REVIEW ARTICLE

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Exploring treatment approaches for Neuromyelitis Optica Spectrum Disorders (NMOSD)

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Abstract

Introduction and Objective. Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune demyelinating disease of the central nervous system, distinct from multiple sclerosis. Its pathogenesis is primarily associated with anti-AQP4-IgG antibodies, though some patients present with anti-MOG-IgG. The most common symptoms include optic neuritis and longitudinal extensive transverse myelitis (LETM) often leading to blindness and tetra- or paraparesis. This review summarizes current and emerging treatment strategies for NMOSD, including therapies used in acute attacks, long-term immunosuppression, and targeted biological agents.

Review Methods. The paper is based on a review of current literature and clinical trial data carried out in March 2025 using electronic databases: PubMed, Scopus and Web of Science. It discusses conventional immunosuppressants (e.g., azathioprine, mycophenolate mofetil, rituximab), targeted therapies (satralizumab, eculizumab, inebilizumab), and the latest Polish drug programme (B.138.FM). Differential diagnostics of NMOSD and radiological imaging of patients is shown.

Brief description of the state of knowledge. Biologic therapies show significant effectiveness in relapse prevention, especially in AQP4-IgG-positive patients. Satralizumab and inebilizumab reduce relapse rates and disability progression, with favourable safety profiles. Eculizumab provides rapid and sustained complement inhibition, offering high efficacy. Satralizumab is now reimbursed in Poland for eligible patients.

Summary. Modern, targeted therapies for NMOSD greatly improve patient outcomes and quality of life. Accurate and timely diagnosis, access to appropriate treatment, and individualized therapeutic approaches remain key to reducing long-term disability in NMOSD.

Key words

biologic therapy, neuromyelitis optica spectrum disorder, autoimmune demyelination, AQP4 antibodies, satralizumab, eculizumab, inebilizumab

INTRODUCTION

The term neuromyelitis optica spectrum disorders (NMOSD) refers to a rare, severe neuro- demyelinating disease of autoimmune origin. Known for many years as Devic's disease, it was initially considered a subtype of multiple sclerosis (MS). However, it is now recognized as a separate clinical entity following the discovery of antibodies against aquaporin 4 (AQP4) [1, 2]. The classic clinical presentation of NMOSD includes acute or subacute attacks of optic nerve inflammation and extensive, transverse inflammation of the spinal cord, the latter being a more specific symptom. Less frequently, area postrema syndrome or other brain or brainstem dysfunctions are observed [3]. Frequent relapses are an additional feature of the disease [4].

NMOSD with the presence of AQP4 antibodies predominantly affects women (with a 9:1 female-to-male ratio) and typically manifests around the age of 40. It should be differentiated from myelin oligodendrocyte glycoprotein antibody disease (MOGAD), which has a more even gender distribution and is more common in children [5].

In 2004, a strong association was discovered between the occurrence of NMOSD and the presence of antibodies against aquaporin-4 water channel (AQP4). The identification of AQP4-IgG in serum demonstrates high specificity for NMOSD and confirms the diagnosis. However, in some patients, AQP4-IgG may be negative, which makes the diagnosis difficult but does not exclude it [6]. AQP-4 is a transmembrane water channel present in the terminal sections of CNS astrocytes, essential for maintaining proper water homeostasis in the CNS and the proper functioning of the blood-brain barrier. A small percentage of patients with neurological symptoms suggestive of NMOSD do not have AQP4-IgG, and are referred to as seronegative. In 10–40% of seronegative patients, the presence of IgG autoantibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) has been demonstrated.

The pathogenesis of MOG-IgG-positive patients has not yet been fully defined [7]. Furthermore, patients with anti-MOG antibodies may phenotypically resemble patients with AQP4-IgG, but differ in their response to immunomodulatory therapy, for example [6].

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Antibodies to AQP4 play a central role in the pathogenesis of NMOSD, being detected in more than 80% of patients. The discovery of AQP4-IgG binding has redefined the pathogenesis, classifying what was once a demyelinating disease as an autoimmune astrocytopathy [1, 6].

Current mechanisms include both complement-dependent and complement-independent responses, with an emphasis on the role of B cells and T lymphocytes [7]. In NMOSD, demyelination usually occurs as a result of axonal injury. Histopathologically, activation of microglial cells or macrophages, deposition of immunoglobulins around vessels, numerous eosinophilic infiltrates, and local activation of the complement system are observed [8].

The inflammatory cascades known so far provide the basis for the search for highly effective immunotherapies [6].

OBJECTIVE

The aim of the review to present the latest advancements in treatment, new therapeutic strategies used both globally and in Poland, and to address the challenges encountered in the management of neuromyelitis optica spectrum disorders (NMOSD), previouly known as Devic's disease. The review provides a current and comprehensive review of NMOSD, a rare but clinically significant autoimmune demyelinating disease of the central nervous system. The review is an important contribution to the fields of neurology, neuroimmunology, and clinical medicine by synthesizing the latest data on the diagnosis and treatment of NMOSD, with particular emphasis on the role of AQP4 and MOG antibodies in disease classification and therapeutic decision-making.

By presenting up-to-date clinical trial results on modern biologic therapies (such as satralizumab, eculizumab, and inebilizumab) and placing them in the context of both Polish and international treatment programmes, the review addresses both global and local aspects of NMOSD management. It also highlights diagnostic challenges and the necessity of multidisciplinary care in the clinical course of the disease.

MATERIALS AND METHOD

The review was conducted to summarize and critically assess current and emerging therapeutic strategies for NMOSD. The literature search was carried out in March 2025, using the following electronic databases: PubMed, Scopus, and Web of Science. The search strategy employed combinations of key words such as: 'neuromyelitis optica spectrum disorder', 'NMOSD treatment', 'AQP4-IgG', 'satralizumab', 'inebilizumab', 'eculizumab', 'rituximab', 'azathioprine', 'mycophenolate mofetil', 'plasmapheresis', and 'clinical trials in NMOSD'.

