Anti-B-cell therapy in patients with neuromyelitis optica spectrum disorders

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Neuromyelitis optica spectrum disorders (NMOSDs) are a group of central nervous system autoimmune diseases characterized by similar clinical manifestations, optic neuritis, and transverse myelitis being the most frequent among them. In most cases, the pathogenesis of NMOSDs is associated with autoantibodies to aquaporin-4 (AQP4-IgG). However, AQP4-IgG is not detected in at least 10–20% of patients with NMOSDs. In this subgroup and in patients with isolated transverse myelitis or optic neuritis, IgG antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) were detected. Patients seronegative for both AQP4-IgG and MOG-IgG have also been described.

Objective: *to evaluate rituximab (RTX) effectiveness in preventing relapses and disability in patients with NMOSDs.*

Patients and methods. *The study included 27 patients with NMOSDs (9 men and 18 women) aged 20–51 years who received RTX in 2019–2021. The treatment protocol included intravenous infusions of 1000 mg of RTX on the 1st and 15th days, the second and subsequent courses (maintenance therapy) – intravenous infusions of 1000 mg of RTX once every six months. Treatment effectiveness was assessed by the average annualized relapse rate, the median changes of the Expanded Disability Status Scale (EDSS), and based on the magnetic resonance imaging (MRI) changes.*

Results and discussion. *The annualized relapse rate at baseline and 18 months after the start of treatment was: all patients (n=27) – 0.6±0.3 and 0.07±0.27 (p<0.0001); AQP4-IgG+ patients (n=6) – 1.1±0.9 and 0.17±0.41 (p=0.028); MOG-IgG+ patients (n=14) – 0.4±0.3 and 0.07±0.28 (p=0.001); AQP4-IgG-, MOG-IgG- patients (n=7) – 0.8±0.4 and 0.0±0.0 (p=0.018). The EDSS score at baseline and 18 months after the start of treatment was: all patients – 4.5 [3.25; 6.0] and 4.0 [3.0; 5.75] (p=0.679); AQP4-IgG+ – 3.5 [2.625; 4.75] and 3.5 [2.5; 4.5] (p=0.869); MOG-IgG+ – 5.5 [3.75; 6.5] and 5.5 [2.75; 6.25] (p=0.465); AQP4-IgG-, MOG-IgG- – 4.0 [3.75; 5.25] and 3.5 [3.0; 3.5] (p=0.043). We observed two clinical relapses during the study period: one in an AQP4-IgG+ male and another one in a MOG-IgG+ woman. There was a significant decrease in the annualized relapse rate in all groups. The disability indicator did not increase during the study period, and in AQP4-IgG and MOG-IgG seronegative patients, it slightly but significantly decreased. Brain and spinal cord MRI monitoring during the treatment period revealed new active foci only in two patients with clinical relapses.*

Conclusion. *RTX treatment in NMOSDs is reasonably efficient and safe, but with the obligatory prior patient evaluation and monitoring of treatment results.*

Keywords: *neuromyelitis optica; neuromyelitis optica spectrum disorders; AQP4-IgG; MOG-IgG; rituximab.*
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Introduction. Neuromyelitis optica spectrum disorders (NMOSDs) are a group of recurrent inflammatory autoimmune diseases of the central nervous system, with similar clinical manifestations, among which the most common are (a) optic neuritis with potential visual impairment or blindness, (b) myelitis with severe motor and sensory disorders, pelvic dysfunction, (c) damage to the brain stem, manifested in oculomotor, coordination and pyramidal disorders or (d) persistent nausea, vomiting, hiccups (area postrema syndrome), (e) brain damage, including cognitive and speech disorders, (e) diencephalic syndrome and narcolepsy. It is believed that in most cases the pathogenesis of NMOSDs is associated with autoantibodies to aquaporin-4 (AQP4-IgG), the most common aquatic channel in the central nervous system, located mainly on the processes of astrocytes. In the pathogenesis of the disease in contrast to multiple sclerosis (MS), the target of autoantibodies is not myelinated fibers of the central nervous system, but astrocytes, therefore this type of NMOSD, Devic's syndrome, is considered astrocytopathy; demyelination is a secondary process. Major lesions predominantly affect areas with high AQP4 expression [1, 2, 3].

