Advances in the long-term treatment of neuromyelitis optica spectrum disorder

Monique Anderson and Michael Levy

Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA.

Journal of Central Nervous System Disease
Volume 16: 1–11

DOI: 10.1177/11795735241231094

Sage

ABSTRACT

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune neuroinflammatory disorder with a prevalence of 1-5/100,000 globally, characterized by attacks of the central nervous system including but not limited to optic neuritis, transverse myelitis and brainstem lesions, including area postrema lesions. These autoimmune attacks can lead to irreversible damage if left untreated, therefore strategies have been developed to prevent relapses. Initial off-label treatments have achieved variable levels of success in relapse prevention, but improved relapse prevention and quality of life remain a goal in the field. A better understanding of the underlying pathophysiology of NMOSD over the last 10 years has led to newer, more specific approaches in treatment, culminating in the first FDA approved treatments in the disease. In this review, we will discuss the seminal trials of PREVENT or Eculizumab in the treatment of aquaporin-4 (AQP4)-IgG positive NMOSD, N-Momentum or Inebilizumab in the study of NMOSD (both AQP4-IgG positive and negative) and SAkura Sky and SAkuraStar which studied satralizumab in AQP4-IgG seropositive and seronegative NMOSD patients. We will also discuss the extension trials of each of these medications and what lead to their approval in AQP4-IgG seropositive NMOSD patients. We will then examine treatments in the pipeline for adult and pediatric NMOSD patients and conclude with discussions on treatment considerations in pregnant patients and how to approach treatment of NMOSD patients during COVID.

PLAIN LANGUAGE SUMMARY

Neuromyelitis optica spectrum disorder (NMOSD) is a rare central nervous system inflammatory disorder caused by the aquaporin-4 antibody (AQP-4 IgG) labeling and immune system attack of astrocytes, and later downstream loss of myelin, the protective sheath surrounding neurons. It occurs in approximately 1-5 individuals per 100,000 globally and is characterized by attacks of the central nervous system including but not limited to optic neuritis, transverse myelitis and brainstem lesions, including area postrema lesions. These autoimmune attacks can lead to irreversible damage if left untreated, therefore strategies have been developed to prevent additional attacks. Initial off-label treatments have achieved variable levels of success in relapse prevention, but improved immune attack prevention and quality of life remain a goal in the field. A better understanding of the underlying causes of NMOSD over the last 10 years has led to newer, more specific approaches in treatment, culminating in the first FDA approved treatments in the disease. In this review, we will discuss the trials PREVENT or Eculizumab in the treatment of aquaporin-4 (AQP4)-IgG positive NMOSD, N-Momentum or Inebilizumab in the study of NMOSD (both AQP4-IgG positive and negative) and SAkura Sky and SAkuraStar which studied satralizumab in AQP4-IgG seropositive and seronegative NMOSD patients. We will also discuss the extension trials of each of these medications and what lead to their approval in AQP4-IgG seropositive NMOSD patients. We will then examine treatments in the pipeline for adult and pediatric NMOSD patients and conclude with discussions on treatment considerations in pregnant patients and how to approach treatment of NMOSD patients during COVID.

KEYWORDS: Neuromyelitis optica spectrum disorder, annualized relapse rate, expanded disability status scale

RECEIVED: August 9, 2023. **ACCEPTED:** December 19, 2023.

TYPE: Review

DECLARATION OF CONFLICTING INTERESTS The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Michael Levy discloses roles as a pharmaceutical consultant for Alexion, Chugai, Horizon, Roche, Genzyme, UCB, and Quest Diagnostics. This role allowed for early disclosure of results for the CHAMPION trial. Additionally, Dr Michael Levy has pharmaceutical grants from Alexion, Shire, Horizon, Genzyme, Sanofi, UCB. These grants were not involved in the funding for the writing and research of this review article.

FUNDING The author(s) received no financial support for the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Monique Anderson, Division of Neuroimmunology, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, 55 Fruit St. Boston, MA 02114, USA.
Email: manderson53@mgh.harvard.edu

Introduction

Neuromyelitis optica (NMO), formally known as Devic's disease, was considered a rare and severe variant of multiple sclerosis (MS) with a predilection for optic neuritis and transverse myelitis. Since the discovery of the aquaporin-4 antibody (AQP4-IgG) biomarker in 2004, NMO has been recognized as a distinct clinical entity.[1] With improvement in the detection of the AQP4-IgG antibody and a >99% specificity, it allowed for categorization of NMO spectrum disorders (NMOSD) which broadly includes all cases of neuroinflammation in the context of a seropositive AQP4 test and allows for seronegative disease of optic neuritis, longitudinally extensive transverse myelitis (LETM), and/or additional immune mediated attacks of the brain stem, and area postrema syndrome.[2,3] The prevalence of NMOSD is approximately 1-5 cases per 100,000 globally,

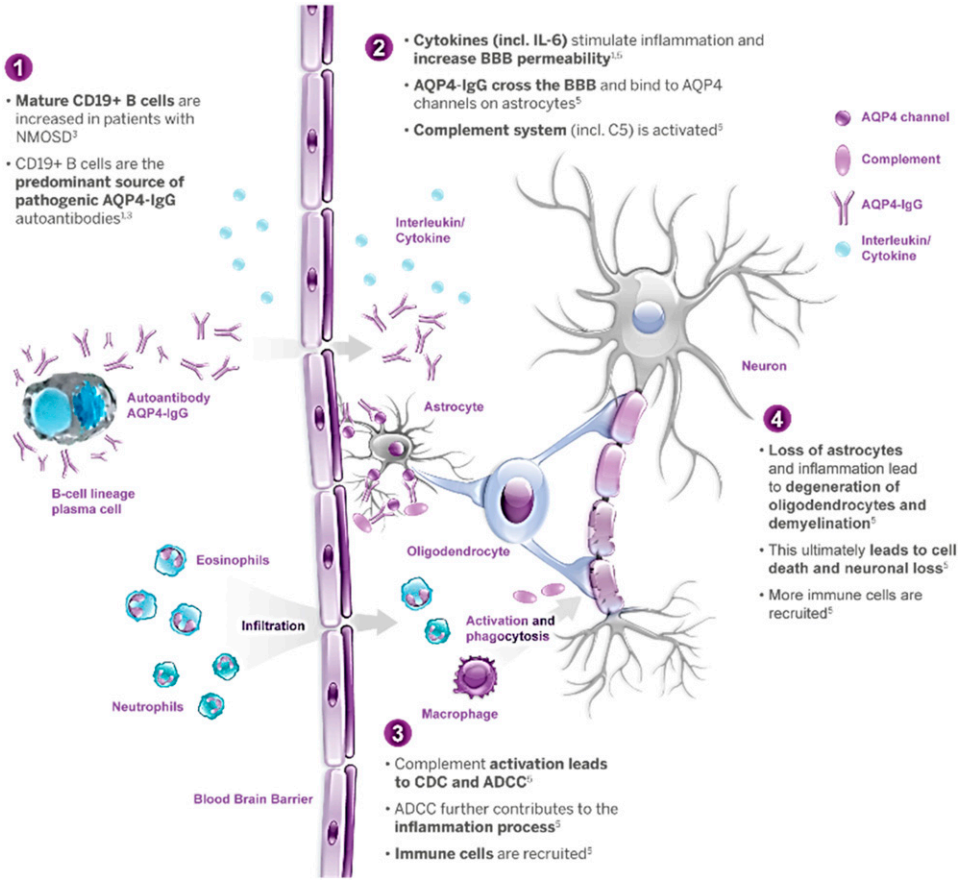

Figure 1. The role of CD19T cells in NMOSD. As noted, $CD19^{+}$ cells are shown to be the predominant source of AQP4-IgG autoantibodies, leading to cytokine release and complement activation and subsequent loss of astrocytes. Uplinza is proposed to act by eliminating these $CD19^{+}$ B cells. And proposed downstream effects in NMOSD. (Reprinted from UplinzaTM).

with race and sex skewed towards non-Caucasian and female.[4] NMOSD is due to an immune mediated attack on the AQP4 water channel on astrocytes, resulting in astrocyte death and secondary demyelination; the pathogenic process recruits humoral immune components such as granulocytes, immunoglobulin and complement.[5]

The disease course of NMOSD is also distinct amongst the CNS demyelinating diseases in that it is characterized by more severe and frequent relapses with permanent neurological damage. Recovery from attacks in NMOSD is more limited compared to recovery usually seen with MS and myelin oligodendrocyte glycoprotein antibody disease (MOGAD).[6-8] Progressive neurological decline during periods of remission in NMO is rare, however, which led to a focus on attack prevention. As a result, several treatments to prevent relapse have been and are continuing to be developed in this disease (Figure 1).

