High-efficacy treatment for aggressive pediatric Multiple Sclerosis

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Pediatric-onset multiple sclerosis (POMS) is rarer than adult-onset disease, and it has different diagnostic and therapeutic challenges. It is known that multiple sclerosis in children is characterized by a greater inflammatory activity than in adult patients, which is reflected in a more frequent polysymptomatic or ADEM-like onset, a high frequency of exacerbations, and a greater radiological burden at the onset of the disease. Also, in children, NEDA (no evidence of disease activity) is achieved with less success when using first line lower-efficacy disease-modifying therapies (DMTs)

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease affecting the central nervous system, which mainly manifests itself in adults. However, from 3 to 10% of all patients diagnosed with MS experience the first demyelinating event before the age of 18 (pediatric multiple sclerosis). In children, multiple sclerosis is characterized mainly by a remitting course (98-99%), with more frequent exacerbations at the beginning of the disease. It is known that the course of pediatric multiple sclerosis is characterized by greater inflammatory activity compared with the onset of the disease after 18 years (high frequency of exacerbations, high workload of focal changes on MRI, higher incidence of ADEM-like onset). In recent years, there has been a change in the therapeutic paradigm of multiple sclerosis in adult patients (an early start of modifying therapy and a rapid transition to more highly effective drugs). Thanks to this, we see a reduction in the risk of achieving permanent disability. Approaches in the treatment of multiple sclerosis in children are also undergoing changes towards more highly effective therapy. However, in practice, quite often we can see some slowdown with the start of high-efficacy treatment (HET). This is due both to insufficient experience in managing aggressive or highly active multiple sclerosis in children, and to the existing restrictions on the use of “2-line” drugs in reimbursement system. Only three drugs are registered for use in children compared to more than ten in adults. Several drugs continue clinical studies of efficacy and safety in childhood. The publication of the results of clinical trials and data from real clinical practice will help fill in the lack of information on the safety and effectiveness of existing modifying therapy.

Materials and methods

At the time of the study, more than 7,000 patients with a diagnosis of multiple sclerosis were observed at the St. Petersburg City Center of Multiple Sclerosis, including about 5,500 residents of St. Petersburg (Russia). 170 patients with childhood multiple sclerosis were monitored in the MS center from different regions of Russia from 2011 to 2022, mainly from St. Petersburg. 132 patients started modifying therapy before the age of 18. Highly effective therapy was started in 11 cases with aggressive (rapidly progressing) MS or highly active multiple sclerosis. The effectiveness of this therapy, tolerability, as well as adverse reactions were evaluated. Clinical recommendations on multiple sclerosis in adults and children of the Ministry of Health of the Russian Federation were used the tactics of therapy. The duration of follow-up was at least 6 months after the start of the "2 line" therapy. 9 patients were treated with natalizumab, 2 patients received ocrelizumab, one child received rituximab. The characteristics of the course of the disease, previous therapy, the effectiveness and tolerability of 2nd line therapy are presented in Table 1.

Results

The mean age of onset of MS was 13,0±2,1 years old. Start of HET was 16,0 13±1,7 years [9,9;17,8]. All 11 patients had a dramatic positive effect of HET on the course of POMS: suppression of the clinical and radiological inflammatory activity of the disease. A year before the start of therapy, patients had frequent severe exacerbations (2,6±1,1; [1;4]), high radiological activity. After the start of HET, no relapses of MS were registered in any child, no new T2 or/and Gd+ appeared. Most patients showed a decrease in the EDSS score in the first months of therapy with further stabilization. In 2 cases the score of the EDSS remained the same. Only one patient progressed during first year from 6.0 to 6.5 of EDSS (Patient 10), more likely due to the relatively late start of HET.

One patient (№2) on the 5th infusion of natalizumab developed an anaphylactic reaction. One patient (№4) was switched from natalizumab to ocrelizumab before 18 y.o. due to the risk of PML . In all patients, high-efficacy therapy showed a dramatic effect on suppressing inflammatory response (there were no exacerbations, no new or Gd+ lesions) throughout the observation period. Apart from 1 anaphylactic reaction on natalizumab, the rest of the safety profile was favorable. Infections, oncology were not revealed.