The primary inclusion criteria were:

- peer-reviewed articles published in English;
- publications from January 2020 – March 2025 to ensure coverage of the most recent therapeutic advances;
- randomized controlled trials, meta-analyses, systematic reviews, observational studies, and official drug programne documentation;
- studies focused on the pharmacological treatment of NMOSD, with particular attention to immunosuppressive and biologic therapies.

Selected key publications from earlier years (pre-2020) were also included due to their seminal character, relevance to historical context (e.g. diagnostic criteria), or because they established the scientific basis for therapies currently in use.

Exclusion criteria were:

- non-English publications (unless a reliable translation was available);
- case reports, conference abstracts, or articles with low methodological transparency;
- studies focused solely on differential diagnosis or basic pathophysiology without reference to treatment.

To ensure the quality of included evidence, each study was assessed for design, sample size, follow-up duration, and robustness of outcome measures. High-quality randomized controlled trials, such as SAkuraSky, SAkuraStar, PREVENT, and N-MOmentum, were prioritized. Clinical guidelines and expert consensus documents, including the updated recommendations by the Neuromyelitis Optica Study Group (NEMOS), were also reviewed.

In addition to searching databases, a manual review of leading neurology and neuroimmunology journals (*Journal of Neurology, Multiple Sclerosis and Related Disorders, Journal of Neuroinflammation,* etc.) was performed to identify any relevant publications not identified through database queries.

Limitations of the study. Limitations of the review include potential publication bias, the exclusion of grey literature, and the narrative nature of the synthesis, which may not fully account for quantitative differences between treatment modalities. However, efforts were made to ensure comprehensive and balanced coverage of the most relevant and up-to-date sources. The exact number of articles initially retrieved through the database search and the detailed reasons for the exclusion of specific studies were not reported. However, as this is a narrative review, some flexibility in the selection process is both acceptable and consistent with the scope and objectives of the review.

Clinical presentation. Clinical symptoms of NMOSD primarily affect the nervous system, with optic neuritis and transverse myelitis being the most characteristic manifestations [4].

Optic neuritis (ON) may initially occur unilaterally but, as the disease progresses, can develop in both eyes. It is most often accompanied by pain in the orbit, which intensifies with eye movement, and is typically followed by symptoms of impaired visual acuity. Significant visual impairment often occurs, eventually leading to the loss of mono- or binocular vision [4, 9]. The bilateral simultaneous occurrence of ON is much more frequently noted (approximately 20%) in MOG-positive patients. In about one-third of cases, optic disc oedema is observed, usually mild in nature; this is not common due to the predominance of changes occurring outside the eyeball [10].

Longitudinal transverse myelitis (LETM) is the most specific feature of NMOSD, usually consisting of inflammation involving primarily the central grey matter and extending to at least three adjacent vertebral body segments. This image is detected on MRI. LETM can be located at any level and, depending on the location, can cause various dysfunctions. It often leads to para – or tetraplegia with patients also reporting bladder dysfunction [4]. Cervical

spinal cord inflammation can extend to the brainstem and medulla oblongata, causing intractable vomiting, narcolepsy, and acute respiratory failure [11]. Some cases also describe the co-occurrence of intense itching and painful spasms in the affected limb, which, although short-lived, tend to recur [12].

Studies have shown a more frequent co-occurrence of other autoimmune diseases, such as myasthenia gravis and systemic lupus erythematosus [11].

The disease can have a monophasic or multiphasic course, with the latter being more common – approximately 90%. It is characterized by unpredictable, recurrent attacks of ON, spinal cord inflammation, or both simultaneously – often very debilitating and worsening the prognosis. Repeated relapses lead to a gradual worsening of neurological disability. For this reason, effective prevention of relapses is crucial to reduce the long-term risk of increasing systemic disability [11].

NMOSD diagnostics. The first diagnostic criteria for NMOSD were introduced in 1999, known as the Wingerchuk and Weinshenker criteria, which have since been updated in subsequent editions. The current criteria are those established in 2015 during a meeting of experts at the International Panel for NMO Diagnostics (IPND). These updated criteria led to a significant increase in the diagnostic sensitivity of NMOSD – by as much as 76%, with a 64% improvement noted in the AQP4-IgG-positive group. The diagnostic criteria are based not only on the presence of antibodies but also on clinical symptoms and imaging test results, with MRI having the greatest diagnostic value [5, 6]. Criteria have been developed for both AQP4-IgG-positive and AQP4-IgG-negative NMOSD patients.

The presence of one of the primary clinical features, together with the confirmed presence of AQP4-IgG antibodies, is sufficient to diagnose NMOSD. In cases where AQP4-IgG is absent or its status is unknown, the diagnostic requirements are slightly more stringent [12].

Diagnostic criteria for NMOSD. Diagnosis relies largely on laboratory tests, primarily the detection of antibodies, such as APQ 4-IgG. Among the available tests, the CBA (Cell-based Assay) has the highest sensitivity (approximately 76.7%) and specificity (99.8%) [12].

AQP4-IgG can be detected using various techniques. CBA can be performed on both live and fixed cells, with detection accomplished via immunofluorescence or flow cytometry (FACS). Other laboratory techniques include ELISA tests and tissue-based tests. The tests mentioned above (except tissue-based tests) allow for the detection of one of the two AQP4 isoforms, M1 or M23. Studies comparing the diagnostic value of these tests have shown that live CBAs, which use the M1 isoform, are the most accurate diagnostic method [13, 14].

