Boyko O.V.[1,2], Petrov S.V.[2], Lashch N.Yu.[1], Guseva M.R.[1], Boyko A.N.[1,2]
[1]N.I. Pirogov Russian National Research Medical University, Ministry of Health of Russia, Moscow, Russia;
[2]Yusupov Hospital, OOO «Neuro-Clinic», Moscow, Russia
[1]1, Ostrovityanov St., Moscow 117997; [2]17, Nagornaya St., Build. 6, Moscow 117186

Experience with anti-B-cell therapy in the pathogenetic treatment of multiple sclerosis

One of the promising areas in the pathogenetic treatment of multiple sclerosis (MS) is anti-B-cell therapy using ocrelizumab, an anti-CD20 monoclonal antibody. The drug is indicated for primary progressive MS (PPMS), secondary progressive MS (SPMS) and exacerbations, and highly active MS.

***Objective**: to analyze the use of the drug in 32 patients with different types of MS in everyday neurological practice.*

***Patients and methods**. The investigation included 32 patients diagnosed with MS using the 2017 McDonald criteria: 12 patients with PPMS, 12 with highly active MS and 8 with SPMS and exacerbations. The median Expanded Disability Status Scale (EDSS) score was 4.0; the most severe course of the disease was observed in patients with SPMS. All the patients received a treatment cycle of 600-mg intravenous ocrelizumab injections (with an infusion pump) every 6 months; the initial dose was by 300 mg every 2 weeks. The follow-up period was 6 to 18 months.*

***Results and discussion.** During ocrelizumab therapy, the patients with PPMS showed stabilization of EDSS score; and 6 (50%) had even its slight decrease by 0.5–1.0 scores, which may be caused by compensation for the existing symptoms due to pathogenetic treatment. In highly active MS, only 1 of the 12 ocrelizumab-treated patients had an ongoing exacerbation of the disease. During a subsequent 6–18-month follow-up, magnetic resonance imaging revealed that none of the patients had manifestations of MS activity; the EDSS score decreased in all the patients, indicating their achievement of stable remission. Six (75%) of the 8 patients with SPMS and exacerbations also displayed a decrease in EDSS score in the absence of exacerbations. No adverse events, including infusion reactions, were recorded during drug administration. The drug has a good tolerance and safety profile and ease-to-use.*

***Conclusion**. Ocrelizumab therapy with will be able to improve the quality of treatment in patients with different types of MS, which is of great medical and social importance.*

***Keywords**: multiple sclerosis; anti-B-cell therapy; pathogenetic treatment; ocrelizumab.*

Contact**: Aleksey Nikolaevich Boyko; **boykoan13@gmail.com

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A promising direction of disease modifying treatment (DMT) of multiple sclerosis (MS) is selective immunosuppression using monoclonal antibodies (MAT). Among the drugs that change the course of MS (DMT), MATs are widely used, especially in the active course of the disease. One of the most promising drugs of MAT today is ocrelizumab – humanized MAT against CD20-receptor, which is expressed mainly on B-cells, mainly on pre-B-cells, mature B-cells and memory B-cells [1]. After binding to the CD20 antigen, ocrelizumab selectively reduces the number of B cells by means of antibody-dependent cell phagocytosis, antibody-dependent cell cytotoxicity, complement-dependent cytotoxicity, and apoptosis. In this case, B-cells precursors and plasma cells are preserved, i.e. it is possible to restore the cell pool and the presence of existing humoral immunity [2]. B-cells are participating in the immunopathogenesis of MS by production of autoantibodies and pro-inflammatory cytokines, as well as presenting antigens to T-cells, including the formation of ectopic lymphoid follicles in the brain meningeal [3, 4]. The formation of these follicles is the most pronouncing phenomena at the progressive stage of MS, associated with the development of cortical lesions of demyelination and diffuse atrophy, being one of the goals of anti-B-cell therapy [5–7]. Some activated T cells also express CD20 receptor and serve as a target for ocrelizumab [8].