In this review, we will discuss the FDA approved long-term treatment options for AQP4-IgG positive NMOSD and ongoing trials that aim to halt disease completely. We will review the recently published extension studies for these trials and finally end with discussing new candidates that are currently being developed.

Approved treatments in adults and their extension studies

With an improved understanding of the underlying pathogenesis of NMOSD, monoclonal antibodies directed against three specific components of the immune response, namely B-cells, the complement pathway and interleukin 6 (IL-6), were pursued resulting in the development of inebilizumab, eculizumab and ravulizumab, and satralizumab respectively. The pivotal trials resulting in approval of each drug have been published; however, extension studies within the trials are ongoing and the data from these extension studies provide additional information about the long-term effects of these treatments, both in terms of efficacy and safety.

Inebilizumab

Inebilizumab is an afucosylated humanized anti-CD19 IgG1 κ monoclonal antibody studied in the N-MOmentum clinical trial or "inebilizumab for the treatment of neuromyelitis optica spectrum disorder", published in 2019.[9] This monoclonal antibody was predicted to be a better alternative to rituximab, currently used off-label in the treatment of NMOSD, given its broader targeting of early B-cell populations, plasmablasts and short-lived plasma cells

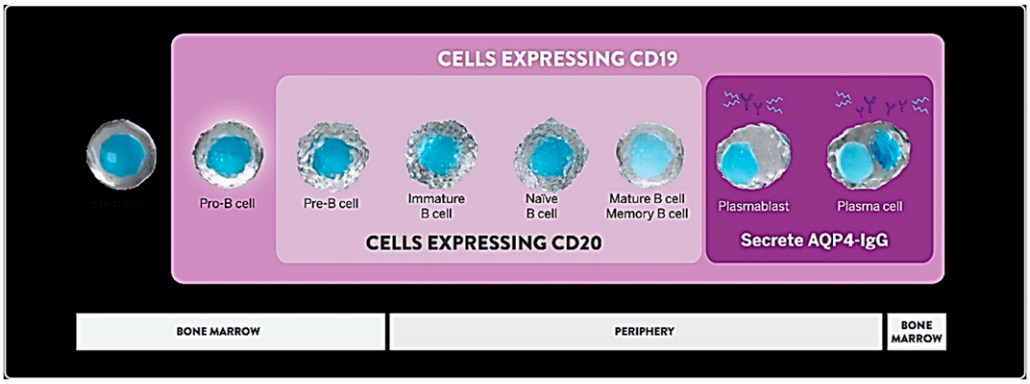

Figure 2. B cell populations as CD19 expression, AQP4-IgG production. The larger box showing pro B-cells through Plasma cells all express CD19, the smaller box which includes Pre-B cells, immature B-cells, naïve B-cells and mature and memory B cells all express CD20 (Reprinted from UplinzaTM).

Figure 2. The study population of this trial included both AQP4-IgG seropositive and seronegative patients. It was structured as a randomized, double-blind placebo phase 2/3 clinical trial. Those randomized to placebo were not allowed to be on other therapies but were switched to inebilizumab if they relapsed during the course of the trial. 12% of both AQP4-IgG seropositive and seronegative patients randomized to inebilizumab had an attack, while 39% of those randomized to placebo experienced and attack (hazard ratio [HR] .72, [95% CI 0.150-.496]:$P < .001$) with a number needed to treat (NNT) of 3.73. Initial data suggested that 11% of AQP4-IgG positive patients receiving inebilizumab had relapses over the 28 w period of monitoring compared to 42% of AQP4-IgG positive patients on placebo (HR .272 [95% CI 0.150-.496]; $P < .0001$), with a NNT of 3.23.[9] Although grouped seronegative and seropositive patient analysis did show significance, due to the low number of seronegative patients randomized to placebo, Cree et al state that efficacy could not be interpreted for the AQP4-IgG seronegative group alone. Therefore, FDA approval was ultimately granted for use of inebilizumab in AQP4-IgG seropositive NMOSD patients and the open-label extension (OLE) proceeded with only AQP4-IgG seropositive patients.

AQP4-IgG seropositive patients from both treatment arms were allowed to enter the (OLE) trial, with 75 patients ultimately included in the final analysis. Findings following 4 y of monitoring were published in 2021.[10] Seropositive patients previously randomized to the inebilizumab arm received 300 mg of inebilizumab on day 1 and placebo on day 15, to maintain masking. Those previously randomized to placebo then received 300 mg of inebilizumab on day 1 and again on day 15. Subsequently, all seropositive patients received inebilizumab every 26 w. 18 attacks were recorded after initiation of inebilizumab treatment, resulting in a calculated ARR of .052 attacks per person year, with most attacks (67%) occurring in the first year following inebilizumab initiation. Of the attacks recorded, 28% were rated as severe and 4 seropositive participants (of 75) had multiple attacks. After being on inebilizumab for 1y, 69 (92%) of seropositive participants remained attack free for the duration of the surveillance period, with a calculated Kaplan-Meier attack-free probability of 87% at 1 y which remained stable in subsequent years.[10] Mean change in EDSS was ≤.5 and the EDSS for seropositive patients overall remained stable in the ≥4 y of follow up.

93% of OLE participants experienced treatment emergent adverse events (TEAEs) with 39% having TEAEs that were felt to be related to inebilizumab by the investigator, however none of these TEAE lead to treatment discontinuation. All adverse events were additionally reviewed by study medical monitor and an independent data monitoring committee. Over the duration of collective infusions (866 in total), 3% were associated with infusion-reactions. Additionally, 79% of seropositive participants experienced infections although the rate of infection did not increase over duration of the treatment. The most common infections were urinary tract infections (UTIs), upper respiratory infections (URIs), influenza, and nasopharyngitis. Median lymphocyte counts were stable through the duration of follow-up, although neutrophil count did decrease following first inebilizumab infusion, and typically increased over follow up. Immunoglobulin levels were decreased by treatment although 76% of participants did maintain normal IgG levels. There were 4 participants with IgG levels <300 mg/dL however no participants required immunoglobulin repletion for hypogammaglobulinemia. Life-threatening infection occurred in 1 participant and no cases of opportunistic infections or cases of progressive multifocal leukoencephalopathy (PML) were reported, although two deaths occurred in the open-label of which PML was on the differential for one of them.[9] This patient experienced neurologic decline in the setting of new brain lesions and ultimately died of cardiopulmonary complications. Although Cree et al could not state that the patient's death was not treatment related, JCV PCR testing was negative in two independent laboratories despite initial PCR positive testing at a local laboratory. The other patient death was attributed to severe NMOSD relapse in a patient initially allocated to placebo and not considered to be treatment related.

