in the study if they were aged 18 to 60 years; had a score <6 on the Expanded Disability Status Scale; and were treatment naive for any disease-modifying MS therapy or had ≤6 weeks of treatment with SC serum-free IFN β-1a before enrollment. Patients were required to provide written informed consent before study initiation.

Patients were excluded from the study[24] if they had ≥1 of the following criteria: primary progressive or secondary progressive MS; previously administered IFN β, glatiramer acetate, any other immunomo-

dulatory or immunosuppressive agents, or any other MS therapy in the past, with the exception of serum-free SC IFN β-1a for no more than 6 weeks before enrollment; received oral or systemic corticosteroids or adrenocorticotropic hormone within the 30 days before enrollment; history of any chronic pain syndrome; serious or acute heart disease; inadequate liver function (defined as an alanine aminotransferase level $>3 \times$ upper limit of normal [ULN], alkaline phosphatase $>2 \times$ ULN, or total bilirubin $>2 \times$ ULN if associated with any elevation of alanine aminotransferase or alkaline phosphatase); white blood cell count $<0.5 \times$ the lower limit of normal; a history of alcohol or drug abuse in the last 2 years; or contraindications to IFN β-1a as defined in the product labeling information. Patients were recruited over a 1-year period, and each patient was observed for 12 months or until early termination.

Administration of the Study Drug

All patients received SC serum-free (without fetal bovine or human serum albumin excipients) IFN β-1a[†] 44 μg or 22 μg 3 times weekly throughout the study period. Serum-free SC IFN β-1a could be administered by using an autoinjection device or by manual injection. The decision on the prescribed dose of serum-free IFN β-1a was at the discretion of the treating physician and reflected the current standard of care in a real-life setting.

Patient Assessment

After a prestudy visit to assess eligibility, patients were required to attend the clinic at study day 1 (baseline), month 6, and month 12 or at any time in the case of early discontinuation (ED). At study day 1, each patient was provided with a diary for reporting experiences with the medication and missed injections (including reasons for missed injections). In addition, demographic data and information on significant medical history/concomitant diseases, MS history, concomitant MS medication, vital signs, details of current treatment with SC serum-free IFN β-1a, and adverse events (AEs) were gathered. The following data were recorded at the month 6 and month 12 visits: concomitant MS medication; vital signs; AEs; adherence to therapy; and details of serum-free IFN β-1a treatment. At the month 12 visit, the investigator performed a global evaluation of safety and adherence for each patient.

[†]Trademark: Rebif® (Merck Serono SA, Geneva, Switzerland, a subsidiary of Merck KGaA, Darmstadt, Germany).

Criteria for Evaluation

The primary study end point was the proportion of patients with ISRs. Secondary end points included the proportion of patients with AEs, including specific categories of AEs; the proportion of missed injections; reasons for missed injections; annualized relapse rate (ARR); the proportion of patients remaining relapse-free from baseline; and time to first relapse.

AEs were defined according to World Health Organization Adverse Reaction Terminology and were displayed by using Medical Dictionary for Regulatory Activities system organ class and preferred term. Causality was assessed in accordance with the recommendations of the World Health Organization AE Monitoring Centre.

A relapse was defined as the appearance of a new symptom or worsening of an old symptom attributable to MS, accompanied by an appropriate new neurologic abnormality or focal neurologic dysfunction lasting at least 24 hours in the absence of fever and preceded by stability or improvement for at least 30 days. Maximal severity of relapses was described according to the activities of daily living criteria.[25]

For the assessment of treatment adherence, patients were asked to record the date of each missed injection and the reason for missing the injection, and were instructed to bring the diary with them at every visit. The investigators assessed patients' adherence as: very good (patient was always taking his or her medication as instructed by the physician); good (patient was taking his or her medication as instructed by the physician but forgot it once or twice since the previous visit); fair (sometimes patient did not take the study medication properly or regularly); or poor (patient did not take the study medication properly or regularly most of the time).

