Usage of Newer Immunotherapies in Myasthenic Crisis – A Review of the Literature

Johnny Dang MD, Sanem P. Uysal MD, Yuebing Li MD, PhD

Department of Neurology, Cleveland Clinic, Cleveland, OH 44195

ABSTRACT

Myasthenic crisis is the most severe manifestation of myasthenia gravis that requires the use of invasive or non-invasive ventilation. Treatment of myasthenic crisis includes removal of triggering factors, airway management, and supportive care. Traditionally, plasmapheresis and/or intravenous immune globulin are the most commonly administered disease modifying treatments, and both are effective in the majority of patients leading to discontinuation of mechanical or non-invasive ventilation. More recently approved therapies for myasthenia gravis, namely, complement or neonatal Fc receptor inhibitors, may serve as additional options of rescue therapies for patients with myasthenic crisis, especially those who do not respond to traditional treatment. In this review, we provide a summary of recently published case reports and case series describing the successful usage of these newly approved therapies in the setting of myasthenic crisis.

Keywords: myasthenia gravis, myasthenic crisis, eculizumab, ravulizumab, efgartigimod

Introduction

Myasthenia gravis (MG) is a rare condition of autoimmunity at the neuromuscular junction, specifically at the postsynaptic components of the neuromuscular junction, with an annual incidence of 2-15 per million but a steadily rising prevalence as treatments and outcomes of the disease improve.[1,2] Most patients with MG first present with ocular symptoms such as ptosis or diplopia.[2,3] About 75% of patients develop generalized disease within the first 2-3 years following presentation, with a predilection for bulbar, neck, and proximal limb muscles, and about 40% of patients develop respiratory muscle weakness, including exertional dyspnea and orthopnea.[3]

Myasthenic crisis (MC), the most severe form of MG, is defined as the "worsening of myasthenic weakness requiring intubation or noninvasive ventilation to avoid intubation" by one international consensus[4] and has an estimated in-hospital mortality of 4.47%.[5] The incidence of MC, which typically occurs within the first 2-3 years of diagnosis, is approximately 12-16%.[5] Impending crisis describes a rapid clinical worsening of MG that could lead to crisis in days to weeks.[4] Impending or manifest MC can be triggered by a number of etiologies, including infections, surgery, medication changes, or pregnancy.[6] Bulbar weakness or severe disease status at onset, muscle-specific kinase (MuSK) antibody positivity, presence of thymoma, and prior history of MC increase risk of MC.[7–9]

The mainstay of MG treatment involves the suppression of various steps of the immune cascade responsible for MG pathogenesis by immunomodulating medications or thymectomy. Traditional MG immunosuppressants include corticosteroids, steroid-sparing agents, intravenous immunoglobulin (IVIG), and plasmapheresis (PLEX). Corticosteroids are the first line immunosuppressant in all clinical subtypes of MG. Due to the long-term side effects associated with corticosteroid use, a non-steroidal immunosuppressant (including azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus) is usually initiated in MG patients requiring long-term immunosuppression. IVIG and PLEX are primarily employed in the acute setting for treatment of MG exacerbation or MC.

Despite the wide range of treatment options available for MG, the management of MC remains a clinical challenge, particularly in the subset of patients resistant to standard rescue therapies. Acute immunomodulation with PLEX or IVIG remains the main rescue therapy options for MG crisis, each leading to significant improvement in approximately 70% of MG patients. The onset of their efficacy typically occurs 3-5 days following initiation. IVIG is easily administered while PLEX should only be provided in centers with experienced teams. However, up to 10-20% of patients in MC do not respond to these treatments, requiring tracheostomy or frequent hospitalizations with repeated rescue therapy administration.[10,11] This challenge underlines the need for additional, more effective acute treatment options for MC.

