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Safety and efficacy of subcutaneous interferon β-1a in children and adolescents with multiple sclerosis: an international retrospective cohort study

S Tenembaum,[1] B Banwell,[2] A Ghezzi,[3] D Pohl,[4] M Meinel,[5] C McIlroy,[6] S Rocak,[5] on behalf of the REPLAY study group

[1]Hospital de Pediatría S.A.M.I.C. "Prof Juan P Garrahan", Buenos Aires, Argentina; [2]Pediatric Multiple Sclerosis Clinic, The Hospital for Sick Children, University of Toronto, Ontario, Canada; [3]Centro Studi Sclerosi Multipla, Ospedale di Gallarate, Gallarate, Italy; [4]Pediatric Multiple Sclerosis Clinic, Children's Hospital of Eastern Ontario, University of Ottawa, Ontario, Canada; [5]Merck Serono S.A. – Geneva, Switzerland;* [6]Merck Serono Ltd,† Feltham, UK

5th Joint Triennial Congress of the European and Americas Committees for Treatment and Research in Multiple Sclerosis (ECTRIMS/ACTRIMS); 19–22 October 2011; Amsterdam, The Netherlands

Background

- The typical age of onset for multiple sclerosis (MS) is between 20 and 40 years; however, 3–10% of patients present with symptoms before the age of 16 years, and <2% before the age of 10 years.[1]
  - More than 97% of paediatric patients with MS present with a relapsing–remitting course, compared with 80–85% of adults.[2]
- Several disease-modifying drugs (DMDs) are licensed for the treatment of adults with MS. However, information on the use of DMDs in patients with paediatric-onset MS is limited.
- Increasing numbers of children and adolescents with MS are being treated with DMDs approved for adult use.
- Based on available data, guidelines for the treatment of paediatric MS[3] recommend that treatment should be started early in the disease course and not delayed until patients reach adulthood.
- Although several cohort studies and isolated case reports indicate that interferon (IFN) β is effective in paediatric MS populations,[4–8] data from larger paediatric cohorts are lacking and no placebo-controlled studies have been conducted.

Aim

- To review and describe the safety, tolerability and efficacy of subcutaneous (sc) IFN β-1a in children and adolescents with MS, using medical records.

Methods

Study design

- This was a single-cohort, retrospective, international study.
- The 'study period' reviewed began in May 1998, when sc IFN β-1a was first available on prescription in Europe, and ended on 31 December 2009.
- The 'observation period' for an individual patient began with the first medical record available on site. Patients were followed until they were lost to follow-up or 31 December 2009, whichever occurred first.
- Patients who received at least one injection of sc IFN β-1a for demyelinating events before the age of 18 years were included in the study.
  - sc IFN β-1a therapy must have been initiated prior to 30 June 2009 to allow the potential for at least 6 months of observation for each patient.
  - All patient data were recorded anonymously.
- The study was retrospective (historical) as exposure and outcomes had already been recorded when the study was initiated. However, all information on exposure, covariates and outcomes were recorded prospectively in patients' medical records as part of routine healthcare delivery.
- To minimize the potential bias inherent to retrospective patient selection, every effort was made to assess all paediatric patients treated with sc IFN β-1a in participating centres.
- No patient started treatment prospectively as part of this study.

Outcomes

- Safety and tolerability outcomes:
  - Prespecified medical events (MEs[†]) that occurred after initiation of sc IFN β-1a treatment, regardless of whether considered related or not related to sc IFN β-1a treatment by the treating physician. These events were prespecified as events of interest based on the safety profile of sc IFN β-1a in adults and on findings from previously published paediatric cohorts. Causality of events was not assigned retrospectively.
  - Serious MEs that occurred after initiation of sc IFN β-1a treatment, regardless of whether considered related or not related to sc IFN β-1a treatment by the treating physician.
  - Non-serious MEs considered causally related to sc IFN β-1a treatment.
  - Laboratory parameters: liver function tests, thyroid tests and haematology.
- Efficacy outcomes included 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). A distinction was made between medically confirmed and patient- or caregiver-reported clinical attacks.

Analyses

- Two analysis sets were considered:
  - Safety and tolerability outcomes were assessed in the total analysis set (TAS; all patients included in the study)
  - Efficacy outcomes were assessed in the MS analysis set (MSAS; patients with a final diagnosis of MS, excluding those with other inflammatory demyelinating disorders at final diagnosis).
- Two age categories were defined based on age at initiation of sc IFN β-1a:
  - Children: aged 2 to <12 years
  - Adolescents: aged 12 to <18 years.