Overall, Rensel et al state that the extension trial data suggests additional benefit and decreased likelihood for relapse

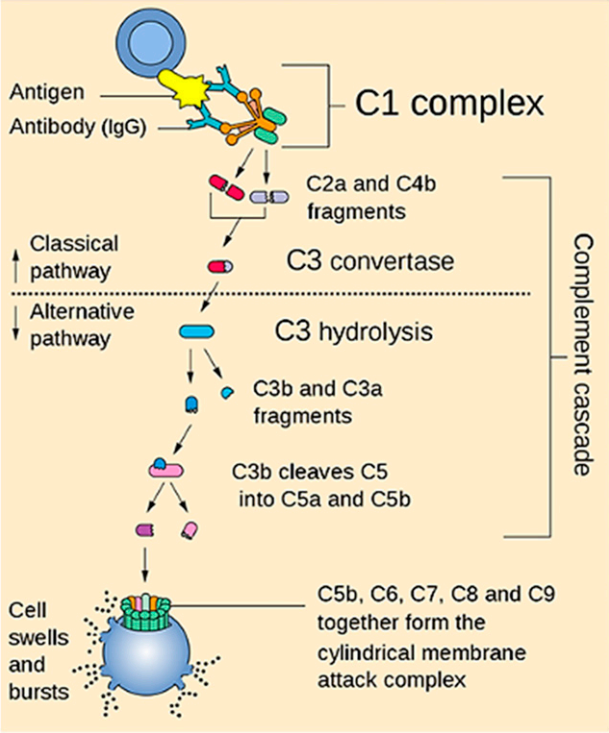

Figure 3. The Complement pathway. Initial antibody binding allows for C1 complex complex formation and initiation of the complement cascade, eventually leading to formation of the membrane attack complex (MAC). (Reprinted from Wikipedia).

with increased length of treatment in AQP4-IgG seropositive NMO patients. Due to the safety data discussed, it is recommended that immunoglobulin levels and CBC with differential be monitored at each infusion. Providers can monitor B-cell levels to check response to medication, however this is not required. Live and live-attenuated vaccines should be avoided while on inebilizumab treatment and TB and hepatitis B status should be tested prior to initiation as it is contraindicated for those populations. Currently, inebilizumab is also approved for the treatment of AQP4-IgG seropositive NMOSD in Japan and the European Union. It is typically dosed at 300 mg x2 doses for the induction and then every 6 months thereafter, coming to a total yearly cost of approximately US$393,000 for the first year and then US$262,000 for every subsequent year.

Eculizumab

Eculizumab is a humanized monoclonal antibody (IgG2/IgG4) targeted to the terminal portion of complement protein C5.[11] Complement activation occurs following the binding of AQP4 antibody to astrocyte feet with C1q, followed by initiation of the classical complement cascade, ending with cleavage of C5 to form the cylindrical membrane attack complex (MAC). It is implicated in astrocyte destruction and neuronal injury and is felt to be the source of lesion formation in the disease, with secondary demyelination.[12] By targeting the endpoint prior to MAC formation, eculizumab would thus have the potential to prevent lesion formation and disability by preventing the cleavage of C5 to C5a and C5b Figure 3.

PREVENT was a phase 3 double-blinded, randomized, placebo-controlled trial in which AQP4-IgG positive patients were randomized to eculizumab or placebo, although patients could continue to receive their prior immunosuppressive therapy (IST) during the trial.[13] Ultimately, 96 seropositive patients were randomized to the eculizumab arm and 47 received placebo. There were 3 relapses in the eculizumab arm, compared to 43% in the placebo arm (hazard ratio, .06; 95% confidence interval [CI], .02 to .20; $P < .001$), with an ARR of .02 in the treatment arm compared to .35 (HR, .04 (.01 to .15), $P < .0001$). Pittock et al[13] surmised that additional IST was unnecessary given that no patients on eculizumab monotherapy experienced a relapse in the initial PREVENT trial. While there were higher overall rates of adverse events in the placebo group compared to the eculizumab group, there were higher rates of headache and URIs in the eculizumab group compared to placebo. Although there have been concerns raised with infection with encapsulated organisms in treatments with complement pathway modulation,[14] there were no reports of meningococcal infection and there was one death due to pulmonary empyema in a patient on eculizumab with concomitant Aza in the initial trial period.

The PREVENT open-label extension (OLE) trial continued with 119 AQP4-IgG seropositive patients from the eculizumab and placebo treatment arms for an additional 28 to 272 weeks.[15] Among 33 on eculizumab monotherapy, one experienced an adjudicated relapse after 380 days in the OLE; 96.2% of the eculizumab monotherapy group remained relapse free at 192 weeks. The annualized relapse rate in the eculizumab monotherapy sub-group was .012 compared to .625 in the PREVENT placebo only group. There were 88 patients in the OLE on eculizumab who were also on background IST during the initial PREVENT trial. 17 (19.3%) of these patients stopped using IST, of whom none had any adjudicated relapses in the 44.3 weeks of additional monitoring. Overall, Pittock et al reported a 94% reduced relapse risk in those treated with eculizumab, with or without concomitant IST, and the safety profile through the OLE was similar to that seen in the initial PREVENT study.

Eculizumab is marketed by Alexion, a subsidiary of AstraZeneca. It is licensed for AQP4-IgG seropositive patients with NMOSD in Australia, Canada, the European Union (EU), Israel, Japan, South Korea, Turkey, the UAE, the United Kingdom and the United States. For NMOSD, it is dosed at 900 mg per week for the first 4 weeks, followed by 1200 mg for week 5 and then 1200 mg every 2 weeks thereafter, coming out to a yearly cost of approximately US$710,000 in the US. Other than the dosing regimen and cost, there is a boxed warning for serious meningococcal infections, although there were none reported in the PREVENT or OLE. Given the risk for infection with

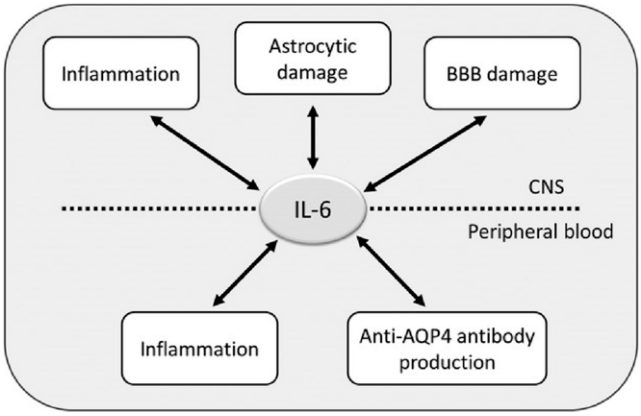

Figure 4. IL-6 and NMOSD pathogenesis. IL-6 is involved in inflammation, AQP4-IgG production, BBB damage and eventual astrocytic damage. (Uzawa et al).

