Advances in the Treatment of Neuromyelitis Optica Spectrum Disorder

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KEYWORDS

- Neuromyelitis optica spectrum disorder • Treatment • Immunosuppression
- Complement inhibition • Anti-IL-6 therapy • Anti-CD20 therapy • Relapses

KEY POINTS

- Acute relapses in neuromyelitis optica spectrum disorder (NMOSD) require immediate treatment. Early deployment of high-dose steroids and plasmapheresis/immunoadsorption is associated with better long-term outcomes.
- Advances in the understanding of NMOSD pathogenesis and identification of the NMO-specific pathogenic autoantibody have led to the development of highly effective disease-modifying strategies.
- Randomized clinical trials support the use of B-cell depletion (rituximab, inebilizumab), interleukin-6 signaling blockade (tocilizumab, satralizumab), and complement inhibition (eculizumab) to decrease relapse rates in NMOSD.
- Mortality in the treated contemporary NMOSD cohorts has been considerably lower (3%–7%) than in the natural history studies (22%–30%).

INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, relapsing-remitting neuro-inflammatory disorder of the central nervous system (CNS) usually associated with aquaporin-4 antibody (AQP4 Ab). The International Panel for Neuromyelitis Optica Diagnosis criteria recognizes 5 core syndromes of NMOSD, of which optic neuritis and longitudinally extensive myelitis are the most common.[1] Despite being an "orphan disease," NMOSD affects about 17,000 people in the United States,[2] and 5

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randomized, placebo-controlled phase 2 and phase 3 clinical trials for 5 different therapies have been successfully completed for NMOSD as of 2020.[3–7] These trials confirmed the efficacy of rituximab[3] and tocilizumab[4] and led to the Food and Drug Administration (FDA) approval of eculizumab,[5] inebilizumab,[6] and satralizumab[7] for NMOSD. These landmark trials cap 2 decades of remarkable progress in the understanding of the pathogenesis of NMOSD. During this short period, NMOSD has been transformed from an obscure, ill-defined, untreatable disorder with a dismal prognosis into a distinct nosologic entity with a highly specific serologic marker and a wide range of immunomodulatory and immunosuppressive treatment options.[8]

MANAGEMENT OF RELAPSES

Relapses in NMOSD tend to be more disabling than in multiple sclerosis (MS) and may lead to vision loss and paralysis, which are often only partially reversible. Traditionally, the inexpensive, widely available intravenous (IV) steroids are used first-line. In observational studies of NMOSD/MOG Ab seropositive optic neuritis, shorter time to treatment correlated with less retinal nerve fiber layer loss[9] and better visual outcomes.[10] However, there is no high-level evidence that steroids affect long-term outcomes.[11] For plasma exchange (PLEX), on the other hand, there is class I evidence for a long-term benefit on disability outcomes based on a pivotal randomized trial of PLEX versus sham PLEX in acute CNS inflammatory relapses recalcitrant to steroids.[12] Immunoadsorption (IA), an alternative to PLEX that does not require blood exchange, seems to have similar efficacy to PLEX.[13] Recent observational studies have shown that earlier use of PLEX/IA as an add-on to steroids in NMOSD is associated with lower long-term disability and a higher proportion of patients with complete recovery.[13–18] These data support prompt initiation of PLEX/IA in any NMOSD relapse that causes moderate-to-severe disability. The typical regimen is 5 to 7 cycles. Side effects of PLEX include complications of central venous catheter placement, which can be mitigated by using peripheral access instead; line infections; hypotension; bleeding due to depletion of coagulation factors; and electrolyte abnormalities. For the subset of patients with NMOSD who are positive for MOG Ab, a course of IV immunoglobulins (IVIg) has been successfully deployed during an acute relapse.[19,20] However, in randomized clinical trials of IVIg for optic neuritis,[21,22] treatment did not improve short- or long-term outcomes.[21,22] "Catastrophic relapses" that are refractory to steroids and PLEX may benefit from high-dose IV methotrexate.[23] Any patient with motor and gait deficits due to a relapse will benefit from a multidisciplinary rehabilitation program,[24] which should be started as soon as the feasible, preferably during the acute hospitalization.

DISEASE-MODIFYING THERAPIES: B-CELL DEPLETION THERAPIES

B-lymphocytes play a prominent role in the immunopathogenesis of NMOSD via AQP4 autoantibody production, enhanced proinflammatory B cell and plasmablast activity, and other mechanisms.[25] Therefore, B-cell depletion is a rational therapeutic strategy for NMOSD.

Rituximab

Rituximab is a chimeric murine/human monoclonal antibody against the CD20 surface molecule, which is found on pre-B cells, mature B cells, and memory B cells, but not on plasma cells. Rituximab was given to 8 patients with NMOSD in an open-label study in 2005 and was found to be safe and effective.[26] Subsequently, dozens of retrospective and prospective observational studies provided evidence for the

effectiveness of rituximab in both pediatric[27] and adult NMOSD, both as a first-line therapy[28] and in refractory cases.[29–32] A meta-analysis of 26 studies of rituximab in NMOSD found that the annualized relapse rate was decreased by 1.56, with 63% of patients being free of relapses during the period of observation.[32] A larger metanalyses with 46 studies showed that treatment with rituximab decreased the annualized relapse rate ratio by 0.79 and Expanded Disability Status Scale (EDSS) by an average 0.64 to 1.2 points.[31] Possibly, even more impressive results could be achieved if all patients are treated to complete suppression of CD19+ (<0.1% of total lymphocytes) and CD27+ (<0.05% of total lymphocytes) cell counts. In a Korean study of 100 patients with NMOSD treated with rituximab with the goal of complete CD27+ (memory B cell) depletion, 70% of patients were relapse-free over a median period of more than 5 years, and the annualized relapse rate was just 0.1.[33] A recently published multicenter, blinded, randomized study of rituximab versus placebo, which enrolled 38 AQP4 Ab seropositive patients in Japan, documented relapses in 7 (37%) patients in the placebo arm and none (0%) in the rituximab arm during the 72-week study period (group difference 36·8%). There were no differences in the final EDSS scores in the 2 groups, but the more sensitive quantification of nerve and spinal cord impairment scores in patients assigned to the rituximab group was significantly better than in the placebo group.[3]

