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REVIEW

# Present and Future Therapies in Neuromyelitis Optica Spectrum Disorders

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**Abstract** Neuromyelitis optica spectrum disorders (NMOSD) are important evolving entities, which have reached much attention in the recent years. NMOSD are characterized by inflammatory lesions in the optic nerves, spinal cord, and central parts of the brain, as well as an autoimmune process directed against aquaporin-4. As disability in NMOSD accumulates by inflammatory damage from attacks, both the treatment and prevention of attacks are decisive for the long-term outcome. NMOSD attacks are treated with high-dose intravenous corticosteroids and apheresis therapies, in particular therapeutic plasma exchange. In cases of incomplete remission, escalation of attack treatment is recommended. Preventive therapy is immunosuppressive and should by commenced as early as possible. Apart from classical immunosuppressants such as azathioprine and mycophenolate mofetil, repurposed biologicals are increasingly used. B-cell depletion with rituximab and other agents, inhibition of the interleukin-6 receptor with tocilizumab, and blockade of complement-mediated damage by eculizumab all are promising therapeutic strategies evaluated in randomized controlled trials. In this review, we will discuss present and future immunotherapies for NMOSD and also consider combination of treatments, plasma, cellular and other therapies. Current advances in immunopathological knowledge are translated into innovative concepts and begin a new era of NMOSD therapy.

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**Key Words** Devic disease · Plasmapheresis · Azathioprine · Rituximab · Tocilizumab · Eculizumab

## Introduction

Neuromyelitis optica (NMO) and NMO spectrum disorders (NMOSD) have been recognized in recent years as a distinguished disease entity owing mainly to identification of pathogenic autoantibodies directed against the astrocytic water channel aquaporin-4 (AQP4-IgG) [1–4]. Although being rare diseases with an incidence and prevalence of 0.05–0.40 and 0.52–4.40 per 100,000, respectively, NMO and NMOSD occur globally in various ethnicities [5], and often pose a high disease burden for affected individuals.

The autoimmune neuroinflammation of NMO and NMOSD involves the spinal cord, typically as longitudinally extensive transverse myelitis (LETM), the optic nerves and optic chiasm, and central parts of the brain. Apart from optic nerve/optic chiasm and spinal cord lesions, magnetic resonance imaging (MRI) shows cerebral lesions in a large proportion of patients, which might present as small and localized or extensive hemispheric lesions, periependymal lesions surrounding the aqueduct, the third and fourth ventricles, and brain stem lesions [6]. Barkhof criteria may sometimes be fulfilled, but generally lesions have an atypical appearance or location for multiple sclerosis (MS), the main differential diagnosis. Several clinical features highly distinctive for NMO and NMOSD have been identified, which include simultaneous LETM and optic neuritis (ON), bilateral ON, and intractable nausea with hiccups and vomiting [7]. Besides clinical evaluation, AQP4-IgG serology and MRI, cerebrospinal fluid diagnostics,

evoked potentials, and optical coherence tomography guide diagnosis of NMO and NMOSD [8].

While ON and LETM are the classical hallmarks of NMO, the spectrum of NMO constantly expanded in recent years [9]. It includes AQP4-IgG-positive patients with isolated ON or LETM, both monophasic or relapsing, with isolated cerebral lesions involving the abovementioned locations, with 1 or several short myelitis lesions [10], or with combinations thereof. Furthermore, NMO and NMOSD can be associated with myopathy and occur in the context of systemic autoimmune disease or cancer [9]. The case for AQP4-IgG-negative NMO is more complex, as these patients form a heterogeneous group with demographic and clinical characteristics different from seropositive patients [11]. Autoantibodies targeting the myelin oligodendrocyte glycoprotein have been reported in some AQP4-IgG-negative patients with a classical clinical presentation of NMO [12, 13], however, anti-myelin oligodendrocyte glycoprotein-antibodies are not specific for NMO and occur in a variety of other demyelinating diseases [14]. Recently, new diagnostic criteria were published that present a uniform concept combining NMO and NMOSD [15], which is why the term "NMOSD" will be used throughout this review. As for MS after definition of the McDonald criteria it is expected that the new diagnostic criteria for NMOSD will lead to an increase in patient numbers, particularly in AQP4-IgG-negative patients.

It was demonstrated long ago that immunosuppressive therapy with corticosteroids is beneficial to induce remission from acute exacerbations and for long-term treatment of NMOSD [16]. Azathioprine (AZA) was among the first immunosuppressants reported to be effective for NMOSD [17]. Subsequently, the new disease-modifying drugs approved for MS were given for NMOSD, with variable success [18–20], while more promising results came from B-cell depletion therapy [21]. The latter approach was a consequence of pathoanatomical and serological studies identifying humoral disease mechanisms, particularly complement activation and NMO-IgG, involved in the pathogenesis of NMOSD [22, 23].

Several national and international guidelines describing diagnosis and treatment of NMOSD have been published [8, 24–27], yet most therapeutic recommendations are still expert-based because until recently all studies reporting treatment outcomes had been conducted in a nonrandomized and often retrospective setting.

With advances in knowledge about the immunopathology of NMOSD [28], innovative therapeutic concepts [29], and the first randomized controlled trials coming up, we are now approaching a new era of NMOSD therapy. In this review, we will discuss present and future immunotherapies for NMOSD. For symptomatic treatments, which are similar to those applied in MS, we refer to respective reviews [30, 31].