Sample Size Determination

A sample size of 250 patients was required to estimate the incidence of ISRs in the study population with an accuracy of 6%, based on an expected incidence of ISRs of 30% in 48- and 96-week data from clinical studies of serum-free SC IFN β-1a.[22,26]

Statistical Analysis

All analyses were performed on the safety population, which included all patients who received at least 1 injection of serum-free IFN β-1a after enrollment. All data were evaluated descriptively by using mean,

median, SD, quartiles, and extreme values for continuous variables, and counts and percentages for categorical variables.

For the primary end point, the proportion of patients with ISRs and corresponding 95% CIs were determined. For the secondary end points, the outcomes "presence/absence of ISR" and "relapse/relapse free at study end" were analyzed by using logistic regression. Time to onset of first relapse was analyzed by using a Cox proportional hazards regression model, with time (days) as the dependent variable, and level of adherence as the independent variable with no interaction terms. Differences between subpopulations with regard to relapse data were analyzed nonparametrically by using the Wilcoxon rank sum test. Imputation was performed for partial dates only.

RESULTS

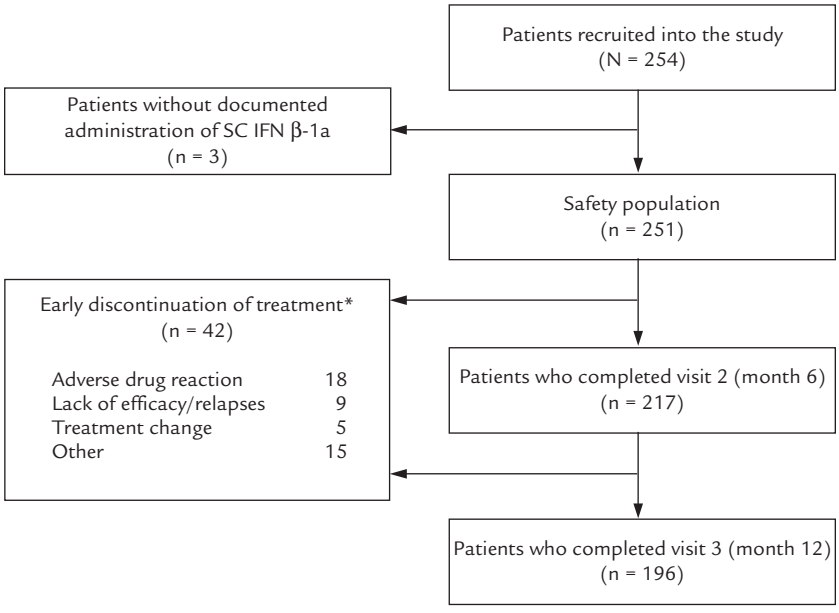
Patient Disposition and Demographic and Baseline Characteristics

Patient disposition is shown in Figure 1. A total of 254 patients were recruited to the study. The safety population, which included patients with documented administration of SC IFN β-1a, comprised 251 patients; ED was documented for 42 patients (16.7%), and 196 (78.1%) completed the month 12 visit. Adverse drug reactions were the most common reason for early study discontinuation (7.2% [18 of 251]).

Demographic and baseline disease characteristics of the safety population are summarized in Table I. Mean (SD) age was 35.8 (10.3) years (n = 251); patients were predominantly white (94.8% [238 of 251]), and two thirds were female (66.1% [166 of 251]). Concomitant medications related to MS (including treatments for AEs), most frequently paracetamol, ibuprofen, and methylprednisolone, were documented for 76.1% of patients (191 of 251). Most patients (87.3% [219 of 251]) opted to administer serum-free SC IFN β-1a by using an autoinjector, 7.6% (19 of 251) by manual injection, and 4.8% (12 of 251) by both methods. Data were missing for 1 patient (0.4%).

Primary End Point: Proportion of Patients With ISRs

Overall, 27.5% of patients (69 of 251) experienced ISRs (Table II) that included injection-site erythema



*Percentages are based on the number of patients in the Safety Population.

Figure 1. Patient disposition. *Percentages are based on the number of patients in the safety population.

