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Review Article

Eculizumab treatment for myasthenia gravis subgroups: 2021 update

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ABSTRACT

Eculizumab is a recombinant humanized monoclonal antibody that targets the complement protein C5, inhibiting its cleavage into C5a and C5b and ultimately preventing the formation of C5b-9 membrane attack complex (MACs), thereby protecting the neuromuscular junction from the damage of complement activation. In 2017, eculizumab became the second FDA-approved medication for AchR-positive generalized myasthenia gravis (gMG) patients based on the successful results of a randomized, double-blinded, placebo-controlled, phase 2, phase 3 study (the REGAIN trial) and its open-label extension study. Despite the efficacy of eculizumab in treating AchR antibody-positive refractory gMG was demonstrated in the REGAIN study, there is few information on its efficacy in other subgroup of MG patients including seronegative MG, thymoma-associated MG and MG crisis. This narrative review summarizes current clinical studies of eculizumab in these refractory gMG patients, with a focus on the therapeutic efficacy and tolerability in different subgroup of MG.

1. Introduction

Generalized myasthenia gravis (gMG) is an autoimmune disorder characterized by skeletal muscle weakness and fatigability caused by autoantibody-induced neurotransmission dysfunction at the neuromuscular junction. The majority of patients with MG have antibodies against acetylcholine receptor (AChR), and a minority have antibodies against muscle-specific kinase receptor (MuSK) or lipoprotein-receptor-related protein 4 (LRP4) (Vincent et al., 2018; Gilhus et al., 2019). AChR antibodies are found in approximately 750% of patients with gMG (Vincent et al., 2018; Gilhus et al., 2019), MuSK antibodies are detected in 30–40% and LRP4 antibodies in 7–33% of gMG patients without AChR antibodies (Gilhus et al., 2016; Rivner et al., 2018). MG in the patients who lack antibodies is often referred to as 'seronegative' (Rivner et al., 2018).

AChR antibodies, which are mainly of the IgG1 and IgG3 subclass, impair neuromuscular transmission at the post-synaptic muscle membrane through three mechanisms, including blockade of AChR channel function, accelerating the internalization and degradation of AChRs that are cross-linked by autoantibodies, and complement activation (Drachman et al., 1978a, 1978b; Toyka et al., 1977; Sahashi et al., 1978). Anti-LRP4 antibodies, since they belong to the IgG1 subclass, are also able to activate complement and reduce AChR clustering by inhibiting LRP4–agrin interactions (Shen et al., 2013). Anti-MuSK antibodies, predominantly IgG4, are unable to activate complement but can impair neuromuscular transmission by blocking activation of the agrin-LRP4-MuSK complex (Huijbers et al., 2013). Complement activation culminates in cleavage of C5 into C5a and C5b, which mediate the terminal complement cascade and contribute to formation of the membrane attack complex (MACs). MACs cause structural damage of the muscle membrane, thereby impairing neuromuscular transmission and the muscle weakness associated with gMG (Engel et al., 1977; Ruff and Lennon, 2008; Conti-Fine et al., 2006).

In most cases, gMG can be treated successfully with an individualized combination of acetylcholinesterase inhibitors, immunosuppressive therapy and thymectomy. However, in 10–15% of patients with gMG, the signs and symptoms are inadequately controlled by currently available therapies (Mantegazza and Antozzi, 2018; Zebardast et al., 2010). Those treatment-refractory gMG subgroup mostly receive combined utilization of multiple drugs accompanying with a considerable socioeconomic burden and intolerable adverse events, for whom the use of more effective and safe therapies is an urgent need.

Eculizumab is a recombinant humanized monoclonal antibody that targets the complement protein C5, inhibiting its cleavage into C5a and C5b and ultimately preventing the formation of C5b-9 MACs (Dhillon, 2018; Thomas et al., 1996; Dubois and Cohen, 2009), thereby protecting the neuromuscular junction from the damage of complement activation. It has been approved by the Food and Drug Administration for refractory

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MG. This narrative review summarizes current clinical studies of eculizumab in these refractory gMG patients (Fig. 1), with a focus on the therapeutic efficacy and tolerability in different subgroup of MG (Table 1).