In clinical practice, variable dosing strategies are deployed. Induction is typically with 1000 mg doses 2 weeks apart, or 375 mg/m^2 weekly for 4 weeks, followed by a maintenance treatment of 500 mg to 1000 mg once (or twice) every 6 months. Treatment to CD19/CD27 suppression targets is recommended and may allow for lower doses or longer interdose intervals in some patients, especially those with lower body mass index. However, smaller doses are associated with a more rapid B-cell reconstitution, and more frequent B-cell monitoring may be required.[34–38] Caution is advised when initiating rituximab within weeks of an acute relapse, as disease exacerbation in the immediate postinfusion period has been reported, presumably due to a rituximab-induced proinflammatory cytokine surge.[39] The most common adverse reactions are nonsevere infusion reactions, which can be mitigated with pretreatment and slow titration, and infections. In a recent meta-analysis, the rate of serious infections and adverse reactions in adult patients with NMOSD was 2%, and the crude mortality rate was 1.6%.[31] In rituximab-treated children with neurologic diseases, serious infections were observed in 7.6% and mortality in 2%.[40] In a large case series of patients with MS and NMO treated with rituximab, the main risk factor for serious infection was nonambulatory status, which increased the risk of serious infections nearly 9-fold in comparison to fully ambulatory patients.[41] Rare complications such as serum sickness[42] and pyoderma grangrenosum[43] have been reported in patients treated with rituximab for neurologic indications.

Inebilizumab

CD19 and CD20 surface antigens are both found on immature B cells and memory B cells, but CD19 is also found on pro-B cells, plasmablasts, and most of the plasma cells.[44] As such, targeting CD19-positive cells could be a more potent strategy for controlling B-cell–mediated diseases than anti-CD20 therapy. Inebilizumab, a humanized, affinity-optimized, afucosylated IgG1 kappa monoclonal antibody against CD19 has undergone extensive clinical development for NMOSD culminating in a double-blind, placebo-controlled phase 2/3 trial (N-Momentum).[6] The trial enrolled 230 adults with active NMOSD (at least one attack requiring treatment the year before enrollment or 2 attacks in 2 years) and EDSS of 8 or less (restricted to bed/chair or better). The cohort was predominantly women (91%), with a mean age of 43 and 92% seropositive

for AQP4 Ab. Approximately 2 out of 3 patients had prior exposure to disease-modifying therapies. The patients were randomized 2:1 into the active group (N = 174) or placebo (N = 56). In the active group, patients were treated with an induction dose of inebilizumab, 300 mg, IV 2 weeks apart, and then a maintenance dose of 300 mg every 26 weeks. Only 12% of participants receiving inebilizumab had an attack, compared with 39% of participants receiving placebo, with a relative risk reduction of 73%. Because of an unequal allocation of seronegative patients across groups (only 4 seronegative patients in the placebo group, none of whom had relapses), efficacy could not be interpreted in the seronegative subset. Serious adverse events were infrequent and similarly distributed during the treatment phase. No deaths occurred during the trial, but during the open-label period, 2 patients who were started on inebilizumab had died after developing new or worsening neurologic symptoms. Based on this trial, inebilizumab (Uplizna) has been FDA approved for NMOSD. Inebilizumab is contraindicated for patients with active hepatitis B and active or untreated latent tuberculosis. Immunoglobulin levels should be measured before and during treatment, as inebilizumab may cause hypogammaglobulinemia, which is a risk factor for recurrent infections or serious opportunistic infections, and may warrant consideration to stop treatment,[45] or, possibly, supplementation with IVIg to replete immunoglobulins.

DISEASE-MODIFYING THERAPIES: INTERLEUKIN-6 ANTAGONISTS

Several lines of evidence implicate interleukin-6 (IL-6) in the pathophysiology of NMOSD. IL-6 levels are increased in cerebrospinal fluid during NMOSD relapses, but not in MS relapses, nor in other neurologic disorders.[46] Only IL-6, among multiple cytokines, demonstrated significantly higher levels in the serum of patients with NMOSD compared with MS controls.[47] IL-6 promotes survival of a plasmablast population responsible for secreting anti-AQP4 antibodies, likely contributing to increased anti-AQP4 antibody titers.[48]

Tocilizumab

Tocilizumab (Actemra) is a humanized anti-IL-6 receptor monoclonal antibody approved for the treatment of rheumatoid arthritis, giant cell arteritis, juvenile idiopathic arthritis, and cytokine release syndrome. In 2013, several case reports documented the effectiveness of tocilizumab in NMOSD, including patients refractory to rituximab.[49–52] In an open-label pilot study of monthly tocilizumab IV infusions in patients who had experienced multiple relapses in the preceding year on immunosuppressants and corticosteroids, 5 of 7 participants achieved relapse freedom for at least 1 year.[53] In another observational study of 8 patients treated with tocilizumab as an add-on therapy for NMOSD,[54] tocilizumab reduced relapses by 90% compared with baseline, with most relapses occurring in patients receiving lower dosing or extended treatment intervals. An open-label randomized phase 2 trial (TANGO) included 118 patients with active NMOSD who were randomized 1:1 to either tocilizumab, 8 mg/kg, monthly IV infusions or azathioprine, 2 to 3 mg/kg, oral daily.[4] Analysis of the primary outcome of time to first relapse favored tocilizumab over azathioprine with a median of 78.9 weeks for tocilizumab versus 56.7 weeks for azathioprine. In the per-protocol analysis, 89% of tocilizumab-treated patients were relapse-free versus 52% on azathioprine at 60 weeks, an 81.2% risk reduction. Adverse events were mostly mild and observed at lower rates in the tocilizumab arm. A single death occurred in each arm of the study. Prescribing information includes warnings regarding the risk of tuberculosis, invasive fungal infections, and opportunistic

infections, but these have been mostly reported in conditions that are commonly treated with multiple concurrent immunosuppressants. Gastrointestinal perforation may be a concern in at-risk patients, as IL-6 prevents apoptosis of the intestinal epithelium,[55] but has not been reported in NMOSD. Although studies on the effectiveness of tocilizumab in NMOSD used the IV preparation of the drug, a recent case series suggested that subcutaneous administration of tocilizumab was similarly efficacious[56] and has the advantage of at-home administration.

