Eculizumab in myasthenia gravis: A review

Avery Zhou[1], Sabrina Ho[1], Aroucha Vickers[2,3]

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Abstract:

Eculizumab, a monoclonal antibody against complement C5, is a novel therapy to treat refractory myasthenia gravis (MG). The present review was undertaken to study the role of eculizumab in MG. This includes the drug's mechanism, pharmacokinetics, clinical trial findings, tolerability, side effects, safety, dosage, administration, and cost. An English-language search for relevant items was undertaken using Embase and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Keywords were eculizumab and MG. The present review found 103 articles after initial screening. Current data support eculizumab as an effective, safe, and tolerable drug in cases of refractory MG. However, its cost can prevent it from being widely accessible to a majority of the general population.

Keywords:

Eculizumab, myasthenia gravis, neuro-ophthalmology, pharmaceutics

Introduction

Myasthenia gravis (MG) is an autoimmune condition that causes characteristic muscle weakness that worsens with repeated muscle work.[1] The most common presenting symptom of MG is ptosis and diplopia; however, it may also present with difficulty swallowing, generalized fatigue, and respiratory weakness.[2] Although symptom severity may fluctuate over time, MG does not involve continuous disease progression.[1] The incidence of MG is estimated to be 4.1–30 cases/million person-years, and prevalence rates range from 150 to 200 cases/million.[3]

MG is caused by autoantibodies that bind to the postsynaptic membrane in the neuromuscular junction and prevent acetylcholine (ACh) from binding to its postsynaptic receptor. The most common autoantibody involved in MG is the ACh receptor (AChR) antibody which is highly specific (>99%) for MG, highly sensitive for generalized MG (85%–90%), but less sensitive for ocular MG (44%–80%).[1,4-7] These AchR antibodies are immunoglobulin (Ig) G1 and IgG3 antibodies that cause activation of the complement system, formation of the membrane attack complex (MAC), and damage of the receptors.[8] Less commonly, patients have antibodies against muscle-specific kinase, lipoprotein-receptor-related protein 4, or agrin.[4,9] Titin and ryanodine receptor antibodies have also been proposed as markers for severe MG.[4]

For research purposes, MG can be classified by clinical symptoms on a scale of intravenous (IV). Class I MG involves ocular symptoms only, whereas Class V MG includes significant respiratory involvement and intubation. This classification system was established by the Task Force of the Medical Scientific Advisory Board of the MG Foundation of America (MGFA) in July 2000 [Table 1].[10] In MG clinical trials, MG severity is monitored quantitatively by the quantitative MG (QMG) scoring system or the MG-Activities of Daily Living (MG-ADL) score. The QMG is conducted by a clinician and is a 13-item test that grades sentinel muscle groups on a scale of 0 (none) to 3 (severe).[10] The MG-ADL is a patient self-survey and is an eight-question survey of MG symptoms graded from 0 to 3.[11] There is a high correlation between the MG-ADL and QMG scores;[11] therefore, both are used in clinical research.

Initial symptomatic treatment of all subgroups of MG involves ACh esterase inhibitors such

[1]Kirk Kerkorian School of Medicine, [2]Department of Neurology, Valley Hospital Medical Center, [3]Department of Neuro-Ophthalmology, Las Vegas Neurology Center, Las Vegas, NV, USA

Address for correspondence: Dr. Aroucha Vickers, Department of Neuro-Ophthalmology, Las Vegas Neurology Center, 2020 Wellness Way, Suite 300, Las Vegas, NV 89106, USA. E-mail: drarouchavickers@lvneuro.com

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as pyridostigmine. This drug inhibits the breakdown of Ach at the neuromuscular junction, resulting in increased availability of Ach. Other ACh esterase inhibitors such as 3,4-diaminopyridine, ephedrine, and terbutaline have shown less efficacy with more side effects.[12]

