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Short Report

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Academic and Employment Status in Patients With Generalized Myasthenia Gravis Treated With Eculizumab: A Case Series

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Abstract

Objectives:
To evaluate the impact of treatment with eculizumab, a terminal complement inhibitor, on academic and employment status in patients with refractory generalized myasthenia gravis (MG).

Methods:
Case review of 7 US patients.

Results:
Six patients were aged ≤65 years; one was a full-time student and the remainder were in employment before MG diagnosis. After diagnosis, all patients gave up work (n = 3) or reduced their study/working hours (n = 4). In the 12 months after eculizumab initiation, patients who had stopped work resumed working in some capacity, whereas those who had changed their work/study hours returned to their original work/study pattern. Patients also experienced a reduction in the number of MG exacerbations, and a clinically significant improvement in MG–Activities of Daily Living scores, and were able to reduce other MG medications.

Conclusions:
These results suggest that treatment with eculizumab may help maintain education/employment activity in patients with refractory generalized MG.

Key Words: myasthenia gravis, classical complement pathway, employment, academic performance, activities of daily living

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INTRODUCTION

Myasthenia gravis (MG) is a rare chronic autoimmune disease estimated to affect approximately 60,000 people in the USA[1] and 56,000–123,000 people in Europe.[2] It is caused by antibodies that target proteins at the neuromuscular junction (NMJ), resulting in localized or (in most cases) generalized muscle weakness that affects the proximal muscles of the extremities and the trunk.[3,4] In approximately 85% of patients with MG, the autoantibodies are directed against acetylcholine receptors (AChRs).[5] Apart from causing functional AChR blockade and accelerated degradation of AChRs, anti-AChR antibodies activate the classical complement cascade, resulting in the formation of the membrane attack complex, which leads to localized damage to the postsynaptic membrane of the NMJ.[6]

Motor symptoms in patients with generalized MG (gMG) include diplopia, ptosis, dysphonia, dysarthria, dysphagia, dyspnea, and weakness in the arms, hands, fingers, legs, and neck.[7–9] Patients may also experience nonmotor symptoms, including pain, headache, autonomic dysfunction, and sleep disturbances,[9] and physical and/or mental fatigue is highly prevalent.[10] As a result, gMG can result in functional disability[11,12] and has a negative impact on patients' health-related quality of life (HRQoL).[13] The burden of the disease is even greater in the 10%–20% of patients who have treatment-refractory MG,[14] variously defined as failure to respond adequately to "conventional" therapies (steroids and nonsteroidal immunosuppressants); inability to reduce immunosuppressant therapy without clinical relapse; need for ongoing rescue therapy with intravenous

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immunoglobulin (IVIg) or plasma exchange; frequent myasthenic crises while receiving therapy; and/or intolerable side effects from immunosuppressive therapy.[15]

Although MG can affect people of all ages, the most common age of onset is 20–39 years in women and 50–70 years in men[16]—age groups that comprise much of the general workforce. These demographics, in the context of the impact of MG on functioning, raise the important question of the extent to which MG affects individuals' ability to study and work. In adults, it has been shown that MG can have a negative impact on work performance and lead to unemployment, premature retirement, and reduced income.[17–19] However, there is a lack of data on the impact of MG treatments on work-related outcomes. Eculizumab, a terminal complement inhibitor indicated in the USA for adults with anti-AChR antibody-positive gMG,[20,21] has been shown to improve patients' abilities to conduct everyday activities.[21] However, its effect on MG-related work impairment has not been evaluated. In this case series, we evaluated academic and employment status following a diagnosis of gMG and assessed whether this changed after the initiation of eculizumab.