Now the new classification of MS by type is becoming more popular, with classifying to MS with relapses (RMS), including relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) with exacerbations, and to progressive MS, including primary progressive (PPMS) [9]. In large randomized double-blind multicenter clinical studies, high efficacy of ocrelizumab in the treatment of both RMS compared to high-dose interferon beta-1A (IFNI) 44 μg subcutaneously 3 times per week [10], as well as in PPMS comparing with placebo [11].

In patients with MSR, ocrelizumab compared with IFN significantly reduced the annual relapse rate by 46% ($p<0.0001$), as well as the risk of disability progression – a relative reduction in the risk of progression according to EDSS (Extended Disability Status Scale) was 40% [10]. During the course of therapy with ocrelizumab, almost complete suppression of MRI activity characterizing autoimmune inflammation was noted: the total number of lesions accumulating contrast on T1-weighted images (T1-WI) was 94% less with ocrelizumab than in the treatment of IFNI ($p<0.0001$) [10]. The status of NEDA (No Evidence of Disease Activity), no clinical and MRI signs of activity or progression of MS, was achieved in 48% of patients in ocrelizumab group over a two-year period, which is significantly higher than in the group of IFNI (25–29%).

In PPMS, ocrelizumab significantly slowed the progression of disability (EDSS) by 24% compared to placebo [11]. The total volume of lesions in T2-weighted images (T2-WI) increased by 7.4% in the placebo group, while in the ocrelizumab group it decreased by 3.4% ($p<0.001$). Less significant atrophy of the

Table 1. Clinical and demographic characteristics of 32 MS patients before initiation of therapy with ocrelizumab

Parameter	MS course		
	PPMS (n=12)	Highly active RRMS (n=12)	SPMS with relapses (n=8)
Women, n (%)	5 (42)	6 (50)	5 (62,5)
Age, years*	49,1 (29–58)	28,5 (19–48)	39,3 (28–58)
MS duration, years*	6,2 (3–10)	1,8 (0,5–2)	7,7 (6–13)
Number of relapses, n*	0	3,6 (2–5)	5,7 (3–10)
EDSS*	3,6 (2,5–5,5)	3,7 (3,0–5,0)	4,6 (3,5–5,5)

* average value and SD are presented..

brain and spinal cord (0,90%) were seen in ocrelizumab and 1.09% – in the placebo group; p=0.02) [11]. Thus, ocrelizumab is the first and so far the only one product for the DMT of PPMS. Thus, ocrelizumab can be recommended for the treatment of almost all forms of MS course (with the exception of SPMS without relapses), but the most actively prescribed to patients with PPMS, highly active MSR (i.e. with frequent relapses), as well as SPMS with exacerbations with the ineffectiveness of high-dose IFNI (first-line DMT for this type of MS course) [12]. At the Department of Neurology, Neurosurgery and Medical Genetics of the Pirogovs' Russian National Research Medical University and the Yusupov Hospital ("Neuro-clinic") ocrelizumab was used DMT in MS for several years.

The aim of the study was to analyze the use of the product in everyday neurological practice in 32 patients with different types of MS.

Patients and Methods. 32 patients with MS according to McDonald criteria 2017 [13] received ocrelizumab (Ocrevus, Roche, Switzerland)/ Clinical and demographic characteristics of patients are given in Table 1. There were 16 (50%) women (in PPMS there were more men), the age of patients ranged from 19 to 58 years (average 38.8 years, the oldest patients were in the group of PPMS, and the youngest – in the group of highly active MS), the duration of MS ranged from 6 months to 13 years (in the group of highly active MS it was less than 2 years, and in SPMS – more than 6). The number of relapses in MSR before treatment ranged from 2 to 10, in highly active MS all patients had more than 2 exacerbations for 6–12 months of the follow-up. By severity of MS (EDSS indices [14]) patients were close, the most severe were patients with SPMS.

