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New Drug Update

Zilucoplan: a novel therapeutic approach to treat generalized myasthenia gravis

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ABSTRACT

Myasthenia gravis (MG) is an autoimmune neuromuscular disease characterized by muscle weakness due to autoantibodies targeting the neuromuscular junction (NMJ). Zilucoplan, a novel complement inhibitor, has shown promise in managing generalized MG (gMG) by blocking the terminal complement cascade. This article provides an overview of Zilucoplan's pharmacological properties, including its mechanism of action, pharmacokinetics, and pharmacodynamics. Clinical trials, including a phase 3 trial (RAISE), have demonstrated Zilucoplan's efficacy in improving muscle strength and function, as measured by the MG-ADL (MG-activities of daily life) score, compared to placebo. The safety profile of Zilucoplan is favorable, with injection-site reactions being the most common adverse event. Notably, Zilucoplan effectively inhibits both wild-type and clinical C5 variants, expanding its potential utility for patients who do not respond well to existing treatments. While further research is needed to assess its long-term safety and efficacy, Zilucoplan represents a valuable addition to the therapeutic armamentarium for managing gMG.

Keywords: MG/gMG, NMJ, Complement, Acetylcholine receptor, Zilucoplan

INTRODUCTION

Myasthenia gravis (MG) is a relatively rare acquired, chronic, autoimmune neuromuscular disease characterized by autoantibodies that target proteins in the NMJ.[1] Although the chief target of the autoimmune assault often centres on the skeletal muscle nicotinic acetylcholine receptor (nAChR), additional antigenic targets within the NMJ have also been implicated.[2] MG impacts around 20 individuals per 100,000 worldwide.[3] While it affects people of all ages, its onset is typically observed in adulthood, more commonly affecting women under 40 and men over 60.[4] The hallmark symptom is fluctuating muscle frailty, exacerbated post-exertion and ameliorated by rest periods.[5] The manifestations can selectively impact distinct muscle groups, including musculature controlling eyelids, ocular and facial movements, speech (resulting in ptosis, diplopia, dysarthria and difficulty in mastication and swallowing), respiratory movements or upper and lower extremities (causing respiratory failure and ambulatory dysfunction).[5] Approximately 15% of patients with MG experience only ocular manifestations (ocular MG). In comparison, 85% progress to gMG, affecting the face, neck, hands and limbs.[4] Occasionally, the respiratory muscles may weaken significantly, reaching a state where assistance through mechanical ventilation becomes imperative-a condition termed as myasthenic crisis, demanding immediate and critical medical intervention.[6] Triggers for such crises include infection, stress, surgery, or an adverse reaction to medication. Roughly 15-20% of people with MG experience at least one episode of myasthenic crisis.[6]

While there is presently no definitive cure for MG, available therapeutic approaches focus on symptom management. These include plasmapheresis, monoclonal antibodies, or thymectomy (surgery to remove the thymus

gland). A noteworthy addition to the pharmacological arsenal is Zilucoplan (marketed as Zilbrysq®). This novel complement inhibitor gained FDA approval in October 2023 for managing gMG in adult patients exhibiting anti-acetylcholine receptor (AChR) antibody positivity.[7]

PHARMACOLOGICAL PROPERTIES OF THE DRUG

Mechanism of action

The complement system is an essential component of the innate immune system, playing a critical role in the body's response to pathogenic bacteria. The activation pathways of the complement system involve the enzymatic cleavage of the complement protein C5 by C5 convertases, resulting in the production of C5a, a potent anaphylatoxin, and C5b.[8-10] The cleavage of C5 also initiates the recruitment of C6, C7, C8, and C9 proteins. Upon binding with C6, C5b produces the terminal complement complex C5b9, a hydrophilic pore that spans the cell membrane. C5b9 prompts an influx of water and ions, leading to osmotic lysis of the targeted cell. Zilucoplan blocks C5 cleavage, inhibiting the generation of C5b9, also known as the membrane attack complex (MAC).[8,11] The terminal complement cascade has been implicated in the pathophysiology of various inflammatory and autoimmune disorders, including gMG.[12] This autoimmune disorder is characterized by pathogenic autoantibodies that bind to AChRs. The accumulation of MAC on the postsynaptic plasma membrane of the NMJ leads to muscle weakness and damage.[8-10,12-14]