## Treatment of NMOSD Attacks

Unlike MS, NMOSD almost never take a progressive disease course and disability is accumulated by inflammatory damage from attacks. Only every 2. to 5. NMOSD attack shows complete recovery [11, 32]. In particular, bilateral ON and myelitis have low remission rates [33]. As successful treatment of attacks determines long-term outcome and disability, NMOSD attacks should be treated "hard and early" and escalation of therapy is recommended. In a retrospective study of 871 NMOSD attacks, escalation of attack therapy significantly improved outcome; after the first treatment course 19.1 % of attacks showed complete remission and 16.4 % no remission, and after the last treatment course 21.6 % showed complete remission and 6.0 % no remission [33].

Recommendations for the treatment of NMOSD attacks were adapted from studies of MS and idiopathic ON. No controlled trials have been performed in NMOSD and most studies examining apheresis therapies have reported outcomes of both entities.

Acute exacerbations of NMOSD are usually treated with high-dose intravenous (IV) methylprednisolone (IVMP) at a dose of 1000 mg for 3–5 days with or without oral tapering [8, 24–26]. It has been shown that each, a first, second, and third course of IVMP significantly improves clinical disability in patients with MS and NMOSD [34], and that early administration is associated with preservation of the retinal nerve fiber layer thickness in NMOSD [35].

When remission is absent or insufficient, therapeutic plasma exchange (TPE; 5–7 cycles) should be used [8, 24–26]. The efficacy of TPE for relapsing–remitting MS and other inflammatory demyelinating diseases was demonstrated in a randomized, controlled trial and several uncontrolled studies [36–40]. TPE was also reported to be beneficial for NMOSD attacks [40–43]. TPE effectively eliminates pathogenic AQP4-IgG from the patient's circulation [44], which is one reason to use TPE in NMOSD. However, TPE improves attack-related disability not only in seropositive but also in seronegative patients [40, 42, 45], where putatively other types of autoantibodies may exist. Attacks other than ON, fewer prior attacks, shorter disease duration, and lower pre-existing disability are factors associated with the favorable outcome of TPE [40, 43–45]. If TPE is not applicable, for example, owing to contraindications, a second course of IVMP at a higher dose of up to 2 g for 5 days can be given [8].

In some countries, immunoadsorption (IA), a method to remove immunoglobulins from the circulation by adsorption to either tryptophan or protein A, is used as an alternative to TPE for the treatment of exacerbations of MS and NMOSD [46, 47]. Several adult and pediatric cases have been reported in whom NMOSD attacks were successfully treated with IA [33, 46, 48–50].

Although mostly given as escalation therapies, TPE and IA might also be used as initial treatment for severe attacks, in

particular when previous attacks have responded well to apheresis therapies but not to IVMP [8]. Interestingly, 3 reports have suggested that TPE in parallel with IVMP is more effective in reaching remission from NMOSD attacks than IVMP alone [32, 42, 43]. In line with these results, a retrospective analysis of 871 NMOSD attacks revealed that first-line therapy with PE or IA is superior to IVMP when the spinal cord is affected [33].

Resistant cases without improvement after ≥ 1 course of both IVMP and apheresis therapies have occasionally been escalated to early highly active immunotherapy such as IV cyclophosphamide [26], mitoxantrone [8], or tocilizumab [51, 52], which induced a dramatic improvement in disability in single patients.

Inhibition of complement-mediated damage, for example by IV immunoglobulins (IVIG), eculizumab, or C1-esterase inhibition, might be another mechanism to induce remission from refractory NMOSD attacks. A retrospective study examining IVIG as an attack therapy in patients nonresponsive to IVMP with or without TPE revealed beneficial effects in 5/11 attacks [53]. Two randomized controlled trials are currently evaluating the efficacy of IVIG for NMOSD attacks. Recently, the C1-esterase inhibitor Cinryze (ViroPharma, Exton, PA, USA) was given as add-on therapy to IVMP in an open-label study of 10 patients with AQP4-IgG-positive NMOSD [54]. Cinryze therapy was safe and associated with disability improvement to preattack levels in 9/10 patients after 1 month. Finally, inhibition of neutrophil elastase with sivelestat was beneficial in animal models of NMOSD [55, 56], and a small open-label trial evaluating sivelestat for NMOSD attacks is currently being conducted in Japan.

## Prevention of NMOSD Attacks

### General Considerations

As attacks are decisive for the long-term outcome of NMOSD, both prevention of attacks and attenuation of attack severity are important treatment goals. Most patients with NMOSD have a relapsing disease course, and the median time between first and second attack is <1 year [11]. Natural history cohorts describing the annual relapse rate (ARR) in untreated patients do not exist for NMOSD; however, it is noteworthy that AQP4-IgG-positive patients with late-onset have attacks even in the oldest age categories [57].

There are probably no differences in relapse rates and clinical features between AQP4-IgG-positive patients with classical NMO and NMOSD, but AQP4-IgG-negative patients more often have bilateral ON or simultaneous ON and myelitis at disease onset than AQP4-IgG-positive patients [11, 58]. While 1 study reported that a monophasic disease course is more common in AQP4-IgG-negative patients [11], this was not found in another study [58]. It is unclear whether AQP4-IgG seronegative and seropositive NMOSD are driven by similar humoral immune mechanisms [29]. Therapeutic recommendations for AQP4-IgG-positive NMOSD cannot *bona fide* be transferred to seronegative patients, who should be treated on an individual basis, guided by severity and remission of the first attack and the clinical course [8]. In patients diagnosed with AQP4-IgG-positive NMOSD, however, preventive therapy should be started as soon as diagnosis is confirmed [8].

