Treatment of early onset multiple sclerosis with subcutaneous interferon beta-1a

Abstract—The authors studied the tolerability of subcutaneous interferon beta-1a (IFNβ-1a) in 51 patients with early-onset multiple sclerosis. The most frequent systemic adverse effects were flu-like symptoms in 65%. Laboratory abnormalities included asymptomatic leukopenia (27%) and elevated hepatic transaminases (35%). Treatment with IFNβ-1a was safe and well tolerated in the majority of children and adolescents.

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Patients with early-onset multiple sclerosis (EOMS) have marked disability at a younger age than patients with adult-onset MS.[1,2] Moreover, cerebral proton magnetic resonance spectroscopy of patients with EOMS reveals metabolic alterations indicating early axonal damage.[3] Therefore, treatment of pediatric MS should be considered, even though none of the disease-modifying drugs are approved for this age group. There are two reports of children who were treated with interferon beta (IFNβ), including only two patients receiving IFNβ-1a subcutaneously.[4,5] To extend these observations, we analyzed the safety and tolerability of subcutaneous IFNβ-1a in 51 patients with EOMS.

Methods. *Patients.* The cohort contained 36 girls and 15 boys with definite relapsing/remitting MS according to Poser et al. criteria[6] and a disease manifestation before age 16 years. Mean age at MS onset was 13.4 years (range 6.8 to 15.8). Treatment was started at a mean age of 14.6 years (range 8.1 to 17.9) after a mean disease duration of 2.0 years (range 0.1 to 6.7). The mean relapse rate before treatment was 1.9 per year (range 0.4 to 7.6). Expanded Disability Status Scale (EDSS) scores before treatment were in the range of 0 to 5.5 (median 1.5). In Germany, the use of IFNβ-1a is approved for patients 16 years of age or older. Informed consent was obtained for patients younger than 16 years of age.

In most patients (n = 46), treatment was initiated with 22 μg IFNβ-1a (Rebif) three times weekly. In five patients with highly active disease, treatment was started with 44 μg IFNβ-1a (Rebif) three times weekly. Patients receiving the low dose were switched to the high dose in the presence of disease activity (relapses, new or contrast-enhancing MRI lesions). At the time of the first 22-μg injection of IFNβ-1a, patients had a mean body weight of 53 kg (range 22 to 88) and a mean age of 14.5 years (range 8.1 to 17.9). At the time of the first 44-μg injection IFNβ-1a, patients had a mean body weight of 61 kg (range 35 to 106) and a mean age of 15.1 years (range 11.6 to 18.8). Treatment was started with the complete dosage from the first injection onward without gradual increase.

Procedure. This was a retrospective analysis of clinical and laboratory data of patients with MS who had been referred to our clinic and treated with subcutaneous IFNβ-1a. Examinations in our clinic were performed before initiation of treatment and every 6 months thereafter, including cerebral MRI with injection of gadolinium. Side effects were evaluated using a questionnaire. Blood count and hepatic enzymes were monitored at 4 weeks, 3 and 6 months, and every 6 months thereafter. Laboratory abnormalities were classified according to the World Health Organization (WHO) toxicity scale.[7] EDSS scores were interpreted as stable if there was less than a 1-point change in the EDSS score. All patients were followed for a minimum of 6 months (maximum 4.4 years).

Results. *Treatment course.* The 51 patients with EOMS were treated with IFNβ-1a for a mean duration of 1.8 years (range 1 month to 4.4 years). Due to ongoing disease activity, 22 of 46 patients who had started on 22 μg IFNβ-1a were switched to 44 μg IFNβ-1a (12 within 6 months, 20 within 12 months, and another 2 after 24 months). At the end of our observation period, 19 patients were treated with 22 μg IFNβ-1a, 25 patients with 44 μg IFNβ-1a, and 9 patients had discontinued therapy (table 1).