2. Eculizumab in AChR antibody-positive MG

In 2017, eculizumab became the second FDA-approved medication for AchR-positive gMG patients based on the successful results of a randomized, double-blinded, placebo-controlled, phase 2, phase 3 study (the REGAIN trial) and its open-label extension study.

Patients enrolled in all trials had to be refractory generalized AChR-positive MG, defined by the international consensus guidance for management of MG as unchanged or worsening post-intervention status after corticosteroids and at least two other immunosuppressive agents used in adequate doses for an adequate duration (Silvestri and Wolfe, 2014; Suh et al., 2013; Sanders et al., 2016). During phase 2 study, eculizumab is given via intravenous infusion with a regimen of 600 mg weekly for 4 weeks, followed by 900 mg every 2 weeks. The primary efficacy endpoint was the percentage of patients with a 3-point reduction from baseline in the QMG total score. Six of seven eculizumab-treated patients (86%) had a 3-point reduction in total QMG score versus only 57% of placebo-treated patients. Four of seven patients (57%) treated with eculizumab achieved an 8-point improvement in total QMG score as compared to only one of seven patients (14%) who received placebo. Overall, changes in mean QMG total score was significantly different between eculizumab and placebo (Howard Jr et al., 2013; Howard Jr et al., 2020). In phase III clinical trials, eculizumab was administered an induction dose of 900 mg on day 1 and weeks 1, 2, and 3; 1200 mg at week 4; and maintenance dosing 1200 mg every second week thereafter. The primary efficacy endpoint, MG-ADL total score, did not differ significantly between patients receiving eculizumab versus placebo at week 26; however, the secondary efficacy outcomes were significantly improved in eculizumab-treated patients compared with placebo. QMG, MG-QoL15 and Neuro-QOL Fatigue scores scales showed initial improvement within 4 weeks with most of the treatment effect seen at week 12 (Howard et al., 2017). At week 26, more eculizumab-treated patients than placebo-treated patients achieved improved status (60.7% vs 41.7%) or minimal manifestations (25.0% vs 13.3%) (Mantegazza et al., 2020). The 3-year open-label extension of the phase 3 trial provided additional data on clinical effectiveness and safety of eculizumab in patients with AChR-positive refractory gMG. After 130 weeks of eculizumab treatment, 87.1% of patients attained a status of improved and 57.1% of patients achieved minimal manifestations (Mantegazza et al., 2020). Improvements of QMG, MG-ADL and MG-QoL15 scores were maintained through 3 years in eculizumab-treated patients. Patients who received placebo during the REGAIN trial had a similar clinical response when transitioned to eculizumab in the open-label extension trial (Muppidi et al., 2019).

A network meta-analysis including 808 patients across 14 studies represented the most comprehensive data analysis for current immunotherapies for MG was performed in Mantegazza and Antozzi, 2018 (Wang et al., 2019). In this article, 684 AChR antibody seropositive samples were identified. QMG score was defined as the primary outcome, and the secondary outcomes included the glucocorticoid reduction and hazard ratios from the counts of adverse events (AEs). With traditional pairwise mean-analysis, statistical significance was observed in eculizumab of −1.50 (−2.81, −0.18) vs placebo for the

