

Myasthenia Gravis Treatment

Both symptomatic and maintenance treatments are available.

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Myasthenia gravis (MG) is the most common autoimmune neuromuscular condition. Fluctuating variable symptoms of MG arise from the failure of neuromuscular transmission caused

by antibodies against the acetylcholine receptor (AChR) and other proteins involved in the AChR aggregation, including muscle specific tyrosine kinase (MuSK) and low-density lipoprotein receptor-related 4 (LRP4). Mortality has been significantly reduced in the last century because of optimized intensive care and recognition of this neuromuscular condition.¹ Currently, drug treatment is focused on eradicating of MG symptoms, improving quality of life, and minimizing medication doses and adverse effects (AEs).

Treatments for MG can be subclassified into symptomatic, maintenance, and rescue treatments. Maintenance and rescue treatments are directed towards modulating or suppressing the immune system. This review focuses on symptomatic and maintenance treatments, emphasizing recent developments.

Symptomatic Treatments

Pyridostigmine

Pyridostigmine is a cholinesterase inhibitor that is a first-line, symptomatic treatment for MG. A common daily dose for people with MG is 60 mg taken 4 times daily while awake. Extended release pyridostigmine (180 mg) can be given at bedtime to relieve nocturnal or early morning symptoms. Total dose should be less than 500 mg per day to avoid cholinergic toxicity. Common AEs include nausea, diarrhea, and cramping. If needed, treatment with loperamide or other antimuscarinic medications can improve tolerability. If clinical remission is achieved with other immunomodulators, pyridostigmine can be tapered. Some individuals with MUSK-related MG report either worsening or ineffectiveness with pyridostigmine.² For those with ocular MG the response rate is approximately 50%. During myasthenic crisis, pyridostigmine can be stopped to avoid secretions and then restarted on an outpatient basis.

Tirasemtiv

Fast skeletal troponin activators (FSTA) may be a new symptomatic treatment in MG. The mechanism of action is

to increase affinity and sensitization for calcium in the troponin-tropomyosin complex. In a phase 2 randomized double-blind treatment-sequenced trial, participants with MG from antibodies to AChRs had improved quantitative myasthenia gravis (QMG) and forced vital capacity (FVC) scores in response to tirasemtiv treatment. Higher doses, however, were limited by dizziness and headache in up to 40% of participants, and further development of the drug was stopped after a negative trial in participants with amyotrophic lateral sclerosis. Other FSTAs are in development with a wider range of uses including neuromuscular diseases.³

3,4 Diaminopyridine

3, 4 Diaminopyridine (3,4 DAP) has been used to treat Lambert Eaton myasthenic syndrome for more than a decade. It acts on voltage-gated potassium channels, prolonging the action potential to increase intracellular calcium, allowing more acetylcholine release. In 1 case, a person with antiMuSK MG responded to symptomatic treatment with 3, 4 DAP.²

Maintenance Treatments

Prednisone

Prednisone is a first-line immunomodulator for MG that is effective in the majority of people with MG, regardless of subtype. Tolerability, however, is a major issue because of AEs that include hypertension, hyperglycemia, weight gain, cataracts, osteopenia, femoral vascular necrosis, gastrointestinal disturbances and infection. Prednisone can be started at 10 mg every other day or daily and then titrated to efficacy up to 1 mg per kg daily or 100 mg daily. Worsening of MG with high doses, especially in corticosteroid-naïve individuals, can occur. Once remission is achieved, taper should commence by reducing the dose by 5 to 10 mg every other day over a 2- to 4-week period with close monitoring to the lowest dose possible that maintains clinical remission. Clinicians may consider starting a steroid-sparing oral agent along with prednisone because these agents often take months to reach therapeutic benefits.

A small randomized controlled trial of prednisone in people with ocular MG showed efficacy of prednisone compared with placebo treatment.⁴ Some have suggested that early prednisone use in ocular MG may reduce symptom generalization.

Azathioprine

Azathioprine (AZA), a popular initial steroid-sparing agent for MG, is an antimetabolite that reduces lymphocyte production. A small trial showed efficacy of AZA over placebo at reducing prednisone dose at 3 years.⁵ Initial AZA doses are 50 mg daily, titrated up to 2 to 3 mg per kg per day divided into twice-daily dosing. There is a 6 to 12 month delay in onset of action and an idiosyncratic flu-like reaction occurs in 10% of patients. Screening for thiopurine methyltransferase enzyme activity can reduce this AE. Other AEs include pancreatitis, transaminitis and pancytopenia, and rarely reported non-melanoma skin cancers and hematologic malignancies with prolonged use. Generally, labs are monitored closely during initiation of treatment and less frequently thereafter.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) reduces lymphocyte production, is generally well tolerated, and has been used widely in transplant medicine. Onset of action may be 6 to 12 months for MG. Infections, lymphopenia, nausea, or diarrhea may occur. In 2 clinical trials of 12 and 36 weeks, MMF did not show efficacy over placebo, although trial design was flawed by unknown latency of action of MMF and rigorous definition of efficacy.⁶ Some centers continue using MMF for MG, titrating the dose up to 1,000 to 1,500 mg twice daily. Rapid mycophenolate discontinuation can lead to relapse, and discontinuation, as with any immunomodulatory drug, should be done slowly. Tapering by 500 mg per 12 months is recommended.⁷