Several immunomodulatory drugs approved for MS were shown to exacerbate the disease course in AQP4-IgG-positive NMOSD. Although only assessed by retrospective studies, the marked worsening of disability reported in some patients treated with interferon-β [19, 20, 59–62], natalizumab [63–65], and fingolimod [66, 67] should prompt us to avoid these therapies. Alemtuzumab, a T- and B-cell-depleting agent, was also shown to exacerbate NMOSD in single patients [51, 68, 69]. At present, there are insufficient data to support or discourage use of glatiramer acetate, teriflunomide, and dimethylfumarate in NMOSD [8].

Although not investigated by randomized, controlled trials, it is now well accepted that treatment for the prevention of NMOSD attacks should be immunosuppressive [8, 24–26]. Several classical immunosuppressants and some repurposed biologicals have been recommended for NMOSD and will be discussed below. Ambiguous cases of autoimmune neuroinflammation not fulfilling criteria for MS or NMOSD are often treated with broad-acting immunosuppressive drugs such as AZA or methotrexate (MTX) [70].

Before starting an immunosuppressive or biological therapy, patients must be informed about the respective risks and potential complications, such as infections, cytotoxicity and myelotoxicity, malignancy, infertility, and, in women, the need for contraception. Pregnancy and chronic infections, particularly HIV, hepatitis B and C, and tuberculosis, should be excluded prior to start of therapy.

The duration of prophylactic immunotherapy in NMOSD is not well defined [26]. Periods of increased attack frequency can be followed by relapse-free times for years before disease activity unpredictably recurs. It has been suggested to continue immunosuppressive therapy for at least 5 years after a first LETM attack [71]. However, any attempt to reduce or stop immunotherapy for NMOSD has to be discussed carefully with the patient, balancing the benefits and risks of the applied therapies [26].

### Classical Immunosuppressants

#### *Oral Corticosteroids*

Corticosteroids bind to the glucocorticosteroid receptor expressed on all cells and induce a wide variety of genomic

changes that lead to immunosuppression [72]. Oral low-dose corticosteroids (usually prednisolone, up to 1 mg/kg/day; Table 1) are used for NMOSD to taper out steroids after IVMP attack therapy, in combination with other immunosuppressants, particularly during dosing in and with breakthrough disease, and sometimes as monotherapy. A small retrospective study of 9 patients with NMOSD reported that the median ARR decreased from 1.48 in untreated patients to 0.49 in corticosteroid-treated patients; doses >10 mg/day were associated with fewer attacks [73]. Long-term use of oral corticosteroids above ~7.5 mg/day is associated with many side effects, for example hyperglycemia, hypertension, weight gain, and osteoporosis, and therefore should be avoided as monotherapy for NMOSD.

*AZA*

The purine synthesis inhibitor AZA preferentially affects proliferation of B and T cells and is the most widely studied immunosuppressant for NMOSD. Several studies including a total of almost 400 patients have shown that AZA reduces the ARR, sometimes associated with improvement of neurological disability [17, 74–80]. A retrospective study evaluating classical NMO and patients with AQP4-IgG-positive NMOSD reported a decrease in the mean ARR from 2.18 to 0.64 in 70 patients treated with AZA for >1 year, with or without concomitant corticosteroid therapy [77]. A reduced dose of <2 mg/kg/day AZA was associated with more, and an increase of the mean corpuscular volume by at least 5 fl from baseline with fewer relapses (both to be confirmed in further studies). Clinical disability measured by the expanded disability status scale (EDSS) and visual acuity improved or remained unchanged in 61 % and worsened in 39 % of patients with >12 months of follow-up on AZA therapy. AZA was discontinued in 38/99 patients, mostly for side effects and lack of efficacy. Another retrospective study of 103 patients with AQP4-IgG-positive NMOSD confirmed these findings, revealed a reduction of the median ARR in 89 % of patients (median of 1.5 pretreatment to 0 on AZA), and an improvement or stabilization of the EDSS in 78 % of patients, but again had a high discontinuation rate of AZA (46 %) [78]. A third retrospective study of 31 patients with AQP4-IgG-positive or AQP4-IgG-negative NMOSD described a reduction in the mean ARR from 2.26 to 0.63 with a failure rate in 53 % of patients, despite concomitant prednisone therapy [79]. Another retrospective study of AZA plus long-term low-dose corticosteroid therapy in 77 Chinese patients found a relapse-free status at median follow-up of 19 months in 44 patients (57.1 %) and significant improvements of the ARR, EDSS, and modified Rankin Scale [80].

While the discussed studies have shown that AZA can reduce the ARR in patients with NMOSD, 2 recent retrospective studies suggested that the risk for further NMOSD attacks was significantly higher with AZA treatment than with B-cell-depleting rituximab therapy [hazard ratio (HR) 2.12 and 1.82, respectively] [79, 81], and that severe attacks occurred more often in patients treated with AZA (HR 11.66) [81].