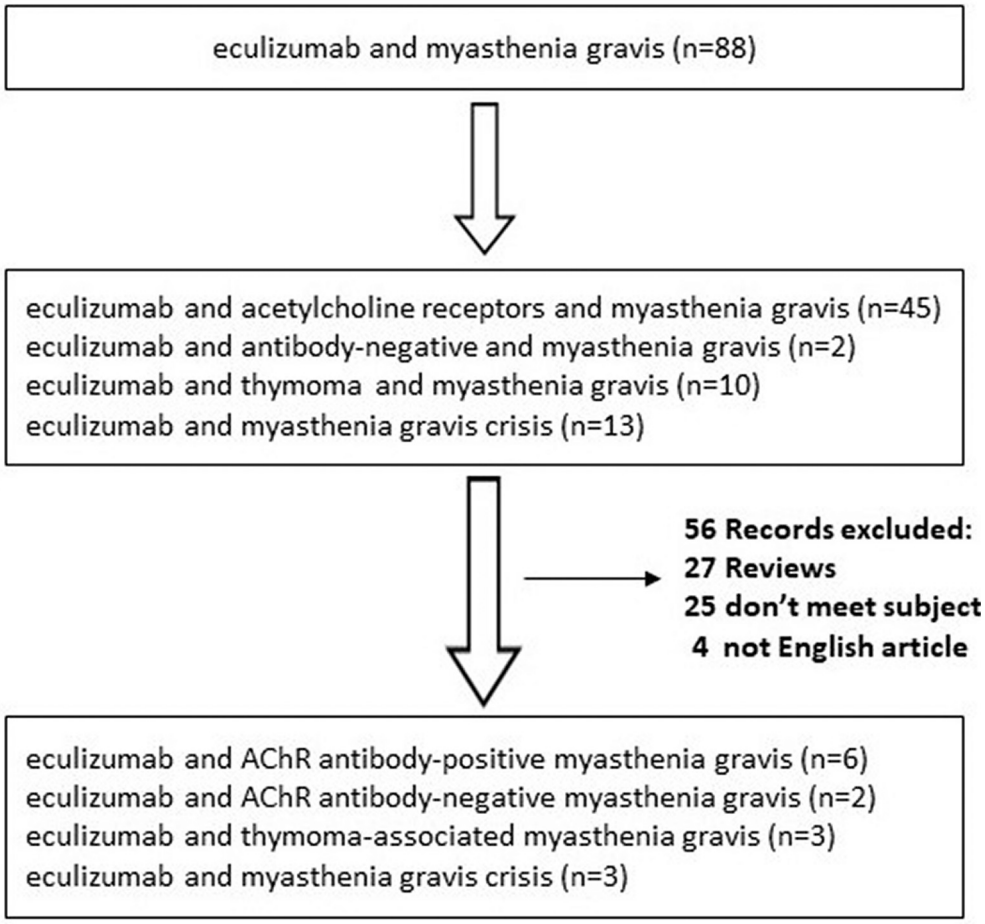

Fig. 1. Study flow.

Table 1
Summary of the main clinical trials on eculizumab in myasthenia gravis subgroup patients.

