Myasthenia Gravis Treatment

There are both disease-modifying and symptom-reducing treatments available and emerging treatment possibilities.

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Myasthenia gravis (MG) is an autoimmune neuromuscular junction disorder that causes skeletal muscle fatigable weakness and is the most common neuromuscular disorder.[1] Management of MG is based on clinical severity of symptoms, type of autoantibody involved, age, comorbidities, and the presence of thymoma. Conventional treatment may be complicated for some because of a wide range of medication regimens with variable onset of action and response. A number of emerging immunotherapies that target different pathways of the immune system have expanded treatment options. In this article, we review the role of novel nonsurgical therapies in the acute and chronic management of MG, including monoclonal antibody (mAb) treatments, complement inhibitors, subcutaneous immunoglobulin, fragment crystallizable neonatal receptor (FcRn) therapeutics, and stem cell therapy.

Historically, treatment options for MG have included thymectomy, symptomatic treatment, acute treatment for myasthenic crisis, and chronic immunomodulating treatments. Although these regimens are effective for many, up to 15% of treated MG is refractory.[2] Individuals who are treated may develop side effects or require modifications of treatment regimens because of comorbid conditions.

Symptomatic Treatment

Symptomatic treatments of MG are limited and include pyridostigmine, an acetylcholinesterase inhibitor, although response is variable and side effects may be limiting. Those who tolerate this medication and have mild disease severity are typically the ideal candidates.

Myasthenic Crisis

Over 25% of people with MG will experience a myasthenic crisis during their disease course.[3] Myasthenic crisis is a life-threatening occurrence traditionally treated with immunomodulators including either plasma exchange (PLEX) or intravenous immunoglobulin (IVIG),[4] which have similar safety and efficacy. This treatment paradigm continues to be the standard of care in the management of an MG crisis.

Disease-Modifying Treatment

Surgical thymectomy is helpful for treating some MG, but is outside the scope of this review.

Immunosuppressants, including azathioprine, mycophenolate (sometimes methotrexate), cyclosporine, cyclophosphamide, and tacrolimus have been used to treat MG. All of these options require blood monitoring and careful surveillance for side effects. Steroids may also be used as short-term bridge therapy to manage symptomatically while waiting for disease-modifying treatments to take effect. Although MG symptoms respond quickly and effectively to steroids, the short- and long-term effects of steroids may be limiting in this vulnerable population.

Although newer immunotherapies (Table 1) have novel mechanisms of action, administration of these can be complex for both the patient and the provider. Challenges to prescribing newer therapies include patient and provider education, insurance or pharmacy benefit manager preauthorization, and financial burden.

Rituximab Is an AntiCD20 Monoclonal Antibody

Improvement of MG after rituximab (RTX) in a person who also had lymphoma led to the development of RTX as a therapeutic option for MG.[5] There are many studies supporting its use to treat MG, although it is not yet approved by the Food and Drug Administration (FDA) for this indication. Benefits of RTX include effective tapering of prednisone and other immunosuppressants for both acetylcholine receptor (AChR) antibody-positive and muscle-specific kinase (MuSK) antibody-positive MG compared with placebo.[6-9] In adolescents and children, RTX has been successfully used to treat seronegative MG.[9,10]

A chimeric murine/human monoclonal antibody, RTX is directed against CD20, which is expressed during early preB-cell development and regulates a step in the activation process required for cel-cycle initiation and differentiation.[11] There are 3 different mechanisms proposed for the depletion of B lymphocytes, including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and stimulation of the apoptotic pathway.[10,11] Clinical improvement is usually noticed within 1 to 3 months of treatment.

The most common side effects are related to the infusion and can be prevented by pretreatment with steroids and antihistamines. Patients should be screened for hepatitis B and C infection and tuberculosis (TB) before starting treatment with RTX and be closely monitored during treatment for infusion reactions, especially with the first dose. A complete blood count (CBC) with differential should be obtained 1 month after treatment to identify the potential adverse effect of myelotoxicity.

