Monoclonal antibody therapies for aquaporin-4-immunoglobulin G-positive neuromyelitis optica spectrum disorder and myelin oligodendrocyte glycoprotein antibody-associated disease

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Abstract:

Monoclonal antibody therapies mark the new era of targeted treatment for relapse prevention in aquaporin-4 (AQP4)-immunoglobulin G (IgG)-positive neuromyelitis optica spectrum disorder (AQP4-IgG+NMOSD). For over a decade, rituximab, an anti-CD20 B-cell-depleting agent, had been the most effectiveness treatment for AQP4-IgG+NMOSD. Tocilizumab, an anti-interleukin-6 receptor, was also observed to be effective. In 2019, several randomized, placebo-controlled trials were completed that demonstrated the remarkable efficacy of eculizumab (anti-C5 complement inhibitor), inebilizumab (anti-CD19 B-cell-depleting agent), and satralizumab (anti-interleukin-6 receptor), leading to the Food and Drug Administration (FDA) approval of specific treatments for AQP4-IgG+NMOSD for the first time. Most recently, ravulizumab (anti-C5 complement inhibitor) was also shown to be highly efficacious in an open-label, external-controlled trial. Although only some patients with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) warrant immunotherapy, there is currently no FDA-approved treatment for relapse prevention in MOGAD. Observational studies showed that tocilizumab was associated with a decrease in relapses, whereas rituximab seemed to have less robust effectiveness in MOGAD compared to AQP4-IgG+NMOSD. Herein, we review the evidence on the efficacy and safety of each monoclonal antibody therapy used in AQP4-IgG+NMOSD and MOGAD, including special considerations in children and women of childbearing potential.

Keywords:

Eculizumab, inebilizumab, myelin oligodendrocyte glycoprotein, neuromyelitis optica, rituximab, satralizumab

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) are central nervous system (CNS) inflammatory disorders that can cause optic neuritis and other demyelinating attacks of the CNS.[1,2] After the discovery of aquaporin-4-immunoglobulin G (AQP4-IgG), the antibody biomarker and pathogenic cause of NMOSD, we have witnessed phenomenal progress from bench research studying pathophysiology to clinical trials and the Food and Drug Administration (FDA)-approved monoclonal antibody therapies for relapse prevention in AQP4-IgG-positive NMOSD (AQP4-IgG+NMOSD) in merely two decades.[3,4]

More recently, MOG-IgG has been found to be a biomarker of MOGAD, a newly described disease that is separate from both NMOSD and multiple sclerosis.[5] MOGAD patients have a different prognosis than AQP4-IgG+NMOSD, with around half being monophasic, and recovery is often good, especially for optic neuritis.[6-8] While many MOGAD patients can be observed after an initial attack, MOGAD patients with a relapsing disease course or attacks causing severe residual disability usually require preventive immunotherapy. Clinical trials for monoclonal antibody therapies in MOGAD are underway. This review focuses on monoclonal antibody therapies for relapse prevention in AQP4-IgG+NMOSD and MOGAD.

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Aquaporin-4-immunoglobulin G+Neuromyelitis Optica Spectrum Disorder

AQP4-IgG+NMOSD is a relapsing disease that can cause severe disability, so all patients require lifelong maintenance immunotherapy for relapse prevention.[9] Broad immunosuppressive therapies, such as azathioprine and mycophenolate mofetil, were observed to be moderately effective in reducing annualized relapse rates (ARR).[10] In recent years, studies have shown that rituximab, an anti-CD20 monoclonal antibody, effectively prevents relapses, and it has been used as the most efficacious off-label treatment for NMOSD for over a decade.[11]

Recently, clinical trials for monoclonal antibodies targeting disease-specific pathophysiology have shown remarkable relapse risk reduction, leading to approvals by the FDA of three monoclonal antibodies in AQP4-IgG+NMOSD: eculizumab (2019), inebilizumab (2020), and satralizumab (2020) [Figure 1].[12-15] Most recently, the clinical trial on ravulizumab has been published, which also demonstrated high efficacy of the treatment.[16] In addition, rituximab and tocilizumab were shown to have a good efficacy in smaller clinical trials.[17,18] To date, there have been no head-to-head studies comparing any of these monoclonal antibody therapies, and the differences in the study design precluded direct comparisons.[19]

Many of the monoclonal antibodies are particularly effective in AQP4-IgG+NMOSD but have mixed results in AQP4-IgG-negative patients, highlighting the importance of the AQP4-IgG as a biomarker. For diagnostic accuracy, the AQP4-IgG should be tested in the serum by cell-based assays, which demonstrate the highest sensitivity and specificity [Table 1].[20]

Monoclonal Antibody Therapies in Aquaporin-4-immunoglobulin G-positive Neuromyelitis Optica Spectrum Disorder

B-cell depletion

Rituximab

Since AQP4-IgG was shown to be synthesized from circulating B-cells in the periphery, B-cell depletion was proposed as a therapeutic strategy.[21-23] Rituximab is a mouse–human chimeric monoclonal antibody, which was the first generation of anti-CD20 therapies,[24] and was the first monoclonal antibody used for relapse prevention in AQP4-IgG+NMOSD.[25] For over a decade, rituximab had been the first-line treatment

