Immunomodulatory therapy of multiple sclerosis in adolescents: single-center experience

Terapia immunomodulująca u młodzieży z rozpoznanym stwardnieniem rozsianym: doświadczenia własne

Karolina Kupczyk, Barbara Steinborn

Chair and Clinic of Developmental Neurology Heliodor Święcicki Hospital University of Medical Sciences in Poznan

STRESZCZENIE

Wstęp. Stwardnienie rozsiane (SM, łac. *sclerosis multiplex*) jest przewlekłą zapalno-immmunologiczną chorobą ośrodkowego układu nerwowego o charakterze demielinizacyjno-neurodegeneracyjnym. W około 3–10% przypadków rozpoczyna się przed 18. rokiem życia. Interferony β (IFN-β) są rekomendowane jako pierwsza linia leczenia immunomodulującego, modyfikującego przebieg choroby u dzieci z SM. **Celem pracy** było przedstawienie przebiegu leczenia IFN-β w grupie młodzieży z SM. **Materiał i metodyka.** Obserwacją objęto 18 chorych w wieku 13–18 lat z rzutowo-remisyjną postacią SM, leczonych w Klinice Neurologii Wieku Rozwojowego Uniwersytetu Medycznego w Poznaniu w latach 2008–2012. Dane uzyskano, przeprowadzając regularne badanie neurologiczne na podstawie skali EDSS (Expanded Disability Status Scale) i badań laboratoryjnych (rezonans magnetyczny, badania krwi i moczu). **Wyniki.** Leczenie immunomodulujące w obserwowanej grupie chorych było skuteczne i dobrze tolerowane. Stwierdzono obniżenie rocznego wskaźnika rzutów u każdego z pacjentów. Stopień sprawności w skali EDSS ustabilizował się u 11 chorych. Najczęstszymi objawami niepożądanymi były przemijające objawy grypopodobne, zmiany skórne w miejscu iniekcji i podwyższenie poziomu aminotransferaz. **Wnioski.** Nasze 4-letnie obserwacje wykazały skuteczność i bezpieczeństwo leczenia INF-β w grupie młodzieży z SM.

Słowa kluczowe: dziecięce stwardnienie rozsiane, leczenie immunomodulujące, leczenie modyfikujące przebieg choroby, interferony β

ABSTRACT

Introduction. Multiple sclerosis (MS) is a chronic inflammatory immune-mediated disease of the central nervous system, characterized by demyelination and neurodegeneration. MS registered before 18 years of age constitutes about 3–10% of the total cases. Immunomodulatory treatment with interferons β (INF-β) is recommended as the first-line disease-modifying therapy (DMT) in pediatric MS. **The study objective** was to present the course of treatment with INF-β in ped-MS patients (adolescents). **Material and methods.** The total of 18 adolescents (age 13–18) with relapsing-remitting course of MS was observed. They were treated within the Therapeutic Program in the Department of Developmental Neurology Poznan University of Medical Sciences in 2008–2012. Data was obtained through the systematic neurological examination based on the Expanded Disability Status Scale (EDSS) and the laboratory tests (magnetic resonance imaging, blood and urine tests). **Results.** Therapy with INF-β was effective and achieved the high level of tolerance in observed adolescents. The reduction of relapse rate was noticed in each patient. EDSS has been stabilized in 11 patients. The most frequent side effects were transient flu-like symptoms, injection-site reactions and increased aminotransferases level. **Conclusions.** The efficacy and safety of INF-β in adolescent with MS have been shown in our 4-year observation.

Key words: pediatric multiple sclerosis, immunomodulatory therapy, disease modifying therapy, interferons β

INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelination-inflammatory disease of the central nervous system leading to progressive degeneration of myelin and axons. Among theories of the etiology of MS prevails the immunological one, assuming impaired immune response due to the action of the environmental factor (such as virus or bacteria) in a person with genetic predisposition [1]. MS occurs most commonly in young adults between 20 and 40 years of age, but the first symptoms may appear as early as in childhood (3–10% of cases below 18 years of age) [2–5].

Poland belongs to the so-called high-risk zone of MS, defined as a prevalence of more than 40 cases per 100 000 inhabitants. According to estimates, 100 new cases may appear in the pediatric population every year [6].

Therapy includes treatment of MS relapse, immunomodulatory treatment-DMT (disease modifying therapy), symptomatic treatment and comprehensive rehabilitation [7, 8].

In the Department of Developmental Neurology in Poznan 13 girls and 5 boys with MS underwent immunomodulatory treatment in 2008–2012. They were inhabitants

of Great Poland Province (14 people), West Pomeranian Province (2 people), Lubusz Province (1 person) and in the Lodz Region (1 person).