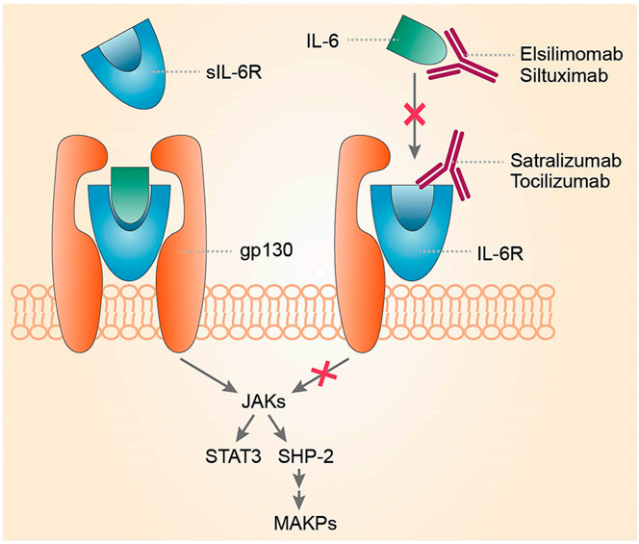

Figure 5. Satralizumab mechanism of action. Satralizumab binds to the IL-6 receptor (IL-6R) to prevent downstream JAK signaling. (Reprinted from Satralizumab Overview by Creative BioLabs).

encapsulated organisms with complement modulation, patients should be vaccinated for *haemophilus influenzae b* (Hib) and *streptococcus pneumoniae* in addition to meningococcus vaccination prior to starting eculizumab.

Satralizumab

IL-6 is an inflammatory cytokine produced by many different cell types including T cells, B cells, monocytes, endothelial cells and mesangial cells and is implicated in the pathogenesis of NMOSD. IL-6 is postulated to promote plasmablast survival, enhance AQP-4 Ab secretion, increase pro-inflammatory T cell differentiation and survival, and reduce blood brain barrier (BBB) integrity in NMOSD pathogenesis.[16] IL-6 levels were found to be increased in the CSF and serum of NMO patients compared to healthy controls.[17] Therefore, targeting IL-6 production or the IL-6 receptor (IL6-R) would allow for immunomodulation of multiple facets of the pathogenic immune response in NMOSD Figure 4.[18]

Satralizumab is a humanized monoclonal antibody (IgG2) directed against the IL6-R, binding to IL6-R at the surface of cells and causing internalization of the receptor.[5] It can bind both membrane-bound and soluble IL6-R[19,20]. It may inhibit T-cell activation and AQP4-IgG production.[21] The medication was studied in NMOSD patients who were seronegative or seropositive for AQP4-IgG in two separate multi-center phase 3 double-blinded placebo controlled clinical trials called SAkuraStar and SAkuraSky. No more than 30% of enrolled patients could be AQP4-IgG seronegative in either study, to reflect global rates of seronegativity. SAkuraStar randomized patients to a satralizumab or placebo arm,[19] while SAkuraSky randomized patients to either satralizumab or placebo + concomitant baseline IST.[20] Both trials demonstrated significantly reduced relapse risk in AQP4-IgG seropositive NMOSD patients compared to placebo,[21] described in more detail below (Figure 5).

In SAkuraStar, 95 AQP4-IgG seropositive and seronegative patients were included. 68 patients were randomized to the satralizumab arm with 30% experiencing a protocol-defined relapse (PDR) while 50% of those in the placebo arm experienced a PDR (HR .45 (.23 to .89); P = .018). On a further breakdown, 9 of 41 (22%) AQP4-IgG seropositive patients on treatment compared to 13 of 23 (57%) seropositive patients on placebo (HR 0 26, 95% CI 0 11-0·63) experienced a PDR. In the seronegative patient subgroup, 10 of 22 (46%) on treatment compared to 3 of 9 (33%) on placebo experienced a PDR (HR 1 19, CI 0 30-4·78). Traboulsee et al could not conclude that there was a risk reduction in the seronegative group and felt that the study was not powered to find a difference in this particular subset, given the low numbers. They concluded that satralizumab monotherapy reduced the rate of relapse in AQP4-IgG seropositive patients included in the study. For SAkuraSky which included adolescents as young as 12 years old, 83 seropositive and seronegative patients were included, including 41 in the satralizumab arm and 42 in the placebo + concomitant baseline IST arm. 20% of those in the treatment arm experienced a PDR while 43% of those in the placebo arm experienced relapse (HR .38 (.16 to .88), P-value .02). However, it was discovered on further analysis that there was a difference in the rates of relapse in the seronegative and seropositive patients. Specifically, 3 of 27 (11%) of AQP4-IgG seropositive patients on satralizumab experienced PDR compared to 12 of 28 (43%) seropositive patients on placebo + IST (hazard ratio, .21; 95% CI, .06 to .75). For AQP4-IgG seronegative patients, 5 of 14 (36%) in the treatment arm and 6 of 14 (42%) in the placebo + IST experienced PDR (hazard ratio, .66;95% CI, .20 to 2.24). Given that the CI for the seronegative group includes the null value of 1 indicating unreliable results to suggest a discernable difference in

relapse rate, Yamamura et al concluded that satralizumab decreased the rate of relapse in the seropositive group only.

AQP4-IgG seropositive and seronegative patients who experienced a relapse regardless of treatment arm, or who reached the end of the study period could elect to continue in the OLE of their respective trial. In the OLE, all patients received satralizumab at the same dosing as that of the double-blinded period, which is 120 mg subcutaneous (SC) every 4 weeks with loading doses at 0 and 2 weeks. Those from SAkuraStar could continue concomitant IST during the OLE period.

Across both trials, AE and SAE were comparable between the satralizumab and placebo group in the double bind period, with similar rates of AE during the OLE.[21] There were 90 AEs (98.9%) in the treatment arm over the entire treatment period in the SAkuraStar study and conversely 24 AEs (75%) in the placebo arm. There were no deaths or anaphylactic reactions and there were no AE leading to discontinuation of satralizumab in either study. The most common AEs in both studies were nasopharyngitis and URI. Rensel et al report that there were no cases of PML or opportunistic infections. There were 5 cases of COVID-19 infection, all mild and occurring prior to widespread vaccine availability.

The results of analysis of the OLE for SAkuraSky and SAkuraStar appear to support the use of satralizumab in the treatment of NMOSD as a monotherapy or in combination with other IST, given the safety profile and reductions in relapses in patients with NMOSD regardless of AQP4-IgG status. Of note, there is still an ongoing trial, SAkuraMoon, which will evaluate seronegative and seropositive patients with NMOSD that completed the OLE for SAkuraStar and SAkuraSky. Subgroup analysis of AQP4-IgG seropositive NMOSD patient efficacy results was published in Jan 2023.[22] Here, 111 AQP4-IgG positive patients entered the OLE, 44 into the SAkuraSky OLE and 57 into the SAkuraStar OLE. It was noted that 12 (24%) of patients from SAkuraSky and 17 (27%) of patients from SAkuraStar experienced a PDR over the total treatment period (double blind period + OLE),[22] with 71% and 73% of patients remaining PDR-free at 192 weeks in the SAkuraSky and SAkuraStar treatment periods respectively[22] (combined for both studies, 72% (95% CI, 62%–80%). The overall ARR was .12 and .08 in the SAkuraSky and SAkuraStar treatment period respectively (combined for both studies, .09 (95% CI, .06-.12)), compared to a baseline ARR of 1.38 for SAkura Sky and .95 for SAkura Star. Kleiter et al concluded that satralizumab reduced rates of PDR in AQP4-IgG seropositive patients in the double-blind period and that these protective effects extended through the duration of the OLE for both studies, although the ARR was lowest for patients initially randomized to satralizumab than those switched from placebo (SAkuraSky: .04 vs .14; SAkuraStar: .02 vs .03).

Satralizumab was developed by Roche, and is available in over 60 countries, including the US and Japan. In the United States, it is priced at US$219,000 for the first year and US$190,000 every subsequent year. Patients can experience injection site redness and labs should be monitored regularly for transaminitis, thrombocytopenia, hypertriglyceridemia, hypercholesterolemia, and low fibrinogen. It is administered subcutaneously at 120 mg every other week for 3 doses and then continued at 120 mg every 4 weeks.

