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Immunobiology of neuromyelitis optica spectrum disorders

Daissy Liliana Mora Cuervo[1], Gisele Hansel[1,2] and Douglas Kazutoshi Sato[1,2,3,a]

Abstract

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune inflammatory disease of the central nervous system. Most of the cases are positive for autoantibodies targeting the water channel aquaporin-4 (AQP4-IgG). Activated B and T cells, innate immunity cells, pro-inflammatory cytokines, and activated complement contribute to the formation of the NMOSD lesions. Optic neuritis, longitudinally extensive myelitis, and area postrema syndrome are core clinical manifestations. NMOSD diagnosis is based on clinical manifestations, magnetic resonance imaging findings, and AQP4-IgG positivity. Cell-based assays are the preferred method for the detection of AQP4-IgG. Acute relapses are treated with IV methylprednisolone or plasma exchange. Recent advances on the NMOSD immunobiology led to approved treatments such as *eculizumab, satralizumab*, and *inebilizumab*.

Addresses

[1] Medicine and Health Sciences Postgraduation Program, School of Medicine, Pontificial Catholic University of Rio Grande Do Sul (PUCRS), Porto Alegre, Brazil

[2] Neuroinflammation and Neuroimmunology Lab, Brain Institute of Rio Grande Do Sul, Porto Alegre, Brazil

[3] Institute of Geriatrics and Gerontology, Pontificial Catholic University of Rio Grande Do Sul (PUCRS), Porto Alegre, Brazil

Corresponding author: Sato, Douglas Kazutoshi (douglas.sato@pucrs.br)

(Mora Cuervo D.L.)

[a] Instituto de Geriatria e Gerontologia (sala 808, prédio 40). Avenida Ipiranga 6681, Zip-code 90619-900, Porto Alegre, RS, Brazil

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Introduction

Neuromyelitis optica spectrum disorder (NMOSD), also known as Devic's syndrome, is a rare inflammatory syndrome mediated by immune-humoral responses directed against central nervous system (CNS) [1]. Most of the cases are positive for immunoglobulin G autoantibodies against aquaporin-4 (AQP4-IgG). Aquaporin-4 (AQP4) is the most abundant water channel protein in the CNS, expressed in the end−feet processes of astrocytes [2]. More recently, another serum autoantibody called anti-myelin oligodendrocyte glycoprotein-antibody (MOG-IgG) has been detected in a fraction of AQP4-IgG-negative NMOSD, but they belong to a distinct disorder known as MOG-IgG-associated disease (MOGAD) [3].

AQP4-IgG-positive NMOSD is an autoimmune astrocytopathy, although secondary damage to oligodendrocytes and neurons loss [4]. A relapsing disease course affecting optic nerve, spinal cord, area postrema of the dorsal medulla, brainstem, diencephalon, or cerebrum could lead to severe disability when untreated [5]. Optic neuritis (ON) and myelitis are the most common initial acute attacks. Complete recovery is possible with early treatment, but with subsequent attacks, the recovery rates are lower [6]. In this review, we will provide an overview of the recent advances on AQP4-IgG NMOSD diagnosis, treatment, and related immunobiological mechanisms involved in the disease pathogenesis.

Epidemiology

The global prevalence of NMOSD varies from 1/100,000 among white people to 10/100,000 in black people. There is a high female-to-male ratio (up to 9:1), and mean disease onset is around 40 years. The positivity of AQP4-IgG is higher in adults than children diagnosed with NMOSD [7].

Several studies have found a significant association between human leukocyte antigen alleles and NMOSD. Although data are limited, infections in early life have been suggested as a protective factor. Despite studies trying to correlate risk factors such as dietary factors, low vitamin D levels, infections and vaccine exposure, has not been established its causality to NMOSD and further investigation is needed [8].

Immunopathogenesis

AQP4 is a bidirectional, osmosis-driven water channel highly expressed in the perivascular and peripheral

Abbreviations

NMOSD	Neuromyelitis optica spectrum disorders
CNS	Central Nervous System
AQP4-IgG	Aquaporin-4 antibody
MOG-IgG	Myelin oligodendrocyte glycoprotein-antibody
HLA	Human leukocyte antigen
IL-6	Interleucin 6
IL-17A	Interleucin 17A
GFAP	glial fibrillary acidic protein
ON	Optic Neuritis
MRI	Magnetic Resonance Imaging
LETM	Longitudinally extensive transverse myelitis
NMO	Neuromyelitis optica
TM	transverse myelitis
PRES	Posterior Reversible Encephalopathy Syndrome
CSF	cerebrospinal fluid
RNFL	retinal nerve fiber layer
GCIPL	ganglion cell/inner plexiform layer
IVMP	Intravenous methylprednisolone
RTX	Rituximab
CBA	cell-based assay
IVMP	Intravenous methylprednisolone
PLEX	plasma exchange
BTK	Bruton's tyrosine kinase

astrocytic endfeet localized in areas such as the optic nerves, spinal cord, diencephalon, and area postrema [9]. It is estimated that around 80% of the patients fulfilling the current diagnostic criteria for NMOSD are positive for serum AQP4-IgG [10].