CHARACTERISTICS OF PARTICIPANTS

Table I presents the basic data on treated patients. Hospital and outpatients medical records were retrospectively analyzed, and the database was regularly updated. In 4 cases the family history of MS was reported.

All patients had cerebrospinal fluid diagnosed. 12 patients had the count of oligoclonal bands of IgG and leukocytosis in excess of 4 cells per microliter, maximum up to 27 cells per microliter.

Prolonged latency P100 in the study of visual evoked potentials were observed in 7 of 15 examined patients.

Demyelinating changes in the magnetic resonance imaging (MRI) of the head in all patients typically meet the criteria for dissemination in space, were localized in the periventricular and juxtacortical white matter, rarely in the corpus callosum and infratentorially. In one case, additionally was described a single focus of "mega lesion" (TDLs, tumefactive demyelinating lesions).

Furthermore, 9 patients underwent MRI of the cervical spine and intramedullary lesions were observed in 6 of them (number of lesions 1–5). Plaques had also been reported in thoracic spine MRI in 3 out of 5 patients (number of lesions 1–4).

THERAPEUTIC PROGRAM

Selection criteria for the therapy were according to the guidelines of the Therapeutic Program of the National Health Fund (the Program) [9]. Requirements to participate in the Program were the following: 16 years of age, diagnosis of relapsing-remitting MS based on McDonald criteria as

Table I. Characteristics of patients with multiple sclerosis treated with interferons β

	Sex	Age of onset (Years ± months)	Age at the begining of therapy (Years ± months)	Duration of therapy (months)	Relapse rate before therapy	Relapse rate during therapy	EDSS before therapy	EDSS in last month therapy	Symptoms of first relapse
1	M	15+7	16+3	24	3,00	0,50	1,0	1,5	double vision
2	K	15+2	16+6	31	3,75	0,77	1,5	1,0	double vision
3	K	16+2	16+9	30	3,42	0,80	1,5	1,0	double vision sensory symptoms
4	M	16+4	16+11	17	5,14	0,00	1,5	1,0	ON[1]
5	M	14+0	16+1	29	1,44	0,83	1,0	1,5	paraparesis
6	K	17+0	17+10	24	3,60	0,50	1,5	2,0	ON, sensory symptoms, dizziness
7	K	16+6	17+0	24	4,00	0,00	0,0	1,0	sensory symptoms
8	M	12+1	16+0	23	0,50	0,00	2,0	1,5	dizziness
9	K	16+11	17+5	11	4,00	0,00	1,0	1,0	paresis n.VII, nystagmus
10	K	14+2	16+7	17	1,24	0,70	1,5	1,0	monoparesis
11	K	15+5	16+8	16	2,40	0,00	0,0	1,0	sensory symptoms
12	K	15+8	16+2	17	4,00	0,00	1,0	1,0	ON
13	K	9+0	13+4	43	1,38	0,00	1,5	1,0	hemiparesis
14	K	13+7	14+7	28	2,00	0,43	1,5	1,5	sensory symptoms dizziness
15	M	11+8	14+7	28	1,00	0,43	0,0	1,0	double vision
16	K	14+8	15+3	19	5,14	1,89	1,0	1,5	dizziness
17	K	12+1	16+6	11	0,90	0,00	1,5	1,0	ON
18	K	15+8	17+1	5	1,41	0,00	2,5	1,5	ON

ON – optic neuritis

modified in 2005, and the occurrence of at least two relapses within the last two years [10]. Each patient had to score at least 21 points in an additional questionnaire concerning the age, the duration of the disease, the number of relapses in the last year and EDSS (Kurtzke Expanded Disability Status Scale) [11].

Patients, who did not meet the age requirement (4 persons aged 13–15) were treated outside the Program. Recruitment of patients was carried out in the period before the publication of the regulation of May 10, 2012, which gave the possibility of using refunded immunomodulatory treatment in children over 12 years of age.

There were two interferons used: IFN-β-1b in a dose of 250 mcg administered subcutaneously every other day, and IFN-β-1a in a dose of 44 mcg administered subcutaneously 3 times a week. Normally, in the first month of treatment a lower dose was given, gradually increased to the normal dose, equal to a dose of an adult, which is for IFN-β-1b 62,5 mcg for the first week, next 125 mcg and 187,5 mcg for the next two weeks, and, finally 250 mcg (1ml) from the 4th week of treatment, whereas IFN-β-1a 8,8 mcg for two weeks, and 22 mcg for 2–4 weeks and 44 mcg (0,5 ml) from 5–7th week.

The youngest patients began treatment at the age of 13 years 4 months, the oldest at 17 years 10 months, 11 patients were on medication immediately after their 16 birthday. The duration of treatment ranged from 11 to 30 months. 10 patients finished their participation in the Program on their 18 birthday. For most of these patients it was possible to continue the therapy in neurological centers for adults.