12 patients had a mean duration of PPMS of 6.2 years. This type of course is characterized by a steady progression of disability from the very beginning of the disease, possibly with episodes of more active increase in severity, which is sometimes referred to as an exacerbation in PPMS, but without remissions [15, 16], according to McDonald criteria 2017 [13]. In such patients, disability occured faster than in patients with MSR, more severe medical and social problems and deterioration of the Quality of Life [16, 17]. In 12 patients included in this study, for 6 years of PPMS, the level of EDSS increased to an average of 3.6 points, i.e. steadily increased by an average of 0.5–1.0 points per year.

In 12 cases, a highly active MS was observed. All these patients with MSR had 2 and more severe relapses, which led to an increase in ⩾1 point of EDSS, with active lesions on MRI. In such cases, it is recommended to start second-line DMT, including ocrelizumab [18, 19].

SPMS with relapses was in 8 patients. In SPMS the period with relapses and remissions (MSR) is changed to a steady progression with relapses (SPMS with relapses). According to International and Russian Recommendations, in such cases, ocrelizumab is prescribed as a second-line DMT with the ineffectiveness of high-dose IFNI [12, 19]. All these patients previously received treatment with high-dose IFNI for 2–12 years, still relapses and EDSS progression were present, which was regarded as a suboptimal response to the therapy [20]. They received an escalation of therapy and were prescribed ocrelizumab as second-line DMT.

Ocrelizumab is used 600 mg every 6 months in intravenous (IV) infusion. The initial dose was administered as two separate infusion: 1st infusion of 300 mg, after 2 weeks – another 300 mg Next dose was administered 6 months after the 1st infusion of the initial dose. Subsequently, the drug is administered as a single infusion at a dose of 600 mg every 6 months. In our study, more than 50% of patients received two courses of ocrelizumab. Prior to the treatment start were done: 1) clinical examination, including a detailed history, a complete neurological examination; 2)

blood test with a detailed leukocyte formula; 3) biochemical blood test to determine the level of creatinine, liver enzymes; 4) analysis for hepatitis B, C, HIV; 5) overview radiography of the chest (to exclude tuberculosis) and Diaskintest; 6) pregnancy test in women of childbearing age; 7) brain MRI at least 3 months before the start of therapy; 8) cancer screening, according to age and gender recommendations. Before each infusion, a detailed clinical and biochemical blood tests, serological studies (HIV, hepatitis B and C), screening for tuberculosis (1 time per year) were repeated.

The drug was prescribed taking into account indications and contraindications, according to the instructions [21]. Ocrelizumab was administered using the infusion pump, slowly, under the careful supervision of an experienced healthcare worker and the availability of access to emergency assistance in the case of infusion reactions, with subsequent observation for at least 1 h after completion of infusion. Before each infusion ocrelizumab the premedication with methylprednisolone 100 mg IV 30 minutes and an antihistamine (diphenhydramine or cetirizine) were done 30–60 min before each infusion. In case of clinical necessity, the premedication was supplemented with antipyretics (acetaminophen or paracetamol) approximately 30–60 minutes before each infusion of ocrelizumab. Blood pressure control was carried out, as ocrelizumab may reduce it.