MATERIALS AND METHODS

This was a retrospective analysis of data from a series of patients with treatment-refractory gMG who started treatment with eculizumab at a single center in the USA between 2018 and 2020. Patients were eligible for inclusion if data were available on their academic or employment status and clinical condition for 12 months both before and after treatment with eculizumab. A patient fulfilled the criteria for having refractory disease if they had received treatment with at least 2 immunosuppressive therapies (including corticosteroids), or at least 1 immunosuppressive therapy with IVIg or plasma exchange administered at least 4 times/year, for 12 months without symptom control.[21]

Information extracted from each patient's electronic medical record included: sex, age, and race; comorbid conditions; MG Foundation of America disease class; concomitant medications for MG; MG—Activities of Daily Living (MG-ADL) scores; number of exacerbations (assessed by the on-call board-certified neurologist, based on the presence of dysphagia, acute respiratory failure, or major functional disability that prevented physical activity, and other objective examination findings[22]) in the 12 months before and after eculizumab initiation; adverse events reported after eculizumab initiation; academic/employment status before diagnosis of MG, at the time of eculizumab initiation, and 12 months after eculizumab initiation; application for leave from work or change to working hours under the US Family and Medical Leave Act; and information on application for Social Security disability benefits.

All patients were vaccinated against *Neisseria meningitidis* before initiating eculizumab, as recommended in the prescribing information for the product.[20] Eculizumab was administered at an induction dose of 900 mg per week for 4 weeks (at Weeks 0, 1, 2, and 3), then at 1200 mg at Week 4, followed by 1200 mg every 2 weeks thereafter, as per the prescribing information for the product.[20]

The study was approved by the University of Missouri Independent Review Board (approval number 2023301).

RESULTS

Seven patients were included in the study; individual patient data are provided in Table 1. All patients were White and 5 (71.4%) were women. The age range at the time of eculizumab initiation was 18–72 years and 6 patients (85.7%) were aged ≤65 years. All 7 patients had comorbid conditions.

All patients had AChR antibody-positive gMG and at the time of eculizumab initiation, their disease was classified as MG Foundation of America class 2 A (n = 1), 2 B (n = 1), 3 A

TABLE 1. Demographics and Clinical Characteristics

Patient	Age (y)	Sex	Race	Comorbidities	MGFA Class	Thymectomy (timepoint)*	Thymus Pathology	MG Duration Before Eculizumab Initiation (y)	Concomitant Treatment on Eculizumab Initiation†	Concomitant Treatment 1 y After Eculizumab Initiation†	Adverse Effects After Eculizumab Initiation
1	56	M	White	Asthma, GERD, hypertension	3B	Yes (2 y)	Normal	3	1. Prednisone 40 mg 2. MM 1 g BID 3. Pyridostigmine 60 mg TID	1. Prednisone 5 mg 2. MM 1 g BID 3. Pyridostigmine 60 mg TID	Headache‡
2	72	M	White	COPD, diabetes mellitus, GERD, hypertension, hypothyroidism	2A	No	NA	5	1. Prednisone 40 mg 2. MM 1.5 g BID 3. Pyridostigmine 60 mg TID	1. Prednisone 20 mg 2. MM 1.5 g BID 3. Pyridostigmine 60 mg TID	None
3	65	F	White	Anemia, COPD	2B	No	NA	4	1. Prednisone 30 mg 2. IVIg 1 g/kg q4w 3. Pyridostigmine 60 mg TID	1. Prednisone 10 mg	Upper respiratory tract infection§
4	26	F	White	Anemia, hypothyroidism	3A	Yes (3 y)	Hyperplasia	3	1. Prednisone 40 mg 2. IVIg 1 g/kg q4w 3. Pyridostigmine 60 mg TID	1. Prednisone 10 mg 2. Pyridostigmine 60 mg TID	Upper respiratory tract infection§
5	38	F	White	Asthma, depression, GERD	3A	Yes (1 y)	Hyperplasia	2.5	1. Prednisone 20 mg 2. IVIg 1 g/kg q4w 3. Pyridostigmine 60 mg TID	1. None	Upper respiratory tract infection§

TABLE 1. (*Continued*)