Adverse events. Side effects were similar to those described for adult patients.[8,9] The cumulative percentages of patients reporting at least one adverse event during treatment were injection site reactions, 71%; flu-like symptoms, 65%; gastrointestinal symptoms, 10%; blood count abnormalities, 39%; and liver enzyme abnormalities, 35%. The percentages of patients reporting distinct side effects in consecutive periods of the treatment course are shown in table 2.

Flu-like symptoms were treated with a premedication of paracetamol (125 to 1,000 mg) or ibuprofen (200 to 600 mg) 1 hour before IFNβ injections. Twenty-four patients did not need any premedication, 15 received it for a maximum of 6 months, 9 received it throughout the first year, and 6 patients extended it into the second treatment year. Except for one boy with a history of migraine who had postinjection headaches and one girl with persisting fatigue, flu-like symptoms could be efficiently prevented by premedication.

Laboratory abnormalities were observed at least once in a total of 21 patients (41%). All laboratory abnormalities were clinically asymptomatic, and the majority were transient with a WHO grade 1 severity.

Hematologic abnormalities comprised only WHO grade 1 findings for hemoglobin and platelets. One patient had a transient WHO grade 2 decrease in leukocytes and one had a WHO grade 2 decrease in lymphocytes. The highest propor-

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Table 1 Characteristics of the nine patients who discontinued treatment with IFNβ-1a

Patient	Age at first injection, y	Weight at first injection, kg	Duration of treatment, mo	Dose of IFNβ1a, μg	Reason for withdrawal	Decision made by
1	12	55	1	22	Systemic reaction*	Physician
2	12	52	13	44	Depression	Physician
3	13	52	2	22	Headache	Patient
4	15	54	3	22	Needle phobia	Patient
5	16	55	13	22	Inefficacy	Physician
6	17	55	25	22	Necrosis	Patient
7	17	58	16	22	Needle phobia	Patient
8	17	56	15	44	Nausea	Physician
9	17	57	34	22	Fatigue	Physician

* Generalized edema, weakness, fatigue, and mild pleural effusion.

IFNβ-1a = interferon beta-1a.

tion of WHO grade 2 to 3 abnormalities was observed for neutrophil counts: five patients with neutropenia grade 2 and one patient with neutropenia grade 3, all with spontaneous normalization under continued IFNβ-1a treatment.

The only patient with a grade 2 elevation of liver enzymes was the youngest patient in our cohort who was 8 years and had a body weight of 22 kg. After reducing his application frequency of 22 μg IFNβ-1a to twice weekly, liver enzyme elevation dropped immediately and stayed at intermittent grade 1 abnormalities during the following treatment course.

Table 2 Frequency of patients reporting adverse events at least once during consecutive periods of IFNβ-1a treatment

Adverse event	Treatment period, mo 0–6, n = 51	6–12, n = 38	13–18, n = 31	Entire treatment, n = 51
Injection-site reactions				
Erythema/Induration, %	69	71	74	71
Abscess, %	2	3	3	6
Necrosis, %	0	5	3	6
Flu-like symptoms				
Headache, %	49	21	16	51
Fever, %	39	8	3	39
Fatigue, %	20	8	3	22
Myalgia/arthralgia, %	12	5	3	14
Gastrointestinal symptoms				
Nausea, %	4	5	0	10
Vomiting, %	4	0	0	4
Liver enzyme abnormalities				
AST (GOT) elevation, %	16	11	6	25
ALT (GPT) elevation, %	18	16	10	27
Gamma GT elevation, %	8	8	10	16
Blood count abnormalities				
Leukopenia, %	18	18	10	27
Lymphopenia, %	14	11	13	22
Neutropenia, %	14	11	6	20
Thrombopenia, %	8	8	6	16
Anemia, %	4	8	6	12

IFNβ-1a = interferon beta-1a; AST = aspartate aminotransferase; GOT = glutamic-oxaloacetic transaminase; ALT = alanine aminotransferase; GPT = glutamic-pyruvic transaminase; GT = glutamyl transferase.

