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Review

Advances in the treatment of neuromyelitis optic spectrum disorder

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***Abstract*:** Neuromyelitis optic spectrum disorder (NMOSD) is a rare autoimmune disease characterized by recurrent episodes and severe debilitation. It primarily involves the central nervous system and is associated with the presence of aquaporin-4 antibodies. Effective management of NMOSD necessitates long-term therapeutic strategies that focus on alleviating symptoms during acute episodes and preventing relapse. In recent years, the approval of emerging biologics targeting B cells, interleukin-6 receptors, and the complement pathway has marked a transformative development in NMOSD treatment. This article provides a comprehensive review of therapeutic advances in NMOSD, integrating the current literature to serve as a theoretical basis for clinical decision-making of NMOSD patients.

Keywords: AQP4-IgG, biotherapy, immunosuppressant, neuromyelitis optic spectrum disease

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Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disease that primarily affects the central nervous system (CNS), particularly targeting the optic nerve and spinal cord, which often results in vision loss and paralysis.[1] This disease, characterized by its severity and high recurrence rate, requires a thorough diagnostic approach involving clinical assessment, imaging, and antibody testing. NMOSD can occur at any age but is most common between 35 and 42 years,[2,3] with a significantly higher prevalence among females. Its incidence varies across ethnic groups, with reported rates ranging from 1 per 100,000 in Caucasians to 10 per 100,000 in African Americans.[4] Such differences in prevalence are due to genetic predisposition, environmental influences, and regional variations in diagnostic practices.

In 2004, the discovery of pathogenic aquaporin-4 antibodies (AQP4-immunoglobulin G (IgG)) constituted a major breakthrough in NMOSD. Studies indicate that over 80% of NMOSD cases test positive for AQP4-IgG.[5] In 2015, the International Panel for NMO Diagnosis revised the diagnostic criteria for NMOSD, emphasizing changes in AQP4-IgG serostatus.[6] Advances in detection methods, particularly the Cell-Based Assay, recognized for its superior specificity and sensitivity, have greatly improved diagnostic rate.[7] Importantly, earlier data on AQP4-IgG-seronegative NMOSD often included patients with myelin oligodendrocyte glycoprotein-IgG. Therefore, the incidence and prevalence of double-negative NMOSD (DN NMOSD) remain underexplored, with approximately 15%–27.9% of patients categorized as double-negative.[8–11] Currently, there is no cure for NMOSD, and treatment primarily aims to manage symptoms during acute episodes and prevent relapses during remission.[12] Therapeutic agents such as eculizumab, inebilizumab, satralizumab, and ravulizumab, approved between 2019 and 2024, are used to treat AQP4-IgG-seropositive NMOSD. Additionally, rituximab (RTX) and other traditional immunosuppressive therapies (ISTs) are also employed, although they are not formally approved for NMOSD treatment.[13]

This article provides a detailed review of the pathogenesis, therapeutic advances in NMOSD. The aim is to contribute to the optimization of medication use and the development of effective treatment strategies.

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Pathogenesis

The identification of AQP4-IgG has solidified that NMOSD is primarily driven by humoral immunity.[14] AQP4-IgG primarily exerts its pathogenic effects by selectively targeting AQP4 in the CNS.[15] In patients with NMOSD, peripheral AQP4-IgG levels are significantly higher than those within the CNS. Although the exact origin of AQP4-IgG remains unclear, it is thought to involve immune tolerance defects and molecular mimicry.[16,17] Pathogenic AQP4-IgG, derived from plasma cells in peripheral tissues, breaches the weakened BBB to bind to AQP4 on astrocyte surfaces. AQP4 exists in two forms, M1 and M23, and AQP4-IgG binding to either form induces antibody-dependent cell-mediated cytotoxicity, leading to astrocyte destruction through the release of cytotoxic substances.[18] Furthermore, AQP4-IgG binding triggers the activation of the classical complement pathway, resulting in C5 protein cleavage and the formation of the membrane attack complex, which inflicts additional damage on astrocytes. This cascade, involving complement activation and inflammatory cell recruitment, releases inflammatory mediators such as cytokines and oxygen-free radicals, causing demyelination and glial cell damage. AQP4-IgG also reduces EAAT2 expression on astrocyte surfaces, which lead to increased extracellular glutamate levels and heightens glutaminergic toxicity, further damaging neurons and glial cells.[19,20] Interleukin-6 (IL-6) promotes glial cell damage by stimulating B cells to differentiate into plasma cells, which produce pathogenic AQP4-IgG. This activity enhances BBB permeability and supports the differentiation and activation of pro-inflammatory T lymphocytes.[21] We illustrate the biological treatment targets for NMOSD in Figure 1 (by Figdraw).

Treatment

Symptom management of acute episodes

Therapies for acute NMOSD are mainly based on approaches used in managing multiple sclerosis (MS). Intravenous methylprednisolone (IVMP) is often the first-line treatment, with a complete remission rate ranging from 17% to 72%.[22–24] However, some patients do not respond to IVMP. In such cases, apheresis therapies, including plasma exchange (PE) and immunoadsorption (IA), are often employed as second-line treatments.[25] Despite the fact that their efficacy has not been proven by randomized controlled trials (RCTs). The choice of apheresis therapy is guided by existing evidence, clinicians' expertise, availability, and cost considerations. The optimal timing for initiating PE or IA remains uncertain, but the interval between attack onset and therapy initiation is critical. While therapeutic responses may occur up to 3 months following a relapse, data indicate that the proportion of patients in complete remission decreased stepwise with the later initiation of apheresis therapy. Early intervention, particularly within the first 2 days, is critical to achieving optimal recovery.[26] Intravenous immunoglobulin (IVIG) is another second-line therapies for NMOSD attacks, although it is less frequently used than apheresis. The efficacy of IVIG as salvage therapy following IVMP has been debated, with mixed results from small-sample studies.[27,28] We summarized the existing evidence on second-line therapies for acute NMOSD (Table 1). Additionally, we compiled information on ongoing clinical trials of new therapies for acute NMOSD and optic neuritis, registered up to November 2024 (https://clinicaltrials.gov/; Table 2).