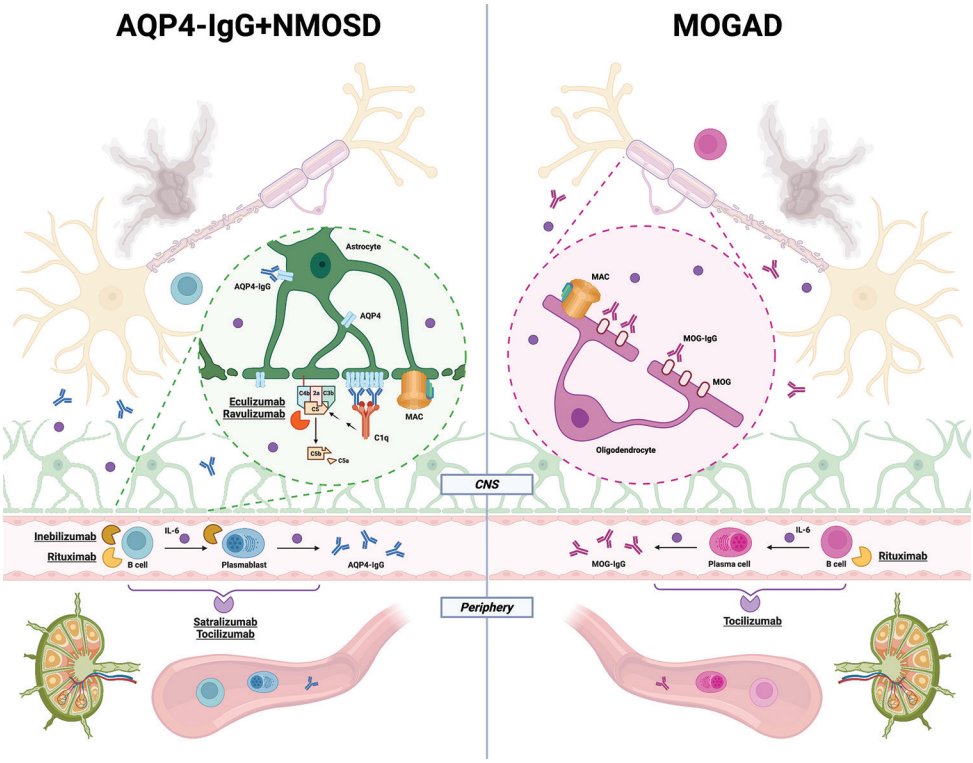

Figure 1: Pathophysiology and therapeutic targets of AQP4-IgG+NMOSD and MOGAD. AQP4-IgG and MOG-IgG are generated in the periphery before entering the CNS. B-cells are important for antibody production and are inhibited by rituximab and inebilizumab. IL-6 is a common important driver involved in T- and B-cell differentiation and inflammation. IL-6 receptor is inhibited by tocilizumab and satralizumab. In AQP4-IgG+NMOSD, complement-dependent cytotoxicity is a prominent mechanism of attacks that leads to astrocyte death followed by demyelination. The complement pathway is blocked by eculizumab and ravulizumab. In MOGAD, complement is also thought to play a role and may act predominantly through oligodendrocytes. However, complement inhibitors have not been explored in MOGAD. AQP4: Aquaporin-4; NMOSD: Neuromyelitis optica spectrum disorder; CNS: Central nervous system; MAC: Membrane attack complex; MOG: Myelin oligodendrocyte glycoprotein; MOGAD: MOG antibody-associated disease; IL-6: Interleukin-6

Table 1: Diagnostic criteria for aquaporin-4-immunoglobulin G-positive neuromyelitis optica spectrum disorder and myelin oligodendrocyte glycoprotein antibody-associated disease

Criteria	AQP4-IgG+NMOSD[1]	MOGAD[2]
Core clinical phenotypes	Optic neuritis	Optic neuritis
	Acute myelitis	Acute myelitis
	Area postrema syndrome	ADEM
	Acute brainstem syndrome	Cerebral monofocal or polyfocal deficits
	Symptomatic narcolepsy or acute diencephalic syndrome with typical lesions	Brainstem or cerebellar deficits
	Symptomatic cerebral syndrome with typical lesions	Cerebral cortical encephalitis, often with seizures
Antibody testing	Serum AQP4-IgG by cell-based assay (live or fixed)	Serum testing for MOG-IgG by cell-based assay (live preferred over fixed)*
	CSF testing for AQP4-IgG is not recommended	CSF testing for MOG-IgG can be considered if high suspicion, but serum MOG-IgG negative*
Recommended imaging	MRI	
	Optic nerve: T1 fat-saturated with Gd, T2/STIR fat-saturated; axial, coronal	
	Spinal cord (cervical, thoracic, or lumbar): T1 with Gd, T2/STIR; axial, sagittal	
	Brain: T1 with Gd, T2 FLAIR; axial, sagittal	
	OCT: RNFL, GCIP	
Common acute MRI findings	Optic nerve	Optic nerve
	T2 hyperintensity with Gd enhancement within the optic nerve(s)	T2 hyperintensity with Gd enhancement in the optic nerve(s), often involve optic nerve sheath and periorbital fat (perineural enhancement)
	Unilateral or bilateral	Unilateral or bilateral
	Longer than 50% of optic nerve	Longer than 50% of optic nerve
	The posterior part of the optic nerve and can involve the chiasm	The anterior part of the optic nerve, mostly with disc edema
	Spinal cord	Spinal cord
	T2 hyperintensity extending >3 vertebral segments (longitudinally extensive) with rim Gd enhancement; can have central T1 hypointensity	T2 hyperintensity extending >3 vertebral segments (longitudinally extensive) with or without Gd enhancement
		Central gray matter of the cord; can have H-sign
		Can involve the conus
	Brain	Brain
	T2 hyperintensity, often with Gd enhancement	Ill-defined T2 hyperintensity with or without Gd enhancement
	Dorsal medulla, particularly the area postrema, may extend from an upper cervical cord lesion	Multiple supratentorial and/or infratentorial white matter lesions
	Periependymal surfaces of the 4th ventricle in the brainstem/cerebellum	Deep gray matter
		Middle cerebellar peduncle, pons, or medulla
	Hypothalamus, thalamus, or periependymal surfaces of the 3rd ventricle	Cortical lesions with or without lesional and meningeal enhancement