Results

Patient and disease characteristics

- Medical records of 309 patients from 18 centres in eight countries were reviewed.
- 307/309 patients were included in the TAS (USA, n=139; Italy, n=47; Russia, n=38; Argentina, n=33; France, n=23; Canada, n=21; Tunisia and Venezuela, n=3 each). Two patients were excluded as age <18 years at the time of sc IFN β-1a treatment initiation could not be confirmed.
- In the TAS, the mean (range) age at clinical disease onset was 14.0 (3–17) years; 52 (16.9%) patients were younger than 12 years (**Table 1**).

Table 1. Disease characteristics at first demyelinating event and MS disease history (total analysis set).

	Age at sc IFN β-1a initiation		Overall (n=307)
	<12 years (n=52)	12 to <18 years (n=255)	
Characteristics at first demyelinating event			
Age group at first event (clinical onset), n (%)			
<12 years			96 (31.3)
12 to <16 years			175 (57.0)
16 to <18 years			36 (11.7)
Age at first event, mean (SD), years	6.8 (2.9)	13.3 (2.4)	12.2 (3.5)
Monofocal, %	28.6	38.6	36.7
Evidence of encephalopathy, %			
Yes	26.9	5.1	8.8
No	63.5	83.5	80.1
Unknown	9.6	11.4	11.1
Hospitalization, %			
Yes	78.8	53.7	58.0
No	17.3	38.8	35.2
Unknown	3.8	7.5	6.8
Steroid use at first event, %			
Yes	80.8	55.7	59.9
No	17.3	38.0	34.5
Unknown	1.9	6.3	5.5
Brain MRI characteristics, %			
No lesions	3.8	2.4	2.6
Monolesional	5.8	1.2	2.0
Polylesional	78.8	72.9	73.9
Not available	11.5	23.5	21.5
Spinal cord MRI characteristics, %			
No lesions	15.4	9.8	10.7
Monolesional	13.5	8.6	9.4
Polylesional	13.5	18.8	17.9
Not available	57.7	62.7	61.9
Affected function, %			
Pyramidal	73.1	40.0	45.6
Cerebellar	48.1	24.3	28.3
Brainstem	40.4	40.8	40.7
Sensory	17.3	42.7	38.4
Bowel and bladder	5.8	5.5	5.5
Visual (optic)	21.2	24.7	24.1
Cerebral (mental)	15.4	5.1	6.8
Other	13.5	7.8	8.8
Unknown	0	2.7	2.3
MS history			
Mean (SD) age at MS diagnosis, years	8.2 (2.6)	14.3 (2.1)	13.2 (3.2)
Oligoclonal bands, n (%)			
Positive	23 (44.2)	130 (50.8)	153 (49.7)
Negative	16 (30.8)	26 (10.2)	42 (13.7)
Not available	13 (25.0)	99 (39.0)	112 (36.6)
Initial MS course, n (%)[a]			
Relapsing–remitting	51 (98.1)	251 (99.2)	302 (99.0)
Primary progressive	0	1 (0.4)	1 (0.3)
Progressive relapsing	0	1 (0.4)	1 (0.3)
Unknown	1 (1.9)	0	1 (0.3)

[a]Data missing for 2 patients aged 12 to <18 years.
IFN, interferon; MRI, magnetic resonance imaging; MS, multiple sclerosis; sc, subcutaneous; SD, standard deviation.

- Median (range) observation time for the cohort was 3.7 (0.4–16) years.
- 9 patients were subsequently believed to have a diagnosis other than MS and were excluded from the MSAS (n=298).

Exposure to sc IFN β-1a

- The mean time on sc IFN β-1a therapy was 2.12 years; median (range), 1.3 (0–12.5) years.
  - 82.7% (254/307) of patients were treated for >6 months and 59.3% (182/307) for >12 months.
- During the observation period, 99 patients permanently discontinued sc IFN β-1a therapy (patient decision, n=15; MRI activity without a clinical attack, n=9; clinical attack, n=31; safety ME, n=36; other reasons, n=8).
  - 'Other reasons' were: neutralizing antibody-positive status (n=3), final diagnosis other than MS (n=2), inability to access the drug (n=2) and medical expert decision (n=1).

Safety and tolerability of sc IFN β-1a

- In total, 190/307 (61.9%) patients experienced at least one safety ME.
- At least one prespecified ME was experienced by 168 (54.7%) patients (**Table 2**).
- In total, 12 (3.9%) patients had serious MEs (**Table 3**).

Table 2. Prespecified medical events of special interest (total analysis set).

