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Interleukin-6 Receptor: A Novel Therapeutic Target for Neuromyelitis Optica

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Abstract

Neuromyelitis optica (NMO) is an inflammatory disorder of the central nervous system causing optic neuritis and transverse myelitis. NMO typically has a worse prognosis than multiple sclerosis due the severity of the acute relapses which lead significant visual and motor impairment. Although the discovery of an NMO-IgG or aquaporin-4 antibody has led to greater understanding about the pathophysiology of the condition, there is currently still no approved treatment for NMO. In this article, will review how IL-6 receptor may be a promising therapeutic target for prevention of NMO relapses.

Introduction

Neuromyelitis optica (NMO), also known as Devic's disease, is an inflammatory disorder of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage primarily targeting optic nerves and spinal cord. While previously considered a severe subtype of multiple sclerosis, NMO has emerged as a distinct entity based on its unique clinical and immunologic profile. The pathogenesis of NMO is still unclear. However, the discovery of NMO-IgG or aquaporin-4 (AQP4) antibody, a circulating antibody targeting the dominant water channel in the central nervous system [1], has been critical in recent advancements in our understanding of the condition. NMO is now considered an anti-AQP4 antibody-mediated astrocytopathy, rather than primarily demyelinating disorder, such as multiple sclerosis. Whereas multiple sclerosis is thought to be largely a cell-mediated autoimmune disorder, the pathophysiology of NMO is not entirely clear though the humoral immune system is largely involved.

While there have been significant advancements in therapies for multiple sclerosis, NMO treatment practices are based on observational studies with no approved therapy currently. Given our increasing understanding of pathophysiology of NMO, including the important role of the humoral immune system, there is more optimism than ever for establishing a targeted therapy. In this article, we will highlight the current unmet need for a proven therapeutic agent to prevent NMO relapses, review how IL-6 receptor antagonists have demonstrated very promising initial data as potential therapeutic agents for NMO, and outline the multicenter, randomized controlled, phase III study underway.

Clinical Features of NMO/NMO Spectrum Disorders

NMO and NMO spectrum disorders (NMOSD) are clinically characterized by optic neuritis and longitudinally extensive transverse myelitis. The median age of onset of neuromyelitis optica is typically in the fourth or fifth decade, though it is occasionally seen in children and the elderly. Women are disportionately affected with a female-to-

male ratio of 5-10:1 [2]. NMO is typically overrepresented in non-Caucasian populations such Africans, East Asians, and Latin Americans, but the relative abundance of NMO may in actuality reflect a paucity of conventional multiple sclerosis in these populations.

NMO often carries a worse prognosis than MS, with greater attack severity and more rapid disease progression. An attack may occur over days, but recovery is variable and may span weeks to months. NMO typically has a relapsing course, with a 60% chance of a relapse within a year after the initial attack, and 90% chance of attack within 3 years [3]. Patients with NMO often have residual symptoms of visual impairment, limb weakness, and bladder dysfunction after an acute relapse, contributing to a rapid development of disability. Fatigue and pain are common in patients with NMO and further impact their quality of life and productivity.

Neuromyelitis Optica: A Distinct Disease Entity from Multiple sclerosis

Neuromyelitis optica and multiple sclerosis have proven to be very different clinical entities. MS is primarily a cell-mediated disorder, whereas NMO is primarily mediated by the humoral immune system. This is highlighted by studies showing NMO patients do not respond to standard treatments for MS such as interferon, natalizumab, and fingolimod, and actually can be harmed from these treatments [4-6]. The prognosis of NMO is typically worse than MS and the often devastating discrete acute attacks lead to significant disabilities.

Treatment for acute relapses include high dose intravenous methylprednisolone, plasma exchange, and in some cases, IVIG. As disability is directly related to number and severity of relapses, the mainstay of treatment of NMO has been preventing attacks through systemic immunosuppression. Agents such as rituximab, azathioprine, mycophenolate mofetil, and corticosteroids have been widely utilized for prevention of relapses. However, the optimal drug regimen and treatment duration are unclear given the lack of randomized controlled trials. This provides an opportunity to increase efforts in developing a targeted and effective treatment for NMO.

The Role of IL-6 in NMO

Our understanding of the pathophysiology of neuromyelitis optica has been significantly advanced with the discovery of the NMO-IgG or aquaporin-4 (AQP4) antibody. This antibody targeting the chief water channel in the central nervous system has been found in the majority of patients with NMO and NMOSD. Complement activation by NMO-IgG binding to AQP4 has been suggested as the ultimate mechanism for astrocyte cell destruction [7]. Transfer of anti-AQP4 antibody has been shown to exacerbate experimental autoimmune

encephalomyelitis in animal models [8]. Yamamura and colleagues have identified a CD19intCD27highCD38highCD180neg (and CD20neg) plasmablast B cell subset, which is associated with production of anti-AQP4 antibodies [9]. Survival of plasmablasts is promoted by interleukin-6 (IL-6), but not by other B cell survival factors. IL-6, secreted by T-cells and macrophages during infection and trauma, acts as both a pro-inflammatory and anti-inflammatory cytokine in different disease models. IL-6 was suggested to enhance antibody production by these plasmablasts, and anti-IL-6 receptor (IL-6R) blockade selectively inhibited survival of AQP4 antibody-producing plasmablasts *in vitro*.