Adapted from the 2015 International Panel for NMO Diagnosis criteria and the 2023 International MOGAD Panel proposed criteria.[1,2] *If the MOG-IgG is low positive in serum, reported without serum titers, or exclusively positive in the CSF, at least 1 additional supporting clinical or MRI criteria suggestive of MOGAD is required for diagnosis. NMO: Neuromyelitis optica, ADEM: Acute disseminated encephalomyelitis, AQP4: Aquaporin-4, FLAIR: Fluid-attenuated inversion recovery, GCIP: Ganglion cell-inner plexiform layer, CSF: Cerebrospinal fluid, Gd: Gadolinium, MOG: Myelin oligodendrocyte glycoprotein, MOGAD: MOG antibody-associated disease, NMOSD: NMO spectrum disorder, RNFL: Retinal nerve fiber layer, STIR: Short-tau inversion recovery, OCT: Optical coherence tomography, MRI: Magnetic resonance imaging, IgG: Immunoglobulin G

of NMOSD in the absence of FDA-approved therapies.[10] Its efficacy has been demonstrated in several observational studies.[26,27] A randomized, open-label trial showed that rituximab was more efficacious than azathioprine in reducing the ARR.[28]

The rituximab in neuromyelitis optica spectrum disorder (RIN-1) study was a randomized, multicenter, double-blind, placebo-controlled trial on rituximab as monotherapy in AQP4-IgG+NMOSD in Japan.[17] Patients received maintenance rituximab or placebo infusion every 6 months until the first relapse or 72 weeks of the study period if they had no relapses. B-cell depletion was confirmed by CD19 and CD20 percentages before each infusion. With 19 patients in each group, none of the patients receiving rituximab had relapses, whereas 37% of the patients receiving placebo did (group difference 36.8%).

Adverse events in patients receiving rituximab were not different from placebo except for the higher rate of infusion reactions in rituximab. Most adverse events were mild-to-moderate. While no cases of progressive multifocal leukoencephalopathy (PML) have been reported in the RIN-1 trial, an observational study in rheumatoid arthritis demonstrated that PML can rarely occur with rituximab (incidence: 2.56/100,000 person-years), often with additional risk factors for immunosuppression.[29]

A few different regimens for rituximab induction and strategies for reinfusion exist for NMOSD [Table 2].[30] The most commonly used induction regimens are: (1) two infusions of 1 g

Table 2: Monoclonal antibody therapies for relapse prevention in aquaporin-4-immunoglobulin G-positive neuromyelitis optica spectrum disorder

Monoclonal antibody (clinical trials)	Target	Route	Regimen	Pretreatment considerations	Adverse events
B-cell depletion					
Rituximab (RIN-1)*	CD20	IV	Induction Regimen 1: 1000 mg on days 1 and 15 Regimen 2: 375 mg every week for 4 weeks Maintenance Dosage: 1000 mg on days 1 and 15 or single 1000 mg dose Interval: Every 6 months or when B-cells repopulate (requires B-cell monitoring)	Baseline CBC, Ig Screening: HBV, HCV, HIV, TB Vaccine Live vaccine >4 weeks before initiation Killed, acellular, or toxoid vaccines >2 weeks before initiation	Infusion reaction Infection Hypogammaglobulinemia Lymphopenia PML (reported with rituximab - rare)
Inebilizumab (N-MOmentum)	CD19	IV	Induction: 300 mg on days 1 and 15 Maintenance: 300 mg every 6 months		
Complement inhibition					
Eculizumab (PREVENT)	C5	IV	Induction: 900 mg weekly for 4 weeks Maintenance: 1200 mg every 2 weeks	Vaccine Meningococcal vaccine (serotypes A, C, Y, W-135, and B); consider bridging antibiotic prophylaxis *H. influenzae* type B (Hib) vaccine Pneumococcal vaccine Live vaccine >4 weeks before initiation	Infusion reaction Infection: Increased risk of invasive encapsulated bacteria infection, i.e., *N. meningitidis, H. influenzae, S. pneumoniae*
Ravulizumab (CHAMPION-NMOSD)†	C5	IV	Induction: 2400–3000 mg (BW-based) on day 1, 3000–3600 mg (BW-based) on day 15 Maintenance: 3000–3600 mg (BW-based) every 8 weeks		
Interleukin 6 blockade					
Tocilizumab (TANGO)‡	IL6R	IV	8 mg/kg every 4 weeks	Baseline liver function Screening: HBV, TB Vaccine Live vaccine >4 weeks before initiation	Infusion (IV) or injection site (SC) reactions Infection Elevated liver enzymes
		SC	162 mg every 1–2 weeks (BW-based)		
Satralizumab (SAkuraSky, SAkuraStar)	IL6R	SC	Induction: 120 mg at weeks 0, 2, 4 Maintenance: 120 mg every 4 weeks		