Preventative therapy: monoclonal antibodies

B cell depletion: inebilizumab. Inebilizumab, approved by the FDA in June 2020 for NMOSD, is a humanized anti-CD19 monoclonal antibody.[29] CD19 is expressed on a broad range of cells, including pre-B cells, plasmablasts, plasma cells, and other B cell subtypes. This broad target range enables inebilizumab to more effective B cells depletion.[30] The N-MOmentum study evaluated the efficacy and safety of inebilizumab in NMOSD.[31] This trail included 230 NMOSD patients aged 18 years or older, of whom 213 were positive for serum AQP4-IgG. Participants were randomized in 3:1 to either inebilizumab or placebo. Ultimately, it represents a 73% reduction in relapse risk for inebilizumab-treated patients compared to those receiving placebo (11% vs 42%). A post hoc analysis also indicated the long-term efficacy of inebilizumab.[32]

Safety analyses from the N-MOmentum trial and its open-label extension (OLE) demonstrated that inebilizumab was well tolerated by adult NMOSD patients.[31,33] No treatment-related deaths occurred during the study. While B cell depletion therapies have been associated with an increased risk of cancer and progressive multifocal leukoencephalopathy

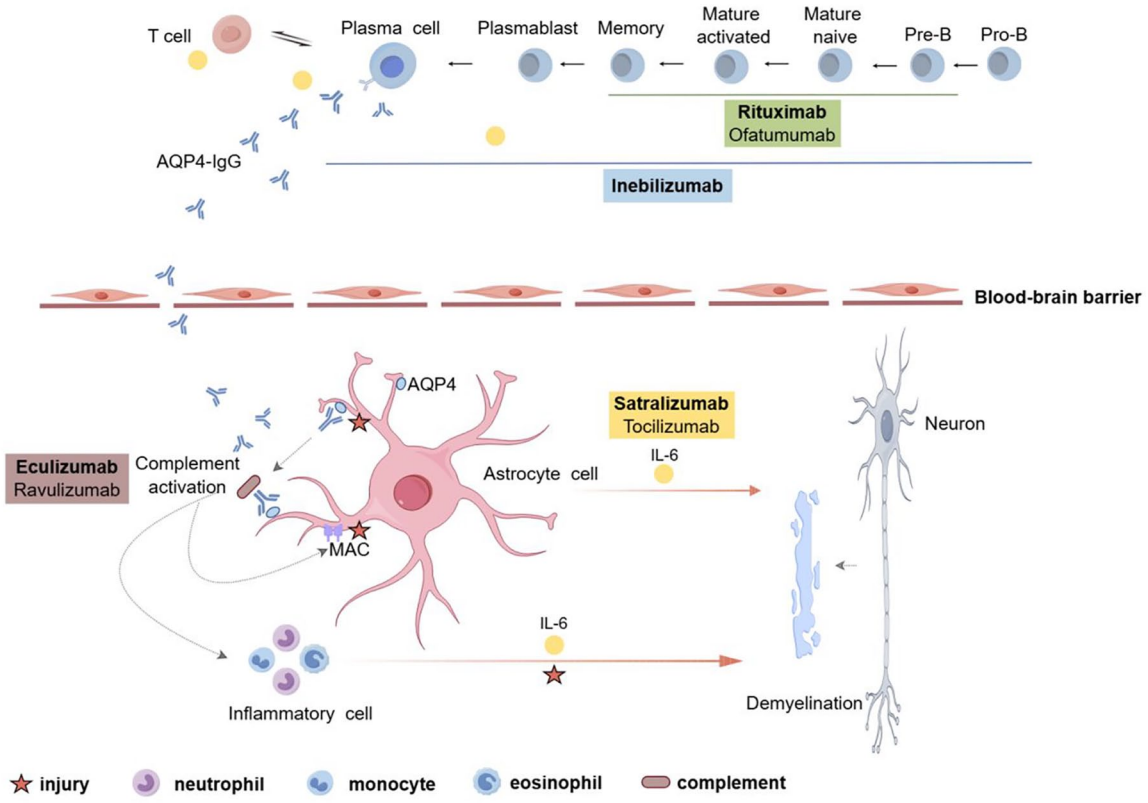

Figure 1. The biological treatment targets in NMOSD. Triggering factors activate peripheral immunity, leading to the production of pathogenic AQP4-IgG, and the recruitment of inflammatory cells and cytokines. These elements cross the impaired blood–brain barrier, entering the central nervous system to target neurons and astrocytes. The resulting neuroinflammation and demyelination drive disease pathology. Various biologics, acting through distinct mechanisms, are highlighted at their respective targets.
AQP4, aquaporin-4; IgG, immunoglobulin G; IL-6, interleukin-6; MAC, membrane attack complex; NMOSD, neuromyelitis optica spectrum disorders.

(PML), no cases of cancer or confirmed PML have been reported in patients treated with inebilizumab to date. Further real-world data are essential to better assess and confirm the long-term safety profile of inebilizumab.

B cell depletion: RTX. RTX is a chimeric monoclonal antibody targeting CD20 positive B-cells, initially developed for B-cell lymphomas.[34] RTX has been approved for NMOSD in Japan but used off-label elsewhere. Several retrospective studies demonstrated its effectiveness in reducing relapse risk in NMOSD.[35,36] The RIN-1 study, conducted in Japan between 2014 and 2017, was a trial to evaluate the efficacy and safety of RTX in NMOSD.[37] Thirty-eight AQP4-IgG-seropositive NMOSD patients aged 16–80 years were randomly assigned in 1:1 to the RTX group or placebo group. Results revealed that at the primary endpoint, no patients in the RTX group relapsed, while 37% (7/19) in the placebo group did. Adverse events include infusion reactions, nasopharyngitis, headaches, and so on, with most being mild to moderate. Besides, the response of patients to RTX can vary due to factors such as the production of antidrug antibodies and polymorphisms in the *FCGR3A* gene encoding the Fc receptor. Consequently, there is no standard RTX dosage or timing regimen for NMOSD. The manufacturer recommends dosing every 6 months or adjusting based on monthly CD19/20 B cell counts.[38]

Complement inhibitor: eculizumab. Eculizumab is the first biologic approved for AQP4-IgG-seropositive NMOSD. It inhibits the cleavage of complement protein C5 into pro-inflammatory components C5a and C5b.[39] The PREVENT study investigated the efficacy and safety of eculizumab in NMOSD.[40] Between 2014 and 2017, 143 adult

Table 1. Summary of published studies on second-line therapies for acute NMOSD.

