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## Letter to the Editor: New Observation

# Managing Myasthenia Gravis with Eculizumab Monotherapy Through Pregnancy

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**Keywords:** Myasthenia gravis; Acetylcholine receptor antibody; Eculizumab; Monotherapy; Pregnancy

Myasthenia gravis (MG) is an autoimmune neuromuscular disorder, caused by autoantibodies targeting the neuromuscular junction. Immunosuppressive therapy (IST) including corticosteroids, mycophenolate mofetil (MMF), azathioprine, methotrexate, and rituximab, combined with cholinesterase inhibitors are the mainstay of MG treatment. In severe cases, intravenous immunoglobulin (IVIG) or therapeutic plasma exchange (TPE) can also be used. Despite the growing list of treatment options, about 10%–15% of the patients with generalized myasthenia gravis (gMG) respond inadequately to a combination of therapies or develop treatment intolerance. Therefore, they are defined as "treatment-refractory".[1] Eculizumab is humanized monoclonal antibody targeting the C5 complement. It was recently shown to be effective and well-tolerated in patients with refractory acetylcholine receptor positive generalized MG (AChR+ gMG) based on the phase 3 randomized, double-blinded, placebo-controlled study (REGAIN) and its open-label extension.[2–3] While the use of the eculizumab has been increasing since its approval, the efficacy of eculizumab monotherapy remains unclear. We report a case of treatment-refractory AChR+ gMG successfully managed with eculizumab monotherapy. In addition, the patient delivered a healthy infant while on treatment.

The patient is a 33-year-old female who was diagnosed with gMG in 2010 in the setting of ocular, bulbar, and generalized weakness. Anti-AChR antibody was positive. Single-fiber electromyography was consistent with a post-synaptic disorder of neuromuscular junction. Anti-muscle specific receptor tyrosine kinase (Musk) antibody was negative. Computed tomography (CT) chest revealed no evidence of thymoma. She underwent thymectomy a year following the diagnosis and the pathology was consistent with lymphoid hyperplasia. Pyridostigmine was used for symptomatic management. The patient was unable to tolerate steroids due to behavioral side effects. She was treated with MMF from 2012 to 2014. However, the treatment was disrupted several times due to pregnancy. The medication noncompliance led to several exacerbations requiring hospitalization. Concerning for teratogenicity, she was transitioned from MMF to IVIG in 2014 during her last hospitalization for exacerbation. Upon discharge, she was maintained on 2 g/kg of IVIG every 6 weeks. However, she was still quite symptomatic and unable to tolerate more frequent dosing due to severe headache with the infusion. She was a transition from IVIG to eculizumab in 2020. Her clinical symptoms rapidly improved with the four induction doses of eculizumab, as reflected in her MG metric scores (Figure 1). Given proximity of the medication induction and clinical improvement, spontaneous remission was deemed unlikely. She has remained clinically stable on maintenance eculizumab monotherapy for more than 2 years. On follow-up examination, she had no ocular or bulbar weakness. Her strength was normal in all muscle groups without fatigability. Pyridostigmine was available to be used on as needed basis, though she had minimal requirements for it. The patient was found to be pregnant a year after initiation of eculizumab. Since the safety profile of eculizumab during pregnancy was unclear, we provided the option of transitioning back to IVIG during pregnancy. The patient elected to continue eculizumab during the pregnancy. She delivered a healthy infant after an uneventful pregnancy. The infant had no MG symptoms neither at delivery nor at the current age of 8 months. The patient experienced mild shortness of breath during the last month of pregnancy, which was attributed to late-stage pregnancy based on her pulmonary function test. She otherwise remained clinically stable.

In the REGAIN study and its open-label extension, eculizumab was used as an add-on therapy to the existing ISTs.[2–3] Therefore, the efficacy of eculizumab monotherapy has not been fully evaluated. We report a case of refractory AChR+ gMG successfully managed with eculizumab monotherapy. Similarly, dose reduction of concomitant ISTs was reported after the initiation of eculizumab in a series of MG patients. Among those, two patients self-discontinued concomitant ISTs and remained on eculizumab alone for unknown periods of time.[4] In neuromyelitis optica spectrum disorder, a compliment-mediated disease mechanistically similar to MG, eculizumab monotherapy was shown to be effective and well-tolerated in a subgroup analysis of 33 patients from PREVENT trial and its open-label extension.[5] Based on these observations, it is reasonable to infer that eculizumab may have the potential to be used as monotherapy in gMG to decrease

