Poor response to Eculizumab in Caucasian Patients with Treatment Refractory Generalized Myasthenia Gravis: A case series

Nakul Katyal and Raghav Govindarajan

Department of Neurology, University of Missouri-Columbia, USA

ABSTRACT

Background

Eculizumab, a C5 complement inhibitor, has been approved to manage patients with treatment-refractory acetylcholine receptor positive (AChR+) Generalized Myasthenia Gravis (gMG). Though most patients receiving eculizumab experience clinical improvement, a small number of patients may respond poorly.

Objective

To report three cases of poor response to eculizumab in young caucasian patients with treatment refractory gMG.

Methods

Case Series

Results

All three patients were young, caucasian, thymectomized, females with MGFA class III, treatment-refractory MG on multiple immunosuppressant medications. All three patients had an initial worsening of MG- ADL score, one-month post eculizumab, followed by an unchanged MG ADL and MGC score three months after eculizumab therapy. No changes were noted in the number of acute exacerbations of MG, pre and post-eculizumab treatment. All patients were eventually started on maintenance Plasma-exchange (PLEX) therapy, post eculizumab failure, and had clinical improvement in MG-ADL and MGC scores and a reduction in the number of acute exacerbations of the disease.

Conclusion

The exact mechanism contributing to poor clinical response to eculizumab in gMG patients remains unclear. Further studies are warranted to undermine the underlying pathogenesis.

Introduction

Myasthenia gravis (MG) is an autoimmune, neuromuscular-junction disorder characterized by skeletal muscle weakness (1). Although established immunosuppressant therapies are effective in most patients with MG, 10–20% of patients are refractory to treatment (2). In Phase 3, a randomized, double-blind, placebo-controlled study (REGAIN) and its open-label extension, eculizumab, a recombinant humanized monoclonal antibody, was shown to be effective in patients with treatment-refractory AChR antibody-positive (AChR+) gMG (3, 4, 5). Eculizumab has been approved by Food and Drug Administration (FDA) for the management of patients with paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (HUS), and AChR+ gMG (6-8). Though most patients receiving eculizumab experience clinical improvement, many patients may respond poorly to eculizumab therapy.

In this case series, we have described three patients with treatment-refractory MG who had poor responses to eculizumab therapy. In addition, we reviewed the current literature highlighting possible mechanisms for poor response to complement inhibitor therapy.

Case Presentation

Patient 1

A 32-year-old thymectomized caucasian female with MGFA Class III, treatment-refractory MG on Prednisone 50 mg daily, pyridostigmine 60mg TID and IVIG 1g/kg/q4weeks with MG-ADL score of 9, MGC score of 30 was started on Eculizumab after vaccination against Neisseria meningitides, at an induction dose of 900 mg per week for four weeks (at Weeks 0, 1, 2, and 3), then at 1200 mg at Week 4, followed by 1200 mg every two weeks after that (7). 1-month post eculizumab initiation, her MG-ADL score worsened to 10, and no changes were noted in the MGC score. Her MG- ADL and MGC scores did not improve after three months of eculizumab use (Figure 1, 2). No changes were noted in the number of acute exacerbations of MG, pre and post-eculizumab therapy (figure 3). Given no clinical improvement, Eculizumab was eventually discontinued after three months. The patient experienced nausea with eculizumab use which was managed conservatively. The patient was then started on PLEX therapy with three exchange sessions every 4-6 weeks. Clinically meaningful improvement was noted in MG-ADL score (>2) six months post PLEX therapy which was maintained for up to 9 months. Clinically significant improvement was noted in MGC score (>3) three months post PLEX therapy and was maintained for up to 9 months (Figure 1, 2). Post

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives (by-nc-nd) License. (CC-BY-NC-ND 4.0: https://creativecommons.org/licenses/by-nc-nd/4.0/)