Myasthenic crisis occurs in 15%–20% of all MG patients and typically occurs within a year of MG symptom onset.[13] After appropriate respiratory support is established, acute medical management of MG flares involves treatment with plasma exchange (PLEX) or IV Ig (IVIg). The typical protocol for PLEX is 5 exchanges of 1 plasma volume every other day for 10 days and the typical protocol for IVIg is 400 mg/kg daily for 5 days. Response usually occurs within a few days and lasts several weeks, but if there is an insufficient response, IVIg can be administered after PLEX.[13]

For patients who do not achieve adequate results on symptomatic treatment alone, steroidal therapy such as prednisone can be initiated.[14] Results from the EPITOME study (a randomized, double-blind, and placebo-controlled trial) revealed that prednisone regressed symptoms of MG within a median of 14 weeks.[15] However, chronic steroid use is associated with numerous adverse effects including but not limited to weight gain, hypertension, diabetes, glaucoma, and cataract.[16] Steroid-sparing agents should be initiated when there is a concern for adverse effects.[17]

Nonsteroidal immunosuppressive therapy using agents such as azathioprine, mycophenolate mofetil, methotrexate, cyclosporine A, or tacrolimus can be used if steroids are not successful. Of these options, azathioprine is the most frequently used agent and is initiated at 50 mg once daily with a target dose of 2–3 mg/kg/day then tapered to 1 mg/kg/day for maintenance.[17] If all previous interventions fail to control the disease, which occurs in about 20% of all MG patients,[18] monoclonal antibody therapies and complement modulation treatment can be considered. Monoclonal antibody treatments include rituximab, which binds the B-lymphocyte membrane protein CD20 and depletes pathogenic B-cells, decreasing AChR antibody production.[18] Complement modulation treatment is the latest therapy approved in treating refractory MG, and eculizumab will be the primary focus of this review.

Methods

A literature search of both the PubMed and Embase electronic databases was performed in January 2023. The main search terms were "eculizumab" and "MG." In total, 134 and 421 articles were found in PubMed and Embase, respectively, and titles were screened by SH, followed by screening of the abstract and full text. We excluded languages other than English, duplicates, case reports that included <4 cases, articles in which no full text was available, and articles that did not include data on eculizumab or MG. A table summarizing the data selection process is included [Table 2].

Eculizumab

Eculizumab, first approved in 2007 to treat paroxysmal nocturnal hemoglobinuria (PNH), was approved in 2017 to treat MG. It is a humanized monoclonal antibody against complement C5 which inhibits the cleavage of C5 into C5a and C5b [Figure 1].[19,20] Eculizumab is the first approved targeted complement inhibitor worldwide to treat complement-mediated diseases[21] and is indicated in the treatment of patients with PNH, atypical hemolytic uremic syndrome (aHUS), neuromyelitis optica spectrum disorder, and

Table 1:Myasthenia gravis clinical classification, as described by the Myasthenia Gravis Foundation of America

I - Any ocular muscle weakness, all other muscle strength is normal
II - Mild weakness affecting other than ocular muscles
IIa - Predominantly affecting limb, axial muscles, or both
IIb - Predominantly affecting oropharyngeal, respiratory muscles, or both
III - Moderate weakness affecting other than ocular muscles
IIIa - Predominantly affecting limb, axial muscles, or both
IIIb - Predominantly affecting oropharyngeal, respiratory muscles, or both
IV - Severe weakness affecting other than ocular muscles
IVa - Predominantly affecting limb, axial muscles, or both
IVb - Predominantly affecting oropharyngeal, respiratory muscles, or both
V - Intubation, with or without mechanical ventilation, except when employed during routine postoperative management

