P 677

Subcutaneous interferon β-1a in paediatric patients with multiple sclerosis: regional outcomes in an international retrospective study (REPLAY)

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Introduction

- Multiple sclerosis (MS) is most commonly diagnosed in early adulthood, with onset between 20 and 40 years of age. However, MS can also affect children and adolescents; approximately 3–5% of patients with MS present under 16 years of age and <1% present under 10 years.[1]
- As with adult MS, most paediatric patients present with the relapsing–remitting course, which accounts for 98% of children and adolescents and 84% of adults with MS.[2]
- No randomized controlled studies of disease-modifying drugs (DMDs) in paediatric MS populations have been conducted, and data from large paediatric cohorts are lacking. Nonetheless, DMDs for adult MS are used in paediatric patients with MS, and guidelines for the management of paediatric MS recommend that treatment should not be delayed into adulthood but started early in the disease course.[3]
- The retrospective REPLAY study found that adult doses of interferon (IFN) β-1a, 44 and 22 µg subcutaneously (sc) three times weekly (tiw), were well tolerated and associated with a reduced clinical attack rate in paediatric patients with MS.[4]
- To date, this is the largest cohort study of safety, tolerability and efficacy outcomes with sc IFN β-1a treatment in children and adolescents with MS.

Purpose

- To perform *post hoc* analyses of regional differences in treatment practice and outcomes in the REPLAY study.

Methods

- This was an international, retrospective, single-cohort study of patients who had received ≥1 injection of sc IFN β-1a for demyelinating events when aged <18 years.
- The observation period for an individual patient began with the first medical record available on site and ended on 31 December 2009, or when the patient was lost to follow-up, whichever occurred first.
- To ensure a minimum of 6 months of potential observation for each patient, therapy had to have been started prior to 30 June 2009.
- Data were collected from medical records of unidentified patients who were evaluated between 1997 and 2009, and all analysed information was recorded as part of routine medical practice.
- Study outcomes included:
  - Prespecified medical events (MEs) occurring after initiation of sc IFN β-1a treatment
    - MEs were prespecified according to the known safety profile of sc IFN β-1a in adults and published findings from paediatric cohorts. Causality of events was not assigned retrospectively
  - Clinical attacks, defined as the emergence of new neurological symptoms and signs >30 days after the last event that persisted for >24 hours in the absence of intercurrent illness.
- Safety outcomes were assessed in the total analysis set (TAS) and efficacy outcomes in the MS analysis set (MSAS), which excluded patients with a final diagnosis other than MS.
- Baseline characteristics, treatment patterns and outcomes were compared in patients from the USA and from the other countries included in the study.

Results

Patients, prestudy characteristics and treatment patterns

- The TAS comprised 307 patients:
  - USA, n=139 (45.3%)
  - Other countries, n=168 (54.7%), including: Italy, n=47 (15.3%); Russia, n=38 (12.4%); Argentina, n=33 (10.7%); France, n=23 (7.5%); Canada, n=21 (6.8%); Tunisia, n=3 (1.0%); Venezuela, n=3 (1.0%).
- Overall, 190 (61.9%) patients were female; the mean (standard deviation) age was 12.2 (3.5) years at the first demyelinating event, 13.2 (3.2) years at MS diagnosis and 14.0 (3.0) years at initiation of sc IFN β-1a treatment.
- 97/307 (31.6%) patients had a monofocal presentation, 178/307 (58.0%) were hospitalized for the first demyelinating event, 184/307 (59.9%) received steroid treatment and 302/305 (99.0%) had an initial relapsing–remitting MS course. Further baseline characteristics were reported in **Poster 220** (Thursday 11 October – Poster Session I [Paediatric MS]).
- **Table 1** shows body mass index (BMI) and treatment patterns before initiation of sc IFN β-1a, stratified by region. Compared with the other countries, patients in the USA:
  - had a higher mean BMI
  - were more likely to have received at least one other DMD prior to initiation of sc IFN β-1a
  - had a shorter median time from their first demyelinating event to first DMD treatment prior to initiation of sc IFN β-1a.

On-study treatment patterns

- Patients in the USA were less likely than patients in the other countries to receive sc IFN β-1a as the first-line DMD treatment (**Table 1**).

Table 1. Prestudy period characteristics and treatment patterns, by region (total analysis set).

	USA (n=139)	Other countries (n=168)	Overall (N=307)
Baseline BMI (kg/m²)			
n (missing)	54 (85)	50 (118)	104 (203)
Mean (SD)	26.17 (7.71)	21.11 (4.01)	23.74 (6.69)
Median (range)	24.84 (15.6, 51.3)	21.04 (13.6, 34.2)	22.46 (13.6, 51.3)
Received ≥1 DMD before sc IFN β-1a initiation, n (%)	47 (33.8)	23 (13.7)	70 (22.8)
Time from first demyelinating event to first DMD treatment (years)[a]			
Mean (SD)	0.98 (1.18)	1.51 (1.36)	1.16 (1.26)
Median (range)	0.69 (0.1, 5.7)	1.14 (–0.1,[b] 6.0)	0.80 (–0.1,[b] 6.0)

[a]Prior to sc IFN β-1a initiation.
[b]One patient received DMD treatment before the first demyelinating event.
BMI, body mass index; DMD, disease-modifying drug; IFN, interferon; sc, subcutaneous; SD, standard deviation.

- In the TAS, the initial dose was 44 µg in 88.9% of patients in the USA and 24.3% of those in the other countries (**Table 2**).

