Two-decade battle with myasthenia gravis: A breakthrough case report on the long-term success of eculizumab and ravulizumab treatment

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Two-decade battle with myasthenia gravis: A breakthrough case report on the long-term success of eculizumab and ravulizumab treatment

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Key clinical message:

Myasthenia gravis is a rare burdensome condition that severely impacts patients' quality of life—often exacerbated by side effects from long-term immunosuppressive therapy. Although effective therapies exist, more real-world evidence is needed to guide decision-making in refractory cases where treatment discontinuation is considered and can significantly worsen a patient's condition.

Introduction

Myasthenia gravis (MG) is a rare, chronic autoimmune disorder affecting the neuromuscular junction (NMJ).[1] MG is characterized by muscle fatigability and weakness, in most cases, initially only affecting the eye muscle but progressing to generalized MG (gMG) involving the muscles of the head, neck, trunk, limbs, and/or respiratory system in roughly 80% of patients approximately 2-3 years following disease onset.[2] Myasthenic crisis is a common complication of MG, affecting 15-20% of patients, and is characterized by respiratory failure requiring mechanical ventilation and intensive care and is often associated with substantial long-term physical and mental consequences.[2,3] The burden of MG is considerable, negatively impacting patients' daily activities; quality of life (QoL); and emotional, social, and economic well-being.[3] Furthermore, the current MG treatment algorithm, particularly long-term treatment with corticosteroids or nonsteroidal/nonspecific immunosuppressive therapies, have known serious, often troublesome, side effects and unpredictable treatment responses that lead to patient dissatisfaction and reduced treatment adherence, further complicating MG management.[1,3]

Targeted approaches to gMG management, namely eculizumab (Soliris®) and ravulizumab (Ultomiris®), were approved in the United States and Europe in 2017 and 2022,[4,5] respectively, with data from two open-label extension studies pointing to the long-term safety and sustained effectiveness of both

medicines.[2,6]Eculizumab is a humanized monoclonal antibody that binds specifically and with high affinity to the human terminal complement protein C5, preventing destruction of the NMJ and consequent muscle weakness and fatigability.[3] Ravulizumab is also a C5 inhibitor, engineered from eculizumab to have a longer half-life, maintaining therapeutic serum concentrations over an 8-week dosing interval (versus a 2-week interval with eculizumab).[5]

Despite the clinical benefits of these more targeted treatments, given the chronic nature of gMG, the likelihood of their success in disease management in the real world is multifactorial. Confirmation of their long-term effectiveness and safety in routine clinical practice and strategies for overcoming challenges associated with their accessibility (e.g., high cost and limited availability) are needed. We report a patient with 20 years of gMG, who after 16 years of refractory disease achieved and, importantly, has maintained a stable condition for the last 3 years with eculizumab/ravulizumab therapy.

Case history

A detailed description of the patient's history, including treatments and outcomes, are presented in **Figures 1 and 2** . Briefly, in 2004, a 77-year-old male was diagnosed with seropositive gMG with primary bulbar symptoms without thymoma. Therapy was initiated with prednisolone 40 mg, azathioprine 150 mg, and pyridostigmine 60 mg 4-6 times daily and the patient was stable for 12 months thereafter before experiencing his first myasthenic crisis (**Figure 1**). This first myasthenic crisis was acutely treated with plasmapheresis, followed by more prednisolone, azathioprine, and pyridostigmine (**Figure 1**). Over the next 10 years, the patient experienced several more myasthenic crises, which were treated similarly with varying responses (mostly with minimal success and in some cases worsening of MG) (**Figure 1**). In 2015, the patient received his first monoclonal antibody therapy (rituximab) without clinical improvement (**Figure 1**). In 2017, the patient discontinued azathioprine due to squamous cell carcinoma on the back of both hands, and azathioprine was replaced by mycophenolate mofetil (a different immunosuppressant) (**Figure 1**). Despite a rigorous treatment regimen, the patient continued to experience recurring myasthenic crises, prompting immunoadsorption every 2-4 weeks (**Figure 1**), with limited success.

Outcome and follow-up

The patient first received eculizumab in 2019, which significantly improved and stabilized his condition as assessed by several pertinent physician- and patient-reported outcome measures of MG symptoms and severity and QoL (Besinger, quantitative MG [QMG], MG activities of daily living [MG-ADL], and MG-QoL [15-item questionnaire] [MG-QoL15] scores) (**Figures 1 and 2**). Following a short discontinuation of eculizumab treatment in 2020 due to cost-associated challenges, the patient experienced MG regression, including a myasthenic crisis (**Figures 1 and 2**). However, the patient's condition quickly improved (within 12 days) upon reinitiating eculizumab. In 2022, the patient switched from eculizumab to ravulizumab without any complications and is currently still being treated with bi-weekly ravulizumab and reduced steroid intake (**Figures 1 and 2**).

Discussion and conclusion

Case reports highlighting eculizumab and ravulizumab as effective rescue therapy for MG are increasing, with emerging evidence supporting their positive impact on the disease's long-term progression.[7] The current case report confirms the long-term effectiveness and safety of eculizumab and ravulizumab as a rescue treatment for gMG in a patient who was unresponsive to conventional immunosuppressive therapies for 16 years. For this patient, eculizumab/ravulizumab treatment was a "game changer" in gMG management, not only because of a rapid improvement in clinical outcomes but also the fact that these targeted treatments have maintained efficacy over the last 3 years, with a significant positive impact on the patient's QoL.

Similar to a previous report,[8] discontinuing eculizumab resulted in significant worsening of the patient's condition. Considering discontinuation occurred due to accessibility issues, developing adequate strategies to support the accessibility and long-term use of targeted immunotherapy in life-long conditions such as gMG should be prioritized for the patient's well-being. Favorably, it is worth noting that the patient's condition

quickly improved upon reinitiating eculizumab treatment, on par with the previous report.[8] Additionally, the patient was successfully switched to ravulizumab—administered at a lower frequency and available at a lower cost—without any negative effect on clinical outcomes. This favorable response is in line with results from a recent study, where switching from eculizumab to ravulizumab was found to be effective for refractory acetylcholine receptor positive gMG patients in a clinical setting.[9] The patient has been receiving ravulizumab treatment since the switch in 2022 and is doing well, with the gMG under control.

As real-world evidence accumulates, the importance of complement C5 inhibitors in gMG treatment is becoming increasingly clear, with eculizumab and ravulizumab offering promising long-term management for patients with severe clinical conditions and refractory disease.

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Figure legends

Figure 1. Patient's medical history including timeline of events and course of illness and treatments. CD19-20, Cluster of Differentiation 19 and 20; MG, Myasthenia Gravis.

Figure 2. Patient's medical history including myasthenic crises (red circles), eculizumab and ravulizumab treatment regimens, and related patient- and physician-reported outcome measure scores assessing myasthenia gravis symptoms and severity, quality of life, and activities of daily living. MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-QoL15, Myasthenia Gravis Quality of Life 15-item questionnaire; QMG, Quantitative Myasthenia Gravis.

Key words: myasthenia gravis, generalized myasthenia gravis, eculizumab, ravulizumab, case report, real-world evidence

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