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REVIEW

Monoclonal Antibody Therapies Beyond Complement for NMOSD and MOGAD

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Abstract

Aquaporin-4 (AQP4)-IgG seropositive neuromyelitis optica spectrum disorders (AQP4-IgG seropositive NMOSD) and myelin oligodendrocyte glycoprotein (MOG)–IgG-associated disease (MOGAD) are inflammatory demyelinating disorders distinct from each other and from multiple sclerosis (MS).While anti-CD20 treatments can be used to treat MS and AQP4-IgG seropositive NMOSD, some MS medications are ineffective or could exacerbate AQP4-IgG seropositive NMOSD including beta-interferons, natalizumab, and fingolimod. AQP4-IgG seropositive NMOSD has a relapsing course in most cases, and preventative maintenance treatments should be started after the initial attack. Rituximab, eculizumab, inebilizumab, and satralizumab all have class 1 evidence for use in AQP4-IgG seropositive NMOSD, and the latter three have been approved by the US Food and Drug Administration (FDA). MOGAD is much more likely to be monophasic than AQP4-IgG seropositive NMOSD, and preventative therapy is usually reserved for those who have had a disease relapse. There is a lack of any class 1 evidence for MOGAD preventative treatment. Observational benefit has been suggested from oral immunosuppressants, intravenous immunoglobulin (IVIg), rituximab, and tocilizumab. Randomized placebo-controlled trials are urgently needed in this area.

Keywords Neuromyelitis optica · Myelin oligodendrocyte glycoprotein · Inebilizumab · Satralizumab · Rituximab

Aquaporin-4-IgG Seropositive Neuromyelitis Optica Spectrum Disorders (AQP4-IgG Seropositive NMOSD) and Myelin Oligodendrocyte Glycoprotein Antibody–Associated Disorder (MOGAD) — Background

Aquaporin-4-IgG seropositive neuromyelitis optica spectrum disorder (AQP4-IgG seropositive NMOSD) and myelin oligodendrocyte glycoprotein antibody (MOG-IgG)–associated disease (MOGAD) are acquired inflammatory demyelinating diseases of the central nervous system (CNS), distinct from multiple sclerosis (MS). Prior to the discovery of their antibody biomarkers, these diseases were initially often categorized as a subtype of MS. They are now recognized as distinct diseases with important treatment and prognostic differences from each other and from MS.

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In 2004 and 2005, an antibody biomarker of NMOSD was discovered that targets aquaporin-4, a water channel on the cell surface of astrocytes [1, 2]. This was the first serum biomarker of any CNS demyelinating disease. AQP4-IgG seropositive NMOSD is relapsing in 90% of cases and attacks are often severe with incomplete recovery and thus disability will accumulate with each attack, further highlighting the importance of attack-prevention treatments in these patients [3, 4]. AQP4-IgG seropositive NMOSD is characterized by three major attack types: (1) transverse myelitis; (2) optic neuritis; (3) area postrema syndrome (which can lead to intractable nausea, vomiting and hiccups from involvement of the brain's vomiting center) (5). Other attack types include acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome, and symptomatic cerebral syndrome with NMOSD-typical brain lesions [5]. AQP4-IgG seropositive NMOSD affects females 5–10 times more frequently than males and has a higher prevalence in non-white populations [6–8]. The median age of disease onset is 35–37 years, but onset has been described in both young children and elderly patients [3, 8, 9]. Unlike MS, it is generally not associated with a secondary progressive course [10]. The latest generation of AQP4-IgG cell-based assays are highly specific (> 99%) for this diagnosis [11–15]. AQP4-IgG seronegative

NMOSD cases are described and account for 20% of NMOSD but represent a heterogeneous group of disorders and will not be a major focus of this review [2, 16, 17].

In 2007, when using assays to detect antibodies to the MOG protein in its native conformational form, it was first recognized that MOG-IgG is a biomarker of a distinct CNS demyelinating disease [18]. Using updated cell-based assays, the true spectrum of MOGAD has been elucidated and its distinction from MS has become clearer. The disease is associated most often with attacks of acute disseminated encephalomyelitis (ADEM), optic neuritis, transverse myelitis, cerebral cortical encephalitis, or combinations thereof [19–22]. It can also account for some patients with the syndrome NMOSD who lack AQP4-IgG. The disease can be monophasic in up to half of patients and the remainder follow a relapsing course. Unlike MS, a secondary progressive course is not encountered [23]. Onset is typically in the third decade of life, with up to half of all cases occurring in children [24–27]. In contrast with AQP4-IgG seropositive NMOSD, males and females are equally affected, and major differences in race/ethnicity have not been described [27–30]. Cell-based assays are optimal for detection of MOG-IgG and have high specificity (≈98%) but false positives occur more commonly than with AQP4-IgG, particularly with low positive results (titer 1:20, 1:40 on flow cytometric assay at Mayo Clinic) or when ordered in low probability situations [31, 32]. Cell-based assays can be carried out using live cells or fixed cells (chemically or physically "fixed" to preserve the shape and contents of the cell even though they are dead) [33]. Live cells preserve the membrane integrity and better recapitulate what happens in humans. Moreover, there is concern that fixed cells may allow the antibody to bind to intracellular components of the cell surface receptor or protein of interest which may be less clinically important given antibodies would not have access to such parts of the receptor in real life. Live cell-based assays appear to have slightly higher specificity than fixed cell-based assays [34].

In this article, we will discuss monoclonal antibody (mAb) treatments used in AQP4-IgG seropositive NMOSD and MOGAD, other than mAbs targeting complement. For a detailed discussion of therapies targeting the complement pathway in NMOSD and beyond, we refer the reader to the "anti-complement agents for autoimmune neurological diseases" accompanying article in this issue of neurotherapeutics.

