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Author Manuscript

Nat Rev Neurol. Author manuscript; available in PMC 2014 November 12.

Published in final edited form as:

Nat Rev Neurol. 2014 September ; 10(9): 493–506. doi:10.1038/nrneurol.2014.141.

Treatment of neuromyelitis optica: state-of-the-art and emerging therapies

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Abstract

Neuromyelitis optica (NMO) is an autoimmune disease of the CNS that is characterized by inflammatory demyelinating lesions in the spinal cord and optic nerve, potentially leading to paralysis and blindness. NMO can usually be distinguished from multiple sclerosis (MS) on the basis of seropositivity for IgG antibodies against the astrocytic water channel aquaporin-4 (AQP4). Differentiation from MS is crucial, because some MS treatments can exacerbate NMO. NMO pathogenesis involves AQP4-IgG antibody binding to astrocytic AQP4, which causes complement-dependent cytotoxicity and secondary inflammation with granulocyte and macrophage infiltration, blood–brain barrier disruption and oligodendrocyte injury. Current NMO treatments include general immunosuppressive agents, B-cell depletion, and plasma exchange. Therapeutic strategies targeting complement proteins, the IL-6 receptor, neutrophils, eosinophils and CD19—all initially developed for other indications—are under clinical evaluation for repurposing for NMO. Therapies in the preclinical phase include AQP4-blocking antibodies and AQP4-IgG enzymatic inactivation. Additional, albeit currently theoretical, treatment options include reduction of AQP4 expression, disruption of AQP4 orthogonal arrays, enhancement of complement inhibitor expression, restoration of the blood–brain barrier, and induction of immune tolerance. Despite the many therapeutic options in NMO, no controlled clinical trials in patients with this condition have been conducted to date.

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M.C.P. has received consulting income from ONO Pharmaceutical. J.L.B. has received consulting income from MedImmune and Chugai Pharmaceuticals. He has a patent application on aquaporin technology and is a member of the board of directors of Apsara Therapeutics. A.S.V. has patent applications on aquaporin and EndoS technology and is a member of the board of directors of Apsara Therapeutics.

Author contributions

All three authors researched the data for the article, provided substantial contributions to discussions of the content, and wrote the article.

Introduction

Neuromyelitis optica (NMO) is a rare inflammatory demyelinating disease of the CNS, with a predilection for the optic nerves and spinal cord. NMO was thought to be a variant of multiple sclerosis (MS), but in 2004, a serum antibody specific to patients with NMO was detected.¹ This antibody, initially termed NMO-IgG, was subsequently shown to recognize extracellular conformational epitopes of the astrocytic water channel protein aquaporin-4 (AQP4).² NMO-IgG—later named AQP4-IgG (or AQP4-Ab)—has a key role in the pathogenesis of NMO.³

The currently used diagnostic criteria for NMO—the revised Wingerchuk 2006 criteria⁴—incorporate the presence of AQP4-IgG. These criteria comprise two absolute criteria (optic neuritis and acute transverse myelitis) and three supportive criteria (brain MRI not meeting criteria for MS at disease onset, spinal cord MRI with contiguous T2-weighted signal abnormality extending over three or more vertebral segments, and AQP4-IgG-seropositive status). The diagnosis of NMO requires the presence of two absolute criteria and at least two of the three supportive criteria. Patients with NMO who have AQP4-IgG antibodies are referred to as seropositive (AQP-IgG⁺) and those without are seronegative (AQP4-IgG⁻). Seropositive patients who do not fulfil enough conditions to satisfy the diagnostic criteria of NMO are said to have NMO spectrum disorder (NMOSD). With improved understanding of NMO pathogenesis, the Wingerchuk criteria are being revised; the new criteria will be published in 2014.

The epidemiology of NMO is not clearly established, because NMO is often misdiagnosed as MS. Reported prevalence ranges from 0.1–4.4 cases per 100,000.^{5–7} The mean age at presentation is 34–43 years, although children and older adults are also affected.^{8–12} Patients with AQP4-IgG⁺ NMO have a marked female predominance with reported female:male ratios of about 10:1 in Japanese⁹ and white¹⁰ populations.

Various autoimmune diseases have been reported in up to 30% of patients with NMO,¹³ suggesting that individuals with this condition might have a genetic predisposition to aberrant autoimmunity. *AQP4* mutations do not account for susceptibility to NMO.¹⁴ Although some studies have reported associations between HLA alleles and NMO,^{15–17} others have found no association,¹⁸ suggesting a complex, multifactorial genetic susceptibility, with only 3% of patients with NMO having relatives with this condition.¹⁹

Individuals of African and East Asian origin have a higher risk of NMO than MS, whereas in white populations, MS is about 40 times more common than NMO.^{5,20–22} Distinguishing NMO from MS is clinically important because the treatments differ and, importantly, some MS treatments, such as IFN- β , natalizumab and oral fingolimod, can exacerbate NMO.

In this Review, we outline the pathogenetic mechanisms of NMO and discuss currently available pharmacological therapies, as well as therapies that have potential for repurposing in NMO. Furthermore, we review the therapies that are currently being developed.

Pathology

The working hypothesis for NMO pathogenesis involves entry of AQP4-IgG into the CNS and binding to AQP4 on perivascular astrocyte endfeet, which causes activation of the classical complement cascade with an inflammatory response that leads to marked granulocyte and macrophage infiltration, causing secondary oligodendrocyte damage, demyelination and neuronal death (Figure 1). The evidence in support of this mechanism, as discussed in recent reviews on the subject,^{12,23–25} comes from pathology of human NMO lesions, and a substantial body of *in vitro* and animal model data.

The events initiating AQP4-IgG production and its access to the CNS remain unclear; speculations have included AQP4 molecular mimicry,²⁶ precipitating infection,²⁷ and circulating blood–brain barrier permeabilizing factors.²⁸ Two independent studies^{29,30} have proposed an extrathecal origin of AQP4-IgG in NMO. Recent data suggest that AQP4-IgG-producing plasmablasts from the periphery might enter the CNS, creating foci of inflammation.³¹ The relative contribution of extrathecal versus intrathecal AQP4-IgG production during an NMO attack is, therefore, unclear. The central involvement of AQP4-IgG binding to AQP4 on astrocytes and complement-dependent cytotoxicity (CDC) in NMO lesion formation is strongly supported by experimental data,^{3,32–34} as is the involvement of infiltrating granulocytes and macrophages.^{35–37} Recent data also indicate the importance of antibody-dependent cellular cytotoxicity (ADCC) in NMO pathogenesis.³⁸

The precise mechanisms by which the inflammatory cascade in NMO produces oligodendrocyte injury and demyelination, possibly quite early in the disease process, remain unclear.³⁹ The role of T cells—which, in addition to their involvement in initial AQP4-IgG generation, might be involved along with other factors in permeabilization of the blood–brain barrier—is also not well understood,⁴⁰ but current data suggest that these cells are probably not involved in the progressive stage of NMO lesion pathology.^{41,42} Various propositions for alternative NMO pathogenesis mechanisms, such as excitotoxic injury,⁴³ AQP4-IgG-mediated inhibition of AQP4 water permeability and AQP4-induced AQP4 aggregation,⁴⁴ are controversial in light of the more-recent data.^{45,46} Interestingly, transgenically induced destruction or dysfunction of astrocytes exacerbates inflammation and demyelination in mice.^{47,48} The contributions of AQP4-IgG-mediated loss of astrocyte function to NMO pathogenesis are understudied and could present novel treatment opportunities.