Patient	Age (y)	Sex	Race	Comorbidities	MGFA Class	Thymectomy (timepoint)*	Thymus Pathology	MG Duration Before Eculizumab Initiation (y)	Concomitant Treatment on Eculizumab Initiation†	Concomitant Treatment 1 y After Eculizumab Initiation†	Adverse Effects After Eculizumab Initiation
6	24	F	White	Asthma, migraine	3A	Yes (1 year)	Normal	2	1. Prednisone 45 mg 2. MM 1 g BID 3. IVIg 1 g/kg q4w 4. Pyridostigmine 60 mg TID	1. Prednisone 20 mg 2. MM 1 g BID 3. Pyridostigmine 60 mg TID	Nausea¶
7	18	F	White	Hyperhidrosis	3A	No	NA	2	1. Prednisone 20 mg 2. IVIg 1 g/kg q4w 3. Pyridostigmine 60 mg TID	1. Pyridostigmine 60 mg TID	Body aches§

*Timepoint relative to eculizumab initiation.
†Daily doses unless otherwise stated.
‡Treated with acetaminophen (paracetamol).
§Self-resolving, no treatment required.
¶Treated with ondansetron.
Note that only eculizumab and pyridostigmine are licensed to treat MG in the USA.
BID, twice daily; COPD, chronic obstructive pulmonary disease; F, female; GERD, gastroesophageal reflux disease; M, male; MGFA, Myasthenia Gravis Foundation of America; MM, mycophenolate mofetil; NA, not applicable; q4w, every 4 weeks; TID, 3 times daily.

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(n = 4), and 3 B (n = 1). Before initiation of eculizumab, the duration of MG ranged from 2 to 5 years and all patients were taking medication to treat the condition (Table 1).

Patients' academic/employment status before and after diagnosis of MG and after initiation of eculizumab is summarized in Table 2. Before diagnosis of MG, 6 patients were working and 1 patient was a full-time student. After diagnosis, all 7 patients had a change to their status: 3 stopped work completely and 4 reduced the number of days worked or in school per week. Among the 6 patients who were working, 3 changed their working circumstances under the Family and Medical Leave Act and 3 applied for disability allowance. In the year after initiating eculizumab, patients who had stopped working were able to resume employment, in at least some capacity, in a different job role or by reducing the number of days worked per week, whereas those who reduced their work/study hours were able to return to their original work/study pattern (see Table 2).

Compared with the 12 months before eculizumab initiation, there was a reduction (improvement) in MG-ADL scores and number of MG exacerbations in the 12 months after its initiation (Figs. 1A, B). Furthermore, after starting eculizumab, 5 patients had their steroid dose reduced and 2 stopped taking steroids completely; and 2 patients were able to discontinue pyridostigmine treatment (Fig. 1C).

Eculizumab was well tolerated. There was one case of headache (treated with acetaminophen [paracetamol]), one case of nausea (treated with ondansetron), one case of body aches (which did not require treatment), and 3 cases of self-resolving upper respiratory tract infection; all occurred

TABLE 2. Academic/Employment Status

Patient	Employment			FMLA†	Disability Application
	Before MG Diagnosis	Change After MG Diagnosis, at Time of Eculizumab Initiation	1 y After Eculizumab Initiation		
1	Welder (4 d/wk)	Stopped working	Shopping center bagger*	NA	Yes
2	School guard (5 d/wk)	Reduced to 3 d/wk	Resumed work as school guard 5 d/wk	Yes	No
3	High-school teacher (5 d/wk)	Stopped working	Resumed work as teacher 3 d/wk	NA	Yes
4	Piano teacher (5 d/wk)	Reduced to 3 d/wk	Resumed work as piano teacher 5 d/wk	Yes	No
5	Customer service advisor (6 d/wk)	Reduced to 3 d/wk	Resumed work as customer service advisor 6 d/wk	Yes	No
6	House maid (7 d/wk)	Stopped working	Resumed work as house maid*	NA	Yes
7	Student preparing for pre-law school	Reduced school hours	Full-time pre-law school student	NA	NA

*Information not available on number of days worked.
†Patients changed their working hours under the FMLA.
FMLA, Family and Medical Leave Act; NA, FMLA not available.