The biological mechanisms underlying the development of AQP4-IgG are not completely understood. However, dysfunctional T helper cells and B cells from patients with NMOSD can recognize AQP4, indicating loss of self-antigen tolerance. Autoreactive B cells from patients with NMOSD can produce AQP4-IgG after IL-6 stimulation in association with CD4+ T cells [11]. Activated B and T cells can produce pro-inflammatory cytokines, cross the cerebral vascular endothelium, and impair blood–brain barrier, leading to the entrance of AQP4-IgG and other immune cells, such as macrophages and granulocytes, into the CNS [6,10,12].

The binding of AQP4-IgG to AQP4 promotes immune-mediated astrocyte damage as demonstrated in Figure 1. This inflammatory process contributes to the formation of typical NMOSD lesions, characterized by astrocytic injury with a loss of AQP4 and glial fibrillary acidic protein (GFAP) immunoreactivity, immune cell infiltration, immunoglobulin G, and activated complement deposition around blood vessels. The astrocyte injury and the complement activation create an inflammatory microenvironment triggering a series of subsequent events inducing secondary damage of oligodendrocytes, axonal dysfunction, and neuronal death [12–14].

Additional studies have shown the involvement of the glutamatergic system in the secondary damage in NMOSD. In astrocytes, AQP4 forms complexes with other membrane proteins, such as glutamate transporters. An imbalance in water transport due to the production of AQP4-IgG may increase extracellular glutamate concentrations providing an excitotoxic environment for neurons [12].

A recent study has shown the calcium increase does not precede axonal degeneration. It seems the axonal damage during NMOSD has a different mechanism when compared to inflammatory demyelinating diseases. This study found damage mainly in thin axons, independently of whether these axons were myelinated, suggesting that myelin damage is not the determining factor for axonal degeneration in NMOSD [15].

However, this immunobiological mechanism does not explain the remaining 20% of cases that are AQP4-IgG negative. Therefore, the discovery of new biomarkers not yet identified or the disease mechanisms involved in seronegative NMOSD is necessary for an accurate diagnosis despite clinical phenotype [5]. In a large cohort, 13–40% of the patients withAQP4-IgG negative showed positivity for serum MOG-IgG [16]. Also, in a subset of patients with AQP4-IgG seropositive NMOSD, a recent study described circulating IgG antibodies in their serum that are cytoprotective against complement-induced injury to AQP4 expressing cells, adding complexity to the immunopathogenesis of the disease [17].

