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Eculizumab: A Review in Neuromyelitis Optica Spectrum Disorder

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Video Abstract

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Abstract

Neuromyelitis optica spectrum disorder, or NMOSD, is a rare auto-immune demyelinating disease of the central nervous system. Now considered a separate disorder from multiple sclerosis, NMOSD can be severely disabling and life-threatening, with a reported mortality of between 7 and 32%. The hallmark of the disease is recurrent attacks of optic neuritis and/or transverse myelitis that result in accumulating, irreversible disability, including blindness and paraplegia. Approximately 75 to 90% of patients with NMOSD have a disease-specific, pathogenic IgG autoantibody against the aquaporin-4 water channel, or AQP4. This antibody is thought to bind to AQP4 on astrocyte foot processes at the blood-brain barrier. This causes damage to astrocytes and the blood-brain barrier itself through several mechanisms, including the formation of the membrane attack complex through activation of the complement component C5b9. Subsequent inflammation-related damage to other parts of the central nervous system leads to demyelination, neuron loss, and neurological deficit, evidenced by clinical symptoms such as vision loss associated with optic neuritis or paralysis of the lower limbs due to transverse myelitis. Eculizumab, a humanized monoclonal antibody, is the first agent to be approved for treating NMOSD in patients with the AQP4 autoantibody. Eculizumab inhibits activation of the terminal part of the complement cascade by binding to complement component C5, blocking the formation of downstream complement proteins that cause the nerve cell damage observed in patients with AQP4-IgG-seropositive NMOSD. While the exact mechanism of eculizumab in these patients is unknown, it is thought to inhibit AQP4-IgG-induced membrane attack complex deposition. Importantly, the critical immunoprotective and immunoregulatory functions of the complement proteins upstream of C5 are preserved, including C3b-mediated immune complex clearance and microbial opsonization. PREVENT was a phase 3, randomized, double-blind, placebo-controlled, multinational trial designed to determine the efficacy and safety of eculizumab for patients with AQP4-IgG seropositive NMOSD. The study enrolled 143 adults with AQP4-IgG seropositive disease, a history of relapses within the last 12 to 24 months, and moderate to severe disability. The primary endpoint of the trial was the time to the first relapse as identified by a treating physician and confirmed by independent adjudicators. Eculizumab significantly reduced the risk of relapse relative to placebo in the PREVENT trial. Relapses occurred in just 3% of eculizumab recipients compared with 43% of patients in the placebo group. Eculizumab was effective regardless of patient age, sex, geographic region, previous treatment with rituximab, and whether or not patients were receiving immunosuppressive therapies for relapse prevention during the trial. In addition, eculizumab improved patients' neurological and functional disability and health-related quality of life. Patients completing either treatment arm in the PREVENT trial were eligible to enter an open-label extension study in which everyone received eculizumab. Over 90% of the group of patients who received at least one dose of eculizumab in the randomized trial or the extension were relapse-free through 4 years of treatment. Eculizumab was generally well tolerated in the PREVENT trial. The most common treatment-emergent adverse events occurring more frequently with eculizumab than placebo were upper respiratory tract infection, nasopharyngitis, diarrhoea, dizziness and back pain. Most of these adverse events were considered unrelated to treatment. Thus, eculizumab is an effective, generally well-tolerated treatment for

AQP4-IgG-seropositive NMOSD, and is the first agent specifically approved for use in patients with this rare condition.