PMID	Author	Country	Therapies	Median time, d	Patients (*N*)	Evaluation index
38850074	Siwach et al.	India	PE; IVIG	PE: 2; IVIG: 5	43	EDSS; ADL; levels of AQP4-IgG
33523317	Lin et al.	China	IVIG	NA	59	ΔEDSS
32653803	Li et al.	China	IVIG	9 (IVIG alone) 14 (IVIG + IVMP)	191	EDSS
38790106	Xu et al.	China	PE/IA	17.5	90	EDSS; VA
29030418	Bonnan et al.	France	PE	7	60	EDSS; VA
25921047	Abboud et al.	America	PE	NA	83	EDSS
27366234	Faissner et al.	Germany	IA	NA	10	VEPs; VA
33992860	Li et al.	China	PE; IVIG	NA	61	3M-SI
30825049	Song et al.	China	PE	NA	31	VF
30345331	Kleiter et al.	Germany	PE; IA	PE: 1; IA: 1.5 (First line) PE: 13; IA: 6 (second line)	105	Complete remission
36993936	Zhang et al.	China	PE	NA	76	EDSS; VOS
34034213	Figueroa et al.	Mexico	PE	20.9	89	EDSS
33948520	Restrepo-Aristizábal et al.	Colombia	PE	7	78	EDSS
29414283	Srisupa-Olan et al.	Thailand	PE	13; 12	52	EDSS; mRS
28427710	Aungsumart et al.	Thailand	PE	11	24	EDSS
38280268	de Almeida et al.	Brazil	PE	25	68	Improvement scale
35353437	Gonzalez et al.	Colombia	PE	7	83	VOS

3M-SI, significant improvement evaluated 3 months after acute attack treatment; ΔEDSS, EDSS (treated) – EDSS (attacked); ADL, activities of daily living; AQP4-IgG, aquaporin-4 antibodies; EDSS, expanded disability status scale; IA, immunoadsorption; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; mRS, modified Rankin Scale; NA, not applicable; NMOSD, neuromyelitis optica spectrum disorders; PE, plasma exchanges; VA, visual acuity; VEP, visual-evoked potentials; VF, visual function; VOS, visual outcome scale.

AQP4-IgG-seropositive NMOSD patients were randomized in 2:1 to receive either eculizumab or placebo. The study was terminated early due to the pronounced efficacy of eculizumab. At week 91, eculizumab reduced the risk of relapse by 94% compared to placebo. The OLE study showed that 94.4% of patients with eculizumab remained relapse-free.[41] Eculizumab was well tolerated, with headache and upper respiratory tract infections as the most common side effects. No meningococcal infection was reported, as all participants received vaccinated against meningococcal disease prior to initiating eculizumab. Recently, Ringelstein et al.[42] has again highlighted the ongoing safety concerns of eculizumab treatment. They reported that 7 of 52 eculizumab-treated patients, experienced postvaccination attacks prior to start of eculizumab. One patient died of meningococcal sepsis despite vaccination. This highlights that vaccination may not fully mitigate the risk of infections, and there is also a risk of postvaccination relapses. Therefore, it is important to increase infection surveillance during treatment and to remain vigilant for the risk of relapse following vaccination. Additional testing of

Table 2. Summary of studies on new therapies for acute NMOSD.

Diagnosis	Therapies	Country	ID	Status
NMOSD	Inebilizumab	China	NCT05891379	Uncompleted
NMOSD	Efgartigimod	China	NCT06497374	Uncompleted
NMOSD	Efgartigimod	China	NCT06118398	Uncompleted
ON	Efgartigimod	America	NCT06453694	Uncompleted
NMOSD	Eculizumab	China	NCT06673394	Uncompleted
ON	OCS-05	France	NCT04762017	Uncompleted
NMOSD	Bevacizumab	America	NCT01777412	Completed
NMOSD	Ublituximab	America	NCT02276963	Completed
NMOSD	HBM9161	China	NCT04227470	Completed

NMOSD, neuromyelitis optica spectrum disorders; ON, optic neuritis.

vaccine response, such as the Serum Bactericidal Assay, may be also helpful in minimizing the risk of meningococcal infection in selected patients.[43]

Complement inhibitor: ravulizumab. Ravulizumab, a long-acting complement C5 inhibitor, has been approved for AQP4-IgG-seropositive NMOSD by the FDA. Using recycling antibody technology, ravulizumab extends its half-life, allowing for an 8-week maintenance dosing schedule compared to eculizumab.[44] The CHAMPION-NMOSD study evaluated the efficacy and safety of ravulizumab in NMOSD.[45] The study enrolled 58 patients who received weight-based doses of ravulizumab. At the primary endpoint, no participants experienced relapse, representing a 98.6% reduction in relapse risk compared to the placebo group. Safety analysis indicated that adverse events associated with ravulizumab were comparable to those observed with eculizumab. No deaths occurred and most adverse events were mild to moderate. Despite being vaccinated against meningococcal disease at least 2 weeks before the trial, two participants contracted meningococcal infections during the study. This suggests a potential high risk of infection despite vaccination. Future studies, evaluating the effectiveness of meningococcal vaccines given during or after immunotherapy, are needed to minimize this risk.[43] In addition, given the lower dosing frequency, ravulizumab may become the preferred choice over eculizumab if future studies support its long-term efficacy and safety.

