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REVIEW ARTICLE

Neuromyelitis Optica spectrum disorders: therapeutic considerations

Marko Andabaka[1], Sarlota Mesaros[1,2], Nikola Veselinovic[1,2], Olivera Tamas[1,2], Maja Budimkic[1,2], Jelena Drulovic[1,2]

[1] Clinic of Neurology, University Clinical Center of Serbia, Belgrade, Serbia

[2] University of Belgrade Faculty of Medicine, Belgrade, Serbia

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Correspondence to:
Jelena Drulovic
Clinic of Neurology, University Clinical Centre of Serbia,
6 Dr Subotica Street, 11000 Belgrade, Serbia
E-mail: drulovicjelena@gmail.com

Summary

Neuromyelitis Optica spectrum disorder (NMOSD) is a rare but debilitating autoimmune disease of the central nervous system (CNS) for which several biological therapies have been approved recently. Historically, NMOSD disease-modifying treatments relied on wide-spectrum off-label conventioanl immunosuppressants, such as azathioprine, and mycophenolate mofetil. Since 2015, evidence has accumulated to support off-label biological therapy (rituximab) and to approve satralizumab, inebilizumab, eculizumab, and ravulizumab. This next generation of drugs provides several targeted disease-modifying treatment options for NMOSD. Here, we first review the mechanistic rationales associated with their specific targets. Then we review the pivotal evidence supporting their use in practice. The current therapeutic options in NMOSD comprise three targeted mechanisms at different stages of a unique tissue-injury cascade: B-cell depleting, anti-cytokine, and anti-complement therapies. One drug from each class has been approved for market release. The current consensus proposes positioning the approved drugs as first-line treatments for newly diagnosed patients and as alternative therapies in case of failure of historical treatment.

Keywords: Neuromyelitis Optica spectrum disorder, treatment, disease-modifying treatment

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INTRODUCTION

Neuromyelitis Optica spectrum disorder (NMOSD) is an immune-mediated disease of the central nervous system (CNS), which is predominantly manifested by the appearance of optic neuritis (ON), transverse myelitis (TM), but also by the involvement of other CNS structures such as diencephalon, brainstem and area postrema (1). The main substrate of etiopathogenesis is related to the auto-antibodies, immunoglobulins G class, directed towards the transmembrane water pore of aquaporin-4 (AQP4-IgG) (1-3). AQP4 is expressed on the astrocytes, especially on the foot-like extensions of astrocytes, and it plays a major role in regulating the flow of water molecules through the cell membranes (4, 5). It has been demonstrated that about 80% of people with NMOSD have AQP4-IgG in their blood, which makes these autoantibodies an important molecular biomarker of the disease, based on which currently valid diagnostic criteria define seropositive and seronegative forms of NMOSD (1-3, 6).

The pathophysiology of seropositive NMOSD is driven by antibody-mediated humoral and cellular immune activation, leading to astrocyte destruction through mechanisms such as complement-dependent cytotoxicity and antibody-induced cellular cytotoxicity. Additionally, the inflammatory milieu contributes to the damage of adjacent CNS cells (7-11). Etiopathogenetic and pathophysiological mechanisms of the seronegative NMOSD have not been fully elucidated. Several various potential explanations for the occurrence of the seronegative NMOSD have been proposed, such as the existence of certain other autoantibodies, lower sensitivity of available tests, cellular mechanisms of pathogenesis, etc. (7, 12-14). The clinical course of the majority of NMOSD cases is recurrent and characterized by unpredictable and potentially very severe relapses that contribute to the development of permanent disability in the affected individuals (10, 12, 15). It has been shown that AQP4-IgG seropositivity in NMOSD patients increases the risk of other comorbid autoimmune diseases (16). In addition to the relapses, patients with NMOSD are burdened with numerous manifestations of the dysfunction of the autonomic nervous system, depression, anxiety and fatigue, which significantly affect the quality of life of these individuals (17-19).

The therapeutic approach to NMOSD is based on the current knowledge related to the pathophysiology and clinical characteristics of the disease and have two main goals: therapy of the relapse and long-term prevention of new relapses (10, 15, 20).