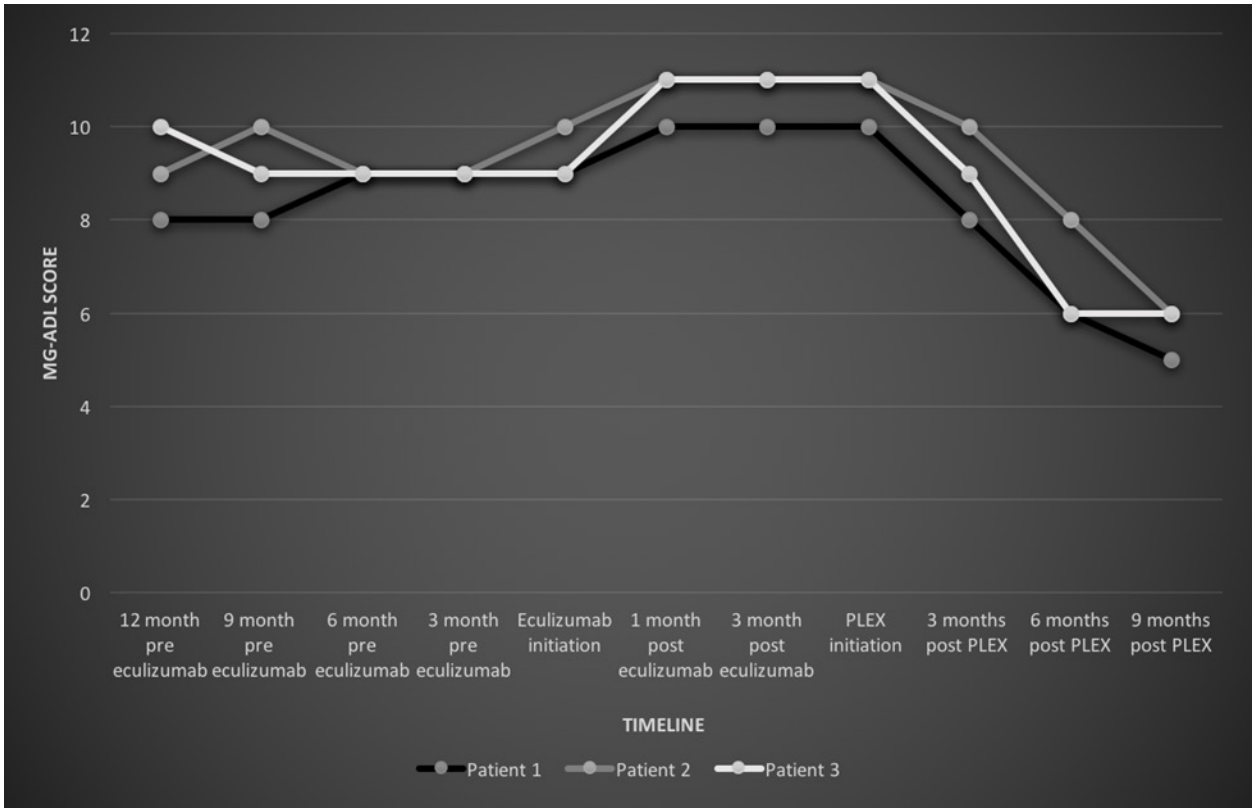

Figure 1: MG-ADL scores, before and after eculizumab initiation. MG-ADL: Myasthenia gravis activity of daily living score; PLEX: Plasma exchange.

PLEX initiation, the patient had two episodes of acute exacerbations at three-month intervals and none at the six-month interval (figure 3).

Patient 2

A 25-year-old thymectomized caucasian female with MGFA Class III, treatment-refractory MG on Prednisone 40 mg daily, pyridostigmine 60mg TID, and Cellcept 1000 mg BID with MG-ADL score of 10, MGC score of 33 was started on Eculizumab after vaccination against Neisseria meningitides, at an induction dose of 900 mg per week for four weeks (at Weeks 0, 1, 2, and 3), then at 1200 mg at Week 4, followed by 1200 mg every two weeks after that (7) (figure 1, 2). The MG-ADL score worsened to 11, 1-month post eculizumab initiation, and both MG- the ADL score and MGC score did not improve after three months of eculizumab use (Figure 1, 2). The patient experienced no side effects with Eculizumab. In the absence of clinical improvement, Eculizumab was discontinued after three months, and the patient was then started on PLEX therapy with three exchange sessions every 4-6 weeks.