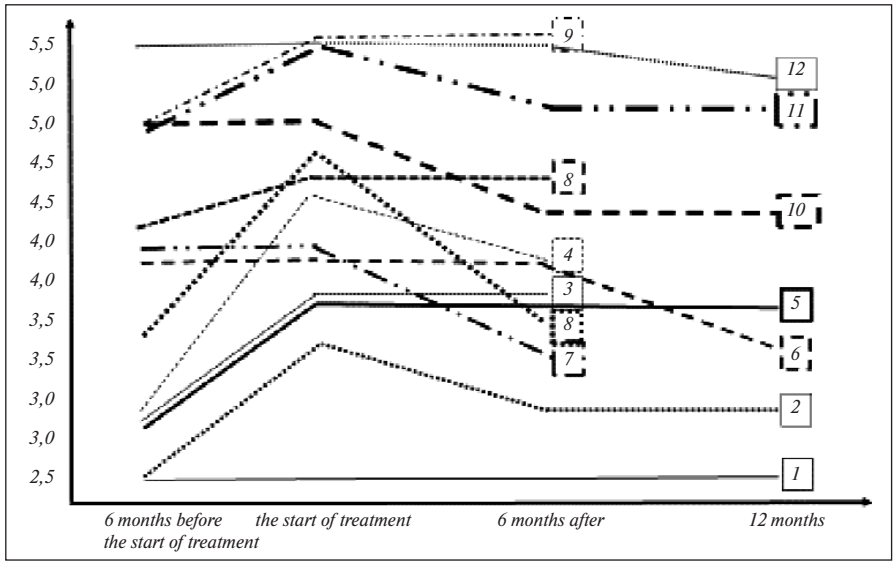

Figure 1. *EDSS levels in 12 patients with PPM treated with ocrelizumab: 6 months before treatment, at the time of the 1st infusion, 6 and 12 months.*

In clinical studies, the most frequent adverse events (AE) were infusion reactions (IR) of different severity, the development of which may be associated with the release of cytokines and/or chemical mediators. Symptoms of IR can develop during any infusion, but most often they occur within 24 hours after the first administration of ocrelizumab [10, 11]. IR can be manifested in the form of itching, rash, urticaria, erythema, throat irritation, pain in the oropharynx, shortness of breath, pharynx or larynx, tides, lowering blood pressure, fever, fatigue, headache, dizziness, nausea and tachycardia. At the time of publication, half of the patients received two or more injections. In any case, no one serious IR were seen.

Results and Discussion. All patients with PPMS the stabilization of the EDSS was seen, and in 6 (50%) – even its slight decrease by 0.5–1.0 points. This may be due to the compensation of existing symptoms during DMT. In the phase III study, which included patients with PPMS, improvement of some neurological symptoms was seen in 20% of cases, most often in young patients with active PPMS and the presence of new lesions on MRI [22]. In our study, 8 (66.7%) from 12 patients 6 months before the start of treatment showed a significant increase in the disease severity, and 5 of 12 (41.7%) – activity on MRI with new lesions in the brain or spinal cord on T2-WI. Figure 1 shows the changes in EDSS (6 months before treatment, at the time of the 1st infusion of ocrelizumab, 6 and 12 months after it). None of the treated patients in the next 6–12 months showed an increase in EDSS scores. According to this study, of course, it no one can speculate that the progression of PPMS has been stopped, but the rate of disability progression clearly decreased.

A clinical case as example.

The patient, 46 years old, has been suffering from MS for 10 years. The onset of the disease with unsteadiness in walking, after 2 years due to the increase in gait disorders, an MRI of the brain was performed, in which multiple lesions with increased intensity were detected on T2-WI periventricular and in the corpus callosum, without the accumulation of contrast agent. He received high-dose IFNβ, weakness in the legs increased. There were no clear relapses and remissions. In 2012. due to the ineffectiveness of IFNβ, therapy with fingolimod was started, which the patient received during the year without significant changes in the rate of weakness in the legs and staggering when walking. At the same time, pulse therapies with glucocorticoids (GC, methylprednisolone and dexamethasone) were also used in different hospitals, despite the diagnosis of PPMS, without significant improvement in the patient status. In 2017 he was sent to the Yusupov hospital, where the additional examination revealed oligoclonal bands of IgG in the cerebrospinal fluid (CSF), changes in visual and somatosensory evoked potentials (EP), we excluded other causes of such progressive tissue damage. At examination, the lower spastic paraparesis with high muscle tone and pathological stop signs prevailed, also in the coordination samples the intention and dysmetry on both sides were noted, more on the right, in the Romberg probe – instable in all directions, depression. When re-examination after 6 months, there was an increase in weakness in the legs and the appearance of weakness in the left hand, urinary retention, EDSS – 5.0. MRI detected a new lesion at T2-WI at the thoracic spinal cord. A decision to use ocrelizumab was made. Currently, three courses of the product have been conducted, after the first course, the EDSS index slightly decreased (to 4.5 points), weakness in the hand regressed, EDSS stabilized (Figure 2). With comprehensive examination no SE have been identified, there remains the decrease in the level of CD19+ cells in the blood.