In the cerebrospinal fluid (CSF) from patients with NMO, Th2 and Th17-related cytokines/chemokines like IL-6 and IL-17A are significantly increased compared with those from patients with non-inflammatory neurological diseases [10-12]. Serum IL-4 is also found elevated in NMO patients [13]. Therefore, Th2 and Th17 may play important roles in the pathogenesis of NMO. IL-6 together with TGF-β mediate Th17/Treg balance by promoting Th17 development and accelerating FoxP3 degradation [14]. Therefore an anti-IL-6R may block Th17 differentiation and facilitate Treg development resulting in a decrease of the ratio of Th17/Treg which maybe therapeutic to NMO. IL-6 can also promote Th2 differentiation by activating transcription mediated by a nuclear factor of activated T cells (NFAT) which leads to production of IL-4 by naïve T cells and promotes differentiation to effector Th2 cells [15]. Anti-IL-6 receptor will block IL-6 dependent Th2 differentiation and reduction of Th2-derived cytokine/chemokine production.

IL-6 Receptor Antagonist as a Possible Therapeutic Target for NMO

The above studies underscore the role of the humoral arm of the immune system in disease pathology for NMO. As IL-6 promotes survival of the plasmablasts producing AQP4 antibodies, it is a natural target for an immunomodulatory agent. This would be upstream of the complement activation step and potentially prevent cell death. Tocilizumab, a monoclonal antibody targeting the IL-6 receptor, is already approved for use in rheumatoid arthritis, systemic juvenile idiopathic arthritis (JIA), polyarticular JIA, and Castleman's disease. Several different global investigators have used tocilizumab off-label to successfully treat patients with NMO [16-18]. In all of these reports, the relapse rates and/or the Expanded Disability Status Scores (EDSS) have dropped dramatically.

Araki and colleagues published their initial positive results with IL-6R blockade in 36-year-old female patient with NMO and multiple relapses who had previously failed treatment with IFNβ, low-dose prednisone, and azathioprine. She received IV tocilizumab 8 mg/kg monthly for 6 months. Relapses ceased apart from one minor case and her EDSS improved from 3.5 to 2.0 [16]. Kieseier et al. describe a 34 year-old female with NMO, who continued to have relapses despite therapy with rituximab and alemtuzumab. She received IV tocilizumab 8 mg/kg every 4 weeks. Her EDSS improved from 8.0 to 4.0 in 2 months, and the patient was ambulatory with EDSS score of 2.5 after 1 year [17]. Ayzenberg et al. presented a case series of 3 patients with aggressive NMO despite complete CD-20 cell depletion from rituximab therapy. The patients were initiated on tocilizumab 6 mg/kg every 4-6 weeks. Their median annualized relapse rate (ARR) decreased from 3.0 to 0.6 [18,19].

A Phase III Multicenter Randomized Controlled trial of SA237, IL-6 Receptor Antagonist

These promising studies have led to a multicenter randomized controlled trial evaluating a new IL-6 receptor antagonist, SA237. Similar to toculizumab, this is a humanized anti-human IL-6R neutralizing monoclonal antibody, which has a longer plasma half-life. The study is a Phase III multicenter, randomized, double-blind, placebo-controlled study which compares the efficacy and safety of SA237 to placebo in patients with NMO and NMOSD. The study's primary objective is to demonstrate the efficacy of SA237 relative to placebo in delaying time to first relapse in the double-blind period. The study population will consist of patients aged 18 to 74 years with a diagnosis of NMO or NMOSD. The full trial is planned to enroll approximately 70 patients.

Potential Applications for Multiple Sclerosis

This trial opens the doors for investigational trial of SA237 in patient with NMO and could lead to a very effective treatment for NMO. Anti-IL-6R treatment may also hold promise for treatment of MS since the drug's mechanism of action may be by blocking the IL-6R on immune modulator cells such as B cells and T cells. In doing this it may cause an inability for the cells to respond the way they normally might in both NMO and MS patients. In MS, the Th17 cells are thought to contribute significantly to the disease pathology. Since anti IL-6 has been shown to have effect an on the Th17 cells, therefore it is very plausible that it can affect the Th17 population in MS patients. A reduction in this population could lead to a decrease in the pathogenesis of MS.

Conclusion

In the past decade, our understanding of the pathogenesis and immunological basis of neuromyelitis optica has improved substantially. It is an exciting time for neuromyelitis optica research as this knowledge may lead to new therapies that will transform this debilitating disease the way that the multitude of new agents for multiple sclerosis has changed its clinical practice. Moreover, we hope that IL-6 receptor antagonist may have applications in the treatment of multiple sclerosis as well. In this article, we reviewed that IL-6 receptor may serve as an important target for treatment of neuromyelitis optica. A multicenter clinical trial evaluating of the efficacy of IL-6 receptor blockade in preventing NMO relapse is currently ongoing. We hope a newfound molecular understanding of NMO will pave the way for drug development and provide a much-needed solution to individuals affected by neuromyelitis optica.

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