Clinical features and radiological findings

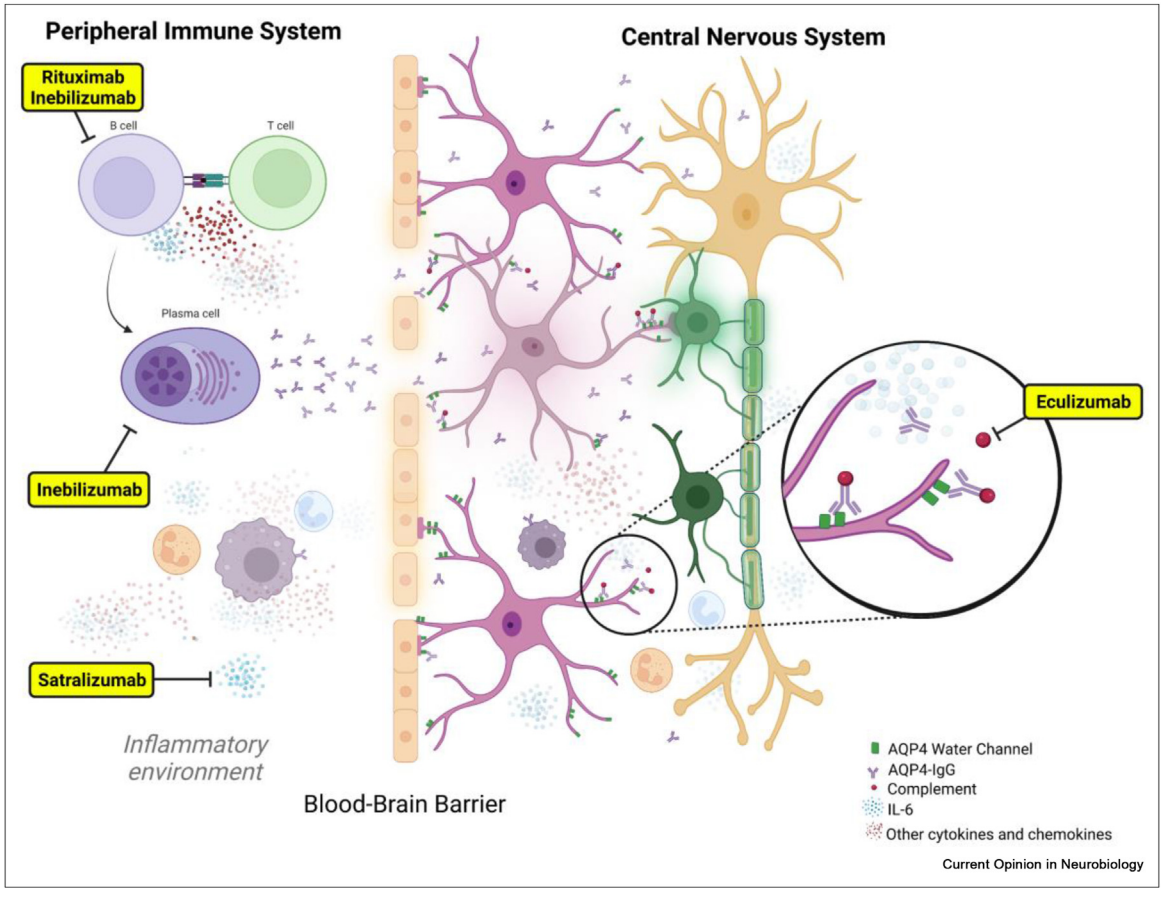
According to the affected regions of the CNS, there are six core clinical characteristics in NMOSD: ON, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome, or symptomatic cerebral syndrome [5]. In most of the cases, the disease starts with an ON or a transverse myelitis. If untreated, most of the patients with AQP4-IgG seropositive NMOSD will have a relapse, with a median interval of 9 months since the first attack but it may occur after several years. Symptoms could completely resolve after acute attacks, but incomplete recovery is reported in 66% of ON and >80% of transverse myelitis attacks [6].

Typical ON in NMOSD is characterized by low visual acuity and color desaturation that can rapidly progress to blindness, associated with pain on eye movement. During ON-NMOSD attacks, we can observe increased signal within the optic nerve with fat-suppressed T2-weighted orbital magnetic resonance imaging (MRI) sequences, typically associated with T1-weighted sequences showing gadolinium enhancement. Bilateral optic nerve involvement, posterior nerve predominance (especially with extension into the optic chiasm), or extensive lesions of the optic nerve (more than half of its length) are all suggestive of NMOSD(5).

Longitudinally extensive transverse myelitis with a complete spinal cord syndrome, especially with paroxysmal tonic spasms is characteristic of NMOSD. Longitudinally extensive transverse myelitis symptoms include sensory and/or motor deficits ranging from mild symptoms to anesthesia and tetraplegia, neuropathic pain, bladder and/or bowel dysfunction. Typical spinal MRI reveal increased signal on sagittal T2-weighted extending over 3 or more vertebral segments in the sagittal view with central cord predominance (more than 70% of the lesion residing within the central gray matter), associated with gadolinium enhancement. In the chronic phase, these lesions may evolve to longitudinally extensive spinal cord atrophy [5].