In highly active MS, patients with an average of 1.8 years of MSR course had from 2 to 5 relapses (average 3.6), which led to the development of disability from 3 to 5 points (average 3.7 EDSS). The active course of MS was also seen on MRI in the form of a large number of new lesions on T2-WI and active (contracting) lesions on T1-WI. These patients started second-line

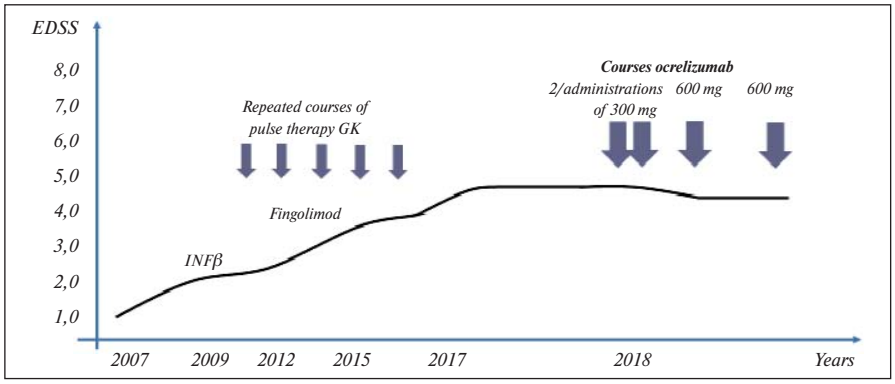

Figure 2. *Disease course and the EDSS in a patient, 46 years old, with EDSS*

methylprednisolone, weakness in the leg regressed. This case was reported to Officals (Roszdravnadzor). Subsequently, none of these patients treated by us during 6–12 months of follow-up revealed clinical and MRI manifestations of MS activity, all patients showed a decrease in EDSS by 0.5–2 points, indicating the achievement of remission (Table 2). No one SE during therapy was seen.

Another clinical case. *Patient N., 24 years old, first sign at May 2017, with right optic neuritis, with severe eye pain and a decrease in visual acuity to 0.3. After pulse therapy with CS, the symptoms regressed.*

Table 2. The course of MS with relapses (highly active relapsing remitting MS and SPMS with relapses) in patients under ocrelizumab.

Parameter	MS course	
	Highly active RRMS	SPMS with relapses
Number of patients, n	12	12
Received at least 2 courses, n (%)	6 (50)	3 (37,5)
Number of relapses, n	1*	0
Progression in EDSS, n	0	0
Decrease in EDSS (≥0,5), n (%)	12 (100)	6 (75)

* Continuous relapse, not stopped after first infusion of ocrelizumab, reported to Officials

