Myasthenia gravis (MG) is a chronic autoimmune disease, with an incidence of approximately 1 in 100,000 and a prevalence estimate of 14 to 20 per 100,000 (approximately 36,000 to 60,000 cases) in the US. The cardinal feature of generalized MG (gMG) is muscular weakness that increases in severity with exertion. Individuals with MG also have a variety of fluctuating symptoms, including ptosis, diplopia, dysphagia, dysphonia/dysarthria, dyspnea, and mobility impairment that significantly affect their quality of life.

**Autoantibodies and gMG**

Most people (~80%) with gMG have IgG autoantibodies directed against the skeletal muscle nicotinic acetylcholine receptor (antiAChR). AntiAChR may impair neuromuscular transmission via mechanisms that reduce the number and density of functional AchR (eg, functional blockade and accelerated internalization of the AChR). AntiAChR binding to the AChR can also activate the complement cascade, leading to the formation of the membrane attack complex (MAC) and postsynaptic membrane damage.

Another 10% of people with gMG have autoantibodies to muscle specific tyrosine kinase (antiMuSK). Onset of anti-MuSK+ gMG is usually acute with rapid progression (ie, often within weeks) predominantly affecting the faciobulbar muscles. The presence of early respiratory crises; muscle atrophy, particularly of the tongue and facial muscles; symptoms that do not fluctuate; and poor or no response to treatment with acetylcholine inhibitors and conventional immunosuppressants should raise clinical suspicion for antiMuSK+ gMG. Black individuals are more likely to have antiMuSK+ MG compared with white individuals, and many with antiMuSK+ MG have HLA-DRB1, DQB1, DQ5 and DR14 alleles.

Of the remaining 10% of people with MG who have neither antiAChR+ or antiMuSK+ status, approximately 15% have antibodies against low-density lipoprotein receptor-related protein 4 (LRP4) or agrin. Individuals with antiLRP4+ or antiagrin+ gMG have mean age 44 at onset, possibly more severe disease as measured by the Myasthenia Gravis Foundation of America (MGFA) classification, and a slight preponderance in women (59%). Most people with anti-LRP4+ or antiagrin+ MG have improvement with standard immunosuppressive or immunomodulatory therapy.

AntiMuSK, antiLRP4, and antiagrin may lead to impaired clustering of AChR at the neuromuscular junction. AntiLRP4 and antiagrin are IgG1, IgG2, and IgG3 subclasses, which may activate complement to various degrees.

**Treatment**

Recent therapeutic advances in the treatment of MG include complement blockade, facilitated removal of pathogenic autoantibodies via blockade of the neonatal Fc receptor (FcRn), and modulation of B cells with rituximab. There is also an association between the development of MG and immune check point inhibitors (ICI).
in MGC and MG-QoL15 was also observed by week 1 and 4, respectively. In an open-label extension study, the rate of MG exacerbation was reduced by 75% (P < .0001) compared with the year before enrollment in the study. Minimal manifestation status or pharmacologic remission was achieved by 56% of those treated with eculizumab. Eculizumab seems to have a favorable tolerability profile during pregnancy; available data indicate that there was no drug accumulation in fetal blood or adverse complement activity in newborns. A recent case report describes a person with MG who was successfully treated with eculizumab before, during, and after pregnancy.

Zilucoplan. Zilucoplan is a macrocyclic peptide that binds to C5 with high affinity and specificity. In a phase 2 clinical trial, 44 participants were randomly assigned 1:1:1 to receive a daily subcutaneous autoinjection of placebo, 0.1 mg/kg zilucoplan, or 0.3 mg/kg zilucoplan for 12 weeks. Individuals who received zilucoplan 0.3 mg/kg had a mean reduction 2.8 points on the QMG scale and 2.3 points on the MG-ADL compared with placebo. Rescue therapy was required in 3 of 15, 1 of 15, and 0 of 14 participants in the placebo, 0.1-mg/kg zilucoplan, and 0.3-mg/kg zilucoplan arms, respectively. Zilucoplan was observed to have a favorable safety and tolerability profile. A phase 3 study of zilucoplan is ongoing.

Ravulizumab. Ravulizumab is a longer acting monoclonal antibody against C5 complement protein that requires infusion every 2 months, instead of every 2 weeks as is needed with eculizumab. A phase 3 trial is ongoing with results expected in 2021.