After initiation of PLEX, clinically meaningful improvement was noted in MG-ADL (>2) and MGC score (>3) three months post-PLEX therapy, which was maintained for up to 9 months (Figure 1, 2). The patient had two episodes of acute exacerbations at the three-month interval and none at the six-month interval (Figure 3).

Patient 3

A 36-year-old thymectomized caucasian female with MGFA Class III, treatment-refractory MG on Prednisone 30 mg daily, pyridostigmine 60mg TID, Azathioprine 200 mg BID and IVIG 1g/kg/q4weeks with MG-ADL score of 9 and MGC score of 32. Her prednisone dose couldn't be increased due to side effects of weight gain and mood changes. Azathioprine was stopped after one month due to nausea. IVIG was stopped after three sessions due to headaches, refractory to medications. The patient was started on Eculizumab after vaccination against Neisseria meningitides at an induction dose of 900 mg per week for four weeks (at Weeks 0, 1, 2, and 3), then at 1200 mg at Week 4, followed by 1200 mg every two weeks after that (7).

Her MG-ADL score worsened 11 1-month post eculizumab initiation, and no improvements were noted in both MG- ADL score and MGC score three months post eculizumab use (Figure 1, 2). The patient experienced nausea with eculizumab use which was managed conservatively. Eculizumab was eventually discontinued, and the patient was started on PLEX therapy with three exchange sessions every 4-6 weeks.

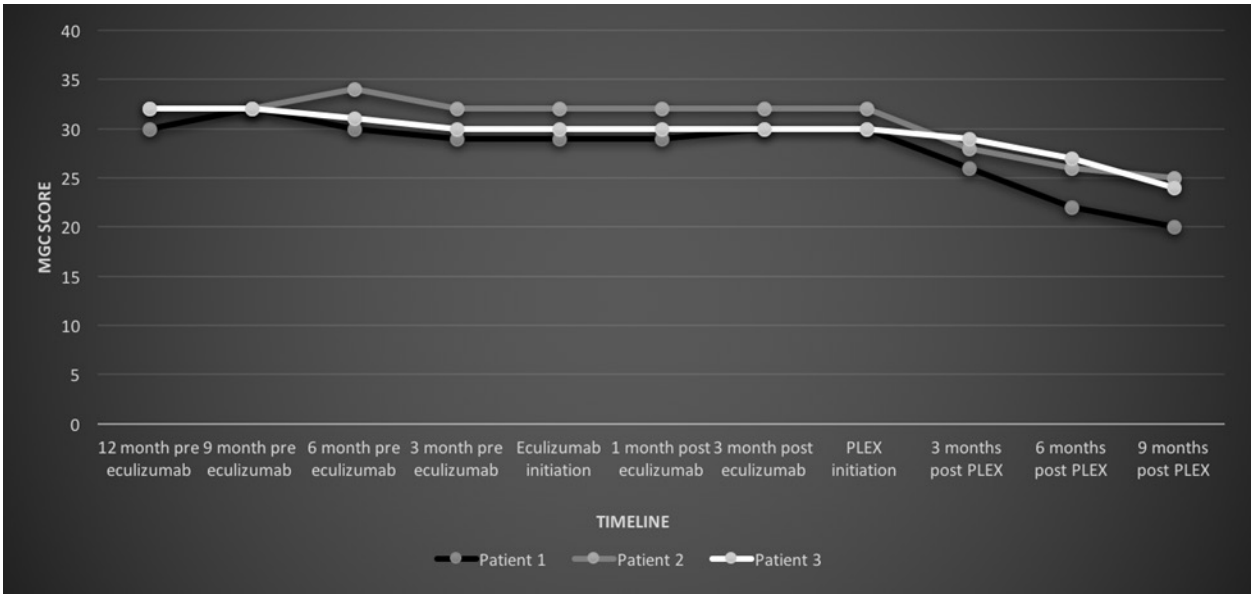

Figure 2: MGC scores, before and after eculizumab initiation. MGC: Myasthenia gravis composite score; PLEX: Plasma exchange.