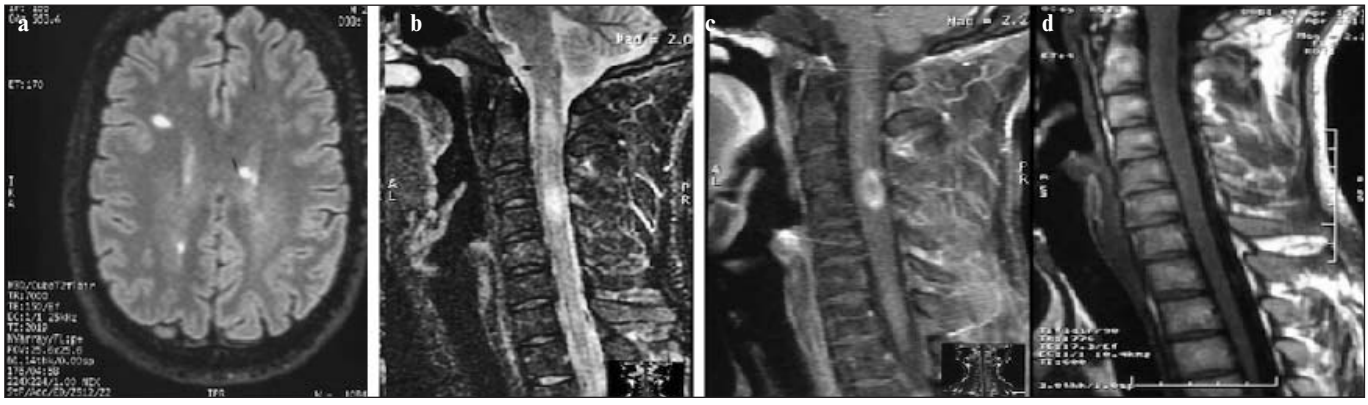

Figure 3. *MRI of the patient's brain and spinal cord of patient N. At January 2018: T2-WI – several lesions periventricular (a), two lesions in the spinal cord (b), one of which actively accumulates paramagnetic contrast agent on T1-WI (c). August 2018: the accumulation of the contrast agent by the lesion in the spinal cord have not been identified (d)*

DMT – ocrelizumab. In 1 patient after the first administration of 300 mg of the drug, increased weakness in the left leg was noted. During the re-MRI revealed a lesion at the spinal cord, actively accumulating contrast agent on T1-WI. After pulse therapy with *MRI revealed multiple lesions with increased intensity on T2-WI. At September 2017 – second relapse with gait disorders. MRI showed new lesions on T2-WI and active lesion with enhancing at T1-WI. Pulse therapy of GC with positive effect was performed. But in*

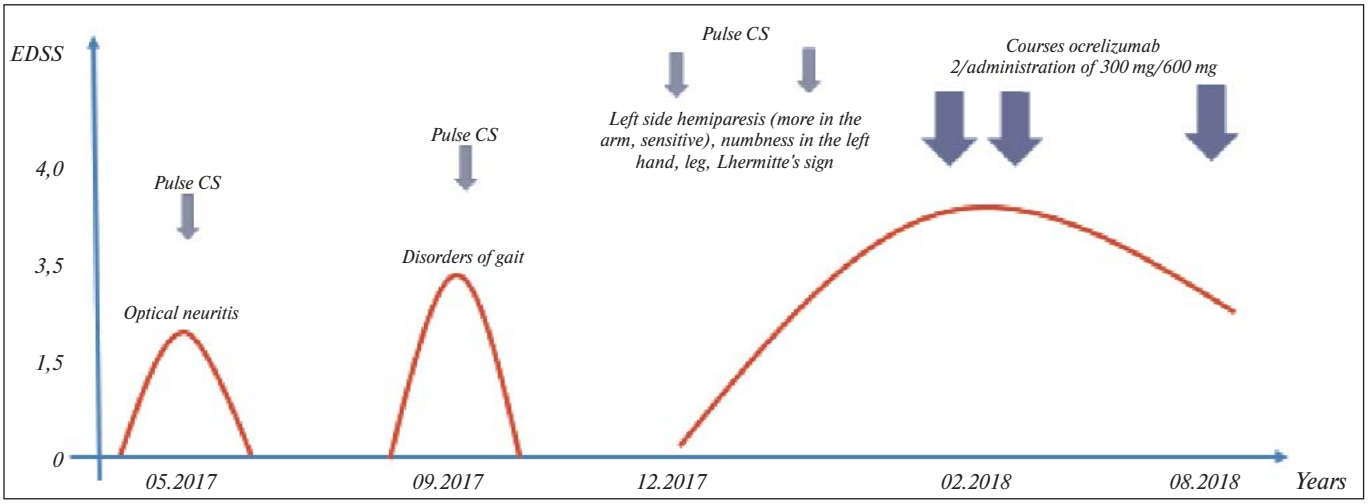

Figure 4. *Disease course and EDSS in patient N., 24 years, with high activity RRMS*