FcγRn Antagonists

FcγRn is an MHC class I-like molecule that participates in the recycling of IgG. Endothelial cells endocytose IgG in the circulation that are subsequently transported to the lysosome. IgG bound to FcγRn in the lysosome are rescued from degradation, giving IgG a longer half-life than other immunoglobulins (eg, IgM or IgA) not bound to FcγRn. Thus, FcγRn prolongs availability of IgG autoantibodies in autoimmune diseases such as gMG. FcγRn blockade offers a promising therapeutic intervention to rapidly and selectively reduce IgG without depleting coagulation factors or causing hemodynamic instability which may occur with IgG removal techniques (eg, therapeutic plasma exchange).

There have been several clinical trials of FcγRn receptor antagonists in the treatment of patients with gMG.

Efgartigimod. Efgartigimod is a human IgG1 antibody Fc-fragment that binds with high affinity to FcγRn. Efgartigimod outcompetes endogenous IgG binding, thereby reducing IgG recycling and increasing IgG degradation. In a phase 2, multicenter, randomized, double-blind, placebo-controlled study of 24 participants, 75% of those who received 4 weekly doses of 10 mg/kg intravenous efgartigimod combined with their standard-of-care therapy had improvement from baseline to week 11 in MG-ADL, QMG, MGC, and MG-QoL15 scores compared with 25% of those who received placebo. Efgartigimod was well tolerated, and all participants treated with efgartigimod also had a rapid decrease in total IgG and antiAChR levels. A subsequent phase 3 study evaluated efficacy, safety, tolerability, quality of life, and impact on activities of daily living of efgartigimod in participants with gMG (n = 167). This trial was unique in enrolling participants who were antiAChR+ (77%) or antiAChR− (23%) if they had evidence of neuromuscular transmission defect (4% had anti-MuSK+ status). Of participants who were antiAChR+ treated with efgartigimod, 67.7% had at least a 2-point improvement on MG-ADL score sustained for at least 4 weeks compared with 29.7% of those treated with placebo (P < .0001). Similarly, among participants who were antiAChR+, 63.1% of those treated with efgartigimod vs 14.1% of those treated with placebo had at least a 3-point improvement on QMG sustained for at least 4 weeks with their first treatment cycle. The median duration between 2 consecutive infusion cycles was 10 weeks for both treatment and placebo arms. Among individuals who had these improvements, more than 80% had onset of effect within the first 2 weeks. After 1 cycle of treatment, 40% of patients in the efgartigimod group showed significant improvement of their MG-ADL score to 0 to 1, consistent with minimal symptom manifestation in comparison to 11% of patients in the placebo group. Of early responders in treatment cycle 1 who received efgartigimod, the duration of response was 6 to 7 weeks in 32%, 8 to 11 weeks in 23%, and more than 12 weeks in 34%. Among participants who were antiAChR−, improvements on both MG-ADL and QMG occurred in 47.4% treated with efgartigimod vs 21.1% with placebo recipients achieving both MG-ADL and QMG responder status. Efgartigimod has been submitted to the Food and Drug Administration (FDA) for approval with a decision date scheduled for December 2021.

Rozanolixizumab. A humanized monoclonal antibody to FcγRn, rozanolixizumab, has been tested in 43 participants with gMG in a phase 2a, randomized, double-blind, placebo-controlled, multicenter trial. Although the change from baseline in QMG after 29 days of treatment with rozanolixizumab vs placebo was not statistically significant, the data overall suggest that rozanolixizumab may provide clinical benefit for people with gMG. The most common adverse event was headache (rozanolixizumab 57% vs placebo 14%). A phase 3 study of rozanolixizumab is ongoing.

Nipocalimab. The engineered human aglycosylated IgG1 antiFcγRn monoclonal antibody nipocalimab was tested in a phase 2 study and well tolerated with no discontinuations because of adverse events. Individuals treated with nipocalimab had significant improvement from baseline in MG-ADL scores across all continuous doses compared with those who...
received placebo. Across all doses of nipocalimab, a greater proportion of participants had improvement in MG-ADL within 2 weeks of treatment, and the effect was durable in 51.9% with nipocalimab vs 15.4% with placebo (P = .017). Treatment with nipocalimab resulted in significant rapid reductions in serum total IgG and antiAChR. A phase 3 confirmatory study of nipocalimab is expected.