Current therapies

Two consensus papers on the treatment of NMO have been published by panels of experts in the field.^{49,50} The overall rationale of NMO therapy is to minimize neurological disability by ameliorating acute attacks and preventing future exacerbations (Table 1). Acute therapies are designed to minimize injury and accelerate recovery, whereas preventative therapies are focused on reducing attack frequency and severity. Since disease progression in the absence of clinical relapse is rare in NMO,⁵¹ beneficial treatments will limit the accumulation of permanent neurological injury in affected individuals.

Treatment of acute attacks

Intravenous methylprednisolone (IVMP) and plasma exchange comprise the standard treatments for acute disease exacerbations in NMO. These therapies have been co-opted from the treatment of acute demyelinating attacks in MS, transverse myelitis and optic neuritis. Corticosteroids have a myriad of anti-inflammatory and immunosuppressive effects, including reduction in circulating lymphocytes and monocytes; decreased expression of cell adhesion molecules and metalloproteinases; and altered transcription of proinflammatory cytokines.⁵² Interestingly, T-helper cell 17 (T_H17) cytokines such as IL-17A, IL-6 and IL-23p19,^{53,54} the levels of which are elevated during NMO exacerbations, are downregulated by corticosteroids.⁵⁵ In addition to a direct role in removing pathogenic AQP4-IgG, plasma exchange could similarly reduce levels of proinflammatory cytokines, alter the numbers of T cells and B cells, and modify T_H-cell phenotypes.⁵⁶

No prospective therapeutic trials for acute NMO exacerbations exist to date, meaning that optimal dosages, duration and sequence for acute therapy have not been established. In general, IVMP (1 g) is delivered daily for 3–5 days and, if the symptoms do not clearly improve, plasma exchange is administered daily or every other day for up to five treatments. If plasma exchange has been successfully used in the past in an individual patient, it can also be considered as a first-line treatment for acute relapse. Although retrospective studies and case series have reported marked improvement in visual and neurological function in patients with NMO following plasma exchange,^{57,58} improvement was independent of AQP4-IgG seropositivity.⁵⁸

Male sex, preserved reflexes and early initiation of therapy have been found to increase the likelihood of improvement in response to plasma exchange.⁵⁹ A recent retrospective study showed that rapid sequencing or concurrent use of plasma exchange with IVMP resulted in better visual acuity, improved visual fields, and greater retinal nerve fibre layer preservation as measured by optical coherence tomography.⁶⁰ Hence, any delay in neurological improvement following IVMP therapy should prompt consideration of rapid initiation of plasma exchange. Additional case series have reported benefits of IVIg therapy⁶¹ and cyclophosphamide infusion⁶² in patients with NMO.

Prevention of attacks

Due to the high morbidity associated with NMO exacerbations, immunosuppressive therapy is typically instituted after the first attack. Unfortunately, interventional studies with level I or II evidence are not yet available; therefore, treatment decisions are typically made after balancing the best available data on clinical efficacy, short-term and long-term adverse effects, comorbid conditions, disease-associated risk factors, functional status, and prior treatment. Possible predictors of disability in NMO patients include male sex, Afro-Caribbean or Asian ethnicity, young age at onset,⁶³ motor symptoms or tetraparesis at first myelitis attack, and more than one myelitis attack in the first year.¹⁰

Active NMO lesions demonstrate antibody-mediated and cell-mediated immunopathology. As a result, current preventative therapies are used to deplete immune cell populations,

diminish circulating AQP4-IgG, or interfere with immune cell proliferation or activation. Interestingly, the most commonly used agents, azathioprine, mycophenolate and rituximab, primarily target lymphocytes and seem to diminish disease activity without consistent effects on AQP4-IgG titre. The clinical response suggests that lymphocytes might promote disease activity through diverse and complex roles, including antigen presentation, proinflammatory cytokine production, and altered regulatory immune networks.

Corticosteroids and plasma exchange—In addition to their use in the treatment of acute exacerbations, oral corticosteroids and plasma exchange can be used on a chronic basis for prophylactic therapy. Low-dose oral prednisolone (2.5–20.0 mg daily) was evaluated retrospectively in a cohort of 25 patients over a median observation period of 19.3 months.⁶⁴ Treatment success showed a dose-dependent relationship; doses greater than 10 mg daily were significantly more efficient than lower doses. Low dose corticosteroid decreased the median annualized relapse rate (ARR) from 1.48 to 0.49.⁶⁴ Regular plasma exchange treatment in association with additional immunosuppression has also shown benefit in reducing relapse activity.⁶⁵

Azathioprine—Azathioprine is converted to nucleotide antimetabolites that interfere with lymphocyte proliferation. A retrospective study of 99 patients with NMO or NMOSD demonstrated an ARR reduction from 2.20 to 0.52 relapses over a median treatment interval of 22 months.⁶⁶ Improvement was noted to be greater in patients receiving doses larger than 2 mg/kg daily, and in those showing an increased erythrocyte mean cell volume. The main reasons for discontinuation of therapy included lack of efficacy, systemic adverse effects and lymphoma. Two smaller studies of azathioprine have reported similar results.^{67,68} ARR was reduced by more than 50% by use of moderate to high dosages of azathioprine (2–3 mg/kg daily), with or without concurrent steroids. Due to a delay in therapeutic effect (3–6 months), therapy is often initiated in combination with corticosteroids.

Mycophenolate mofetil—Mycophenolate mofetil, a prodrug of the active metabolite mycophenolic acid, suppresses lymphocyte proliferation by inhibiting guanosine nucleotide biosynthesis. In a retrospective study of 24 patients, a reduction in the median ARR from 1.28 to 0.09 over a median follow-up of 28 months (median dose 2 g daily) was observed.⁶⁹ Disability remained relatively unchanged. 19 patients remained on medication, 25% of patients noted adverse events, and one patient died of disease complications.

Methotrexate—Methotrexate inhibits folate-dependent enzymes and interferes with purine and thymidylate synthesis. 14 AQP4-IgG-seropositive patients with NMO or NMOSD treated with methotrexate (median dose: 17.5 mg weekly; median duration: 21.5 months) showed a significant reduction in the median ARR from 1.39 before treatment to 0.18 during treatment.⁷⁰ Nearly half of the patients were relapse-free, and none discontinued therapy. However, 13 of the 14 patients were co-treated with prednisolone, tacrolimus or rituximab, the impact of which is unknown. In an earlier case series, seven NMO patients treated with methotrexate (50 mg weekly) and oral prednisolone (1 mg/kg daily) demonstrated disease stabilization, as measured by disease activity and the expanded disability status scale (EDSS).

Mitoxantrone—Mitoxantrone inhibits topoisomerase II, suppresses lymphocyte and macrophage development, and inhibits B-cell activation. 20 patients with NMO or NMOSD treated with mitoxantrone (three to six monthly cycles of 12 mg/m² followed by 6–12 mg/m² maintenance doses) for an average of 17 months showed a reduction in ARR (2.8 before treatment to 0.7 after treatment) and mean EDSS score (5.6 to 4.4).⁷¹ In another small case series, four of five patients with NMO showed clinical benefit and three of five patients became relapse-free.⁷¹ A significant decline in left ventricular ejection fraction was observed in one patient after a cumulative dose of 72 mg/m². Mitoxantrone-related leukaemia, a serious consequence of treatment, has not been reported in any NMO patient, probably owing to the low number of patients treated with mitoxantrone to date.