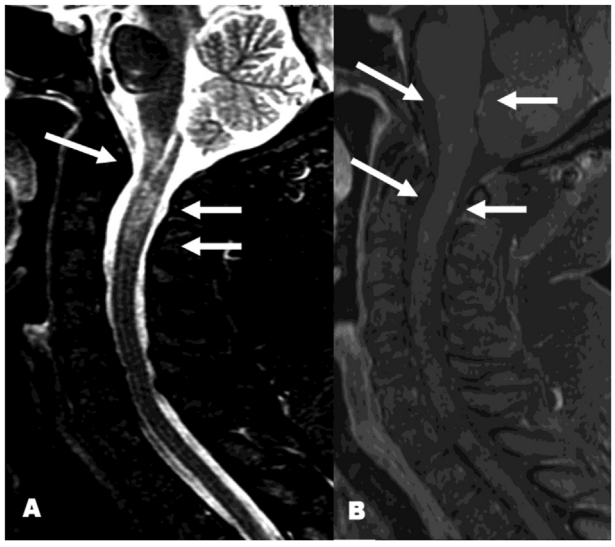
Area postrema syndrome is characterized by persistent (>72h) hiccups or nausea and vomiting. On brain MRI, there is an increased signal on T2-weighted sequences involving the dorsal surface of the medulla oblongata at the caudal end of the fourth ventricle, either small and localized, often bilateral or contiguous with an upper cervical spinal cord lesion, as seen in Figure 2 [5]. Recently, the 'inverted V' sign in axial T2-weighed images of the medulla oblongata was described as characteristic of the syndrome and could help in the early diagnosis [18].

Figure 1



Immunobiology of NMOSD with aquaporin-4 antibodies and treatment targets. NMOSD, neuromyelitis optica spectrum disorder. Abnormal activation of the acquired immune system results in the production of AQP4-IgG. The pro-inflammatory environment causes blood–brain barrier disruption and penetration of AQP4-IgG into the CNS. The AQP4-IgG promotes astrocyte damage and secondary oligodendrocyte and neuronal loss. Yellow boxes indicate treatments used in NMOSD. Aquaporin-4 (AQP4); Aquaporin-4 antibody (AQP4-IgG); interleukin-6 (IL-6).

Figure 2



Radiological findings in NMOSD. NMOSD, neuromyelitis optica spectrum disorder. A 53-year female with area postrema syndrome and upper myelitis who was positive for aquaporin-4 antibodies. A - Short tau inversion recovery (STIR) showing a lesion in the medulla extending to the upper cervical spinal cord. B - T1 showing contrast enhancement in the acute lesion.

Less frequent core clinical manifestations are acute brainstem syndrome, symptomatic narcolepsy, or acute diencephalic clinical syndrome and symptomatic cerebral syndrome with NMOSD-typical brain lesions. Manifestations could include encephalopathy, psychiatric symptoms, headache, narcolepsy, hemiparesis, and ataxia; diencephalitis could lead to hypothyroidism, galactorrhea, inappropriate antidiuretic hormone secretion autonomic symptoms, obesity, and behavioral changes. NMOSD-typical brain MRI lesion patterns include lesions in periependymal surfaces of the fourth ventricle in the brainstem/cerebellum; lesions involving the hypothalamus, thalamus, or periependymal surfaces of the third ventricle; large, confluent, unilateral, or bilateral subcortical or deep white matter lesions; long (1/2 of the length of the corpus callosum or greater), diffuse, heterogeneous, or edematous corpus callosum lesions; long corticospinal tract lesions, unilateral or bilateral, contiguously involving internal capsule and cerebral peduncle and extensive periependymal brain lesions, often with gadolinium enhancement [5].

Rare clinical manifestations include hydrocephalus, lumbo-sacral myeloradiculitis, symptomatic hyperCKemia, corticosteroid-responsive myalgia, hyposmia and hearing loss, and posterior reversible encephalopathy syndrome [19,20]. Also, NMOSD is associated with organ- and non-organ-specific autoimmunity. The most common coexisting autoimmune conditions in NMOSD are autoimmune hypothyroidism, systemic lupus erythematosus, and Sjogren's syndrome [19].

Diagnosis

In 2015, the International Panel for NMOSD proposed a diagnostic criteria for patients with AQP4-IgG positive and those with unknown or negative AQP4-IgG status. These criteria consider clinical presentation and MRI findings in addition to AQP4-IgG serology. This diagnostic criteria is accompanied by a comprehensive list of 'red flags' which, if present, should prompt additional investigation for differential diagnoses and AQP4-IgG re-testing if previously negative [5]. Depending on the world region, we need to rule out local endemic infections and nutritional diseases in the differential diagnosis [21].

In patients, without detectable AQP4-IgG, despite the use of the best available assays or unavailable tests, the diagnosis remains a challenge. In a small group of these patients, serum antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) have been reported [22]. However, these patients with MOG-IgG are currently known as a distinct disorder known as MOG-IgG-associated disorder with different immunobiological pathogenesis of AQP4-IgG NMOSD.