Author	Year	MG subgroups	Patients	Treatment	Duration	Study design
Howard JF et al.	2013	AchR-positive gMG Key Exclusion Criteria: MGFA Class IVb history of thymoma thymectomy within 12 months myasthenic crisis received IVIG within 8 weeks plasma exchange within 3 months rituximab within 6 months	14	600 mg weekly for 4 doses followed by 900 mg every two weeks for 7 doses	16 weeks	Randomized, double blind, placebo controlled, multicenter, phase II study 6 of 7 patients treated with eculizumab (86%) achieved 3-point reduction in the QMG score. Overall change in mean QMG total score was significantly different between eculizumab and placebo ($p < 0.001$) ECU was well tolerated
Howard JF et al.	2017	AchR-positive gMG Key Exclusion Criteria: thymoma or other neoplasms of the thymus thymectomy within 12 months MGFA Class I or MG crisis (MGFA Class V) rituximab within 6 months Use of IVIg or PE within 4 weeks	125	900 mg on day 1 and weeks 1, 2, and 3, 1200 mg at week 4, and 1200 mg every second week	26 weeks	Randomized, double blind, placebo controlled, multicenter, phase III study The primary endpoint: change in MGADL score from baseline at week 26 was not signifcant difference between Ecu and placebo. The secondary endpoints: significant changes in QMG ($P = 0.0129$) and MG-QoL15 ($P = 0.0281$) score; Significant improvement in Neuro-QOL Fatigue scores at week 26 ECU was well tolerated
Muppidi S et al.	2019	AchR-positive gMG Key Exclusion Criteria: thymoma, or other thymic neoplasm thymectomy in the 12 months MGFA class I or myasthenic crisis (MGFA class V) IVIg or PE within the 4 weeks	117	1200 mg every 2 weeks	4 years	Phase III, Open-label Extension Trial Improvements in QMG, MG-ADL and MG-QoL15 scores was maintained through 3 years in ECU-treated patients. Improvement of MG-ADL, QMG, MGC, and MG-QoL15 scores over 30 months in patients switched from placebo to ECU ($P < 0.0001$) ECU was well tolerated
Wang L et al.	2019	684 (94.3%) AchR-positive MG Key Exclusion Criteria: HDMP, IVIg, plasma pheresis thymectomy	808	900 mg/ wk. −1200 mg/2 wk 600 mg/wk-900 mg/2 wk	6.5 months 8 months	Meta-analysis ECU of −1.50 (−2.81, −0.18) vs placebo reached a statistical significance in QMG scores. ECU ranked the most tolerable therapies causing the least counts of AEs vs placebo.
Govindarajan R	2020	AchR-positive gMG	15	900 mg/week for 4 weeks then 1200 mg every 2 weeks	12 months	Retrospective study Significant reductions in total MG-ADL scores at 3 months and maintained up to 12 months in all patients. Mean (SD) SBCT score improved from 28.13 (0.33) to 50.26 (2.86) after 12 months. All patients reduced their daily prednisone dose. ECU was well tolerated
Murai H et al.	2021	AchR-positive gMG Key Exclusion Criteria: thymoma or other thymic neoplasms	40	900 mg/week for 4 weeks then 1200 mg every 2 weeks	26 weeks	Prospective study The mean (SD) change from baseline in MG-ADL total score was −3.7 (2.61) ($n = 27$) at 12 weeks and − 4.3 (2.72) ($n = 26$) at 26 weeks; The mean (SD) change from baseline in QMG total score was −5.6 (3.50) (n = 26) at 12 weeks and − 5.6 (4.02) ($n = 24$) at 26 weeks; Frequency of IVIg use decreased following eculizumab initiation ECU was well tolerated
Datta S et al.	2020	AChR-negative gMG	6	900 mg/week for 4 weeks then 1200 mg every 2 weeks	12 months	Retrospective study Significant reductions in total MG-ADL scores (≥2 points) before or at 5 months and were maintained to Month 12 in all patients. Mean (SD) number of exacerbations per patient from 2.8 (1.2) to 0.3 (0.5) in the 12 months. ECU was well tolerated
Greenwood GT et al.	2020	AchR-negative, Musk-negative gMG	1	900 mg 1 day after first PLEX, plus 600 mg on the day of the second PLEX session, for 4 weeks and then 1200 mg every 2 weeks	39 weeks	Retrospective study MG-ADL score decreased from 9 to 1 or 2 at most assessments and PLEX was discontinued at Week 39. ECU was well tolerated
Vélez-Santamaría V et al.	2020	Thymoma-associated, AchR-positive gMG	1	900 mg/week for 4 weeks then 1200 mg every 2 weeks	48 weeks	Case report ECU notably improved her motor symptoms by week 8 of therapy. QMG and MG-ADL scores decreased from 23 and 12 to 7 and 2 at week 48, respectively. ECU was well tolerated
Amano E et al.	2019		1		34 weeks	

(*continued on next page*)

Table 1 (*continued*)

Author	Year	MG subgroups	Patients	Treatment	Duration	Study design
		Thymoma-associated, AChR-positive striational-positive gMG		900 mg on day 1 and weeks 1, 2, and 3, followed by 1200 mg every 2 weeks		Case report QMG and MG-ADL scores reduced from 13 to 4 and 18 to 5 at week 12, respectively. Prednisolone was tapered from 20 mg/d to 5 mg/d after week 34. ECU was well tolerated
Yeo CJJ et al.	2018	AchR-negative, myasthenic crisis no thymoma gMG	1	900 mg weekly for 4 weeks then 1200 mg every 2 weeks	6 weeks	Case report At 4 weeks, tolerated it for 12–15 h daily, walking around without ventilator support.; At 6 weeks, she tolerated 48 h tracheostomy collar. QMG and MG-ADL scores both dropped from 20 to 13 over 41 days; ECU was well tolerated
Oyama M, et al.	2020	11 AChR-positive, 7 myasthenic crisis 5 thymoma gMG	12	900 mg on day 1 and weeks 1, 2, and 3, then 1200 mg every 2 week	26 weeks	Retrospective study Mean QMG and MG-ADL scores ranged from 18.6 to 9.1 ($p = 0.008$) and 10.8 to 4.2 ($p = 0.002$) at week 26. All but one patient did not need additional rescue treatment. ECU was well tolerated
Hofstadt-van Oy U et al.	2021	AchR-positive, myasthenic crisis no thymoma gMG	1	900 mg weekly for 4 weeks, followed by 1200 mg every 2 weeks	10 weeks	Case report Bulbar symptoms such as dysarthria or dysphagia were completely resolved 10 weeks after the start of eculizumab; MGFA from 4b to 2a at 10 weeks after the start of eculizumab ECU was well tolerated