However, AQP4-IgG is not detected in at least 10-20% of patients with NMOSDs. Recent studies have shown that in this subgroup of patients, as well as in patients with isolated transverse myelitis or optic neuritis, IgG antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) were detected, thus, this variant of NMOSD can be characterized as oligodendrocytopathy with demyelination [4, 5, 6]. According to L. Pandit et al. [7], in patients with the presence of MOG-IgG, clinical manifestations included recurrent optic neuritis and myelitis, and lesions of the lumbosacral region were observed more often than in AQP4-IgG associated NMOSDs. As with AQP4-IgG-positive NMOSDs, the number of affected women is more than double the number of men. According to DK Sato et al. [8], stem symptoms in the form of area postrema syndrome is not typical for such patients. MOG-IgG was detected in patients with acute and recurrent disseminated encephalomyelitis.

In seronegative (for AQP4-IgG and MOG-IgG) patients, as observed by H. Cross et al. [9], at the onset of the disease isolated myelitis occurred almost three times more often (57%) than optic neuritis (20%). A multi-focal lesion at the onset was also

more often observed in seronegative patients, who, with a similar level of disability, had a worse response to glucocorticoid therapy.

A common feature of NMOSDs, both associated with AQP4-IgG and MOG-IgG, and seronegative, is rapid progression of neurological deficits because of repeated exacerbations. Therapy for exacerbations of NMOSDs is the use of high doses of glucocorticoids in the pulse therapy mode, the use of plasmapheresis, and administration of normal human immunoglobulin. Long-term immunosuppression is critical to prevent recurrent exacerbations [10, 11, 12].

The aim of our study was to evaluate the results of using rituximab (RTX) in patients with NMOSD to prevent recurrent exacerbations and an increase in disability.

Materials and methods. The study protocol was approved by the Independent Ethics Committee of Moscow Regional Research and Clinical Institute (MONIKI) on June 13, 2019, protocol №8). The study was prospective. We observed 27 patients with NMOSD, 9 men and 18 women, aged 20 to 51 years, who received rituximab therapy in 2019–2021.

All patients met the *inclusion criteria*:

– signed informed consent;
– age over 18;
– compliance with the diagnostic criteria for NMOSD (seropositive or seronegative) [3];
– the absence of clinical and MRI signs of an exacerbation of the disease during the last 30 days;
– no deviations in the results of the preliminary examination:
  • Chest X-ray and tuberculin skin test, consultation of a phthisiatrician at least 6 months before hospitalization;
  • Complete blood count (with differentiated count of lymphocytes (absolute count) 10 days before hospitalization;
  • Biochemical blood test (creatinine, ALT, AST) 10 days before hospitalization;
  • General urine analysis 10 days before hospitalization;
  • Serological tests for HIV, hepatitis B and C, syphilis (3 months);
  • ELISA blood test for herpes simplex virus types 1 and 2 (IgG and IgM), *Varicella Zoster* virus (IgG and IgM);
  • Oligoclonal antibodies in the cerebrospinal fluid;
  • Results of blood tests for AQP4-IgG (laboratory INVITRO) and MOG-IgG (laboratory of the Scientific Center of Neurology);
  • Phenotyping of B-lymphocytes (main subpopulations);
  • In the presence of any oncological disease – consultation of an oncologist about the possibility of anti-B-cell therapy;
  • Consultation of a gynecologist, mammography for women over 40 years old.

The exclusion criteria were:

– deviations in preliminary examination, which increase the risks of adverse events during RTX therapy;
– history of pulmonary insufficiency;
– decompensated cardiovascular diseases (angina pectoris, arrhythmia, arterial hypertension, heart defects);
– decompensation of somatic pathology;
– neutropenia ($<1.5 \cdot 10^9$/l);
– thrombocytopenia ($<75 \cdot 10^9$/l);
– acute infectious diseases;
– febrile syndrome;
– non-compliance;
– protocol deviations.

During the observation period (before the start of the therapy, and after 6, 12, 18 and 24 months from the start of therapy), the patients underwent: 1) physical examination; 2) brain MRI; 3) EDSS scale evaluation; 4) blood and urine tests, biochemistry, B-lymphocyte subtypes.