Satralizumab

Satralizumab (Enspryng) is a humanized anti-IL6 monoclonal antibody, which has been studied in 2 phase III randomized clinical trials for NMOSD, SAkuraSky, and SAkuraStar. In SAkuraSky, adolescents and adults with an EDSS less than or equal to 6.5 (bilateral crutches or better) were randomized 1:1 to receive either satralizumab, 120 mg, subcutaneously or placebo as add-on to baseline immunosuppression (azathioprine, mycophenolate, or glucocorticoids).[57] During the 96-week trial, there was a 62% relative reduction in relapses in the treated group, with 89% of patients remaining relapse-free on satralizumab compared with 66% in the placebo arm. Efficacy was more pronounced in seropositive participants, with a 79% relative risk reduction, compared with a 34% risk reduction in seronegative NMOSD. SAkuraStar tested satralizumab as monotherapy versus placebo for adults with active NMOSD and EDSS less than or equal to 6.5 and demonstrated a 55% relapse relative risk reduction compared with placebo,[7] with higher efficacy—a 74% relative risk reduction—when restricting the analysis to AQP4 seropositive participants, suggesting different pathophysiology in seronegative patients. Neither SAkuraSky nor SAkuraStar found a significant effect of satralizumab on secondary outcome measures of pain or fatigue. In SAkuraSky and SAkuraStar, overall infection rates, including serious infection and neoplasm rates, were similar in both arms. Injection reactions occurred in 12% to 13% of satralizumab-treated patients and 5% to 16% of placebo patients. There was no anaphylaxis and no mortalities in either trial.

Satralizumab is approved to treat adults and children with NMOSD in Japan and AQP4-positive adults in the United States. It is contraindicated in patients with hepatitis B and active or untreated latent tuberculosis. It is administered subcutaneously at weeks 0, 2, and 4, then monthly, with instructions on holding treatment in the event of active infection, elevated liver enzymes, or neutropenia.[58]

DISEASE-MODIFYING THERAPIES: COMPLEMENT INHIBITORS

Neuropathological analysis of acute lesions in NMO has shown extensive complement activation in a perivascular pattern.[59] These observations predated the discovery of a pathogenic autoantibody and led to the dual hypotheses that CNS vasculature may be an early and specific target of NMOSD and that complement activation plays an important role in the pathogenesis of the disease.[59] Both of these hypotheses were confirmed with the discovery of an NMOSD-specific autoantibody directed to an antigen on the blood-brain barrier—the AQP4 Ab—and demonstration of the spectacular efficacy of complement inhibitors in preventing relapses of NMOSD.

Eculizumab

Eculizumab (Soliris) is a humanized monoclonal antibody that binds plasma C5 and thereby blocks the formation of the cytotoxic membrane-attack complex and the generation of a proinflammatory C5a paracrine factor. An open-label study of eculizumab enrolled 14 AQP4 seropositive patients with NMOSD who collectively suffered 55

attacks in the 2 years preceding the trial (despite treatment in 10 of the patients).[60] During the 12-month on-trial period, 12 of the patients had no attacks and 2 patients had possible attacks but without worsening disability scores. Within 1 year of stopping eculizumab in the clinical trial, 5 patients experienced a total of 8 relapses despite restarting immunosuppressive therapies. Serious adverse events in treated patients included meningococcal sepsis in a patient who received prior immunization, and a fatal myocardial infarction during follow-up that was deemed unrelated to the study drug.

Following the very encouraging results of the open-label trial, eculizumab was tested in a phase III randomized double-blind, placebo-controlled trial that enrolled adult AQP4-positive patients with NMOSD with EDSS less than or equal to 7 (wheelchair-bound, or better) and highly active disease (at least 2 relapses in the prior year or 3 in the prior 24 months).[61] Patients were randomized 2:1 to eculizumab, 900 mg, IV weekly x 4 doses followed by 1200 mg every 2 weeks or to placebo infusions. All patients were allowed to continue prior oral immunosuppression during the trial. The primary endpoint—an adjudicated clinical relapse—occurred in 3% of patients in the eculizumab group and 43% of patients in the non-eculizumab group, yielding a 94% relative risk reduction. In a subset analysis of patients who were on concomitant immunosuppression, 4% of the eculizumab group and 54% of the non-eculizumab group of patients experienced a relapse. Serious adverse events included one death from pulmonary empyema in a patient on eculizumab and concomitant azathioprine. During the open-label extension trial involving 137 patients (282 patient-years), serious adverse events were reported in 36% of treated patients, including 2 cases of sepsis and 1 case of Neisseria gonorrhea infection[5] but no deaths. All subjects received meningococcal vaccination at the start of the trial, and there were no cases of meningococcal infection during either the trial or open-label follow-up period.

All patients who are starting eculizumab must receive the meningococcal vaccination (MenACWY and MenB) and be enrolled in the Risk Evaluation and Mitigation Strategy program (https://www.solirisrems.com/).[62] Widespread clinical use of this extremely effective medication has so far been limited by concerns about its safety, the need for bimonthly IV infusions, and high cost.