ECU: eculizumab; gMG: generalized myasthenia gravis; AChR: acetylcholine receptor; MuSK: muscle-specific kinase receptor; QMG: Quantitative Myasthenia Gravis; MG-ADL: Myasthenia Gravis-Activities of Daily Living; MG-QoL15: 15-item Myasthenia Gravis Quality of Life; MGC: Myasthenia Gravis Composite; MGFA: Myasthenia Gravis Foundation of America; SBCT: single -breath count test; PE: plasma exchange; HDMP: high dose methylprednisolone; IVIG: intravenous immunoglobulin; PE: plasma exchange.

primary outcome. Futhermore, eculizumab ranked the most tolerable therapies causing the least counts of AEs compare with placebo. Another retrospective study reported 15 refractory AChR-positive gMG patients treated with eculizumab for 12 months. Following initiation, clinically significant reductions were observed in total MG-ADL scores at 3 months and maintained 12 months in all patients. After 12 months, there was a gradual increase in single-breath count test score in all patients and acute exacerbations were significantly reduced. All patients reduced daily prednisone dose (Katyal et al., 2021). These findings indicated that eculizumab represented the most effective therapeutic alternative to improve clinical symptoms of MG patients with good tolerability and could be recommended for refractory MG.

Recently, an interim analysis assessed the safety and effectiveness of eculizumab treatment in 40 patients with AChR-positive gMG in Japan. Comparing with baseline, the mean (SD) changes of MG-ADL and QMG scores were −3.7 (2.61) and −5.6 (3.50), respectively, at 12 weeks, and −4.3 (2.72) and −5.6 (4.02), respectively, at 26 weeks. Frequency of IVIg use decreased after eculizumab initiation (Murai et al., 2021).

Eculizumab has been approved for the treatment of adult AChR-positive gMG in USA (Alexion Pharmaceuticals Inc., 2015), AChR-positive refractory gMG in the European (Alexion Europe SAS, 2017), and AChR-positive gMG patients whose symptoms are difficult to be control with IVIg or PE in Japan (Japan Ministry of Health Labour and Welfare, 2017; Murai et al., 2019). In Farmakidis et al., 2020, International Consensus Guidance for Management of Myasthenia Gravis has recommended that eculizumab should be considered in the treatment of severe, refractory, AChR-positive gMG (Median 9, range 2–9) (Narayanaswami et al., 2020).

3. Eculizumab in AchR antibody-negative MG

Despite the efficacy of eculizumab in treating AchR antibody-positive refractory gMG was demonstrated in the REGAIN study, there is few information on its effects in patients who are seronegative for anti-AChR antibodies.

Datta S et al. described six patients with refractory AChR antibody-negative gMG treated with eculizumab for 12 months (Datta et al., 2020). After eculizumab treatment, clinically meaningful reductions (≥2 points) in total MG-ADL scores were observed at month 5 and were maintained to month 12 in all patients; the mean number of exacerbations was reduced from 2.8 to 0.3 in the 12 months before and after eculizumab initiation, respectively. Physical assessment ratings were improved in all patients. Adverse events occurred in four patients, but all were mild and none were treatment-related. Greenwood GT et al. reported a successful transition from 3-times weekly plasma exchange (PLEX) to eculizumab because of worsening symptoms in a female patient with treatment-refractory, AChR antibody and MuSK antibody-negative gMG. During eculizumab treatment, the patient's MG-ADL score decreased from 9 to 1 or 2 at most assessments and PLEX was discontinued at Week 39 after eculizumab initiation (Greenwood and Lynch, 2020).

These retrospective analysis initially explored the efficacy of eculizumab in refractory AChR antibody-negative gMG. Due to the small sample size of these studies, more evidence is required to confirm the effectiveness of eculizumab in antibody-negative MG.