The treatment protocol consisted of the first course of RTX 1000 mg on days 1 and 15, the second and subsequent courses - intravenous infusion of RTX 1000 mg once every 6 months. Safety control included vital signs, blood test (with a differentiated count of lymphocytes (absolute number), blood biochemistry (creatinine, ALT, AST), urine test 10 days before hospitalization and every 3 months. Brain MRI was performed before the start of the therapy, then every 6 months. The observation period was from 12 to 24 months (mean 18.4±3.2 months).

The effectiveness of the therapy was assessed based on:1) annual frequency of exacerbations; 2) EDSS scores; 3) brain MRI results.

BioStat Pro 7.3.0 software package was used for statistics. Quantitative data are presented as mean values and standard deviation (M±σ), categorical ordinal data are presented as median and quartiles (Me [Q1, Q3]). Normality of distribution was assessed using the D'Agostino–Pearson test. When analyzing qualitative ordinal data distributed according to a law different from the normal distribution law, we used the Wilcoxon nonparametric test for dependent samples, and to compare two independent samples, the Mann–Whitney test. Statistical tests were carried out for a two-sided hypothesis, the level of statistical significance was taken equal to 0.05.

Results. All 27 patients included in the study met the criteria for the diagnosis of NMOSD [3]. Six of them had AQP4-IgG+, 14 – MOG-IgG+, 7 patients were seronegative for AQP4-IgG and MOG-IgG. All patients fully completed all research procedures. No serious adverse events were reported during the therapy. Clinical manifestations of the disease are shown in Table 1.

Table 1. *NMOSDs clinical features in the study population*

	AQP4-IgG+ (n=6)	MOG-IgG+ (n=14)	AQP4-IgG-, MOG-IgG- (n=7)	Total (n=27)
Optic neuritis	5	4	4	13
Myelitis	5	9	7	21
Cerebral syndrome	1	13	6	20
Hypothalamic syndrome		7	2	9
Brainstem syndrome	1	2	1	4
Area postrema syndrome		1		1

As follows from the data given in Table 1, the most frequent manifestations of NMOSD were clinical signs of myelitis; 18 patients had transverse myelitis, including bilateral conduction pyramidal and sensory deficits and pelvic disorders. Optic neuritis was detected in half of the patients, and bilateral optic neuritis – in 6 patients. Cerebral syndrome (confusion, cognitive disorders, pyramidal and sensory loss) was more often detected in MOG-IgG seropositive patients. They also showed a hypothalamic syndrome, however, there was no «classical» manifestation in the form of narcolepsy, though episodes of hypersomnia and insomnia, hemodynamic dysfunction, hyperhidrosis, etc. were noted. Clinical manifestations of area postrema syndrome were noted only in 1 patient, although hyperintense periependymal foci on T2–WI in the region of the fourth ventricle in the brainstem and cerebellum were found in 5 patients.

Table 2 shows the demographic data of the examined patients.

As can be seen from the data presented in Table 2, most of the patients were female, the ratio of men to women was 1:2. The age of the patients at the time of seeking help ranged from 20 to 51 years, Only in 1 patient the disease debuted at the age of 17, in 3 – in the second, in 10 – in the third, in 13 – in the fourth decade of life, while the latest debut was noted at the age of 39. The period from the onset of the disease to seeking help in 12 patients was 1–2 years, in 9 – 3–9 years, in 6 – more than 10 years, at the same time, the longest duration was recorded in patients with MOG-IgG+, and they also had the highest level of disability. The number of exacerbations in the period preceding the initiation of anti-B-cell therapy ranged from 1 to 8, with the highest rate being in AQP4-IgG+ patients.

The results of the therapy for patients with NMOSDs are presented in Table 3.

During the 18-month follow-up period, 2 clinical exacerbations were recorded in 27 patients with NMOSDs, 1 in a patient with AQP4-IgG+ and 1 in a patient with MOG-IgG+. Statistically significant decrease in the average annual number of exacerbations was noted both in the whole group and in patients with AQP4-IgG+, MOG-IgG+ and seronegative patients. The disability indicator did not increase during the observation period, and in AQP4-IgG and MOG-IgG seronegative patients, it slightly, but statistically significantly, decreased.

Monitoring MRI of the brain and spinal cord during the therapy revealed the appearance of new active foci only in two patients who had clinical exacerbations.