Ravulizumab

Ravulizumab is a second-generation terminal complement inhibitor based on eculizumab. It binds to the same C5 epitope but has a longer half-life, allowing for extended dosing intervals of 8 weeks compared to 2 weeks for eculizumab, potentially lowering costs and increasing patient convenience.[23] Ravulizumab has recently completed the CHAMPION-NMOSD trial, a global phase 3 multicenter study.[24] The PREVENT study placebo arm is used as a comparator as it was determined that a placebo arm for CHAMPION would be unethical. Patient inclusion criteria were different than the PREVENT trial, and included age ≥18, prior immunization with meningococcal vaccine in the 3 y prior to inclusion, AQP4 antibody positive NMOSD diagnosis, ≥1 relapse in the last 12 months prior to inclusion, and EDSS ≤7. Seropositive patients received weight-based dosing of IV ravulizumab at day 1 (2400-3000 mg), day 15 (3000-3600 mg), and once every 8 weeks thereafter. Similar to the PREVENT trial, patients were allowed to be on concomitant IST, however the proportion of patients on monotherapy is higher in the CHAMPION study (51.7%) compared to the PREVENT study (27.7%), likely because there was no risk of being randomized to a placebo arm.[24]

Ravulizumab was found to decrease the rate of adjudicated relapse in seropositive patients by 98.6% ($P < .0001$) compared to the placebo group in the PREVENT trial with zero adjudicated relapses in the ravulizumab group over a median of 74 weeks follow-up compared to 20 relapses in the PREVENT placebo group (HR, .014 (95% confidence interval [CI], .000 to .103).[24] In a subgroup analysis of seropositive patients on ravulizumab monotherapy, it was found that there was a 97.9% reduction in relative risk of relapse compared to PREVENT placebo group (HR, .021 [95% CI, .000 to .176]; $P < .0001$). Physician-determined relapses occurred in 2 patients of the treatment arm but neither of these were adjudicated by the committee. Furthermore, worsening of the Hauser Ambulatory Index (HAI) was lower in those treated with ravulizumab compared to the PREVENT placebo group (2/58 vs 11/47, HR = .155, $P = .0228$). Similarly, the majority of patients on ravulizumab (52/28, 89.7%) experienced no clinical worsening based on EDSS scores compared to placebo (HR .332, $P = .0588$).

There were 328 TEAEs in the treatment group, with 38 of those felt to be related to treatment. These TEAEs included COVID-19 infection, headache, UTIs, back pain and arthralgia. 3 patients withdrew due to TEAEs. There were 8 treatment-emergent serious adverse events (TESAEs), 3 of which were meningococcal sepsis, meningococcal pneumonia (PNA) and encephalitis. *Neisseria meningitidis* infection occurred in 2 vaccinated individuals in the treatment group. One developed an infection 21 days after first dose of ravulizumab

while the other developed infection 482 days after first dose. Both were treated and ultimately recovered without sequelae. Despite the increased frequency in this trial, meningococcal infection rate was still within range of rates of infection with real world use of eculizumab (.25 cases per 100 patient years for eculizumab vs .05 cases per 100 patient years for ravulizumab as of December 31, 2021). The cases of meningococcal infection in previously vaccinated patients, while concerning, will continue to be monitored in the open-label extension period and is actively monitored in the post-marketing of the medication.

Ravulizumab has been approved for treatment in antibody-positive NMOSD in the EU, Japan, and Canada. It is under review for treatment of NMOSD in the United States. Although pricing for the expected dose regimen is not yet available, it is expected to tentatively cost around US$44000 per dose, or around US$290,000 yearly[25] however these prices may change.

New therapies in the pipeline

While the addition of three new FDA approved therapies to a previously empty market for NMOSD treatment has been life-altering for many patients and medical providers, there remains progress to be made. There are additional ongoing trials seeking to fill present treatment gaps in the NMOSD patient population. Here we will discuss trials that have not yet been published, from those closest to publication to those still in formulation. Upcoming therapies were either included from recently completed trials or from clinicaltrials.gov. Any treatments that were listed under patent names or whose mechanism of action could not be verified were not included here.

Orelabrutinib

Orelabrutinib is a Bruton's tyrosine kinase (BTK) inhibitor, developed by InnoCare Pharma, which was recently approved for a phase 2 trial in China (NCT 05284175). BTK is a key kinase in the B cell receptor (BCR) signal transduction. Patient enrollment has not yet begun but the plan will be to enroll 23 AQP4-IgG positive NMOSD patients in an open label, prospective, self-controlled study to explore the efficacy and safety of orelabrutinib.[26] Patients will receive oral orelabrutinib 50 mg daily. Primary outcome will be annualized relapse rate at 48 weeks compared to prior relapse history. Planned completion is August 2023. BTK inhibitors are being developed for other CNS autoimmune diseases including multiple sclerosis.

Zanubrutinib

Zanubrutinib is a BTK inhibitor developed by BeiGene. It is already approved for treatment in Chronic Lymphocytic Leukemia (CLL), Waldenstrom's macroglobulinemia (WM), Mantle Cell Leukemia and Marginal Zone Lymphoma. It will also be studied in AQP4-IgG positive NMOSD patients in an open label, single-center phase 2 trial in China (NCT05356858) and began recruiting in May 2022. Patients will receive oral zanubrutinib 80 mg daily for 48 w and relapse-free rate at 48 w will be the primary outcome. They plan to enroll 23 AQP4-IgG positive NMOSD patients, ages 18 to 75, and will plan to complete in October 2024.

Belimumab

Belimumab is a human IgG1λ recombinant antibody directed against B cell activating factor (BAFF), which was previously approved for treatment in systemic lupus erythematosus (SLE).[27] Binding of Belimumab to BAFF prevents BAFF from binding to its three receptors, and therefore indirectly decreases B-cell survival and antibody production. It is planned for use in a phase 1/2 open label single treatment arm clinical trial where its safety and efficacy will be studied in 12 NMOSD participants (NCT05154734). Dosing of IV belimumab is 10 mg/kg on days 1, 14, 28 then every 28 days until week 48, with final evaluation at week 52. Primary outcome is time to first relapse and participants must be ≥ 18 yo, have a diagnosis of NMO by 2015 International Criteria, clinical evidence of at least 2 relapses in the last 12 months or at least 3 in the last 24 months, and EDSS ≤6. Planned primary completion date is June 2023.

Baricitinib

Baricitinib is a JAK1/JAK2 inhibitor that blocks a portion of the JAK/STAT pathway involved in B cell proliferation and differentiation. Though recruitment has not yet begun, the trial will recruit 12 NMOSD patients (based on 2015 diagnostic criteria) ages 18-85 (NCT05792462), EDSS ≤6.0, and at least one attack requiring treatment over the last year or two attacks over the last two years. AQP4-IgG serostatus has not yet been defined as an inclusion criterion. It will be a phase 1/2 interventional trial looking into the safety and efficacy of this medication. Participants will receive 2 mg or 4 mg daily over the course of 48 weeks with primary outcome of time to first relapse. Planned primary completion date is March 2024.