Aquaporin-4-IgG Seropositive Neuromyelitis Optica Spectrum Disorders

Immunopathogenesis

AQP4-IgG seropositive NMOSD is an autoimmune astrocytopathy [35]. AQP4-IgG plays a direct causative role in the pathogenesis of NMOSD [36, 37]. Evidence for the pathogenic mechanism comes from studies involving injection of animals with human AQP4-IgG, from pathology specimens, and from biomarkers in sera and CSF of affected patients. AQP4-IgG is produced by B cells and plasmablasts in the periphery and enters the CNS at areas of increased blood–brain barrier (BBB) permeability or BBB damage. It binds to AQP4 on astrocyte foot processes and causes injury through (1) AQP4 internalization [38, 39], (2) glutamate toxicity via downregulation of excitatory amino acid transporter 2 (EAAT2) [40], (3) generation of reactive astrocytes and activation of the NF-kB pathway [41], (4) complement-dependent cytotoxicity (CDC) [37, 42, 43], and (5) antibody-dependent cellular cytotoxicity (ADCC) [44]. Gaining an understanding of the pathogenic mechanisms has allowed us to develop and use targeted therapies (Fig. 1).

B Cells

Naïve B cells, as part of their development, go through the important checkpoints of central and peripheral tolerance, where naïve cells that react to a self-antigen are eliminated. In autoimmune diseases, such as AQP4-IgG seropositive NMOSD, there is a failure of this tolerance process, and autoreactive and polyreactive naïve B cells are able to survive [45, 46].

B cell recruiting and activating factor (BAFF), a proliferation-inducing ligand (APRIL), and C-X-C motif chemokine 13 (CXCL13) are upregulated in the CSF of patients with NMOSD [47–49].

A subpopulation of B cells ($CD19^{int}CD27^{high}CD38^{high}CD180^{-}$ B cells) with properties of plasmablasts is thought to be responsible for most of the AQP4-IgG production in NMOSD [50]. Notably, these cells do not express CD20 [50]. There is evidence to suggest that AQP4-IgG-producing plasmablasts enter the CNS from the periphery and establish inflammatory foci [51].

There is also an overall imbalance of the pro-inflammatory and anti-inflammatory B cells in AQP4-IgG seropositive NMOSD [52]. Most of the AQP4-IgG-producing plasma cells originate in the periphery but some intrathecal production has also been described, likely from both novel and peripherally derived B cell clones [53, 54]. There is some evidence that peripherally activated B cells form ectopic tertiary lymphoid structures in the intrathecal compartment, where they undergo clonal expansion and differentiation into plasmablasts [55].

Complement

Most AQP4-IgG is of the IgG1 isotype which is effective at activating the classical complement pathway [39]. This leads to opsonization of astrocytes and their lysis through the formation of the membrane attack complex. Complement

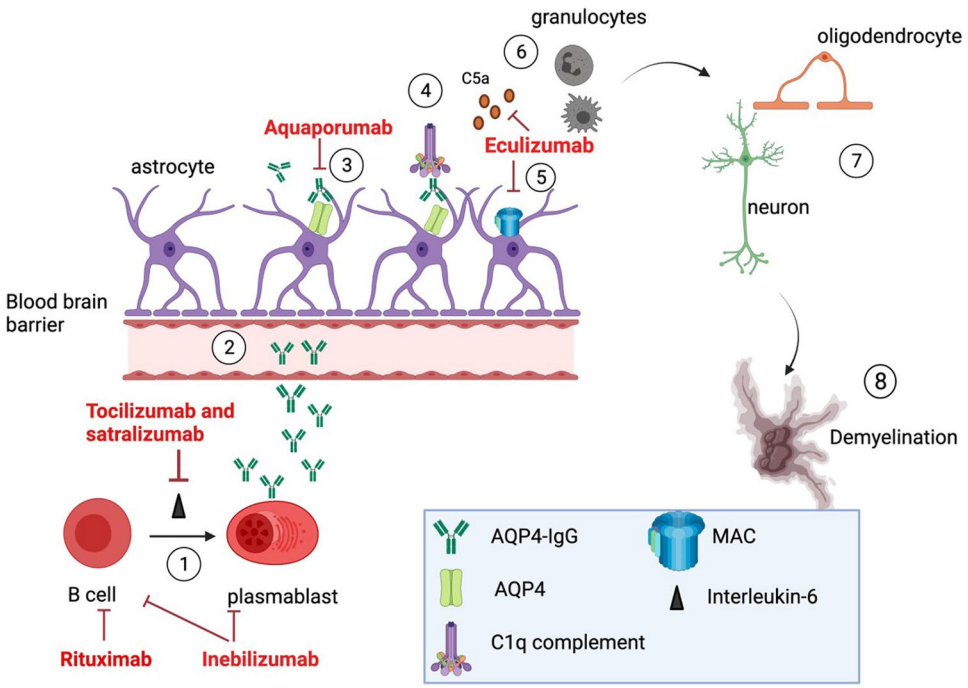

Fig. 1 Main pathogenic mechanism by which AQP4-IgG causes NMOSD. 1 — B cells differentiate into AQP4-IgG-secreting plasmablasts which is helped by interleukin-6; 2 — AQP4-IgG enters the circulation and traverses the blood–brain barrier; 3 — AQP4-IgG binds to AQP4 on the surface of astrocytes; 4 — C1q binds to AQP4-IgG and activates the classical complement pathway; 5 — astrocyte damage occurs from opsonization with complement and formation of the membrane attack complex (c5–c9); 6 — C5a is an anaphylatoxin and recruits granulocytes; 7 — granulocytes damage neurons and oligodendrocytes; 8 — the end result is demyelination

activation also causes inflammation through C5a, recruiting other inflammatory cells, such as granulocytes and macrophages, which then cause damage to oligodendrocytes and neurons as well as further compromising BBB integrity [56–59]. For further information on the role of complement in NMOSD, we refer the reader again to "anti-complement agents for autoimmune neurological diseases" in this issue.