The aim of acute relapse therapy is a better and faster recovery of the neurological deficit (15, 21, 22). Following the latest recommendations, relapse therapy in both AQP4-IgG seropositive and seronegative NMOSD patients, comprise administration of corticosteroids (glucocorticoids) and/or blood apheresis according to established protocols as early as possible (20). Medicines used in chronic therapy to prevent relapse in NMOSD include:

conventional immunosuppressive drugs, as well as recently approved, evidence-based, specific therapies, and various monoclonal antibodies (20).

CONVENTIONAL IMMUNOSUPPRESSIVE THERAPIES

Drugs that achieve non-specific immunosuppression, such as azathioprine, and mycophenolate mofetil, potentially in combination with oral glucocorticoids, have retained their role in NMOSD therapy regardless of serostatus (20). For years, these drugs have been the primary treatment for all forms of NMOSD to prevent new relapses. However, their use has been limited by the risk of numerous side effects, particularly long-term administration (20, 23, 24). Under current conditions, glucocorticoids are primarily used as adjunctive therapy for preventing new NMOSD relapses (20). In certain areas of the world, where no other drugs are available for the treatment of NMOSD, glucocorticoids are still used as chronic monotherapy for this disease (20). Glucocorticoids achieve their effect even in lower doses that are taken chronically, but they can often induce the occurrence of adverse events, such as lymphopenia and hepatotoxicity (20). Additionally, long-term use of glucocorticoids is associated with more frequent occurrences of diabetes mellitus, hypertension, osteoporosis, and other disorders (20, 24). Recent recommendations suggest oral glucocorticoids should not be used as monotherapy in the prevention of NMOSD relapse, except when no other therapeutic options are available (20).

Azathioprine is a drug that is used in the treatment of NMOSD in a dose of 2.5-3 mg/kg/day with full therapeutic effect achieved after 6-12 months. It is recommended to overlap it during the first six months with oral glucocorticoids, which quickly achieve their effect, thus bridging the therapeutic gap (20, 25, 26). Frequent adverse effects of azathioprine refer to the occurrence of lymphopenia, thrombocytopenia, hepatotoxicity, gastrointestinal disturbances, and long-term effects that may lead to the potential occurrence of malignancy and secondary infections (20, 23, 25, 27). Studies have shown that lymphopenia occurs in about 13% of NMOSD patients treated with azathioprine (28). Although the frequency of secondary infections in patients treated with azathioprine varies, the incidence of infections is not high (27). However, very rare cases of progressive multifocal leukoencephalopathy (PML) have been described in patients treated exclusively with azathioprine (29, 30). In general, since all side effects are mainly related to the length of treatment and the dose of azathioprine, dose reduction or temporary discontinuation of the drug can alleviate these side effects (27).

Mycophenolate mofetil in therapeutic doses of 1000 to 2000 mg/day has a similar effectiveness and side effect profile to azathioprine (20, 27). The time required to achieve a full therapeutic effect is shorter compared to azathioprine and amounts to 6-12 weeks (20, 31). The most common side effects of mycophenolate mofetil are: leukopenia with secondary infections, vomiting, and diarrhea (27). In a meta-analysis that included 11 studies of patients with NMOSD treated with mycophenolate mofetil, it was shown that side effects were present in 17.8%, while individual studies reported the frequency of side effects in up to 43% (27, 32, 33).

MONOCLONAL ANTIBODIES

Recently, several prospective randomized controlled trials (RCT) have led to FDA approval of the first three immunotherapies for patients with AQP4-IgG-positive NMOSD: eculizumab in June 2019, inebilizumab in June 2020, and satralizumab in August 2020 (34-37). In addition, rituximab was approved for NMOSD in Japan in June 2022 based on the results of an investigator-initiated phase II/III clinical study (38), and in May 2023, the EMA approved ravulizumab for the treatment of AQP4-IgG-positive NMOSD.

Satralizumab

Satralizumab is a humanized monoclonal antibody against interleukin-6 receptor (IL-6R) (20). Satralizumab was approved for the treatment of AQP4-IgG seropositive NMOSD in adult patients and adolescents (aged 12 and older) in 2020 in the USA and in 2021 in Europe (20, 39, 40). Satralizumab reduces the relapse rate by over 70% during a follow-up period of more than 4 years (41). In more than 50% of patients with NMOSD, serum antibodies against Satralizumab were detected, but their clinical significance is unknown (20). Possible side effects of the drug are related to laboratory parameters such as neutropenia, thrombocytopenia, and side effects in the form of infusion reactions, headache, and arthralgia, while no serious opportunistic infections have been reported until now (20, 27).