As opposed to the traditional MG therapies providing broad-spectrum immunosuppression, novel MG immunotherapies target specific steps of the MG immune cascade. Five new MG drugs received United States Food and Drug Administration approval in the last six years for use in generalized MG, including eculizumab, ravulizumab, zilucoplan, efgartigimod, and rozanolixizumab.[12–18] Eculizumab, ravulizumab, and zilucoplan are complement inhibitors that lead to clinical improvement by preventing the formation of the membrane attack complex at the neuromuscular endplate, thereby maintaining the integrity of the acetylcholine receptors at the postsynaptic junction.[19] The role of complement activation in the pathogenesis of MG renders it as a favorable therapeutic target particularly in acetylcholine receptor antibody positive (AChR+) MG.[20]

Efgartigimod and rozanolixizumab are neonatal Fc receptor (FcRn) inhibitors which function by the blockage of FcRn-mediated recycling of pathogenic antibodies, leading to their increased lysosomal degradation. FcRn inhibitors are comparable to PLEX in reducing IgG levels, but with a prolonged effect and less significant complications.[21]

The efficacy of these new therapies in treating generalized MG were all demonstrated in pivotal trials (e.g., REGAIN, CHAMPION, ADAPT, RAISE, MycarinG) eventually leading to FDA approval for their use in AChR+ generalized MG.[13–18] These early trials, however, excluded patients in MC, leaving the role of these newer immunotherapies in the treatment of patients amid MC unclear. We present here a review of the current literature on the application of these newer immunotherapies in the treatment of MC.

Methods

The PubMed, Google Scholar, and Embase databases were queried for cases of MC and treatment with either eculizumab, ravulizumab, efgartigimod, zilucoplan, or rozanolixizumab up to March 28, 2024. Case reports and case series of adult patients in MC or impending MC were included. Publications were reviewed in their entirety, and patient characteristics such as demographics, prior MG treatment, and effect of immunotherapy treatment, as well as complications during the treatment course were recorded. All publications were in English except for one, which was written in Japanese.

Results

There were 8 total publications from 2018 to 2023 reporting on a total of 16 patients presenting with manifesting or impending MC treated with eculizumab (Table 1). Of these 16 patients, 9 (56.3%) were female and average age at eculizumab administration was 51.9 years (range: 22 to 79 years). A total of 15 (93.8%) patients had AChR+ MG (one patient had seronegative MG) and 6 (37.5%) patients were found to have a thymoma. Prior to MC, 7 (43.8%) patients were taking tacrolimus, 2 (12.5%) patients were taking azathioprine, and 1 (6.25%) patient was taking mycophenolate mofetil. A total of 14 (87.5%) patients received PLEX and/or immunoadsorption, 14 (87.5%) patients received IVIG, 3 (18.8%) patients received pulse intravenous steroids, 1 (6.25%) patient received intravenous pyridostigmine, and 2 (12.5%) patients received rituximab as rescue treatments. On average, patients received 2.12 rescue treatments, defined as a combination of either PLEX, IVIG, pulse steroids, IV pyridostigmine, or rituximab, prior to initiation of eculizumab.

Eculizumab was administered as an initial dose of 900 mg weekly for four weeks followed by 1200 mg every two weeks thereafter, consistent with the dosing regimen used in the REGAIN trial in all reports except for one where dosage was not defined. While there was heterogeneity in how outcomes of eculizumab treatment were reported, all patients were able to be liberated from invasive mechanical ventilation after treatment with eculizumab, although one patient remained on intermittent non-invasive ventilation through a trach collar. Time to response to eculizumab varied, with one patient reportedly being extubated the day following eculizumab treatment while other patients took anywhere from 1 to 6 weeks for weaning of mechanical ventilation. All patients experienced clinical improvement and no relapse of MC was reported. The most common complication reported was infection, including sepsis or pneumonia which occurred in 3 (18.8%) patients. There were no reports of meningococcal infection although there was 1 case reporting polymicrobial infection partially consisting of encapsulated organisms. Other complications reported during therapy included intestinal perforation, thymoma-associated multiorgan autoimmunity, and delay in immune therapy due to logistical reasons. No other complications were reported in the remaining 10 (62.5%) patients.