Due to the higher incidence of false-negative results, tests like ELISA and tissue-based tests are not preferred. Diagnosing MOGAD largely depends on the detection of MOG-IgG, which makes the accuracy of diagnostic tests crucial. Again, the use of live CBA is more accurate (approximately 96%), and in this case, the ELISA test should be completely abandoned.

The timing of the test is also important. Samples should be collected before starting treatment, and the biomaterial of choice is serum [15]. During testing, a promising diagnostic biomarker, glial fibrillary acidic protein (GFAP), was identified [13].

Diagnostics is further supported by imaging tests (with MRI being the most important) and electrophysiological tests, such as visual evoked potentials (VEP) and optical coherence tomography (OCT). The diagnostic criteria and clinical features of NMOSD are shown in Tables 1 and 2 [15].

Table 1. Diagnostic criteria for adult patients in NMOSD

Diagnostic Criteria	NMOSD with AQP4-IgG [12]	NMOSD without AQP4-IgG or unknown AQP4-IgG status [12,15]
Main vlinical features[a]	At least 1 main clinical feature	At least 2 main clinical features
AQP4-IgG Test	Positive AQP4-IgG test (preferred cell-based test)	Negative AQP4-IgG test or test not available
Exclusion of alternative diagnoses	Yes	Yes
Clinical requirement	-	At least 1 main clinical feature must be optic neuritis, acute transverse myelitis (LETM), or area postrema syndrome
Spatial dissemination	-	At least 2 different main clinical features
Addidtional MRI requirements[b]	-	Must meet MRI criteria (if applicable)

AQP4 – aquaporin 4; IgG – immunoglobulin G; LETM – longitudinally extensive transverse myelitis lesions; NMOSD – neuromyelitis optica spectrum disorders; MRI – magnetic resonance imaging. a, b – See Table 2 for main clinical features and additional MRI requirements

Table 2. Main clinical features and MRI requirements in NMOSD diagnosis

Main clinical feature	Additional MRI requirements [12, 15, 16]
Optic neuritis	Acute optic neuritis: Brain MRI – normal findings or non-specific white matter lesions. Optic nerve MRI – T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 of the optic nerve length or involving the optic chiasm
Acute myelitis	Acute myelitis: Intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) History compatible with acute myelitis involving ≥3 contiguous spinal cord segment
Area postrema syndrome	Area postrema syndrome: MRI – associated dorsal medulla/area postrema lesions
Acute brainstem syndrome	Acute brainstem syndrome: MRI – associated periependymal brainstem lesions
Symptomatic narcolepsy or acute diencephalic clinical syndrome (with NMOSD-typical diencephalic MRI lesions)	-
Symptomatic cerebral syndrome (with NMOSD-typical brain lesions)	-

LETM – longitudinally extensive transverse myelitis lesions; NMOSD – neuromyelitis optica spectrum disorders; MRI – magnetic resonance imaging.

Markers differentiating NMOSD from multiple sclerosis. Initially, NMOSD was considered a subvariant of multiple sclerosis (MS), but in recent years, it has been recognized as two distinct diseases that differ in terms of course, immunopathogenesis, treatment and prognosis. Differentiating these two disease entities is crucial for the patient's prognosis, as the treatments differ significantly. An incorrect diagnosis may exacerbate the course of the disease and increase the risk of complications [15]. Although both diseases often present with similar symptoms and clinical features, in NMOSD, visual disturbances, lower limb paresis, and sensory disturbances below the waist are usually more severe.

On MRI, spinal cord damage in NMOSD is typically more extensive and occurs in a relatively short period. In contrast, in MS, extensive spinal cord damage is generally observed only after several years of disease progression. Relapses in NMOSD occur more frequently and are characterized by a more severe course, with a greater risk of irreversible disability.

The most specific markers differentiating these two diseases are pathogenic antibodies that can be detected in patients' blood serum. In Devic's disease (NMOSD), the most commonly detected antibodies are those against the AQP4 protein.

An additional test that helps differentiate these two diseases is the assessment of cerebrospinal fluid (CSF). In MS, oligoclonal bands are frequently detected in CSF samples, whereas in NMOSD, they are relatively rare. Additionally, pleocytosis is detected with similar frequency in both diseases, but in MS, it is almost always <50/μl [16].

Imaging diagnostics. Among imaging studies, MRI currently plays the most important role in the initial differential diagnosis. Certain characteristic features seen on MRI scans can guide the initial empirical immunotherapy for the likely disease entity, even before the antibody test result are available [15]. In a significant number of patients diagnosed with NMOSD, the MRI of the brain may appear normal [17].

In AQP4-positive NMOSD, changes seen on MRI of the brain and spinal cord are usually non-specific. However, characteristic findings are typically observed around the third and fourth ventricles of the brain (area postrema), the corticospinal tract and linear ependymal enhancement. Intramedullary MRI lesion extending over at least 3 contiguous segments (longitudinally extensive transverse myelitis, LETM) is characteristic for acute myelitis (Fig. 1 and 2). MRI is particularly important in differential diagnosis when the result of serological testing for specific antibodies are equivocal, when the test is performed outside the acute phase of the disease, or when access to the test is limited [16].

Differential diagnosis. During the initial diagnostic process, the differentiation and dynamics of clinical symptoms, along with basic laboratory tests, can help guide the identification of the likely disease. In cases of suspected CNS inflammatory myelopathy, the following disease entities should be considered during MRI analysis: MS, MOGAD, NMOSD, anti-GFAP astrocytopathy / anti-GFAP antibody-associated encephalomyelitis, paraneoplastic myelopathies, neurosarcoidosis, Behçet's disease, rheumatic diseases, and paraneoplastic neurological syndromes.