Cyclophosphamide—Cyclophosphamide is a cytotoxic alkylating agent that is used in the treatment of severe autoimmune disorders. This drug has been evaluated in NMO in two small clinical case series, with differing results. One small study of four patients with NMOSD reported a reduction in median EDSS score from 8.0 to 5.75;⁷² by contrast, no improvement in relapse rate or disability was observed in another study of seven patients with NMO.⁷³

Rituximab—Rituximab is a chimaeric anti-CD20 monoclonal antibody that depletes both naive and memory B cells. Multiple dosing regimens have been explored for NMO rituximab therapy. In most studies, rituximab was administered at regular 6-month intervals beginning with four weekly doses of 375 mg/m² followed by two biweekly doses of 1 g.^{74–78} Other studies used more-frequent infusions (usually 1 g every 12 months)⁷⁷ or administration depending on circulating B-cell numbers.^{74–76,79} In each study, patients treated with rituximab demonstrated a significant reduction in ARR, and stabilization of disability. In general, the reduction in ARR was substantial—in two studies, the post-treatment ARR was zero. EDSS scores stabilized or improved in most patients.^{75,77–79}

To date, no definitive biomarker of disease activity has emerged in rituximab-treated individuals. According to one study, AQP4-IgG titres and CD19⁺ B-cell counts rise before relapse and fall with remission,⁸⁰ whereas another study suggests that the suppression of disease activity by rituximab correlates with the extent of B-cell depletion, but not with serum AQP4-IgG titre or serum levels of B-cell-activating factor (BAFF) or a proliferation-inducing ligand.⁸¹ Additional studies are needed to determine whether the benefits of CD20⁺ B-cell depletion are mediated by a reduction in AQP4-IgG production or through effects on other proinflammatory B cell functions.⁸² Most of the serious adverse events were attributable to disease relapse; however, severe infections and cardiovascular failure were also reported. Progressive multifocal leukoencephalopathy has been reported in rituximab-treated patients (though not yet in NMO), and can present a potential limitation, especially in combination therapies.⁸³

Combination therapies—Combination therapy with cytotoxic, immunomodulatory, and B-cell-depleting therapies is a fundamental approach to the treatment of many autoimmune disorders such as rheumatoid arthritis. In NMO, the rarity of disease, the risk of infectious complications, and the cost of therapeutics have limited the employment of combination therapy. To date, the use of combination therapy in NMO has been limited to oral

corticosteroids (prednisolone or prednisone) plus immunosuppressive agents such as azathioprine⁶⁶ and cyclosporine;⁸⁴ combination of corticosteroids with both azathioprine and cyclosporine have demonstrated a reduction in ARR and EDSS. Prospective studies comparing combination therapy, sequential therapy and induction therapy will be needed to balance benefits and risks.

Selection of therapies

Although no prospective clinical trials have been conducted in NMO, retrospective and prospective case series have been used to develop a framework to guide treatment decisions. Owing to the more-extensive availability of clinical data, azathioprine, mycophenolate mofetil and rituximab tend to be the most-recommended first-line therapies for NMO prophylaxis. Second-line therapies include methotrexate, mitoxantrone and cyclosporine. Due to the potential toxicity of mitoxantrone and the limited clinical data on methotrexate and cyclosporine, physicians should consider restricting their use to refractory cases. Certain emerging therapies could also be considered for off-label use in patients with refractory NMO; however, long-term safety issues remain of particular concern.

Special circumstances

Pregnancy—NMO exacerbations are not substantially increased during pregnancy; however, the frequency of exacerbations increases in the postpartum period and during the year following childbirth.^{85,86} In relation to pregnancy, the FDA classifies drugs as category A (no adverse effect on fetus in human trials), B (no adverse effect on fetus in animal studies), C (adverse effects on fetus in animal studies without good data from human studies), D (adverse effects on fetus in human studies) and X (adverse effects on fetus in human and animal studies). Azathioprine, mycophenolate and methotrexate are pregnancy category D or X and should not be continued during pregnancy. Although rituximab and prednisone are pregnancy class C, the absence of an increase in ARR during pregnancy makes continued therapy during pregnancy questionable unless the patient displays evidence of renewed disease activity. Given the increased relapse rate following delivery, rapid introduction of prophylactic therapy could be warranted; however, the benefits of these therapies should be balanced against the benefits of breastfeeding. Ringelstein *et al.*⁸⁷ reported an uneventful pregnancy in an AQP4-IgG-seropositive NMO patient who received low-dose rituximab (100 mg) 7 months before pregnancy without complications to the mother or newborn. Interestingly, despite a low rituximab dosage, the newborn's umbilical cord blood showed decreased CD19⁺ B cells and evidence of adoptive transfer of AQP4-IgG.

Fetal and paediatric NMO—Unlike the CNS of fetal rodents, which express little or no AQP4,⁸⁸ the human fetal CNS strongly expresses AQP4,^{89,90} thus raising the possibility that AQP4-IgG might attack the human fetal CNS. To date, no published evidence is available to support this hypothesis. Both mouse and human placenta also express AQP4,^{90–92} and intraperitoneal administration of AQP4-IgG in pregnant mice caused dose-dependent placental inflammation and spontaneous abortion.⁹⁰ In addition, one case of AQP4-IgG attacking the placenta causing spontaneous abortion in humans has been reported.⁹³ Several case studies have reported normal pregnancies in women receiving treatment for

NMO.^{87,94,95} Overall, it is unclear whether the effects of maternal NMO on the fetoplacental unit in humans are sufficient to justify treatment in the presence of AQP4-IgG, but without active maternal disease.

Although children as young as 2 years⁹⁶ can develop NMO, the median age of children presenting with the disease is 10–14 years.⁹⁷ Children with NMO have been suggested to be more likely to be seronegative and to have brain involvement than adult patients.^{98–100} Therapies for children are similar to those used in adults, with IVMP and plasma exchange for an acute attack, and long-term immunosuppression to prevent relapses.

MS treatments that worsen NMO—Several MS therapies have poor efficacy or adverse effects in NMO. IFN- β increases relapse rate¹⁰¹ and promotes severe exacerbations,^{102–104} possibly by increasing production of BAFF and IL-17.¹⁰⁵

Natalizumab, an antibody against very late antigen-4, has been reported to have no effect or to worsen disease activity in AQP4-IgG-seropositive^{106,107} and AQP4-IgG-seronegative¹⁰⁸ patients with NMO. A small study of five patients with NMO treated with natalizumab reported nine relapses and an increase in mean EDSS from 4.0 to 7.0.¹⁰⁹ Lesions observed during natalizumab treatment show florid active demyelination, severe neutrophilic and eosinophilic infiltrates, and severe astrocyte loss.¹⁰⁷ Natalizumab can accelerate disease activity by increasing the numbers of peripheral proinflammatory T cells or eosinophils.¹¹⁰ Peripheral eosinophils might be able to migrate to the CNS and exacerbate lesion formation^{111,112} or facilitate stabilization of AQP4-specific bone marrow plasma cells.¹¹³

Oral fingolimod has also been reported to cause an increase in NMO disease activity. In two studies,^{114,115} fulminant disease activity was observed quickly after the initiation of therapy. Like natalizumab, fingolimod promotes bone marrow egress of eosinophils¹¹⁶ and might thereby enhance lesion activity and AQP4-IgG production.

Drugs with potential for repurposing

Improved understanding of the mechanisms of NMO pathogenesis has led to discovery of novel therapeutic targets (Figure 2). In this section, we discuss the potential for repurposing of approved therapeutics in NMO, including some approaches that are currently undergoing clinical trials (Table 2).

Complement-targeted therapy

As discussed above, complement activation seems to be involved in NMO pathogenesis. In cultured cells, AQP4-IgG binds AQP4 and activates complement via the classical pathway, resulting in cell lysis.³ In mouse spinal cord tissue slices³⁵ and *in vivo* mouse models,³³ complement activation is required for AQP4-IgG to cause the characteristic histological changes comprising loss of AQP4 and glial fibrillary acidic protein, inflammatory cell infiltration, and demyelination.