The antiMuSK$^+$ serotype of MG has a higher rate of clinical remission and sustained improvement from treatment with RTX compared with antiAChR$^+$ MG.[11,12] A striking reduction in antiMuSK titer has been noted after treatment of antiMuSK$^+$ MG, whereas in antiAChR$^+$ MG, there is a slow decline to no change in antiAChR titers.[6] Specifically, antiAChR$^+$ MG treated with RTX can have early and sustained clinical improvement, prolonged time to relapse, and even occasional clinical remission, but these benefits are not as pronounced as those seen in antiMuSK$^+$ MG.[8]

The optimal dose of RTX for MG has not been formally established and can range from weight-based (375 mg / m^2 weekly for 4 weeks) or nonweight-based (100-1,000 mg in 1-2 infusions 2 weeks apart).[7,9,14] Circulating CD19$^+$ B cells are depleted for up to 6 to 9 months posttreatment and B-cell recovery begins approximately 6 months after treatment. A return of median B-cell counts to normal by 12 to 24 months after treatment is associated with clinical worsening, which can be treated with repeat RTX.[7] Monitoring of B cells 6 months after infusion or with clinical worsening can be used to determine if there is a need for repeat RTX.[12,15] With longer courses of treatment (also in renal transplant recipients), a severe hypogammaglobulinemia has been seen. Monitoring serum IgG levels should be considered along with appropriate redosing if IgG levels fall below 300 mg/dL in these patients.[16]

Eculizumab

Eculizumab is a humanized monoclonal antibody with high affinity to human terminal complement protein C5 and is the first complement inhibitor approved in the US. By binding to C5, eculizumab prevents enzymatic cleavage of C5 into C5a and C5b, inhibits terminal complement formation, and thereby protects the neuromuscular junction from the destructive effects of antibody-mediated complement activation. Vaccination for *Neisseria meningitidis* at least 2 weeks before starting eculizumab because complement

TABLE 1. NEWER IMMUNOMODULATORY THERAPIES FOR MYASTHENIA GRAVIS

Drug/class	Ideal candidate	Dose/route	Onset	Adverse events	Monitoring
Rituximab (AntiCD20 monoclonal antibody) (off-label use)	Refractory gMG; more effective for MuSK than AChR-MG	375 mg/m^2 weekly x 4 weeks or nonweight-based 100 -1,000 mg in 1-2 infusions 2 weeks apart every 6 months; pretreatment with antihistamine, acetaminophen, and corticosteroid recommended	4-8 weeks	Infusion-related, severe mucocutaneous reaction, PMLE, myelosuppression, hepatitis B virus/tuberculosis reactivation	Pretreatment screen for TB and hepatitis, Pre- and posttreatment CBC with differential/ANC; Posttreatment CD19/20 counts 1 month later and before next cycle
Eculizumab (complement inhibitor) (FDA approved)	AChR$^+$ gMG of any severity	I,900 mg IV every week for 4 weeks followed by 1,200 mg in week 5, then 1,200 mg every 2 weeks	2-4 weeks	Severe meningococcal infection, mild infusion related adverse events: headache, nasopharyngitis	No routine laboratory monitoring
Subcutaneous Ig (off-label use)	gMG for maintenance treatment	130%-150% of IVIG dose, 0.2-0.4 g/kg (1-2 mL/kg) body weight per week, administered in 1-3 sessions/week; injection sites include the abdomen, thigh, upper arm, and/or upper leg/hip; avoid bony prominence; can be injected simultaneously over multiple sites but >2 in apart	4 weeks	infusion site skin reactions, systemic reactions are less common than with IVIG but can occur and include nephrotoxicity, headache, hemolytic anemia, leukopenia, aseptic meningitis, and thromboembolism	CBC and BUN/Cr at baseline and if no specific indication, then semiannually

Abbreviations: AChR, acetylcholine receptor; ANC, absolute neutrophil count; BUN, blood urea nitrogen; CBC, complete blood count; Cr, creatinine; FDA, Food and Drug Administration; gMG, generalized myasthenia gravis; Ig, immunoglobulin; IVIG, intravenous immunoglobulin; IV, intravenous; mAb, monoclonal antibody; MG, myasthenia gravis, MuSK, muscle-specific kinase; PMLE, progressive multifocal leukoencephalopathy; TB, tuberculosis.

depletion increases the risk of Neisseria infections. Because of the mechanism of action, eculizumab is not expected to be effective for antiMuSK$^+$-IgG$_4$-positive MG, because this IgG subclass does not activate complement.

