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Tolerability results from Year 1 of the PRISMS 2-year randomized controlled trial of IFN β-1a SC tiw compared with placebo

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Introduction

- Interferon beta-1a (IFN β-1a) injected subcutaneously (SC) at a dose of 44 or 22 µg three times weekly (tiw) was approved for the treatment of relapsing forms of multiple sclerosis (MS) in 2002.[1]
- The long-term safety profile of IFN β-1a SC tiw is well established, with considerable clinical trial and post-marketing data available.[1–3]
- In the 2-year, double-blind, placebo-controlled PRISMS (Prevention of Relapses and disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) trial, IFN β-1a SC tiw significantly reduced relapse rates and the number of active T2 lesions, and slowed disability progression compared with placebo, in patients with relapsing–remitting MS (RRMS).[2]
- Safety results from PRISMS demonstrated that flu-like symptoms (FLS) were common in all groups, and that injection-site reactions (ISRs) were frequent in both IFN β-1a SC tiw groups, with no apparent dose effect.[2]
- During the PRISMS study, ISRs (n=2) and FLS (n=2) led to four patients discontinuing IFN β-1a SC tiw, highlighting these adverse events (AEs) as a possible tolerability issue for IFN β-1a SC tiw.[2]
- The frequency of ISRs and FLS appear to reduce with increased time on IFN β-1a SC tiw; however, detailed analysis of the frequency of IFN β-1a SC tolerability issues at early time points remains limited.[4]

Objective

- To evaluate tolerability data by timing and severity of AEs during the first year of PRISMS in order to further characterize the safety profile of IFN β-1a SC tiw.

Methods

- Patients enrolled in the PRISMS study (n=560) were IFN-naïve adults with RRMS, active disease (≥2 relapses in the previous 2 years), and an Expanded Disability Status Scale score between 0 and 5.0.
- Patients were randomized to receive IFN β-1a 44 µg SC tiw (n=184) or 22 µg SC tiw (n=189), or placebo (n=187), for 2 years.
- This *post hoc* analysis investigated the frequency and severity of ISRs and FLS at 3-month incremental time periods (0–3, 3–6, and 6–12 months) during the first year of the PRISMS trial.
- AEs were categorized by severity (mild, moderate, or severe) and reported for incremental and cumulative time periods.
- The rates of discontinuation due to ISRs and FLS were calculated during the first year of PRISMS.

Results

- More patients treated with IFN β-1a SC tiw than with placebo experienced injection-site erythema, unspecified ISRs, and injection-site pain during the first year of therapy (**Table 1**). The majority of injection-site AEs were mild; severe events were rare in all groups (**Table 1**).
- Over the cumulative 0–12-month period, FLS were more common in the IFN β-1a 44 µg SC tiw group compared with the placebo group (38.0% vs 26.7%; p=0.026); however, no significant difference between IFN β-1a 22 µg SC tiw (31.2%) and placebo (26.7%) was seen (p=0.364; **Table 2**). Additionally, there was no statistically significant difference between the two IFN β-1a SC tiw doses in the incidence of FLS (p=0.192).
  - No serious FLS, unspecified ISRs, injection-site pain, or injection-site erythema AEs were reported in any group.

Table 1. First-year cumulative tolerability results: treatment-emergent injection-site reactions occurring in ⩾10% of patients in any treatment group.

Severity	Placebo (n=187), %	IFN β-1a 22 µg SC tiw (n=184), %	p value vs placebo[a]	IFN β-1a 44 µg SC tiw (n=184), %	p value vs placebo[a]
Injection-site erythema					
Total	12.3	48.1	<0.001	52.2	<0.001
Mild	10.7	43.4	<0.001	46.2	<0.001
Moderate	1.6	4.2	0.220	4.3	0.137
Severe	0.0	0.5	1.000	1.6	0.121
Unspecified injection-site reaction					
Total	6.4	31.2	<0.001	37.0	<0.001
Mild	5.3	23.3	<0.001	24.5	<0.001
Moderate	1.1	6.9	0.006	10.9	<0.001
Severe	0.0	1.1	0.499	1.6	0.121
Injection-site pain					
Total	11.2	20.1	0.023	20.7	0.016
Mild	10.7	15.9	0.172	12.0	0.745
Moderate	0.5	3.7	0.067	8.2	<0.001
Severe	0.0	0.5	1.000	0.5	0.496

IFN β-1a, interferon beta-1a; SC, subcutaneously; tiw, three times weekly.
[a]Fisher's exact test.

