The Treatment of Neuromyelitis Optica: Present and Future Perspective

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Abstract

The treatment of neuromyelitis optica (NMO) should be considerably different between the acute phase and chronic phase.

In the acute phase, steroid pulse therapy with high-dose methylprednisolone is the first-line therapy to achieve swift remission and to prevent irreversible disabilities. If one or two courses of steroid pulse therapy are insufficient, plasma exchange should be urgently considered.

In the chronic phase, long-term immunosuppressive therapies, including low-dose oral corticosteroid therapy, is the mainstay therapy. These preventive therapies may be necessary several years or more and should not be casually interrupted, because the relapse rate without immunosuppressants is quite high in NMO. Azathioprine is one of the most widely used immunosuppressants that can spare the steroid dose when combined with oral corticosteroid, benefitting patients by reducing steroid-induced side effects. Rituximab is a monoclonal antibody that has been widely used as a preventive therapy, while other monoclonal antibodies such as eculizumab and tocilizumab have shown their superior efficacy in recent trials. The treatment of pain is also an important aspect in managing NMO patients.

Differing from multiple sclerosis, fingolimod, interferon-beta, and natalizumab should be avoided in NMO, because they could trigger relapse or exacerbate symptoms in some NMO patients.

It may be possible to develop preventive therapies for NMO in the future, including AQP4-Ab blocker therapy, and a more precise understanding of the pathomechanisms of NMO may lead to the development of more effective drugs. Furthermore, discovery of useful biomarkers that reflect the disease activity of NMO is definitely required for developing effective drugs for NMO treatment.

ABBREVIATIONS

NMO: Neuromyelitis Optica; AQP4-Ab: Anti-Aquaporin-4 Autoantibodies; MS: Multiple Sclerosis; AZA: Azathioprine; MMF: Mycophenolate Mofetil; CPA: Cyclophosphamide; EAE: Experimental Autoimmune Encephalomyelitis; PNH: Paroxysmal Nocturnal Hemoglobinuria; BBB: Blood-Brain Barrier; BCSFB: Blood-Cerebrospinal Fluid Barrier

INTRODUCTION

Neuromyelitis optica (NMO) is one of the most common autoimmune inflammatory neurological disorders, especially in Asian countries; it predominantly affects the optic nerves and spinal cord. Thus, its treatments are mainly focused on suppressing the hyperactivated humoral immunity and plasma cells that produce anti-aquaporin-4 autoantibodies (AQP4-Ab). Although it is uncertain whether the production of serum AQP4-Ab is the primary etiology in NMO, immunosuppression as well as depletion of serum AQP4-Ab is known to be highly effective both in the acute phase and in remission to prevent relapses. In this review, we summarize conventional NMO therapies which have already been established, and also describe some possible future therapies.

ESTABLISHED THERAPIES IN ACUTE PHASE OF NMO

The most important therapy in the acute phase is steroid pulse therapy (1 g/day of intravenous methyl-prednisolone (IVMP) for three to five days). Three to five days of IVMP can be repeated several times in refractory cases. If the IVMP isn't effective, plasmapheresis should be selected. A previous report about plasmapheresis for NMO patients showed it can be effective in almost half of NMO patients in the acute phase [1].
An important point of the acute phase therapy in multiple sclerosis (MS) and NMO is that immune-suppressive therapies should be swiftly administered in the earliest active phase known as “window of opportunity”. A previous report showed that early IVMP in NMO patients well preserved the thickness of the retinal nerve fiber layer, and reduced the irreversible loss of optic nerve axons [2]. As with firefighting, acute phase therapies should be done quickly within the period showing contrast-enhanced lesions. “Swiftly administer steroid in the acute phase, and deliberately reduce steroid during remission” is the basic concept in NMO treatment.

**ESTABLISHED RELAPSE PREVENTIVE THERAPIES IN CHRONIC STAGE OF NMO**

At present, low dose steroid therapy (5-15 mg/day of prednisolone) should be the mainstay of preventive therapy in NMO [3]. Such oral steroid administration may be necessary for long periods, because, in NMO, the relapsing risk significantly increases without steroid therapy. Differing from MS, interferon-beta or fingolimod could exacerbate the condition of NMO and should not be tried, as will be described later.