Table 1

		Features of MS in the debut			Features of MS before the shift to the 2nd line therapy						Features of MS after switching to the 2nd line therapy									
Patient №	Sex	Age of MS onset, y	MRI in debut	OCB (yes /no)	MS duration, months	Number of MS drugs	Last MS drug	Duration of last MS treatment, months	Number of relapses in previous year	MRI before changing treatment	Next MS treatment (Mabs)	Age of onset Mabs	Duration of Mabs treatment	Number of relapses for whole period of Mabs treatment	Number of relapses for 12 months	Number of relapses for 24 months	Safety	MRI after 6 months of treatment by Mabs	MRI after 12-24 months of treatment by Mabs	Comments
1	m	9	>20 T2 lesions, 6 Gd+	yes	4,2	1	interferon bet a 1 a 30 mkg	1	4	>20 new T2 lesions, 20 Gd+	ocrelizumab	9	8,1	0	n/a	n/a	-	No new T2 lesions, Gd-	n/a	Without exacerbations, the therapy continues
2	f	11	17 T2 lesions	no	29,1	2	teriflunomide	9	4	> 10 new T2 lesions, 6 Gd+	natalizumab	14	3,6	0	n/a	n/a	Anaphylaxis on the 5th infusion	n/a	n/a	The drug was canceled due to an anaphylactic reaction, there was a change of therapy to rituximab
2	f	11	17 T2 lesions	no	34,2	3	natalizumab	4	3	-	rituximab	14	26,8	0	0	0	-	No new T2 lesions, Gd-	No new T2 lesions, Gd-	The patient's weight was 54 kg, the therapy regimen was 2000 mg every 9 months. The total dose was 6000 mg. After the 3rd cycle, she was transferred to ocrelizumab (after its registration)
2	f	11	17 T2 lesions	no	66,8	4	rituximab	26	-	-	ocrelizumab	17	8,7	0	n/a	n/a	-	No new T2 lesions, Gd-	n/a	Without exacerbations, the therapy continues
3	m	11	25 T2 lesions, 10 Gd+	yes	31,3	1	interferon bet a 1 a 44 mkg	26	2	4 new T2 lesions, 15 Gd+	natalizumab	14	32,7	0	0	0	-	No new T2 lesions, Gd-	No new T2 lesions, Gd-	Without exacerbations, therapy continues, the titer of abs to JCV is negative
4	m	15	12 T2 lesions, Gd-	yes	9,8	1	teriflunomide	6	4	6 new T2 lesions, with perifocal edema	natalizumab	15	5,0	0	n/a	n/a	-	n/a	n/a	The drug was canceled due to the risk of PML (high titer of abs to JCV - 2.86, therapy of juvenile rheumatoid arthritis with methotrexate at 11 years old). In this case, natalizumab was used as an urgent and transient therapy before the start of ocrelizumab.
4	m	15	12 T2 lesions, Gd-	yes	15,8	2	natalizumab	5	4	-	ocrelizumab	16	6,7	0	0	n/a	Mild infusion reaction during 1 cycle	No new T2 lesions, Gd-	n/a	without exacerbations, the therapy continues
5	f	9	6 T2 lesions, 1 Gd+	yes	83,2	2	interferon bet a 1 b	4	2	4 new T2 lesions, 2 Gd+	natalizumab	16	19,9	0	0	0		No new T2 lesions, Gd-	No new T2 lesions, Gd-	Without exacerbations, therapy continues, it is planned to change therapy within the 2nd line due to the high titer of abst to JCV
6	m	15	14 T2 lesions, 1 Gd+	yes	25,4	1	interferon bet a 1 a 44 mkg	19	2	5 new T2 lesions	natalizumab	17	44,2	0	0	0	-	No new T2 lesions, Gd-	No new T2 lesions, Gd-	without exacerbations, therapy continues, the titer of abs to JCV is negative
7	m	11	15 T2 lesions, 2 Gd+	yes	75	3	interferon bet a 1 b	37	1	5 new T2 lesions, 2 Gd+	natalizumab	17	23,2	0	0	0	-	No new T2 lesions, Gd-	No new T2 lesions, Gd-	without exacerbations, therapy continues, the titer of abs to JCV is negative
8	f	11	4 T2 lesions	yes	73,9	1	glatiramer acetate	35	4	4 new T2 lesions, 2 Gd+	natalizumab	17	24,5	0	0	0	-	No new T2 lesions, Gd-	No new T2 lesions, Gd-	After 2 years, ocrelizumab therapy was started due to the risk of PML (high titer of abs to JCV)
9	m	15	15 T2 lesions, 11 Gd+	yes	21,6	1	interferon bet a 1 a 44 mkg	13	2	12 new T2 lesions, 10 Gd+	natalizumab	17	40,6	0	0	0	-	No new T2 lesions, Gd-	No new T2 lesions, Gd-	without exacerbations, therapy continues, the titer of abs to JCV is negative
10	f	15	Brain MRI: 2 T2 lesions, Gd-; Spinal MRI: 1 T2, 1 Gd+	yes	28,7	1	interferon bet a 1 a 44 mkg	16	3	3 new T2 lesions, 1 Gd+	natalizumab	17	30,2	0	0	0	-	No new T2 lesions, Gd-	No new T2 lesions, Gd-	After 2,5 years, ocrelizumab therapy was started due to the risk of PML (high titer of abs to JCV)
11	f	14	11 T2 lesions, 5 Gd+	yes	36,7	1	interferon bet a 1 a 44 mkg	33	2	new T2 lesions, 2 Gd+	ocrelizumab	17	6,9	0	n/a	n/a		No new T2 lesions, Gd-	n/a	without exacerbations, the therapy continues

Abs – antibodies; Gd+ - gadolinium-enhancing lesions on T1 ; JCV – John Cunningham virus; Mabs – monoclonal antibodies; MS – multiple sclerosis; OCB – oligoclonal bands; PML – progressive multifocal leukoencephalopathy

Concusion

Natalizumab, ocrelizumab and rituximab can be an effective and safe disease-modifying therapy for POMS.

For prevention disability it is important to start HET for aggressive POMS early/

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