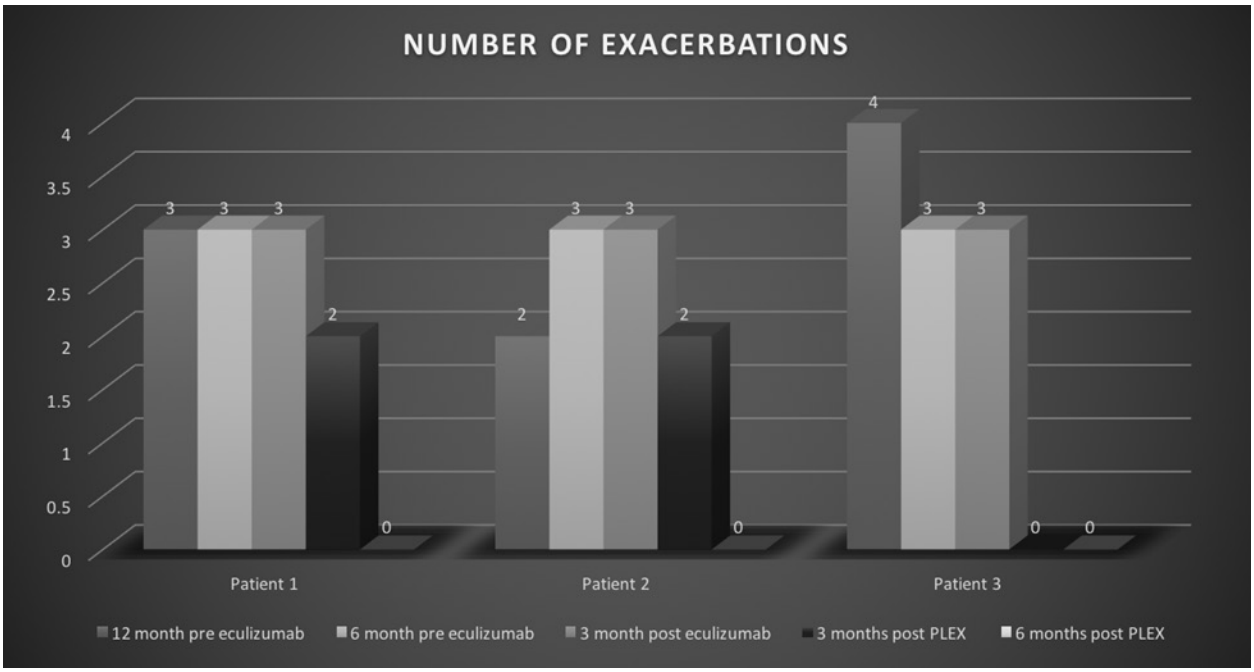

Figure 3: Number of exacerbations, pre and post eculizumab.

The patient had clinically meaningful improvement in MG-ADL score (>2) and MGC score (>3) three months post-PLEX therapy which was maintained for up to 9 months (Figure 1, 2). Post PLEX initiation, the patient had no acute exacerbations of MG at six months intervals (Figure 3).

Table 1 describes baseline demographics of patients included in the analysis.

Discussion

This case series highlighted poor response to eculizumab therapy in 3 patients with treatment-refractory MG. All patients had similar demographic and disease profiles. All three were young, caucasian, thymectomized, female patients with MGFA class III, treatment-refractory MG on multiple immunosuppressant medications. All three patients had an initial worsening of MG- ADL score, one-month post eculizumab, followed by an unchanged MG ADL