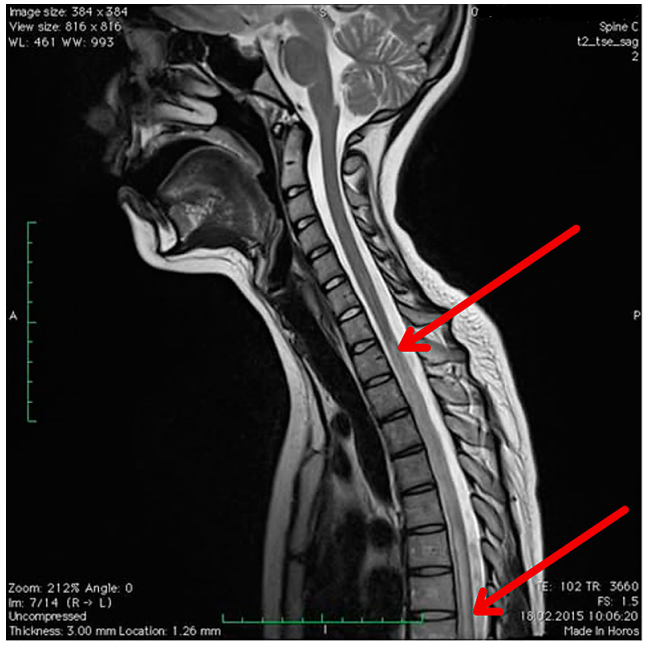

Figure 1. MR of the spinal cord of a female age 15, diagnosed with NMOSD: T2-weighted image, sagital view – the picture of longitudinally extensive transverse myelitis, extending from C6 to Th11 level

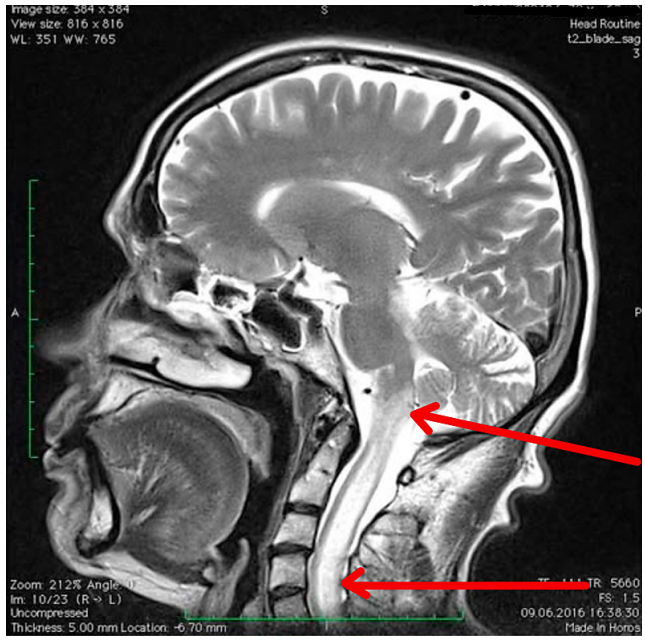

Figure 2a. MR of the brain and the spinal cord of a female age 62, diagnosed with NMOSD: T2-weighted images – hyperintensive inflammatory lesion in the brain (sagital view)

Serological testing for the presence of antibodies offers the highest specificity in the differential diagnosis of these conditions. However, limitations of this test include issues with availability, the waiting time for results, and the potential for false-negative results, especially when performed outside an acute flare. In these cases, MRI of the CNS can be crucial for expediting the initial diagnosis and initiating appropriate treatment [16]. Comparison of seropositive NMOSD, MOGAD and MS is shown in Table 3 [16].

Treatment of NMOSD (Devic's syndrome). Pharmacotherapy in the acute phase of the disease (corticosteroid therapy,

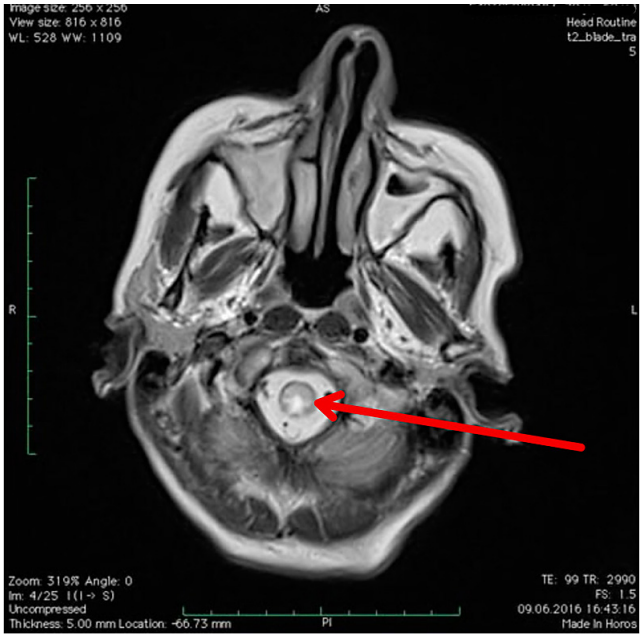

Figure 2b. MR of the brain and the spinal cord of a female age 62, diagnosed with NMOSD: T2-weighted images – hyperintensive inflammatory lesion in the brain (transverse view)