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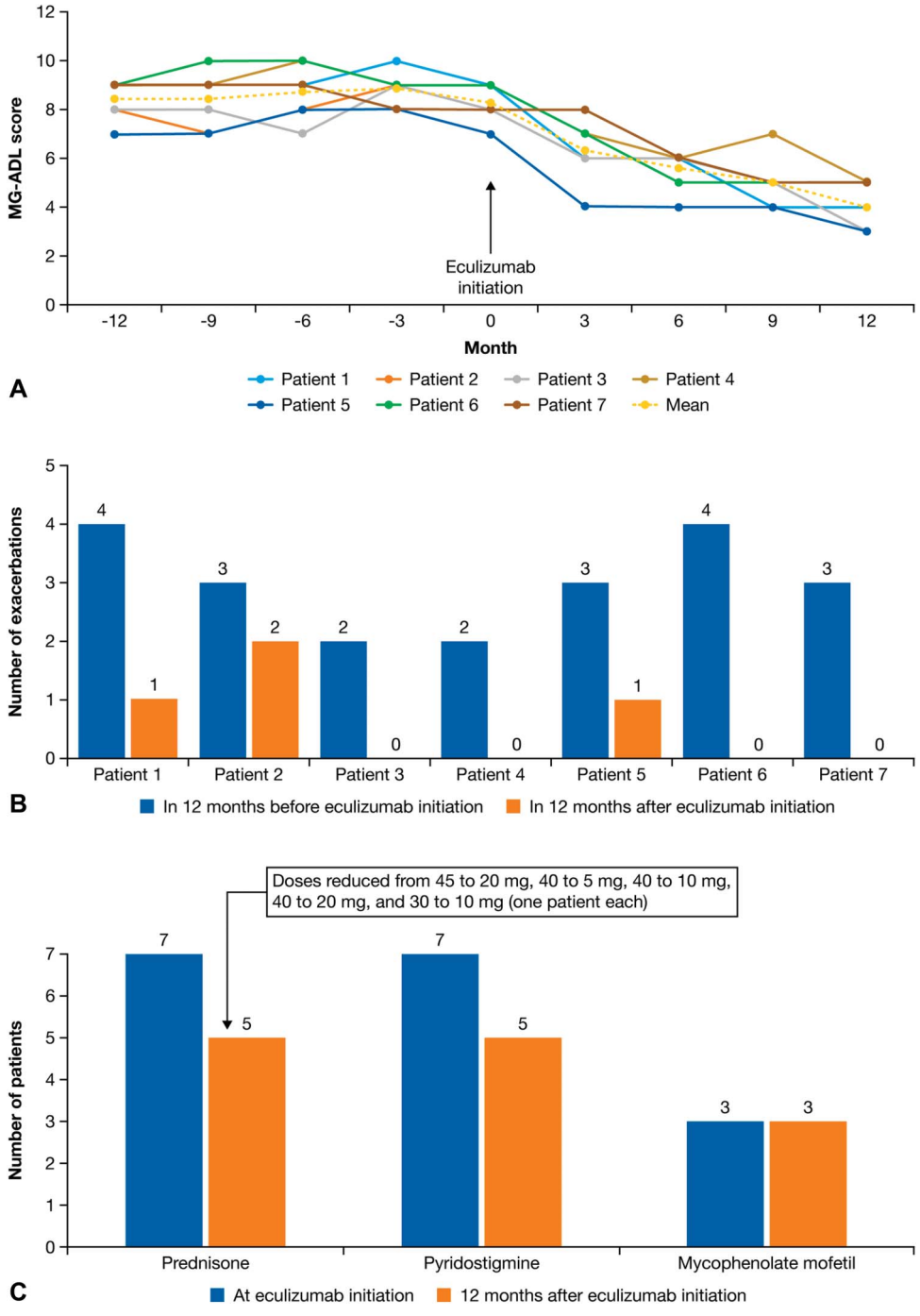

FIGURE 1. (A) Total MG-ADL scores, and (B) number of exacerbations in the 12 months before and after eculizumab initiation; and (C) concomitant medications at and 12 months after eculizumab initiation.

within 1 week after eculizumab infusion. All were mild in severity and resolved spontaneously or after standard care, and none resulted in the discontinuation of eculizumab. One patient reported no side effects.