DISEASE-MODIFYING THERAPIES: BROAD-SPECTRUM IMMUNOSUPPRESSANTS

Multiple therapies with broad immunosuppressive properties have been used for NMOSD as monotherapy or in conjunction with low-dose corticosteroids. Low-dose corticosteroids have also been deployed as monotherapy, and there is limited evidence that corticosteroid doses greater than 10 mg/d may be protective against relapses.[63] Retrospective comparisons involving the different therapies are subject to confounding by indication and other biases and have produced mixed results. One study demonstrated the superiority of rituximab and mycophenolate mofetil (MMF) over azathioprine,[64] whereas another, albeit with a small number of azathioprine-treated cases, found that rituximab and azathioprine were more efficacious than MMF.[65] A prospective study of low-dose rituximab, azathioprine, and MMF found the 3 treatments to be of comparable efficacy, but MMF and rituximab were better tolerated.[66] Based on the randomized trials that allowed for oral immunosuppression in the "placebo" arms,[57,61] the efficacy of the older, broad-spectrum oral immunosuppressants is likely less robust compared with that of the more targeted approaches discussed earlier (B-cell depletion, IL-6 blockade, complement inhibition).

Azathioprine

Azathioprine is an antimetabolite, which causes a decrease in lymphocyte proliferation. Azathioprine was efficacious for NMOSD in doses of 2 mg/kg/d when used in conjunction with high-dose prednisone in a small open-label prospective cohort study.[67] In clinical practice, it is often used as monotherapy. Azathioprine has been widely prescribed for NMOSD, especially in resource-poor settings, although it seems to be less effective than rituximab[64,66,68,69] or tocilizumab.[4] Serious adverse events are hepatotoxicity and malignancies: lymphoma was observed in 3% of patients in a large NMOSD series.[70]

Mycophenolate Mofetil

MMF is a noncompetitive inhibitor of an enzyme essential for *de novo* synthesis of guanosine-5′-monophosphate, a purine nucleotide. MMF inhibits proliferation of lymphocytes and is used for the treatment of autoimmune conditions and the prevention of organ transplant rejection. Following a case report of MMF effectiveness in a patient with NMOSD,[71] a case series of 24 patients with NMOSD documented a decrease from baseline aldosterone-to-renin ratio (ARR) 1.28 to 0.09 posttreatment and stabilization of disability in 63% of patients. One death in a patient with severe NMOSD was recorded during the 29-month median follow-up.[72] A retrospective, multicenter Korean study[73] reported a decrease in the ARR in 88% of patients (median ARR improvement from 1.5 to 0) and EDSS improvement or stabilization in 91%. MMF seems effective in doses of 1750 mg to 2000 mg per day and may be used in conjunction with prednisone.[74] MMF has been associated with increased risk of lymphoma in transplant patients and nonmelanoma skin carcinomas, so routine dermatologic screening in patients on long-term therapy is advisable. Other known adverse events include infections, gastrointestinal symptoms, including ulcers and hemorrhage, and cytopenias. MMF is teratogenic—congenital malformations have been reported in 26% of live births and the risk of first-trimester pregnancy loss is 45% in exposed patients, thus women of childbearing age must be counseled accordingly before starting therapy.[75]

Methotrexate

Methotrexate is a dihydrofolate reductase inhibitor used in weekly oral doses for the treatment of rheumatoid arthritis, Crohn's disease, and other autoimmune diseases. The evidence for methotrexate in NMOSD comes from small observational studies, the largest of which included 14 patients.[76–79] The improvement in ARR ranged from 64% to 100%, and relapse freedom was attained in 22% to 75% of patients.[76,77,79] Patients should be monitored for bone marrow suppression and liver function. Rare serious adverse events include hepatotoxicity, pneumonitis, aplastic anemia, and opportunistic infections. Methotrexate is teratogenic and is not recommended for women of childbearing age when safer options are available.

Tacrolimus

Tacrolimus is an oral immunosuppressant that inhibits the intracellular calcineurin pathway required for T-cell activation and is widely used in organ transplantation and systemic autoimmune diseases. A Japanese retrospective cohort study of patients with NMOSD treated with "induction prednisolone" followed by tapering doses of prednisolone and tacrolimus in 25 patients, dosed 1 to 6 mg/d, achieved relapse freedom in 92%, with relapses only seen in patients with subtherapeutic serum concentrations.[80] A Chinese retrospective study of 25 patients with NMOSD treated with

tacrolimus 2 to 3 mg/d (except for one pediatric patient treated with 1 mg/d) and concomitant prednisone in 60% of patients, found that tacrolimus decreased the ARR by 86% and improved the EDSS from 4.5 pretreatment to 2.3 at the last follow-up.[81] One patient died of a serious infection.[81] Tacrolimus prescribing information includes a boxed warning related to an increased risk of serious infections and malignancies.[82]

Mitoxantrone

Mitoxantrone inhibits topoisomerase II, an enzyme crucial in DNA repair, leading to a reduction in B- and T-cell counts. A recently published systematic review[83] of mitoxantrone in NMOSD identified 8 studies with 117 patients. Three of the five studies with pre- and posttreatment ARR reported significant improvement 6 months to 5 years following treatment. A comparison of AQP4 seropositive patients treated with rituximab, azathioprine/prednisolone, or mitoxantrone suggested a greater decrease in relapse rates with rituximab and azathioprine/prednisolone than with mitoxantrone.[84] Mitoxantrone is not widely used due to dose-limiting cardiotoxicity and risk of acute myeloid leukemia (incidence of nearly 1% in a large Italian series of patients with MS).[85] The risk of acute leukemia seems to be higher with a cumulative dose[86] greater than 60 mg/m^2, but acute leukemia was also reported in a patient with NMOSD who received a lower dose.[87]

Cyclophosphamide

Cyclophosphamide is an alkylating agent widely used in oncology. In a nonblinded prospective cohort study[88] of Chinese patients with NMOSD that included 119 patients treated with azathioprine, 38 with MMF, and 41 with IV cyclophosphamide, all in combination with oral steroids, the 3 drugs had a similarly positive effect in decreasing ARR during 15-month follow-up, but cyclophosphamide did not improve EDSS, whereas the other 2 treatments did. However, another group found cyclophosphamide to have poor efficacy; in a cohort of 7 patients treated with cyclophosphamide only 1 (14%) was clinically stable.[89]

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANT AS A DISEASE-MODIFYING THERAPY