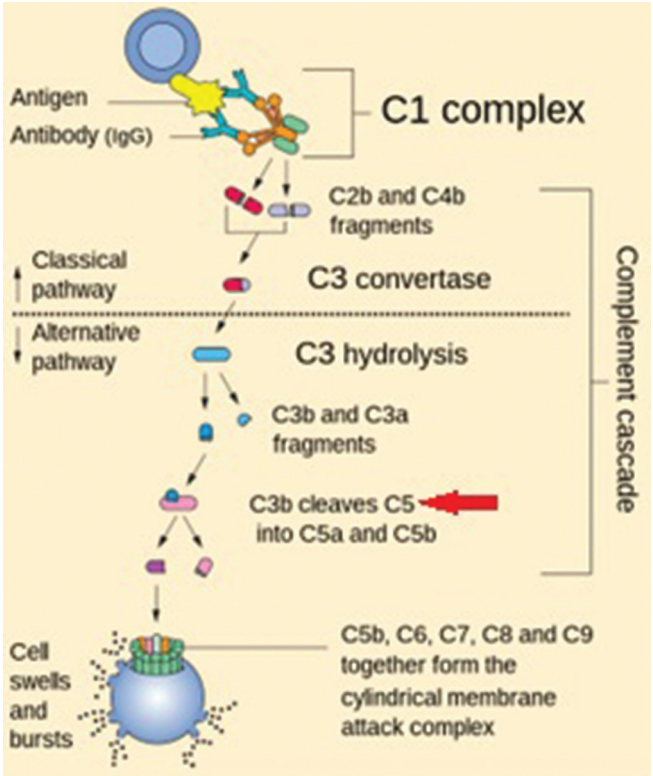

Figure 1: Simplified diagram of the complement cascade. The red arrow denotes the step in the complement cascade that is halted by eculizumab. "Complement pathway" by the US Federal Government is in the public domain

Table 2: Data selection process for the review of eculizumab in myasthenia gravis. Keywords of "eculizumab" and "myasthenia gravis" were searched on PubMed and EMBASE from 1946 to present. Searches were last updated on January 15, 2023

Total records identified	555
Duplicates removed	104
Excluded during initial screening (e.g., press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial; not English)	348
Excluded during writing (e.g., reviews; duplicate data; small patient number; nonrandomized/phase I/II trials; abstracts; article corrections)	58
Cited articles	45

Search Strategy: EMBASE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Eculizumab, myasthenia gravis. Records were limited to those in the English language. Searches last updated 15 January 2023

AChR antibody-positive MG.[22] As AChR antibody-positive MG causes postsynaptic damage through activation of the complement cascade, eculizumab is able to halt the formation of C5b, thereby preventing the formation of the MAC. Eculizumab also halts the formation of C5a, a potent pro-inflammatory, and anaphylactic mediator.[23]

Eculizumab Clinical Trials

The 2013 Phase 2 trial of eculizumab in MG was a randomized, double-blind, placebo-controlled, crossover trial including 14 patients with refractory generalized MG treated over 16 weeks, followed by a 5-week washout period then an additional 17 weeks after crossover. A QMG score reduction of at least 3 points was seen in 86% of the eculizumab group and 57% of the placebo group. A QMG score reduction of 8 points was seen in 57% of the eculizumab group and 14% of the placebo group. Results were also seen to be sustained, as QMG scores did not return to baseline throughout the washout period.[24]

The 2017 Phase 3 trial, termed the REGAIN trial (ClinicalTrials.gov identifier: NCT01997229), included 125 patients across 76 hospitals in 17 countries.[25] This was a randomized, double-blind, placebo-controlled study that included patients who were at least 18 years old, scored 6 or more on the MG-ADL scale, had MGFA Class II-IV disease, were vaccinated against Neisseria meningitides, and failed previous treatment of at least two immunosuppressive therapies or one immunosuppressive therapy and chronic IVIG/PLEX. Patients with a history of thymomas or thymic neoplasms, thymectomy within the past 12 months, MGFA Class I or V, treatment with IVIg or PLEX within 4 weeks, or rituximab therapy within 6 months were excluded from the study. Sixty-three patients were assigned to the placebo group and 62 were assigned to the treatment group. Groups were stratified according to demographics, disease status, and medical history. The eculizumab group received loading doses of 900 mg on day 1 and then every week until week 3. At week 4, the dosage was increased to 1200 mg and given every other week for maintenance. Prespecified statistical analyses found no significant difference in change in MG-ADL score between the two groups; however, *post hoc* sensitivity analyses found that eculizumab was effective in improving MG symptoms, was well tolerated, and could partially alleviate disease progression.[25] The benefit of eculizumab over placebo occurred within the first 4 weeks of treatment, and the majority of patients (67%) responded by week 12 with sustained improvement until the end of the study (week 26). The mean change in MG-ADL and QMG scores was greater with eculizumab than with placebo, regardless of other immunosuppressive therapies. No deaths or cases of meningococcal infection occurred, and the most common adverse events reported were headache, upper respiratory tract infection, and nasopharyngitis. Serious adverse events were reported in 15% of the eculizumab cohort and 29% of the placebo cohort. The most common serious adverse event was infections (3% of the eculizumab cohort and 10% of the placebo cohort). Rescue therapy was required in 10% of the eculizumab cohort and 19% of the placebo cohort.