The C5 complement inhibitor eculizumab, which is approved for use in paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome, has recently been tested in NMO in an open-label trial.¹¹⁷ Eculizumab is a humanized IgG2/4 antibody that

binds C5 and inhibits its cleavage into C5a and C5b. AQP4-IgG-seropositive patients with NMOSD who had experienced at least two attacks in the preceding 6 months or three in the previous 12 months received 600 mg intravenous eculizumab weekly for 4 weeks, 900 mg in the fifth week, and then 900 mg every 2 weeks for 48 weeks. In the 14 patients studied, eculizumab significantly reduced attack frequency, and stabilized or improved neurological disability measures. The main drawbacks of eculizumab are its high cost (around US \$400,000 per patient-year), and risk of meningococcal sepsis, which was seen in one patient in the trial. Given these disadvantages, testing the safety and efficacy of eculizumab for acute NMO relapses could be worthwhile.

IL-6 receptor-targeted therapy

Interleukin-6 (IL-6) has been implicated as a driver of NMO disease activity.¹¹⁸ Cerebrospinal fluid (CSF) IL-6 and soluble IL-6 receptor levels are elevated in NMO during an attack,^{119,120} and the plasma cell population in the blood and CSF expands during NMO relapse.³¹ *In vitro*, IL-6 enhances the survival of these cells and increases AQP4-IgG secretion, whereas blockade of the IL-6 receptor reduces their survival.¹¹⁸ Several case reports^{121–124} show reduced relapse rate in NMO patients treated with tocilizumab, a humanized murine anti-IL-6 receptor monoclonal antibody. Another anti-IL-6 receptor monoclonal antibody, SA237, which has a fourfold greater duration of action than tocilizumab, has recently entered a clinical trial in NMO.

Granulocyte-targeted therapies

One of the major histological differences between MS and NMO lesions is the presence of perivascular neutrophils, as reported in patients with NMO¹¹¹ as well as in mouse^{33,37} and rat¹²⁵ models of the condition. Neutrophil counts are elevated in the CSF of about 60% of untreated patients during relapse, but only in about 20% of patients during remission.¹²⁶ In mouse models of NMO³⁷ and in mouse spinal cord slices,³⁵ elimination of neutrophils ameliorates tissue damage, whereas increased neutrophil counts enhance tissue damage. Inadvertent administration of granulocyte colony-stimulating factor in a patient with NMO was found to be detrimental.¹²⁷

Sivelestat, a small-molecule inhibitor of neutrophil elastase, which is involved in neutrophil migration¹²⁸ and neutrophil-mediated tissue damage,^{128,129} reduced NMO pathology in a mouse model of NMO.³⁰ Sivelestat was originally developed to treat acute respiratory distress syndrome and is approved for that purpose in Japan.¹³⁰ Sivelestat is well tolerated, but has a short half-life of 6 h, thus requiring continuous infusion to maintain therapeutic levels.¹³¹ Studies in animal models of NMO suggest that neutrophil entry into the CNS occurs early (within 24 h of lesion initiation),³⁷ whereas macrophages might predominate at later stages. The pathological observations and animal data suggest the utility of sivelestat in an acute NMO attack, which is being tested in a small clinical trial in Japan.

In addition to neutrophils, eosinophils are found in inflammatory demyelinating lesions in NMO, but are absent in MS.¹¹¹ Postulating that eosinophil inhibitors could be useful in NMO, researchers initiated a series of *in vitro* and *in vivo* studies to investigate the role of eosinophils in NMO pathogenesis and the efficacy of eosinophil inhibitors in reducing NMO

pathology.¹¹² Eosinophils cultured from mouse bone marrow produced robust AQP4-IgG-dependent ADCC in AQP4-expressing cells and spinal cord slice cultures and, in the presence of complement, eosinophils produced complement-dependent cellular cytotoxicity (CDCC). NMO-like pathology was also produced in spinal cord slice culture by eosinophil granule toxins, suggesting that eosinophil degranulation contributes to NMO pathogenesis.

The second-generation antihistamines cetirizine and ketotifen, which have eosinophil-stabilizing actions,¹³² were found to greatly reduce cytotoxicity mediated by AQP4-IgG and eosinophils.¹¹² In mice, demyelinating NMO lesions with marked eosinophil infiltration were produced by continuous intracerebral injection of AQP4-IgG and complement. Lesion severity was increased in transgenic hypereosinophilic mice, and was reduced in mice made hypo-eosinophilic by an anti-IL-5 antibody or by gene deletion, and in normal mice receiving cetirizine orally. Cetirizine is currently being tested in patients with NMO in a small clinical study. Alternative agents that reduce eosinophil numbers or activity could also be useful in NMO.

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) is another approved therapy with potential for repurposing in NMO. IVIg, which consists of pooled human IgG from more than 1,000 blood donors and is administered to the circulation of the patient, has been used for over 30 years to treat idiopathic thrombocytopenic purpura,¹³³ and has been used to treat various immune-mediated demyelinating diseases of the nervous system including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, diabetic polyneuropathy, multifocal motor neuropathy, and myasthenia gravis.¹³⁴ IVIg has pleiotropic actions on the immune system, including autoantibody neutralization, blockade of antibody–target binding, acceleration of autoantibody clearance, inhibition of dendritic cell activation and leukocyte migration, complement inhibition, and blocking of Fc γ receptors.¹³⁵

The data supporting the clinical benefit of IVIg in NMO are limited. In one study, IVIg showed efficacy in the prevention of relapses in eight NMO patients, with a reduction in mean ARR from 1.8 in the year before IVIg treatment to 0.006 during a mean follow-up of 19.3 months.¹³⁶ Other case studies also support a beneficial effect of IVIg in preventing relapse in NMO,^{137,138} and potentially in acute NMO relapses.⁶¹ In a proof-of-concept study, AQP4-IgG was administered to rats by intracerebral injection, and the size of the resulting neuroinflammatory demyelinating lesions was reduced by about 50% when IVIg was subsequently administered by intraperitoneal injection to yield serum levels of 10–25 mg/ml IgG, which is comparable to human therapeutic levels.¹³⁹ *In vitro* studies suggested that inhibition of AQP4-IgG-mediated CDC and ADCC were the primary mechanisms mediating the beneficial effects found *in vivo*. Further evaluation of IVIg in NMO thus seems warranted.

CD19-targeted therapy

Bone marrow-derived and tissue-resident AQP4-IgG-expressing plasma cells are considered to be the source of circulating AQP4-IgG in seropositive patients, and numbers of peripheral blood plasmablasts capable of producing AQP4-IgG are increased in the CSF and peripheral

blood of relapsing patients with NMO.^{34,118} CD19 is a B-cell surface marker that is expressed on the surface of plasmablasts and some plasma cells¹⁴⁰ and might provide an alternative target for B-cell-depletive therapy in NMO. Owing to the expression of CD19 on some antibody-producing cell populations, antibodies targeted against this antigen might diminish serum titres of AQP4-IgG and reduce levels of circulating plasmablasts that can contribute to intrathecal inflammation.⁸⁰ Several CD19-targeted therapies are currently under active investigation,¹⁴¹ and could potentially be rapidly repurposed for clinical trials in NMO.

TNF-targeted therapy

Many of the therapies currently used for preventing NMO relapses, such as azathioprine, mycophenolate mofetil, methotrexate, and rituximab, are used for the treatment of rheumatoid arthritis. The success of these agents in both NMO and rheumatoid arthritis suggests that some critical immunopathology is shared between these autoimmune disorders.

Anti-tumour necrosis factor (TNF) therapies are central to the modern-day treatment of rheumatoid arthritis and could potentially be repurposed for the treatment of NMO. Addition of TNF to an *ex vivo* NMO spinal cord slice model has been demonstrated to exacerbate AQP4-IgG-mediated tissue injury.³⁵ TNF might also impede lesion repair through oligodendrocyte precursor cell toxicity.¹⁴² Anti-TNF therapies could, therefore, offer a novel avenue for treatment of acute NMO attacks. Since serum levels of TNF are not elevated in patients with NMO,¹⁴³ however, anti-TNF therapies might have limited use in the prevention of exacerbations.