Autologous hematopoietic stem cell transplant (AHSCT) is under investigation for NMOSD as well as many other autoimmune conditions. Results of the 2 larger studies of AHSCT for NMOSD were discrepant. In the European retrospective AHSCT registry that included 16 patients with NMOSD refractory to immunosuppressants, only 10% remained relapse-free at 5 years.[90] Yet, in the US-based clinical trial of 12 patients with NMOSD treated with AHSCT, 83% were relapse-free at 5 years.[91] Each study recorded one fatality. The differences in outcomes could be partially due to differences in the regimen—European Registry did not use rituximab, whereas the US group did—as well as differences in patient characteristics. Complications of AHSCT include neutropenic fever[91,92] and other serious infections that are estimated to occur at a rate of 0.2 per year per patient[91]; electrolyte abnormalities; blood pressure fluctuations; and emergence of new autoimmune diseases, including myasthenia gravis and hyperthyroidism.[91] Mortality from AHSCT improved considerably over the last several decades: the overall mortality after AHSCT was only 0.2% in 2012 to 2016.[93] Given the uncertainty of benefit and concerns of long-term safety, AHSCT should currently be restricted to carefully selected patients with NMOSD, preferably in the context of a research protocol.[94]

SUMMARY

Discovery of the NMO-specific antibody against AQP4 in 2004 was a watershed event in the history of NMOSD. AQP4-antibody testing allows for earlier diagnosis, redefinition of NMOSD,[1] and easier distinction from MS.[95] Distinguishing NMOSD from MS is critically important, as some of the MS disease-modifying therapies, including interferon β, fingolimod, and natalizumab, are ineffective in NMOSD and may even exacerbate the disease.[96–98] Anti-AQP4 antibody mediates its injurious effect in part through complement-dependent cytotoxicity.[95] Thus, the most effective therapeutic approaches in NMOSD involve depleting B cells, decreasing IL-6, which prolongs survival of AQP4 antibody–secreting cells,[48] and blocking complement activation. These strategies have now been rigorously proved in randomized clinical trials to decrease the relapse rate in NMOSD by 74% to 94%.[6,7,61] The older immunosuppressants and corticosteroids are still widely used for NMOSD, especially in resource-limited settings but will likely be increasingly replaced by the newer, more targeted and likely more efficacious therapies.

The remarkable advances in NMOSD therapeutics coincided with a dramatic decrease in mortality. In a large natural history study from the 1990s, 5-year survival in NMOSD was only 68%,[99] whereas a recent population-based study recorded a mortality of 3%. The success comes at a cost of life-long immunosuppression and increased risk of infections and other complications. The next frontier in NMOSD therapeutics is to move away from the "blunt hammer" of immunosuppression to "precise scalpels" that target the pathogenic AQP4 immunity leaving the rest of the immune system intact.[100] Various stratagems are being tested that involve inverse DNA, autoreactive T cells, dendritic cell vaccines, enhancement of regulatory T and B cell function, oral tolerizations, and others.[101,102] The importance of advancing these targeted immunomodulatory approaches to the clinical arena has never been more acute than at the time when this article is being written, at the height of the global COVID-19 pandemic.

CLINICS CARE POINTS

- There is strong evidence that early treatment with plasmapheresis (typically 5 – 7 courses) is associated with better long-term outcomes in NMOSD.
- Disease-modifying therapies should be deployed early in the disease, preferably after the first attack because they are likely to significantly impact the long term prognosis.
- Review the patient's vaccination history prior to starting lifelong immunosuppressant treatment. Live vaccines (eg. MMR) are not advised during treatment with rituximab, inebilizumab, tocilizumab or satralizumab. Two meningococcal vaccines are recommended prior to starting eculizumab at least 2 weeks prior to the first dose.

DISCLOSURE

REFERENCES

1. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015; 85(2):177–89.
2. Flanagan EP, Cabre P, Weinshenker BG, et al. Epidemiology of aquaporin-4 autoimmunity and neuromyelitis optica spectrum. Ann Neurol 2016;79(5): 775–83.
3. Tahara M, Oeda T, Okada K, et al. Safety and efficacy of rituximab in neuromyelitis optica spectrum disorders (RIN-1 study): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet Neurol 2020;19(4):298–306.
4. Zhang C, Zhang M, Qiu W, et al. Safety and efficacy of tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorder (TANGO): an open-label, multicentre, randomised, phase 2 trial. Lancet Neurol 2020;19(5):391–401.
5. Wingerchuck DM. Long-term safety and effectiveness of eculizumab in neuromyelitis optica spectrum disorder. Paper presented at: ECTRIMS2019. 11-13 September 2019, Stockholm, Sweden.
6. 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(10206):1352–63.
7. 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(5):402–12.
8. Kister I, Paul F. Pushing the boundaries of neuromyelitis optica: does antibody make the disease? Neurology 2015;85(2):118–9.
9. Nakamura M, Nakazawa T, Doi H, et al. Early high-dose intravenous methylprednisolone is effective in preserving retinal nerve fiber layer thickness in patients with neuromyelitis optica. Graefes Arch Clin Exp Ophthalmol 2010;248(12): 1777–85.
10. Stiebel-Kalish H, Hellmann MA, Mimouni M, et al. Does time equal vision in the acute treatment of a cohort of AQP4 and MOG optic neuritis? Neurol Neuroimmunol Neuroinflamm 2019;6(4):e572.
11. Gal RL, Vedula SS, Beck R. Corticosteroids for treating optic neuritis. Cochrane Database Syst Rev 2012;(4):CD001430.
12. Weinshenker BG, O'Brien PC, Petterson TM, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. Ann Neurol 1999;46(6):878–86.
13. Kleiter I, Gahlen A, Borisow N, et al. Apheresis therapies for NMOSD attacks: A retrospective study of 207 therapeutic interventions. Neurol Neuroimmunol Neuroinflamm 2018;5(6):e504.
14. Abboud H, Petrak A, Mealy M, et al. Treatment of acute relapses in neuromyelitis optica: Steroids alone versus steroids plus plasma exchange. Mult Scler 2016; 22(2):185–92.
15. Kumawat BL, Choudhary R, Sharma CM, et al. Plasma Exchange as a First Line Therapy in Acute Attacks of Neuromyelitis Optica Spectrum Disorders. Ann Indian Acad Neurol 2019;22(4):389–94.
16. Bonnan M, Cabre P. Plasma Exchange in Severe Attacks of Neuromyelitis Optica. Mult Scler Int 2012;2012:1–9.