IL-6R inhibitor: satralizumab. Satralizumab, a humanized IgG2 monoclonal antibody, inhibits the IL-6 inflammatory pathway by targeting membrane-bound and soluble IL-6R.[46] Two key phase III RCTs, SAkura-Sky and SAkura-Star, evaluated the efficacy and safety of satralizumab.[47,48] The SAkura-Sky trail included 83 NMOSD patients aged 12–74, randomly assigned in 1:1 to the satralizumab or placebo group. At the primary endpoint, satralizumab demonstrated a 79% reduction in relapse risk compared to placebo (11% vs 43%). The SAkura-Star trail enrolled 95 NMOSD patients aged 18–74. Participants were randomly assigned in 2:1 to receive satralizumab or placebo. At the primary endpoint, 22% (9/41) in the satralizumab group relapsed, compared to 57% (13/23) in the placebo group. A recent Japanese study involving 131 NMOSD patients treated with satralizumab for an average of 197 days reported that 95.4% of participants remained relapse-free.[49] Long-term efficacy data from the OLE phases of these trials have been published.[50] A total of 111 AQP4-IgG-seropositive NMOSD patients received extended satralizumab treatment, including 49 from SAkura-Sky and 62 from SAkura-Star. During follow-up, 24% (12 patients) in SAkura-Sky and 27% (17 patients) in SAkura-Star experienced relapses. Additionally, 90% participants in SAkura-Sky and 86% in SAkura-Star maintained stable Expanded Disability Status Scale scores. No serious adverse events or deaths were reported, with the most frequent adverse events being urinary

and upper respiratory tract infections. Long-term safety data confirm that satralizumab is well tolerated in NMOSD.

IL-6R inhibitor: tocilizumab. Tocilizumab, a humanized monoclonal antibody targeting IL-6R, is commonly used for rheumatoid arthritis and has shown efficacy in treating refractory NMOSD.[51,52] The TANGO study provides evidence supporting tocilizumab's efficacy and safety in NMOSD.[53] The study enrolled 118 adult NMOSD patients, randomly assigned in 1:1 to tocilizumab or azathioprine (AZA). At the primary endpoint, the tocilizumab group showed a 76% reduction in relapse risk compared to AZA group (14% vs 47%). Adverse events were similar in both groups and were generally mild. Although both satralizumab and tocilizumab are IL-6R inhibitors, satralizumab has a longer half-life due to pH-dependent antibody recycling technology.

Preventative therapy: oral immunosuppressants

Oral immunosuppressants such as mycophenolate mofetil (MMF), AZA, and tacrolimus are used off-label for NMOSD, particularly in regions with limited economic resources or unavailable biologics. Retrospective data showed that ISTs reduce the relapse risk in NMOSD, with MMF demonstrating greater efficacy compared to other oral drugs.[36,54,55] However, tolerability and safety concerns main key factors limiting the frequency of oral immunosuppressants.

Comparison of therapies in NMOSD

Currently, no head-to-head RCTs directly compare the efficacy and safety of biologics for NMOSD, particularly among those with similar mechanisms of action. Nevertheless, indirect comparisons and network meta-analyses provide useful insights. A network meta-analysis found that inebilizumab and satralizumab were less effective than eculizumab in reducing relapse risk.[56] A model-based meta-analysis compared the long-term efficacy of five monoclonal antibodies (eculizumab, inebilizumab, satralizumab, RTX, and tocilizumab) with two ISTs (AZA and MMF). The findings showed that monoclonal antibodies, particularly eculizumab, were more effective than ISTs in delaying recurrence.[57] While literature-based comparative studies lack the robustness of direct RCT evidence, they remain valuable in guiding clinicians to tailor treatment plans based on individual needs. Table 3 summarizes RCTs conducted on six biologics for NMOSD.

Drug selection, conversion, and discontinuation in AQP4-IgG-seropositive NMOSD

In 2023, the Neuromyelitis Optica Study Group updated management guidelines for NMOSD.[13] Biologics are recommended as the first choice for AQP4-IgG-positive NMOSD patients, preferred over ISTs. Patients may start eculizumab, inebilizumab, ravulizumab, or satralizumab at diagnosis, after the first attack, or following failure of prior treatments. Satralizumab is the preferred option for adolescents aged 12 and older.[58] Current evidence does not indicate any benefit of combination therapies over biologic monotherapy for NMOSD. The dosage of ISTs should be tapered gradually based on the response to biologics, although standardized protocols for tapering remain unavailable. A study demonstrated that reducing steroids from 11.7 to 4.6 mg/day is feasible for patients receiving satralizumab combination therapies.[49] While this finding highlights the potential for minimizing steroid exposure in NMOSD patients treated with biologics, it is important to note that steroid tapering must be individualized and guided by careful monitoring of disease activity and treatment response.

Drug conversion is a common challenge in NMOSD, particularly for patients who respond poorly to previous maintenance therapy. For those with treatment failures, new biologics with distinct mechanisms of action can be started immediately after discontinuing prior therapies. However, patients who remain relapse-free and tolerate off-label medications such as AZA, MMF, RTX, or tocilizumab, may not require a transition to new therapies.[13,58]

An additional critical issue is determining whether and when to discontinue maintenance therapy. Unlike MS, disease activity in NMOSD does not decline with age, 25% of patients over the age of 50 continue to exhibit disease activity.[59] Several studies emphasize that even during prolonged periods of inactivity, discontinuing ISTs carries a substantial risk of relapse or antibody reactivation.[60] Based on current evidence, discontinuing

Table 3. Summary of RCTs on six biologics in NMOSD.