Interleukin 6

Interleukin 6 (IL-6) is a pro-inflammatory cytokine and another key player in the pathogenesis of AQP4-IgG seropositive NMOSD. IL-6 levels are elevated in patients with NMOSD, particularly during attacks [60–64]. AQP4-IgG binding promotes IL-6 release from astrocytes [65]. IL-6 contributes to the pathology of NMOSD by (1) effect on B cells, promoting differentiation and maintenance of plasmablasts from B cells and enhancing secretion of AQP4-IgG [50, 66]; (2) effect on T cells, promoting the differentiation and maintenance of naive T cells to proinflammatory T-helper-17 cells and inhibiting activation of regulatory T cells [67–69]; (3) effect on innate immune system, activates innate immune cells [70]; and (4) effect on BBB, increased permeability [65].

Therapeutic Strategies

Treatment of AQP4-IgG seropositive NMOSD can be divided into acute treatments of attacks and chronic maintenance attack-prevention treatments, the latter of which will be the focus of this review.

Acute Treatment of Attacks

Treatment of acute attacks consists of high-dose IV steroids and plasma exchange. Given the attacks are often severe with incomplete recovery, we have a very low threshold for giving plasma exchange in addition to corticosteroids. Indeed, retrospective studies have suggested evidence for the early use of plasma exchange in improving outcomes [71, 72]. Dosing of attack-prevention mAb treatments should be undertaken after plasma exchange has been completed, to avoid plasma exchange removing the attack-prevention monoclonal antibody.

Bevacizumab is a mAb which has undergone some studies to assess its potential utility in the acute treatment of AQP4-IgG seropositive NMOSD, although is not yet part of the standard treatment regimen. Bevacizumab is a humanized mAb that targets vascular endothelial growth factor A (VEGF-A), inhibiting the formation of new blood vessels [73]. The rationale for the use of bevacizumab in AQP4-IgG seropositive NMOSD is that astrocyte-derived VEGF-A drives BBB disruption in CNS inflammatory disease [74]. In 2015, a single-center, open-label phase 1b trial for bevacizumab in acute treatment of attacks was published [75]. It was a safety and proof of concept study involving 10 patients with AQP4-IgG seropositive NMOSD. Bevacizumab (10 mg/kg intravenously) was administered on day 1, in addition to a 5-day course of methylprednisolone (1 g intravenously). Three patients recovered to pre-attack neurological function or better, and no patients required escalation to plasmapheresis. Bevacizumab was safe in all 10 participants, with only one

serious adverse event occurring within the 90-day follow-up, and this was not attributed to the medication. Larger randomized control trials are needed to properly assess the efficacy and safety of bevacizumab prior to it being incorporated into clinical practice.

Chronic Treatment to Prevent Attacks

In general, it is recommended that all patients with AQP4-IgG seropositive NMOSD be started on attack prevention treatments from onset given the potential severity of attacks and risk of incomplete recovery (a single attack can result in permanent blindness, paraplegia, or death from neurogenic respiratory failure) [76]. Initial studies showed that some MS treatments, such as IFN-β, natalizumab, alemtuzumab, and fingolimod can worsen AQP4-IgG seropositive NMOSD [77–80]. Early treatments used for AQP4-IgG seropositive NMOSD were focused on broad oral immunosuppressants utilized in the treatment of other autoimmune neurologic disorders and retrospective studies reported some possible benefit of mycophenolate and azathioprine [81]. However, these treatments take a long time to take effect and thus require concomitant corticosteroids for 3–6 months which can have a high side effect burden. With increasing knowledge of the immunopathogenesis of AQP4-IgG seropositive NMOSD, targeted mAb treatments to prevent attacks were developed and have been studied in clinical trials. In the following sections, we will discuss novel mAb treatments used in AQP4-IgG seropositive NMOSD other than monoclonal antibodies targeting complement. For a detailed discussion of therapies targeting the complement pathway in NMOSD and beyond, we refer the reader to the "anti-complement agents for autoimmune neurological diseases" accompanying article in this issue of neurotherapeutics. It is of note that transitional oral corticosteroids at low doses (20–30 mg oral prednisone daily followed by a taper) are often used to reduce the risk of early attacks while the prevention treatments take effect, which usually takes just a few weeks with these novel mAb treatments.

There are four mAbs with class 1 evidence for use (rituximab, inebilizumab, satralizumab, and eculizumab) [82], three of which have been approved by the US Food and Drug Administration (FDA) for the treatment of AQP4-IgG seropositive NMOSD (inebilizumab, eculizumab, and satralizumab) (Table 1). These treatments are very effective and although also very expensive, their use likely reduces downstream costs that would be incurred from breakthrough attacks which often require prolonged hospitalization and expensive attack treatment [83].

Treatment Options

Anti-CD20 Therapies

Rituximab

Therapeutic Mechanism Rituximab is a chimeric monoclonal IgG1 that binds to CD20 on B cells. Rituximab depletes CD20 + B cells in peripheral blood, with one goal to try to reduce the levels of AQP4-IgG. Other mechanisms of action may include inhibition of B/T-cell interactions, decreasing pro-inflammatory cytokines, and modulating the T-cell compartment [84–86]. BAFF is a B cell survival factor which supports autoreactive B cells and prevents their deletion [87]. Rituximab increases BAFF levels [88]. Belimumab, a BAFF inhibitor that has shown efficacy when used after rituximab in patients with systemic lupus erythematosus, may also be a consideration for investigation for NMOSD [89].