In one case the treatment was discontinued due to leucopenia (WBC count < 3 G/L) persisting despite the reduction of the dose of IFN-β. After 2 years of treatment one of the patients decided to discontinue the use of IFN-β due to bothersome flu-like symptoms, loss of appetite and increased headaches. In addition, a clear progression of changes was present on MRI.

The scheme of patient care was based on monthly visits connected with taking the medications. Every 3 or 6 months a full neurological examination and basic blood and urine tests were carried out. Whenever needed, the patients and their parents had psychological care provided.

Control MRI of the head was normally performed after 1 or 2 years of treatment and during neurological deterioration. Not in all cases it was possible to reliably compare subsequent MRI results because the gadolinium had not been used or the first examination was carried out in other laboratory.

Before the treatment, the patients and their parents underwent training conducted by the qualified nurse in giving self-administered injection and preventing undesirable effects, particularly associated with the injection site reaction. Only in one case the cooperation with a public health nurse was required.

TREATMENT

Neurological condition was monitored using the EDSS scale and MRI. We analyzed the number, severity and relapse rate during the treatment compared with the period before immunomodulatory therapy individualized for each patient. The efficacy of the treatment was based on the guidelines from the Program.

None of the patients had progression of the disease, defined as persisting for at least 3 months deterioration in EDSS by more than 2.0 points for patients with scores to 3.5, or more than 1.0 point for patients with scores greater than 4.0. There was also not observed the relapsing-remitting MS transition into the secondary – progressive MS (EDSS > 6.0 points).

During the treatment more relapses were observed in 9 patients, in 5 of them a single attack, in 3 patients – 2 attacks, in 1 patient – 3 attacks. The most frequent symptoms regarded the sensory symptoms characterized by paresthesia of one limb, face and upper lip or trunk, additionally monoparesis, hemiparesis, ataxia and optic neuritis were also observed.

In most cases, the relapses were qualified as mild, which means not impairing daily activities, and resulting in an increase of up to 1.0 points in one to three different functional systems of EDSS. The reduction in annualized relapse rate in each patient was noted (table I). Regular neurological assessment during treatment showed stabilization of the neurological condition according to EDSS in 11 patients.

Tolerance to treatment was satisfactory in the majority of patients. Among the most commonly observed were flu-like symptoms (headache, myalgia, shivers, fever) lasting usually for the first 6 months of therapy. Prophylactic use of analgesics usually effectively mitigated or eliminated these symptoms. In individual cases periodically the dose of IFN-β was reduced.

Other undesired symptoms regarded the increased level of liver enzymes without the clinical features of liver failure (7 patients, AST 58–83 UI/l, ALT 44–134 UI/l), leucopenia (1 patient WBC count 2,74 G/L), thyroid dysfunction (2 patients, subclinical hyperthyroidism or hypothyroidism). In individual cases transient insomnia, menstruation disorders and isolated headaches were observed.

Figure 1 graphically presents the distribution of side effects of immunomodulatory therapy in all patients.

During relapses the standard dose of intravenous methylprednisolone was used (20–30 mg/kg of body weight, up to 1 g/day), usually for 3–5 days with a good tolerance. Temporary the redness of the face, dyspepsia and sleep disorders was observed. None of the patients required administration of immunoglobulin and plasmapheresis during exacerbation of the disease.