Novel therapies in the pipeline

Blockade of AQP4-IgG–AQP4 binding

Several therapeutic approaches have been developed to block the binding of AQP4-IgG to AQP4, thereby reducing CDC, ADCC and downstream pathogenicity (Table 3). In one approach, a nonpathogenic human monoclonal antibody, aquaporumab, was generated from a recombinant monoclonal AQP4-IgG that binds tightly to AQP4. Mutations were introduced into the Fc region of the antibody to eliminate its CDC and ADCC effector functions (Figure 3).¹⁴⁴ Aquaporumab competitively displaces AQP4-IgG in the serum of patients with NMO, in part by steric hindrance, because the IgG1 antibody is large compared with the AQP4 tetramer (Figure 3). Aquaporumab greatly reduced AQP4-IgG-dependent cytotoxicity and NMO pathology in animal and *in vitro* models of NMO.¹⁴⁴ As targeting of AQP4 by aquaporumab is highly selective, immunosuppression should not occur and minimal toxicity is anticipated, although as with any biological drug, studies are needed to exclude off-target effects and immunogenicity. Aquaporumab is currently in preclinical development.¹⁴⁴

In an alternative approach, a target-based small-molecule screen identified several potential drugs and natural products that reduced AQP4-IgG binding to AQP4 by binding to the extracellular surface of AQP4; these agents included the antiviral agent arbidol and the nutraceutical berberine.¹⁴⁵ Screens also identified idioselective compounds that bind to the variable region of monoclonal AQP4-IgG.¹⁴⁶ The compounds identified so far have

relatively weak affinity for AQP4 and unfavourable pharmacological properties for use in NMO, so more-extensive screening might be required to identify further small-molecule drug candidates. The level of plasma membrane AQP4 expression and its supramolecular assembly in orthogonal arrays of particles (OAPs) are important determinants of AQP4-IgG pathogenicity,^{147–150} so targeting of astrocyte AQP4 expression at the transcriptional or post-translational levels would be predicted to be beneficial in NMO, as would targeting of OAP formation by AQP4. Whether selective drug-like regulators of AQP4 expression or assembly can be identified, however, is currently unclear.

Antibody inactivation

Antibody inactivation is considered to be a potential therapeutic approach for autoimmune diseases caused by pathogenic antibodies. Several bacterial enzymes selectively target IgG-class antibodies. Some of these enzymes interfere with the binding site for complement component C1q on the antibody, thereby neutralizing the Fc effector functions that are involved in CDC, whereas others target the Fc γ receptor binding motif that is involved in ADCC. One such enzyme, endoglycosidase S (EndoS), is a 108 kDa protein, derived from *Streptococcus pyogenes*, that selectively digests asparagine-linked glycans on IgG heavy chains (Figure 3).¹⁵¹ The enzymatically deglycosylated antibody has virtually no cytotoxicity effector functions. In a proof-of-concept study, treatment of serum from NMO patients with EndoS prevented CDC and ADCC *in vitro*, and counteracted the development of NMO pathology *in vivo* in animal models.¹⁵² The deglycosylated antibody also competitively displaced pathogenic NMO-IgG bound to AQP4, thus converting pathogenic AQP4-IgG into a therapeutic blocking antibody.

Another *S. pyogenes*-derived enzyme, IgG-degrading enzyme (IdeS), selectively cleaves IgG antibodies to yield Fc and F(ab')₂ fragments.¹⁴⁸ As found with EndoS, IdeS treatment of NMO patient serum abolished CDC and ADCC *in vitro* and NMO pathology *in vivo*.¹⁵³ Notwithstanding the challenges related to IgG inactivation kinetics, manufacturing, and effects of general IgG neutralization, EndoS or IdeS treatment of blood by therapeutic apheresis using surface-immobilized enzyme might be useful in NMO. The blocking activity of nonpathogenic AQP4-IgG fragments in EndoS-treated or IdeS-treated blood could confer additional therapeutic benefit over that obtained with plasma exchange.

Other complement-targeted therapies

Motivated by the central role of complement activation in NMO pathogenesis and the initial success of C5 inhibition by eculizumab, as discussed above, other complement-targeted therapeutics are under consideration in NMO (Figure 4). The infectious adverse effects of eculizumab are thought to result from inhibition of the lectin pathway and alternative complement activation pathway, which are necessary for killing bacteria.¹⁵⁴ C1-targeted monoclonal antibodies have been shown to be efficient in both *in vitro* and *in vivo* models of NMO.¹⁵⁵ In contrast to C5 inhibition, C1 inhibition has multiple therapeutic effects: it prevents the generation of C3a and C3b, which participate in CDCC by causing effector cell chemotaxis, binding and degranulation; prevents amplification of the classical complement pathway by the alternative complement pathway; and does not interfere with defence against bacteria because the lectin and alternative activation pathways remain intact. Selective

inhibition of the classical complement pathway in NMO is, thus, predicted to be superior to generalized complement inhibition. Alternative agents that might be useful in NMO include a peptide inhibitor of C1 esterase activity (C1inh), a cyclic oligopeptide targeting C3 (compstatin), inhibitors of C3a and C5a receptors, and monoclonal antibodies and small molecules against other complement components, which are currently under development (Figure 4).^{156,157}

Complement inhibitor CD59

Another potentially attractive target in NMO is CD59, the major complement inhibitor protein in astrocytes. CD59 is a glycoposphoinositol-anchored membrane protein that inhibits formation of the terminal C5b–9 membrane attack complex.¹⁵⁸ Other complement inhibitor proteins that might be present in astrocytes, albeit to a lesser extent, include CD55 (also called decay acceleration factor), CD46 (membrane cofactor protein) and CD35 (type 1 complement receptor).¹⁵⁹ Various human diseases, including atypical haemolytic uraemic syndrome, membranoproliferative glomerulonephritis, C3 glomerulonephritis and dense deposit disease, involve mutation or dysregulation of complement regulatory proteins.¹⁶⁰ Pharmacological upregulation of CD59 or other complement inhibitors on astrocytes is predicted to be beneficial in NMO by reducing AQP4-IgG-dependent CDC. In two proof-of-concept studies in mouse models of NMO created by passive transfer of AQP4-IgG,^{161,162} CD59 deletion or neutralization greatly increased NMO pathology in the spinal cord, optic nerve and brain. Small-molecule screening might yield upregulators of astrocyte CD59 expression that are of potential therapeutic value in NMO.

Antibody-dependent cellular cytotoxicity

Although CDC has a central role in NMO pathogenesis, an expanding body of evidence also indicates an important role for ADCC, which involves binding of AQP4-bound AQP4-IgG to Fc γ receptors on effector cells, causing their accumulation, phagocytosis and degranulation. In addition to *in vitro* studies showing AQP4-IgG-dependent ADCC by granulocytes and natural killer cells,¹⁶³ *in vivo* evidence from rodent models demonstrates ADCC-initiated NMO pathology,^{36,125} as well as involvement of AQP4-IgG ADCC effector function in the initiation of NMO pathology.³⁸ Administration of a neutralizing Fc γ III-receptor antibody reduced NMO pathology in a mouse model.³⁸ Notwithstanding the complexity of Fc γ receptor expression on human effector cells,¹⁶⁴ targeting of Fc γ receptors using antibodies or small molecules might have therapeutic benefit in NMO.