4. Eculizumab in thymoma-associated MG

MG is frequently accompanied with thymoma, however, patients with a history of thymoma or thymic neoplasms were excluded from the REGAIN study. Until now, only a few case reports suggests that eculizumab is effective for thymoma-associated gMG.

Vélez-Santamaría V et al. reported a 25-year-old woman of refractory thymoma-associated MG treated with eculizumab. Her blood testing revealed AchR antibody positivity and chest computed tomography showed a large anterior mediastinal mass suggestive of thymoma. After treatment with eculizumab, her motor and bulbar symptoms notably improved by 8 weeks, and the QMG and MG-ADL scores decreased from 23 and 12 to 9 and 3, respectively (Vélez-Santamaría et al., 2020). Another case was a 34-year-old male of refractory thymoma-associated

gMG with anti-AChR and anti-striational antibodies. Before eculizumab treatment, the patient was receiving predonisolone (20 mg/day) and tacrolimus (2.5 mg/day) and exhibited severe physical exhaustion. After a standard dosing schedule of eculizumab treatment, his motor symptoms substantially improved, and prednisolone was safely tapered. After week 34, the patient exhibited minimal manifestations with 3 mg/day tacrolimus and 5 mg/day prednisolone (Amano et al., 2019).

5. Eculizumab in Myasthenia gravis crisis

Yeo CJJ et al. reported promising results with eculizumab in treating AchR-antibody negative refractory myasthenic crisis in 2018. Despite the usage of corticosteroids, plasma exchanges and IVIG, the patient remained severe respiratory distress and ventilator-dependent. At 25 days of ventilation, she received eculizumab and the symptoms improved soon. At week 4, she could walk 12–15 h daily without ventilator support, and at week 6, she tolerated 48 h without ventilator support after tracheostomy collar. The modified QMG and MG-ADL scores improved by 7 points over 6 weeks. Rapid improvement of symptoms in this patient suggests that eculizumab may be a potentially useful rescue treatment in myasthenic crisis (Yeo and Pleitez, 2018).

In another article, eculizumab was administered to 12 Japanese patients over the course of 1 year, soon after its approval in Japan. A total of 11 patients who were anti-AchR antibody-positive with refractory gMG completed the 26-week treatment with eculizumab. Seven patients had experienced myasthenic crisis. After eculizumab infusion, the mean QMG and MG-ADL scores ranged from 18.6 to 9.1 and 10.8 to 4.2 at week 26 ($p = 0.008$, $p = 0.002$ respectively). All but one patient did not need additional rescue treatment (Oyama et al., 2020).

Most recently, a case reported a 62-year-old caucasian male refractory MG patient with positive AchR antibodies suffered a severe myasthenic crisis due to COVID-19 pneumonia and persistent septicaemia. After receiving IVIG, PLEX and escalation therapy with eculizumab, the patient had a complete recovery (Hofstadt-van et al., 2021).

6. Safety and adverse events (AEs) in MG

Intravenous eculizumab was generally well tolerated in refractory gMG patients, with a tolerability profile generally similiar to that observed in the other approved indications, PNH and aHUS (Hill et al., 2005; Palma and Langman, 2016; Ninomiya et al., 2016). The most common AEs are headache, nasopharyngitis, arthralgia, diarrhea and infections. Most AEs are mild to moderate. Serious infections such as aspergillus and pseudomonas were reported in eculizumab-treated MG patients, but direct relationship with eculizumab cannot be definitely established considering infections may occur in other immunosuppressive therapies. However, complement inhibition increased the risk of meningococcus infection, so all patients are required to have received meningococcal vaccination at least 2 weeks before eculizumab initiation (McNamara et al., 2017; Farmakidis et al., 2020).

In the phase 3 REGAIN study in patients with refractory gMG, the incidence of treatment-emergent AEs in eculizumab recipients were generally similar comparing with placebo (86% VS 89.0%), and most AEs were mild or moderate in severity. Serious AEs were occured in nine (15%) patients treated with eculizumab and 18 (29%) patients received placebo. Four patients treated with eculizumab discontinued because of AEs, including one patient who had MG crisis and died 90 days after the last eculizumab dose due to crisis-related complications (Howard et al., 2017).