17. Mori S, Kurimoto T, Ueda K, et al. Short-term effect of additional apheresis on visual acuity changes in patients with steroid-resistant optic neuritis in neuromyelitis optica spectrum disorders. Jpn J Ophthalmol 2018;62(4):525–30.

18. Srisupa - Olan T, Siritho S, Kittisares K, et al. Beneficial effect of plasma exchange in acute attack of neuromyelitis optica spectrum disorders. Mult Scler Relat Disord 2018;20:115–21.

19. Hacohen Y, Banwell B. Treatment Approaches for MOG-Ab-Associated Demyelination in Children. Curr Treat Options Neurol 2019;21(1):2.

20. Elsone L, Panicker J, Mutch K, et al. Role of intravenous immunoglobulin in the treatment of acute relapses of neuromyelitis optica: experience in 10 patients. Mult Scler 2014;20(4):501–4.

21. Noseworthy JH, O'Brien PC, Petterson TM, et al. A randomized trial of intravenous immunoglobulin in inflammatory demyelinating optic neuritis. Neurology 2001;56(11):1514–22.

22. Roed HG, Langkilde A, Sellebjerg F, et al. A double-blind, randomized trial of IV immunoglobulin treatment in acute optic neuritis. Neurology 2005;64(5):804–10.

23. Beh SC, Kildebeck E, Narayan R, et al. High-dose methotrexate with leucovorin rescue: For monumentally severe CNS inflammatory syndromes. J Neurol Sci 2017;372:187–95.

24. Amatya B, Khan F, Galea M. Rehabilitation for people with multiple sclerosis: an overview of Cochrane Reviews. Cochrane Database Syst Rev 2019;(1):CD012732.

25. Bennett JL, O'Connor KC, Bar-Or A, et al. B lymphocytes in neuromyelitis optica. Neurol Neuroimmunol Neuroinflamm 2015;2(3):e104.

26. Cree BA, Lamb S, Morgan K, et al. An open label study of the effects of rituximab in neuromyelitis optica. Neurology 2005;64(7):1270–2.

27. Nosadini M, Alper G, Riney CJ, et al. Rituximab monitoring and redosing in pediatric neuromyelitis optica spectrum disorder. Neurol Neuroimmunol Neuroinflamm 2016;3(1):e188.

28. Zephir H, Bernard-Valnet R, Lebrun C, et al. Rituximab as first-line therapy in neuromyelitis optica: efficiency and tolerability. J Neurol 2015;262(10):2329–35.

29. Collongues N, Brassat D, Maillart E, et al. Efficacy of rituximab in refractory neuromyelitis optica. Mult Scler 2016;22(7):955–9.

30. Wong E, Vishwanath VA, Kister I. Rituximab in neuromyelitis optica: A review of literature. World J Neurol 2015;5(1):39–46.

31. Damato V, Evoli A, Iorio R. Efficacy and Safety of Rituximab Therapy in Neuromyelitis Optica Spectrum Disorders: A Systematic Review and Meta-analysis. JAMA Neurol 2016;73(11):1342–8.

32. Gao F, Chai B, Gu C, et al. Effectiveness of rituximab in neuromyelitis optica: a meta-analysis. BMC Neurol 2019;19(1):36.

33. Kim S-H, Jeong IH, Hyun J-W, et al. Treatment Outcomes With Rituximab in 100 Patients With Neuromyelitis Optica: Influence of FCGR3A Polymorphisms on the Therapeutic Response to Rituximab. JAMA Neurol 2015;72(9):989–95.

34. Ellrichmann G, Bolz J, Peschke M, et al. Peripheral CD19(+) B-cell counts and infusion intervals as a surrogate for long-term B-cell depleting therapy in multiple sclerosis and neuromyelitis optica/neuromyelitis optica spectrum disorders. J Neurol 2019;266(1):57–67.

35. Yang CS, Yang L, Li T, et al. Responsiveness to reduced dosage of rituximab in Chinese patients with neuromyelitis optica. Neurology 2013;81(8):710–3.

36. Greenberg BM, Graves D, Remington G, et al. Rituximab dosing and monitoring strategies in neuromyelitis optica patients: creating strategies for therapeutic success. Mult Scler 2012;18(7):1022–6.

37. Novi G, Bovis F, Capobianco M, et al. Efficacy of different rituximab therapeutic strategies in patients with neuromyelitis optica spectrum disorders. Mult Scler Relat Disord 2019;36:101430.

38. Ciron J, Audoin B, Bourre B, et al. Recommendations for the use of Rituximab in neuromyelitis optica spectrum disorders. Rev Neurol 2018;174(4):255–64.

39. Perumal JS, Kister I, Howard J, et al. Disease exacerbation after rituximab induction in neuromyelitis optica. Neurol Neuroimmunol Neuroinflamm 2015; 2(1):e61.

40. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology 2014;83(2):142–50.

41. Vollmer BL, Wallach AI, Corboy JR, et al. Serious safety events in rituximab-treated multiple sclerosis and related disorders. Ann Clin Transl Neurol 2020. https://doi.org/10.1002/acn3.51136. Epub ahead of print. PMID: 32767531.

42. Wolf AB, Ryerson LZ, Pandey K, et al. Rituximab-induced serum sickness in multiple sclerosis patients. Mult Scler Relat Disord 2019;36:101402.

43. Parrotta E, Zhovtis Ryerson L, Krupp LB. It's not always an infection: pyoderma gangrenosum of the urogenital tract in two patients with multiple sclerosis treated with rituximab. ACTRIMS Forum. West Palm Beach, FL, February 27, 2020.