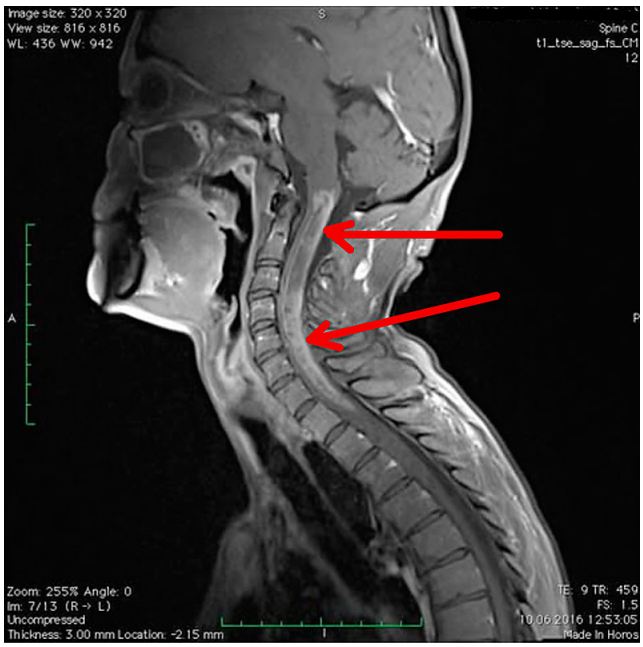

Figure 2c. MR of the brain and the spinal cord of a female age 62, diagnosed with NMOSD: T2-weighted images – the cervical spinal cord extending from the medulla oblongata to the Th1 level

Table 3. Comparison of MOGAD, NMOSD (AQP4-IgG+), and multiple sclerosis (MS)

Feature / Disease	NMOSD (AQP4-IgG+) [5, 12]	MOGAD [5, 12]	Multiple Sclerosis (MS) [5, 12]
Age of onset	Typically, between 30 – 50 years	More frequent in children (<18 years)	Typically, between 20 – 40 years
Gender distribution	Strong female predominance (up to 9:1)	Female predominance (9:1)	Female predominance (2–3:1)
Clinical course	Commonly relapsing	Monophasic or relapsing	Relapsing, secondary progressive, or progressive from onset (adults only)
Antibody status	Presence of AQP4-IgG antibodies (typically high-titre, cell-based assay)	Presence of MOG-IgG antibodies (usually low to moderate titre)	Disease-specific antibodies not detected
CSF oligoclonal bands	<20% of cases; typically, transient	<20% of cases; typically, transient	>85% (persistent)
Optic nerve involvement	Unilateral or bilateral involvement, often posterior	Unilateral or bilateral, frequently with optic disc swelling and involving the optic nerve sheath	Usually unilateral, anterior, short optic nerve lesions that do not involve the optic nerve sheath
Initial visual acuity	Often severely impaired	Often severely impaired	Mild to moderately impaired
Optic disc swelling	Less common and usually less severe	Common; may be associated with haemorrhages	Rare, mild
Spinal cord MRI lesion characteristics	Single longitudinally extensive lesion, which commonly involves entire transverse diameter of the cord and might have bright spotty lesion appearance, conus rarely involved	Single or multiple longitudinally extensive lesions, grey matter involvement leading to the H-sign and conus lesions are characteristics	Often multiple focal cord lesions, posterior and involving only a portion of the cross-sectional area of the cord, conus rarely involved
Neurological presentation	Area postrema symptoms, hiccups, hypersomnolence or focal neurological deficits	Encephalopathy, seizures, focal deficits and cerebral cortical encephalitis can occur	Focal or polyfocal deficits common, encephalopathy or seizures are rare
Brain MRI features	Fluffy or poorly demarcated T2 hyperintensities, often with a leukodystrophy-like pattern; common periependymal involvement near the floor of the fourth ventricle	Multifocal T2 lesions frequently involving deep grey matter, thalamus, internal capsule, and splenium of the corpus callosum	Ovoid, well-demarcated T2 lesions; periventricular, juxtacortical, infratentorial, and spinal cord involvement; Dawson's fingers typically present
Neuropathological findings	Astrocytopathy	Oligodendrocytopathy	Demyelination, astrogliosis

plasmapheresis, intravenous immunoglobulins ([IVIG]). The key goal in treating the disease is the effective control of disease relapses to manage symptoms and reduce the risk of permanent disability. Treatment can be divided into 2 main categories: non-specific immunosuppressive therapy including azathioprine, mycophenolate mofetil, glucocorticosteroids, and therapies targeted at the specificity and pathophysiology of the disease. Reducing the risk of attacks and improving long-term prognosis primarily relies on effective chronic immunotherapy.

During severe disease flares, treatment methods may include intravenous (i.v.) steroids, plasmapheresis, or intravenous immunoglobulin (IVIG). Glucocorticosteroids are the main drugs used in treating acute relapses. The most commonly used regimen is high-dose intravenous methylprednisolone (500–1000 mg) for 5 – 10 days [18]. A meta-analysis evaluating the efficacy of plasmapheresis in NMOSD patients during acute flares showed a temporary reduction in disease activity.

Plasmapheresis is important due to its ability to partially eliminate pathogenic antibodies, complement system components, and proinflammatory cytokines, all of which play a key role in NMOSD pathogenesis. However, in seropositive patients (AQP4+) NMOSD patients, plasmapheresis does not yield the same dramatic results as in seronegative cases. This is likely due to the renewal of CD19+ B cells and the subsequent increase in pathogenic antibody levels over time [18]. The use of intravenous immunoglobulins (IVIG) are not considered first-line treatment for acute disease flares, but may serve as an adjunctive therapy for NMOSD cases refractory to steroids and plasmapheresis. IVIG has shown positive effects when used in combination therapy, shortening the duration and severity of symptoms during disease flares and potentially reducing the risk of neurological disability [19].

Long-term immunosuppressive therapy – azathioprine, mycophenolate mofetil, rituximab).

Azathioprine. A heterocyclic derivative of 6-mercaptopurine, with cytostatic and immunosuppressive effects. It is used in NMOSD due to its proven effectiveness in reducing relapse frequency and improving neurological function [20]. However, its widespread use is limited by the relatively high incidence of adverse effects compared to other drugs approved for the treatment of NMOSD disease.