Drug	Inebilizumab	Rituximab	Eculizumab	Ravulizumab	Satralizumab	Tocilizumab
Target	CD19	CD20	C5	C5	IL-6R	IL-6R
Study name	N-MOmentum	RIN-1	PREVENT	CHAMPION-NMOSD	SAkuraSky; SAkuraStar	TANGO
Number of patients (treatment:control)	230 (174:56)	38 (19:19)	143 (94:47)	105 (58:47)	83 (41:42); 95 (63:32)	118 (59:59)
Patient age (y)	⩾18	18–80	⩾18	⩾18	12–74; 18–74	⩾18
AQP4-IgG-seropositive (*n*)	213	38	143	105	55; 64	115
AQP4-IgG-seronegative (*n*)	17	0	0	0	28; 31	3
Primary outcome	Time to first relapse	Time to first relapse	Time to first relapse	Time to first relapse	Time to first relapse	Time to first relapse
Double-blind period in RCT	28 weeks	72 weeks	103 weeks	52 weeks	48 weeks; 1.5 y after random assignment of the last patient enrolled	60 weeks
Control arm	Placebo	Placebo + prednisolone	Placebo ± IST	Placebo ± IST	Placebo ± IST; Placebo	Azathioprine
Concomitant IST	No	Low-dose steroid allowed	Allowed	Allowed	Allowed; no	Allowed
Application	IV; Initially 300 mg at day 1 and day 14, followed by 300 mg every 6 months	IV; 375 mg/m² weekly for 4 weeks, then at 6-month intervals (1000 mg every 2 weeks)	IV; 900 mg weekly for the first four doses, followed by 1200 mg every 2 weeks	IV; Weight-based, loading dose of 2400–3000 mg at day 1, then maintenance doses of 3000–3600 mg at day 15 and once every 8 weeks thereafter	SC; 120 mg 0, 2, 4, and every 4 weeks thereafter	IV; 8 mg/kg every 4 weeks
Common side effects	Arthralgias, back pain	Nausea, exanthema, headache	Headaches, upper respiratory tract infections	Headaches, upper respiratory tract infections	Injection-related reactions, headache, arthralgia	Injection-related reactions, headache
Risk of infections	Upper respiratory tract and urinary tract infections, opportunistic infections (including PML)	Upper respiratory tract and urinary tract infections, hepatitis B reactivation, opportunistic infections (including PML), no PML in NMOSD reported so far	Meningococcal infection and infections with other encapsulated bacteria	Meningococcal infection and infections with other encapsulated bacteria	Mild to moderate infections, no opportunistic infections so far reported	Upper respiratory tract and urinary tract infections
Suggested monitoring	Differential WBCC, serum immunoglobulins, CD19/20-positive B-cells count	Differential WBCC, serum immunoglobulins, CD19/20-positive B-cell count	BCC and differential WBCC; Meningococcal infection (exclusion before each infusion)	BCC and differential WBCC; Meningococcal infection (exclusion before each infusion)	BCC and differential WBCC, liver enzymes, lipids	BCC and differential WBCC, liver enzymes, lipids

AQP4, aquaporin-4; BCC, blood cell count; IL6-R, interleukin-6 receptor; IST, immunosuppressive therapy; IV, intravenous; NMOSD, neuromyelitis optica spectrum disorders; PML, progressive multifocal leukoencephalopathy; RCT, randomized controlled trial; SC, subcutaneous; WBCC, white blood cell count.

therapy is generally not recommended, even for patients who have achieved AQP4-IgG-seronegative, due to the persistent risk of relapse.

Preventative therapy: AQP4-IgG-seronegative NMOSD

Currently, no drugs are approved for DN NMOSD, which differs immunologically and pathologically from seropositive cases. For DN NMOSD patients, maintenance therapy may be initiated following the first severe attack or after a second relapse.[13] Recommended therapies include traditional immunosuppressants such as AZA, MMF, or RTX. For patients who continue to experience relapses despite maintenance therapy, combination therapy, or switching to tocilizumab may be considered. Previous evidence indicates that RTX and tocilizumab may be effective against DN NMOSD, though this is still debated.[61,62]

Other potential therapies

New potential therapies including efgartigimod, chimeric antigen receptor T-cell (CAR-T) therapy, zanubrutinib, BAT4406F, and stem cell therapy are currently under ongoing (https://clinicaltrials.gov/; Tables 2 and 4).

Efgartigimod is a novel human IgG1 antibody Fc fragment that binds to the neonatal Fc receptor (FcRn), reducing pathogenic IgG antibodies and blocking their recycling. Two cases suggest that efgartigimod is effective as a rescue therapy for AQP4-IgG-seropositive NMOSD attacks.[63,64] Currently, three clinical studies are recruiting participants to explore its efficacy.

CAR-T therapy is a transformative cell-based treatment. By genetically modifying the surface receptors of T cells, CAR-T cells can provide long-term B cell depletion. Qin et al.[65] were the first to report the successful use of CAR-T therapy in NMOSD. Currently, several preliminary studies are evaluating the safety and feasibility of CAR-T therapy for NMOSD.

Telitacicept is a novel fusion protein targeting B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL), thereby preventing their interaction with B cell ligands.[66] Ding et al.[67] reported the experience of successful treatment of NMOSD with telitacicept, despite their study included only eight NMOSD patients. A phase III trial investigating the efficacy and safety of telitacicept in NMOSD is ongoing.

Daratumumab, a CD38-directed monoclonal antibody, has demonstrated the ability to reduce autoantibody levels in conditions such as lupus, MG, and autoimmune encephalitis.[68] A study evaluating the efficacy of daratumumab in NMOSD is ongoing.

Zanubrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, has shown potential in NMOSD treatment. Liu et al.[69] reported that upregulated BTK expression in the blood and CSF of NMOSD patients, and that zanubrutinib improved demyelination, edema, and axonal injury in mouse models of NMO. A study evaluating the efficacy and safety of zanubrutinib in NMOSD patients is currently recruiting participants.

BAT4406F is a glycosylated, optimized IgG1 subclass recombinant anti-CD20 fully human monoclonal antibody.[70] A phase I trial of BAT4406F for NMOSD has been completed,[71] and a phase II/III clinical trial is underway.

Stem cell therapy, traditionally employed to treat hematological malignancies, is gaining recognition for its potential in neuroimmune diseases. Burt et al.[72] reported that among 12 NMOSD patients who underwent stem cell transplantation, only 2 experienced relapses within 5 years. Stem cell therapy is emerging as a promising treatment, with several clinical studies currently in progress.

Ofatumumab, approved for relapsing-remitting MS in adults, has not been validated for NMOSD through RCTs, with evidence limited to case reports.[73,74] Similarly, ocrelizumab, another CD20-targeting biologic, achieves B cell depletion levels comparable to RTX. Although not specifically tested in NMOSD, its theoretical potential warrants further investigation.[75]

In addition to the therapies mentioned above, studies investigating novel anti-CD20 monoclonal antibodies, including B001, MIL62, and IMC-002, are also recruiting participants with AQP4-IgG-seropositive NMOSD (https://clinicaltrials.gov/; Table 4).