Evidence Prior to the evidence from randomized controlled trials (RCTs) for newer treatments, rituximab was commonly used and recommended as first-line maintenance therapy for AQP4-IgG seropositive NMOSD, given its efficacy in other autoimmune diseases [90, 91]. Rituximab showed efficacy for relapse prevention in multiple case series and retrospective analyses [92–98]. An open-label trial showed benefit of rituximab over azathioprine for relapse prevention [99].

RIN-1 Trial Design The RIN-1 study is a multicenter, randomized, double-blind, placebo-controlled clinical trial performed at eight hospitals in Japan, and published in 2020 [100]. Only AQP4-IgG seropositive patients were included. Patients were matched 1:1 for rituximab (intravenous treatment with 375 mg/m^2 every week for 4 weeks followed by two 1000 mg infusions 2 weeks apart at six monthly intervals) and placebo. Both groups had 19 patients. Relapse had occurred during the 2 years prior to enrollment in 12/19 (63%) patients assigned to rituximab and 11/19 (58%) assigned to placebo. The study period was 72 weeks.

Efficacy None (0/19 [0%]) of the patients on rituximab had relapses during the study period, compared to 7/19 (37%) of patients on placebo (CI: 12.3–65.5%; p value = 0.0058). However, the small sample size did not allow a reliable calculation of risk reduction by rituximab treatment. A post hoc analysis of AQPR-IgG titers found that in patients assigned placebo, titers increased or remained high and did not decrease in any patients. By contrast, in patients assigned rituximab, AQP4-IgG titers decreased gradually in six (32%) patients, suggesting that rituximab prevented relapses without reducing AQP4 antibody titers in the remaining 13 patients.

Table 1 Comparison of class 1 evidence for attack prevention treatments for AQP4-IgG seropositive NMOSD

Drug	Eculizumab	Rituximab	Inebilizumab	Satralizumab	
Target	C5	CD20	CD19	IL-6R	
Trial (reference)	PREVENT [78]	RIN-1 [93]	N-MOmentum [102]	SAkuraSky [121]	SAkuraStar [122]
Monotherapy or add-on?	Add-on or monotherapy	Monotherapy	Monotherapy	Add-on to baseline immunotherapy	Monotherapy
Randomization	2:1	1:1	3:1	2:1	1:1
Number of patients (drug group, control group)	(96, 47)	(19, 19)	(174, 56)	(41, 42)	(63, 32)
% of patients AQP4-IgG + (drug group, control group)	(100%, 100%)	(100%, 100%)	(93%, 93%)	(66, 67%)	(65%, 72%)
% of AQP4-IgG + patients who had a relapse (drug group vs control group)	(3% vs 43%)	(0% vs 37%)	(11% vs 42%)	(11% vs 43%)	(22% vs 57%)
Risk reduction in AQP4-IgG + patients	94%	Not reported	77%	79%	74%
Adverse effects	Infections, particularly with encapsulated bacteria (N. meningitidis, P. pneumonia, H. influenzae), therefore need for vaccination prior to treatment	Infections, hypogammaglobulinemia, infusion reactions	Infections, hypogammaglobulinemia, arthralgia	Infections, injection site reactions, elevated liver enzymes, neutropenia	
Maintenance administration	1200 mg every 2 weeks, IV	1 g × 2 doses every 6 months, IV	300 mg every 6 months, IV	120 mg every 4 weeks, subcutaneously	
Annual cost estimate in US$ (ref 80)	$700,000	$18,000	$262,000 ($393,000 the first year)	$190,000 ($219,000 the first year)	
Approval status for AQP4-IgG + NMOSD in USA	FDA approved in June 2019*	Not yet FDA approved	FDA approved in June 2020*	FDA approved in August 2020*	

*Not currently approved by the British National Formulary and orphan drug status with the European Medicines Agency. *FDA*, Food and Drug Administration; *IV*, intravenously; *MOGAD*, myelin oligodendrocyte–IgG-associated disease; *NMOSD*, neuromyelitis optica spectrum disorders

Adverse Events Adverse events were reported in 17/19 (90%) patients in both groups. Infusion reactions were more common in the rituximab group. No deaths occurred.

Ublituximab

Therapeutic Mechanism Ublituximab is a chimeric IgG1 targeting CD20 with a low fucose content of oligosaccharides [101]. The low fucose content allows it to bind with higher affinity to FcγRIIIa, which increases its ADCC activity to 100 times more than rituximab [102–104].

Evidence In 2019, results from an open-label phase 1 study were published. This was a safety and proof of concept trial in five patients with AQP4-IgG seropositive NMOSD [105]. Ublituximab (450 mg intravenously) was administered once, within 5 days of relapse onset, in addition to methylprednisolone (1 g intravenously for 5 days).

The primary outcome was safety with secondary efficacy measures. Expanded Disability Status Scale (EDSS) scores dropped from admission (median = 6.5) to 90-day follow-up (median = 4). Two subjects did not achieve total B cell depletion and relapsed within 3 months.

Although the adverse events of ublituximab were mostly immunosuppressive, there were no opportunistic infections or serious adverse events. Common side effects included diarrhea, constipation, fatigue, and neutropenia.