AQP4-IgG assays

Nowadays, the positive serological status for AQP4 is considered the diagnostic biomarker of NMOSD. The cell-based assay (CBA) is considered the best technology for the analysis of AQP4-IgG due to its greater sensitivity and specificity, especially those using live transfected cells. In terms of detection analysis, both direct microscope immunofluorescence and flow cytometry assays have been shown to be sensitive and specific techniques. In the NMOSD, serum analysis is more sensitive than CSF for detecting AQP4-IgG and serum titer does not correlate with disease severity or clinical outcomes [5,21]. Alternative methodologies have been investigated to cover the lack of CBA availability in some world regions. A recent study evaluated a new nanosensor technology for the analyses of AQP4-IgG detection using silver nanoparticles AgNPs. The results have shown higher sensitivity than commercial CBA; however, more studies are still required to confirm this new methodology [23].

Cerebrospinal fluid analysis

Cerebrospinal fluid (CSF) analysis is useful but not required to diagnose NMOSD. AQP4-IgG may be detected in CSF, but exclusive positivity of AQP4-IgG in the CSF is rare. CSF white cell count of >50 cells/μL with granulocytes and eosinophils is common during acute attacks [24]. Many pro-inflammatory cytokines (e.g. IL-6, IL-17A, G-CSF) are elevated during NMOSD attacks, and the cytokine profile is distinct from multiple sclerosis [23]. CSF exclusive oligoclonal IgG bands are mainly negative in NMOSD, but its positivity do not exclude the diagnosis [24].

Other biomarkers

GFAP, a major constituent of the astrocyte cytoskeleton, has been studied as a biomarker of astrocyte injury in AQP4-NMOSD when measured in body fluids, such as CSF and serum. There is an increase in serum and CSF GFAP during clinical attacks, but subclinical astrocyte damage is not evidenced during remission periods. Additionally, the CSF GFAP levels in seronegative NMOSD are low or undetectable, evidencing distinct pathophysiology in these patients [25].

Interleukin-6 (IL-6) in the CSF and serum of AQP4-NMOSD can promote the survival of plasmablasts able to produce AQP4-IgG. Moreover, IL-6 participates in many other biological processes such as T cell activation and proliferation, endothelial expression of adhesion molecules, among other pleiotropic functions. However, elevated IL-6 levels are not clearly seen in the seronegative NMOSD [26, 27].

Treatment

Acute relapses

There is no curative treatment for NMOSD. The goals are to improve symptoms associated with acute attacks and prevent further relapses. Early treatment for acute attacks is highly recommended, although there are no randomized controlled trials on acute treatments. In clinical practice, NMOSD attacks are initially treated with 1 g of intravenous methylprednisolone (IVMP) for 3 to 5 consecutive days. After IVMP treatment, it is common to use a slow tapering course of oral steroids [21]. Early treatment reduces the risk of poor visual recovery [28] and minimize axonal loss in NMOSD associated ON [29].

Patients with severe NMOSD relapses and those who do not respond to treatment with IVMP may benefit from 5 to 7 sessions of plasma exchange (PLEX) (approximately 1.5 plasma volumes every other day). The clinical benefit of PLEX diminishes after day 20, whether or not IVMP has been administered; therefore, starting PLEX early is recommended [21]. Some centers have implemented early PLEX in NMOSD, as time from relapse onset to start PLEX is a strong predictor of complete remission [30].

Long-term treatments

Long-term attack prevention treatment is recommended for all patients with AQP4-IgG positive and negative and with relapsing disease. Therapies tested in Phase III and phase II/III multicenter, randomized, double-blind, placebo-controlled trials in NMOSD include eculizumab, satralizumab, inebilizumab, and rituximab plus oral prednisolone, as summarized in Table 1.

Eculizumab is a humanized monoclonal antibody. The PREVENT (Prevention of Relapses in Neuromyelitis Optica) study was a phase 3, randomized, double-blind,