In addition to long-term low-dose corticosteroid therapy, immunosuppressive agents like azathioprine (AZA) or cyclosporine-A can be added as “escalation therapy”. Basically, most of the immunosuppressive agents have been reported to be effective in suppressing relapses in NMO. They are also known as “steroid-sparing” agents, and they can enable a decrease in the median dose of oral corticosteroid [4]. In some cases, immunosuppressants can enable patients to be steroid-free within several months. Though not yet reported in Japan, oral tacrolimus at 3 mg/day has been widely used to successfully reduce the oral corticosteroid dosage in NMO. Mycophenolate mofetil (MMF), which specifically prohibits T-cell and B-cell proliferation, is also widely used in western countries. There is a report describing the successful use of cyclophosphamide (CPA) in a refractory case of NMO accompanied by lupus erythematosus [5]. There is another report mentioning that a pulse dose of CPA (1g/day) showed no effect on relapse in NMO, and even could be lethal because of the side effects of the agent [6].

Rituximab (anti-CD20 monoclonal antibody), which achieves B-cell depletion in many autoimmune-mediated disorders, also came to be regarded as one of the preventive therapies for NMO. Many reports support the high efficacy of rituximab in preventing relapses of NMO [7-9]. The association with B-cells, in collaboration with T-cells, is thought to be stronger in NMO than in MS, and the efficacy of this agent will likely become more generally recognized. Usually, rituximab (375 mg/m²) is intravenously administered once weekly for 4 weeks as the initial “induction treatment”, and is regularly or irregularly added as “maintenance therapy” in reference to the serum level of CD19+ B-cell [7]. In a previous report high efficacy of relapse prevention was achieved by monitoring the serum CD27+ memory B-cells with flow cytometry to determine the timing for re-administering rituximab [9]. Though it is expensive, reinforcing regular low-dose oral corticosteroid with occasional rituximab according to the serum B-cell level may become more widespread in the future.

Though not a mainstay preventive therapy, intravenous mitoxantrone is also known to effectively reduce relapses in NMO [10]. This therapy should be cautiously considered in each patient before administration to avoid severe side effects.

NMO is likely to be accompanied by some other autoimmune-mediated disorders like SLE and Sjögren syndrome, and controlling such accompanying disorders is also important in the management of NMO patients.

**THERAPIES FOR CHRONIC PAIN IN NMO PATIENTS**

In NMO, acute or chronic pain is known to be more frequent and severe than in MS [11]. More than 80% of NMO patients are known to have suffered from some types of pain during their clinical course. Relieving such pain is also an important aspect in the management of NMO patients. For painful tonic spasms (PTS) in the acute phase of NMO, known to occur at a higher rate than in MS, carbamazepine would be the mainstay treatment, as in MS cases with PTS [12]. For chronic pain during the interval, pregabalin, gabapentin, duloxetine, tricyclic antidepressants, and tramadol are known to be effective.

**NON-RECOMMENDED THERAPIES IN NMO**

Fingolimod, a modulator of the sphingosine 1-phosphate receptor, is now regarded as one of the first-line therapies to prevent relapse in MS. On the other hand, fingolimod is suggested to exacerbate or trigger relapses in NMO patients [13]. In other words, if the disease condition has deteriorated in suspected MS patients after administering fingolimod, NMO should be suspected and serum AQP4-Ab should be examined.

Interferon-beta, one of the old first-line therapies to prevent relapses in MS, is also known to possibly exacerbate the disease condition and trigger relapses in NMO [14].

Though rituximab was expected to be an effective preventive monoclonal therapy for NMO, another monoclonal antibody, natalizumab (anti-VLA4 antibody), has been found to be less than optimal as a preventive measure in NMO. In one report, all of five NMO patients given monthly natalizumab under a primary diagnosis of MS showed accumulating disabilities with no suppression of the disease activity [15]. One of the patients even died during the clinical course. Natalizumab is now commonly used for MS patients, but should be avoided if AQP4-Ab is detected.

**POSSIBLE FUTURE THERAPIES IN ACUTE PHASE OF NMO**

Recently, intravenous immunoglobulin (IVIG) in the acute phase of NMO has been suggested to be effective for NMO patients refractory to IVMP [16, 17]. Also, in the remission period, monthly or bimonthly IVIG has been suggested to be effective for preventing relapses [17-19]. IVIG may take the place of plasmapheresis in the acute phase treatment of NMO, and regular IVIG could also become an effective preventive therapy in the future. Several clinical trials of IVIG in NMO patients are now underway.

