

In This Issue

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Generalized Myasthenia Gravis



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Eculizumab for Refractory, Generalized Myasthenia Gravis

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Background: Generalized myasthenia gravis (gMG) is a rare, chronic, autoimmune neuromuscular disease causing weakness in skeletal muscles due to disruption of neurotransmission at the neuromuscular junction (NMJ).^{1,2} A majority of gMG patients have auto-antibodies which block and degrade acetylcholine receptors (AChRs); it is postulated that these auto-antibodies activate the complement cascade disrupting the neurotransmission process. Unfortunately, 10% to 15% of gMG patients are refractory or intolerant to conventional therapies (e.g., cholinesterase inhibitors, corticosteroids) creating the need for a new therapeutic modality.³⁻⁵ Since there was strong evidence suggesting the complement cascade plays a key role in the pathogenesis of gMG, eculizumab, a complement cascade inhibitor, previously approved by the Food and Drug Administration (FDA) for atypical paroxysmal nocturnal hemoglobinuria in 2007 and atypical hemolytic uremic syndrome in 2011, was evaluated for the treatment of anti-AChR antibody positive (anti-AChR+) gMG. It received FDA approval for adult patients with gMG who are anti-AChR+ in October 2017.⁶

Mechanism of Action: Eculizumab (Soliris®; Alexion Pharmaceuticals) is a humanized, mouse-derived, monoclonal antibody that binds to the terminal complement protein C5 inhibiting C5a and C5b formation.^{6,7} C5a acts as a potent pro-inflammatory mediator that attracts other inflammatory cells to the

site of damage, while C5b combines with other complement proteins to form C5b-9, also known as the membrane attack complex (MAC).^{3,5} It is thought that eculizumab can help maintain neurotransmission in patients with gMG by reducing potential C5b-9 or MAC-mediated deposition at the NMJ.

Key Clinical Trial: Eculizumab's FDA approval was based on one phase III randomized, double-blind, placebo-controlled, multicenter study (REGAIN).⁴ The 125 patients included in the trial were required to be diagnosed with anti-AChR+ refractory gMG disease. Of note, patients were allowed to continue the same dose and schedule of conventional gMG medications as long as they were maintained on a steady dose prior to and throughout the study period. Patients were randomized to receive either eculizumab (n=62) or placebo (n=63) for a total of 26 weeks. The majority of patients were white (76%), female (66%), and had an average gMG disease duration of 9.6 years. Patients were monitored for up to a total of 38 weeks during the trial. Efficacy was assessed by four validated gMG scoring systems. Two of these scoring systems were the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale and the Quantitative Myasthenia Gravis (QMG) score. The primary outcome of the mean-ranked difference in change between MG-ADL total score (analyzed by worst-rank ANCOVA) for eculizumab versus

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placebo, -11.7 (95%CI: -24.3 to 0.96; p=0.0698), did not achieve statistical significance. However, the secondary efficacy endpoints of the difference in change of scores from baseline for the eculizumab group versus the placebo group for MG-ADL, -1.8 (95%CI: -3.2 to -0.5; p=0.0077), and for QMG, -2.9 (95%CI: -4.6 to -1.2; p=0.0007), were statistically significant. Eculizumab was found to be superior to placebo for the incidence of any treatment-emergent serious adverse events (AEs) (15% vs. 29%, respectively), the amount of exacerbations (10% vs. 24%, respectively), the use of rescue therapy (10% vs. 19%, respectively), and the amount of admissions to the hospital (15% vs. 29%, respectively). Headache and upper respiratory tract infections were the most common AEs seen in both treatment groups, 16% of patients in the eculizumab group and 19% of patients in the placebo group. No deaths or cases of meningococcal infection occurred during the study period. The authors concluded that even though the primary outcome did not reach statistical significance, eculizumab should be considered as a potential therapy for gMG based on significant improvement depicted in the secondary outcomes.

Dosing and Administration: Eculizumab is administered as an intravenous infusion only. It may be diluted in sodium chloride 0.9% injection or dextrose 5% in water injection to a final admixed concentration of 5 mg/mL (e.g., 300 mg in 60 mL total volume). Eculizumab should be administered over 35 minutes for adult patients, but can be slowed to infuse over 2 hours if an adverse reaction occurs.^{6,7} It is important to note that supplemental doses are needed for those patients who receive plasmapheresis, plasma exchange, or fresh frozen plasma. For recommended dosing information please refer to Tables 1 and 2. All doses of eculizumab should be administered within 2 days of the specified time intervals listed in Table 1.⁶

Risk Evaluation and Mitigation Strategies (REMS): Due to the risk of meningococcal infection, eculizumab may be prescribed only through the Soliris® OneSource Safety Support Program by enrolled prescribers. Patients treated with eculizumab are indicated to receive the full series of both the MenACWY vaccine (e.g., Menactra®) and the MenB vaccine (e.g., Bexsero®). These vaccines should be administered at least 2 weeks prior to initiating therapy, unless the risks of delaying eculizumab therapy outweigh the risk of infection. Furthermore, if unvaccinated patients must undergo urgent treatment with eculizumab, they should be given antibiotic prophylaxis (e.g., ciprofloxacin or penicillin) until at least 2 weeks after meningococcal vaccination.^{6,8}

Table 1: Dosage for Eculizumab for gMG⁶

Indication	Induction (weeks 1-4)	Post-induction (week 5)	Maintenance
gMG	900 mg weekly	1200 mg 1 week after induction	1200 mg every 2 weeks

gMG=Generalized Myasthenia Gravis

Table 2: Supplemental Eculizumab Doses for PP/PE/FFPI⁶

Type of Intervention	Most Recent Dose	Additional Dose	Timing
PP or PE	300 mg	300 mg per session	Within 60 minutes after each session
	600 mg or more	600 mg per session	
FFPI	300 mg or more	300 mg per infusion	60 minutes prior to each infusion

PP=Plasmapheresis PE=Plasma Exchange FFPI=Fresh Frozen Plasma

Availability and Cost: Eculizumab is available as 300 mg single-dose vials each containing 30 mL of a 10 mg/mL sterile, preservative-free solution.⁶ The product has a suggested wholesale price (SWP) of approximately \$7828 per vial.⁷ Therefore, 6 months of eculizumab therapy would cost approximately \$400,000.

Formulary Status: The formulary status of eculizumab for the treatment of gMG is currently under review by the Cleveland Clinic Health-System (CCHS) Pharmacy and Therapeutics Committee.

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