The open-label extension (OLE) study conducted using the REGAIN study group tracked outcomes for up to 4 years (ClinicalTrials.gov identifier: NCT02301624). All patients who completed the REGAIN study were eligible to participate in the OLE and everyone received eculizumab. A total of 116 patients participated in the OLE. Most patients responded by the 12th week; 17% of patients responded between the 12th and 130th week, and 15% did not respond to eculizumab within 130 weeks.[26] However, many patients were able to decrease the use of concomitant immunosuppressive therapies such as prednisone, azathioprine, and mycophenolate mofetil while on eculizumab due to symptom improvement; 48.7% of participants stopped or decreased an immunosuppressive therapy within the extension study period.[27] Of the 18 patients who received chronic IVIg before eculizumab (>4 times in 1 year, with at least one IVIg treatment cycle within 6 months of starting the REGAIN study), the rate of MG exacerbations reduced from 150 exacerbations/100 patient-years to 47 exacerbations/100 patient-years during REGAIN and the OLE.[28] This suggests that eculizumab may also benefit patients who otherwise require chronic IVIg treatments.

Further findings from the OLE are mentioned in their respective sections below.

Eculizumab Tolerability, Side Effects, and Safety

The OLE found that the safety profile of eculizumab was similar in patients who previously received rituximab compared to those who had not.[29] The most common adverse events include headache, nasopharyngitis, diarrhea, worsening MG, upper respiratory tract infection, nausea, musculoskeletal pain, and arthralgia.[22,29] Side effects were similar between the 11 Japanese patients and 88 Caucasian patients after 52 weeks.[30] Infection rates in the eculizumab study group were similar to those in the

placebo group, regardless of concomitant immunosuppressive therapies,[31] and there were no cases of meningococcal infections in either the REGAIN study or the OLE.[25,26]

One of the most serious risks associated with eculizumab is fatal meningococcal infection. Since eculizumab interferes with the formation of the MAC, the body's natural immunological defense against *Neisseria meningitidis* is compromised. As of 2019, the incidence of meningococcal infection was 3.0/1000 person-years and as of 2017, the mortality rate was 0.34/1000 person-years.[32] For this reason, eculizumab is contraindicated in patients who are not vaccinated against *N. meningitidis* or have unresolved *N. meningitidis* infection, unless risks of delaying eculizumab treatment outweigh the risk of developing a meningococcal infection.[22]

To manage this potential serious risk, eculizumab has a risk evaluation and mitigation strategy (REMS), a program by the United States Food and Drug Administration (FDA).[33] Eculizumab may only be prescribed by health-care workers who are specially certified and have enrolled in the eculizumab REMS program. Patients must be immunized with meningococcal vaccines at least 2 weeks before the first dose of eculizumab and if eculizumab must be initiated immediately, patients must be given 2 weeks of antibacterial drug prophylaxis.[33]