B-Cell Modulation

**Rituximab**. B cells express CD20 on the cell membrane until they differentiate into antibody-secreting plasma cells. Rituximab, a monoclonal antibody to CD20, has been used to treat people with gMG refractory to conventional immunosuppressants, including a small series of people with antiMuSK+ gMG, generally with positive results. In a multicenter, blinded, prospective review, comparing people with antiMuSK+ gMG treated with rituximab vs other medications, 58% of those treated with rituximab (n=24) achieved prespecified clinical improvements compared with 16% of those who received other medications (n=31; P < .002). Clinical improvement was defined as reaching level 2 on the Myasthenia Gravis Status and Treatment Intensity (MGSTI) scale, a composite measure of the MGFA postintervention status and the number and dosages of other immunosuppressant therapies. Additionally, 29% of participants treated with rituximab were taking prednisone (29%) compared with 74% of those who had other treatments (P < .001) and the dose of prednisone was lower with rituximab (mean 4.5 mg/day) compared with other treatments (mean 13 mg/day; P < .005). Based on the available data, the International Consensus Guidance for Management of Myasthenia Gravis (2020 Update) suggested rituximab should be considered an early treatment option in antiMuSK+ gMG with unsatisfactory response to initial immunotherapy.

Therapeutic effects of rituximab on antiAChR+ gMG are less robust. In a randomized, double-blind, placebo-controlled, multicenter, phase 2 clinical trial in which participants with antiAChR+ gMG had rituximab (n=26) or placebo (n=26) added to a steroid regimen for 8 weeks followed by 44 weeks of steroid taper, there were no statistically significant differences in the proportion of participants who had at least a 75% reduction in mean daily prednisone dose by week 48 without clinical worsening. This primary futility outcome was achieved in a cohort with predominantly mild disease. In a post hoc subgroup analysis of those with moderate-to-severe gMG (MGFA class III-IV; n=10 for rituximab; n=10 for placebo) the primary outcome was achieved by 60% of participants in the rituximab group and 50% of those in the placebo group (not significant). Change from baseline to week 52 in QMG was −3.9 (rituximab) vs −0.5 (placebo) and in MGC was −7.0 (rituximab) vs −4.8 (placebo). The authors concluded rituximab treatment effect on successful steroid taper could not be excluded, but the study lacked the power to make firm conclusions.

**Checkpoint Inhibitors and MG**

ICI, including ipilimumab, pembrolizumab, atezolizumab, and nivolumab are used for effective treatment of melanoma and other cancers. The development of MG after treatment with ICI, however, has been described. PostICI-MG mean symptom onset was a mean 4 weeks (range 1-16 weeks) after treatment, and 37% (24/65) of those described developed concurrent myositis. Notably, not all who developed MG were antiAChR+. Respiratory failure occurred in 45%, and 38% died; 15 deaths were caused by MG complications. Better outcomes were observed in those treated with intravenous immunoglobulin (IVIG) or plasma exchange as first-line therapy compared with those who received steroids alone (95% vs 63% improvement of MG symptoms). It is unknown whether patients who developed antiAChR continued to have MG symptoms after ICI discontinuation in the long term. The International Consensus Guidance suggests the risk of MG and other immune-mediated neurologic illnesses should be discussed with people who are candidates for ICI and that close observation is mandatory because of the severity and high rate of respiratory crisis in ICI-associated MG. Of note, the preexisting MG is not considered as an absolute contraindication to the use of ICI, at least in those with minimal manifestation status or better. However, combined therapy (anti–CTLA-4 plus anti-PD-1/PD-L1 monoclonal antibodies) should be avoided in anyone who has MD. Furthermore, MG treatment should be maintained and perhaps restarted in those who are in remission before treatment with ICI.

**Conclusions**

The FDA approval of eculizumab for treatment of gMG in 2017 marked the beginning of a new era in MG treatment. Complement inhibition is a new intervention that has improved patients’ function and quality of life. Data from clinical trials of FcRn antagonists efgartigimod, rozanolixizumab, and nipocalimab promise another effective therapeutic venuel. Features that distinguish these medications from conventional immunosuppressants are the rapid onset of action, availability of high-quality data from well-controlled studies, and the relatively safe therapeutic profile. The effects of these medications on gMG associated with antiMuSK, antiLRP4, and antiagrin are yet to be determined. Challenges remain in the diagnosis and treatment of those with myasthenic symptoms without detectable antibodies. More studies are needed to determine whether combinations of novel mechanistically distinct therapies are safe and efficacious for refractory MG. Where these novel therapies fit in the treatment paradigm will also need to be better understood (ie, first- vs second-line treatments or maintenance vs rescue therapy during a myasthenic crisis). With the current pace of drug development, the treatment options for MG will likely soon increase significantly.
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Disclosures
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