Discussion. Despite a certain similarity in the clinical picture and course of MS and NMOSD, these diseases have different pathogenesis, which determines different approaches to therapy. After the approval of drugs that modify the course of multiple sclerosis, there have been attempts to use them for the treatment of patients with NMOSDs. However, it was found that some MS disease modifying drugs (DMD) such as inter-

Table 2. *General characteristics of the NMOSDs patients*

Показатель	Total (n=27)	AQP4-IgG+ (n=6)	MOG-IgG+ (n=14)	AQP4-IgG-, MOG-IgG- (n=7)
Age (years)	35.9±8.2	34.2±6.4	38.9±7.1	31.6±10.0
Sex m/f	9/18	2/4	4/10	3/4
Age at onset (years)	28.8±6.2	30.2±7.5	29.6±4.7	26.0±7.7
Duration of the disease (years)	5.9±5.7	3.0±2.7	7.8±6.7	4.4±4.2
Age at initiation of therapy (years)	34.5±8.1	33.2±6.1	37.2±7.2	30.3±9.9
Number of exacerbations prior to initiation of therapy total	3.3±1.8	3.2±2.1	3.4±1.9	3.4±1.5
Average annual number of exacerbations before starting therapy	0.6±0.3	1.1±0.9	0.4±0.3	0.8±0.4
EDSS before starting therapy	4.5 [3.25; 6.0]	3.5 [2.625; 4.75]	5.5 [3.75; 6.5]	4.0 [3.75; 5.25]

Table 3. *Annualized relapse rate and EDSS scores in NMOSDs patients treated with RTX*

Показатель	Total (n=27)	AQP4-IgG+ (n=6)	MOG-IgG+ (n=14)	AQP4-IgG-, MOG-IgG- (n=7)
Average annual number of exacerbations before starting therapy	0.6±0.3	1.1±0.9	0.4±0.3	0.8±0.4
Average annual number of exacerbations 18 months after initiation of therapy	0.07±0.27 (p<0.0001)	0.17±0.41 (p=0.028)	0.07±0.28 (p=0.001)	0.0±0.0 (p=0.018)
EDSS before starting therapy	4.5 [3.25;6.0]	3.5 [2.625;4.75]	5.5 [3.75;6.5]	4.0 [3.75;5.25]
EDSS 18 months after initiation of therapy	4.0 [3.0;5.75] (p=0.679)	3.5 [2.5;4.5] (p=0.869)	5.5 [2.75;6.25] (p=0.465)	3.5 [3.0;3.5] (p=0.043)

Note: p – significance level of the differences between the values before and 18 months after the start of RTX therapy.

feron-beta, natalizumab, fingolimod, were not only ineffective, but in some cases led to a worsening of the course in AQP4-IgG+ NMOSD [12, 13].

Despite insufficient knowledge of the immunological mechanisms of this group of diseases, it was noted that in MS a high level of cytokines, chemokines and related molecules released by Th1 lymphocytes (IL-2, IFN-γ, IL-8, IL-15, fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), etc.) was revealed. However, patients with AQP4-IgG and MOG-IgG associated NMOSD, in contrast to patients with MS, had a more pronounced increase in the activity of Th17 lymphocytes and an increase in the level of associated cytokines (IL-6, IL-8, granulocyte-stimulating colony-forming factors), Th1-associated cytokines (IFN-γ and TNF-α), circulating T-regulatory cells (IL-10), and such changes were found in both adults and children [14].

In experimental animal studies, it was found that interferon-beta (IFN-β) was effective against the clinical course of Th-1-induced encephalomyelitis but had no effect on Th-17-induced encephalomyelitis [15]. Probably, these differences in the pathogenesis of MS and NMOSD explain the ineffectiveness of MS-DMD in relation to relapses of NMOSD.

The modern approach to the therapy of NMOSD consists of two directions: the fastest relief of the current exacerbation and prevention of repeated exacerbations leading to an increase in disability. The first line of therapy includes intravenous administration of high doses of methylprednisolone - pulse therapy at 1000 mg/day for 3–5 days, if necessary, the dose can be increased to 2000 mg/day. In the case of insufficient effectiveness, it is possible to use exchange plasma transfusion (EPT) 30–40 ml/kg of body weight or immunosorption from 3 to 8 sessions. With ineffectiveness of pulse therapy in a previous exacerbation, EPT becomes the method of choice [16, 17, 18]. In a small number of our observations, in severe disabling exacerbations with transverse myelitis, a combination of alternating EPT and pulse therapy was used, which increased the chances of achieving positive dynamics with an early start of the therapy [4, 10].