A multicenter randomized controlled trial and open-label extension demonstrated significant clinical improvement of refractory antiAChR$^+$ MG within the first week of treatment with maximal improvement by 12 weeks and sustained improvement over 3 years. There were also reductions in both MG exacerbations and MG-related hospitalizations.[17]

The recommended dose of eculizumab is 900 mg intravenously every week for 4 weeks followed by 1,200 mg every 2 weeks. Side effects range from mild (eg, headaches) to more severe (eg, myasthenic crisis orsystemic infection). The FDA has approved eculizumab for generalized antiAChR$^+$ MG of any severity.[18] Although results are promising, more studies are needed to evaluate safety and efficacy of eculizumab in different subtypes of MG.

Subcutaneous Immunoglobulin

Subcutaneously administered immunoglobulin (SCIG) has been used in the treatment of chronic inflammatory demyelinating polyneuropathy and in immunodeficient states and is an attractive alternative to IVIG. There is similar efficacy between IVIG and SCIG, and the subcutaneous administration is more accessible, can be done at home by the patient or an assistant, and has reduced cost and fewer systemic side effects. The efficacy of SCIG for MG is mostly based on prospective and retrospective studies; no randomized controlled trials have been conducted yet. However, SCIG has been successfully used in mild to moderate MG exacerbation, refractory MG, and maintenance therapy.[19] Slow release of immunoglobulin (Ig) from the subcutaneous tissue into vasculature takes approximately 4 weeks to reach peak concentration and provides stable Ig serum levels thereafter. Stable Ig levels reduce wearing-off effects and adverse events related to rapid peaks of Ig in serum (eg, headache, aseptic meningitis, renal failure, thromboembolic, and hemolytic reactions), which are more common with IVIG. Local skin reactions are more common with SCIG and the prolonged time to onset of action may be perceived as "less efficacious" by patients.

With SCIG, the peak serum Ig concentration is 40% lower than with IVIG and requires a dose increase of 30% to 50% compared with IVIG to achieve equivalent systemic levels at treatment initiation. Once serum Ig peak is reached, the dose can be adjusted based on clinical response.[20] Because of SCIG time to onset, it may not be beneficial for treatment of myasthenic crisis. Administration of SCIG requires dividing the total monthly Ig dose into smaller weekly or twice weekly doses. Most patients are able to self infuse after 1 to 2 training sessions using automated pumps. Common sites of infusion are the abdomen, thigh, buttock, and arms.

Investigational Treatments

Complement inhibitors ravulizumab and zilucoplan are in clinical trials for treatment of MG (Table 2).

Fragment Crystallizable Neonatal Receptor Blockers

The FcRn plays a crucial role in IgG homeostasis by rescuing IgGs from lysosomal degradation and thereby increasing the long halflives of IgGs compared with other Ig isotypes. This inhibition of IgG "recycling" is a potential therapeutic target to inhibit all IGg levels including IgG$_4$.[21] Lower IgG levels (60%-85% decrease) occur with administration of FcRN blockers within 2 to 3 weeks and lower antiAChR titers within 4 to 5 weeks. Lower Ig levels coincide with subsequent clinical improvement, and when antiIgG and antiAChR titers return to normal 8 weeks posttreatment, clinical improvement persists.