Table 4. Summary of ongoing studies on new or potential therapies in NMOSD remission.

Therapies	ClinicalTrials.gov ID	Target	Mechanism of action
Inebilizumab	NCT06212245	CD19	B-cell depletion
Inebilizumab	NCT06180278	CD19	B-cell depletion
Inebilizumab	NCT06068829	CD19	B-cell depletion
Ofatumumab	NCT05504694	CD20	B-cell depletion
Daratumumab	NCT05403138	CD38	Reduction of IgG production
CAR-T	NCT06249438	CD20	Genetically engineered T cells to recognize and kill cells expressing specific target antigens
CAR-T	NCT06279923	CD19	
CAR-T	NCT04561557	BCMA	
CAR-T	NCT05828212	CD19	
CAR-T	NCT06633042	CD19	
Telitacicept	NCT03330418	BLyS, APRIL	Inhibition of BLyS and APRIL
Zanubrutinib	NCT05356858	BTK	B-cell and microglia inactivation
IMC-002	NCT06557174	CD20, CD47	B-cell depletion
B001	NCT06413654	CD20	B-cell inactivation/depletion
B001	NCT05145361	CD20	B-cell inactivation/depletion
BAT4406F	NCT06044350	CD20	B-cell depletion
MIL62	NCT05314010	CD20	B-cell depletion

APRIL, a proliferation-inducing ligand; BCMA, B-cell maturation antigen; BLyS, B lymphocyte stimulator; BTK, Bruton's tyrosine kinase; CAR-T, chimeric antigen receptor T-cell; NMOSD, neuromyelitis optica spectrum disorders.

Summary and future directions

In recent years, advancements in understanding NMOSD pathogenesis have led to the development of emerging therapies that significantly improve patient outcomes. Despite these advances, several challenges remain. Long-term real-world data on the efficacy and safety of newly approved biologics are still lacking. Additionally, some refractory NMOSD patients continue to experience relapses even after switching to biologics with different mechanisms of action. The optimal therapeutic approaches for DN NMOSD patients remain unclear. Furthermore, the role of serum AQP4-IgG titers in predicting disease prognosis and recurrence is still debated. Future research may benefit from international, multicenter, and prospective study designs to provide more comprehensive evidence. We anticipate new therapies targeting other immune pathways, offering additional options to minimize permanent disability caused by NMOSD relapses.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Xiaolin Yang: Writing – original draft.

Shaoru Zhang: Conceptualization; Writing – original draft.

Jinzhou Feng: Conceptualization; Writing – review & editing.

Xinyue Qin: Conceptualization; Writing – review & editing.

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References

1. Wingerchuk DM and Lucchinetti CF. Neuromyelitis optica spectrum disorder. *N Engl J Med* 2022; 387(7): 631–639.
2. Asgari N, Lillevang ST, Skejoe HP, et al. A population-based study of neuromyelitis optica in Caucasians. *Neurology* 2011; 76: 1589–1595.
3. Kashipazha D, Mohammadianinejad SE, Majdinasab N, et al. A descriptive study of prevalence, clinical features and other findings of neuromyelitis optica and neuromyelitis optica spectrum disorder in Khuzestan Province, Iran. *Iran J Neurol* 2015; 14: 204–210.
4. Jarius S, Paul F, Weinshenker BG, et al. Neuromyelitis optica. *Nat Rev Dis Primer* 2020; 6: 85.
5. Jarius S and Wildemann B. Aquaporin-4 antibodies (NMO-IgG) as a serological marker of neuromyelitis optica: a critical review of the literature. *Brain Pathol* 2013; 23: 661–683.
6. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 2015; 85: 177–189.
7. Höftberger R, Sabater L, Marignier R, et al. An optimized immunohistochemistry technique improves NMO-IgG detection: study comparison with cell-based assays. *PLoS One* 2013; 8: e79083.
8. Hamid SHM, Whittam D, Mutch K, et al. What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients. *J Neurol* 2017; 264(10): 2088–2094.
9. Mao Z, Lu Z, Hu X, et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. *Neurology* 2014; 83(12): 1122.
10. Sepúlveda M, Aldea M, Escudero D, et al. Epidemiology of NMOSD in Catalonia: influence of the new 2015 criteria in incidence and prevalence estimates. *Mult Scler* 2018; 24(14): 1843–1851.
11. Demuth S, Guillaume M, Bourre B, et al. Treatment regimens for neuromyelitis optica spectrum disorder attacks: a retrospective cohort study. *J Neuroinflammation* 2022; 19(1): 62.
12. Lotan I and Levy M. New Treatment perspectives for acute relapses in neuromyelitis optica spectrum disorder. *Transfus Med Rev* 2022; 36: 230–232.
13. Kümpfel T, Giglhuber K, Aktas O, et al. Update on the diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD)—revised recommendations of the Neuromyelitis Optica Study Group (NEMOS). Part II: Attack therapy and long-term management. *J Neurol* 2024; 271(1): 141–176.
14. Zhao C, Li HZ, Zhao DD, et al. Increased circulating T follicular helper cells are inhibited by rituximab in neuromyelitis optica spectrum disorder. *Front Neurol* 2017; 8: 104.
15. Saadoun S and Papadopoulos MC. Role of membrane complement regulators in neuromyelitis optica. *Mult Scler* 2015; 21(13): 1644–1654.
16. Vaishnav RA, Liu R, Chapman J, et al. Aquaporin 4 molecular mimicry and implications for neuromyelitis optica. *J Neuroimmunol* 2013; 260: 92–98.
17. Cotzomi E, Stathopoulos P, Lee CS, et al. Early B cell tolerance defects in neuromyelitis optica favour anti-AQP4 autoantibody production. *Brain* 2019; 142(6): 1598–1615.
18. Wu Y, Zhong L and Geng J. Neuromyelitis optica spectrum disorder: pathogenesis, treatment, and experimental models. *Mult Scler Relat Disord* 2019; 27: 412–418.
19. Hinson SR, Roemer SF, Lucchinetti CF, et al. Aquaporin-4-binding autoantibodies in patients

with neuromyelitis optica impair glutamate transport by down-regulating EAAT2. *J Exp Med* 2008; 205(11): 2473–2481.