A strong association with eosinophils is known in the pathology of the acute phase of NMO. A previous paper revealed
that the antihistamines cetirizine and ketotifen, both of which have an einosphin-stabilizing effect, decreased the severity of lesions in a mouse model of NMO [20].

In addition to eosinophils, numerous neutrophils are also known to appear in NMO lesions. A previous study reported that sivelestat, neutrophil elastase inhibitor, reduced the expression of cytokines (IL-17, IL-5, and IL-2) in Th17-induced experimental autoimmune encephalomyelitis (EAE), which is thought to be analogous to NMO [21].

Though these anti-granulocyte agents were used before a clinical trial, they could become a treatment for the acute phase in the future.

**POSSIBLE FUTURE PREVENTIVE THERAPIES IN NMO**

One of the candidates is glatiramer acetate (Copaxone), which is already one of the first-line MS preventive therapies in US and Europe. This drug has not yet been approved in Japan as of 2014, and a clinical trial is expected in the near future. The evidence for glatiramer acetate in NMO is insufficient, but there is a report suggesting its efficacy in preventing relapses of NMO [22]. As in MS, this agent could be one of the possible future therapies in NMO.

Another promising therapy using a monoclonal antibody other than rituximab is eculizumab (anti-C5 complement antibody), which is already widely used for patients of paroxysmal nocturnal hemoglobinuria (PNH). However, in an open-label trial, eculizumab was shown to be efficacious for NMO patients who were refractory to other treatments including rituximab, and to have a low rate of severe side effects [23].

Recombinant monoclonal anti-AQP4 antibody, which prevents pathogenic AQP4-Ab to bind AQP4 on astrocytes, has also been suggested as another possibility. In one report where recombinant AQP4-Ab was administered to a mouse model, the development of NMO was prevented without cytotoxicity [24]. Though the practicability is still uncertain, blocking antibodies could become new therapies in the future.

Other small-molecule inhibitors of AQP4-Ab binding, like antiviral arbidol, flavonoid tamarixetin, and several plant-derived berbamine alkaloids, were also shown to reduce astrocyte cytotoxicity in NMO, and could become candidate drugs [25].

Plasma cells in the peripheral tissues could also become possible targets. Previously, antibody-secreting plasma cells were believed to be short-lived and continuously replenished by signals from memory B-cells in chronic autoimmune-mediated neurological disorders. Later, a paper showed that a substantial fraction of plasma cells can survive in peripheral tissue for more than months or years, known as "long-lived plasma cells", and are possibly associated with long-term autoantibody production [26]. Such cells have already been detected in bone marrow and spleen. Though such plasma cells have already been detected in myasthenia gravis, but not yet in NMO.

Short-lived (recently activated) plasma blast is another possible target, and possibly a more likely target than long-lived plasma cells in NMO. Previously, it was detected in MS patients [27]. Recently, the abnormal expression of plasma blast in the serum of NMO patients has been reported [28], and another report showed that tocilizumab (anti-IL-6 receptor antibody) rapidly reduced the serum plasma blast count and AQP4-Ab level, together with reductions in the clinical severity [29]. This finding is quite suggestive and strongly supports the association of short-lived plasma blast in the pathogenesis of NMO.

In plasma cells or plasma blasts, which are terminally differentiated B cells, the expression of CD20 is thought to have already faded out. Though rituximab (anti-CD20 monoclonal antibody) is effective in NMO, more disease-specific cell surface target molecules likely exist. CD19, CD38, or CD138 could be possible target molecules, and monoclonal antibodies against these specific molecules may possibly benefit NMO patients in the future.

Dysfunctions of glia limitans are suggested to have a role in the pathophysiology of NMO, and could be another target in the future [30]. No matter where the primary origin of serum AQP4-Ab is, dysfunctions in the blood-brain barrier (BBB) or blood-cerebrospinal fluid barrier (BCSFB) seem to have a role in the etiology of NMO. Accordingly, agents modifying the BBB- and BCSFB-functions could benefit NMO patients as a preventive therapy in the future.

To develop more effective and well-tolerated NMO therapies, not only further elucidating its pathomechanism but also discovering more sensitive and specific biomarkers reflecting the disease condition will be necessary.

**CONFLICT OF INTEREST**

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