Advances in the Treatment of Neuromyelitis Optica Spectrum Disorder

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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.<sup>1</sup> Despite being an “orphan disease,” NMOSD affects about 17,000 people in the United States,<sup>2</sup> and 5

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%).

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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 rituximab3 and tocilizumab4 and led to the Food and Drug Administration (FDA) approval of eculizumab,5 inebilizumab,6 and satralizumab7 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 loss9 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 Immunoabsorption (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 and adult NMOSD, both as a first-line therapy and in refractory cases. 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. A larger meta-analysis 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. 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. 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.

In clinical practice, variable dosing strategies are deployed. Induction is typically with 1000 mg doses 2 weeks apart, or 375 mg/m² 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. 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. 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%. In rituximab-treated children with neurologic diseases, serious infections were observed in 7.6% and mortality in 2%. 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. Rare complications such as serum sickness and pyoderma gangrenosum 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. 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). 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, 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. Only IL-6, among multiple cytokines, demonstrated significantly higher levels in the serum of patients with NMOSD compared with MS controls. IL-6 promotes survival of a plasmablast population responsible for secreting anti-AQP4 antibodies, likely contributing to increased anti-AQP4 antibody titers.

**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. 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. In another observational study of 8 patients treated with tocilizumab as an add-on therapy for NMOSD, 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. 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, 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 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). 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, 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.

**DISEASE-MODIFYING THERAPIES: COMPLEMENT INHIBITORS**

Neuropathological analysis of acute lesions in NMO has shown extensive complement activation in a perivascular pattern. 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. 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). 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). 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 gonorrhoea infection 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/). 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. 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, whereas another, albeit with a small number of azathioprine-treated cases, found that rituximab and azathioprine were more efficacious than MMF. 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. Based on the randomized trials that allowed for oral immunosuppression in the “placebo” arms, 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. 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 or tocilizumab. Serious adverse events are hepatotoxicity and malignancies: lymphoma was observed in 3% of patients in a large NMOSD series.

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, 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. A retrospective, multicenter Korean study 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. 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.

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. The improvement in ARR ranged from 64% to 100%, and relapse freedom was attained in 22% to 75% of patients. 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. 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. One patient died of a serious infection. Tacrolimus prescribing information includes a boxed warning related to an increased risk of serious infections and malignancies.

**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 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. 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). The risk of acute leukemia seems to be higher with a cumulative dose greater than 60 mg/m², but acute leukemia was also reported in a patient with NMOSD who received a lower dose.

**Cyclophosphamide**

Cyclophosphamide is an alkylating agent widely used in oncology. In a nonblinded prospective cohort study 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.

**AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANT AS A DISEASE-MODIFYING THERAPY**

Autologous hematopoietic stem cell transplant (AH SCT) is under investigation for NMOSD as well as many other autoimmune conditions. Results of the 2 larger studies of AH SCT for NMOSD were discrepant. In the European retrospective AH SCT registry that included 16 patients with NMOSD refractory to immunosuppressants, only 10% remained relapse-free at 5 years. Yet, in the US-based clinical trial of 12 patients with NMOSD treated with AH SCT, 83% were relapse-free at 5 years. 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 AH SCT include neutropenic fever and other serious infections that are estimated to occur at a rate of 0.2 per year per patient; electrolyte abnormalities; blood pressure fluctuations; and emergence of new autoimmune diseases, including myasthenia gravis and hyperthyroidism. Mortality from AH SCT improved considerably over the last several decades: the overall mortality after AH SCT was only 0.2% in 2012 to 2016. Given the uncertainty of benefit and concerns of long-term safety, AH SCT should currently be restricted to carefully selected patients with NMOSD, preferably in the context of a research protocol.
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, and easier distinction from MS. 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. Anti-AQP4 antibody mediates its injurious effect in part through complement-dependent cytotoxicity. Thus, the most effective therapeutic approaches in NMOSD involve depleting B cells, decreasing IL-6, which prolongs survival of AQP4 antibody–secreting cells, 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%. 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%, 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. 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. 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

Dr A.I. Wallach has received consulting fees from Biogen. She serves as a site investigator for trials by Biogen, Hoffman La-Roche, TG Therapeutics, and MedDay Pharmaceuticals. Dr M. Tremblay has received consulting fees from Biogen and Genentech. Dr I. Kister served on advisory boards for Biogen and Genentech and received consulting fees from Roche and research support for investigator-initiated grants from Sanofi Genzyme, Biogen, EMD Serono, National MS Society, and Guthy-Jackson Charitable Foundation.
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