Eculizumab Dosage, Administration, and Pharmacokinetics

Eculizumab is administered as an IV infusion over 35 min in adults and 1–4 h in pediatric patients.[22] The dosing regimen currently recommended that was used in the Phase 3 REGAIN study (900 mg weekly for the first four doses, followed by 1200 mg 1 week later and 1200 mg every 2 weeks afterward) was investigated by Monteleone *et al*. using data from the REGAIN study.[34] Blood samples were collected to measure baseline, trough, and peak eculizumab concentrations up to week 26. Eculizumab acted similarly to a two-compartment population pharmacokinetic model with first-order elimination.[34] The terminal elimination half-life was found to be 18.2 days, which allows for slight fluctuations in intervals without risk of incomplete complement inhibition. Complete terminal complement inhibition (serum-free C5 <0.5 μg/mL or *in vitro* chicken red blood cell hemolysis <20%) was detected by the end of the first dose infusion and sustained throughout the treatment period. Eculizumab was also found to be very well-tolerated regardless of serum concentration; adverse events were similar in the eculizumab and placebo groups, and no trends were observed with increased serum eculizumab concentrations.[34]

Modified doses are required if the patient receives PLEX or fresh frozen plasma infusion. For PLEX patients, there is a supplemental dose of 300 or 600 mg of eculizumab within 60 min after PLEX if the most recent eculizumab dose was 300 mg or >600 mg, respectively. For patients who receive fresh frozen plasma, there is a supplemental dose of 300 mg of eculizumab 60 min before fresh frozen plasma.[22]

Long-term Outcomes of Eculizumab

Patients treated with eculizumab maintained minimal symptom expression with sustained, long-term tolerability (through 130 weeks).[35-37] Furthermore, more patients experienced improvement after long-term eculizumab (88% of patients experienced improved symptoms after 130 weeks, increased from 60.7% of patients after 26 weeks) with 57.3% experiencing MGFA's classification of minimal manifestations (MM) (no symptoms indicating functional limitations) by the end of the OLE.[38]

Eculizumab Compared to Other Immunotherapies

A network meta-analysis conducted by Wang *et al*. in 2019 found that cyclosporine A, eculizumab, and tacrolimus showed significantly superior efficacy in reducing QMG compared to placebo scores (−1.19, −0.80, and −0.41, respectively), whereas belimumab, methotrexate, azathioprine, and mycophenolate mofetil did not.[39] Eculizumab also had a preferable safety profile compared to placebo, azathioprine, methotrexate, tacrolimus, mycophenolate mofetil, and cyclosporine A; belimumab had a preferable safety profile to eculizumab (hazard ratio of 1.09).[39]

In a model-based meta-analysis conducted by Chen *et al*. in 2021, eculizumab was superior to efgartigimod, zilucoplan, belimumab, and iscalimab in QMG scores.[40,41] Eculizumab was also noted to have a more rapid onset and be more effective than immunosuppressants such as mycophenolate mofetil, prednisone, tacrolimus, and cyclosporine. When evaluating based on MG-ADL scores, eculizumab was superior to belimumab, iscalimab, and zilucoplan but inferior to efgartigimod.[40] A similar Bayesian network meta-analysis found that eculizumab had superior improvement in MG-ADL and QMG scores compared to belimumab, efgartigimod, rozanolixizumab, and placebo.[41] Eculizumab was associated with a higher probability of adverse events than placebo, efgartigimod, and belimumab. However, rates of serious adverse events occurred at higher rates in placebo than in eculizumab.[41]

A 2021 systematic review compared eculizumab with rituximab in refractory MG.[42] Quantitative synthesis of the eight studies on rituximab (196 patients) and five studies on eculizumab (170 patients) was analyzed. Eculizumab was found to reduce QMG by 6.93, reduce MG-ADL by 4.34, and induce MM in 49% of patients. This was not significantly different than rituximab, which reduced QMG by 4.16, reduced MG-ADL by 4.40, and induced MM in 67% of patients. There was no significant difference in rates of adverse severe event density between eculizumab and rituximab, but there were more adverse events overall associated with eculizumab than rituximab (1.195 vs. 0.134/patient-year).[42]