20. da Silva APB, Souza DG, Souza DO, et al. Role of glutamatergic excitotoxicity in neuromyelitis optica spectrum disorders. *Front Cell Neurosci* 2019; 13: 142.
21. Fujihara K, Bennett JL, de Seze J, et al. Interleukin-6 in neuromyelitis optica spectrum disorder pathophysiology. *Neurol Neuroimmunol Neuroinflamm* 2020; 7(5): e841.
22. Contentti EC, Lopez PA, Pettinicchi JP, et al. Assessing attacks and treatment response rates among adult patients with NMOSD and MOGAD: data from a nationwide registry in Argentina. *Mult Scler J Exp Transl Clin* 2021; 7(3): 20552173211032334.
23. Kleiter I, Gahlen A, Borisow N, et al. Neuromyelitis optica: evaluation of 871 attacks and 1,153 treatment courses. *Ann Neurol* 2016; 79: 206–216.
24. Abboud H, Petrak A, Mealy M, et al. Treatment of acute relapses in neuromyelitis optica: steroids alone versus steroids plus plasma exchange. *Mult Scler* 2016; 22(2): 185–192.
25. Kleiter I and Gold R. Present and future therapies in neuromyelitis optica spectrum disorders. *Neurotherapeutics* 2016; 13(1): 70–83.
26. Kleiter I, Gahlen A, Borisow N, et al. Apheresis therapies for NMOSD attacks: a retrospective study of 207 therapeutic interventions. *Neurol Neuroimmunol Neuroinflamm* 2018; 5(6): e504.
27. Lin J, Xue B, Zhu R, et al. Intravenous immunoglobulin as the rescue treatment in NMOSD patients. *Neurol Sci* 2021; 42(9): 3857–3863.
28. Li X, Tian DC, Fan M, et al. Intravenous immunoglobulin for acute attacks in neuromyelitis optica spectrum disorders (NMOSD). *Mult Scler Relat Disord* 2020; 44: 102325.
29. Frampton JE. Inebilizumab: first approval. *Drugs* 2020; 80(12): 1259–1264.
30. Tullman MJ, Zabeti A, Vuocolo S, et al. Inebilizumab for treatment of neuromyelitis optica spectrum disorder. *Neurodegener Dis Manag* 2021; 11(5): 341–352.
31. Cree BAC, Bennett JL, Kim HJ, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. *Lancet* 2019; 394: 1352–1363.
32. Rensel M, Zabeti A, Mealy MA, et al. Long-term efficacy and safety of inebilizumab in neuromyelitis optica spectrum disorder: analysis of aquaporin-4-immunoglobulin G-seropositive participants taking inebilizumab for ⩾4 years in the N-MOmentum trial. *Mult Scler J* 2022; 28: 925–932.
33. Cree BAC, Kim HJ, Weinshenker BG, et al. Safety and efficacy of inebilizumab for the treatment of neuromyelitis optica spectrum disorder: end-of-study results from the open-label period of the N-MOmentum trial. *Lancet Neurol* 2024; 23: 588–602.
34. Plosker GL and Figgitt DP. Rituximab: a review of its use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. *Drugs* 2003; 63: 803–843.
35. Poupart J, Giovannelli J, Deschamps R, et al. Evaluation of efficacy and tolerability of first-line therapies in NMOSD. *Neurology* 2020; 94(15): e1645–e1656.
36. Huang W, Wang L, Xia J, et al. Efficacy and safety of azathioprine, mycophenolate mofetil, and reduced dose of rituximab in neuromyelitis optica spectrum disorder. *Eur J Neurol* 2022; 29: 2343–2354.
37. Tahara M, Oeda T, Okada K, et al. Safety and efficacy of rituximab in neuromyelitis optica spectrum disorders (RIN-1 study): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2020; 19: 298–306.
38. Kessler RA, Mealy MA and Levy M. Treatment of neuromyelitis optica spectrum disorder: acute, preventive, and symptomatic. *Curr Treat Options Neurol* 2016; 18(1): 2.
39. Nelke C, Schroeter CB, Stascheit F, et al. Eculizumab treatment alters the proteometabolome beyond the inhibition of complement. *JCI Insight* 2023; 8: e169135.
40. Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. *N Engl J Med* 2019; 381(7): 614–625.
41. Wingerchuk DM, Fujihara K, Palace J, et al. Long-term safety and efficacy of eculizumab in aquaporin-4 IgG-positive NMOSD. *Ann Neurol* 2021; 89(6): 1088–1098.
42. Ringelstein M, Asseyer S, Lindenblatt G, et al. Eculizumab use in neuromyelitis optica spectrum disorders: eculizumab use in neuromyelitis optica spectrum disorders. *Neurology* 2024; 103(9): e209888.
43. Baker CJ. Prevention of meningococcal infection in the United States: current recommendations

and future considerations. *J Adolesc Health* 2016; 59: S29–S37.