Long-term immunosuppression is used to prevent recurrences of NMOSD. There is experience with the use of azathioprine at 2–3 mg/kg/day, alone or in combination with prednisolone 30–60 mg/day, for at least 6–9 months, mycophenolate mofetil 1000–3000 mg/day in combination with prednisolone, 30 mg/day, RTX (induction therapy 375 mg/m^2 per week – 4 weeks, or 1000 mg twice with a two-week break, then maintenance therapy). It was noted that RTX therapy was more effective in preventing the recurrence of NMOSD than the use of azathioprine or mycophenolate mofetil [19, 20]. Our observations also confirm insufficient effectiveness of azathioprine therapy, long-term administration of glucocorticoids and the introduction of normal human immunoglobulin in adequate doses to maintain remission of NMOSD [4, 10].

Recently, an international multicenter double-blind placebo-controlled clinical trial of three monoclonal antibodies for the treatment of NMOSD has been carried out. Satralizumab, a humanized monoclonal antibody to the IL-6 receptor, has been shown to reduce the risk of exacerbation in AQP4-IgG seropositive and seronegative patients with NMOSD [21]. Eculizumab, a recombinant humanized monoclonal antibody to the IgG2/4k immunoglobulin that binds to the human complement protein C5 and inhibits the activation of complement-mediated cell lysis, significantly reduced the risk of recurrent exacerbations in AQP4-IgG seropositive patients compared with placebo [22]. Inebilizumab is a humanized monoclonal antibody to the surface antigen CD19 on B-lymphocytes. In contrast to RTX, which acts on CD20 receptors, inebilizumab depletes a wider range of B cells, including plasmablasts and plasma cells, therefore, it is probably more effective in inhibiting the production of AQP4-IgG [23].

For patients with AQP4-IgG and MOG-IgG seronegative NMOSD, as well as in the case of clinical and MRI signs of both MS and NMOSD, many experts are inclined to recommend immunosuppressive therapy rather than MS-DMD [24].

Currently, there are many studies that have shown the effectiveness of the use of anti-B-cell therapy in patients with AQP4-IgG seropositive neuromyelitis optica. RTX is a monoclonal antibody against CD-20, a surface antigen that is primarily expressed on B-lymphocytes. The drug was originally developed to treat B-cell lymphoma because it depletes the pool of B-cells in the peripheral blood and bone marrow. Subsequently, B-cell depletion was found to be effective against several autoimmune diseases, as well as in prevention of exacerbations in patients with NMOSDs. Since then, off-label use of RTX has been reported in a few studies, reviews and meta-analyzes [25, 26, 27]. Later, recommendations were proposed for treatment of NMOSD, in which RTX was regarded as the first-line therapy [28].

In our rather small study, we presented patients with NMOSDs, seropositive for AQP4-IgG and MOG-IgG, as well as seronegative for these antigens. Considering the polymorphism of clinical manifestations, neuroimaging data and laboratory parameters, we should agree with N. Borisow [12] and O. Schmetzer [29], who believe that several independent diseases with different pathogenetic mechanisms are combined under the name NMOSD. What they have in common is apparently the involvement of autoimmune mechanisms, which justifies the use of RTX to prevent recurrent exacerbations.

As a result of the study, a significant decrease in the average annual frequency of exacerbations was noted, which was statistically significant in all groups. We will not speak about greater or lesser effectiveness of RTX therapy, depending on the type of immune disorders identified in specific patients, since the number of patients included in the study was small. Nevertheless, the level of disability, assessed by the EDSS scale, did not change during the 18–24-month period of observation. We also note good tolerance of RTX therapy and the absence of serious adverse events in our patients.

Conclusion. During RTX therapy in patients with NMOSD aimed at preventing recurrent exacerbations of the disease, a statistically significant decrease in the average annual frequency of exacerbations was revealed compared with the period before the start of the therapy, while the level of disability in patients remained stable during the observation period. Such results were achieved in both AQP4-IgG and MOG-IgG seropositive and seronegative patients. The data obtained allow us to speak about sufficient efficacy and safety of RTX therapy for patients with NMOSDs, but with obligatory full-fledged previous examination of such patients and monitoring of the results of therapy.

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