Table 1: Baseline demographics of patients included in the analysis

Patient	Age (years)	Gender	Ethnicity	MGFA class	Thymectomy	Therapy at eculizumab initiation	Duration of Eculizumab Therapy	Therapy post eculizumab
1	32	F	Caucasian	IIIa	Yes	Prednisone 50mg daily + Pyridostigmine 60mg TID + IVIG 1g/kg/q4weeks	3 months	PLEX every 4-6 weeks, 3 exchanges
2	25	F	Caucasian	IIIa	Yes	Prednisone 40mg daily + Cellcept 1000mg BID + Pyridostigmine 60mg TID	3 months	PLEX every 4-6 weeks, 3 exchanges
3	36	F	Caucasian	IIIa	Yes	Prednisone 30mg daily + Pyridostigmine 60mg TID, Azathioprine 200 mg + IVIG 1 gm/kg/q4 weeks	3 months	PLEX every 4-6 weeks, 3 exchanges

BID, twice daily; F, female; IVIg, intravenous immunoglobulin; M, male; MGFA, Myasthenia Gravis Foundation of America; qnw, every n weeks; TID, three times daily.

and MGC score three months after eculizumab therapy. No changes were noted in the number of acute exacerbations of MG, pre and post-eculizumab treatment. All patients were eventually started on maintenance PLEX therapy, post eculizumab failure, and had clinical improvement in MG-ADL and MGC scores and a reduction in the number of acute exacerbations of the disease.

In the REGAIN trial, six patients (10%) in the eculizumab group experienced acute exacerbation requiring rescue therapy (3). One of the patients had a worsening MG-ADL score from 13 at baseline to 18 and had to discontinue the study due to the MG crisis (3). The patient, unfortunately, died from crisis-related complications 90 days after the last eculizumab dose (3).

Genetic variations in the C5 complement can lead to poor response to eculizumab (9). Nishimura et al. assessed the sequences of the gene encoding C5 in Japanese patients with PNH with poor response to eculizumab. They noted all patients with inadequate response had a single missense C5 heterozygous mutation, c.2654 G->A, which predicts the polymorphism p.Arg885His (9). Another patient of Asian ancestry with a poor response to eculizumab had a similar mutation

c.2653C→T, which indicates p.Arg885Cys (9). Similar C5 polymorphism was reported in a Dutch patient with PNH with poor response to eculizumab who was noted as having a single C5 heterozygous missense mutation, c.2653C>A, which predicts p.Arg885Ser (10). The mutation at Arg885 results in the failure of binding and blockade of eculizumab at the C5 domain, accounting for the poor response (9). No similar studies have been conducted in MG patients with inadequate response to eculizumab.

Another potential mechanism for poor response could be the development of antidrug antibodies. However, studies looking into this possible mechanism have thus far been negative. The administration of any large-molecule therapeutics potentially induces an unwanted immune response by developing antidrug antibodies (11-14). Hillmen et al. evaluated the immunogenicity of eculizumab in PNH patients after long-term treatment and found no anti-eculizumab human anti-human antibodies (HAHs) in the enrolled patient population (11). Neutralizing antibodies to the C5 monoclonal antibody have not been found to the degree that inhibits the therapeutic effects of the drug (15).

The three pathogenic mechanisms for AChR antibodies include blockade of AChR channel function, antigenic modulation, and complement activation (15). In patients with poor response to eculizumab, the primary mechanism contributing to the clinical worsening of MG may not be complement activation.

This study has several limitations, including a need for proof of theory utilizing genetic testing. This was a case series of medical records at a single institution, with a small sample size and the need for a control group, limiting the findings' generalizability. More extensive controlled studies with a more robust design are warranted to explore the mechanism for poor response to eculizumab in treatment-refractory AChR+ gMG.

Conclusion

The exact mechanism contributing to poor clinical response to eculizumab in generalized MG patients remains unclear. Further studies are warranted to undermine the underlying pathogenesis.

Corresponding Author

Nakul Katyal[1]
CE 540, One Hospital Drive
Department of Neurology- University of Missouri
Columbia, USA, 65212

Declaration

All authors contributed to the work, agree with the presented findings, and that the work has not been published before nor is being considered for publication in another journal. The University of Missouri IRB approved the project, Approval #2058362. No animal subjects were involved. No financial support was obtained for this study. Both authors have no conflict of interest to report.