**Table 1** Pharmacological therapies used for prevention of attacks in neuromyelitis optica spectrum disorders (NMOSD)

| Therapy | Regimen | Route | Comments |
|---|---|---|---|
| Prednisolone | Up to 1 mg/kg/day, usually 15–30 mg/day | Oral | Steroid side effects, taper after 1 year |
| Azathioprine | 2–3 mg/kg/day in 1 or 2 doses | Oral | First-line therapy, taper in, measure TPMT activity, target dose guided by ALC and MCV increase, liver toxicity |
| Rituximab | Various (250–2000 mg every 6–12 months; 4 weekly doses of 375 mg/m$^2$) | IV | First-line therapy, B-cell count as biomarker |
| Mycophenolate mofetil | 1500–3000 mg/day in 2 doses | Oral | Taper in, target dose guided by ALC and trough blood concentration (1–2 μg/ml) |
| Methotrexate | 7.5–25.0 mg weekly | Oral | Substitute folic acid, liver toxicity |
| Ciclosporin A | 2–5 mg/kg/day in 2 doses | Oral | Nephrotoxic, target dose guided by trough blood concentration (70–100 ng/ml) |
| Tacrolimus | 1–6 mg/day in 2 doses | Oral | Nephrotoxic, target dose guided by trough blood concentration (5–10 ng/ml) |
| Mitoxantrone | 12 mg/m$^2$ every 1–3 months | IV | Cardiac monitoring (LVEF), target dose guided by leukocyte count, total cumulative dose 100 mg/m$^2$ |
| Tocilizumab | 8 mg/kg every 4 weeks | IV | Monitoring for infections, CRP no reliable biomarker for infection |
| Combination therapies | Usually prednisolone + immunosuppressant OR biological + immunsuppressant | IV or oral | Only few reports in NMOSD, monitoring for infections |

TPMT = thiopurine methyl transferase; ALC = absolute lymphocyte count; MCV = mean corpuscular volume; IV = intravenously; LVEF = left ventricular ejection fraction; CRP = C-reactive protein

AZA is given at a dose of 2–3 mg/kg/day, should be slowly tapered in with monitoring of hematological parameters and transaminases, and reaches clinical activity after 3–6 months. Prior to starting AZA, testing for thiopurine methyltransferase enzyme activity may be useful as patients with low activity are of higher risk for severe side effects [8, 26]. We suggest adjusting the target dose of AZA by the total lymphocyte count, which should decrease to 600–1000/μl, the leukocyte count, which should remain at >3000/μl, and the mean corpuscular volume, which should increase by about 5 % from baseline. A correlation between the dosage of AZA and clinical efficacy was reported for NMOSD and other indications [77, 82]. Regular differential blood cell count and transaminase monitoring are mandatory. Side effects of AZA include nausea, diarrhea, fatigue, leuko- and lymphopenia, infections, liver toxicity, bone marrow suppression, and malignancies with long-term use.

*Mycophenolate Mofetil*

Mycophenolate mofetil (MMF) is a prodrug of the active metabolite mycophenolic acid. It inhibits lymphocyte proliferation by suppression of guanosine nucleotide biosynthesis and is used for psoriasis, proliferative lupus nephritis, and renal transplant rejection. Four retrospective cohorts evaluating 24–58 patients with mostly AQP4-IgG-positive NMOSD have reported beneficial outcomes of MMF therapy with or without concomitant corticosteroids [79, 81, 83, 84]. MMF treatment for a median of 20–27 months resulted in a reduction of the ARR by 80–93 % and improvement of the median EDSS in 3/4 studies (not reported in 1). More than 90 % of patients had stable or improved disability [83, 84], and 46–65 % were relapse-free [79, 81, 83, 84]. Discontinuation rates due to disease activity or side effects were 15–25 %.

In comparison with B-cell-depleting rituximab therapy there was no significant difference for the risk of further NMOSD attacks (HR 1.48 and 1.27, respectively) [79, 81], although 1 study found that severe attacks occurred significantly more often with MMF than with rituximab (HR 5.96) [81].

MMF is tapered in with a target dose of 1500–3000 mg/day, guided by the total lymphocyte count, which should decrease to 1000–1500/μl, but also following a plasma trough level of 1–2 μg/ml in neuroimmunological indications. The treatment effect usually occurs within 2–3 months. Monitoring of the differential blood cell count and liver function is mandatory. Gastrointestinal complications, hypercholesterolemia, elevation of transaminases, myelotoxicity, and infections, including progressive multifocal leukoencephalopathy, are potential side effects of MMF therapy.

*MTX*

MTX, a folic acid antagonist, is used for hematological malignancies, rheumatoid arthritis, psoriasis, myasthenia gravis, and other autoimmune diseases. Kitley et al. [85] treated 14 patients with AQP4-IgG-positive NMOSD for a median of 21.5 months with 17.5 mg MTX (median). The ARR was reduced by 87 %; 79 % of patients had a stable or improved EDSS; 43 % were relapse-free. However, 13/14 patients had received concomitant immunotherapy, 11 with oral prednisolone, 1 with rituximab, and 1 with tacrolimus. In another retrospective study of 9 patients with NMOSD, 17.5 mg MTX accompanied by low-dose prednisone therapy reduced the ARR by 64 %, 2 patients were relapse-free, and 5 had a stable or improved EDSS [86]. In 3 patients, MTX was used as a de-escalation strategy after 6 months of cyclophosphamide therapy; however, 2 of these 3 patients had further attacks while on MTX. An older, less well-documented study revealed stable disease (without new clinical or MRI events) and improvement of EDSS over a period of 24 months in all 7 patients with Devic disease who were treated with a combination of 50 mg IV MTX weekly and prednisone 1 mg/kg/day (with subsequent tapering) [87]. MTX was generally well tolerated in patients with NMOSD [85–87].