Live vaccines, such as varicella and MMR vaccines, are contraindicated during immunotherapy. Given the risk of viral replication, live vaccines should be given at least 4 weeks before the treatment initiation. B-cell-depleting agents are known to attenuate vaccine response, but evidence on complement inhibitors and interleukin 6 blockers is less robust. Vaccines should be updated before starting B-cell depletion therapy. During treatment, delaying the next infusion to allow B-cell repopulation may be considered for maximal vaccine response. *Rituximab has not been approved by the FDA for relapse prevention in AQP4-IgG+NMOSD but has robust evidence, including the RIN-1 randomized controlled trial, suggesting good efficacy and is commonly used. In the RIN-1 trial, regimen 2 was used for induction, followed by two doses of 1000 mg rituximab (days 1 and 15) every 6 months, †The CHAMPION-NMOSD trial was published in March 2023. As of May 2023, ravulizumab has not been approved by the FDA for AQP4-IgG+NMOSD, ‡The TANGO trial was an open-label, head-to-head, randomized trial comparing IV tocilizumab to azathioprine in AQP4-IgG+NMOSD. BW: Body weight, CBC: Complete blood count, Ig: Immunoglobulin, IL6R: Interleukin 6 receptor, IV: Intravenous, MMR: Measles, mumps, and rubella, PML: Progressive multifocal leukoencephalopathy, SC: Subcutaneous, *H. influenzae: Haemophilus influenzae, N. meningiditis: Neisseria meningitidis, S. pneumoniae: Streptococcus pneumoniae*, MOGAD: Myelin oligodendrocyte glycoprotein antibody-associated disease, NMOSD: Neuromyelitis optica spectrum disorder, TB: Tuberculosis, FDA: Food and Drug Administration, HBV: Hepatitis B virus, HCV: Hepatitis C virus

of rituximab at 2 weeks apart and (2) 375 mg/m^2 of rituximab infusion every week for 4 weeks, both of which would amount to around 2 g in 1 month.[11,31] For the maintenance phase, reinfusion can be given every 6 months or guided by B-cell monitoring.[11,17,28] If reinfusion is guided by B-cell monitoring, initial monitoring for B-cell repopulation should be done every 2–3 months. The threshold for rituximab reinfusion depends on the tests: CD19$^+$ >1%, CD20$^+$ >1%, CD19$^+$ CD27$^+$ memory B-cells >0.05% (or >0.1% after 2 years of rituximab), or B-cell counts >10 cells/L.[32] B-cell depletion effect may last for years.[32,33] Reinfusion regimen could be the same as the induction or utilize a reduced dose at 1 g, which was also shown to sustain B-cell depletion.[11,32,34] Reduced dose and rituximab biosimilar can be cost-effective in resource-limited settings.

Inebilizumab

Inebilizumab is a humanized monoclonal antibody targeting the CD19 which is expressed on the surface of a broader range of B-cells than CD20, including plasmablasts and memory B-cells. The extended coverage of anti-CD19 has been theorized to be more efficacious than anti-CD20, but the concept has not been proven in a head-to-head trial.[35] The N-MOmentum trial was a randomized, double-blind, placebo-controlled phase 2/3 study evaluating the efficacy and safety of inebilizumab in NMOSD patients, which included both AQP4-IgG+ and AQP-IgG-negative.[13] Of note, 7/17 AQP-IgG-negative patients in the trial tested positive for MOG-IgG, which might have fulfilled the updated criteria for MOGAD.[2] Although inebilizumab was administered as monotherapy, all participants received concomitant oral corticosteroids (prednisolone 20 mg/day or equivalent) during the first 2 weeks. Patients who previously received rituximab had to be at least 6 months from the last dose at the time of enrollment.