References

1. Juel VC, Massey JM. Myasthenia gravis. Orphanet J Rare Dis. 2007;2:44. doi: 10.1186/1750-1172-2-44.

2. Schneider-Gold C, Hagenacker T, Melzer N, Ruck T. Understanding the burden of refractory myasthenia gravis. Ther Adv Neurol Disord. 2019;12:1756286419832242. Doi: 10.1177/1756286419832242.

3. Howard JF, Jr., Utsugisawa K, Benatar M, Murai H, Barohn RJ, Illa I, et al. Safety and efficacy of eculizumab in anti- acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. Lancet Neurol. 2017;16(12):976-86. Doi: 10.1016/S1474-4422(17) 30369-1

4. Muppidi S, Utsugisawa K, Benatar M, Murai H, Barohn RJ, Illa I, et al. Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. Muscle Nerve. 2019; 60(1):14-24. doi: 10.1002/mus.26447

5 Howard JF, Jr., Barohn RJ, Cutter GR, Freimer M, Juel VC, Mozaffar T, et al. A randomized, double-blind, placebo-controlled phase II study of eculizumab in patients with refractory generalized myasthenia gravis. Muscle Nerve. 2013;48(1):76-84. doi: 10.1002/mus.23839

6. US Food and Drug Administration, "Drugs@FDA: soliris (BLA 125166)," 2018, https://www.accessdata.fda.gov/scripts/ cder/daf/index.cfm?event=BasicSearch.process.

7. Alexion Pharmaceuticals," Soliris (Eculizumab), Alexion Pharmaceuticals, Cheshire, CT, USA, 2018, https://www. accessdata.fda.gov/drugsatfda_docs/label/2018/125166s426lbl.pdf.

8. Katyal N, Narula N, Govindarajan R. Clinical Experience with Eculizumab in Treatment-Refractory Acetylcholine Receptor Antibody-Positive Generalized Myasthenia Gravis. J Neuromuscul Dis. 2021;8(2):287-294. doi: 10.3233/JND-200584. PMID: 33325394; PMCID: PMC8075396.

9.Nishimura J. [Genetic variants in C5 and poor response to eculizumab]. Rinsho Ketsueki. 2015 Jul;56(7):855-60. Japanese. doi: 10.11406/rinketsu.56.855. PMID: 26251149.

10.Saskia Langemeijer, Jun-Ichi Nishimura, Wynne Weston-Davies, Miles A Nunn, Yuzuru Kanakura, Ian J Mackie, Petra Muus; C5 Polymorphism in a Dutch Patient with Paroxysmal Nocturnal Hemoglobinuria (PNH) and No Asian Ancestry, Resistant to Eculizumab, but in Vitro Sensitive to Coversin. *Blood* 2015; 126 (23): 1209. Doi: https://doi.org/10.1182/blood.V126.23.1209.1209.

11.Hillmen P, Muus P, Szer J, Hill A, Höchsmann B, Kulasekararaj A, Risitano AM, Van Den Neste E, Liljeholm M, Ebrahim KS, Bedrosian CL, Gao X, Ames D, Socié G. Assessment of human antihuman antibodies to eculizumab after long-term treatment in patients with paroxysmal nocturnal hemoglobinuria. Am J Hematol. 2016 Mar;91(3):E16-7. doi: 10.1002/ajh.24280. PMID: 26690023.

12. Koren E, Zuckerman LA, Mire-Sluis AR. Immune responses to therapeutic proteins in humans–clinical significance, assessment and prediction. *Curr Pharm Biotechnol* 2002; 3: 349– 360.

13. Hwang WY, Foote J. Immunogenicity of engineered antibodies. *Methods* 2005; 36: 3– 10.

14. Nechansky A. HAHA—nothing to laugh about. Measuring the immunogenicity (human anti-human antibody response) induced by humanized monoclonal antibodies applying ELISA and SPR technology. *J Pharm Biomed Anal* 2010; 51: 252– 254.

15. Albazli K, Kaminski HJ, Howard JF Jr. Complement Inhibitor Therapy for Myasthenia Gravis. *Front Immunol*. 2020;11:917. Published 2020 Jun 3. doi:10.3389/fimmu.2020.00917