December 2017 appeared the left-side hemiparesis (greater in the hand, afferent), numbness in the left hand with the spread of foot and torso, Lhermitte's sign. MRI revealed new lesions periventricular and lesion in the cervical spinal cord, with contrasting at T1-WI. Additional examination revealed oligoclonal IgG in CSF, changes in visual and somatosensory evoked potentials/ Other reasons of CNS damage were excluded. Despite two courses of GC, symptoms persisted. At observation January 2018 horizontal nystagmus in both directions, inter-nuclear ophthalmoplegia were seen. Paresis of the left hand, decreased muscle tone more on the left, tendon and periosteal reflexes from the hands are animated on both sides, from the legs are increased, more on the left, abdominal reflexes are absent, the Babinski sign on the left. Paresthesia in the left hand. Lhermitte's Sign. The decrease of deep sensitivity on the limbs on the left. Dysmetria in coordinatory probes on the left. Dysphoria, asthenia. EDSS-3.5 points. In January 2018 9 lesion on MRI were seen, in the corpus callosum, brain stem and cerebellum, and in 2 lesions in spinal cord (Figure 3). One lesion in the brain and a new one in the spinal cord were Gd+ at T1-WI. The highly active course of RRMS with three exacerbations for 8 months of the disease was proposed, it was decided to use ocrelizumab: the first administration – in February, the second- in August. SAE with the introduction of the drug is not noted. There was a significant regression of symptoms (EDSS 1.5 points), during the year of observation – no exacerbations.

Figure 4 shows the dynamics of the patient's conditions. Timely administration of a highly effective drug second line DMT has reduced autoimmune and inflammatory activity of the disease. No new or active foci were detected in the brain and spinal cord when MRI was performed again in August 2018. Another infusion of ocrelizumab is planned for February 2019.

The third group of patients included 8 patients (5 women) with SPMS with relapses. The duration of MS ranged from 6 to 13 years (average 7.7), relapses still present, despite a long course