	Age at sc IFN β-1a initiation		Overall (n=307)
	<12 years (n=52)	12 to <18 years (n=255)	
Patients with ≥1 prespecified event[a]	31 (59.6)	137 (53.7)	168 (54.7)
Medical event category of interest			
Injection-site reactions	11 (21.2)	74 (29.0)	85 (27.7)
'Flu-like' symptoms	14 (26.9)	61 (23.9)	75 (24.4)
Hepatic disorders	8 (15.4)	36 (14.1)	44 (14.3)
Blood cell disorders (e.g. thrombocytopenia, leukopenia, anaemia)	2 (3.8)	12 (4.7)	14 (4.6)
Allergic reactions (e.g. rash, urticaria, anaphylaxis)	1 (1.9)	4 (1.6)	5 (1.6)
Epilepsy and convulsive disorders	1 (1.9)	4 (1.6)	5 (1.6)
Thyroid dysfunction	1 (1.9)	2 (0.8)	3 (1.0)
Autoimmune diseases	–	2 (0.8)	2 (0.7)
Bone/epiphyseal and cartilage disorders	1 (1.9)	1 (0.4)	2 (0.7)
Serious infections	–	2 (0.8)	2 (0.7)
Malignancies	1 (1.9)[b]	–	1 (0.3)

Data are n (%).
[a]Some patients had >1 event, thus the total number of events is higher than the number of patients.
[b]Nine-year-old patient who underwent partial resection of the greater omentum and appendectomy after 5 months on sc IFN β-1a 22 µg. Although no tumour was involved, omentectomy was classified under "malignancy" as it is part of the malignancy standardized Medical Dictionary for Regulatory Activities (MedDRA) query. The treating physician considered the event not related to sc IFN β-1a.

Table 3. Serious medical events (total analysis set).

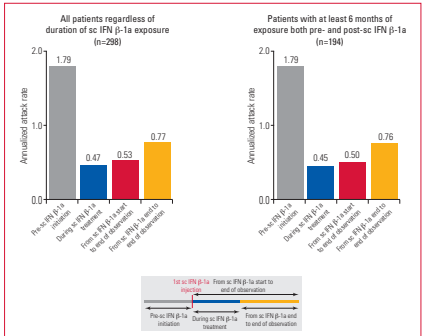
	Age at sc IFN β-1a initiation		Relationship to sc IFN β-1a[a]
	<12 years (n=52)	12 to <18 years (n=255)	
Patients with ≥1 event	2 (3.8)	10 (3.9)	
Idiopathic thrombocytopenic purpura	–	1 (0.4)	Related
Injection-site injury	–	1 (0.4)	Related
Injection-site necrosis	–	1 (0.4)	Related
Injection-site cellulitis	–	1 (0.4)	Related
Irritability	–	1 (0.4)	Related
Autoimmune hepatitis	–	1 (0.4)	Related
Cholelithiasis	–	1 (0.4)	Related
Hypersensitivity	1 (1.9)	–	Related
Liver function test, abnormal	–	1 (0.4)	Related
Hallucination, auditory[b]	–	1 (0.4)	Related
Suicidal behaviour[b]	–	1 (0.4)	Related
Anaphylactic reaction	–	1 (0.4)	Not related
Cellulitis	–	1 (0.4)	Not related
Convulsion	–	1 (0.4)	Not related
Epilepsy	1 (1.9)	–	Not related
Suicidal ideation	–	1 (0.4)	Not related
Appendectomy	1 (1.9)	–	Not related
Omentectomy	1 (1.9)	–	Not related

Data are n (%).
[a]According to the treating physician.
[b]Some patients had >1 event, thus the total number of events is greater than the number of patients.
IFN, interferon; sc, subcutaneous.

- 184 (59.9%) patients had non-serious MEs that were considered to be causally related to sc IFN β-1a.
  - Events experienced by >10% of patients were: influenza-like illness (24.4%), injection-site erythema (15.6%) and injection-site pain (11.1%).
- Medical safety events led to dose reductions in 8 (2.6%) patients and treatment discontinuation in 36 (11.7%) patients.
- Events leading to treatment discontinuation in >1% of patients were: injection-site reaction (6.2%), liver test abnormalities or increases in alanine aminotransferase/aspartate aminotransferase levels (3.3%), and influenza-like illness (2.0%).