MTX is tapered in and folic acid supplementation is recommended. As for other immunosuppressants regular differential blood cell count and transaminases should be monitored and infections anticipated.

*Ciclosporin A and Tacrolimus*

The calcineurin inhibitors ciclosporin A and tacrolimus are frequently used for patients with various autoimmune diseases or to prevent organ transplant rejection. Kageyama et al. [88] described 9 patients with AQP4-IgG-positive NMOSD treated with a combination of ciclosporine A (median dose 150 mg/day) and prednisone for 13–51 months, which improved the ARR in 8 patients (3 were relapse-free, mean ARR reduction 86 %) and stabilized the EDSS in 7.

Tacrolimus (1–6 mg/day) was given as add-on therapy to prednisolone (median initially 13 mg/day, after tapering 1.5 mg/day) in 25 Japanese patients with NMOSD [89]. Twenty-three patients (92 %) remained relapse-free in a treatment time of 2–44 months (median 12 months) and 2 patients had side effects (diabetes and cholangitis). Another patient with AQP4-IgG-positive NMOSD associated with Sjögren syndrome and failure of intravenous cyclophosphamide was stable for 3 years with tacrolimus [90], while in 1 patient with systemic lupus erythematosus-associated NMOSD tacrolimus was not effective [91].

*Mitoxantrone*

Mitoxantrone is an antineoplastic topoisomerase II inhibitor that inhibits both DNA and RNA synthesis and suppresses T- and B-cell immunity. Two recent observational studies of 20 and 51 patients with NMOSD found a reduction in ARR of 75 % and 80 % and a relapse-free status in the first year of treatment of 50 % and 70 %, respectively, during mitoxantrone treatment (duration up to 22 months, cumulative dose up to 120 mg/m$^2$) [92, 93]. In one study all patients were AQP-IgG-positive [92]; in the other AQP4-IgG-positive patients had more relapses than AQP4-IgG-negative patients [93]. Another small open-label study of 5 patients with NMOSD demonstrated beneficial effects of mitoxantrone on disability and MRI in 4 patients, with 3 patients staying relapse-free [94].

Mitoxantrone is usually started as induction therapy with 3 monthly pulses of 12 mg/m$^2$ body surface area supplemented with 1 g IVMP, followed by further infusions every 3 months until the maximum dose of 100 mg/m$^2$ (120 mg/m$^2$ in exceptional cases) is reached. Different dosing regimens exist. Cardiac function and differential blood cell count have to be monitored prior each infusion. Decrease in left ventricular ejection fraction and hematological malignancies occur as dose-dependent effects in some patients and limit the use of mitoxantrone to severe cases of NMOSD.

*Cyclophosphamide*

Immunoablative or immunosuppressive therapy with IV cyclophosphamide was reported to induce stable disease in single patients with NMOSD, often in the context of systemic lupus erythematosus [91, 95]. However, 3 retrospective studies of 4, 5, and 7 patients, respectively, revealed breakthrough disease of NMOSD with IV cyclophosphamide therapy in all but one patient each [87, 96, 97]. Therefore, IV cyclophosphamide is only recommended when other therapies fail or are not available [8].

*Combination Therapies of Immunosuppressants*

Immunosuppressants are often combined with oral corticosteroids, in particular during tapering in and in patients not responding to monotherapy. Adjunctive therapy of AZA [17, 75, 77, 79], MMF [79, 83], MTX [85–87], ciclosporine A [88], and tacrolimus [89] with oral corticosteroids have all been reported to be (partly) effective and safe in NMOSD. In breakthrough disease intermittent TPE might be added to immunosuppressive treatment [8, 98], but usually escalation to a biological is preferable.

**Biologicals**

After recovering the importance of humoral immune mechanisms for NMOSD [22, 23], soon more specific therapies aiming to suppress either B cells, plasma cells, or downstream effector mechanisms were advocated. Nowadays, a couple of approaches derived from basic research data are being translated into clinical practice and biologicals are about to become the mainstay of NMOSD therapy.

*Rituximab and Other B-cell-depleting Therapies*

Rituximab is a chimeric anti-CD20 monoclonal antibody that depletes both naïve and memory B cells. It was the first specific immunosuppressant used for NMOSD. The pivotal open-label study from Cree et al. [21] established B-cell depletion as a therapeutic principle for NMOSD; 6/8 patients were relapse-free after 1 year of treatment. Several clinical case series and retrospective analyses (including 10–55 patients each, treatment up to 8 years) have confirmed these findings and reported a reduction of ARR in 87–96 %, freedom from relapses in 44–72 %, and an improvement of disability in 80–100 % of patients [79, 81, 97, 99–102]. Most patients in these studies were AQP4-IgG-positive, but response rates in patients with AQP4-IgG-negative NMOSD seem to be similar [97, 102]. Treatment responses to rituximab appear to be more favorable than for classical immunosuppressive therapies [79, 81, 97], but caution has to be applied as all reported studies are prone to different kinds of bias owing to their retrospective design. Although previously often used as escalation therapy, its high efficacy makes rituximab an option for first-line treatment of highly active NMOSD [8].