Other C5 Inhibitors for Myasthenia Gravis

Ravulizumab-cwvz is a C5 complement inhibitor that was

Table 3: Postmarketing studies of the efficacy and safety of eculizumab

	Country	Patients enrolled	Length of follow-up	ΔMG-ADL	ΔQMG	Serious AE
Murai, 202147	Japan	40	26 weeks	-4.3	-5.6	10%
Murai, 202248	Japan	134	52 weeks	-5.0	-6.35	18.7%
Narayanaswami, 202249	USA	59	7-2,435 days	-5.2	N/A	10.2%

ΔMG-ADL=change in Myasthenia Gravis-Activities of Daily Living score, ΔQMG=change in Qualitative Myasthenia Gravis score, AE=adverse events.

approved by the FDA in April 2022[43] and by the European Commission in September 2022,[44] following the results of the CHAMPION-MG Phase III trial (ClinicalTrials.gov identifier: NCT03920293).[45] Ravulizumab has a longer half-life and thus requires maintenance dosing every 8 weeks in adult patients compared to eculizumab which requires dosing every 2 weeks.[45] Results of the Phase III trial show that, by week 26, patients treated with ravulizumab experienced significant improvements in MG-ADL and QMG scores (−3.1 and −2.8, respectively). Improvements occurred within 1 week of initiation and were sustained throughout the trial. This is a significantly faster onset of action compared to the results of eculizumab's Phase III clinical trial, which did not demonstrate a significant improvement for most patients until week 12. Although ravulizumab was previously approved for PNH and aHUS, it is still a novel drug for MG, and more research is required to determine its safety and efficacy compared to eculizumab.

The most recent drug undergoing investigation to treat MG through the complement cascade is zilucoplan, a macrocyclic peptide that binds to and inhibits C5. It is administered through a daily subcutaneous injection and has shown rapid, statistically significant, and sustained results in its 12-week Phase II study (average of −6.0 QMG and −3.4 MG-ADL scores) that was published in May 2020.[46] The Phase III study is currently ongoing at the time of this review (ClinicalTrials.gov identifier: NCT04115293).

Eculizumab Real-world Studies

Only a few postmarketing studies have been published at the time of this review,[47,48] with one being an analysis of registry data.[49] Of those that have been published, eculizumab's efficacy and safety outcomes were found to be generally consistent with the findings from REGAIN. The current up-to-date studies that analyzed data using patients beyond the REGAIN study group are summarized in Table 3.[47-50]

Eculizumab Cost-effectiveness

The Institute for Clinical and Economic Review is an independent nonprofit organization that assesses drug costs in the United States.[51] Although the group concluded that there was at least a high certainty of a small net health benefit from eculizumab, the cost of eculizumab added to conventional therapy was not cost-effective compared to conventional therapy alone. As of 2021, the annual cost of eculizumab was $653,100 and the incremental cost-effectiveness ratio was $5,210,000 per quality-adjusted life year (QALY). Even with adjustments made to increase the effectiveness of eculizumab to what was presented in the REGAIN study, the effectiveness ratio never reached <$3,800,000 per QALY. The current price of eculizumab is remarkably high and far exceeds the $13,200–$19,400 (calculated based on the amount of health improvement received by therapy) needed to reach traditional cost-effectiveness thresholds in the United States per their standards.[51]

Conclusion

Eculizumab is the first approved complement inhibitor to treat refractory anti-AChR antibody-positive MG. Results from the clinical trial *post hoc* analyses, extension studies, and postmarketing studies currently available in the literature have supported eculizumab as being a safe, tolerable, and effective therapy to treat refractory MG. However, eculizumab remains to be a prohibitively expensive drug that, from a cost–benefit perspective, does not make it a preferred treatment option over conventional therapy. Current gaps in the literature include the total length of treatment required, efficacy in nonrefractory MG, long-term efficacy, and long-term safety.

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Conflicts of interest

There are no conflicts of interest.

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