Batoclimab

Batoclimab or HBM9161 is a novel human anti-neonatal Fc receptor (anti-FcRn) that blocks FcRn-IgG interactions and accelerates autoantibody degradation.[28] This was a phase 1b trial (NCT04227470) that recruited 9 participants, randomized two treatment arms dosed at 340 mg or 680 mg weekly administration of batoclimab for 4 w as an add-on therapy. The primary outcome was the number of treatment-related adverse events. Participants were ≥18 yo, diagnosed with NMOSD based on 2015 international criteria, AQP4-IgG positive, new acute ON or TM, with an EDSS between 2.5 and 7.5. Results of this phase 1b trial, recently published by Wang et al,[28] included undetectable AQP4-IgG titers in 6/7 patients treated with batoclimab 680 mg weekly add-on therapy and reduced

EDSS by 1.3 ± .4 at week 4 (2.7 ± 1.3) compared with baseline (4.0 ± 1.0) in all participants. While this trial focused on acute treatment of NMOSD relapses, it does suggest that this novel treatment option is safe for short-term use in NMOSD. It may warrant closer examination as a maintenance therapy option in NMOSD.

Daratumumab

Daratumumab is a human monoclonal antibody directed against CD38, which is highly expressed on antibody secreting cells and is currently approved for treatment in multiple myeloma. It is being developed for treatment of SLE, myasthenia gravis and autoimmune encephalitis and has been shown to decrease antibody levels in these conditions.[29] "Safety and Efficacy of Daratumumab in Patients with Anti-Aquaporin 4 Antibody Positive Neuromyelitis Optica Spectrum Disorder" or DAWN will be a phase 2/3 multicenter randomized double-blind placebo controlled clinical trial to evaluate the safety and efficacy of daratumumab in patients with AQP4-IgG positive NMOSD (NCT05403138). They plan to recruit 72 participants and participants must be ≥ 18 years, have a diagnosis of NMOSD with AQP4-IgG seropositivity, at least 1 relapse in the last 12 months or 2 in the last 24 months, and EDSS ≤7.5. Patients will be randomized to treatment with daratumumab 8 mg/kg for 2 cycles every 2 weeks followed by 4 mg/kg every 4 weeks, while the placebo arm will receive buffer components without active ingredients. It has just begun recruitment in November 2022 with a planned primary completion date of August 2024.

MIL62

MIL62 is a 3rd generation anti-CD20 monoclonal antibody under investigation by Beijing Mabworks in a multicenter phase 1b/3 randomized control trial (NCT05314010) which began recruitment in April 2022. It will be quadruple masked with a goal of including 140 AQP4-IgG seropositive NMOSD patients ages 18-60 with a goal of evaluating the safety and efficacy of this agent in NMOSD patients. Participants must have an EDSS ≤6.5 and have had at least 1 relapse in the last 12 months or more than 2 in the last 24 months. Primary outcomes will be time to first relapse and CD19 and CD20 subset ratios. Participants will either receive IV MIL62 500 mg or 1000 mg or IV placebo on Day 1, Day 15, followed by a single dose every 6 months. Planned primary completion date is March 2025.

Mitoxantrone

Mitoxantrone Hydrochloride Liposome Injection is a chemotherapy classified as a topoisomerase inhibitor which inhibits cell growth and spread. It has been used in the treatment of MS, prostate cancer and certain types of leukemias. It will be studied in a double-blind randomized placebo-controlled phase 2 clinical trial investigating the efficacy and safety of this treatment in NMOSD (NCT05551598). It will recruit AQP4-IgG seropositive or seronegative patients ages 18-60 based on 2015 International Diagnostic criteria. Participants will need an EDSS ≤7.5, have experienced at least 2 attacks within the last year or three attacks within the last 24 months with one of these attacks within 12 months of screening. Patients will be randomized to receive either IV mitoxantrone 8 mg/m^2 Q12w or IV mitoxantrone 12 mg/m^2 Q12w or IV placebo Q12 over 48 w with primary outcome of time to first relapse. Recruitment began in September 2022 with a planned primary completion date of October 2024.

Ofatumumab

Ofatumumab is a humanized anti-CD20 that is injected subcutaneously and is currently approved in the treatment of multiple sclerosis (MS). This trial is designed as an open-label single-arm multicenter prospective phase 1/2 trial to study the safety and efficacy of ofatumumab in AQP4-IgG seropositive NMOSD patients in China (NCT05504694). Patients will receive 20 mg SC injections at days 1, 7, 14 and then monthly thereafter. Participants must be ≥18 years, have an EDSS ≤7.5, have a diagnosis of NMOSD with AQP4-IgG seropositivity, and at least 1 relapse in the last 12 months or more than 2 in the last 24 months. Planned primary completion date is June 2024.

Advances in treatment of pediatric NMOSD

Despite recent successes in development of treatments for NMOSD, there remains a treatment gap in the pediatric NMOSD population. Pediatric onset occurs in 3%–5% of NMOSD cases.[30] Currently, there are ongoing trials for satralizumab, inebilizumab, eculizumab and ravulizumab in children. In the SAkuraSun trial (NCT05199688), 8 children ages 2-11 years with AQP4-IgG seropositive NMOSD are being recruited to participate in a phase 3 open label, multicenter, uncontrolled study with planned primary completion date in September 2024. There are three planned dosing arms of satralizumab administered SC at 0, 2, and 4 weeks and then every 4 weeks thereafter; the dosing is weight-based with categories of 10 – 20 kg, 20 – 40 kg and ≥40 kg. Additional inclusion criteria are: AQP4-IgG seropositive status, EDSS 0 to 6.5, neurologic stability for ≥30 days prior to enrollment, and stable treatment on other IST for 4 weeks prior to baseline.

Inebilizumab is also beginning clinical trials in pediatric subjects. This will be a phase 2, open label, multicenter clinical trial with a goal of enrolling 15 subjects over a 28-week treatment period (NCT05549258). Inclusion criteria will be patients ages 2 to 17 years, seropositive AQP4-IgG NMO diagnosis, and history of ≥1 relapse in the last year or ≥2 in the last 2 years. Enrollment began in September 2022.

Alexion Pharmaceuticals began recruitment for their phase 2/3 open label single-arm trial into the efficacy and safety of eculizumab in pediatric patients in November 2019 and is still listed to be recruiting. It is designed to enroll 12 participants aged 2-17 with

Table 1. Ongoing or recently completed clinical trials in the treatment of NMOSD in adult and pediatric patients.

TREATMENT	CLINICAL TRIAL IDENTIFIER	ANTIBODY	MECHANISM OF ACTION	ROUTE	DOSING	AGE RANGE	AQP4-IGG STATUS	COMPLETION DATE
Ravulizumab	NCT04201262	Anti-C5	Complement inhibition	IV	2400 mg-3000 mg d1 3000-3600 mg d15 Q8 w thereafter	≥18	+	Completed
Orelabrutinib	NCT 05284175	BTK inhibitor	Blocks BCR signalling, inhibits proliferation, trafficking, chemotaxis, and adhesion of B cells	PO	50 mg daily	18 to 75	+	Aug 2023
Zanubrutinib	NCT05356858	Irreversible BTK inhibitor	Blocks BCR signaling, inhibits proliferation, trafficking, chemotaxis, and adhesion of B cells	PO	80 mg daily	18 to 75	+	Oct 2024
Belimumab	NCT05154734	Anti-BAFF	Decreases B-cell survival and antibody production	IV	10 mg/kg at d1, 14, 28 and q28 thereafter	≥18	+/-	Jan 2023
Baricitinib	NCT05792462	JAK1/JAK2 inhibitor	Inhibits STAT phosphorylation and downstream inflammatory cytokine production, decreases T_H1 and T_H17 populations, decreases, attenuates immune cell entry into CNS	PO	2 mg or 4 mg daily	18 to 85	+	Mar 2024
[a]Batoclimab	NCT0422740	Anti-FcRn	Blocks FcRn-IgG binding and accelerates IgG degradation	SC	340 mg or 680 mg weekly for 4w	>18	+	Completed
Daratumumab (DAWN)	NCT05403138	Anti-CD38	Targets antibody-secreting cells	IV	8 mg/kg every 2w for 2 cycles and 4 mg/kg every 4w	≥18	+	Aug 2024
MIL62	NCT05314010	Anti-CD20	Targets B cells	IV	500 mg or 1000 mg Day 1, 15 then q6mo	18 to 60	+	Mar 2025
Mitoxantrone	NCT05551598	Inhibition of topoisomerase II	Inhibits proliferation of macrophages, and B and T cells	IV	8 mg/m^2 or 12 mg/m^2 Q12w	18 to 60	+/–	Oct 2024
Ofatumumab	NCT05504694	Anti-CD20	Targets B cells	SC	20 mg at d1,7, 14 and then every 4w thereafter	≥18	+	Jun 2024
Satralizumab (SAkuraSun)	NCT05199688	Anti-IL-6	Decrease plasmablast survival, inflammatory T cell response, and AQP4-IgG production	SC	Q6w 10-20 kg	2-11	+	Sep 2024

(Continued)

Table 1. Continued.