There are various treatment regimens for rituximab in NMOSD, yet it has not been identified which has the optimal ratio of efficacy, side effects, and costs. Usually, rituximab infusions are applied either at a dosage of 2 treatments of 1 g with a 2-week interval or, for oncological indications, 4 times per 375 mg/m$^2$ body surface area with weekly intervals. More than 80 % of patients remain B-cell depleted 6 months after rituximab treatment [103], and re-dosing is often done at regular 6-month intervals [79], which however runs the risk that B cells in some patients are already repopulating. Another approach is to monitor B-cell counts closely and to re-dose rituximab before recurrence of circulating B cells (CD19$^+$ or CD20$^+$ B cells >0.1 % of total lymphocytes, CD27$^+$ memory B cells >0.05 % of peripheral blood mononuclear cells) [99]. A genetic polymorphism in the fragment c gamma receptor 3A (FCGR3A) allele has been shown to be associated with insufficient memory B-cell depletion and an elevated risk of attacks during rituximab treatment [104]. It is controversial whether a reduction in the dose during long-term treatment or even lower initial doses of rituximab are sufficient to suppress disease activity [100, 103, 105, 106]. Generally, optimal

dosing of rituximab is important to lower the failure rate [79, 103]. Relapses occurring in the setting of (incipient) B-cell repopulation should not be regarded as a nonresponse to rituximab but rather as dosing failure.

Moreover, relapses were reported to occur in the first weeks after the first rituximab application, probably owing to transient elevation of proinflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-6, and B-cell activating factor, all of which promote maturation and survival of B cells and plasmablasts [107, 108]. In line with these findings AQP4-IgG transiently increase after initiation of rituximab, with a subsequent decrease [107]. Lower titers of AQP4-IgG are probably associated with less disease activity but have not yet been established as a reliable biomarker of treatment response in rituximab-treated patients [74, 100, 101]. It is unknown whether the clinical effects of B-cell depletion are mediated by a reduction of AQP4-IgG or by inhibition of other proinflammatory B-cell functions. Notably, rituximab does not deplete antibody-producing plasma cells.

Despite the apparent success of rituximab in NMOSD it has to be stated that none of the abovementioned studies was controlled with a placebo arm or active comparator, making assessment of the real therapeutic effect difficult. In this regard it is of great importance that a randomized controlled trial was started, which evaluates the efficacy of a novel anti-CD19 humanized monoclonal antibody (MEDI-551) against placebo to prevent NMOSD attacks (Table 2) [109]. Further B-cell-depleting therapies targeting CD19 or CD20 are being developed for MS and other autoimmune diseases, for example ocrelizumab and ofatumumab, all of which potentially could be used for NMOSD in the future. A phase I trial with ublituximab (anti-CD20 antibody) to treat acute NMOSD attacks is in preparation [110].

Although rituximab generally is well tolerated, patients receiving this drug or other B-cell-depleting monoclonal antibodies should be monitored closely for allergic reactions (preventive premedication is obligatory), infections, low IgG/IgM levels, and late-onset neutropenia [111, 112]. Progressive multifocal leukoencephalopathy is another potential complication, which has not yet been reported in patients with NMOSD or MS treated with rituximab. Vaccinations with inactivated vaccines are safe during rituximab therapy in patients with NMOSD, but a reduction in the immune response should be anticipated [113].

### *IL-6 Receptor Inhibition*

Another method to target the humorally mediated immune process of NMOSD is inhibition of the IL-6/IL-6 receptor axis [114]. IL-6 is produced by stromal, epithelial, muscle, and immune cells, binds to either soluble or membrane-bound IL-6 receptor, and mediates its pleotropic effects through the transmembrane protein gp130 [115]. It has multiple functions in the immune system, including promotion of T- and B-cell activation, T helper 17 differentiation, and plasmablast survival.

Increased levels of IL-6 were detected in the serum and cerebrospinal fluid of patients with NMOSD, which correlated with disease activity and AQP4-IgG titers [116, 117]. Production and secretion of AQP4-IgG by B-cell-derived plasmablasts was shown to be dependent on IL-6, and blockade of IL-6 receptor signaling by an anti-IL-6 receptor antibody reduced the survival of plasmablasts in vitro [118]. Subsequently, several case reports revealed a reduction of disease activity in patients with severe, AQP-IgG-positive NMOSD using the anti-IL-6 receptor antibody tocilizumab, which is approved for the treatment of rheumatoid arthritis (IV and subcutaneous application) [51, 119, 120].

The efficacy of tocilizumab is supported by the congruent results of 2 recent open-label studies reporting a total of 15 patients from Germany and Japan with AQP-IgG-positive NMOSD [121, 122]. Araki et al. [121] treated 6 females and 1 male with high disease activity (mean ARR 2.9±1.1, mean EDSS 5.1±1.7) monthly with 8 mg/kg tocilizumab as add-on therapy to either prednisolone, AZA, ciclosporin, or tacrolimus. During 12 months of therapy, both ARR (0.4±0.8) and EDSS (4.1±1.6) significantly decreased and fatigue improved. Ringelstein et al. [122] reported the disease course of 8 female patients with severe NMOSD nonresponsive to rituximab (median ARR 4.0, median EDSS 7.3), which significantly improved during monotherapy with tocilizumab (median ARR 0.4, median EDSS 5.5) for up to 4 years. Relapses were mostly mild and occurred either in the first 2.5 months of therapy or after a reduction of application frequency (>40 days) or dosage (6 mg/kg instead of 8 mg/kg). Signs of disease activity on MRI were absent in 7/8 patients and AQP4-IgG titers significantly dropped.