In the N-MOmentum trial, inebilizumab reduced the risk of relapse by 73% compared to placebo (12% of the inebilizumab

group relapsed vs. 39% of the placebo group).[13] The effect was apparent among the AQP4-IgG+ patients but could not be determined for the AQP4-IgG-negative due to the low number of cases. Results from the open-label extension showed that 67% of relapses occurred within the first year of inebilizumab initiation.[36] The relapse-free probability was 87% at 1 year and remained stable for up to 4 years during the follow-up period.[36]

The rates of adverse events and serious adverse events were not statistically different between inebilizumab and placebo.[13] The most common adverse events were infection and infusion-related reactions (grade 1–2).[36] Although there was a stable decrease of IgG titers, no patients received intravenous immunoglobulin (IVIG) for hypogammaglobulinemia. The incident and severity of infection also did not increase over the 4 years of treatment.[36] Furthermore, there have been no cases of opportunistic infection or PML. Even though no treatment-related deaths were reported, one patient receiving inebilizumab died after having large new brain lesions with cardiopulmonary complications. The differentials included acute disseminated encephalomyelitis (ADEM), atypical NMOSD attack, and PML, so the possibility of being related to treatment could not be excluded.[13]

Complement inhibition

Eculizumab

Eculizumab is a humanized monoclonal antibody targeting the complement protein C5. It acts by inhibiting the cleavage of C5 into C5a and C5b, which are inducers of downstream inflammation and membrane attack complex (MAC) formation, respectively. Complement inhibition was proposed to prevent astrocyte killing from complement activation that follows AQP4-IgG binding to astrocytes.

The Prevention of Relapses in Neuromyelitis Optica (PREVENT) trial was a phase 3 randomized, double-blind, placebo-controlled, time-to-event trial that evaluated the safety and efficacy of eculizumab in AQP4-IgG+NMOSD patients.[12] The primary endpoint was the first adjudicated relapse. Participants were allowed to continue to receive their prior immunosuppressive therapies, except for rituximab, mitoxantrone, or IVIG. Those who received rituximab or mitoxantrone within 3 months or IVIG within 3 weeks before screening were excluded. Of note, the short duration from prior treatments could potentially introduce carry-over effects from rituximab.[11] All participants were vaccinated against *Neisseria meningitidis* before receiving a trial agent.

The PREVENT trial showed that eculizumab significantly reduced the risk of adjudicated relapse by 94%, with 3% of patients receiving eculizumab having a relapse compared to 47% of patients receiving placebo. The ARR in patients receiving eculizumab was 0.02. Among patients without concomitant immunotherapy, those receiving eculizumab also had a significantly lower risk of relapse. The open-label extension showed that 96% of those receiving eculizumab monotherapy remained relapse free at almost 4 years.[37]

The rates of adverse events were similar between the eculizumab and the placebo groups with headaches, upper respiratory tract infection, nasopharyngitis, and urinary tract infection being the most common.[12,38] Patients receiving eculizumab were not observed to have an increased risk of serious infection. However, there was one mortality case from pulmonary empyema in a patient receiving eculizumab with concomitant azathioprine.[12]

Since the C5b is important for MAC formation, eculizumab carries a risk of bacterial infection, particularly from the encapsulated *Neisseria meningitidis*. Although meningococcal meningitis is rare in the general population, the risk in patients receiving eculizumab has been shown to increase by 1000-fold in a study in those treated with eculizumab for paroxysmal nocturnal hemoglobinuria.[39] Of note, all patients required meningococcal vaccination before treatment, but serotype coverage varies by vaccine availability, and infection can be from a non-covered serotype.[39,40] Although the PREVENT protocol did not specify the meningococcal vaccine regimen, none of the patients developed meningococcal infection during the trial and its open-label extension.[12,37,38] However, in the previous pilot study, one patient had meningococcal sepsis and sterile meningitis.[41] There was also one patient with *Neisseria gonorrhoeae* infection which resolved with antibiotics.[38] A case series from the US FDA report showed that eculizumab might be associated with an increased risk of disseminated gonococcal infection, although this has not yet been observed in AQP4-IgG+NMOSD patients.[42]

Ravulizumab

With the FDA approval of eculizumab and other treatments for NMOSD, placebo-controlled trials were no longer ethical. The CHAMPION-NMOSD trial was a phase 3 open-label, external-controlled interventional study evaluating the efficacy of ravulizumab.[16] Ravulizumab is a complement C5 inhibitor that binds to the same epitope as eculizumab but has a longer action and dosing interval, extending it from 2 to 8 weeks. The placebo group from the PREVENT trial was used as an external comparator with sensitivity analysis using propensity scores, and therefore the inclusion criteria of the two trials were similar. Only AQP4-IgG+NMOSD patients were included. Among 58 patients, there were no adjudicated on-trial relapses in the ravulizumab group, so the primary treatment period was ended when all patients had completed at least 50 weeks of ravulizumab treatment or discontinued before that time. During the median 74 weeks of ravulizumab treatment, the risk of relapse was reduced by 98.6% compared to the placebo group in the PREVENT study, which was consistent across the prespecified subgroups of patients receiving ravulizumab monotherapy and regardless of rituximab use in the prior year.

The most common adverse events in patients receiving ravulizumab were COVID-19 and headache. Meningococcal infection occurred in two patients despite vaccination against five serotypes (A, C, W, Y, and B), leading to discontinuation before the 50 weeks in one patient. The other patient had

concomitant B-cell depletion due to prior rituximab exposure. Both fully recovered from the infection with rapid antibiotic initiation and intensive care.