Pharmacokinetics and pharmacodynamics

Zilucoplan is a subcutaneously injectable drug that reaches maximum effectiveness within 3-6 hours.[9-15] Healthy volunteers received single or multiple doses of Zilucoplan 0.2 mg/kg. The plasma concentrations were consistent with the in silico pharmacokinetic models, with maximum plasma concentration observed 3 hours post dose.[16] The approximate half-life was 7 days across all dose levels.[17] Steady-state plasma levels were predicted to be achieved at day 11 at a 0.2 mg/kg dose level.[16] Zilucoplan pharmacodynamic effects were studied in healthy volunteers using a sheep red blood cell lysis assay.[18] It showed rapid and dose-dependent inhibition of complement activity. A 12 week phase 2 study on patients with gMG confirmed the inhibition effect. A Zilucoplan dose of 0.3 mg/kg resulted in 97% inhibition, and 0.1 mg/kg resulted in approximately 88%. Zilucoplan effectively inhibited hemolysis induced by C5 variants, including the mutation associated with poor response to eculizumab.[16,19]

Drug interactions

Zilbrysq (zilucoplan) is found to interact with 59 other drugs. Upon investigating the interactions, it was discovered that 28 of these interactions were classified as major, 24 as moderate, and 7 as minor. Co-administering Zilucoplan with other C5 inhibitors is not recommended as it can have an additive effect on complement inhibition, which may increase the risk of infection. Administering drugs that affect the complement system, such as eculizumab and eculizumab, should be done cautiously as they can significantly impair the immune system's ability to fight infections. Additionally, certain drugs can moderately increase the risk of side effects from Zilucoplan or decrease its effectiveness. Examples of such drugs include immunosuppressant like azathioprine, cyclophosphamide, and methotrexate, as well as antibiotics like clarithromycin and erythromycin because antibiotics can inhibit an enzyme involved in metabolizing Zilucoplan, potentially increasing its blood levels and risk of side effects.[16]

Adverse effects

It is important to be aware of the potential adverse effects of Zilucoplan. Some of the most common ones, which affect more than 10% of patients, include reactions at the injection site, upper respiratory tract infections, and diarrhea. Other adverse effects seen in 1-10% of patients are urinary tract infections, nausea, vomiting, increased lipase, and amylase. Additionally, some adverse effects are not frequently reported, such as pancreatitis, pancreatic cysts, and a temporary increase in blood eosinophils.[19]

CLINICAL TRIAL

In a randomized, double-blind, placebo-controlled, phase 2 clinical trial, Zilucoplan demonstrated clinically meaningful complement inhibition in patients with AChR-positive gMG. Zilucoplan, a first-of-its-kind cyclic peptide targeting C5, appears to be a therapeutic option for the treatment of gMG based on available pharmacokinetic/pharmacodynamic data and phase 1 and 2 efficacy, safety, and tolerability data with limited long-term follow-up.[9]

RAISE was a double-blind, placebo-controlled, randomized phase 3 trial conducted at 75 locations in Europe, Japan, and North America. The 174 eligible patients with AChR-positive gMG, aged 18-74, and were enrolled in the study. Patients were randomly assigned to receive subcutaneous Zilucoplan 0.3 mg/kg or a matched placebo for 12 weeks. The primary efficacy endpoint was a change in MG-ADL score from baseline to week 12 in the modified intention-to-treat population. Treatment-emergent adverse events (TEAEs) were assessed in all patients. Patients assigned to zilucoplan showed a greater reduction in MG-ADL score than placebo. The most common TEAE was injection-site bruising. The incidence of serious TEAEs and serious infections was similar in both groups. The trial is registered at ClinicalTrials.gov.NCT04115293.[20]

CONCLUSION

Zilucoplan is a novel inhibitor of the C5 complement that shows promising treatment for gMG. Clinical trials demonstrate that it improves muscle strength and function, as measured by the MG-ADL score, compared to placebo. Additionally, it has a favorable safety profile, with injection-site reactions being the most common side effect.

The study highlights Zilucoplan's unique dual mode of action. Unlike eculizumab, it can effectively inhibit the activation of both wild-type and clinical R885 C5 variants. This characteristic broadens its potential use for patients who may not respond well to existing treatments. While the long-term safety and efficacy of Zilucoplan require further investigation, the current data suggests that it is a valuable addition to the treatments available for managing gMG.

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