Anti-CD19 Therapies

Inebilizumab

Therapeutic Mechanism Inebilizumab is a humanized IgG1 targeting CD19, which has broader expression than CD20. CD20 is present on pre–B cells; naïve, mature, memory B cells; and some plasmablasts [106], whereas CD19 is a pan B cell marker, also present on pro-B cells, plasmablasts, and some plasma cells [107]. CD19 is also more selective for B cells, while CD20 can also be expressed on some T cells [52, 85, 108, 109]. Hence, CD19 might be a more attractive target than CD20 for B cell–directed therapies in AQP4-IgG seropositive NMOSD.

Evidence N-MOmentum Trial Design N-MOmentum is a multicenter, double-blind, randomized placebo-controlled, phase 2/3 trial for inebilizumab published in 2019 [110]. It was carried out across 99 centers in 25 countries. Patients were randomized 3:1 to the inebilizumab ($n=174$) and placebo ($n=56$) groups. Inebilizumab was administered intravenously at a dose of 300 mg (initial loading of 2 doses 2 weeks apart and then 6 monthly). The primary endpoint was time to onset of an NMOSD relapse.

Efficacy The trial was terminated early by the independent data-monitoring committee, due to a clear demonstration of efficacy. Only 21/174 (12%) of patients in the inebilizumab group had an attack of NMOSD, compared to 22/56 (39%) in the placebo group (hazard ratio 0.272 [95% CI 0.15–0.496]; $p<0.0001$). The efficacy was even better for AQP4-IgG seropositive patients, with relapse occurring in 18/161 (11%) in the inebilizumab group vs 22/52 (42%) in the placebo group ($p<0.001$). Although prior studies suggest that titers do not impact relapses [111, 112], AQP4-IgG titers after treatment have not yet been analyzed and may offer insights into the mechanism of action of inebilizumab.

Adverse Events Both groups had similar adverse event rates (72% inebilizumab vs 73% placebo). Serious adverse events were reported more frequently in the placebo group (9% vs 5%). One death occurred in each group. The cause of death for the patient in the placebo group was respiratory insufficiency related to NMOSD relapse. The cause of death for the patient in the inebilizumab arm was a CNS process of unclear etiology (the differential diagnoses were acute disseminated encephalomyelitis, atypical NMOSD attack, and progressive multifocal leukoencephalopathy).

Additional Analyses A post hoc analysis of 75 AQP4-IgG seropositive patients receiving inebilizumab for ≥ 4 years (randomized controlled period and open-label extension of the N-MOmentum study) found that 18 attacks occurred in 13 patients [113]. Of these, 12 attacks occurred in the first year of treatment and two per year in years 2–4. This suggests that the efficacy of inebilizumab may be enhanced after the first year of treatment. This may apply to all B cell–targeted treatments as early relapse after treatment has also been described with rituximab [114]. Reasons for this phenomenon are unclear but potentially include the time taken for the autoantibody to be removed from circulation, an increase in pro-inflammatory cytokines such as BAFF, and the release of AQP4-IgG from B cells [114]. Further studies assessing B cell depletion, AQP4-IgG titers, and BAFF levels, over time with inebilizumab treatment, are warranted to answer this question. Inebilizumab was well tolerated, with two serious adverse events related to inebilizumab in the study period and no deaths. IgG levels decreased over time; however, correlation between severe infections and low IgG levels could not be determined because of the small numbers [113]. A subgroup analysis found that the benefit of inebilizumab vs placebo remained, regardless of attack definition, type of attack, baseline disability, ethnicity, treatment history, or disease course [115]. Another analysis showed that compared with placebo, inebilizumab reduced the risk of 3-month EDSS-confirmed disability progression [116].

Infection Risk in CD19 and CD20 Targeted Treatments

Anti-B cell therapies have the potential to cause hypogammaglobulinemia. Although unproven, the risk theoretically may be greater with anti-CD19 than anti-CD20 treatments, given that CD19 is expressed on a wider repertoire of B cells. In the N-MOmentum trial, at day 197, IgG levels had decreased by 4.0% in the inebilizumab group and increased by 6.2% in the placebo group [110]. Hypogammaglobulinemia can lead to secondary antibody deficiency (SAD) with an increase in bacterial infections of the sinopulmonary and gastrointestinal tract and of viral infections such as enterovirus. Hypogammaglobulinemia can be transient and potentially reversible (partially or fully) but has the potential to limit the long-term use of B cell–depleting therapies [117, 118]. A study of ocrelizumab (anti-CD20) in patients with MS found that 5.4% of patients had low IgG levels after 5 years of treatment [119]. Lower baseline immunoglobulin levels result in lower post treatment levels and autoimmunity can occasionally be the first manifestation of primary immunodeficiency [120–122]. We therefore recommend checking pre-treatment immunoglobulin levels, in addition to hepatitis B/C and HIV serology. The role of testing for latent tuberculosis (TB) is less clear. While some physicians only do QuantiFERON testing in high-risk patients, the American College of Rheumatology recommends a more cautious approach with testing for all patients prior to rituximab treatment [123, 124]. A study in a TB endemic

area of the UK showed a 10% prevalence of latent TB in patients being treated with biologic therapy [125]. Even in non-endemic areas, latent TB infection can be frequent (> 1%) in patients receiving immunotherapy, which would support the need for screening of all patients [126]. We also recommend three monthly CBC and yearly IgG monitoring [127]. If IgG levels are low (especially < 500 mg/dL and/or recurrent infections), consider clinical immunology consult who can advise on the need for prophylactic antimicrobials and/or replacement with IVIg (0.4 g/kg once a month initially, titrated to effect on infection rate and/or to achieve a minimum IgG concentration of 800 mg/dL) [127]. The number of patients requiring immunoglobulin replacement following rituximab was 4.5% in a study of 8663 patients [128]. Note that the replacement dose is much lower than the immunomodulatory dose of IVIg used for the treatment of immune-mediated disorders. Hypogammaglobulinemia (pre- or post treatment) is not a contraindication to further B cell–targeted therapies [118, 129].