Mycophenolate mofetil (MMF). Another commonly used immunosuppressive drug in NMOSD. Its mechanism of action involves the selective and reversible inhibition of inosine monophosphate dehydrogenase, which results in a cytostatic effect on cells, including T and B lymphocytes involved in the pathogenesis of NMOSD. MMF is particularly useful when combined with steroids to reduce steroids, making it an optional dose for patients unable to tolerate high-dose glucocorticosteroids (GKS), or those with significant contraindications to long-term steroid therapy [21].

Rituximab (RTX). A monoclonal antibody, genetically engineered to selectively bind to the CD20 antigen on the surface of B lymphocytes, leading to the depletion of these cells.

A meta-analysis evaluating the efficacy and safety of rituximab in NMOSD patients demonstrated that the annualized relapse rate was significantly reduced, regardless of the disease's serological nature (AQP4+ or AQP4-). Approximately 25% of patients reported adverse events during therapy, but only a small percentage (5 out of 681 patients, i.e. 0.7%) discontinued treatment due to severe adverse events [22].

Satralizumab. Satralizumab is a humanized IgG2 monoclonal antibody that binds to both soluble and membrane-bound interleukin-6 (IL-6) receptors, thereby blocking IL-6-dependent signalling. IL-6 is a cytokine involved in inflammatory processes, and elevated levels of this cytokine are observed in NMOSD patients during active disease phases. By inhibiting IL-6 signalling, satralizumab reduces the production of anti-aquaporin-4 (AQP4) autoantibodies and limits blood-brain barrier permeability to inflammatory mediators [23].

The efficacy and safety of satralizumab in NMOSD treatment have been confirmed in 2 randomized Phase 3, double-blind clinical trials: SAkuraSky and SAkuraStar. SAkuraSky evaluated satralizumab as an add-on to standard immunosuppressive therapies, while SAkuraStar assessed its efficacy as monotherapy. Both studies demonstrated a significant reduction in relapse frequency in AQP4-antibody-positive patients.

In SAkuraSky, satralizumab combined with immunosuppressive therapy reduced relapse risk by 62%, compared to placebo. In SAkuraStar, satralizumab monotherapy reduced relapse risk by 55%, compared to placebo, with a more pronounced effect in AQP4-antibody-positive patients. In the open-label extension phases of both trials where patients were treated for up to 4 years, the sustained reduction in relapses and the absence of new safety concerns were observed [23, 24].

Satralizumab is administered via subcutaneous injections every 4 weeks, which aids in patient adherence. Its safety profile is favourable, with the most common adverse events being upper respiratory tract infections, headaches, gastritis, skin rashes, joint pain, and fatigue. Clinical trials found no significant differences in adverse event rates between the satralizumab and placebo groups [25].

In Poland, satralizumab has been refunded for patients since November 2022, providing access to this modern and effective therapy. The eligibility criteria include age over 12 years, an NMOSD diagnosis based on current criteria, the presence of AQP4 antibodies, an EDSS score of 6.5 or lower. Satralizumab can be used as monotherapy or in combination with immunosuppressants, such as prednisolone, azathioprine, or mycophenolate mofetil. It is expected that 86% on monotherapy and 90% of those on combination therapy will not experience a severe relapse within the first 4 years [26].

Eculizumab. Eculizumab is a humanized monoclonal antibody that binds to complement protein C5 preventing its cleavage into C5a and C5b, thereby inhibiting further complement system activation. It is characterized by a rapid onset of action and continuous inhibition of complement protein C5 from the first infusion [1, 27].

The PREVENT study, a phase 3 randomized, double-blind, placebo-controlled, time-to-event trial with an open-label extension (OLE), evaluated the efficacy and safety of eculizumab in monotherapy, as well as its impact during long-term use. A total of 143 adults were randomly assigned (2:1) to receive eculizumab or placebo. The use of stable-dose immunosuppressive therapy (IST) was allowed, although 34 participants remained on monotherapy. Rituximab and mitoxantrone were excluded from IST, but patients who had previously received these medications could participate in the study, provided the last dose was administered at least 3 months prior to the study. The use of intravenous immunoglobulin and plasmapheresis to prevent relapses was prohibited. All patients were vaccinated against Neisseria meningitidis [28].

Eligibility criteria included adults with confirmed AQP4-IgG antibodies in NMOSD and at least 2 relapses within the past 12 months or 3 relapses within 24 months (including one in the last 12 months), and an Expanded Disability Status Scale (EDSS) score of 7 or less. Female participants were required to confirm the absence of pregnancy and use effective contraception for 5 months after conclusion of the study [28].

The primary endpoint of the study was the time to first relapse, assessed by the investigator and confirmed by an objective committee. The study was concluded after 23 confirmed relapses. Following the conclusion, patients participated in the open-label extension (OLE) phase. Initially, patients randomly assigned to the eculizumab group received 4 induction doses of 900 mg weekly, followed by a 1,200 mg maintenance dose every 2 weeks, continuing throughout the OLE. IST was continued at a stable dose during the PREVENT study unless a relapse, in which case the decision was made by the investigator. During the OLE, IST could be changed at the discretion of the investigator. A total of 124 patients completed the study, with 119 patients receiving the maintenance dose of eculizumab in OLE in combination with IST approved by their treating physician [28].