Targeting the blood–brain barrier

Targeting of the blood–brain barrier could be beneficial in NMO. Two *in vitro* studies^{28,163} have reported that serum from AQP4-IgG-seropositive patients increases permeability of human astrocyte–endothelial cell cocultures and reduces expression of tight junction proteins in cultured brain microvascular endothelial cells, thereby recapitulating the mechanisms involved in blood–brain barrier opening. Dysfunction of the blood–brain barrier—detected as raised albumin levels in CSF or blood—was more common in patients with NMO during relapse than during remission (55% versus 33% of patients), and CSF and blood albumin levels were significantly increased during a relapse.¹²⁶ Although the

mechanisms are unclear, the secretion of vascular endothelial growth factor (VEGF) by astrocytes or endothelial cells has been suggested to be involved.²⁸ The matrix metalloproteinase MMP-9, levels of which are elevated in the serum of patients with NMO,¹⁶⁵ might be released from neutrophils in the NMO lesion and degrade the blood–brain barrier basement membrane. The humanized murine monoclonal antibody bevacizumab, a VEGF inhibitor, is currently in a clinical trial to determine whether it reduces blood–brain barrier opening in NMO.

Tolerance and transplantation

Antigen-specific tolerance against AQP4 provides a novel approach for suppression of the immune response in NMO. AQP4 tolerance could effectively halt the pathological immune response that drives CNS tissue injury while leaving the remainder of the immune surveillance system intact. Methods for inducing antigen-specific tolerance include DNA vaccination, altered peptide ligands, and low-dose oral or nasal antigen administration.¹⁶⁶ In MS, initial attempts at antigen-induced tolerance either failed to produce clinical efficacy^{167,168} or worsened disease activity.¹⁶⁹ The failure of antigen-specific therapy in MS could be related in part to the lack of a definitive disease-specific antigen in affected individuals, and similar strategies targeting AQP4 in seropositive NMO might yield more-substantial clinical and immunological effects.

An alternative and aggressive strategy for restoring immune tolerance in NMO is autologous haematopoietic stem cell transplantation (HSCT). HSCT has shown benefit in the treatment of severe MS¹⁷⁰ and systemic lupus erythematosus,¹⁷¹ and aggressive cases of NMO might demonstrate a similar robust and prolonged response. Owing to the considerable mortality associated with HSCT, however, careful selection of cases is mandatory.

Challenges and future directions

Clinical trials

The burgeoning environment of NMO therapeutics mandates clinical studies that provide definitive evidence of efficacy. These future clinical trials, however, present substantial challenges. First, the potential severity of NMO disease activity can limit the ability of investigators to accumulate extensive longitudinal data. Second, there are no defined criteria for clinical end points in NMO trials. Third, the number of potential trial participants is limited, necessitating the incorporation of sensitive primary end points. Last, there are concerns in trials designs involving a placebo arm because untreated NMO produces irreversible neurological deficits. The landscape is further complicated by the lack of a definitive preventative therapy, requiring investigators to try to balance the increased enrolment requirements of active comparator trials with the potential safety concerns associated with immunosuppressant or placebo therapy. Eventually, NMO clinical trials will need to address the above issues within an experimental design that allows regulators to determine the definitive risks and benefits of the investigational agent. Currently, NMO clinical trials are focused on preventative therapy and use time to first relapse as the primary end point. Future prophylactic trials will need to incorporate additional metrics to assess NMO relapse severity and progressive disability to begin to differentiate the entire spectrum

of therapeutic efficacy. In addition, NMO clinical trials will need to focus on the evaluation of acute therapeutics and the development of new clinical metrics for evaluation of relapse recovery.

Seronegative NMO

Management of AQP4-IgG-seronegative patients poses a challenge, because it is currently unclear whether their disease is caused by an AQP4-IgG-like antibody that recognizes an antigen different from AQP4, or whether these patients have a different disease altogether that shares clinical features with seropositive NMO. No animal models of AQP4-IgG-seronegative NMO currently exist. Several studies^{172–177} have reported IgG antibody against myelin oligodendrocyte glycoprotein (MOG-IgG) in the serum of 10–15% of patients with AQP4-IgG-seronegative NMO. The MOG-IgG-positive patients often have better clinical outcomes than the AQP4-IgG-seropositive patients, including resolution of their radiological abnormalities. The role of MOG-IgG in NMO disease pathogenesis is unclear,¹⁷⁸ although a recent study¹⁷⁹ reported that NMO MOG-IgG injected in the mouse brain causes changes in the expression of axonal proteins that are required for the integrity of the nodes of Ranvier and normal action potential firing. Interestingly, MOG-IgG did not produce inflammation in this model, and the tissue changes were independent of complement activation. Unlike AQP4-IgG-induced damage in the mouse brain, which was complement-dependent and irreversible, the MOG-IgG-induced changes disappeared within 2 weeks. The differences in lesion pathology and recovery are reflected in the clinical outcomes of MOG-IgG⁺ NMO and AQP4-IgG⁺ NMO patients.^{173–177} Further studies are needed to understand the pathogenesis of seronegative NMO, and to determine whether MOG-IgG⁺ NMO is pathologically related to or is a phenocopy of AQP4-IgG⁺ NMO.

Conclusions

In summary, the NMO therapeutics pipeline is quite full, with approved drugs being evaluated for repurposing in NMO, and new agents targeting a wide range of pathways in disease pathogenesis. Development of effective, highly selective drug therapy without general immunosuppression or off-target toxicity is a central goal in NMO therapeutics. Despite the inherent challenges of future clinical trials in NMO, such as patient enrolment and clinical variability, significant advances in treatment of NMO are anticipated.

Acknowledgments

M.C.P., J.L.B. and A.S.V. have received funding from the Guthy-Jackson Charitable Foundation, and J.L.B. and A.S.V. have received funding from the NIH.

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Key points

- Most patients with neuromyelitis optica (NMO) have serum IgG antibodies against astrocytic aquaporin-4 (AQP4) channels, a minority have antibodies to myelin oligodendrocyte glycoprotein, and some have neither
- Current NMO treatments include corticosteroids and plasma exchange, which reduce the severity of acute attacks, and prednisolone, rituximab, cyclophosphamide, azathioprine, mycophenolate, mitoxantrone, methotrexate and cyclosporine, which prevent relapses
- Some multiple sclerosis treatments, such as IFN- β , fingolimod and natalizumab, can be harmful in NMO
- Approved therapies with potential for repurposing in NMO include eculizumab (complement inhibitor), tocilizumab (IL-6 receptor inhibitor), sivelestat and cetirizine (granulocyte inhibitors), intravenous immunoglobulin, CD19-depleting agents, and anti-TNF therapy
- Potential therapeutic approaches include inhibition of AQP4-IgG binding (aquaporinab, small molecules), AQP4-IgG inactivation (endoglycosidase S, IgG-degrading enzyme), alternative complement inhibitors (C1inh, compstatin, CD59), anti-Fc γ RIII antibody, VEGF inhibition (bevacizumab), and antigen-specific tolerization
- Challenges for NMO therapeutics include optimization of drug penetration into NMO lesions, clinical trial design (given the small patient numbers), and management of seronegative patients

Review criteria

We searched PubMed (all years) using the search terms “NMO”, “neuromyelitis optica” and “aquaporin-4”. We also read abstracts from the Guthy-Jackson Charitable Foundation NMO and the ECTRIMS meetings (2009–2013).