DISCUSSION

The results from the current case series indicate that refractory gMG greatly affects patients' ability to study or work. After their

MG diagnosis, all 6 patients in this cohort who were previously employed reduced the number of days they worked or gave up work completely, either by changing the number of hours worked (under the Family and Medical Leave Act) or claiming disability benefits. These findings are consistent with larger studies evaluating the effect of MG on work-related outcomes. For example, in a cross-sectional study of 49 patients with MG, 39% became unemployed, 47% had to retire prematurely, and 47% had a reduction in monthly income after diagnosis.[19] In another study in >900 patients with MG, 47% reported that their income had decreased by ≥50%.[23] Moreover, in a meta-analysis of data from 3600 patients with MG, only 50% were in employment, which is low considering that the average age was ~48 years.[17] In addition to the impact on the individual's socioeconomic status, the consequences of reduced productivity (presenteeism), absenteeism, or early retirement place a burden on society in terms of indirect costs, including disability benefits and costs incurred via the Family and Medical Leave Act in the USA. Published data on this topic are sparse. In a recent systematic review of the economic impact of MG, only 2 relevant studies were identified; these reported per-patient indirect annual costs (2018) as $80 in India and $3550 in Germany.[24]

In our case series, after initiating eculizumab, all previously employed patients were able to return to work (if they had previously given it up) or resume their prediagnosis number of working hours. In addition, the young woman who had to reduce her school hours was able to enroll in pre-law school as planned before the MG diagnosis. These changes were also accompanied by improvements in clinical outcomes. After eculizumab initiation, we observed a reduction (improvement) in MG-ADL scores. At Month 12, the magnitude of the decrease was ≥2 points (the threshold for a clinically relevant change[25]) in all patients. We also observed a reduction in the number of exacerbations in all patients; 4 patients had no exacerbations in the 12 months after treatment initiation (compared with 2–4 events in the 12 months before eculizumab initiation). Furthermore, at the time of the last assessment, all patients were able to reduce their dose of prednisone or stop taking it completely, an important observation given the burdensome side-effect profile of corticosteroids.[26,27] All patients stopped maintenance IVIg treatment shortly after initiating eculizumab. Although it may be effective for acute MG exacerbations[28] and as maintenance therapy, IVIg can cause side effects such as headache, chills, myalgia, transient hypertension, and fluid overload.[29] In a study evaluating the impact of MG treatment side effects on patients' daily lives, patients in the "refractory with IVIg" group had higher mean scores (ie, their lives were more impacted) than those in the "refractory without IVIg" and nonrefractory groups.[30] In addition, maintenance IVIg is typically administered over 2 days each month, which may be inconvenient for patients.

Eculizumab is a recombinant humanized monoclonal antibody that binds to the C5 complement protein, thus preventing activation of the terminal complement pathway and subsequent destruction of the NMJ.[31] In the USA, it is indicated for anti-AChR antibody-positive gMG,[20] based on the results of the Phase 3 REGAIN study.[21] Data from REGAIN and its open-label extension have also shown that eculizumab treatment is associated with improvement in patients' HRQoL versus placebo.[32] In the context of the current study, it is notable that academic/employment status affects HRQoL in patients with MG.[33–35] Likewise, the number of MG medications, presence of uncontrolled disease, and exacerbations during the previous year, all of which improved after eculizumab initiation in the current study, have been shown to negatively affect HRQoL.[36] The demonstrated positive impact of eculizumab on fatigue,[37] a symptom of MG that may contribute to work (and other functional) impairments,[17,37] is also of interest and warrants further investigation.