Interestingly, both studies reported a reduction of chronic pain and about half of the patients became free of pain with tocilizumab therapy. Neuropathic pain is a frequent and often intractable symptom of NMOSD [123, 124]. Among other pleiotropic effects of IL-6, direct modulation of nociceptive neurons is likely, because deletion of its signal transducing receptor gp130 in peripheral neurons significantly reduced pain in mice [125].

Infections, hypercholesterolemia, elevation of transaminases, and leukopenia are the most common adverse effects of tocilizumab, and were observed in patients with NMOSD [121, 122]. Possible tuberculosis reactivation and opportunistic infections make careful observations essential. As C-reactive protein is directly downregulated by tocilizumab, it cannot be used as a sensitive diagnostic marker.

The above results from nonrandomized studies suggest that inhibition of the IL-6/IL-6 receptor axis might be beneficial from early stages of the disease to prolonged treatment of severely affected patients. Apart from the reduction of ARR,

**Table 2** Current randomized controlled trials for prevention of attacks in neuromyelitis optica spectrum disorders (NMOSD)

| Study number | Compound (company) | Target structure | Trial design | Regimen | Patients | Estimated recruitment (*n*) | Study duration | End point, comments |
|---|---|---|---|---|---|---|---|---|
| NCT01892345 | Eculizumab (Alexion) | C5 | Phase III, placebo-controlled, double blind, add-on to immunosuppressive therapy OR as monotherapy | 900 mg IV every week for 4 weeks, followed by 1200 mg IV every 2 weeks | AQP4-pos. NMO/NMOSD, age≥18 years, EDSS≤7.0 | 132 | 104 weeks | Time to first attack, randomization 2:1, study followed by open-label extension, completion of double-blind part of study estimated 2016 |
| NCT02028884 | SA237 (Chugai) | IL-6R | Phase III, placebo-controlled, double blind, add-on to oral corticosteroids or AZA, or MMF (EU, Japan, Taiwan) | 120 mg SC at weeks 0, 2, and 4; thereafter, every 4 weeks | NMO or AQP4-pos. NMOSD, age 12–74 years | 70 | Up to 30 months | Time to first attack, randomization 1:1, double blind followed by open-label extension, completion of double-blind part of study estimated 2017 |
| NCT02073279 | SA237 (Chugai) | IL-6R | Phase III, placebo-controlled, double blind, monotherapy (North America) | 120 mg SC at weeks 0, 2, and 4; thereafter, every 4 weeks | NMO or AQP4-pos. NMOSD, age 18–74 years | 70 | Up to 30 months | Time to first attack, randomization 1:2, double blind followed by open-label extension, completion of double-blind part of study estimated 2017 |
| NCT02200770 | MEDI-551 (MedImmune) | CD19 | Phase II/III placebo-controlled, double blind, monotherapy | 300 mg IV on days 1 and 15, and then every 6 months | NMO or AQP4-pos. NMOSD, age≥18 years, EDSS≤7.5 | 212 | 3 years | Time to first attack, randomization 3:1, maximum 197 days placebo, followed by open-label period, completion estimated 2019 |

IV = intravenously; AQP4 = aquaporin-4-antibody; EDSS = expanded disability status scale; IL-6R = interleukin-6 receptor; AZA = azathioprine; MMF = mycophenolate mofetil; EU = European Union; SC = subcutaneously

tocilizumab might additionally improve disability and alleviate fatigue and chronic pain. Currently, tocilizumab represents an off-label therapy for NMOSD and was suggested as a third-line treatment for severe cases [8]. A new subcutaneous IL-6 receptor-blocking monoclonal antibody (SA 237; Chugai, Tokyo, Japan), which has a fourfold greater duration of action than tocilizumab, is currently being evaluated for NMOSD in 2 randomized controlled trials [126, 127]. Other monoclonal antibodies targeting IL-6 or the IL-6 receptor are being developed for non-neurological conditions.

*Complement Inhibition*

As membrane-bound AQP4-IgG activates the complement cascade, ultimately forming the membrane attack complex, astrocytes expressing the target antigen AQP4 are destroyed during the immune attack [128, 129]. Therefore, inhibition of complement activation should reduce damage to the central nervous system in patients with AQP4-IgG-positive NMOSD.

Eculizumab, a humanized monoclonal antibody targeting the complement protein C5, was approved as an orphan drug for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Eculizumab inhibits the cleavage of C5 and prevents formation of the cytolytic terminal membrane attack complex C5b–C9. As the soluble peptide C5a has multiple roles in inflammation, including recruitment of basophils, macrophages, neutrophils, and lymphocytes to inflammatory sites, differentiation of T helper 1 cells, and interaction with Toll-like receptors [130, 131], upstream proinflammatory pathways might also be inhibited by eculizumab, potentially lowering attack frequency. An open-label pilot study investigated the efficacy and safety of eculizumab (600 mg IV weekly for 4 weeks, 900 mg in fifth week, then 900 mg every 2 weeks for 48 weeks) in 14 female patients with AQP4-IgG-positive NMOSD with high disease activity [132]. Eculizumab treatment reduced the median number of attacks from 3 to 0 and the median EDSS from 4.3 to 3.5. Twelve of 14 patients were relapse-free and disability stabilized or improved in all. Beside meningococcal sepsis with sterile meningitis, rheumatoid arthritis, and transient ischemic attack, in single patients each, no other serious adverse events occurred. While complement activity was suppressed during eculizumab treatment, AQP4-IgG titers remained unchanged. This interesting study demonstrates that complement-dependent cytotoxicity contributes to tissue damage in NMOSD and is a valuable target for both attack and preventive therapy. Nevertheless, infectious complications, particularly meningococcal meningitis (meningococcal vaccine is obligatory prior to the start of therapy), are an area of concern with complement-inhibiting therapies. The efficacy of eculizumab for AQP-IgG-positive NMOSD is currently being investigated in the randomized, controlled PREVENT trial [133].