The number of cases reported involving the use of efgartigimod and ravulizumab in MC thus far is limited. Watanabe et. al described the use of efgartigimod in a 54-year-old female with AChR+ MG diagnosed 5 months prior who presented with neck muscle weakness and dysphagia. She continued to worsen despite 6 PLEX sessions and 2 g/kg IVIG, eventually requiring intubation due to progression of her bulbar symptoms. Subsequently, she was administered efgartigimod at 10 mg per kilogram of body weight weekly, each cycle of four weekly infusions for a total of three cycles, which led to resolution of her weakness 18 days after the first infusion and, eventually, successful extubation. Her anti-AChR antibody titers showed a consistent decline in parallel with the clinical improvement.

Konen et. al described the use of ravulizumab in a 34-year-old female with AChR+ MG with symptom onset eight months prior who presented with progressive bulbar and limb weakness. Her MG was refractory to treatments of IVIG, PLEX, and rituximab and she was in impending MC. Consequently, she was administered one dose of 3g ravulizumab infusion and achieved clinical improvement and stability over a course of two weeks, which was sustained up to 19 weeks following the first administration of ravulizumab. To date, there are no case reports on the use of rozanolixizumab or zilucoplan in MC.

Discussion

In this review, we summarized the use of eculizumab, efgartigimod, and ravulizumab for treatment of MC. As the initial pivotal trial that led to their approval as standard treatment for generalized MG did not include patients with MC, only a small number of case reports have been included. More cases describing the use of eculizumab

compared to efgartigimod and ravulizumab were found, which corresponds to its earlier approval and availability. Overall, the positive results from the described case reports suggest the potential therapeutic value of these newer immunotherapies in the setting of MC.

Complement and FcRn inhibitors may have advantages over PLEX or IVIG for acute MG treatment. Compared to PLEX or IVIG, which are nonselective immunomodulators that may act on multiple aspects of MG pathogenesis, these newer therapies act on a unique key step of antibody reduction or complement inhibition. Both PLEX and IVIG can be associated with significant side effects. Vascular access is required for PLEX administration, and its use may be contraindicated in patients with concern of infection. IVIG treatment is associated with hypercoagulability, volume overload, and worsening kidney function. In contrast, data from the phase 3 trials and open label extension studies demonstrated that efgartigimod, eculizumab, and ravulizumab are associated with mild side effects, most commonly nasopharyngitis, upper respiratory infection, or headache.[13–15] While initial studies have demonstrated the relative safety of these newer immunotherapeutic agents, complement inhibition has been well known to increase the risk of meningococcal infection, highlighting the importance of immunization or chemoprophylaxis for those unable to receive immunization two weeks prior to drug initiation in this population in addition to close monitoring for infections as the patient is undergoing the course of therapy.[22–24]

One limitation of the cases reported in literature is that several rescue therapies were tried concomitantly or consecutively before initiation of efgartigimod, eculizumab, or ravulizumab. Therefore, it is possible that the combination of multiple mechanisms of action involving the MG pathogenesis could be responsible for the demonstrated clinical improvement. Multiple patients were continued on the complement or FcRn inhibitors that were used in the acute setting after clinical stabilization with sustained clinical benefit. Neither complement inhibitors nor FcRn inhibitors can render remission as they are not capable of stopping the production of pathogenic antibodies. However, this limitation does not preclude their use in the acute setting for the goal of eliminating the need of mechanical or non-invasive ventilation. Finally, the extremely high costs of the novel MG immunotherapeutics are one of the biggest barriers to their widespread use.

Conclusion

This review summarizes the available literature on the application of eculizumab, ravulizumab, and efgartigimod in the treatment of MC and suggests that patients in MC refractory to typical rescue treatments may benefit from the use of these newer immunotherapies. As most of the complement inhibitors and FcRN therapies are relatively new (apart from eculizumab), we expect that more case reports or case series will likely be generated in the near future, further solidifying their role in the treatment of MC or impending MC.