Rituximab

Rituximab is a monoclonal antibody against a cluster of differentiation (CD) 20 molecules on the surface of B lymphocytes, causing depletion of these cells (20, 43). The full therapeutic effect of Rituximab is achieved in 8-12 weeks, which is why the initial introduction of oral is advised glucocorticoids in the first few months (20). Rituximab is the only monoclonal antibody that has shown efficacy in the treatment of seropositive and seronegative NMOSD, which is of great importance (20, 43). Rituximab achieves a reduction in the relapse rate in NMOSD by over 80% (20). A potential reason for the absence of a positive therapeutic response is the possible occurrence of serum-neutralizing antibodies against Rituximab, which occurs in a different percentage of treated patients (44, 45). The main side effects of Rituximab therapy are headache, nausea, infections, and infusion reactions (20, 27). The most common side effects of Rituximab in patients with NMOSD are infusion reactions 10-13%, followed by infections mainly of the respiratory and urinary tract, 9% (27, 46, 47).

Inebilizumab

Inebilizumab is a humanized monoclonal antibody that causes depletion of the CD19 subpopulation of B lymphocytes (20). The drug was approved in 2020 in the USA, and in 2022 in Europe as a therapy for seropositive NMOSD (20, 48). It is most likely that inebilizumab achieves its full effect within 6-8 weeks of starting therapy (20). Inebilizumab caused a significant reduction in the relapse rate in NMOSD patients over time, with the most frequent occurrence of relapse occurring only during the first year of follow-up (49). The most common adverse effects of inebilizumab are related to arthralgia and back pain, headache, and infusion reactions (20, 48). There may also be a slightly higher risk of infections, among which, according to the findings of certain studies, urinary infections are the most common, accounting for up to 20% (27). So far, no cases of severe opportunistic infections have been reported, although a case of potential PML has been described, for which, to the best of our knowledge, this diagnosis has not been confirmed with certainty (20, 27, 48).

Eculizumab

Eculizumab is a humanized monoclonal antibody directed against the C5 complement component, blocking the cascade reaction of the complement system in the pathogenesis of NMOSD (10, 20). Eculizumab was approved for the treatment of seropositive NMOSD in 2019 in the USA, while in Europe, it was approved for relapsing forms of seropositive NMOSD (50-52). Eculizumab achieves its effect very quickly after application by strongly blocking the activity of the C5 component of the complement (20, 51). Eculizumab has shown remarkable efficacy over a follow-up period of just over a year, with complete relapse control in patients with NMOSD (20, 53). One of the most common side effects of eculizumab is headache, while back pain, diarrhea, and nausea occur less frequently (27). Notably, eculizumab increases the risk of infections caused by bacteria from the genus Meningococcus and other encapsulated bacteria regardless of prior vaccination. It also heightens the risk of certain fungal infections (20, 27, 52, 54).

Ravulizumab

Ravulizumab is a monoclonal antibody that achieves its effect in treating NMOSD by inhibiting the C5 complement component (20). Ravulizumab also potently and rapidly inhibits the cascade reaction of the complement system (20). Ravulizumab is a very effective drug in preventing the occurrence of relapse in the seropositive form of NMOSD with a complete, 100% cessation of relapse during a one-year follow-up (20, 55). Ravulizumab and eculizumab, both targeting the complement system, have similar molecular structures, as well as comparable therapeutic and safety profiles (20). Adverse effects of Ravulizumab include headache, anemia, leukopenia, as well as a tendency to respiratory infections as well as meningococcal and fungal infections (20).

RECOMMENDATIONS AND MODALITIES OF LONG-TERM THERAPY

Recently published recommendations for pharmacological therapy of NMOSD suggest different treatment modalities for AQP4-IgG seropositive and seronegative NMOSD (20). For the prevention of relapse in the seropositive form of NMOSD, all the above-mentioned drugs can be used, depending on the condition, age, and preferences of the patient, comorbidities, as well as characteristics of the disease itself, such as the frequency and severity of relapse and socioeconomic circumstances (20). Potent monoclonal antibodies are recommended as first-line monotherapy to prevent NMOSD relapses (20). These recommendations suggest that the first line of therapy in seronegative NMOSD should be drugs from the group of conventional immunosuppressive drugs or rituximab monotherapy (20). If there is no therapeutic effect, conventional immunosuppressive drugs should be switched to rituximab (20).