Several other complement inhibitors, for example monoclonal antibodies targeting C1, and compounds inhibiting C1 esterase activity, C3, or C3a and C5a receptors, were assessed in preclinical models or have been suggested for theoretical reasons [29].

*Combination Therapy with Biologicals*

As commonly practiced in rheumatology, combination therapy of a biological with another immunosuppressive or immunomodulatory approach might be used in refractory NMOSD with high disease activity. Examples include combination of rituximab with MTX or IVIG [8], or tocilizumab with prednisolone, AZA, ciclosporin, or tacrolimus [121]. Care has to be taken as combination therapies implicate an increased risk of complications, particularly infections.

## Plasma, Cellular and Other Therapies

Further empiric therapies are used or have been proposed for prevention of NMOSD attacks, some of which are summarized below.

First, plasma therapies aiming to reduce humoral factors, particularly circulating AQP4-IgG, cytokines and proteins of the complement system, may be beneficial for maintenance therapy of NMOSD. Apheresis therapies such as TPE are classically used to treat severe NMOSD attacks; however, TPE was also evaluated for prevention of attacks [98, 134]. Khatri et al. [134] reported 7 patients with AQP4-IgG-positive NMOSD who received 21–154 TPE treatments for a mean of 7.1 years concomitantly with either oral or IV corticosteroids, cyclophosphamide, or both. Initially, TPE was applied as induction therapy, followed by gradual tapering to once every 3–12 weeks. Only one patient was relapse-free, but the ARR was reduced in all patients and 5/7 patients had an improvement of disability. Although not reported so far, regular IA therapy may have a similar effect as maintenance therapy. Another plasma therapy, monthly IVIG, inhibited clinical attacks in single patients with NMOSD for treatment periods of up to 5.5 years [135, 136]. Therefore, in patients with contraindications for classical or selective immunosuppressants, particularly children, regular IVIG infusions might be tried [8].

Second, similar to other severe autoimmune diseases, cellular therapy, either as rescue hematopoietic stem cell therapy after immunoablative chemotherapy or as stem cell transplantation with immunoregulatory or regenerative function, was proposed for NMOSD. Greco et al. [137] reported improvement of clinical disability, cessation of attacks, and disappearance of AQP4-IgG in 2 patients with severe NMOSD after allogeneic hematopoietic stem cell transplantation. In contrast, 14/17 patients with NMOSD described in 2 studies and treated with autologous hematopoietic stem cell transplantation had

further disease activity [138, 139]. Several registered clinical trials are underway to evaluate autologous mesenchymal or hematopoietic stem cell transplantation for NMOSD.

Third, granulocyte-, plasma cell-, cytokine-, or chemokine-directed therapies designed to modulate pathophysiologically relevant pathways are further potential treatments for NMOSD. Examples include antihistamines, bortezomib, and inhibitors of IL-8 or IL-17; however, these have not yet been investigated in the clinical setting.

Finally, antigen-specific therapies with curative properties might be developed and are of particular interest, given that the autoantigen is known in NMOSD. One approach is to block competitively the binding of AQP4-IgG to AQP4 (e.g., by the nonpathogenic human monoclonal antibody aquaporumab); others include enzymatic deglycosylation or cleavage of AQP4-IgG [29]. Furthermore, various techniques to restore immune tolerance to AQP4 derived from animal models and other human autoimmune diseases have been suggested or are in (pre-)clinical development [29, 140]. Examples are DNA vaccination [141], T-cell-based vaccines [142], peptide-coupling strategies [143], and adoptive transfer of tolerogenic dendritic cells or regulatory T cells [144].

## Conclusions

Treatment and prevention of attacks are equally important to control NMOSD, which often has an unfavorable prognosis. As the remission status of attacks determines long-term outcome and disability, aggressive therapy of NMOSD attacks is warranted. Apart from IVMP, TPE, and IA, which were derived from MS therapy and target cellular and humoral immune processes, inhibition of complement activation or other mechanisms relevant for disease pathogenesis might be helpful to treat NMOSD attacks. Approved immunosuppressive drugs and increasingly repurposed biologicals targeting specific immune processes are used for preventive therapy.

In contrast to MS, gradual progression of disability is uncommon in NMOSD, which should allow freedom of disease activity being reached simply through the prevention of attacks. Theoretically, the absence of attack-related inflammation could also release repair processes such as remyelination. Indeed, several studies investigating broad or selective immunosuppression reported an improvement of disability during the course of treatment [21, 81, 83, 84, 87, 92, 102, 121, 122].

A future goal is to transfer the current empiric treatment recommendations for NMOSD to an evidence based standard of care, which will only be possible by conducting randomized controlled trials [145]. First treatment trials are underway and will potentially broaden our therapeutic spectrum for NMOSD.

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**Compliance with Ethical Standards**

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