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As with all case series, limitations of the current study include the small number of patients, the nonrandom retrospective selection of patients, and the lack of control group. As such, it is not possible to infer a causative association between eculizumab treatment and improved work/study status. One may expect that any treatment that improves symptoms in patients with MG may positively affect the ability to work or study, but there is a lack of data on the effect of MG treatments on work-related impairment. The current results offer insights into the potential positive impact of eculizumab, and add to the body of data on the effects of eculizumab on traditional clinical and real-world, patient-centric outcomes in patients with refractory gMG.

In conclusion, the results from this small case series provide additional evidence on the positive impact of eculizumab treatment on the daily lives of patients with gMG, allowing them to resume study or employment/livelihood. Given the demographics of this disease and the potential impact of unemployment or early retirement on individuals and society as a whole, this is an interesting finding that warrants further study.

REFERENCES

1. Phillips LH. The epidemiology of myasthenia gravis. *Semin Neurol*. 2004;24:17–20.
2. Nel M, Heckmann JM. Epidemiology and genetics of myasthenia gravis. In: Kaminski HJ, Kusner LL, eds. Myasthenia Gravis and Related Disorders Third edition. Switzerland: Springer; 2018:71–84.
3. Beloor Suresh A, Asuncion RMD. Myasthenia Gravis. Treasure Island (FL). StatPearls Publishing LLC; 2020.
4. Gilhus NE. Myasthenia gravis. *N Engl J Med*. 2016; 375:2570–2581.
5. Phillips WD, Vincent A. Pathogenesis of myasthenia gravis: update on disease types, models, and mechanisms. *F1000Res*. 2016;5:F1000Res.
6. Gilhus NE, Tzartos S, Evoli A, et al. Myasthenia gravis. *Nat Rev Dis Primers*. 2019;5:30.
7. Al-Haidar M, Benatar M, Kaminski HJ. Ocular myasthenia. *Neurol Clin*. 2018;36:241–251.
8. National Institute of Neurological Disorders and Stroke. Myasthenia Gravis Fact Sheet; 2020. Available at: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Myasthenia-Gravis-Fact-Sheet. Accessed April, 2021.
9. Tong O, Delfiner L, Herskovitz S. Pain, headache, and other non-motor symptoms in myasthenia gravis. *Curr Pain Headache Rep*. 2018;22:39.
10. Ruiter AM, Verschuuren JJGM, Tannemaat MR. Fatigue in patients with myasthenia gravis. A systematic review of the literature. *Neuromuscul Disord*. 2020;30:631–639.
11. Leonardi M, Raggi A, Antozzi C, et al. Identification of international classification of functioning, disability and health relevant categories to describe functioning and disability of patients with myasthenia gravis. *Disabil Rehabil*. 2009;31:2041–2046.
12. Vinge L, Jakobsen J, Andersen H. Muscle weakness and functional disability in patients with myasthenia gravis. *Muscle Nerve*. 2019;59:218–223.
13. Boldingh MI, Dekker L, Maniaol AH, et al. An up-date on health-related quality of life in myasthenia gravis -results from population based cohorts. *Health Qual Life Outcomes*. 2015;13:115.
14. Schneider-Gold C, Hagenacker T, Melzer N, et al. Understanding the burden of refractory myasthenia gravis. *Ther Adv Neurol Disord*. 2019;12: 1756286419832242.
15. Mantegazza R, Antozzi C. When myasthenia gravis is deemed refractory: clinical signposts and treatment strategies. *Ther Adv Neurol Disord*. 2018;11: 1756285617749134.
16. Bubuioc AM, Kudebayeva A, Turuspekova S, et al. The epidemiology of myasthenia gravis. *J Med Life*. 2021;14:7–16.
17. Guastafierro E, Tramacere I, Toppo C, et al. Employment in myasthenia gravis: a systematic literature review and meta-analysis. *Neuroepidemiology*. 2020;54:304–312.
18. Harris L, Aban IB, Xin H, et al. Employment in refractory myasthenia gravis: a Myasthenia Gravis Foundation of America registry analysis. *Muscle Nerve*. 2019;60:700–706.
19. Vitturi BK, Kim AIH, Mitre LP, et al. Social, professional and neuropsychiatric outcomes in patients with myasthenia gravis. *Neurol Sci*. 2021;42:167–173.
20. Alexion Pharmaceuticals Inc. SOLIRIS® (Eculizumab) Injection Prescribing Information; 2020. Available at: https://alexion.com/Documents/Soliris_USPI.pdf. Accessed April, 2021.
21. Howard JF, Jr., Utsugisawa K, Benatar M, 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;16:976–986.
22. Gajdos P, Tranchant C, Clair B, et al. Treatment of myasthenia gravis exacerbation with intravenous immunoglobulin: a randomized double-blind clinical trial. *Arch Neurol*. 2005;62:1689–1693.
23. Nagane Y, Murai H, Imai T, et al. Social disadvantages associated with myasthenia gravis and its treatment: a multicentre cross-sectional study. *BMJ Open*. 2017; 7:e013278.
24. Landfeldt E, Pogoryelova O, Sejersen T, et al. Economic costs of myasthenia gravis: a systematic review. *Pharmacoeconomics*. 2020;38:715–728.
25. Muppidi S, Wolfe GI, Conaway M, et al. MG-ADL: still a relevant outcome measure. *Muscle Nerve*. 2011;44:727–731.
26. Moghadam-Kia S, Werth VP. Prevention and treatment of systemic glucocorticoid side effects. *Int J Dermatol*. 2010;49:239–248.