TREATMENT	CLINICAL TRIAL IDENTIFIER	ANTIBODY	MECHANISM OF ACTION	ROUTE	DOSING	AGE RANGE	AQP4-IGG STATUS	COMPLETION DATE
Inebilizumab	NCT05549258	Anti-CD19	Targets early B cells and plasmablasts	IV	Not specified	2 to 17	+	Sep 2024
Eculizumab	NCT04155424	Anti-C5	Complement inhibition	IV	Wt based	2 to 17	+	Jul 2023
Ravulizumab	NCT05346354	Anti-C5	Complement inhibition	IV	Wt based	2 to 17	+	Mar 2026

[a]Batoclimab trial investigated as treatment for acute relapse.

seropositive AQP4-IgG NMOSD status. Initial primary completion date was planned for July 2023 (NCT04155424); however, given the success of ravulizumab in adults and the easier dosing frequency, a new trial with ravulizumab will begin recruitment starting in November 2022. It is planned as a multicenter open-label, historical controlled, phase 2/3 study to look at the efficacy and safety of ravulizumab in children with AQP4-IgG positive NMOSD (NCT05346354), ages 2 to 17 years. Dosing will be weight-based with infusions on days 1, 15 and every 8 weeks until over 50 w or 104 w. Planned primary completion date is March 2026 Table 1.

Treatment considerations

With the increasing number of FDA-approved treatments for AQP4-IgG positive NMOSD in addition to off-label immunotherapies, providers now have multiple options in the treatment of NMOSD. Among the many factors that drive physician recommendations, AQP4-IgG serostatus, meningococcus immunization status in the case of eculizumab, insurance approval and treatment schedule are common. Providers often elect to continue with off-label therapies such as Rituximab and/or mycophenolate mofetil if insurance will not cover the newer approved medications that have come to market.

Based on the number of publications on the topic, the recent SARS CoV-2 global pandemic has raised questions in the field regarding how to approach patients on long-term immunotherapy. Though there is limited data of antibody levels for NMOSD patients on B-cell therapies and these effects on hospitalization and COVID outcomes, data accumulated from MS patients on B-cell therapies could provide insight. For example, a recently published article cited higher rates of severe COVID infection in some MS patients on B-cell therapies – rituximab in particular.[31] However, updates have suggested that severe infections were most likely in patients with leukopenia (<1.0 $\times 10^9$/mL).[32] Overall, while it has been noted that patients on B-cell therapies in MS such as ocrelizumab did have lower B-cell responses to vaccination, they did have preserved overall T-cell responses which still allowed for an immune response to the vaccine.[33] Time and additional research are required to conclude if similar observations will be made in NMOSD patients on B-cell therapies, but at this time there is insufficient data analysis in NMOSD to provide advice on the use of B-cell therapies in patients with or at-risk for COVID. Patients are advised to obtain vaccination at least 2-4 w prior to B-cell infusion, but if not possible, they should still obtain COVID vaccination.

Special considerations must be made for pregnant patients with NMOSD. Regarding the pregnant population, unlike MS, rates of relapse and disability are increased during pregnancy and the postpartum period for NMOSD patients.[34,35] Therefore, close preparation and monitoring must be employed for women who are planning to or become pregnant and have been diagnosed with NMOSD. Importantly, there are several medications with evidence of fetal harm that should be avoided or transitioned if the patient is already on these: cyclophosphamide, methotrexate, mitoxantrone, and mycophenolate mofetil.[34] Additionally, caution should be taken using azathioprine given evidence of fetal immunosuppression with exposure in the 3rd trimester. Evidence for the safety inebilizumab and satralizumab are still under review. However, monoclonal biologics are not felt to cross the placenta during the first trimester,[36] suggesting that timing infusions of monoclonal biologics in the first trimester could be considered, if dosing was not possible prior to pregnancy.[37] Although it should be noted that rituximab has been associated with increased risk of pre-term birth in some studies.[35] Anti B-cell biologic infusions have been shown to decrease fetal B-cell production when given after the first trimester, however data has shown that babies born to mothers who received infusions in the second or third trimester recover their B-cell population within 2-3 mos.[37] Therefore, there are options available to pregnant NMOSD patients, but providers must weigh the timing and frequency of dosing to avoid certain at-risk periods during and after pregnancy.

For the pediatric population, there is only one FDA-approved medication for AQP4-IgG seropositive pediatric patients, satralizumab, in children ages 12 and above. Otherwise, children are frequently placed on mycophenolate mofetil and/or rituximab, azathioprine, or monthly IVIG.[38]

Conclusion

There have been several advances in NMOSD treatment in recent years based on proposed NMOSD disease mechanisms. Regulatory approval of eculizumab, inebilizumab and satralizumab in adults has greatly expanded our treatment options as well as revolutionized treatment outcomes in NMOSD patients with meaningful reductions in relapse rates. Building on these successes, there are pending clinical trials in children

using inebilizumab, eculizumab and satralizumab. In addition to these treatments, new drugs are being developed for NMOSD to target novel pathways. While treatments for seronegative NMOSD patients remain lacking, the recent and ongoing trials in the field continue to reconcile gaps in treatment within the NMOSD patient population and there remains hope that in the future, NMOSD, regardless of age or AQP4-IgG antibody status, will become a more treatable disease.

Acknowledgements

We would like to acknowledge the field representatives from Alexion Pharmaceuticals, Genentech and Horizon therapeutics for providing information on global availability of their respective approved medications.

Author contributions

Monique Rochelle Anderson: Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Michael Levy: Conceptualization, Supervision, Writing – review & editing.