(n = 30), reaction (n = 17), pain (n = 16), swelling (n = 3), hematoma (n = 2), hemorrhage (n = 1), induration (n = 1), pruritus (n = 1), rash (n = 1), and abscess (n = 1). Five patients discontinued treatment because of ISRs that involved, pain, swelling, erythema, and induration; an additional patient discontinued treatment due to injection site hematoma and influenza-like illness. One patient interrupted treatment because of mild pain and erythema at the injection site. Most ISRs were mild (14.7% [37 of 251]) or moderate (11.2% [28 of 251]) in intensity; 4 patients experienced severe ISRs (1.6%). No serious ISRs were reported. All ISRs were assessed as possibly or probably related to administration of SC IFN β-1a. Unexpectedly, female patients had higher odds of experiencing ISRs compared with male patients (odds ratio [OR], 2.15 [95% CI, 1.1–4.2]). Age, treatment adherence at study end, mean dose per week, and educational level had no influence on the occurrence of ISRs.

Table I. Demographic and baseline multiple sclerosis (MS) characteristics.*

Characteristic	Total (N = 251)
Age	
No.	251
Mean (SD), y	35.8 (10.3)
Median (minimum, maximum), y	35.0 (17, 60)
Q1; Q3, y	27; 45
Sex, no. (%)	
Female	166 (66.1)
Male	85 (33.9)
Ethnic origin, no. (%)	
White	238 (94.8)
Black	11 (4.4)
Asian	0
Other	1 (0.4)
White/other	1 (0.4)
Duration since MS diagnosis	
No.	249
Mean (SD), mo	18 (40.8)
EDSS score	
No.	236
Mean (SD)	1.64 (1.12)
Relapse episodes in the last 12 months	
No.	246
Mean (SD)	1.6 (0.8)
Time since last relapse episode	
No.	230
Mean (SD), mo	3.8 (2.4)

Q = quartile; EDSS = Expanded Disability Status Scale.
*Percentages are based on the total number of patients.

Secondary End Points

General Safety Profile

A total of 147 patients (58.6%) experienced a total of 389 related AEs (assessed by the investigator to have a possible, probable, or unlikely relationship with SC IFN β-1a) (Table III). Seventeen patients (6.8% [17 of 251]) cited AEs as the reason for discontinuation of treatment; in 16 (6.4%) of these patients, the AEs had an assumed causal relationship with IFN β-1a.

Nonserious, related AEs reported in >1% of the study population are shown in Table IV. The most frequently reported related AEs were influenza-like illness (30.3% [76 of 251]) and injection site erythema (12.0% [30 of 251]), headache (9.2% [23 of 251]), ISR (6.8% [17 of 251]), injection site pain (6.4% [16 of 251]), and fatigue (5.6% [14 of 251]). Seven patients (2.8%) experienced 11 serious AEs (SAEs), which led to discontinuation of treatment in 2 patients. Only the SAE of psychotic disorder was deemed possibly related to treatment. No deaths occurred during the study, and all patients recovered from SAEs without sequelae. The investigators rated the overall safety of SC serum-free IFN β-1a as excellent in 62.1% (139 of 224), very good in 25.9% (58 of 224), and good in 5.8% (13 of 224) of patients at the month 12/ED visit. Tolerability was rated as excellent in 40.2% (90 of 224), very good in 35.3% (79 of 224), and good in 11.6% (26 of 224) of patients. Overall, the safety and tolerability of IFN β-1a were rated as excellent, very good, or good in >85% of patients.

Adherence

Adherence data are summarized in Table V. The proportion of patients with missed injections since the previous visit was similar at the month 6 (20.3% [44 of 217]) and month 12/ED (21.0% [47 of 224]) visits. The most common reason for missed injections was

Table II. Summary of injection site reactions (ISRs).*

Variable	Total (N = 251)
Patients with ISR, no. (%)†	69 (27.5)
95% CI	22.1–33.5
Patients with ISR by intensity, no. (%)†	
Mild	37 (14.7)
Moderate	28 (11.2)
Severe	4 (1.6)

*All ISRs were assessed as treatment related (causal relationship with subcutaneous interferon β-1a was assessed by the investigator as possible, probable, or unlikely).
†Percentages are based on the total number of patients (safety population).