Anti-interleukin 6 Therapies

Tocilizumab

Therapeutic Mechanism Tocilizumab is a humanized mAb targeting the IL-6 receptor.

Evidence Several retrospective case series and reports suggested efficacy of tocilizumab in the treatment of NMOSD [130–133].

Three studies showed that tocilizumab led to an absolute risk reduction (ARR) for NMOSD relapses [130, 134, 135]. Two of the studies were in patients who had failed B cell therapies.

TANGO Trial Design The TANGO trial, published in 2020, is an open-label, multicenter, randomized, phase 2 trial for tocilizumab in NMOSD [136]. Patients were randomized 1:1 to receive treatment with tocilizumab (8 mg/kg every 4 weeks intravenously) or azathioprine (2–3 mg/kg/day orally), with 59 patients in each group. In total, 85% of patients in the tocilizumab group and 90% of patients in the azathioprine group were AQP4-IgG seropositive. The study period was 60 weeks.

Efficacy Relapse rates were lower in the tocilizumab group (8/59, 14%) than the azathioprine group (28/59, 47%) (hazard ratio [HR] 0.236 [95% CI 0.107–0.518]; $p < 0.0001$).

Adverse Events Tocilizumab had a lower rate of treatment-associated adverse events than azathioprine (61% vs 83%). The most commonly reported adverse events were increased alanine transaminase concentrations, upper respiratory tract infections, and urinary tract infections. There was one death in each group. The cause of death in the tocilizumab group was myelitis ascending to the medulla oblongata. In the azathioprine group, the cause of death was acute meningoencephalitis caused by Listeria monocytogenes.

Satralizumab

Therapeutic Mechanism Satralizumab is another humanized mAb targeting the IL-6 receptor. It was designed using recycling antibody technology™ to last longer in the circulation, and thus, have a longer half-life than tocilizumab [137, 138].

Evidence SAkuraSky Trial Design This was an international, randomized, double-blind, placebo-controlled, phase 3 trial [139]. It included AQP4-IgG seropositive and seronegative NMOSD patients. Patients received satralizumab ($n = 41$) or placebo ($n = 42$) in addition to their baseline oral immunosuppressive therapy. Satralizumab dosing was 120 mg subcutaneously at 0, 2, and 4 weeks and every 4 weeks thereafter. The median treatment duration with satralizumab was 107.4 weeks.

Efficacy Patients in the satralizumab treatment arm had a lower rate of relapse (8/41, 20%) than the placebo arm (18/42, 43%) (hazard ratio, 0.38; 95% confidence interval [CI], 0.16 to 0.88). Subgroup analysis showed better efficacy in patients with AQP4-IgG seropositive NMOSD (relapse occurred in 11% (3/27) of those in the satralizumab group and in 43% (12/28) of those in the placebo group (hazard ratio, 0.21; 95% CI, 0.06 to 0.75)). No differences were found in the AQP4 seronegative subgroup subanalysis.

Adverse Events The rates of serious adverse events (satralizumab 17%, placebo 21%) and infections (satralizumab 68%, placebo 62%) were similar in both groups. Injection site reactions were more frequently reported by patients in the satralizumab group (12% vs 5%). Other common adverse effects included neutropenia and elevated liver enzymes. No deaths occurred.

SAkuraStar Trial Design This was an international, randomized, double-blind, placebo-controlled, phase 3 trial [140]. It was carried out across 44 centers in 13 countries and included AQP4-IgG seropositive and seronegative NMOSD patients. In contrast to SAkuraSky, satralizumab was administered as monotherapy and taking other immunosuppressants concomitantly was prohibited. Patients were randomly assigned to receive satralizumab ($n = 63$) or placebo ($n = 32$). Treatment duration was until 44 protocol-defined relapses occurred or 1.5 years after random assignment of the last patient enrolled, whichever occurred first.

Efficacy Relapse occurred in 19/63 (30%) of patients in the satralizumab arm and 16/32 (50%) in the placebo arm

(hazard ratio 0.45, 95% CI 0.23–0.89; $p=0.018$). For AQP4-IgG seropositive patients, relapse occurred in 9/41 (22%) in the satralizumab group versus 13/23 (57%) in the placebo group (95% CI, 0.11–0.63).

Adverse Events Both groups had similar rates of serious adverse events (19% satralizumab vs 16% placebo) and infections (54% satralizumab vs 44% placebo). Patients on satralizumab did not report a higher frequency of injection site reactions in this trial (13% vs 16%).

Monitoring Requirements for Anti-IL-6 Therapies

Due to the effect on liver transaminases, monitoring of liver function tests is recommended (every 4 weeks for the first 3 months of treatment, every 3 months for 1 year, annually thereafter) in addition to CBC monitoring for neutropenia (4–8 weeks after initiation of therapy and annually thereafter) [127].

Emerging Treatments

Aquaporumab Aquaporumab is a non-pathogenic human mAb that binds to AQP4 with high affinity. It was generated from a recombinant pathogenic monoclonal AQP4-IgG [141, 142]. The Fc (fragment crystallizable) region of aquaporumab has been artificially mutated to prevent its CDC and ADCC effects. It competitively displaces AQP4-IgG from AQP4. Aquaporumab reduced NMO lesions in vitro models and in mice [143]. Given its highly specific mechanism of action, minimal side effects of treatment are anticipated but could include formation of antiidiotypic host antibodies against aquaporumab. Aquaporumab looks to be a promising treatment; however, a decade after its creation, there is no start date for clinical trials [144]. Moreover, we do not know of targeting a specific variable region epitope or epitopes is enough to block the polyclonal anti-AQP4 response and do not know for sure if it could be immunogenic itself. All of this will need to be addressed in human studies.