Females with NMOSD in the reproductive period should plan pregnancy in consultation with a neurologist in the phases of remission of the disease. Additionally, the chronic administration of drugs to control the relapse of the disease should not be interrupted or delayed (20, 56). Methotrexate and mycophenolate mofetil are teratogenic and should be avoided in women of reproductive age, as well as during pregnancy and breastfeeding (20, 57).

Azathioprine or monoclonal antibodies could be used in pregnancy, when necessary, with careful consideration of each drug's profile and all clinical characteristics of the individual patient (20, 57). When using these drugs, special monitoring by neurologists, gynecologists/obstetricians, and other members of the medical team is necessary (20, 57).

OTHER TREATMENT MODALITIES

Administration of intravenous immunoglobulins (IVIG), 1g/kg for 4 weeks, showed positive effects in relapse control in NMOSD in children and adults (20). The combination of IVIG with conventional immunosuppressive drugs, such as azathioprine, can have a positive effect on the prevention of relapse in NMOSD (20). Methotrexate may also have a role in relapse prevention therapy, particularly in individuals with autoimmune comorbidities and NMOSD (20, 58, 59). The application of a combination of intermittent apheresis (TIP) with conventional immunosuppressive drugs can be a form of treatment when other options are not available or not applicable (20, 58, 59).

CONCLUSION

The existence of a molecular biomarker and clearly defined diagnostic criteria enables a quick and accurate diagnosis of NMOSD. On the other hand, knowledge regarding the pathophysiological mechanisms underlying different forms of NMOSD enables the design of goal-directed new therapies, which support precision medicine and emphasize the importance of an individual approach. Biological therapy represents an important step in the prevention of relapse in NMOSD via using monoclonal antibodies, which reduce the deleterious effect of this disease on the degree of disability, quality of life, and prognosis of the disease. Further research is necessary in order to find potential therapeutic targets in the seronegative NMOSD, as well as the development of new and safer therapeutic agents and treatment modalities for all forms of NMOSD.

Author Contributions

MA, SM, NV, OT, MB, and JD conceived and wrote the paper, revised it for important intellectual content, and approved the final submission.

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BOLESTI IZ SPEKTRA NEUROMIJELITISA OPTIKA (NMOSD): TERAPIJSKA RAZMATRANJA

Marko Andabaka[1], Šarlota Mesaroš[1,2], Nikola Veselinović[1,2], Olivera Tamaš[1,2], Maja Budimkić[1,2], Jelena Drulović[1,2]

Sažetak

Bolesti iz spektra neuromijelitisa optika (NMOSD) su retka, ali potencijalno teška autoimuna oboljenja centralnog nervnog sistema (CNS) za koja je nedavno odobrena primena nekoliko bioloških terapija. Istorijski gledano, tretmani koji modifikuju NMOSD oslanjali su se na konvencionalne imunosupresive širokog spektra, kao što su azatioprin i mofetil mikofenolat. Od 2015. godine, akumulirani su dokazi koji, s jedne strane, podržavaju biološku terapiju koja nije dokazano-efektivna (rituksimab) u okviru kontrolisane studije, a sa druge su omogućili odobravanje satralizumaba, inebilizumaba, ekulizumaba i ravulizumaba, posle sprovedenih kontrolisanih, randomizovanih klinikih studija kojima je dokazana njihova efikasnost i bezbednost. Ova sledeća generacija lekova pruža nekoliko ciljanih opcija lečenja za NMOSD koje modifikuju bolest. Ovde prvo prikazujemo mehanizam dejstva povezan sa njihovim specifičnim ciljevima. Zatim prikazujemo ključne dokaze koji podržavaju njihovu upotrebu u praksi. Trenutne terapijske opcije u NMOSD obuhvataju tri ciljana mehanizma u različitim fazama jedinstvene kaskade oštećenja tkiva CNS: uništavanje B-ćelija, anti-citokinske i terapije protiv komplementa. Po jedan lek iz svake klase odobren je na tržištu. Trenutni konsenzus predlaže pozicioniranje odobrenih lekova kao tretmana prve linije za novodijagnostikovane pacijente i kao alternativne terapije u slučaju neuspeha prethodnog lečenja.

Ključne reči: bolesti iz spektra neuromijelitisa optika, tretman, lekovi koji menjaju prirodni tok bolesti

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