Table III. Summary of related adverse events (AEs). Unless otherwise noted, data are given as number (%).

AE	Total (N = 251)
No. of AEs	389
Patients with AEs*	147 (58.6)
Patients with AEs by intensity*†	
Mild	55 (21.9)
Moderate	70 (27.9)
Severe	21 (8.4)
Life-threatening	1 (0.4)
Patients with nonserious AEs*	147 (58.6)
Patients with serious AEs*	5 (2.0)
No. of deaths	0
Patients who discontinued treatment due to AE*	16 (6.4)

Related adverse events were assessed by the investigator to have a possible, probable, or unlikely relationship with subcutaneous interferon β-1a.
*Percentages are based on the total number of patients (safety population).
†Each patient is counted only with the maximum intensity.

Table IV. Nonserious, related adverse events reported in >1% of patients. Data are given as number (%).

MedDRA Preferred Term	Total (N = 251)
Influenza-like illness	76 (30.3)
Injection site erythema	30 (12.0)
Headache	23 (9.2)
Injection site reaction	17 (6.8)
Injection site pain	16 (6.4)
Fatigue	14 (5.6)
Pyrexia	12 (4.8)
Myalgia	10 (4.0)
Transaminase level increased	8 (3.2)
Pain in extremity	7 (2.8)
Liver function test abnormality	6 (2.4)
Urinary tract infection	5 (2.0)
Anxiety	4 (1.6)
Chills	4 (1.6)
Hyperhidrosis	4 (1.6)
Arthralgia	3 (1.2)
Dizziness	3 (1.2)
Injection site swelling	3 (1.2)
Nausea	3 (1.2)
Platelet count decreased	3 (1.2)
Sleep disorder	3 (1.2)
Skin reaction	3 (1.2)

MedDRA = Medical Dictionary for Regulatory Activities.

"patient forgot to inject" (51.1% [24 of 224] at month 12/ED), "patient did not want to have injection" or "other" (both 19.1% [9 of 224]), "flu-like symptoms" (10.6% [5 of 224]), and "tired" (6.4% [3 of 224]). Only 2 patients (4.3% [2 of 47]) cited "pain on injection site" as a reason for missed injections, and 1 patient (2.1% [1 of 47]) cited "fear of injection." The investigators assessed adherence to treatment at the month 6 visit as very good in 79.6% (172 of 217) of patients, good in 13.0% (28 of 217), and fair in 6.9% (15 of 217). At month 12/ED, adherence was assessed as very good in 78.5% (175 of 224) of patients, good in 12.6% (28 of 224), and fair in 7.2% (16 of 224). Investigators assessed adherence as poor in 2 patients (0.9%).

Table V. Adherence to study medication.

	Month 6 (n = 217)	Month 12/ED (n = 224)
Patients with missed injections since last visit[*]		
N	44 (20.3%)	47 (21.0%)
Percentage of missed injections[†‡]		
N	209	219
Mean (SD)	0.9 (3.5)	0.7 (2.0)
Median (minimum, maximum)	0.0 (0, 30)	0.0 (0, 22)
Reasons for missed injections[§‖]		
Forgot to inject	23 (52.3%)	24 (51.1%)
Tired	4 (9.1%)	3 (6.4%)
Fear of injection	1 (2.3%)	1 (2.1%)
Did not want to have injection	6 (13.6%)	9 (19.1%)
Pain on injection site	2 (4.5%)	2 (4.3%)
Flu-like symptoms	4 (9.1%)	5 (10.6%)
Other	14 (31.8%)	9 (19.1%)
Missing data	1 (2.3%)	0
Adherence to study medication[*¶]		
Very good	172 (79.6%)	175 (78.5%)
Good	28 (13.0%)	28 (12.6%)
Fair	15 (6.9%)	16 (7.2%)
Poor	0	2 (0.9%)
Missing data	1 (0.5%)	2 (0.9%)

*Adherence: very good = patient was always taking his or her medication as instructed by the physician; good = patient was taking his or her medication as instructed by the physician but forgot it once or twice since the previous visit; fair = sometimes patient did not take the study medication properly or regularly; poor = patient did not take the study medication properly or regularly most of the time.
†Cumulative for month 12/early discontinuation visit.
‡One patient was excluded from the analysis because a value (247.8%, month 12) was considered implausible.
§Percentages are based on the number of patients with missed injections at the respective visit.
‖More than 1 reason could have been documented for a patient.
¶Percentages are based on the number of patients with the respective visit.