References

1. Phillips LH, Torner JC. Epidemiologic evidence for a changing natural history of myasthenia gravis. Neurology 1996;47(5):1233–8.
2. Grob D, Arsura EL, Brunner NG, Namba T. The Course of Myasthenia Gravis and Therapies Affecting Outcomes. Annals of the New York Academy of Sciences 1987;505(1):472–99.
3. Hehir MK, Silvestri NJ. Generalized Myasthenia Gravis. Neurologic Clinics 2018;36(2):253–60.
4. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. Neurology 2016;87(4):419–25.
5. Alshekhlee A, Miles JD, Katirji B, Preston DC, Kaminski HJ. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospitals. Neurology 2009;72(18):1548–54.
6. Wendell LC, Levine JM. Myasthenic crisis. Neurohospitalist 2011;1(1):16–22.
7. Geng Y, Zhang H, Wang Y. Risk factors of myasthenia crisis after thymectomy among myasthenia gravis patients: A meta-analysis. Medicine (Baltimore) 2020;99(1):e18622.
8. Nelke C, Schroeter CB, Stascheit F, et al. Eculizumab versus rituximab in generalised myasthenia gravis. J Neurol Neurosurg Psychiatry 2022;93(5):548–54.
9. Claytor B, Cho S-M, Li Y. Myasthenic crisis. Muscle & Nerve 2023;68(1):8–19.
10. Vanoli F, Mantegazza R. What are the pharmacotherapeutic considerations for the treatment of myasthenia gravis? Expert Opinion on Pharmacotherapy 2022;23(13):1471–4.
11. Schneider-Gold C, Hagenacker T, Melzer N, Ruck T. Understanding the burden of refractory myasthenia gravis. Ther Adv Neurol Disord 2019;12:1756286419832242.
12. Suzuki S, Uzawa A, Murai H. Efgartigimod for generalized myasthenia gravis with or without anti-acetylcholine receptor antibodies: a worldwide and Japanese perspective. Expert Rev Clin Immunol 2022;18(12):1207–15.
13. Howard JF, 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(12):976–86.
14. Meisel A, Annane D, Vu T, et al. Long-term efficacy and safety of ravulizumab in adults with anti-acetylcholine receptor antibody-positive generalized myasthenia gravis: results from the phase 3 CHAMPION MG open-label extension. J Neurol 2023;270(8):3862–75.

15. Howard JF, Bril V, Vu T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. Lancet Neurol 2021;20(7):526–36.
16. Howard JF, Bresch S, Genge A, et al. Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study. The Lancet Neurology 2023;22(5):395–406.
17. Bril V, Drużdż A, Grosskreutz J, et al. Safety and efficacy of rozanolixizumab in patients with generalised myasthenia gravis (MycarinG): a randomised, double-blind, placebo-controlled, adaptive phase 3 study. Lancet Neurol 2023;22(5):383–94.
18. Vu T, Meisel A, Mantegazza R, et al. Terminal Complement Inhibitor Ravulizumab in Generalized Myasthenia Gravis. NEJM Evid 2022;1(5):EVIDoa2100066.
19. Kim MS, Prasad V. The Clinical Trials Portfolio for On-label and Off-label Studies of Eculizumab. JAMA Intern Med 2020;180(2):315–7.
20. Uysal SP, Morren JA. Promising therapies for the treatment of myasthenia gravis. Expert Opinion on Pharmacotherapy 2024;0(0):1–14.
21. Peter H-H, Ochs HD, Cunningham-Rundles C, et al. Targeting FcRn for immunomodulation: Benefits, risks, and practical considerations. J Allergy Clin Immunol 2020;146(3):479-491.e5.
22. Benamu E, Montoya JG. Infections associated with the use of eculizumab: recommendations for prevention and prophylaxis. Curr Opin Infect Dis 2016;29(4):319–29.
23. Crew PE, McNamara L, Waldron PE, McCulley L, Jones SC, Bersoff-Matcha SJ. Antibiotic prophylaxis in vaccinated eculizumab recipients who developed meningococcal disease. J Infect 2020;80(3):350–71.
24. Crew PE, Abara WE, McCulley L, et al. Disseminated Gonococcal Infections in Patients Receiving Eculizumab: A Case Series. Clin Infect Dis 2018;10.1093/cid/ciy958.