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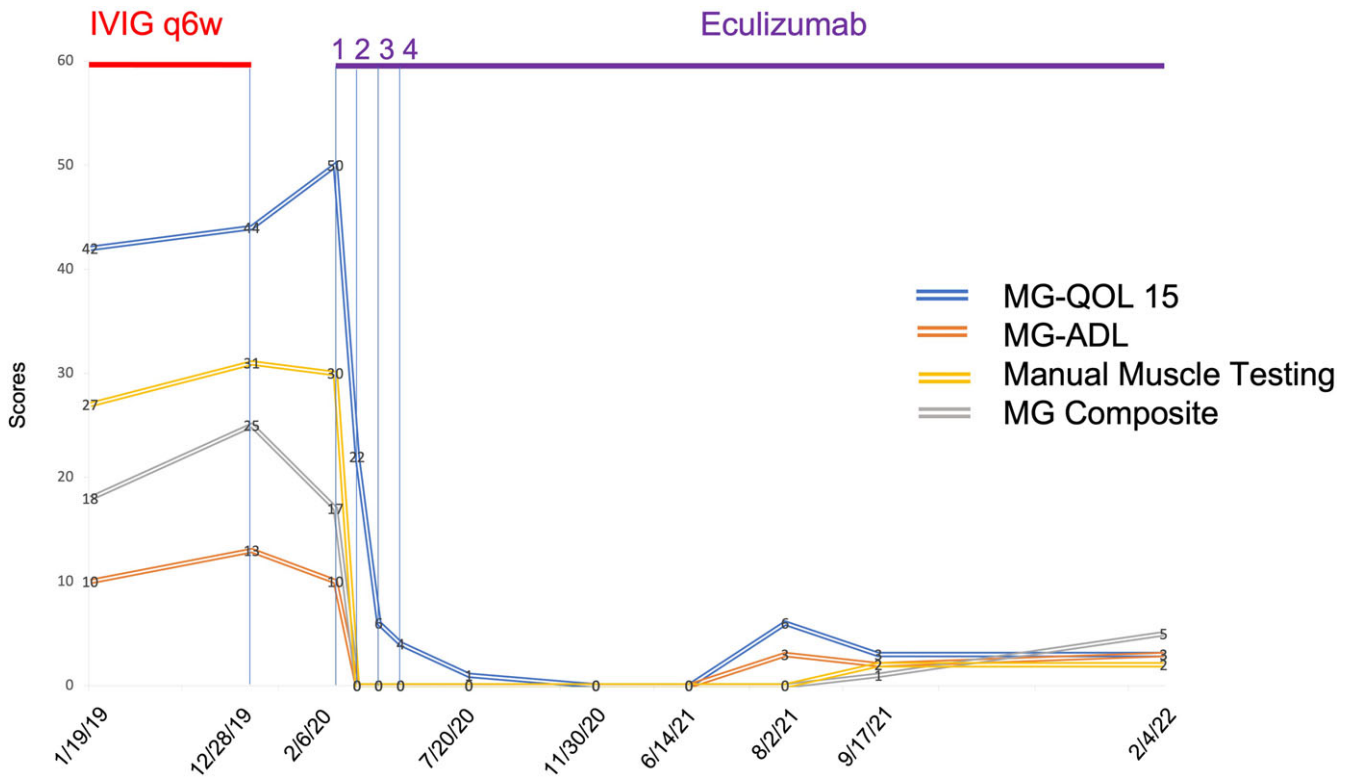


**Figure 1:** Treatment timeline and changes in MG metrics. Eculizumab was initiated 1 month after the discontinuation of maintenance IVIG. Improvement was seen immediately following the first dose of eculizumab. The patient has been in sustained remission on eculizumab monotherapy. MG-QOL 15: Myasthenia Gravis Quality of Life 15-item Scale; MG-ADL: Myasthenia Gravis Activities of Daily Living Scale; MG Composite: Myasthenia Gravis Composite Scale.

IST burdens in treatment-refractory patients. However, larger retrospective or prospective cohorts are needed to further validate this clinical observation.

The optimal transition from IVIG to eculizumab is another area of discussion. In this patient, eculizumab was administered 4 weeks after the last dose of IVIG infusion to avoid overlap as some evidence suggested that IVIG may decrease serum eculizumab concentration.[6] This is in line with the design in the REGAIN study where a 4-week washout period was required.[2] However, the prolonged washout period may cause treatment disruption and lead to clinical deterioration in patients with severe symptoms. A recent study showed that a more abbreviated transition period of 10–14 days may be feasible.[7] Alternatively, concomitant TPE can be considered as a bridging therapy to quickly achieve symptomatic control in patients with severe symptoms.

The safety of maintenance therapy during pregnancy is also of great interest since MG affects many female patients of childbearing age. The management of treatment-refractory patients is particularly challenging because one needs to balance the effective control of disease activity against the potential teratogenic effects of already limited IST options. Positive pregnancy outcome has been reported recently in a woman on eculizumab.[8] However, the real-world pregnancy safety data and experience on eculizumab in MG patient are still lacking. Limited experience with eculizumab in women with paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS) and hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome showed that eculizumab might be safe during pregnancy because it is not present in breast milk, and the levels in the umbilical cord blood are not sufficient to affect complement level in newborns.[9] Similarly, favorable maternal and fetal outcomes were demonstrated in a 10-year pharmacovigilance analysis in patients with PNH and aHUS.[10] The positive pregnancy outcome reported in this case further contribute to the current scarce safety data. Large-scale studies and long-term follow-up are needed to determine the safety profile of eculizumab during pregnancy.

**Conflict of Interest.** The authors have no conflicts of interest to declare.

**Statement of Authorship.** XL performed chart review, analyzed the data, and drafted the manuscript. AM acquired clinical data and revised the manuscript. Both authors have approved the final version of the manuscript.

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