Table 2. First-year cumulative tolerability results: treatment-emergent flu-like symptoms.

Severity	Placebo (n=187), %	IFN β-1a 22 µg SC tiw (n=189), %	p value vs placebo[a]	IFN β-1a 44 µg SC tiw (n=184), %	p value vs placebo[a]
Flu-like symptoms					
Total	26.7	31.2	0.364	38.0	0.026
Mild	18.7	22.2	0.444	26.1	0.105
Moderate	8.0	7.4	0.849	12.0	0.228
Severe	0.0	1.6	0.248	0.0	-

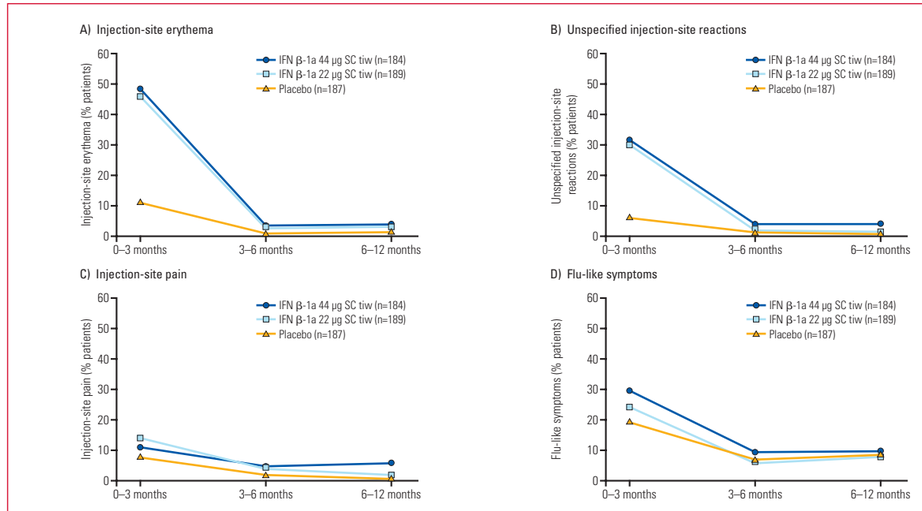
IFN β-1a, interferon beta-1a; SC, subcutaneously; tiw, three times weekly.
[a]Fisher's exact test.

- Over the cumulative 0–12-month period, treatment discontinuation due to tolerability-associated AEs was rare, exceeding 1% only for unspecified ISRs in the IFN β-1a 44 µg SC tiw group (2.2%, n=4; **Table 3**). No patients discontinued treatment due to FLS (**Table 3**).
- The percentage of patients who experienced injection-site erythema, unspecified ISRs, or injection-site pain declined sharply after the first 3 months of IFN β-1a SC tiw treatment: during Months 3–6 and Months 6–12, the percentage of patients with an injection-site associated AE did not exceed 6% in any treatment group (**Figure 1A–C**).
  - In the IFN β-1a 44 µg SC tiw group, 3.8% of patients experienced unspecified ISRs during Months 3–6 and 6–12 of the PRISMS study, compared with 31.5% during Months 0–3 (**Figure 1B**).
- The incidence of moderate or severe injection-site erythema, unspecified ISRs, or injection-site pain was low during Months 0–3 of IFN β-1a SC tiw treatment and decreased further during Months 3–6 and 6–12 (**Figure 2B, C**). No severe AEs were recorded in the placebo group (**Figure 2A**).

Table 3. First-year cumulative tolerability results: injection-site reactions and flu-like symptoms leading to treatment discontinuation.