Table 1

Long-term attack prevention treatments for NMOSD

Drugs with phase II/III Trials in NMOSD

Name	***Mechanism of Action***	***Dose***
Eculizumab	Inhibits the terminal complement protein C5 and prevents its cleavage into C5a, which is pro-inflammatory, and C5b, which coordinates the formation of membrane cytolytic attack complex.	900 mg intravenously weekly for the first 4 doses starting on day 1, followed by 1200 mg every 2 weeks starting at week 4.
Satralizumab	Binds to membrane-bound and soluble IL-6 receptors, preventing IL-6 from binding and inhibiting the IL-6 signaling pathways involved in inflammation.	120 mg subcutaneously at weeks 0, 2, and 4 and every 4 weeks thereafter.
Inebilizumab	Binds to the B-cell surface antigen CD19 targeting B cells and CD19+ plasmablasts	300 mg administered intravenously on days 1 and 15 every 6 months
Rituximab	Binds to the B-cell surface antigen CD20 surface expressed on B-lymphocytes.	375 mg/m^2 intravenously every week for 4 weeks, then 6-month interval dosing (alternatively, 2 doses of 1,000 mg with 2 weeks interval)

Off-label treatments

Azathioprine, mycophenolate mofetil, tocilizumab, intravenous immunoglobulin, mitoxantrone, methotrexate and cyclophosphamide.

placebo-controlled, time-to-event trial that evaluated the efficacy and safety of eculizumab in patients with AQP4-IgG NMOSD. Adjudicated relapses occurred in 3 of 96 patients (3%) in the eculizumab group and 20 of 47 (43%) in the placebo group (hazard ratio, 0.06; 95% confidence interval [CI], 0.02 to 0.20; $P < 0.001$). The adjudicated annualized relapse rate was 0.02 in the eculizumab group and 0.35 in the placebo group (rate ratio, 0.04; 95% CI, 0.01 to 0.15; $P < 0.001$). Most common adverse effects include upper respiratory infection, nasopharyngitis, headache, diarrhea, back pain, nausea, and diarrhea [31].

Satralizumab is a subcutaneously administered, humanized monoclonal antibody targeting IL-6 receptor. Its bioengineering technology allows to dissociate from the IL-6 receptors at an acidic pH within endosomes and satralizumab is returned to circulation, prolonging the drug half-life. Two phase III trials evaluated the efficacy and safety of satralizumab as add-on (SAkuraSky) [32] or monotherapy (SAkuraStar) [33] in NMOSD. Both studies demonstrated reduction in relapses risk and activity of disease in patients with AQP4-IgG positive NMOSD. However, benefit in seronegative patients was less pronounced than in the seropositive NMOSD.

Inebilizumab is an anti-CD19 humanized, affinity-optimized, afucosylated IgG1 kappa monoclonal antibody. It depletes B cells in a slightly higher range than anti-CD20 antibodies, including circulating CD19+ plasmablasts. N-Momentum was a multicenter, double-blind, randomized placebo-controlled phase II/III study that reported a significant reduction in relapse risk, 21 (12%) of 174 participants receiving inebilizumab had an attack versus 22 (39%) of 56 participants receiving placebo (hazard ratio 0·272 [95% CI 0·150–0·496]; $p < 0·0001$) [34].

Rituximab is a monoclonal chimeric antibody against CD20, a surface antigen that is mainly expressed on B-lymphocytes. RIN-1 is a multicenter, randomized, double-blind, placebo-controlled clinical trial that compared rituximab plus oral prednisolone versus placebo plus oral prednisolone. The primary outcome (time to first relapse) met with no relapse in the rituximab arm and 7 relapses in the control arm (group difference 36.8%, 95% CI 12.3–65.5; logrank $p = 0.0058$) after 72 weeks [35]. Also, a systematic review and meta-analysis including 46 retrospective studies provides evidence that rituximab reduces the frequency of NMOSD relapses and neurological disability [36].

As future treatment perspectives, studies with *Orelabrutinib*, a Bruton's tyrosine kinase inhibitor; *MIL-62*, a fucosylated recombinant anti-CD20 antibody, and *RC18*, a recombinant human B lymphocyte stimulator receptor, are registered in *clinicaltrials.gov*.

Conclusions

Since the discovery of AQP4-IgG, the understanding of NMOSD immunobiology evolved to the clinical use of monoclonal antibodies against B cells, cytokine receptors and activated complement. However, there is a lack of information about the disease triggers and the immunopathogenesis in seronegative patients requires further investigation. In the future, new therapies may be developed based on other immunological targets to prevent the NMOSD attacks with fewer adverse effects and reduce the risk of permanent disability.

Author contributions

Concept: DLMC, GH, DKS. Writing—original draft: DLMC, GH. Writing—review and editing: DKS. Figures: DLMC, GH, DKS. All authors contributed to the article and approved the submitted version.

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Conflict of interest statement

DLMC and GH have nothing to disclose. DKS has received speaker honoraria from Roche, and participated in advisory boards for Roche, Viela-Bio/Horizon and Alexion.

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