Among the 34 individuals not on IST in the PREVENT study (21 in the eculizumab group, 13 in placebo group), 15 and 12 patients, respectively, joined the OLE phase. In total, 33 patients received monotherapy with eculizumab (15 participated in both PREVENT and OLE, 6 were only in the PREVENT study, and 12 patients from the placebo group in PREVENT, joined the OLE). These patients were observed for a total of 87.3 patient-years (median 2.9 years per patient, range: 23.1–272.1 weeks). The total duration of eculizumab therapy was 85.3 patient-years (median 2.8 years per patient, range: 14.1 – 271.3 weeks). Twelve patients withdrew from the studies (6 from PREVENT and 6 from OLE). Among the 33 monotherapy patients, 1 experienced a confirmed relapse after 380 days in the OLE, coming from the placebo group in PREVENT. A total of 96.2% of these patients had no relapses after 192 weeks of monotherapy. Of those patients who initially received IST, 19.3% discontinued IST, with no confirmed relapses reported in this subgroup over a median of 44.3 weeks of eculizumab therapy [28].

The study also examined EDSS and Hauser Ambulatory Index (HAI) scores. In the PREVENT group not on IST, only 4.8% of patients experienced worsening scores in EDSS and HAI, significantly better than the placebo group, where worsening occurred in 38.5% in the EDSS scale and 30.8% in the HAI scale [28].

By the end of the PREVENT study, the average EDSS and HAI scores improved in the eculizumab group, while they worsened in the placebo group. Improvement was also observed in the modified Rankin scale and the EQ VAS and EQ-5D-3L scales.

No cases of meningococcal infections or deaths were reported in patients receiving monotherapy with eculizumab. The frequency of serious infections was also lower in the eculizumab group (2.3 events/100 patient-years) compared to the placebo group (7.8 events/100 patient-years),, with patients on eculizumab having about 3.4 times lower risk of serious infections. The most commonly reported adverse events were respiratory tract infections, particularly upper respiratory infections, urinary tract infections, nausea, and headaches [28, 29].

The data from the PREVENT and OLE studies demonstrate that monotherapy with eculizumab provides exceptional efficacy in treating AQP4-IgG (+) NMOSD, showing 94% reduction in relapse risk. Its efficacy surpasses not only placebo, but also other monoclonal antibody therapies, such as satralizumab and inebilizumab. Eculizumab therapy when used without IST outside of specific indications, provides long-term efficacy, significantly improving patients' quality of life without worsening their functional status. Furthermore, it has a favourable safety profile with a low incidence of serious infections, making it an ideal therapeutic option for patients at increased risk of adverse events [28, 29].

Inebilizumab. Inebilizumab is a monoclonal anti-CD-19 antibody approved for the treatment of NMOSD in adults with AQP4-IgG serotype of the disease. It is registered in the USA, European Union, China, Japan and South Korea [30, 31].

The N-Momentum study, an international, multicentre, double-blind, randomized, placebo-controlled trial, assessed the impact of inebilizumab on NMOSD activity, particularly through the reduction of CD19+ B lymphocytes in peripheral blood. The study confirmed the efficacy of inebilizumab in NMOSD, evaluating disease activity based on clinical attacks, worsening disability, CNS changes on MRI, and hospitalizations related to NMOSD. A strong, long-lasting therapeutic response was observed within just one week of initiating inebilizumab treatment. Long-term therapy also showed a correlation between the extent of B-cell depletion and a reduction in NMOSD activity.

It is particularly significant that the efficacy of inebilizumab in reducing disease activity was most pronounced in patients who achieved CD20+ B-cell counts of ≤4 cells/μL, compared to those with counts >4 cells/μL over a 6-month period. However, this effect was mainly observed during the first 2.5 years of inebilizumab exposure. After this time, the activity of NMOSD was similar between these subgroups, but still significantly lower than in patients receiving placebo [30].

Beyond its effects on B cell numbers, Inebilizumab has also demonstrated probable efficacy in reducing other biomarkers associated with the severity of NMOSD activity. These biomarkers include neurofilament light chains (sNfL), C-terminal ubiquitin hydrolase L1 (sUCHL1), tau protein (sTau) and glial fibrillary acidic protein (sGFAP). These biomarkers increase in the week preceding, during, and the week following an attack. Notably, sNfL is a strong predictor of CNS damage and disability worsening, while sGFAP is the most accurate predictor of future attacks. Reducing the concentrations of these biomarkers during inebilizumab treatment may therefore help reduce disease severity and improve disability outcomes, compared to placebo [31].

Inebilizumab treatment significantly reduces the number of CD20+ B cells, CD27+ memory B cells, naive B cells, and plasma cells and their precursors (PBs/PCs), indicating its effectiveness in eliminating B cells that contribute to disease development and relapse. The drug also reduces the frequency of NMOSD attacks, regardless of AQP4-IgG levels, suggesting that its mechanism of action extends beyond the effect on biomarkers alone. Additionally, inebilizumab offers advantages over such therapies as rituximab, which do not eliminate all CD19+ PB cells. This makes inebilizumab more effective in controlling the activity of cells involved in the pathogenesis of NMOSD [32].

In summarizing the key results from the N-momentum study, it should be noted that 47 (21%) of the 225 participants receiving inebilizumab experienced an attack. A correlation was observed between the duration of inebilizumab therapy and a reduction in the number of relapses; 40 (63%) of the 63 attacks occurred in 34 (15%) of the 225 participants in the first year, with progressively fewer attacks as treatment continued. The unadjusted annualized relapse rates were lower in the inebilizumab group compared to placebo (inebilizumab: 0.26 [95% CI 0.14–0.48]; placebo: 1.03 [0.65–1.54]). In terms of long-term tolerability, inebilizumab showed good safety, with the most common adverse events reported being urinary tract infection (26%), nasopharyngitis (21%), arthralgia (17%), upper respiratory tract infections (16%), headaches (15%), back pain (14%), and infusion-related reactions (13%) [30, 33].