Interleukin-6 blockade

Tocilizumab

Interleukin-6 (IL-6) was found to be elevated in the serum and cerebrospinal fluid (CSF) of NMOSD patients and is involved in several steps of the pathophysiology.[43,44] Tocilizumab was the first humanized monoclonal antibody against the IL-6 receptor approved for other autoimmune conditions, such as giant cell arteritis. Although most data on tocilizumab in AQP4-IgG+NMOSD were case series, there was one head-to-head, randomized, open-label, phase 2 trial comparing tocilizumab to azathioprine in highly relapsing NMOSD patients (TANGO trial).[18,45,46]

During the TANGO trial, patients were allowed to have concomitant immunotherapies during the first 12 weeks of tocilizumab or the first 24 weeks of azathioprine initiation before receiving the trial agent as monotherapy. Patients with a prior history of azathioprine failure or recent B-cell depletion were excluded from the study. Patients receiving tocilizumab had a 76% reduced risk of relapse compared to those receiving azathioprine; 14% vs. 47% had relapses during the trial. Interestingly, around 40% of the participants had concomitant autoimmune diseases, such as Sjogren's syndrome or rheumatoid arthritis, and the efficacy of tocilizumab was more pronounced in those with concomitant autoimmune diseases. The risks of adverse events were similar in both groups. There was one death in each group, both related to a severe transverse myelitis relapse with complications.

Overall, tocilizumab seemed to be effective for relapse rate reduction in AQP4-IgG+NMOSD with a favorable safety profile.[46] Most studies, including the TANGO trial, used intravenous tocilizumab at 8 mg/kg every 4 weeks. There was a case series on subcutaneous tocilizumab at 162 mg every 1–2 weeks, depending on the weight.[47]

Satralizumab

Satralizumab is also a humanized monoclonal antibody that targets the IL-6 receptor, blocking the downstream effects of IL-6.[44,48,49] Satralizumab harbors the antibody recycling capability by pH-dependent dissociation within acidic endosomes which prolongs the duration of action.[14,50] This allows subcutaneous treatment with satralizumab every 4 weeks. Two double-blind, randomized, placebo-controlled phase 3 trials for satralizumab in NMOSD patients have been completed: the SAkuraSky for satralizumab as an add-on therapy and the SAkuraStar for satralizumab monotherapy.[14,15] Both AQP4-IgG+ and AQP4-IgG-negative NMOSD patients were included in these studies. Currently, a phase 4 prospective, open-label study with comprehensive imaging and fluid biomarker assessments of AQP4-IgG+NMOSD patients receiving satralizumab (SAkuraBonsai) is ongoing.[51]

The SAkuraSky trial evaluated the efficacy and safety of satralizumab as an additional treatment to baseline immunosuppressive therapy in adolescent and adult NMOSD patients (aged 12–74 years). Those immunosuppressive therapies included azathioprine (<3 mg/kg/day), mycophenolate mofetil (<3000 mg/day), or oral corticosteroids (equivalent to prednisolone <15 mg/day) that had been at a stable dose for at least 8 weeks before enrollment but did not include rituximab. Randomization was stratified by baseline ARR, and the primary endpoint was the first adjudicated relapse. In the SAkuraSky, satralizumab reduced the risk of relapse by 62%, with 20% of patients in the satralizumab group having a relapse compared to 43% in the placebo group. However, 66% of the participants were AQP4-IgG+, and relapse reduction was only significant in the AQP4-IgG+subgroup.[14] Among the AQP4-IgG+NMOSD participants, there was a 79% relapse reduction compared to placebo. After the double-blind period ended with 26 protocol-defined relapses, 80% of participants entered the open-label extension. During the whole satralizumab treatment period, 71% of patients were relapse free at almost 4 years.[52]

The SAkuraStar trial which evaluated satralizumab as a monotherapy in NMOSD patients was published the following year.[15] Only adults (aged 18–74 years) were included, and participants had to be free from immunosuppressive therapy for at least 3 months since concomitant immunosuppressive therapy was prohibited. The last dose of anti-CD20 agent or eculizumab had to be at least 6 months. Randomization was stratified by previous relapse prevention therapy. Thirty percent of the satralizumab group relapsed compared to 50% of the placebo group, reducing the risk of relapse by 55%. Similar to the SAkuraSky trial, the significant relapse risk reduction was only observed among AQP4-IgG+NMOSD patients, which had a 74% reduction in relapse compared to placebo. After 1.5 years, 89% of participants entered the open-label extension of SAkuraStar, which showed that 73% of patients were relapse free at almost 4 years.[52]

The rates of adverse events and serious adverse events were not different between satralizumab and placebo in the SAkuraSky and the SAkuraStar trials, and the rates remained similar during the open-label extensions.[14,15,53] The most commonly reported adverse events were infections, with upper respiratory tract and urinary tract as the leading sources. Grade 1–2 neutropenia or thrombocytopenia was observed but was mostly transient and not associated with serious infection or bleeding. No deaths, anaphylactic reactions, opportunistic infections, or PML had been reported. The rates of satralizumab discontinuation due to adverse events were consistently low at 9% in the SAkuraSky and 3% in the SAkuraStar and their respective open-label phases.[53]

Special Patient Populations

Children with aquaporin-4-immunoglobulin G-positive neuromyelitis optica spectrum disorder