Although no adverse events of FcRn blockers have been reported in trials thus far, there may be albumin depletion, and the effects of long-term panIgG suppression are unknown. There are currently four FcRn blockers in clinical trials for treatment of MG (Table 2) which are all administered intravenously, although rozanolixizumab and batoclimab also have subcutaneous formulations.[21]

A phase 3 trial of efgartigimod is complete and had positive results according to a press release from the manufacturer.[22]

TABLE 2. EMERGING THERAPIES FOR MYASTHENIA GRAVIS

Drug/administration	Indication	Study status
FcRN inhibitors		
Efgartigimod/IV	gMG[a]	OLE (NCT03770403)
Rozanolixizumab IV or SC	Seropositive gMG	Phase 3 (NCT04124965)
Nipocalimab IV	gMG	Phase 2 (NCT03772587)
Batoclimab/IV or SC	gMG	Phase 2a (NCT03863080)
Terminal complement inhibitor		
Ravulizumab/IV	AChR-MG	Phase 3 (NCT03920293)
Zilucoplan	AChR-MG	Phase 3 (NCT04115293)
CAR-T cell derived immunotherapy		
Descartes-08 CAR-T cells	gMG	Phase 1/2 (NCT04146051)
Stem cell therapy		
Autologous hematopoietic stem cell transplant	Refractory MG	Phase 2 (NCT00716066)

[a] Phase 3 trial included both seropositive and seronegative MG. Abbreviations: AChR, acetylcholine receptor; CAR-T, chimeric antigen receptor T; gMG, generalized myasthenia gravis; IV, intravenous; MG, myasthenia gravis; OLE, open-label extension; SC, subcutaneous.

In the press release, improvement in the MG activities of daily living (MG-ADL) scale score (67.7% improvement with efgartigimod vs 29.7% with placebo; *P*<.0001) and improvement in the quantitative MG scale (63.1% with efgartigimod vs 14.1% with placebo; *P*<.0001) were announced. It was also stated that more participants treated with efgartigimod had minimal symptoms compared with those treated with placebo and that the safety profile was comparable to placebo. Clinical improvement was noted within 2 weeks suggesting a possible use in myasthenic crisis. Results from trials studying efficacy and safety of other FcRN therapeutics are pending yet promising. Long-term studies are needed to determine the role of FcRn in acute and chronic management of MG.

Chimeric Antigen Receptor T Cell-Derived Immunotherapy

Chimeric antigen receptor T (CAR-T) cells are in early development for MG treatment (Table 2). Historically used as cancer treatment, CAR-T-cell therapy is in phase 2 trials for several autoimmune diseases, including MG.[23] The mechanism of action for CAR-T cells involves engineering an individual's own T cells to express specific CARs that recognize pathogenic cell antigens on surfaces of antibody-producing plasma cells to eliminate production of disease-causing antibodies. The CAR-T cells can proliferate and survive in vivo for several years to sustain clinical remission. The precise nature of CAR-T cell therapy could address the current challenge of repeatedly administering immunosuppressants to individuals with MG, persistently weakening the immune system. Side effects of cytokine release syndrome and cytopenia have been seen with CAR-T cell therapy when used to treat hematologic malignancies.[23]

Stem Cell Treatment

Autologous hematopoietic stem cell transplantation (HSCT) for treatment of MG has been reported in a few retrospective studies and a phase 2 trial is underway (Table 2). In published studies, individuals with refractory and severe MG who had HSCT achieved clinical remission within 1 to 12 years, although it is not clear if this was a result of HSCT or the strong immunosuppressants these individuals received with HSCT.[24,25] Infection, malignancy, and cytopenia were common side effects. A clinical trial of HSCT for refractory MG was terminated early because of poor recruitment and 33% mortality rates. Although HSCT is an emerging therapy for MG and other autoimmune disorders, it requires more vigorous investigation.

Conclusion

A variety of therapeutics are being developed to target specific immune system functions in contrast to the broader immunosuppressive approach that has traditionally been available. The burgeoning field of autoimmune therapies is promising for a number of diseases and specifically MG considering that this population has a need for broader therapeutic options. As more is understood about the immunopathology of MG, specific direct and indirect B- and T-cell therapies and other immune targets will continue to be investigated. ■

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