ORCID iD

Monique Anderson https://orcid.org/0000-0001-7713-2878

REFERENCES

1. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet*. 2004;364:2106-2112. doi:10.1016/S0140-6736(04)17551-X
2. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85:177-189. doi:10.1212/WNL.0000000000001729
3. Fujihara K. Neuromyelitis optica spectrum disorders: still evolving and broadening. *Curr Opin Neurol*. 2019;32:385-394. doi:10.1097/WCO.0000000000000694
4. Hor JY, Asgari N, Nakashima I, et al. Epidemiology of neuromyelitis optica spectrum disorder and its prevalence and incidence worldwide. *Front Neurol*. 2020;11:501. doi:10.3389/fneur.2020.00501
5. Carnero Contentti E, Correale J. Neuromyelitis optica spectrum disorders: from pathophysiology to therapeutic strategies. *J Neuroinflammation*. 2021;18:208. doi:10.1186/s12974-021-02249-1
6. Masuda H, Mori M, Uzawa A, et al. Recovery from optic neuritis attack in neuromyelitis optica spectrum disorder and multiple sclerosis. *J Neurol Sci*. 2016;367:375-379. doi:10.1016/j.jns.2016.06.036
7. Jurynczyk M, Craner M, Palace J. Overlapping CNS inflammatory diseases: differentiating features of NMO and MS. *J Neurol Neurosurg Psychiatry*. 2015;86:20-25. doi:10.1136/jnnp-2014-308984
8. Banwell B, Bennett JL, Marignier R, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: international MOGAD Panel proposed criteria. *Lancet Neurol*. 2023;22:268-282. doi:10.1016/S1474-4422(22)00431-8
9. Cree BAC, Bennett JL, Kim HJ, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. *Lancet*. 2019;394:1352-1363. doi:10.1016/S0140-6736(19)31817-3
10. Rensel M, Zabeti A, Mealy MA, et al. Long-term efficacy and safety of inebilizumab in neuromyelitis optica spectrum disorder: analysis of aquaporin-4-immunoglobulin G-seropositive participants taking inebilizumab for ⩾4 years in the N-MOmentum trial. *Mult Scler*. 2022;28:925-932. doi:10.1177/13524585211047223
11. Dhillon S. Eculizumab: a review in generalized myasthenia gravis. *Drugs*. 2018;78:367-376. doi:10.1007/s40265-018-0875-9
12. Asavapanumas N, Tradtrantip L, Verkman AS. Targeting the complement system in neuromyelitis optica spectrum disorder. *Expet Opin Biol Ther*. 2021;21:1073-1086. doi:10.1080/14712598.2021.1884223
13. Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. *N Engl J Med*. 2019;381:614-625. doi:10.1056/NEJMoa1900866
14. Ram S, Lewis LA, Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. *Clin Microbiol Rev*. 2010;23:740-780. doi:10.1128/CMR.00048-09
15. Pittock SJ, Fujihara K, Palace J, et al. Eculizumab monotherapy for NMOSD: data from PREVENT and its open-label extension. *Mult Scler*. 2022;28:480-486:doi:10.1177/13524585211038291
16. Fujihara K, Bennett JL, de Seze J, et al. Interleukin-6 in neuromyelitis optica spectrum disorder pathophysiology. *Neurol Neuroimmunol Neuroinflamm*. 2020;7:20200820. doi:10.1212/NXI.0000000000000841
17. Ringelstein M, Ayzenberg I, Lindenblatt G, et al. Interleukin-6 receptor blockade in treatment-refractory MOG-IgG-associated disease and neuromyelitis optica spectrum disorders. *Neurol Neuroimmunol Neuroinflamm*. 2022;9:20211116. doi:10.1212/NXI.0000000000001100
18. Akiyuki Uzawa MM, Kuwabara S. Role of interleukin-6 in the pathogenesis of neuromyelitis optica. *Clinical and Experimental Neuroimmunology*. 2013;4:167-172
19. Traboulsee A, Greenberg BM, Bennett JL, et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. *Lancet Neurol*. 2020;19:402-412. doi:10.1016/S1474-4422(20)30078-8
20. Yamamura T, Kleiter I, Fujihara K, et al. Trial of satralizumab in neuromyelitis optica spectrum disorder. *N Engl J Med*. 2019;381:2114-2124. doi:10.1056/NEJMoa1901747
21. Yamamura T, Weinshenker B, Yeaman MR, et al. Long-term safety of satralizumab in neuromyelitis optica spectrum disorder (NMOSD) from SAkuraSky and SAkuraStar. *Mult Scler Relat Disord* 2022; 66: 104025. doi: 10.1016/j.msard.2022.104025
22. Kleiter I, Traboulsee A, Palace J, et al. Long-term efficacy of satralizumab in AQP4-IgG-seropositive neuromyelitis optica spectrum disorder from SAkuraSky and SAkuraStar. *Neurol Neuroimmunol Neuroinflamm*. 2023:10 20221208. doi:10.1212/NXI.0000000000200071
23. Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. *Blood*. 2019;133:530-539. doi:10.1182/blood-2018-09-876136
24. Pittock SJ, Barnett M, Bennett JL, et al. Ravulizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. *Ann Neurol*. 2023;93(6). doi:10.1002/ana.26626
25. Wang Y, Johnston K, Popoff E, et al. A US cost-minimization model comparing ravulizumab versus eculizumab for the treatment of atypical hemolytic uremic syndrome. *J Med Econ*. 2020;23:1503-1515. doi:10.1080/13696998.2020.1831519
26. A study of Orelabrutinib Patients with AQP4-IgG Positive Neuromyelitis Optica Spectrum Disorder. https://clinicaltrials.gov/ct2/show/NCT05284175?term=Orelabrutinib&draw=2&rank=9
27. Singh JA, Shah NP, Mudano AS. Belimumab for systemic lupus erythematosus. *Cochrane Database Syst Rev*. 2021;2:CD010668doi:10.1002/14651858.CD010668.pub2
28. Wang Y, Zhong X, Wang H, et al. Batoclimab as an add-on therapy in neuromyelitis optica spectrum disorder patients with acute attacks. *Eur J Neurol*. 2023;30:195-203. doi:10.1111/ene.15561
29. Scheibe F, Ostendorf L, Pruss H, et al. Daratumumab for treatment-refractory antibody-mediated diseases in neurology. *Eur J Neurol*. 2022;29:1847-1854. doi:10.1111/ene.15266
30. Ferilli MAN, Paparella R, Morandini I, et al. Pediatric neuromyelitis optica spectrum disorder: case series and literature review. *Life*. 2021:12:20211223. doi:10.3390/life12010019
31. Smith TE, Madhavan M, Gratch D, et al. Risk of COVID-19 infection and severe disease in MS patients on different disease-modifying therapies. *Mult Scler Relat Disord* 2022; 60: 103735. doi:10.1016/j.msard.2022.103735
32. Mears V, Jakubecz C, Seeco C, et al. Predictors of hypogammaglobulinemia and serious infections among patients receiving ocrelizumab or rituximab for treatment of MS and NMOSD. *J Neuroimmunol*. 2023;377:578066-20230308. doi:10.1016/j.jneuroim.2023.578066
33. Faissner S, Heitmann N, Rohling R, et al. Preserved T-cell response in anti-CD20-treated multiple sclerosis patients following SARS-CoV-2 vaccination. *Ther Adv Neurol Disord*. 2022;15. doi:10.1177/17562864221141505
34. D'Souza R, Wuebbolt D, Andrejevic K, et al. Pregnancy and neuromyelitis optica spectrum disorder - reciprocal effects and practical recommendations: a systematic review. *Front Neurol*. 2020;11:544434-20201016. doi:10.3389/fneur.2020.544434
35. Borisow N, Hellwig K, Paul F. Neuromyelitis optica spectrum disorders and pregnancy: relapse-preventive measures and personalized treatment strategies. *EPMA J*. 2018;9:249-256. doi:10.1007/s13167-018-0143-9
36. Pham-Huy A, Top KA, Constantinescu C, et al. The use and impact of monoclonal antibody biologics during pregnancy. *CMAJ (Can Med Assoc J)*. 2021;193:E1129-E1136. doi:10.1503/cmaj.202391
37. Galati A, McElrath T, Bove R. Use of B-Cell-Depleting therapy in women of childbearing potential with multiple sclerosis and neuromyelitis optica spectrum disorder. *Neurol Clin Pract*. 2022;12:154-163. doi:10.1212/CPJ.0000000000001147
38. Tenembaum S, Yeh EAGuthy-Jackson Foundation International Clinical C. Pediatric NMOSD: a review and position statement on approach to work-up and diagnosis. *Front Pediatr*. 2020;8:339. doi:10.3389/fped.2020.00339