All of the clinical trials for monoclonal antibodies in AQP4-IgG+NMOSD were conducted in adults, with an extension to adolescents for satralizumab. Eculizumab is approved in children with paroxysmal nocturnal

hemoglobinuria but not yet with AQP4-IgG+NMOSD. Open-label studies in children with AQP4-IgG+NMOSD are underway for eculizumab, satralizumab, inebilizumab, and ravulizumab [Table 3]. Case series has shown that rituximab appears to be effective and safe in children with NMOSD.[54,55] However, there are challenges with dosing and timing of repeated rituximab infusion in children. Since the regimens used in children were heterogeneous and relapses occurred with B-cell repopulation, a close B-cell monitoring may be required in children.[54,56] A few case reports have suggested that tocilizumab can prevent relapses in children who relapsed despite B-cell depletion from rituximab.[57,58]

Women of childbearing potential with aquaporin-4-immunoglobulin G-positive neuromyelitis optica spectrum disorder: Pregnancy and lactation

Although AQP4-IgG+NMOSD preferentially affects women of childbearing potential, no prospective studies included AQP4-IgG+NMOSD patients undergoing pregnancy or lactation. Retrospective studies suggest the ARR may increase during 3-month postpartum, but immunotherapy was associated with a lower risk of peripregnancy relapse.[59] The decision to continue, stop, or switch immunotherapy during pregnancy should be individualized. There are case series suggesting that rituximab, eculizumab, and tocilizumab are not associated with adverse pregnancy or neonatal outcomes.[60-63] The expression of monoclonal antibody in breast milk is negligible, given their large molecular weights.[64]

Recommended peripregnancy vaccination in NMOSD patients has been reviewed elsewhere.[61,65] The timing of vaccination and monoclonal antibody therapy has to optimize relapse prevention, vaccine response, and avoid complications from live vaccines, especially with B-cell depleting agents.[66]

Myelin oligodendrocyte glycoprotein antibody-associated disease

Unlike AQP4-IgG+NMOSD, only around half of MOGAD patients have a relapsing disease course.[7,8] Although there are currently no clear predictors of relapses, some evidence suggests that an onset attack with optic neuritis and delayed acute steroid treatment might be associated with a higher risk of relapse.[7,67] In contrast, pediatric onset, an onset attack with transverse myelitis, and MOG-IgG seroreversion to negative might be associated with a lower risk of relapse, but these findings were not consistently found.[8,68-70] In general, MOGAD attacks are more responsive to acute steroid treatment and have a milder residual disability than AQP4-IgG+NMOSD.[71,72] However, some attacks may require aggressive treatment with plasma exchange, and rare instances of critical attacks requiring ventilatory support can also occur with ADEM or cortical encephalitis phenotypes.[73,74]

Table 3: Ongoing phases 2 and 3 clinical trials for relapse-preventing monoclonal antibody in aquaporin-4-immunoglobulin G-positive neuromyelitis optica spectrum disorder and myelin oligodendrocyte glycoprotein antibody-associated disease

Monoclonal antibody	Phase (ClinicalTrial.gov identifier; name)	Target	Route	Trial design
AQP4-IgG + NMOSD				
Inebilizumab	2 (NCT05549258)	CD19	IV	Open-label trial in children 2–17 years old
Eculizumab	2/3 (NCT04155424)	C5	IV	Open-label trial in children 2–17 years old
Ravulizumab	2/3 (NCT05346354)	C5	IV	Open-label, historical-controlled trial in children 2–17 years old
Satralizumab	3 (NCT05199688; SAkuraSun)	IL6R	SC	Open-label, uncontrolled trial in children 2–11 years old
Daratumumab	2/3 (NCT05403138; DAWN)	CD38	IV	Randomized, double-blind, placebo-controlled trial in adults >18 years old
Divozilimab	2/3 (NCT05730699; BCD-132-6/ AQUARELLE)	CD20	IV	Randomized, double-blind, placebo-controlled trial in adults >18 years old
MIL62	1b/3 (NCT05314010)	CD20	IV	Randomized, double-blind, placebo-controlled trial in adults 18–60 years old
Ofatumumab	1/2 (NCT05504694)	CD20	SC	Open-label, single-arm, pilot study in adults >18 years
Belimumab	1/2 (NCT05154734)	BLyS	IV	Open-label, single-arm, pilot study in adults >18 years
MOGAD				
Satralizumab	3 (NCT05271409; Meteoroid)	IL6R	SC	Randomized, double-blind, placebo-controlled trial in >12 years old
Rozanolixizumab	3 (NCT05063162; cosMOG)	FcRn	SC infusion	Randomized, double-blind, placebo-controlled trial in adults 18–89 years old
Rituximab	3 (NCT05545384; IDAR)	CD20	IV	Randomized, open-label study comparing rituximab after the 1st attack compared to standard of care (no maintenance immunotherapy after the 1st attack) in children 6–17 years old

Data were retrieved from ClinicalTrial.gov in May 2023. Apart from monoclonal antibody, other novel approaches for the potential treatment of AQP4-IgG + NMOSD include small-molecule BTK inhibitors (NCT05284175, NCT05356858, NCT04670770), JAK1/JAK2 inhibitor (NCT05792462), proteasome inhibitor (NCT02893111), B-cell depletion with TACI-Ig fusion protein (NCT03330418), and autologous hematopoietic stem cell transplantation (NCT00716066). AQP4-IgG+NMOSD: Aquaporin-4-IgG-positive neuromyelitis optica spectrum disorder, BLyS: B lymphocyte stimulator, FcRn: Neonatal Fc receptor, Ig: Immunoglobulin, IL6R: Interleukin-6 receptor, IV: Intravenous, MOGAD: Myelin oligodendrocyte glycoprotein antibody-associated disease, SC: Subcutaneous, TACI: Transmembrane activator calcium modulator and cyclophilin ligand interactor