MOG-IgG-Associated Disease (MOGAD)

Pathogenesis

MOG is expressed on the surface of oligodendrocytes and is a minor component of the myelin sheath. The function of MOG has not been fully elucidated but evidence suggests it plays a role in adhesion of myelin fibers, regulation of microtubule stability, and myelin-immune system interactions via the complement pathway [145–147]. The majority of human MOG antibodies do not recognize rodent MOG, which has hampered applying animal MOG-IgG studies to human MOGAD. However, studies that used only human MOG-IgG that does recognize rodent MOG, and injected them intrathecally along with myelin reactive T-cells, found that this resulted in demyelination and complement deposition, suggesting pathogenic potential of the antibody [148]. This study used high titer antibodies and thus could suggest that higher titers are more likely to be pathogenic, whereas prior studies have shown that low titer results may be found in healthy and disease controls [30, 148, 149]. Though there is some evidence that persistently positive MOG-IgG titers are predictive of relapse, further studies, to evaluate the impact of seroconversion, are needed before MOG-IgG titers can be used as a marker to assess therapeutic efficacy [22, 150, 151]. It will be important to include MOG-IgG titers as a surrogate biomarker and correlate the values with outcome in upcoming clinical trials of MOGAD in order to determine if it could be a marker of therapeutic efficacy. The location of MOG-IgG production is yet to be fully elucidated though two sources of circulating autoantibodies have been proposed: plasmablasts that emerge from germinal center reactions in secondary lymphoid organs and long-lived plasma cells located in the bone marrow [55]. B cells activated in secondary lymphoid tissue may also migrate into the intrathecal compartment to undergo clonal expansion and differentiate into plasmablasts, potentially associated with the formation of ectopic tertiary lymphoid structures [152]. Recent studies have shown higher CSF MOG-IgG levels than expected from the patient's serum level as well as occasional circumstances when MOG-IgG is detected in the CSF and not serum, which is also suggestive of intrathecal synthesis of MOG-IgG [153, 154]. MOG-IgGs from most patients require bivalent binding. Since bivalently bound antibodies have been reported to only poorly bind C1q, the complement pathway may play a less active role in MOGAD than AQP4-IgG seropositive NMOSD [155]. However, the role of complement in MOGAD is controversial and remains yet to be fully determined. Specimens from biopsy and autopsy reveal perivenous as well as confluent cortical and white matter demyelination, CD4 + T cell and granulocyte infiltration, and complement deposition, and some studies have suggested loss of MOG immunostaining and others have not [156–158]. Unlike AQP4-IgG seropositive NMOSD, with MOGAD, the AQP4 immunostaining is preserved and astrocytes are also typically preserved [156–158]. In contrast to MS in which MRI T2-lesions persist over time, MOGAD T2-lesions often resolve completely in follow-up which might provide some insight into the better long-term prognosis and absence of a secondary progressive course in MOGAD [159]. The pathophysiologic underpinning of this much

higher frequency of lesion resolution when compared to MS is uncertain but it could relate to enhanced ability to remyelinate in MOGAD [159].

B Cells

In comparison to healthy controls, patients with MOGAD (similar to AQP4-IgG seropositive NMOSD) may have an imbalance in proinflammatory and anti-inflammatory B cells, with decreased regulatory and IL-10 + B cells and increased memory B cells as well as increased T-follicular helper cels (Tfh) [160]. However, it is important to remember that these results were from an immunophenotyping study with intracellular staining. Immunophenotyping studies are rarely reproduced and only allow for limited conclusions about the function of the cells studied. Naïve B cells are activated by Tfh cells, the activated B cells then differentiate to MOG-IgG-secreting plasmablasts (Fig. 2). Less than 50% of MOGAD patients harbor MOG-specific B cells in the peripheral blood, which are not linked to levels of MOG-IgG in serum, suggesting different sources of MOG-IgG [161]. Identification of MOG-specific B cells in blood could be of future relevance for selecting patients with MOG-IgG for B cell–directed therapy [161].

Interleukin-6

There are raised levels of Th17-related cytokines, such as IL-6, in the CSF of MOGAD patients during an attack. As described above, this is also seen in AQP4-IgG seropositive NMOSD but not in MS [162].

Therapeutic Strategies

Treatment of MOGAD can also be divided into acute treatments of attacks and chronic maintenance attack prevention treatments, again we will focus on the latter.

Acute Treatment of Attacks

We recommend acute treatment of all attacks. There is evidence to suggest that early glucocorticoid treatment could prevent residual damage [163]. First-line treatment is with 1 g of IV methylprednisolone daily for 5 days, with high-dose oral prednisolone 1250 mg daily for 5 days as an alternative. An oral steroid taper over weeks to months is sometimes considered to prevent early recurrence on steroid withdrawal. Most patients respond well to glucocorticoids [30]. For those that do not, second-line options are plasma exchange and IVIg (particularly in children) [164].