Disease Activity

The results of the relapse assessments for the safety population are summarized in Table VI. At month 12/ED, 71.7% (180 of 251) of patients were relapse-free, and the mean ARR was 0.4 (1.0) (range, 0–9; n = 237).

Effect of Adherence on Disease Activity

A greater proportion of patients with very good or good adherence (n = 217) were relapse-free at month 12/ED (77.6% [170 of 219]) compared with those with fair or poor adherence (50.0% [9 of 18]; $P = 0.0107$) (Figure 2A). However, because of the low number of patients in the subgroup with fair or poor adherence, this result should be interpreted with caution. The ARR was significantly lower in the patient subgroup with very good or good adherence versus fair or poor adherence (0.3 [1.0] vs 0.9 [1.2]; $P = 0.0055$) (Figure 2B). There were no significant differences between the adherence subgroups with regard to the mean time to onset of the first episode or mean duration of the episodes. In a multivariate logistic regression analysis, the odds of a patient with a fair or poor adherence experiencing a relapse epi-

Table VI. Relapse assessment.

Variable	Total (N = 251)
Relapse-free patients at month 6*	191 (76.1%)
Relapse-free patients at month 12/ED*	180 (71.7%)
Annualized relapse rate (normalized to 12 months)	
No. of patients	237
Mean (SD)	0.4 (1.0)
Median (min, max)	0.0 (0, 9)
Time to onset of first relapse, d	
No. of patients	46
Mean (SD)	152.8 (113.3)
Median (min, max)	255 (4, 377)
Duration of relapse episode, d	
No. of relapse episodes	53
Mean (SD)	35.2 (35.4)
Median (min, max)	22 (2, 154)
Total number of relapse episodes between baseline and month 6	
No. of relapse episodes	35
No. of relapse episodes between baseline and month 6 by severity†	
Mild	17 (48.6%)
Moderate	17 (48.6%)
Severe	1 (2.9%)
Total no. of relapse episodes between month 6 and month 12/ED	
No. of relapse episodes	31
No. of relapse episodes between month 6 and month 12/ED by severity†	
Mild	35 (53.0%)
Moderate	26 (39.4%)
Severe	5 (7.6%)

Note: For the annualized relapse rate, the number of relapse episodes per patient was normalized to 12 months, regardless of whether the patient discontinued the study earlier. Partial dates for "time to first relapse" and "duration of relapse episodes" were imputed.
ED = early discontinuation; min = minimum; max = maximum.
*Percentages are based on the total number of patients.
†Percentages are based on the total number of relapse episodes in the respective time period.

sode during the study were 4.6 times higher than for patients with very good or good adherence (OR, 4.58 [95% CI, 1.48–14.20]). A Cox proportional hazards regression analysis identified significant effect of adherence on the time to onset of the first relapse episode, with hazard ratios (95% CI) of 3.20 (1.326–7.739; $P = 0.0097$) for good versus very good adherence and 3.57 (1.313–9.720; $P = 0.0127$) for fair versus very good adherence.

DISCUSSION

The aim of the present study was to assess the local tolerability of SC serum-free IFN β-1a in patients with RRMS in a minimally organized setting without the frequent and regular medical surveillance commonly performed in clinical trials. During the 12-month observation period, 27.5% of patients experienced nonserious ISRs, which was comparable to, or lower than, that observed with the same serum-free SC IFN β-1a therapy