Given the unclear risk of relapse and the good recovery with acute treatment, whether to put patients on chronic immunotherapy is a clinical judgment which requires a shared decision-making between the physician and the patient. In general, relapse prevention immunotherapy is not routinely prescribed after the first MOGAD attack but should be considered for patients who are relapsing or have significant residual disability from the first attack. The duration of immunotherapy is also undetermined, but it may be reasonable to try tapering off treatment in patients who have been in remission for 3–4 years with minimal disability. Early acute steroid treatment without chronic relapse prevention immunotherapy might be a suitable strategy for some patients who have excellent recovery, long intervals between attacks, and an easy access to prompt acute treatment.

To date, there has been no FDA-approved immunotherapy for relapse prevention in MOGAD. Observational studies suggested that maintenance IVIG might be one of the more effective treatments in MOGAD, whereas rituximab was less effective in MOGAD compared to NMOSD and might be comparable to azathioprine and mycophenolate mofetil.[75,76] Tocilizumab has also been used successfully, particularly as an escalation therapy in refractory cases.[77,78] Currently, two randomized clinical trials are ongoing for satralizumab and rozanolixizumab as maintenance immunotherapies in relapsing MOGAD.

Monoclonal Antibody Therapies in Myelin Oligodendrocyte Glycoprotein Antibody-associated Disease

B-cell depletion: Rituximab

A recent meta-analysis of observational studies in MOGAD showed that the ARR was significantly lower while on rituximab (mean reduction 0.92 relapses/year), but up to 60% of relapsing MOGAD patients continued to have relapses despite treatment.[75,79-81] With similar rituximab regimens to AQP4-IgG+NMOSD, the effectiveness in relapse prevention in MOGAD is less robust.[80,82] Of note, relapses in MOGAD were not associated with B-cell repopulation, with 80% of relapses occurring while B-cells ($CD19^+$ or $CD27^+$) were still depleted, suggesting a different mechanism of disease.[79,82] Rituximab has also been reported to reduce the ARR in children with relapsing MOGAD and could be continued during pregnancy, although evidence regarding pregnancy in MOGAD patients is scarce.[83,84] However, there are no randomized clinical trials for B-cell depleting agents for relapse prevention in MOGAD.

Interleukin-6 blockade: Tocilizumab

Similar to AQP4-IgG+NMOSD, CSF IL-6 is elevated in MOGAD patients, suggesting a potential therapeutic target.[85] Observational studies have shown that MOGAD patients who relapsed on rituximab had a remarkable response to tocilizumab, with 79% being relapse free.[77,78,86] Both intravenous and subcutaneous forms of tocilizumab have been reported in MOGAD. Some retrospective studies suggest that children with relapsing MOGAD refractory to rituximab and IVIG may respond to tocilizumab.[78,87]

Randomized clinical trials for monoclonal antibody therapies in myelin oligodendrocyte glycoprotein antibody-associated disease

Satralizumab, another IL-6 receptor blocker, is being studied in the Meteoroid trial (NCT05271409), which is enrolling relapsing MOGAD patients who are at least 12 years old.[88] Another ongoing clinical trial is investigating the efficacy and safety of rozanolixizumab (cosMOG trial; NCT05063162) in relapsing MOGAD patients aged 18–89 years.[89] Rozanolixizumab is a monoclonal antibody against the neonatal Fc receptor (FcRn) which is involved in the recycling of endocytosed IgGs.[90,91] Endocytosed IgGs, both normal and pathogenic, which are not bound to FcRn are susceptible lysosomal degradation.[91] Rozanolixizumab has recently been shown to be effective in a randomized, placebo-controlled trial for generalized myasthenia gravis with acetylcholine receptor antibody or muscle-specific kinase antibody, suggesting a role in antibody-mediated diseases.[92] MOGAD will be the first demyelinating disease to be treated with rozanolixizumab in a clinical trial.

Conclusion

The discoveries of AQP4-IgG and MOG-IgG have paved the ways for studying the pathophysiology of AQP4-IgG+NMOSD and MOGAD. Several therapeutic targets involved in the mechanisms of disease have been identified. B-cell depletion (rituximab and inebilizumab), complement C5 inhibition (eculizumab and ravulizumab), and IL-6 blockade (tocilizumab and satralizumab) are highly effective relapse prevention strategies for AQP4-IgG+NMOSD. Rituximab seemed to be less effective in relapsing MOGAD, and patients can have breakthrough relapses despite B-cell depletion. While maintenance IVIG is often used for patients with relapsing MOGAD disease, refractory MOGAD patients may respond to tocilizumab. Clinical trials for monoclonal antibody therapies in MOGAD are underway, including satralizumab and rozanolixizumab.

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Conflicts of interest

There are no conflicts of interest.

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