In open-label extension of REGAIN study, there were no occurrences of meningococcal infection by the end of trial, only one non-fatal case was reported afterward (Mantegazza et al., 2020). The drug showed a good tolerability and no specific safety concerns were found (Howard et al., 2017; Mantegazza et al., 2020). Therefore, eculizumab appears to be substantially safe in the long-period treatment of MG.

7. Future challenges

7.1. Is AChR antibody-negative MG suitable for eculizumab treatment?

Although AChR antibody-negative MG is classified as a separate subtype of MG, there is increasing evidence that it is similar with AChR antibody-positive MG in clinical characteristics, thymic pathology and immunosuppressive treatment response (Romi et al., 2005; Lauriola et al., 2005; Leite et al., 2008). AChR antibody-positive and AChR antibody-negative MG also have the same pathophysiological features. Leite MI et al. found that the sera from patients with AChR antibody-negative were capable of activating complement C3 and MACs (Leite et al., 2008). More recently, Hoffmann S et al. identified the complement and MACs at the motor endplate in muscle biopsies from 'triple-seronegative' refractory MG patients (no antibodies to AChR, MuSK, or LRP4) (Hoffmann et al., 2020). These clinical founding suggest that the complement system plays a crucial role in pathogenesis development of patients with AChR antibody-negative MG (Jacob et al., 2012; Vincent et al., 2008).

In addition, the assays most commonly used to measure anti-AChR autoantibodies including enzyme-linked immunosorbent assay (ELISA) and radioimmunoprecipitation assay (RIA) sometimes get false negative results as they are not sufficiently sensitive (Leite et al., 2010; Vincent et al., 2018). It has been shown that there are low-affinity AChR antibodies present in 35% of patients who previously detected negative using conventional assays (Dalakas, 2019), and cell-based assays (CBA), rather than ELISA or RIA, should be recommended in the assessment of patients with AChR antibody-negative MG (Leite et al., 2008; Vincent et al., 2018; Cossins et al., 2012; Jacob et al., 2012). However, AChR antibody detection was based on RIA in the current study, so it is possible that some would have tested positive if more sensitive assays had been used.

Based on these evidences, complement inhibition should be considered in individualized therapies of refractory AChR antibody-negative gMG with histopathologically confirmed complement deposition at the NMJ and the patients that get false negative results by conventional assays.

7.2. Antibodies subtypes selection for eculizumab

As we know that AChR antibodies belong to the IgG1 and IgG3 subclasses and LRP4 antibodies belong to the IgG1 subclass. A more severe thymoma MG and late-onset MG usually reveal titin and ryanodine receptor (RyR) antibodies (Zisimopoulou et al., 2013; Romi et al., 2000). The titin antibodies occurred in the IgG 1 and IgG 4 subclasses, whereas RyR antibodies are mainly IgG1 and IgG3 subclasses, which are all presenting the capacity to activate complement protein signaling pathway.

The role of the complement system in MuSK antibody-related MG is not well understood. Serum MuSK antibodies are predominantly of the IgG4 isotype, and do not activate the complement cascade (Plomp et al., 2012). Nevertheless, current studies have confirmed that IgG1–3 antibodies present in some MuSK antibody-related MG patients even though they are at lower levels than IgG4 (Koneczny et al., 2013; Huijbers et al., 2019; Leite et al., 2008; Viegas et al., 2012). Sera from MuSK antibody positive patients were able to activate complement on MuSK transfected human embryonic kidney (HEK) cells in vitro (Leite et al., 2008), and levels of complement breakdown products were elevated in the patients' serum samples (Erdem et al., 2011). Furthermore, some MuSK antibody positive patients have been detected C3 deposition at limb NMJs (Shiraishi et al., 2005). These results suggest that the complement system might be involved in the pathogenesis of the disease at least in a fraction of MuSK-Ab-associated MG patients (Koneczny et al., 2013; Erdem et al., 2011; Leite et al., 2008).

Collectively, other gMG subgroups including LRP4 antibody positive MG and a fraction of MUSK antibody positive MG except for AChR

antibodies positive MG may be suitable recipients for eculizumab administration. Further studies are needed to confirm the efficacy of eculizumab in different MG antibody subtypes.