44. Chen D, Gallagher S, Monson NL, et al. Inebilizumab, a B Cell-Depleting Anti-CD19 Antibody for the Treatment of Autoimmune Neurological Diseases: Insights from Preclinical Studies. J Clin Med 2016;5(12):107.

45. Uplizna Prescribing Information. 2020. Available at: https://www.uplizna.com/ Uplizna_Prescribing_Information.pdf. Accessed August 16, 2020.

46. Uzawa A, Mori M, Ito M, et al. Markedly increased CSF interleukin-6 levels in neuromyelitis optica, but not in multiple sclerosis. J Neurol 2009;256(12): 2082–4.

47. Uzawa A, Mori M, Arai K, et al. Cytokine and chemokine profiles in neuromyelitis optica: significance of interleukin-6. Mult Scler 2010;16(12):1443–52.

48. Chihara N, Aranami T, Sato W, et al. Interleukin 6 signaling promotes anti-aquaporin 4 autoantibody production from plasmablasts in neuromyelitis optica. Proc Natl Acad Sci U S A 2011;108(9):3701–6.

49. Kieseier BC, Stuve O, Dehmel T, et al. Disease amelioration with tocilizumab in a treatment-resistant patient with neuromyelitis optica: implication for cellular immune responses. JAMA Neurol 2013;70(3):390–3.

50. Araki M, Aranami T, Matsuoka T, et al. Clinical improvement in a patient with neuromyelitis optica following therapy with the anti-IL-6 receptor monoclonal antibody tocilizumab. Mod Rheumatol 2013;23(4):827–31.

51. Ayzenberg I, Kleiter I, Schroder A, et al. Interleukin 6 receptor blockade in patients with neuromyelitis optica nonresponsive to anti-CD20 therapy. JAMA Neurol 2013;70(3):394–7.

52. Lauenstein AS, Stettner M, Kieseier BC, et al. Treating neuromyelitis optica with the interleukin-6 receptor antagonist tocilizumab. BMJ Case Rep 2014;2014. bcr2013202939.

53. Araki M, Matsuoka T, Miyamoto K, et al. Efficacy of the anti-IL-6 receptor antibody tocilizumab in neuromyelitis optica: a pilot study. Neurology 2014; 82(15):1302–6.

54. Ringelstein M, Ayzenberg I, Harmel J, et al. Long-term Therapy With Interleukin 6 Receptor Blockade in Highly Active Neuromyelitis Optica Spectrum Disorder. JAMA Neurol 2015;72(7):756–63.

55. Kuhn KA, Manieri NA, Liu TC, et al. IL-6 stimulates intestinal epithelial proliferation and repair after injury. PLoS One 2014;9(12):e114195.

56. Lotan I, Charlson RW, Ryerson LZ, et al. Effectiveness of subcutaneous tocilizumab in neuromyelitis optica spectrum disorders. Mult Scler Relat Disord 2019;39:101920.

57. Yamamura T, Kleiter I, Fujihara K, et al. Trial of Satralizumab in Neuromyelitis Optica Spectrum Disorder. N Engl J Med 2019;381(22):2114–24.

58. Enspryng Prescribing Information. 2020. Available at: https://www.gene.com/download/pdf/enspryng_prescribing.pdf. Accessed August 16, 2020.

59. Lucchinetti CF, Mandler RN, McGavern D, et al. A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. Brain 2002;125(Pt 7):1450–61.

60. Pittock SJ, Lennon VA, McKeon A, et al. Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: an open-label pilot study. Lancet Neurol 2013;12(6):554–62.

61. Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. N Engl J Med 2019;381(7):614–25.

62. Avasarala J, Sokola BS, Mullins S. Eculizumab package insert recommendations for meningococcal vaccinations: call for clarity and a targeted approach for use of the drug in neuromyelitis optica spectrum disorder. CNS Spectr 2019;1–3 [Epub ahead of print].

63. Watanabe S, Misu T, Miyazawa I, et al. Low-dose corticosteroids reduce relapses in neuromyelitis optica: a retrospective analysis. Mult Scler 2007;13(8):968–74.

64. Mealy MA, Wingerchuk DM, Palace J, et al. Comparison of relapse and treatment failure rates among patients with neuromyelitis optica: multicenter study of treatment efficacy. JAMA Neurol 2014;71(3):324–30.

65. Poupart J, Giovannelli J, Deschamps R, et al. Evaluation of efficacy and tolerability of first-line therapies in NMOSD. Neurology 2020;94(15):e1645–56.

66. Yang Y, Wang CJ, Wang BJ, et al. Comparison of efficacy and tolerability of azathioprine, mycophenolate mofetil, and lower dosages of rituximab among patients with neuromyelitis optica spectrum disorder. J Neurol Sci 2018;385:192–7.

67. Mandler RN, Ahmed W, Dencoff JE. Devic's neuromyelitis optica: a prospective study of seven patients treated with prednisone and azathioprine. Neurology 1998;51(4):1219–20.

68. Nikoo Z, Badihian S, Shaygannejad V, et al. Comparison of the efficacy of azathioprine and rituximab in neuromyelitis optica spectrum disorder: a randomized clinical trial. J Neurol 2017;264(9):2003–9.

69. Bichuetti DB, Lobato de Oliveira EM, Oliveira DM, et al. Neuromyelitis optica treatment: analysis of 36 patients. Arch Neurol 2010;67(9):1131–6.

70. Costanzi C, Matiello M, Lucchinetti CF, et al. Azathioprine: tolerability, efficacy, and predictors of benefit in neuromyelitis optica. Neurology 2011;77(7):659–66.

71. Falcini F, Trapani S, Ricci L, et al. Sustained improvement of a girl affected with Devic's disease over 2 years of mycophenolate mofetil treatment. Rheumatology (Oxford) 2006;45(7):913–5.

72. Jacob A, Matiello M, Weinshenker BG, et al. Treatment of neuromyelitis optica with mycophenolate mofetil: retrospective analysis of 24 patients. Arch Neurol 2009;66(9):1128–33.

