NMOSD: CURRENT AND EMERGING THERAPIES AND STRATEGIES

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Neuromyelitis optica (NMO; Devic's syndrome) consists of optic neuritis and transverse myelitis, the latter of which is associated with a longitudinally extensive spinal cord lesion on MRI (longitudinally extensive transverse myelitis (LETM)) [1]. NMO is typically severe, relapsing, results in early and permanent neurological disability, and relatively spares the brain. It is associated with a highly specific serum autoantibody marker, NMO-IgG, which targets the water channel aquaporin-4 [2-4], which has allowed for identification of a broader clinical and radiological spectrum of the disease (especially brain involvement), termed "NMO spectrum disorders (NMOSD) [1,5,6]. Numerous additional lines of evidence support the hypothesis that NMO is caused by antibody-mediated mechanisms and a central role for complement and that AQP4 antibodies have pathogenic potential [7-11]. In turn, these data support the use of immunosuppressive therapies aimed at the humoral immune mechanisms as the primary preventative therapeutic approach in NMO.

NMOSD Natural History and Relevance to Treatment

NMOSD is usually a relapsing disorder with recurrent attacks of optic neuritis and myelitis. Although a few patients may have only one near-simultaneous attack of optic neuritis and myelitis, fulfilling NMOSD criteria but having a 'monophasic' course, this is exceptional. NMO-IgG provides helpful prognostic information for patients presenting with a first-ever event of LETM; seropositive patients have a greater than 50% risk of myelitis relapse or conversion to NMOSD over the subsequent 12 months [12].

Recurrent optic neuritis and myelitis attacks in relapsing NMOSD result in stepwise accumulation of neurological disability. Within 5 years, more than 50% of such patients are functionally blind (visual acuity worse than 20/200) or have lost the ability to ambulate without assistance [13,14]. Cervical myelitis attacks may also involve the brain stem, a risk factor for neurogenic respiratory failure and associated medical complications. A later secondary progressive phase is rare in NMOSD, in contrast to multiple sclerosis, in which it is common and the major predictor of future disability [15]. Therefore, relapse prevention is of primary importance in NMOSD, likely having a much greater relative impact on disability than do current multiple sclerosis therapies on the course of that disease.

TREATMENT
Overview [16]
Acute attacks:
First line: Intravenous corticosteroids
Rescue: plasma exchange
Other considerations: intravenous immune globulin (IVIG), immunosuppression

Attack Prevention:
First line: Immunosuppression
Milder/less active disease: Azathioprine or mycophenolate mofetil in combination with prednisone
Severe/more active disease: Rituximab or general immunosuppression
Other considerations: maintenance plasma exchange

Treatment of Acute Relapses

1. Corticosteroids

The approach to treatment of NMOSD attacks is extrapolated from studies of MS and idiopathic optic neuritis because inflammatory demyelination underlies all of these disorders; there are no specific studies in NMOSD. Corticosteroids increase the likelihood of clinical improvement during the first five weeks after therapy for acute

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MS attacks; methylprednisolone may be of greater benefit than ACTH [17]. Intravenous administration is favored over oral therapy but increasing the treatment duration beyond five days does not appear beneficial. The Optic Neuritis Treatment Trial (ONTT) demonstrated that for acute optic neuritis attacks, intravenous methylprednisolone (1000 mg/d for 3 days followed by oral prednisone 1mg/kg/d for 11 days and a 4-day taper), but not oral prednisone monotherapy, increased the speed of visual recovery compared with placebo [18]. At 6 months follow-up, methylprednisolone therapy was associated with slightly better visual function (color vision and contrast sensitivity - but not visual acuity) compared with placebo but there was no significant impact on long-term visual function (more than 5-year follow-up) [18,19]. A meta-analysis showed that IV methylprednisolone reduced the risk of failure to improve by day 30 but did not improve long-term visual outcome [20].

The standard dosage of intravenous methylprednisolone (1g/d) for five consecutive days. Oral prednisone may be added afterward in preparation for long-term immunosuppressive therapy (e.g., with azathioprine).

2. Plasma Exchange

Patients with corticosteroid-refractory myelitis exacerbations benefit from rescue plasma exchange administered seven times on alternate days [21]. Fifty to 60% of NMOSD patients achieve functionally important benefit, usually after 1-3 exchange procedures [22,23] Early initiation of plasma exchange is associated with better clinical outcome.

3. Other approaches

Intravenous immunoglobulin (IVIG) is sometimes used for steroid-refractory attacks of MS but a report suggesting benefit [24] was not supported by two subsequent small controlled trials of 76 patients [25] and 19 patients [26] that compared combination methylprednisolone and IVIG to methylprednisolone alone. A recent small retrospective series suggested it may enhance recovery in some NMOSD patients with attacks refractory to steroids (with or without PLEX).[27]

A recent retrospective study showed that some patients with inflammatory myelitis, especially if severe, recurrent, and associated with features suggestive of systemic autoimmunity (abnormal serologies or diagnosis of lupus or Sjogren's syndrome) may respond to a combination of IV methylprednisolone, plasma exchange, and cyclophosphamide [28]. Selection bias is evident in the study but it may provide clues to responsive subgroups.