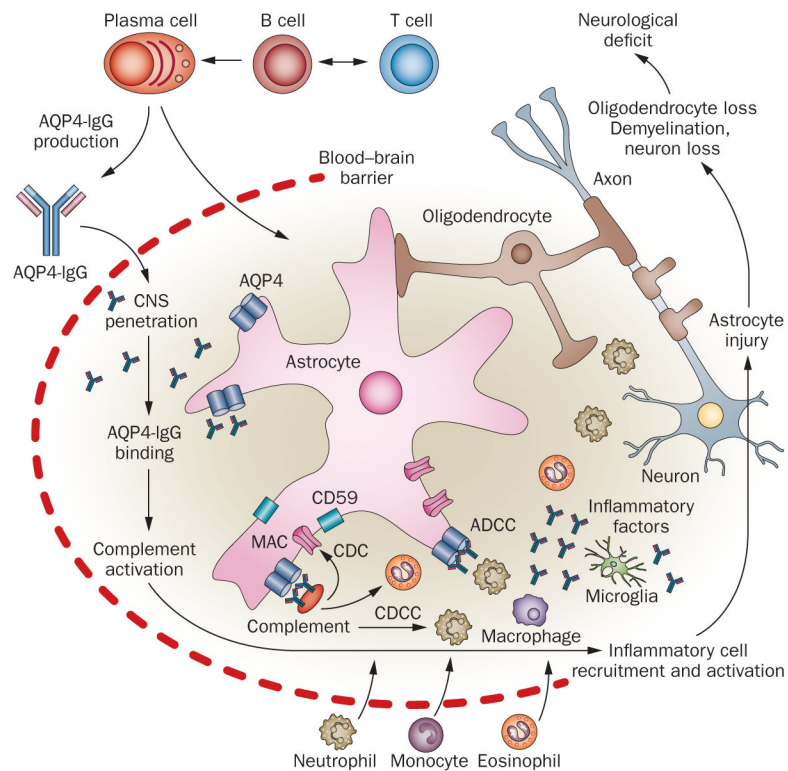


Figure 1. Mechanisms of NMO pathogenesis. Serum AQP4-IgG and plasma cells that produce AQP4-IgG penetrate the CNS, resulting in binding of AQP4-IgG to AQP4 channels on astrocytes. Antibody-dependent astrocyte damage involving complement-dependent cytotoxicity, CDCC and ADCC mechanisms lead to inflammation, oligodendrocyte injury, demyelination and neuronal loss. The CD59 glycoprotein inhibits cell lysis by inhibiting formation of the MAC. Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; AQP4, aquaporin-4; CDC, complement-dependent cytotoxicity; CDCC, complement-dependent cellular cytotoxicity; MAC, membrane attack complex; NMO, neuromyelitis optica.

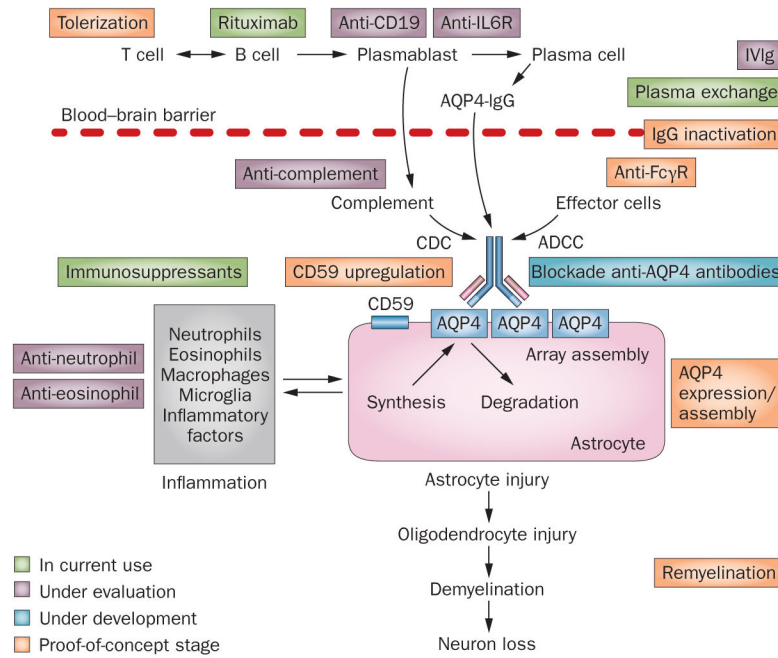


Figure 2. Pharmacological targets in NMO. Green boxes show mechanism-based approaches currently used to treat NMO (anti-CD20 antibody [rituximab]; immunosuppressive agents; plasma exchange), purple boxes show approved drugs under evaluation for repurposing for NMO, blue boxes show drugs in preclinical development, and orange boxes show pharmacological intervention strategies at early, proof-of-concept stage. See Table 1 for additional information. Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; AQP4, aquaporin-4; CDC, complement-dependent cytotoxicity; IVIg, intravenous immunoglobulin; NMO, neuromyelitis optica.

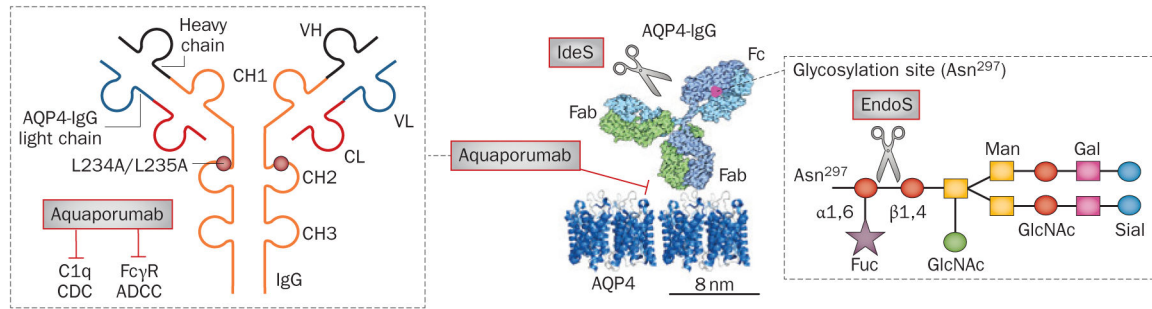


Figure 3.

AQP4-IgG blocking and inactivation strategies for NMO therapy. An AQP4 array with bound AQP4-IgG antibody is shown in the middle of the figure. High-affinity, nonpathogenic anti-AQP4 antibody (aquaporumab) competes with pathogenic AQP4-IgG for AQP4 binding. *Streptococcus pyogenes*-derived enzymes IdeS and EndoS selectively inactivate IgG through proteinase and endoglycosidase actions, respectively, producing blocking nonpathogenic antibody remnants. Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; AQP4, aquaporin-4; C1q, complement component C1q; CDC, complement-dependent cytotoxicity; CDCC, complement-dependent cellular cytotoxicity; CL, constant region of light chain; EndoS, endoglycosidase S; Fab, fragment antigen-binding region; Fuc, fucose; Gal, galactose; GlcNAc, *N*-acetylglucosamine; IdeS, IgG-degrading enzyme; Man, mannose; NMO, neuromyelitis optica; Sial, sialic acid; VH, variable region of heavy chain; VL, variable region of light chain.