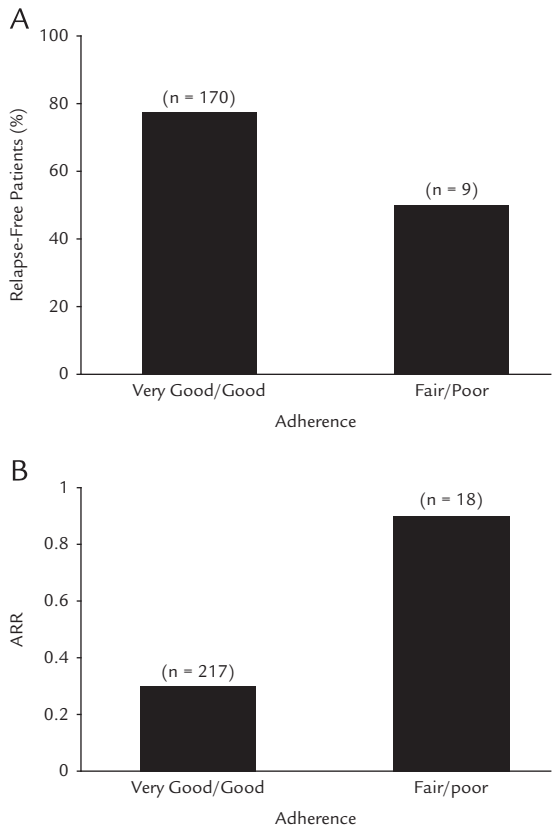


Figure 2. Effect of adherence on relapse activity. (A) At the month 12/early discontinuation visit, the proportion of relapse-free patients in the subgroups with very good/good adherence and fair/poor adherence was 77.6% (170 of 219) and 50% (9 of 18), respectively ($P = 0.0107$; Fisher's exact test). (B) The mean annualized relapse rate (ARR) in the subgroups with very good/good adherence and fair/poor adherence was 0.3 and 0.9, respectively ($P = 0.0055$; Wilcoxon rank sum test).

in clinical studies (29.6% and 43.3% at 48 and 40 weeks, respectively, and 31% and 36% at 96 weeks and 2 years, respectively),[21,22,26,27] demonstrating that the good local tolerability of serum free SC IFN β-1a seen in clinical studies is also observed in a real-life setting.

The observed discontinuation rate of 16.7% is at the lower end of the expected range of 14% to 44% when starting IFN β-1a therapy.[28] Less than 2% of patients in the study discontinued treatment due to ISRs, which accounted for 12% of AEs that led to early discontinuation. These rates compare favorably with findings of a hospital-based survey, which reported that ISRs accounted for 16% of AEs leading to discontinuation of IFN β administered by SC injection 3 times weekly or weekly IM or SC injection.[29] Data from previous studies indicate that patients who discontinue IFN β treatment because of AEs tend to do so soon after therapy initiation (median, 13 months),[29] and most patients who discontinue or switch treatment from SC IFN β-1a do so in the first 12 months.[2] Among patients with MS treated with IFN β, the majority of treatment interruptions occurred within the first 6 months of therapy,[4] and ISRs with SC IFN β-1a were most common during the first month of treatment.[30] Thus, the 1-year observation period in the present study is adequate to assess the effect of local tolerability and general safety of SC IFN β-1a on treatment discontinuation and adherence.

The investigators rated the overall safety and tolerability of SC IFN β-1a during the study as excellent, very good, or good in >87% of patients. AEs accounted for 45% of early discontinuations, which compares favorably with a previous study, which reported that adverse clinical reactions were responsible for 71.5% of discontinuations of long-term treatment with SC IFN β-1a.[31] The overall 63.7% incidence of AEs was lower than the incidence of 76.6% to 95.0% observed in controlled MS populations treated with the same serum-free SC IFN β-1a formulation for a similar duration,[26,27] demonstrating that the good safety profile and tolerability of SC IFN β-1a reported in clinical studies were also observed in a real-life setting. However, we could not rule out the possibility of underreporting of AEs in an observational study versus a randomized controlled trial setting; a recent study reported that the mean incidence of ISRs among patients receiving SC IFN β-1a in randomized controlled trials was 70% (8%) versus 41% (30%) in observational studies.[32]

More than 90% of patients in the study had very good or good adherence. The most common reason for nonadherence, cited by approximately one half of the patients, was forgetting to administer the injection, followed by not wanting to have an injection, which is consistent with the findings of a multicenter, observational study.[20] In the same study, 30% to 38% of patients cited general injection-related problems, including skin reaction and pain at the injection site, as reasons for nonadherence to SC IFN β-1a. Almost