7.3. Genetic variations that lead to treatment resistance

As regard to genetic variations directly affecting the effectiveness of complement inhibitors, few studies have been performed so far. Nishimura et al. reported a rare missense C5 heterozygous sequence variant c.2654G→A (p. Arg885His) identified in 11 paroxysmal nocturnal hemoglobinuria (PNH) patients with poor response to eculizumab treatment (3.2% of the PNH population receiving eculizumab). Further investigation revealed this variant was found in 3.5% of the Japanese population (Nishimura et al., 2014). In addition, an Asian PNH patient with a poor response to eculizumab also had a very similar gene variant in C5 (c.2653C→T) (Du et al., 2016). Both variants caused a replacement of arginine by histidine or cysteine and the structural changes in C5, so that eculizumab cannot bind to C5 (Schatz-Jakobsen et al., 2016).

A few small retrospective series indicated that relapse risk of atypical hemolytic uremic syndrome (aHUS) after eculizumab discontinuation appears to be higher in carriers of rare complement gene variants (Ardissino et al., 2015; Merrill et al., 2017; Fakhouri et al., 2017). Fadi Fakhouri et al. analyzed 38 patients with aHUS who discontinued eculizumab and identified that patients with complement factor H (CFH) variants and membrane cofactor protein (MCP) variants had a high risk of relapse. Another 33-year-old female aHUS patient was reported that thrombotic microangiopathy recurred following eculizumab discontinuation, and her genetic analysis revealed a novel mutation in exon 21 of complement factor H (CFH) (c.3454T>A; p.C1152S) (Sahutoglu et al., 2016).

Currently, studies associating gene variants with response to eculizumab treatment are lacking in MG patients, and the genetic profile in different population ethnicity also should be taken into consideration in eculizumab treatment.

7.4. Infection risk related to eculizumab treatment

Infection is a main concern of complement inhibitors treatment. In 2017, a CDC report showed a high risk for invasive meningococcal disease among patients receiving eculizumab despite receipt of meningococcal vaccine. 16 meningococcal disease cases were identified from 10 jurisdictions during 2008–2016 (10 patients were receiving eculizumab for PNH, 5 for aHUS, and 1 for another condition, through a clinical trial), 1 patient died (case-fatality ratio = 6%) (Lucy et al., 2017). Recently, a pharmacovigilance analysis of eculizumab in PNH and aHUS patients revealed meningococcal risk was 0.25/100 patient-years (PY) in the 10 years (Gérard et al., 2019). Other commonly reported infections include pneumonia (11.8%); bacteraemia, sepsis and septic shock (11.1%); urinary tract infection (4.1%); staphylococcal infection (2.6%); and viral infection (2.5%) (Muppidi et al., 2019). Therefore, in many jurisdictions, prophylactic antibiotics are also recommended to guard against other infections in eculizumab administration except for mandatory meningococcal vaccinations.

7.5. Medication cost

The costs of eculizumab for MG treatment is over $720,000 per year ($60,000 per month) in the United States, and 60,000,000 Yen per year in Japan. Consequently, eculizumab is considered as one of the most expensive drugs (Edmundson and Guidon, 2019; Munenori et al., 2020). Therefore, the use of eculizumab need well weighed and the patient should be carefully selected. Currently, eculizumab is recommended in the treatment of severe, refractory, AChR antibody positive gMG. In other MG populations such as patients with thymoma, seronegative MG, and patients with myasthenia crisis who have not tolerated or responded to acetylcholine esterase inhibitors, corticosteroids, IVIG, PE and conventional immunosuppressive drugs, eculizumab is an alternative, and its efficacy need further research to assessment.

Cost-effectiveness should be considered besides the efficacy and tolerability when choosing a drug. There are no pharmacoeconomic analyses of eculizumab in patients with gMG currently. Well-designed studies assessing the cost-effectiveness of eculizumab are needed so as to reduce the expensive financial burden of eculizumab on MG patients.

Additionally, defining optimal treatment duration and maintenance dose, seeking biomarkers of disease activity and response to treatment, combinating with other Immunosuppressant are needed for the better control of medication cost in MG patients.

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Declaration of Competing Interest

The authors have no conflicts of interest.

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