44. Rondeau E, Scully M, Ariceta G, et al. The long-acting C5 inhibitor, Ravulizumab, is effective and safe in adult patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment. *Kidney Int* 2020; 97(6): 1287–1296.
45. Pittock SJ, Barnett M, Bennett JL, et al. Ravulizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. *Ann Neurol* 2023; 93: 1053–1068.
46. Schett G. Physiological effects of modulating the interleukin-6 axis. *Rheumatology* 2018; 57: ii43–ii50.
47. Yamamura T, Kleiter I, Fujihara K, et al. Trial of satralizumab in neuromyelitis optica spectrum disorder. *N Engl J Med* 2019; 381(22): 2114–2124.
48. Traboulsee A, Greenberg BM, Bennett JL, et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. *Lancet Neurol* 2020; 19: 402–412.
49. Nakashima I, Nakahara J, Yasunaga H, et al. Real-world management of patients with neuromyelitis optica spectrum disorder using satralizumab: results from a Japanese claims database. *Mult Scler Relat Disord* 2024; 84: 105502.
50. Kleiter I, Traboulsee A, Palace J, et al. Long-term efficacy of satralizumab in AQP4-IgG-seropositive neuromyelitis optica spectrum disorder from SAkuraSky and SAkuraStar. *Neurol Neuroimmunol Neuroinflamm* 2022; 10(1): e200071.
51. Uzawa A, Mori M, Masuda H, et al. Interleukin-6 analysis of 572 consecutive CSF samples from neurological disorders: a special focus on neuromyelitis optica. *Clin Chim Acta* 2017; 469: 144–149.
52. Yang S, Zhang C, Zhang TX, et al. A real-world study of interleukin-6 receptor blockade in patients with neuromyelitis optica spectrum disorder. *J Neurol* 2024; 270(1): 348–356.
53. Zhang C, Zhang M, Qiu W, et al. Safety and efficacy of tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorder (TANGO): an open-label, multicentre, randomised, phase 2 trial. *Lancet Neurol* 2020; 19: 391–401.
54. Songwisit S, Kosiyakul P, Jitprapaikulsan J, et al. Efficacy and safety of mycophenolate mofetil therapy in neuromyelitis optica spectrum disorders: a systematic review and meta-analysis. *Sci Rep* 2020; 10(1): 16727.
55. Wang L, Tan H, Huang W, et al. Low-dose tacrolimus in treating neuromyelitis optica spectrum disorder. *Mult Scler Relat Disord* 2021; 48: 102707.
56. Wingerchuk DM, Zhang I, Kielhorn A, et al. Network meta-analysis of food and drug administration-approved treatment options for adults with aquaporin-4 immunoglobulin G-positive neuromyelitis optica spectrum disorder. *Neurol Ther* 2022; 11(1): 123–135.
57. Xue T, Yang Y, Lu Q, et al. Efficacy and safety of monoclonal antibody therapy in neuromyelitis optica spectrum disorders: evidence from randomized controlled trials. *Mult Scler Relat Disord* 2020; 43: 102166.
58. Paul F, Marignier R, Palace J, et al. International Delphi consensus on the management of AQP4-IgG+ NMOSD: recommendations for eculizumab, inebilizumab, and satralizumab. *Neurol Neuroimmunol Neuroinflamm* 2023; 10(4): e200124.
59. Papp V, Magyari M, Aktas O, et al. Worldwide incidence and prevalence of neuromyelitis optica. *Neurology* 2021; 96(2): 59–77.
60. Kim KH, Chung YH, Min JH, et al. Immunosuppressive therapy in elderly patients with neuromyelitis optica spectrum disorder: a retrospective multicentre study. *J Neurol Neurosurg Psychiatry* 2024; 95(12): 1168–1175.
61. Mealy MA, Kim SH, Schmidt F, et al. Aquaporin-4 serostatus does not predict response to immunotherapy in neuromyelitis optica spectrum disorders. *Mult Scler* 2018; 24(13): 1737–1742.
62. Broome CM, McDonald V, Miyakawa Y, et al. Efficacy and safety of the neonatal Fc receptor inhibitor efgartigimod in adults with primary immune thrombocytopenia (ADVANCE IV): a multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2023; 402:1648–1659.
63. Li Z, Xu Q, Huang J, et al. Efgartigimod as rescue treatment in acute phase of neuromyelitis optica spectrum disorder: a case report. *Heliyon* 2024; 10(9): e30421.
64. Huang SQ, Yuan ZH, Hong Y, et al. Successful treatment with efgartigimod as an add-on therapy in acute attack of anti-AQP4 antibody-positive NMOSD: a case report. *Neurol Sci* 2024; 45(11): 5511–5515.
65. Qin C, Tian DS, Zhou LQ, et al. Anti-BCMA CAR T-cell therapy CT103A in relapsed or

refractory AQP4-IgG seropositive neuromyelitis optica spectrum disorders: phase 1 trial interim results. *Signal Transduct Target Ther* 2023; 8(1): 5.

66. Wu D, Li J, Xu D, et al. Telitacicept in patients with active systemic lupus erythematosus: results of a phase 2b, randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2024; 83(4): 475–487.
67. Ding J, Jiang X, Cai Y, et al. Telitacicept following plasma exchange in the treatment of subjects with recurrent neuromyelitis optica spectrum disorders: a single-center, single-arm, open-label study. *CNS Neurosci Ther* 2022; 28(10): 1613–1623.
68. Holzer MT, Ruffer N, Huber TB, et al. Daratumumab for autoimmune diseases: a systematic review. *RMD Open* 2023; 9(4): e003604.
69. Liu Y, Huang Z, Zhang TX, et al. Bruton's tyrosine kinase-bearing B cells and microglia in neuromyelitis optica spectrum disorder. *J Neuroinflammation* 2023; 20(1): 309.
70. Carnero Contentti E and Correale J. Neuromyelitis optica spectrum disorders: from pathophysiology to therapeutic strategies. *J Neuroinflammation* 2021; 18(1): 208.
71. Yu H, Chen Y, Qi Y, et al. First-in-human study of BAT4406F, an ADCC-enhanced fully humanized anti-CD20 monoclonal antibody in patients with neuromyelitis optica spectrum disorders. *CNS Neurosci Ther* 2024; 30(11): e70126.
72. Burt RK, Balabanov R, Han X, et al. Autologous nonmyeloablative hematopoietic stem cell transplantation for neuromyelitis optica. *Neurology* 2019; 93(18): e1732–e1741.
73. Zhang W, Jiao Y, Jiao J, et al. Successful treatment of rituximab-unresponsive elderly-onset neuromyelitis optica spectrum disorder and hypogammaglobulinemia with ofatumumab plus intravenous immunoglobulin therapy in a patient with mutant *FCGR3A* genotype: a case report. *Front Immunol* 2022; 13: 1047992.
74. Maillart E, Renaldo F, Papeix C, et al. Dramatic efficacy of ofatumumab in refractory pediatric-onset AQP4-IgG neuromyelitis optica spectrum disorder. *Neurol Neuroimmunol Neuroinflamm* 2020; 7(3): e683.
75. AbdelRazek MA, Casasola M, Mollashahi R, et al. Extended B-cell depletion beyond 6-months in patients receiving ocrelizumab or rituximab for CNS demyelinating disease. *Mult Scler Relat Disord* 2022; 59: 103505.