27. Yasir M, Goyal A, Bansal P, et al. Corticosteroid Adverse Effects. Treasure Island, FL: StatPearls Publishing LLC; 2020.
28. Alabdali M, Barnett C, Katzberg H, et al. Intravenous immunoglobulin as treatment for myasthenia gravis: current evidence and outcomes. *Expert Rev Clin Immunol*. 2014;10:1659–1665.
29. Jowcar A, Goldenberg WD. Myasthenia Gravis Treatment & Management; 2018. Available at: https://emedicine.medscape.com/article/1171206-treatment#d17. Accessed April, 2020.
30. Bacci ED, Coyne KS, Poon JL, et al. Understanding side effects of therapy for myasthenia gravis and their impact on daily life. *BMC Neurol*. 2019;19:335.
31. Thomas TC, Rollins SA, Rother RP, et al. Inhibition of complement activity by humanized anti-C5 antibody and single-chain Fv. *Mol Immunol*. 1996;33:1389–1401.
32. Garzón-Orjuela N, van der Werf L, Prieto-Pinto LC, et al. Quality of life in refractory generalized myasthenia gravis: a rapid review of the literature. *Intractable Rare Dis Res*. 2019;8:231–238.
33. Dong D, Chong MK, Wu Y, et al. Gender differences in quality of life among patients with myasthenia gravis in China. *Health Qual Life Outcomes*. 2020;18:296.
34. Fan X, Xing C, Yang L, et al. Fatigue, self-efficacy and psychiatric symptoms influence the quality of life in patients with myasthenia gravis in Tianjin, China. *J Clin Neurosci*. 2020;79:84–89.
35. Szczudlik P, Sobieszczuk E, Szyluk B, et al. Determinants of quality of life in myasthenia gravis patients. *Front Neurol*. 2020;11:553626.
36. Alanazy MH, Binabbad RS, Alromaih NI, et al. Severity and depression can impact quality of life in patients with myasthenia gravis. *Muscle Nerve*. 2020;61:69–73.
37. Muppidi S, Utsugisawa K, Benatar M, et al. Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. *Muscle Nerve*. 2019;60:14–24.