90% of patients in the present study administered IFN β-1a with an autoinjector. Findings from some studies suggest that the use of injection devices may help to overcome some injection-related barriers to adherence. In a 12-week, observational study of 120 patients using an electronic autoinjection device to self-administer serum-free SC IFN β-1a, the incidence of ISRs was 10.6%, and >90% of patients adhered to treatment.[33]

More than 70% of the study population remained relapse-free, and the mean ARR over the study period was 0.4, which is comparable with outcomes in a clinical study setting in which 66.8% of patients were relapse-free after 48 weeks and the mean relapse rate was 0.37.[26] Adherent patients were more likely to be relapse-free at the 6-month and 12-month/ED visits and had a lower ARR compared with those with fair/poor adherence. The difference in the number of patients in the adherence subgroups is a source of bias in the analysis; however, an increased risk of relapse in patients who did not adhere to their MS medication has also been reported in other studies.[6–9] Our findings emphasize the need to adhere to SC IFN β-1a treatment for the disease-modifying effects to be realized and provide a strong rationale for attempting to maximize treatment adherence.

Limitations of the study should be considered when interpreting the findings. The electronic autoinjector for SC IFN β-1a (RebiSmart, Merck Serono SA, Geneva, Switzerland) was not available in all countries during the study period; therefore, adherence data were not recorded automatically for all patients, which could have resulted in patient-reporting errors. We observed no significant effect of adherence on the mean time to onset of the first relapse episode or mean duration of relapse episodes. However, interpatient variability for the mean time to onset of first relapse and the mean relapse duration was high (4–377 days and 2–154 days, respectively,) and imputation of partial dates in 11 patients resulted in inaccuracies of up to 1 month, which could obscure differences in these comparisons.

CONCLUSIONS

This study confirmed that the good local and general tolerability of SC serum-free IFN β-1a seen in clinical studies were also observed in an international population in a real-life clinical setting. Adherence to treatment was high, and adherent patients were more likely to remain relapse-free, have a lower relapse rate, and have a longer time to first relapse than non-adherent patients. These findings suggest that the good local and general tolerability of SC serum-free IFN β-1a may encourage good treatment adherence, which is associated with better treatment outcomes.

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Drs. Hupperts, Gazi-Visser and Arvantis contributed to the study concept or design. Drs. Hupperts, Martins Silva, and Kuusisto were involved in the acquisition of data. Drs. Gazi-Visser, Martins Silva, Arvanitis, and Marhardt contributed to the analysis or interpretation of data. Drs. Ghazi-Visser, Avanitis, Marhardt, and Vlaikidis supervised or coordinated the study. All authors contributed to drafting and revising the manuscript for content and have read and approved the final version.

CONFLICTS OF INTEREST

Dr. Hupperts has received honoraria for consultancies, presentations, participation in advisory boards, and/or PhD grants from Novartis, Biogen-Idec, TEVA, Sanofi/Genzyme, and Merck Serono. Dr. Ghazi-Visser is an employee of Merck Serono, a division of Merck BV. Dr. Martins Silva has received support from Sanofi-Aventis, Biogen-Idec, Merck Serono, Bayer-Schering, and Novartis for clinical research conducted in Centro Hospitalar do Porto/Hospital de Santo António. Dr. Arvanitis was an employee of Merck AE Hellas throughout the period of the study. Dr. Kuusisto received financial compensation for participation in the STAR study; financial compensation from Sanofi-Aventis, Teva, Biogen-Idec, Novartis, and Genzyme for serving as a member of advisory boards; and speaking fees from Biogen-Idec, Novartis, Merck, Bayer, and Orion. Dr. Marhardt is an employee of Merck Serono SA. Dr. Vlaikidis has received honoraria for lecturing and participation in advisory councils and trial steering committees, and travel expenses for attending meetings from Merck AE Hellas, Bayer, Novartis, Pfizer, and Sanofi-Aventis. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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