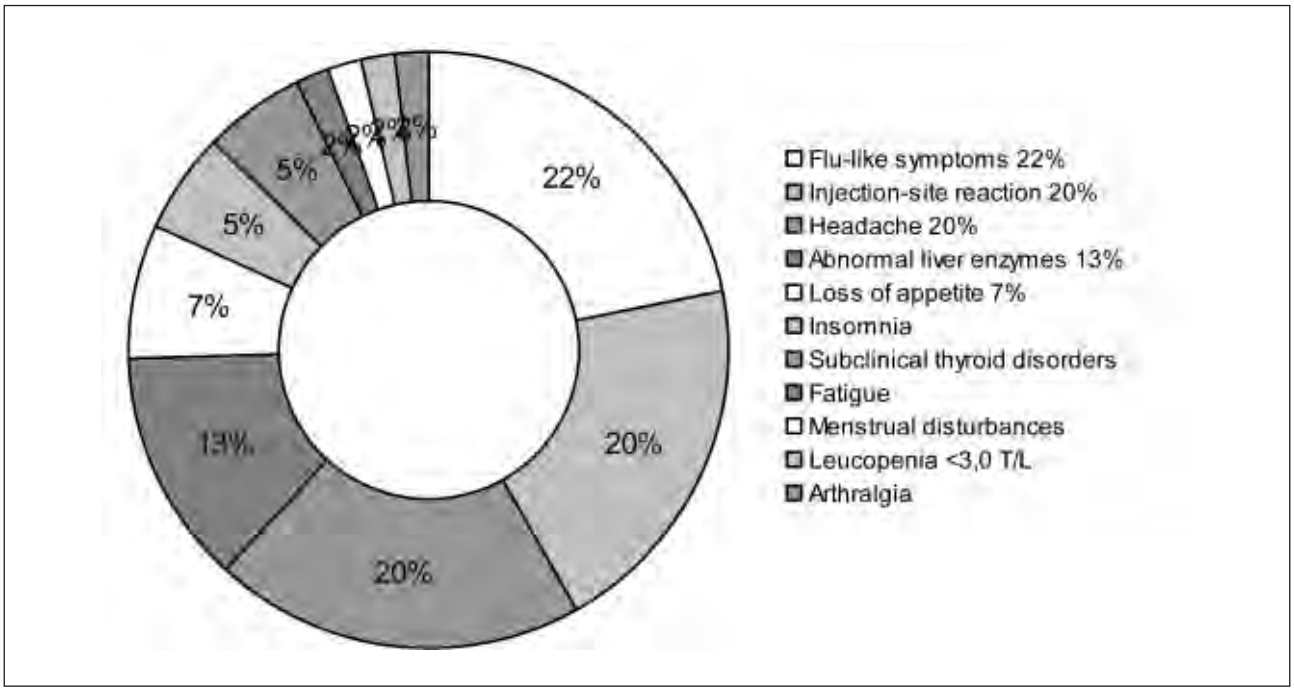
Not many patients underwent the symptomatic treatment, mostly they were given medications to improve liver function.

In addition to the physiotherapy implemented in relapse, the patients were provided the guidance on the regular physical exercises and healthy lifestyle.

DISCUSSION

Experience in the treatment of IFN-β in developmental age patients in the world, despite a few prospective studies, is

Figure 1. Side effects of the immunomodulatory therapy in the study group of patients.



sufficient enough to conclude that their efficacy and safety is comparable to the treatment in adult population with MS [3, 8, 12].

An international group of researchers dedicated to MS in children (the International Pediatric Multiple Sclerosis Study Group) had published the 2010 guidelines for the use of medications of first and second-line DMT [7]. We analyzed the most important retrospective and prospective studies, single and multi-center on the use of IFN-β and glatiramer acetate.

Decline in the annual relapse rate during treatment compared to pre-treatment was reported in most studies. For example, in a group of 39 patients from the Italian centers treated with IFN-β-1a (dose of 22 mcg) or IFN-β-1b, the average annual relapse before treatment was 3,2 ± 2,5, and after treatment 0,9 ± 1,1 [13].

Among the most commonly observed side effects were flu-like symptoms (7–70%), injection site reaction, abnormal liver enzymes and myalgia. Serious side effects, such as systemic reactions, were reported in single cases [8, 14].

Meta-analyzes conducted for adult MS patients showed the frequency of flu-like symptoms during IFN-β in the range of 32–57 %, and the injection site reaction in 22–65% of patients. Among other frequent side effects were observed: isolated headache, myalgia, depression, fatigue, joint pain, fever and insomnia [15].

Observations on the efficacy and tolerability of IFN-β in the group of our patients were similar to the experience of other centers worldwide. Due to low numbers of participants in the group, their heterogeneity and varied treatment time, we were unable to carry out statistical calculations.

SUMMARY

Presented 18 MS patients constituted the first group subjected to immunomodulatory therapy in Poznan Department of Developmental Neurology.

The 4-year-observation has shown the safety and efficacy of IFN-β in adolescents, which is comparable with the experiences of other neurological centers in the world.

Over the time, the principles of MS treatment programs in Poland have changed for the benefit of the patients. Among other things, the age limit was lowered from 16 to 12 years for IFN-β, the upper limit of the age of recruitment was removed, the duration of treatment was extended from 2 to 5 years. The possibility of an epileptic seizure as a MS relapse in children was taken into account by excluding epilepsy from the list of contradictions to treat with IFN-β. Separate rules were established to dose IFN-β and monitor treatment for the pediatric group.

From practical point of view, too restrictive criteria for treatment failure may give ground for some reservations. Due to the different dynamics of the disease in children (including a greater annual relapse rate than in adults, relapses with impaired consciousness), it seems that the criteria regarding the lack of IFN-β efficacy should be more lenient for developmental age patients.

In using the first line DMT medication in immunomodulatory therapy in MS are applied: natalizumab, mitoxantrone, cyclophosphamide, and the lately registered oral fingolimod. Experience with administering them in children with MS is limited [16–19].

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Adres do korespondencji:
Karolina Kupczyk, Department of Developmental Neurology, 61–355 Poznań, ul. Przybyszewskiego 49, Phone: 61 8691255,
e-mail: karolina.kupczyk@op.pl