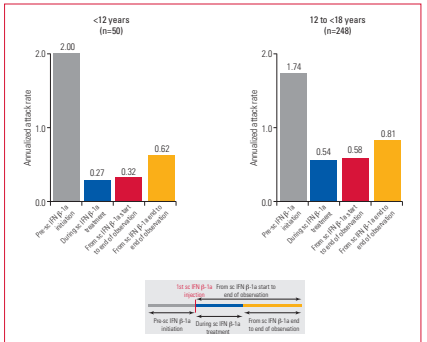
Efficacy of sc IFN β-1a

- The annualized attack rate decreased after the initiation of sc IFN β-1a treatment (**Figure 1**).
- The reduction in annualized attack rate appeared to be more pronounced in patients aged <12 years at treatment initiation (**Figure 2**).
- The median time to the first medically confirmed attack was 19.5 months (**Figure 3**).



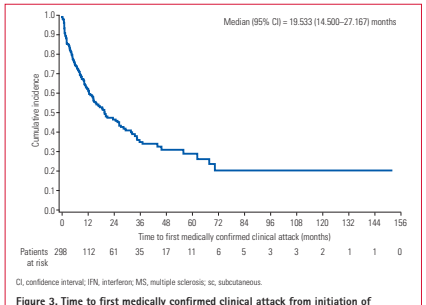
IFN, interferon; MS, multiple sclerosis; sc, subcutaneous.

Figure 1. Medically confirmed clinical attacks (MS analysis set).



IFN, interferon; MS, multiple sclerosis; sc, subcutaneous.

Figure 2. Medically confirmed clinical attacks in patients <12 years and 12 to <18 years (MS analysis set).



CI, confidence interval; IFN, interferon; MS, multiple sclerosis; sc, subcutaneous.

Figure 3. Time to first medically confirmed clinical attack from initiation of sc IFN β-1a (MS analysis set).

Conclusions

- This is the largest multicentre, multinational review of safety, tolerability and efficacy outcomes with sc IFN β-1a, including 307 children and adolescents.
- Most children and adolescents were able to tolerate sc IFN β-1a doses currently used in adults with MS (22 and 44 µg tiw), with 36 (11.7%) patients discontinuing treatment due to adverse safety MEs. There were no new or unexpected adverse drug reactions related to sc IFN β-1a.
- The annualized attack rate after initiation of therapy was lower than prior to initiation of treatment; this ARR decrease appeared to be more pronounced in patients <12 years. The observed overall ARR reduction of 74% is either higher or in line with ARR reductions previously reported in paediatric patients treated with sc IFN β-1a[4,5] and is also in line with the ARR decrease reported with intramuscular IFN β-1a and sc IFN β-1b.[9,10] However, this finding must be interpreted with caution in light of the natural history of MS and the lack of a control group.

Acknowledgements

This study was sponsored by Merck Serono S.A. – Geneva, Switzerland.* The authors thank Ulrich Freudensprung for his valuable input into study design; Daniel Mikol, Cedric Marchand, Shalini Jayasekar, Jocelin McDonough, Eric Henninger and Delphine Issard for their help in study implementation; and Andrea Plant and Veronica Porkess of Caudex Medical Ltd, Oxford, UK (supported by Merck Serono S.A. – Geneva, Switzerland*), for assistance with the preparation of this poster.

The REPLAY study group comprises: B Banwell, A Boyko, M Capobianco, T Chitnis, K Deiva, A Ghezzi, N Gouider-Khouja, L Krupp, GM Marrosu, V Martinelli, J Ness, M Patterson, F Patti, J Pena, C Pozzilli, S Tenembaum, E Waubant, B Weinstock-Guttman.

Disclosures

ST: lecture fees from Bayer Schering Pharma, Teva Pharmaceutical Industries and Merck Serono; honoraria for serving as a consultant for Genzyme Corporation and Biogen Idec. **BB:** speaker honoraria from Biogen Idec, Merck Serono and Bayer Schering; serves on an advisory board for Biogen Idec and for Merck Serono for the REPLAY study. **AG:** speaker honoraria and support for congress participation from Bayer Schering, Biogen-Dompè, Merck Serono, Novartis and sanofi-aventis; consultancy fees from Actelion, Merck Serono, Teva and Novartis. **DP:** honoraria or support for travel and accommodation for congress participation from Bayer Schering, Biogen Idec, Merck Serono and Teva. **MM, SR:** salaried employees of Merck Serono S.A. – Geneva, Switzerland.* **CM:** salaried employee of Merck Serono Ltd,† Feltham, UK.

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*A branch of Merck Serono SA, Coinsins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany.
†An affiliate of Merck KGaA, Darmstadt, Germany.
‡Medical events in the retrospective setting are equivalent to adverse events in a prospective clinical study (as recommended in Good Pharmacoepidemiological Practice).

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