Relapse Prevention

Current approved immunomodulatory MS therapies such as beta-interferon or glatiramer acetate appear to be ineffective for NMOSD. Although a Japanese randomized controlled trial showed benefit of beta-interferon for MS, the study was not powered to detect an effect in the optic-spinal subgroup relevant to NMOSD [29]. However, NMO SDexacerbation has been reported with beta-interferon drugs,[30-32] natalizumab,[33] and fingolimod.[34]

Treatment strategies: Current concepts of NMOSD pathobiology and anecdotal treatment observations strongly suggest that immunosuppression is necessary to induce and maintain NMOSD remission.[35] For patients with relatively mild or recently quiescent disease, or for those patients with a first-ever LETM event and who are NMO-IgG seropositive (and therefore at high risk of relapse), the combination of azathioprine and oral prednisone may be used. Mycophenolate mofetil can be used in place of azathioprine if drug tolerability problems warrant. For more severe and active disease, the monoclonal antibody rituximab will induce rapid B lymphocyte-specific immunosuppression. At least five years of immunosuppressive therapy is recommended for NMO-IgG seropositive patients with a first LETM event and indefinite treatment for those with established relapsing NMOSD.

1. Azathioprine

One uncontrolled, open-label case series of seven patients showed that the combination of oral azathioprine and prednisone appeared to stabilize previously very active relapsing NMO. In addition, neurological function, as measured by the Expanded Disability Status Scale, also improved [36]. A study of 36 patients from Argentina included 29 who were treated with azathioprine (mean 2 mg/kg daily), with or without prednisone, with an apparent benefit on both relapse rate and clinical disability.[37] A series of 99 patients treated with azathioprine also showed lower relapse rate compared to pre-treatment rates.

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Azathioprine and prednisone combination therapy is a commonly used immunosuppressive regimen for relapsing NMO patients who do not need immediate 'induction'-type therapy because they have not had recent clusters of severe attacks or have been attack-free for a few months. Corticosteroids are used to provide rapid general immunosuppression until azathioprine is fully active.

The target dose of azathioprine is 2.5-3.0 mg/kg/d. Thiopurine methyltransferase levels should be checked before treatment initiation since deficiency increases risk of azathioprine-induced toxicity (one should consider substituting mycophenolate mofetil in this setting). Dose adjustments are required if the leukocyte count falls below 3000/mm^3 or the platelet count drops below 100,000/mm^3. There is a small increased risk of malignancy with long-term use. The onset of immunosuppression is delayed by 1-6 months and is associated with mild reduction in the leukocyte count and increase in mean corpuscular volume (MCV). Increase in the MCV by at least 5 points is associated with successful relapse prevention.

2. Prednisone

Low-dose oral corticosteroids (range: 5 mg every other day to 20 mg daily) are associated with reduced relapse frequency in NMO [38], however, we utilize them as a bridge to establish immunosuppression with a steroid-sparing agent because of their long-term adverse effects. The standard is to initiate oral prednisone at 1 mg/kg/d (usually 40-60 mg/d) along with the steroid-sparing agent. After 4-6 months, the dose may be gradually reduced by no more than 5 mg/week to achieve alternate day prednisone dosing; then more slowly, usually by 5 mg every 2 weeks, and discontinued if possible. Some patients have breakthrough attacks below a threshold prednisone dose (10-15 mg/d), in which case switching to another immunosuppression strategy may be warranted.

3. Mycophenolate mofetil

Mycophenolate suppresses B and T cell proliferation while theoretically leaving hemopoiesis and neutrophil number and activity unchanged, a potential advantage over azathioprine. Mycophenolate mofetil is a good substitute for patients at risk for azathioprine-induced toxicity due to thiopurine methyltransferase deficiency.

In a multicenter observational study of mycophenolate for neuromyelitis optica, 24 patients were followed for a median of 28 months (range, 18-89 months), 19 patients (79%) were continuing treatment.[39] The median duration of treatment was 27 months (range, 1-89 months) and the median dose of mycophenolate was 2000 mg/d. The median annualized posttreatment relapse rate was lower than the pretreatment rate (0.09; range, 0-1.5; and 1.3; range, 0.23-11.8, respectively; $P < .001$). Disability stabilized or decreased in 22 of 24 patients (91%). One patient died of disease complications during follow-up. Six patients (25%) noted adverse effects during treatment with mycophenolate.

The dosage is 1000 mg twice daily. Side effects include constipation, diarrhea, nausea, vomiting, hypertension, peripheral edema, headache, confusion, tremor, gastrointestinal bleeding, increased susceptibility to infections, sepsis, myelosuppression, increased risk for developing lymphomas or other malignancies.