Table 1. Case report on the efficacy of newer immunotherapies in refractory myasthenic crisis or impending crisis. AChR (+) = Aceytylcholine Receptor Positive, MG = Myasthenia Gravis, PLEX = Plasmapheresis, IVIG = Intravenous Immunoglobulins, IA = Immunoadsorption, MGFA = Myasthenia Gravis Foundation of America Grading, MD-ADL = Myasthenia Gravis Activities of Daily Living Score, QOL = Quality of Life Score, QMG = Quantitative Myasthenia Gravis. * = Patient administered eculizumab as 900mg on day 1 then weekly for weeks 1-3 followed by 1200mg week 4, then 1200mg every other week thereafter as per REGAIN trial protocol unless otherwise specified

Reference	# of Patients	Age/ Sex	MG Features (Duration, Antibody Status, and Thymoma Status if known)	Prior MG Treatment	Rescue Treatment Trialed	Crisis or Impending crisis	MC Treatment (Medication, Dose, Frequency)	Improvement Following MG Treatment	Time Course of Initial Improv-ement	Follow Up Duration	Complications
Yeo & Pleitez, 2018	1	79F	Seronegative, no thymoma, onset 3 years ago	Methylpredniso-lone, pyridostigmine	PLEX, IVIG	Crisis, then tracheostomy	Eculizumab*	Weaning of respiratory support, then off ventilation, improved limb strength	1 Week	Hospitalized for 2 months for sepsis, discharge to community rehab ventilator dependent	Coexisting hemolytic uremic syndrome, polymicrobial sepsis after PEG tube placement requiring stopping of Eculizumab
Oyama et al., 2020	7	22F	AChR (+), onset 1 year ago	Prednisone	PLEX	Crisis	Eculizumab*	QMG score improved from 36 to 26 at 6 months. No longer needs wheelchair	Not reported	6 months	None reported
		23F	AchR (+), onset 4 years ago	Prednisone, tacrolimus, thymectomy	IVIG, IA	Crisis, then extubated prior to eculizumab usage	Eculizumab*	QMG score improved from 28 to 16	Not reported	12 months	None reported
		33F	AChR (+), onset 21 years ago	Prednisone, tacrolimus, thymectomy	IVIG	Crisis	Eculizumab*	Disappearance of ptosis, ability to use mascara and eye liner	Not reported	6 months	None reported
		40F	AChR (+), type B3, thymoma, onset 21 years ago	Prednisone, tacrolimus, thymectomy	IVIG, PLEX, IA	Crisis	Eculizumab*	Strength improved, recovered after delivery of child	Not reported	6 months	None reported
		53F	AChR (+), type B1 thymoma, onset 7 years ago	Prednisone, tacrolimus, thymectomy	IVIG. IA	Crisis	Eculizumab*	Limb strength improved	Not reported	6 months	None reported
		55M	AChR (+), type B2 thymoma, onset 5 years ago	Prednisone, tacrolimus, thymectomy	IVIG, IA, pulse dose of corticosteroid	Crisis	Eculizumab*	Strength improved and regained employment	Not reported	6 months	None reported
		67F	AChR (+), type A thymoma, onset 1 year ago	Prednisone, tacrolimus, thymectomy	IVIG, IA, PLEX	Crisis	Eculizumab*	Strength improved, speech and swallowing improved	Not reported	6 months	None reported