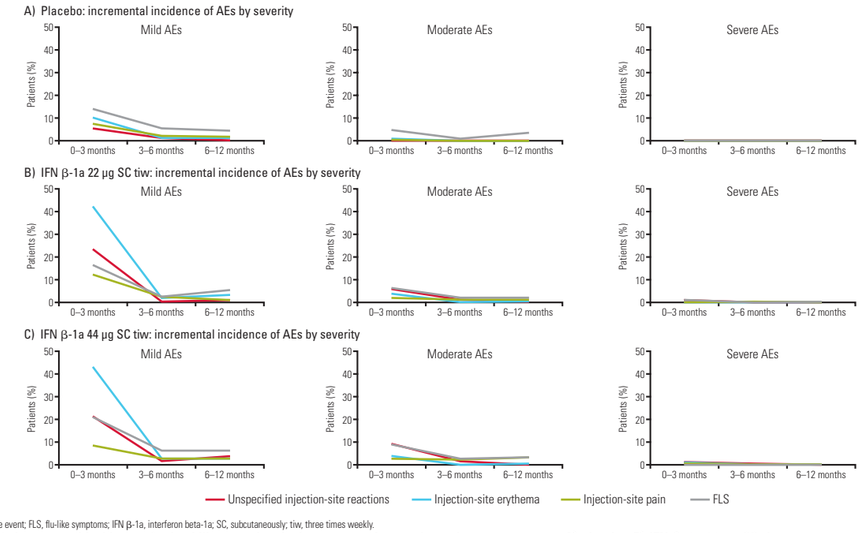
	Placebo (n=187), n (%)	IFN β-1a 22 µg SC tiw (n=189), n (%)	IFN β-1a 44 µg SC tiw (n=184), n (%)
Injection-site reaction (unspecified)	1 (0.5)	1 (0.5)	4 (2.2)
Injection-site induration	0 (0.0)	0 (0.0)	1 (0.5)
Injection-site inflammation	0 (0.0)	0 (0.0)	1 (0.5)
Injection-site irritation	0 (0.0)	0 (0.0)	1 (0.5)
Injection-site nodule	0 (0.0)	0 (0.0)	1 (0.5)
Flu-like symptoms	0 (0.0)	0 (0.0)	0 (0.0)

IFN β-1a, interferon beta-1a; SC, subcutaneously; tiw, three times weekly.



IFN β-1a, interferon beta-1a; SC, subcutaneously; tiw, three times weekly.

Figure 1. Incidence of tolerability-associated adverse events over 0–3, 3–6, and 6–12 months of treatment: A) injection-site erythema; B) unspecified injection-site reactions; C) injection-site pain; and D) flu-like symptoms.



AE, adverse event; FLS, flu-like symptoms; IFN β-1a, interferon beta-1a; SC, subcutaneously; tiw, three times weekly.

Figure 2. Incremental incidence of tolerability-associated adverse events by severity and treatment group: A) placebo; B) IFN β-1a 22 µg SC tiw; and C) IFN β-1a 44 µg SC tiw.

- The incidence of FLS was greatest during the first 3 months of treatment and decreased during the subsequent 9 months of IFN β-1a SC tiw treatment (**Figure 1D**).
  - In the IFN β-1a 44 µg SC tiw group, 8.7% and 9.2% of patients experienced FLS during Months 3–6 and 6–12 of the PRISMS study, respectively, compared with 29.3% during Months 0–3. Similarly, 4.8% and 7.9% of patients in the IFN β-1a 22 µg SC tiw group experienced FLS during Months 3–6 and 6–12, respectively, versus 23.8% during Months 0–3 (**Figure 1D**).
- The incidence of moderate or severe FLS in the IFN β-1a 44 and 22 µg SC tiw groups remained low (≤3.3%) during Months 3–6 and 6–12, and was comparable with that in the placebo group (**Figure 2A–C**).

Conclusions

- AEs likely to affect the tolerability of IFN β-1a SC tiw, including injection-site erythema, unspecified ISRs, injection-site pain, and FLS, occurred more frequently in patients treated with IFN β-1a SC tiw than in patients treated with placebo.
  - The majority of these AEs were mild, with severe AEs occurring rarely during the first 12 months of treatment.
- Very few patients discontinued IFN β-1a SC tiw due to injection-site erythema, unspecified ISRs, injection-site pain, or FLS.
- The percentage of patients experiencing injection-site erythema, unspecified ISRs, injection-site pain, or FLS decreased considerably after 3 months of IFN β-1a SC tiw treatment and remained low during Months 3–12.
- This analysis suggests that tolerability issues with IFN β-1a SC tiw are greatest during the first 3 months of treatment, and that patients who continue treatment after this early time period may experience considerably fewer tolerability issues.

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