Chronic Treatment to Prevent Attacks

MOGAD is more likely to have a monophasic course with better recovery from attacks, when compared to AQP4-IgG seropositive NMOSD [151]. Due to the high proportion of people whose disease will remain monophasic (40–50%), preventative treatment is usually commenced only after a relapse occurs. There are exceptions to this rule, particularly if the first attack was life threatening or leaves the patient with severe residuals deficits (e.g., unilateral blindness). Similar to AQP4-IgG seropositive NMOSD, certain disease-modifying drugs used in MS (IFN-β, fingolimod, and natalizumab) do not appear to be effective [80, 165, 166]. Treatment options include oral immunosuppression, IVIg, and mAbs. In a study assessing the efficacy of

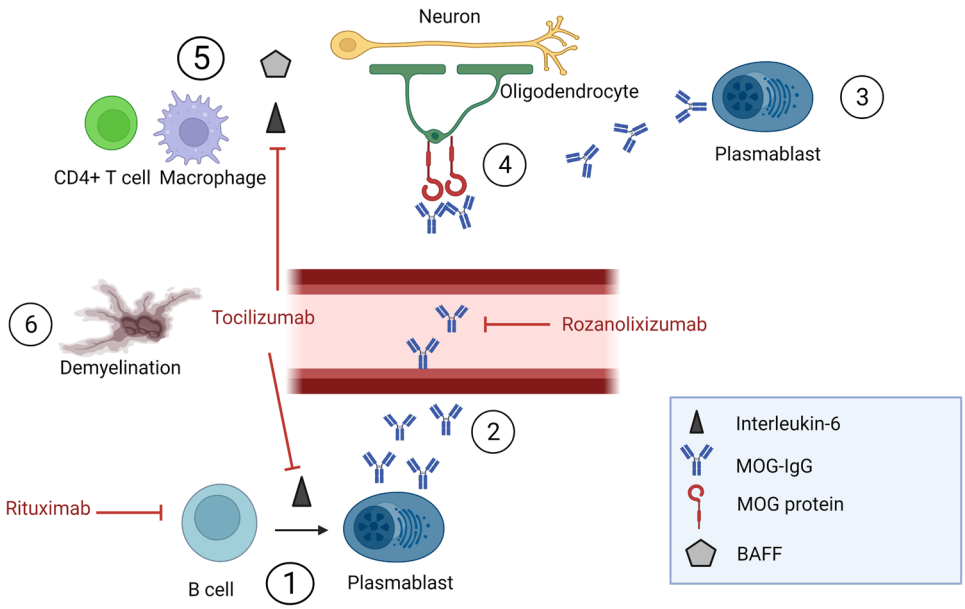

Fig. 2 Main pathogenic mechanism of MOGAD. 1 — B cells differentiate into MOG-IgG-secreting plasmablasts which is helped by interleukin-6; 2 — MOG-IgG enters the circulation and traverses the blood–brain barrier; 3 — there is also some intrathecal production of MOG-IgG; 4 — MOG-IgG binds to MOG protein on the surface of oligodendrocytes; 5 — inflammation occurs with release of cytokines such as interleukin-6 and BAFF and CD4 + T cells and macrophages are recruited; 6 — these cells damage neurons and oligodendrocytes; the end result is demyelination

different immunosuppressive therapies for relapse prevention in MOGAD, IVIg appeared to have the lowest annualized relapse rate, followed by azathioprine, then rituximab [166]. Evidence for treatment comes from case series and case reports, mostly retrospective. With no class 1 evidence and no FDA-approved treatments, prospective, placebo-controlled randomized controlled trials are urgently needed.

Treatment Options

Anti-CD20

Rituximab Several studies, including a meta-analysis, have shown a reduced risk of relapse with rituximab. However, it appears to be less effective than for AQP4-IgG seropositive NMOSD with relapse occurring in up to half of all patients, sometimes despite B cell depletion [167].

Anti-IL-6 Receptor

Tocilizumab Tocilizumab reduced the risk of MAGAD relapse in retrospective case series [133, 168].

Emerging Treatments

Rozanolixizumab Rozanolixizumab is a humanized IgG4 mAb targeting the neonatal Fc receptor (FcRn). FcRn is responsible for IgG recycling intracellularly and inhibiting it leads to accelerated elimination of IgG. Rozanolixizumab hence reduces plasma IgG levels [169, 170]. Phase 2 trials have shown its efficacy and safety in myasthenia gravis, and clinical trials for MOGAD are due to begin. Headaches are the most common side effect, occurring in up to 39% of patients [171, 172].

Discussion

There have been no head-to-head trials to compare the different monoclonal treatment options for NMOSD and MOGAD. Direct comparison is difficult due to differences in trial design and baseline patient characteristics. For example, when comparing B cell–depleting therapies for NMOSD, patients in the treatment group in RIN-1 had no relapses, whereas 12% of those in the treatment group in N-MOmentum had a breakthrough relapse. However, RIN-1 had a much smaller number of patients and patients had lower relapse rates in the 2 years prior to recruitment so there is no sufficient evidence to conclude that rituximab is a superior treatment to inebilizumab. By understanding the pathophysiology of these diseases, we have been able to develop highly targeted, effective treatments. In turn, the efficacy of these target treatments contributes to our understanding of the pathophysiological mechanisms. In the absence of definitive evidence of superiority of one drug, other factors that may influence treatment choice include whether the treatment is licensed, physician experience/comfort with the treatment, adverse effect profile, accessibility, patient preference, and cost.

Conclusions

Disease-modifying treatments used in MS are not effective for AQP4-IgG seropositive NMOSD or MOGAD. Acute treatment of NMOSD is with high-dose IV steroids and plasma exchange. AQP4-IgG seropositive NMOSD has four attack-prevention treatment options with class 1 evidence for use: eculizumab, inebilizumab, rituximab, and satralizumab. Tocilizumab also has some evidence for use and aquaporumab is a promising emerging therapy. Treatment is initiated after the first attack. Acute treatment of MOGAD is with corticosteroids and if refractory to steroids, plasma exchange or IVIg. There have been no randomized controlled trials for attack-prevention treatment of MOGAD, with observational evidence for oral immunosuppressants, IVIg, anti-B cell, and anti-IL-6 therapies. Since MOGAD can often have a monophasic course, treatment is often not started unless the patient has a relapse of disease.

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