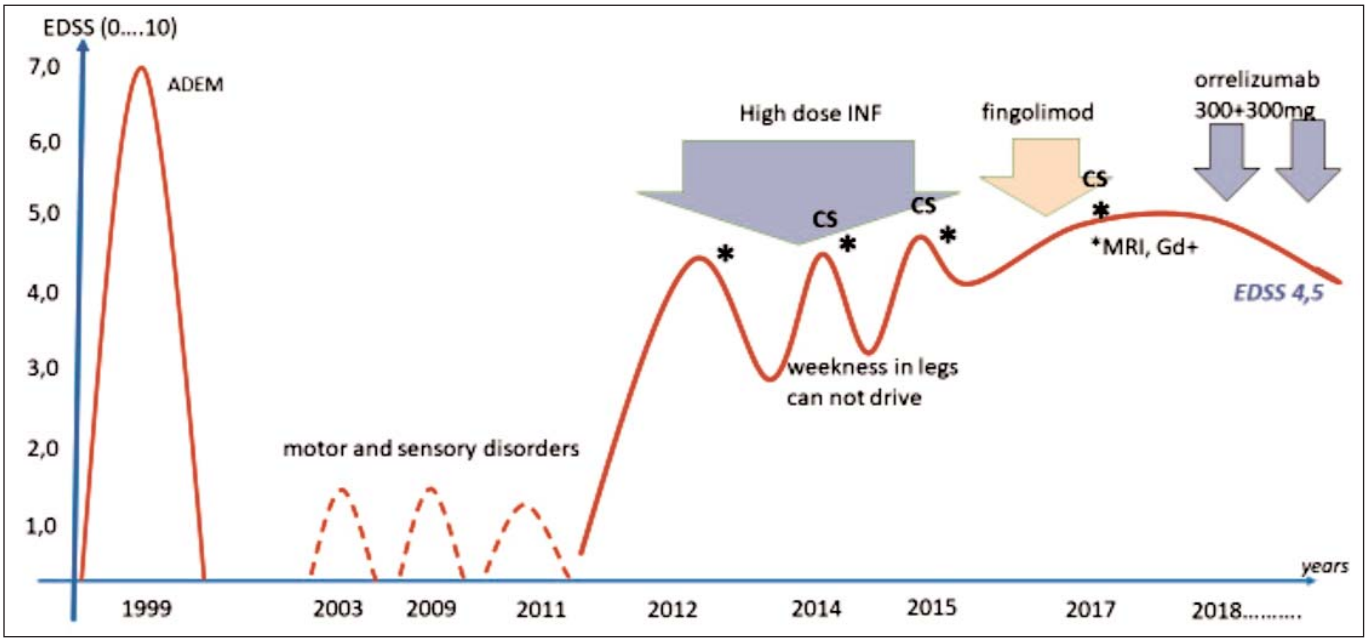

Figure 5. *Disease activity and EDSS levels in the patient N., 41, SPMS with relapses and insufficient efficiency of therapy of high-dose IFNβ*

of treatment with high-dose IFNβ. At the same time, there was a steady increase in disability (EDSS) outside the exacerbations, which allowed to diagnose SPMS with relapses. In accordance with the European and Russian recommendations, the only second-line DMT in this type of MS course is ocrelizumab [12, 19]. During 6–12-month course of therapy with this drug, in no case was a relapse of SPMS, and in 6 (75%) of 8 patients the score on EDSS decreased, which, of course, can be regarded as a very positive result in CHD (see Table 2)

A case.

Patient N., 41 years old, first relapse in 1999, the onset of the disease was severe, according to the type of acute disseminated encephalomyelitis (ADEM) with a good regression of symptoms after a course of pulse therapy of CS. In 2003–2011, the patient noted several times transient deterioration in the form of increased weakness and coordination disorders, which regressed without therapy. In 2012 – severe exacerbation with motor disorders, after which a course of treatment with high-dose IFNβ was started. Despite DMT, repeated relapses were seen in 2014 and 2015. Weakness in the legs began to grow independently on relapses. The last pulse therapy of CS the end of 2017, there was a moderate effect, the EDSS remained at the level of 5. Due to insufficient response to INF_, second line DMT was started – ocrelizumab. Two courses of treatment with this drug were conducted, there were no exacerbations for 10 months of observation, there was an improvement in the condition with a decrease in the EDSS index up to 4 points. Figure 5 shows the dynamics of the patient.

Conclusion. Thus, indications for MAT ocrelizumab are PPMS, highly active RRMS or SPMS with relapses. Atall these MS types, there is a positive clinical dynamics with a decrease in the activity of the pathological process, the absence of relapses, stabilization, and in some cases, a decrease in the degree of disability. In PPMS ocrelizumab is the only allowed DMT [12]. Based on a subgroup analysis of clinical study data, it was shown that the drug may be most effective in those patients with PPMS who had signs of activity (clinically in the form of relapses or according to MRI), and were younger than 45 years old [23]. This drug is still the only one method of escalation of therapy in patients with MS with relapses, resistant to INFI [12]. With a highly active course of MS, ocrelizumab is one of the drugs of the first choice along with other MAT.

The drug has a good tolerability and safety profile. The most common SAE during treatment with ocrelizumab are IR, the number of which in clinical studies was the maximum during the 1st infusion of the initial dose of ocrelizumab (27.5%) and decreased over time to <10% during the administration of the 4th dose [10, 11]. Most of the infusion reactions in phase III studies were mild or moderate. In our group, 32 patients did not have a single case of IR as SAE. Anti-B-cell therapy in studies of II and III phases involving a large number of patients [10, 11] showed no increase in the frequency of serious infections. Particularly discussed is the issue of increasing the risk of cancer on ocrelizumab. When combining the data of three phase III studies, it was found that breast cancer was diagnosed in 6 patients in the ocrelizumab group [10, 11], although these indicators did not go beyond the expected, according to epidemiological studies in MS [24]. In our 32 patients during 6–12 months no such cases were detected, which does not exclude the need for careful monitoring in the future. While ocrelizumab easy to use – IV infusion once per 6 months. The active introduction of ocrelizumab in the daily practice of neurologists will significantly improve the quality of treatment of patients with different types of MS, which is of great medical and social importance, especially in the active course of MS in young patients.

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