Two patients with EOMS treated with IFNβ-1a experienced serious adverse events. Patient 1, a 12-year-old boy (55 kg), presented with a systemic reaction including generalized edema, weakness, fatigue, and mild pleural effusion 4 weeks after initiating therapy with 22 μg IFNβ-1a. Drug application was discontinued, and his symptoms resolved within 2 weeks without any sequelae. Patient 2, a 12-year-old boy (52 kg), developed a depressive mood disorder after 13 months of IFNβ-1a treatment and 5 months after increasing the dose to 44 μg. His depression did not require drug treatment and subsided within 4 weeks after termination of IFNβ-1a therapy. Both patients were not rechallenged with IFNβ.

Disease activity. In the patients with EOMS treated with IFNβ-1a, yearly relapse rates decreased from a mean pretreatment value of 1.9 to 0.8. Twenty-one patients were relapse free during treatment; the mean treatment duration in this group was 1.5 years (range 6 months to 4.1 years). At the end of the treatment observation period, the median EDSS score was 1.5 (range 0 to 5.0). EDSS scores remained stable in 48 of the 51 treated patients.

Discussion. The spectrum and most of the frequencies of IFNβ-1a side effects in our patients with EOMS were comparable with those reported for adult patients with MS, including the decreasing frequency of flu-like symptoms during the treatment course and the higher prevalence of laboratory abnormalities in patients treated with 44 μg IFNβ-1a compared with those treated with 22 μg IFNβ-1a (table 3).[8,9] The lower frequency of flu-like symptoms in our 44-μg IFNβ-1a cohort most likely results from the fact that 81% of the patients in this group were previously treated with 22 μg IFNβ-1a and therefore had already become accustomed to the substance. Liver enzyme elevations were seen less frequently in our cohort than in adults treated with IFNβ-1a.[10] None of our patients had to drop out of therapy due to hematologic or hepatic adverse events; however, the

Table 3 *Frequency of patients reporting adverse events at least once during treatment with 22 μg IFNβ-1a (n = 41, mean treatment duration 1.3 years) or 44 μg IFNβ-1a (n = 27, mean treatment duration 1.4 years)*

Adverse event	IFNβ-1a, 22 μg	IFNβ-1a, 44 μg*
Injection-site reactions		
Erythema/Induration, %	68	70
Abscess, %	2	7
Necrosis, %	2	7
Flu-like symptoms		
Headache, %	46	37
Fever, %	41	19
Fatigue, %	24	11
Myalgia/arthralgia, %	12	15
Gastrointestinal symptoms		
Nausea, %	5	11
Vomiting, %	5	4
Liver enzyme abnormalities		
AST (GOT) elevation, %	17	22
ALT (GPT) elevation, %	20	22
Gamma GT elevation, %	7	19
Blood count abnormalities		
Leukopenia, %	22	26
Lymphopenia, %	15	19
Neutropenia, %	14	19
Thrombopenia, %	7	22
Anemia, %	5	15

* Twenty-two of 27 patients of the IFNβ-1a (44 μg) group were initially treated with IFNβ-1a (22 μg), so the percentage of side effects occurring more frequently in the beginning of treatment might be underestimated (see discussion).

IFNβ-1a = interferon beta-1a; AST = aspartate aminotransferase; GOT = glutamic-oxaloacetic transaminase; ALT = alanine aminotransferase; GPT = glutamic-pyruvic transaminase; GT = glutamyl transferase.

occurrence of WHO grade 2 and 3 abnormalities calls for regular controls of blood count and liver enzymes.

All but one of our patients could be treated with the application frequency and doses recommended for adults; only the youngest patient with an age of 8 years and a very low body weight of 22 kg was switched to a twice-weekly application of 22 μg IFNβ-1a due to liver enzyme elevations. We thus recommend that juvenile patients with EOMS be treated with IFNβ-1a as approved in adult-onset MS. In children younger than age 10 years or with a body weight of less than 30 kg, a reduction in the cumulative weekly dose should be considered. Phase III clinical trials are warranted to assess the efficacy of IFNβ-1a in childhood and juvenile MS.

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