73. Huh SY, Kim SH, Hyun JW, et al. Mycophenolate mofetil in the treatment of neuromyelitis optica spectrum disorder. JAMA Neurol 2014;71(11):1372–8.

74. Jiao Y, Cui L, Zhang W, et al. Dose effects of mycophenolate mofetil in Chinese patients with neuromyelitis optica spectrum disorders: a case series study. BMC Neurol 2018;18(1):47.

75. Kylat RI. What Is the Teratogenic Risk of Mycophenolate? J Pediatr Genet 2017; 6(2):111–4.

76. Ng ASL, Tan K. Methotrexate is effective for the treatment of neuromyelitis optica spectrum disorders in Asian patients. Clin Exp Neuroimmunol 2015;6(2): 149–53.

77. Kitley J, Elsone L, George J, et al. Methotrexate is an alternative to azathioprine in neuromyelitis optica spectrum disorders with aquaporin-4 antibodies. J Neurol Neurosurg Psychiatry 2013;84(8):918–21.

78. Minagar A, Sheremata WA. Treatment of Devic's Disease with Methotrexate and Prednisone. Int J MS Care 2000;2(4):43–9.

79. Ramanathan RS, Malhotra K, Scott T. Treatment of neuromyelitis optica/neuromyelitis optica spectrum disorders with methotrexate. BMC Neurol 2014;14:51.

80. Tanaka M, Kinoshita M, Tanaka K. Corticosteroid and tacrolimus treatment in neuromyelitis optica related disorders. Mult Scler 2015;21(5):669.

81. Chen B, Wu Q, Ke G, et al. Efficacy and safety of tacrolimus treatment for neuromyelitis optica spectrum disorder. Sci Rep 2017;7(1):831.

82. Highlights of Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210115s000,050708s047,050709s040lbl.pdf. Accessed April 25, 2020.

83. Enriquez CAG, Espiritu AI, Pasco PMD. Efficacy and tolerability of mitoxantrone for neuromyelitis optica spectrum disorder: A systematic review. J Neuroimmunol 2019;332:126–34.

84. Jarius S, Aboul-Enein F, Waters P, et al. Antibody to aquaporin-4 in the long-term course of neuromyelitis optica. Brain 2008;131(Pt 11):3072–80.

85. Martinelli V, Cocco E, Capra R, et al. Acute myeloid leukemia in Italian patients with multiple sclerosis treated with mitoxantrone. Neurology 2011;77(21): 1887–95.

86. Ellis R, Boggild M. Therapy-related acute leukaemia with Mitoxantrone: what is the risk and can we minimise it? Mult Scler 2009;15(4):505–8.

87. Cabre P, Olindo S, Marignier R, et al. Efficacy of mitoxantrone in neuromyelitis optica spectrum: clinical and neuroradiological study. J Neurol Neurosurg Psychiatry 2013;84(5):511–6.

88. Xu Y, Wang Q, Ren HT, et al. Comparison of efficacy and tolerability of azathioprine, mycophenolate mofetil, and cyclophosphamide among patients with neuromyelitis optica spectrum disorder: A prospective cohort study. J Neurol Sci 2016;370:224–8.

89. Bichuetti DB, Oliveira EM, Boulos Fde C, et al. Lack of response to pulse cyclophosphamide in neuromyelitis optica: evaluation of 7 patients. Arch Neurol 2012;69(7):938–9.

90. Greco R, Bondanza A, Oliveira MC, et al. Autologous hematopoietic stem cell transplantation in neuromyelitis optica: a registry study of the EBMT Autoimmune Diseases Working Party. Mult Scler 2015;21(2):189–97.

91. Burt RK, Balabanov R, Han X, et al. Autologous nonmyeloablative hematopoietic stem cell transplantation for neuromyelitis optica. Neurology 2019;93(18): e1732–41.
92. Aouad P, Li J, Arthur C, et al. Resolution of aquaporin-4 antibodies in a woman with neuromyelitis optica treated with human autologous stem cell transplant. J Clin Neurosci 2015;22(7):1215–7.
93. Muraro PA, Martin R, Mancardi GL, et al. Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis. Nat Rev Neurol 2017;13(7): 391–405.
94. Sharrack B, Saccardi R, Alexander T, et al. Autologous haematopoietic stem cell transplantation in multiple sclerosis and other immune-mediated neurological diseases: guidelines and recommendations of the European Society for Blood and Marrow Transplantation and the Joint Accreditation Committee of the International Society for Cellular Therapy (4540). Neurology 2020;94(15 Supplement):4540.
95. Jarius S, Wildemann B, Paul F. Neuromyelitis optica: clinical features, immuno-pathogenesis and treatment. Clin Exp Immunol 2014;176(2):149–64.
96. Kim SH, Kim W, Li XF, et al. Does interferon beta treatment exacerbate neuromyelitis optica spectrum disorder? Mult Scler 2012;18(10):1480–3.
97. Kleiter I, Hellwig K, Berthele A, et al. Failure of natalizumab to prevent relapses in neuromyelitis optica. Arch Neurol 2012;69(2):239–45.
98. Min JH, Kim BJ, Lee KH. Development of extensive brain lesions following fingolimod (FTY720) treatment in a patient with neuromyelitis optica spectrum disorder. Mult Scler 2012;18(1):113–5.
99. Wingerchuk DM, Hogancamp WF, O'Brien PC, et al. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 1999;53(5):1107–14.
100. Steinman L, Axtell RC, Barbieri D, et al. Piet Mondrian's trees and the evolution in understanding multiple sclerosis, Charcot Prize Lecture 2011. Mult Scler 2013; 19(1):5–14.
101. Steinman L, Bar-Or A, Behne JM, et al. Restoring immune tolerance in neuromyelitis optica: Part I. Neurol Neuroimmunol Neuroinflamm 2016;3(5):e276.
102. Bar-Or A, Steinman L, Behne JM, et al. Restoring immune tolerance in neuromyelitis optica: Part II. Neurol Neuroimmunol Neuroinflamm 2016;3(5):e277.