4. Rituximab

This monoclonal antibody deletes CD-20+ B cells. Two reports showed that most patients experience disease stabilization for at least several months after rituximab administration, even in the setting of failure of one or more prior immunosuppressive agents [40,41]. A course typically consists of 1000 mg IV, repeated 2 weeks later.

B lymphocyte suppression lasts about 8 months for most patients; retreatment can occur when flow cytometry monitoring shows that CD19 counts (B cell marker) have re-emerged to >1% of the lymphocyte count. In a recently published prospective observational study, Kim et al evaluated whether safe and effective rituximab readministration could be guided by periodically measuring the frequency of CD27+ memory B cells in peripheral blood. [42] Patients received intravenous infusions of rituximab over a 24-month period. After induction with standard doses, retreatment need was monitored with CD27+ B cell counts every 6 weeks for the first year and every 8 weeks for the second year; the threshold for retreatment was 0.05% of peripheral blood mononuclear cells. Of 30 patients, 26 (87%) exhibited a marked reduction in ARR over 5 years (mean [SD] pretreatment vs posttreatment ARR, 2.4 [1.5] vs 0.3 [1.0]). Eighteen patients (60%) became relapse free after rituximab treatment. In 28 patients (93%), the disability was either improved or stabilized after rituximab treatment.

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5. Intravenous immune globulin

A small study suggested that IVIG may be effective for attack prevention, reporting near complete remission of previously active disease in 8 NMO patients over a mean of 19.3 months of therapy using a dose of 0.7 g/kg body weight IVIG daily for 3 consecutive days every 2 months [43].

6. Mitoxantrone

Mitoxantrone is FDA-approved for treatment of rapidly worsening relapsing-remitting or secondary progressive MS [44,45]. It inhibits B cell, T cell, and macrophage proliferation and impairs antigen presentation. One prospective 2-year case series reported that 4/5 patients with relapsing NMO experienced disease stabilization and MRI improvement after mitoxantrone therapy using 12 mg/m^2 monthly for 6 months followed by 3 additional treatments every 3 months [46]. A more recent Korean study [47] retrospectively assessed series of 20 patients treated most (n=13) patients with mitoxantrone 6 cycles of 12 mg/m^2 monthly intravenous infusions as an induction, followed by maintenance treatment of 6 to 12 mg/m^2 every 3 months up to a maximum dose of 100 to 120 mg/m^2. Median annualized relapse rate declined by 75% compared with pre-treatment rate; 50% of patients were relapse free. Median follow-up was 41 months, during which no serious adverse events were noted. Immunological studies showed a preferential reduction in CD27+CD19+ memory B cells in peripheral blood.

Contraindications include hypersensitivity to mitoxantrone, hepatic impairment, and left ventricular ejection fraction less than 50% and prior significant cardiovascular disease. Main side effects include alopecia, diarrhea, nausea, vomiting, headache, myelosuppression (frequent), menstrual disorders (amenorrhea, irregular periods), mucositis, reduced fertility, urinary tract infection, abnormal liver function tests, cardiac toxicity (related to cumulative total lifetime dose), hepatotoxicity, secondary leukemia and myelodysplasia. Cardiac ejection fraction (either with echocardiography or MUGA scan) is required prior to therapy and each subsequent dose or if symptoms or signs of congestive heart failure develop. Use of mitoxantrone requires a plan for transitioning to another therapy because of the limited time that it can be used.

7. Other Approaches

Systemic immunosuppression may be achieved using a variety of chemotherapeutic agents, including methotrexate [48]. It remains unclear whether NMO will respond to all forms of general systemic immunosuppression. Maintenance PLEX has been reported but there are few data.[49]

Emerging Therapies

Advances in the understanding of NMO disease mechanisms are contributing to rapid expansion of experimental options. A prospective study demonstrated good safety, tolerability, and preliminary efficacy of the monoclonal antibody eculizumab, which targets the terminal component of complement [50]. Only 2 possible attacks occurred amongst 14 AQP4-IgG seropositive individuals during one year of therapy and several relapses occurred after eculizumab was discontinued and the subjects transitioned to other immunotherapies. A phase 3 trial is ongoing.

An anti-CD19 monoclonal antibody called inebilizumab depletes a broader range of B cells and precursors than rituximab and is also being evaluated in a large randomized controlled trial.

Several case reports and series indicate that aggressive NMO, especially if it fails to respond to rituximab, can stabilize after therapy with tocilizumab, a monoclonal antibody that blocks the interleukin-6 receptor (IL-6 is associated with relapses) [51].

If NMO-IgG is confirmed to be the cause of NMO, more specific therapeutic strategies may be developed. Recent developments include the creation of aquaporumab, a monoclonal antibody that prevents AQP4-IgG binding, the identification of a number of small molecules that interfere with AQP4-IgG binding, and the possibility that sivelestat, a neutrophil protease inhibitor, could reduce NMO-IgG-mediated damage.[52-54] Reparative strategies are needed for NMO patients, most of whom are faced with lasting visual and ambulatory disability.

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