Yoshizumi et al., 2020	1	40M	AChR (+), thymoma, onset three years ago	Prednisone, thymectomy	Intravenous corticosteroids, IVIG, PLEX	Crisis	Eculizumab (dosage not defined)	MG-ADL improved in 3 weeks, Resumed eating 42 days after treatment, weaned from noninvasive ventilation at day 47	3 weeks	Discharged 82 days after treatment with QMG 6 and MG-ADL 4	None reported
Furuta et al., 2021	1	77F	AChR (+), type B2 thymoma, onset five years ago	Pyridostigmine, prednisone, tacrolimus, thymectomy	IA, PLEX, IVIG	Crisis then tracheostomy	Eculizumab* - 900mg x4 and 1200mg x2 then not continued on discharge	Improved strength, discharge 70 days after treatment, no recurrence at 1 year	70 days	No recurrence of coexisting autoimmune diseases	Thymoma associated multiorgan autoimmunity, polymyositis, and myocarditis
Hofstadt-van Oy et al., 2021	1	62M	AChR (+), no thymoma, onset 11 months ago	Pyridostigmine, prednisone, azathioprine, dexamethasone	IVIG, IV pyridostigmine, PLEX, rituximab	Crisis then tracheostomy	Eculizumab*	Bulbar and limb strength improved, removal of tracheostomy and nasogastric tube	1 week	Persistent return of spontaneous breathing and oral feeding at 1 month	Aspiration pneumonia, sepsis, Enterobacter cloacae bacteremia requiring pausing azathioprine therapy
Usman et al., 2021	3	24F	AChR (+), thymoma, onset 11 years ago	Prednisone, azathioprine, thymectomy	PLEX, IVIG, rituximab	Crisis then tracheostomy	Eculizumab*	Successful extubation at 1-week, minimal manifestation status at week 4, asymptomatic at week 55	1 week	Asymptomatic at 55 weeks	Steroids held at week 8 due to intestinal perforation
		77M	AChR (+), no thymoma, onset three weeks ago	Pyridostigmine, prednisone	PLEX, IVIG	Crisis	Eculizumab*	Extubated the following day, discharged 15 days later, asymptomatic at 24 weeks	Next day	Asymptomatic at 24 weeks	None reported
		56M	AChR(+), no thymoma, onset one year ago	pyridostigmine, prednisone, mycophenolate mofetil	IVIG, PLEX	Crisis then tracheostomy	Eculizumab*	Non-invasive ventilation through trach collar at week 3, improved limb strength	3 weeks	Intermittent non-invasive ventilation at 40 weeks	Eculizumab 7th and 8th doses delayed logistically due to COVID 19 pandemic
Strano et al., 2022	1	48M	AChR (+), onset 3 months ago	Pyridostigmine, prednisone	IVIG, PLEX	Crisis then tracheostomy	Eculizumab*	MG-ADL improved in 10 days, ambulated in 20 days, weaned from invasive ventilation in 10 days with successful extubation	10 days	Maintained need for non-invasive ventilation at night only at 6 months	None reported

Vinciguerra et al., 2023	1	74M	AChR (+), onset two years ago	Pyridostigmine	IVIG	Crisis	Eculizumab*	Improved limb strength, weaned off mechanical ventilation and improved to MGFA IIa at day 5	5 days	Discharged at 5 weeks	Severe pneumonia and sepsis making IVIG and PLEX infeasible for a period of timed
Konen et al., 2024	1	34F	AChR (+), no thymoma, onset 8 months ago	Prednisolone, pyridostigmine	IVIG, PLEX, rituximab, IA	Impending crisis	Ravulizumab 3 g	MGFA improved from IVb to MGFA IIa, immunotherapy reduced	14 days	Sustained improvement at 19 weeks, improved MG-ADL and QOL	None reported
Watanabe et al., 2024	1	54F	AChR (+), type B1 thymoma, onset 5 months ago	Prednisolone, tacrolimus, pyridostigmine, thymectomy	PLEX, IVIG, IA	Crisis	Efgartigimod 10mg/kg/ week, 4 infusions per cycle, 3 total cycles	Improvement of limb and neck weakness, immunotherapy reduced	18 days	Off ventilation at day 60, minimal symptomatic expression at 196 days	First cycle efgartigimod limited to three doses due to ventilator associated pneumonia