Molecularly targeted treatment. Molecularly targeted therapies represent modern approaches that specifically target molecular mechanisms involved in the pathophysiology of spinal cord and optic nerve inflammation. This class of drugs includes interleukin-6 (IL-6) inhibitors, B-cell-targeting agents, FcRn inhibitors, antihistamines, and agents that bind to vascular endothelial growth factor (VEGF). One example of an IL-6 inhibitor is tocilizumab, a monoclonal antibody that blocks IL-6 signalling. Tocilizumab has shown efficacy in reducing the risk of a subsequent NMOSD relapses compared to such traditional treatments as azathioprine, which is commonly used as a first-line therapy for preventing relapses in NMOSD. Studies have indicated that tocilizumab may offer a promising, safe and effective alternative for preventing relapses in patients with NMOSD, providing an important treatment option in managing the disease [34].

Symptomatic and supportive treatment – neurological rehabilitation, pain and spasticity treatment. Symptomatic treatment aims to alleviate or eliminate disease symptoms rather than directly address its underlying cause. In individuals with NMOSD, improving muscle strength is essential. Strengthening exercises for both the upper and lower limbs are recommended to help achieve this goal. Physiotherapy also focuses on restoring balance and coordination, reducing spasticity, and enhancing walking ability.

Rehabilitation techniques, such as laser therapy and electrotherapy, are often employed to alleviate pain and spasticity. Neuropathic itching, which affects 27–64% of patients with NMOSD according to various studies, may also be a significant concern [35, 36]. For managing this symptom, symptomatic treatments can include antiepileptic drugs, antidepressants, opioids, and topical therapies, e.g. capsaicin and lidocaine [7].

Problems and challenges in the treatment of NMOSD. Challenges in the treatment of NMOSD often begin at the diagnostic stage. Confirming the diagnosis can be time-consuming and delays initiation of the appropriate treatment. Additionally, biological treatments, which are commonly used in managing NMOSD, can be expensive, making them inaccessible to some patients due to financial constraints.

Moreover, treatment for NMOSD may carry the risk of side-effects, which need to be carefully monitored. Patients often require specialized rehabilitation to manage the neurological impairments associated with the disease. These challenges highlight the importance of regular psychological monitoring in NMOSD patients, along with the need for preventive measures, early diagnosis and intervention. Such approaches are essential to improve medical outcomes but also to address the psychosocial aspects of living with the disease [37].

Efficacy and safety of available drug programmes. In Poland, the B.138. FM drug programme includes treatment with satralizumab, a humanised monoclonal antibody that targets both membrane-bound and soluble receptors (IL-6R). By inhibiting IL-6 signalling pathways, satralizumab can reduce AQP4-IgG production and modulate T cell activation, both of which are implicated in NMOSD. In the SAkuraSky and SAkuraStar studies, satralizumab – either as monotherapy or in combination with baseline IST – demonstrated a significant reduction in the risk of relapse in AQP4-IgG-seropositive NMOSD patients, compared to placebo. Moreover, satralizumab showed a favourable safety profile during the double-blind phases of both studies [39]. Research involving NMOSD patients has confirmed that satralizumab is safe for use in monotherapy, as well as in combination with other immunosuppressive treatments. Adverse events observed were comparable between patients receiving satralizumab and those on placebo. The most commonly reported adverse reactions included headache (19.2%), arthralgia (13.5%), decreased white blood cell count (13.5%), hyperlipidaemia (13.5%) and injection-related reactions (12.5%) [8].

Availability of drug programmes. The drug programme (B.138.FM) available in Poland is dedicated to seropositive NMOSD individuals [1]. The programme covers satralizumab treatment for individuals who meet criteria:
- age: patients must be over 12 years old:
- diagnosis: a confirmed diagnosis of NMOSD, based on current diagnostic criteria;
- presence of anti-AQP4 antibodies;
- EDSS score between 0 and 6.5;
- no contraindications for satralizumab as specified in the Summary of Product Characteristics (SPC);
- no prior IL-6 inhibitor treatment – patients should not have been treated with other drugs from interleukin 6 inhibitors group;
- contraception for women: women of reproductive age must use contraception during treatment. Once a patient is enrolled in the programme, the treatment must be monitored annually. If the therapy is considered effective, it can be extended after 12 months [25].

CONCLUSIONS

Satralizumab represents a significant advance in the treatment of NMOSD, demonstrating high efficacy in reducing relapse rates and improving patients' quality of life. As a humanized IgG2 monoclonal antibody targeting the interleukin-6 receptor (IL-6R), satralizumab effectively inhibits the inflammatory cascade that plays a critical role in the pathogenesis of NMOSD. By addressing the underlying mechanisms of the disease, satralizumab helps control its activity and reduce its clinical manifestations. Clinical trials, including SAkuraSky and SAkuraStar, have

consistently shown that satralizumab significantly reduces the risk of disease relapses, whether used as monotherapy or in combination with immunosuppressive agents. Its effectiveness is particularly pronounced in AQP4–IgG – positive patients, demonstrating a high level of specificity for this subgroup of NMOSD patients.

From the safety perspective, satralizumab has a favourable profile, with the most commonly reported adverse events being mild to moderate in nature, such as injection site reactions, headaches, and upper respiratory tract infections. Its low immunogenicity potential and subcutaneous administration make it a convenient and well-tolerated treatment option for patients.

When compared to other biologic therapies, such as eculizumab or inebilizumab, satralizumab stands out due to its at-home administration, less frequent dosing schedule, and well-balanced efficacy-safety profile. Its introduction marks an important step toward personalized treatment in NMOSD, enabling therapy to be tailored to the unique needs of each patient. Based on the available data, satralizumab can be considered a highly effective and safe therapeutic option, significantly reducing the disease burden, improving prognosis, and enhancing the quality of life for NMOSD patients. Long-term studies are needed to further define its role in the future treatment landscape for this rare but severe disorder.

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