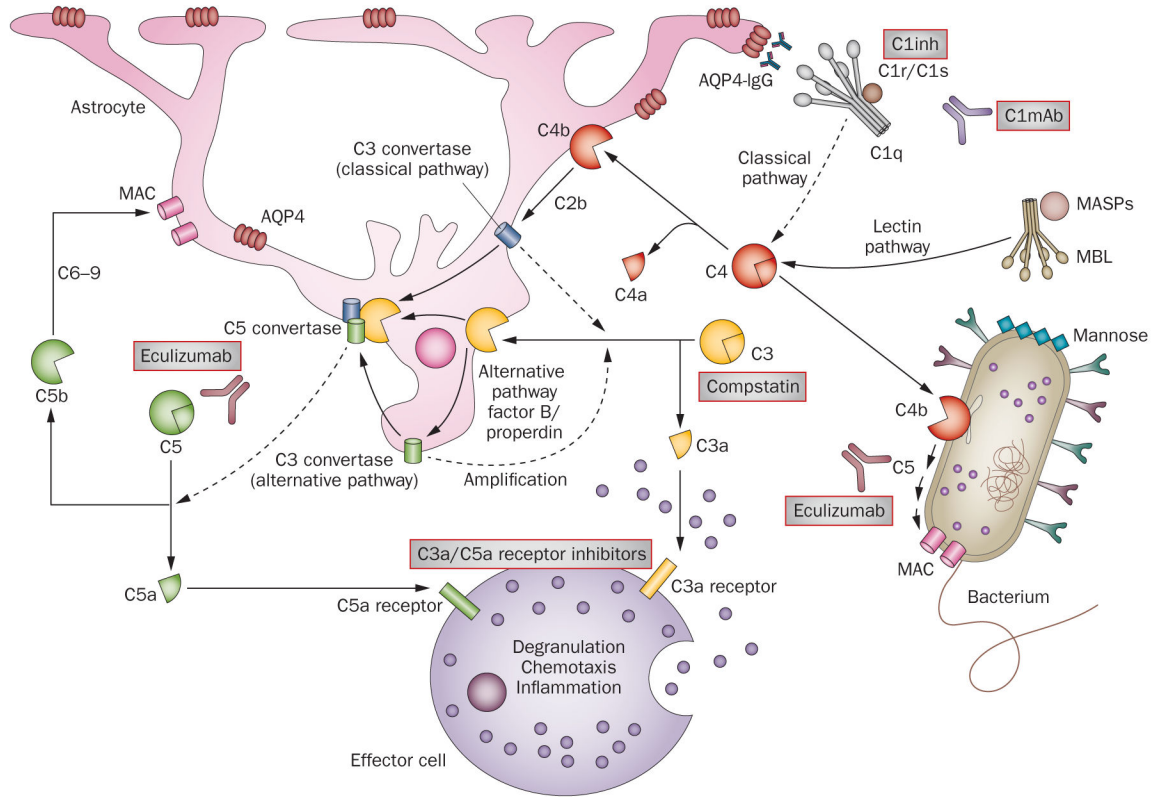


Figure 4. Complement activation pathways and complement drug targets. The major components of the classical, alternative and lectin complement activation pathways are shown, along with C1mAb and eculizumab—monoclonal antibodies that target complement components C1 and C5, respectively; C1inh, which targets C1; and the cyclic oligopeptide compstatin, which targets C5. C3a and C5a anaphylatoxins cause granulocyte activation by binding to specific receptors. Abbreviations: AQP4, aquaporin-4; C1inh, complement protein 1 inhibitor; MAC, membrane attack complex; MASP, mannan-binding lectin serine protease; MBL, mannose-binding protein.

Table 1

Commonly used NMO treatments in adults

Treatment	Typical dose	Mode of action
<i>For acute exacerbation</i>		
Methylprednisolone ⁶⁰	1 g daily, for 3–5 days	Multiple
Plasma exchange ^{57–60}	Five to seven cycles	Depletion of AQP4-IgG and cytokines
Intravenous immunoglobulin ^{61,136}	0.7g/kg for 3 days; treatment period 8 weeks	Multiple
Cyclophosphamide ⁶²	2 g daily for 4 days	Inhibits mitosis
<i>Relapse rate reduction</i>		
Prednisolone ⁶⁴	2–20 mg daily	Multiple
Rituximab ^{74–80,180,181}	For example, 1 g at day 1 and day 14, repeat every 6 months (optional: monitoring of CD19 counts)	Anti-CD20, B-cell depletion
Plasma exchange ⁶⁵	Immunosuppression	Depletion of AQP4-IgG and cytokines
Cyclophosphamide	2 g daily for 4 days	Inhibits mitosis
Azathioprine ^{66–68,180}	2.5–3.0 mg/kg daily	Blocks synthesis of adenine and guanine
Mycophenolate ^{69,180}	750–3000 mg daily	Inhibits inosine monophosphate dehydrogenase, primarily the type II isoform found in T cells and B cells
Mitoxantrone ^{71,182}	Initiation with 12 mg/m ² monthly for 3–6 months, maintenance with 6–12 mg/m ² every 3 months; maximum cumulative dose of 120 mg/m ²	Intercalates DNA, inhibits mitosis
Methotrexate ⁷⁰	7.5–25 mg once weekly	Folic acid antagonist
Cyclosporine A ⁸⁴	2–5 mg/kg daily	Inhibits T cells
<i>Harmful in NMO or insufficient safety data</i>		
IFN- β ^{101–104}	NA	Harmful in NMO
Fingolimod ^{114,115}	NA	Might be harmful in NMO (insufficient data)
Natalizumab ^{106,107}	NA	Might be harmful in NMO (insufficient data)

Abbreviations: AQP4, aquaporin-4; CD20, B-lymphocyte antigen CD20; NA, not applicable; NMO, neuromyelitis optica.

Table 2

Current therapeutic trials in NMO

Company	Intervention	Mode of action	Type of trial	Recruitment	Purpose of trial
Alexion	Eculizumab (Soliris [®])	Inhibits C5	Phase III	Not yet started	Long-term safety and efficacy for relapse rate reduction in AQP4-IgG ⁺ NMO
Nihon	Intravenous immunoglobulin (NPB-01) combined with steroids	Multiple	Phase II	Recruiting	Safety and efficacy in AQP4-IgG ⁺ NMO
Mayo Clinic	Plasma exchange	IgG depletion	Phase I	Recruiting	Feasibility, tolerability, safety and preliminary efficacy as maintenance therapy in NMO
Viropharma	C1inh (Cimryze [®]) as an add-on therapy	C1 inhibition	Phase I	Completed	Tolerability, safety and preliminary efficacy in acute NMO/NMOSD
Genentech	Bevacizumab (Avastin [®]) as add-on therapy	Inhibits VEGF	Phase II	Not yet started	Tolerability, safety and preliminary efficacy in acute NMO/NMOSD
Chugai	SA237	Anti-IL-6 receptor	Phase III	Not yet started	Safety, efficacy; pharmacodynamic, pharmacokinetic and immunogenic profiles in NMO/NMOSD
ONO	Sivelestat (Elaspol [®]) combined with methylprednisolone	Anti-neutrophil	Phase I, II	Recruiting	Safety and efficacy in acute NMO
Genentech	Tocilizumab (Actemra [®] , Toactemra [®])	Anti-IL-6 receptor	Phase I, II	Completed	Safety and efficacy in intractable NMO; exploration of mechanisms of action

Abbreviations: AQP4, aquaporin-4; AQP4-IgG⁺, AQP4-IgG-seropositive; C, complement protein; NMO, neuromyelitis optica; NMOSD, NMO spectrum disorder; VEGF, vascular endothelial growth factor.

Table 3

Compounds in the pipeline

Compound	Target molecule	Mechanism of action
Anti-CD19 ^{34,118}	B-cell surface marker	Depletion of naive and memory B cells, plasmablasts, and some plasma cells
Anti-IL-17 ^{54,183}	Cytokine	Blocks IL-17 signal transduction
Aquaporumab ¹⁴⁴	AQP4	Binds to AQP4 on CNS astrocytes and blocks AQP4-IgG binding
IdeS ¹⁵³	AQP4-IgG	Cleaves circulating AQP4-IgG
EndoS ¹⁵²	AQP4-IgG	Deglycosylates AQP4-IgG to eliminate CDC and ADCC function
Small-molecule blockers ¹⁴⁵	AQP4-IgG	Competitive inhibition of AQP4-IgG binding
Peptoid inhibitors ¹⁸⁴	AQP4-IgG	Competitive inhibition of AQP4-IgG binding

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; AQP4, aquaporin-4; CDC, complement-dependent cytotoxicity; NMO, neuromyelitis optica.