Table 2. Dose and duration of sc IFN β-1a treatment and status at the end of the observation period, by region (total analysis set).

	USA (n=139)	Other countries (n=168)	Overall (N=307)
First treatment dose			
n (other dosage)[a]	126 (13)	136 (32)	262 (45)
44 µg tiw, n (%)	112 (88.9)	33 (24.3)	145 (55.3)
22 µg tiw, n (%)	14 (11.1)	103 (75.7)	117 (44.7)
Time on treatment, years			
Mean (SD)	1.34 (1.04)	2.76 (2.52)	2.12 (2.11)
Median	1.07	1.73	1.30
Status of sc IFN β-1a treatment at end of observation period, n (%)			
Ongoing treatment	81 (58.3)	127 (75.6)	208 (67.8)
Switched DMD[b]	40 (28.8)	22 (13.1)	62 (20.2)
Stopped treatment[c]	18 (12.9)	19 (11.3)	37 (12.1)

[a]Data from some patients are not included here because they received an initial dose other than 44 or 22 µg tiw.
[b]From sc IFN β-1a to a different DMD.
[c]Ceased all DMD therapy.
DMD, disease-modifying drug; IFN, interferon; sc, subcutaneous; SD, standard deviation; tiw, three times weekly.

- Compared with patients in the other countries, patients in the USA had a shorter time on treatment, were less likely to be receiving ongoing sc IFN β-1a therapy at study end, and were more likely to switch to another DMD (**Table 2**). The proportion of patients who stopped all DMD treatment was similar in both regions.
- In the MSAS, 262/298 patients received IFN β-1a, 44 or 22 µg sc tiw, as the first dose; the initial dose was 44 µg in 76.3% of patients in the USA and 23.7% of those in the other countries.

Prespecified medical events

- Overall, 54.7% of patients had at least one prespecified ME after initiation of sc IFN β-1a treatment (USA 52.5%; other countries 56.5%). MEs were presented in detail in **Poster 220**.
- There were only minor regional differences in prespecified MEs.

Efficacy outcomes

- Annualized relapse rates were similar in the USA and the other countries prior to sc IFN β-1a initiation, and decreased in both groups after starting sc IFN β-1a treatment; however, annualized relapse rates were higher in the USA than in the other countries during sc IFN β-1a treatment and from treatment termination to the end of the observation period (**Figure 1**).
- The median time to first relapse after treatment initiation was shorter in the USA (14.2 months) than the other countries (27.2 months).

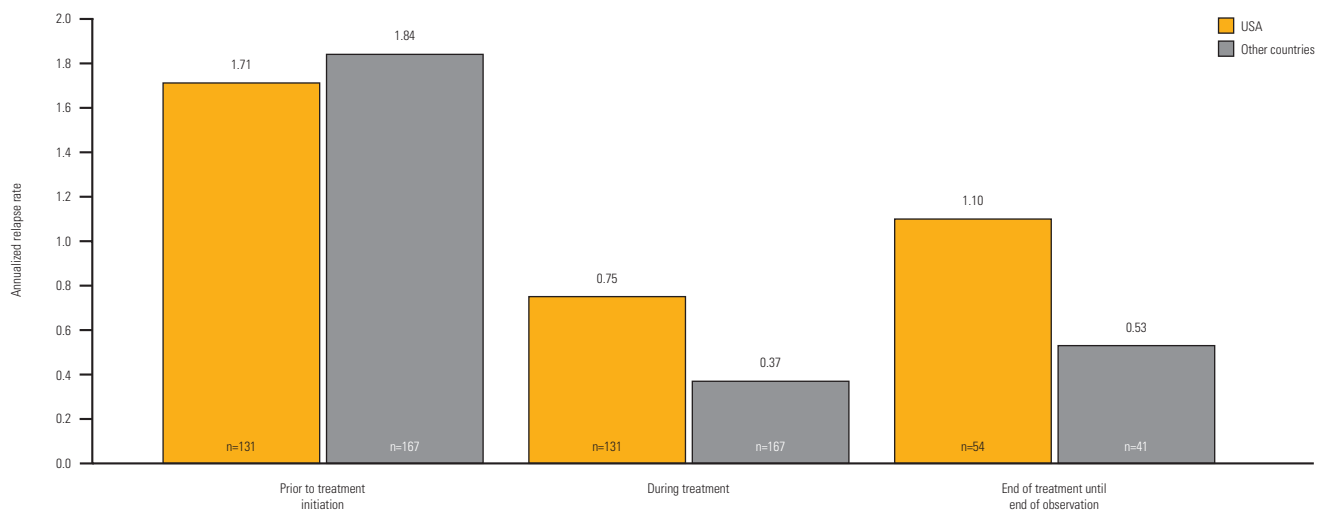

Figure 1. Medically confirmed clinical relapses (multiple sclerosis analysis set).

Conclusions

- Across all regions, sc IFN β-1a was well tolerated and associated with a reduction in clinical relapses in paediatric patients with MS.
- Compared with in other regions, patients in the USA had a higher BMI, a higher frequency of DMD use prior to initiation of sc IFN β-1a and a higher relapse rate during the observation period. The basis for these differences remains unclear.
- Further research is needed to determine whether these differences can be explained by differing access to healthcare resources (which may have led to increased reporting of relapses or greater opportunity to switch therapy), differences in disease severity, or a combination of these and other factors.

References

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