Cyclosporine and Tacrolimus

Cyclosporine reduces T-lymphocyte-specific proliferation pathways. Cyclosporine was shown efficacious in a small placebo-controlled trial for people with refractory MG.⁸ Cyclosporine is dosed at 5 to 6 mg per kg per day and titrated to trough levels (400-600 ng/mL) with close monitoring of kidney function and blood counts. Tacrolimus dosing is 1 to 2 mg per day.^{2,9} Serious AEs, however, including nephrotoxicity and hypertension, limit widespread use.

Methotrexate

Methotrexate, an antifolate antimetabolite, is immunomodulatory at low doses and can be dosed at 10 mg per week and titrated to 20 mg per week. The AEs include bone marrow suppression, hepatotoxicity, stomatitis, and pulmonary fibrosis. A randomized controlled trial of methotrexate and prednisone compared with prednisone alone showed no significant differences.¹⁰ Methotrexate is still used to treat refractory MG in some centers.

Cyclophosphamide

Cyclophosphamide is a cytotoxic treatment in which the active metabolite, phosphoramide mustard, crosslinks DNA

at specific sites, leading to cell death. Monthly cyclophosphamide dosed at 500 mg and administered intravenously (IV) led to significant improvement in QMG score and reduction of prednisone dose at 6 and 12 months.¹¹ Cyclophosphamide has significant toxicity, however, including hemorrhagic cystitis, leukopenia, and dose-dependent cardiotoxicity and so is used only rarely for severely refractory MG.

Eculizumab

Complement-mediated damage to membranes causes complex formation, leading to endocytosis and degradation of AChRs and flattening of synaptic fold architecture. These changes lead to reduced safety factor, reduced end plate potentials, and clinical weakness. Complement knockout mice (C5 deficient) with passive administration of AChRs have less incidence of disease.¹² Eculizumab is a monoclonal antibody to C5 that has been studied in people with refractory generalized MG from antiAChR who had moderate to severe symptoms, despite multiple treatments, evidenced by MG-ADL score more than 6 and QMG score more than 12. After receiving eculizumab (900 mg on day 1, weeks 1, 2, and 3 followed by 1,200 mg per week) participants had significant improvement in many prespecified secondary outcomes including QMG score. The primary outcome was initially not significant due to the worst-rank ANCOVA design, which automatically assigned participants who discontinued treatment the worst score. In post-hoc analysis, 3 participants were identified who discontinued eculizumab for unrelated reasons (prostate adenocarcinoma, bowel perforation, and *Moraxella* bacteremia). When these individuals were assigned based on their clinical status, all outcomes were met.¹² The Food and Drug Administration (FDA) approved eculizumab in 2018 for treatment of generalized, antiAChR-positive MG. In Japan and Europe, the medication was approved for all refractory antiAChR-positive MG. All participants had to receive *Neisseria meningitidis* vaccine prior to starting eculizumab. Headache and nasopharyngitis were the most common AEs. Improvement began as early as 2 to 4 weeks and could be determined by 12 weeks.¹² An open-label extension study continued to show similar AE as the previous trial, with some reported patients receiving the medication for up to 4 years.¹³ Limitations to widespread use include cost, but eculizumab is an important treatment option for generalized, refractory, antiAChR-positive MG.^{12,13}

Thymectomy

Thymectomy is recommended for thymomatous MG (found in 10%-15% of patients) but the literature was less clear for nonthymomatous MG. A landmark clinical trial showed that treatment with thymectomy plus prednisone for people with AChR antibody-positive MG had better 3-year outcomes compared with those who had prednisone treatment alone. In this study of participants age 18 to 65 years with less than

5 years duration of MG, thymectomy was performed with an extended transsternal approach to avoid residual ectopic thymic tissue. A larger percentage of people treated with thymectomy and prednisone reached minimal manifestation status (MMS) compared with prednisone alone. The thymectomy group also had fewer hospital admissions for MG exacerbations. In a 2-year extension study of 50 of the original participants, 5-year data continued to show significant improvement in QMG score and time-weighted prednisone dose. The mean prednisone dose at 60 months was 11 mg every other day in the thymectomy group. A significantly greater proportion of thymectomy patients (88% vs 54%) achieved MMS. Thymectomy should be offered and discussed with most people with antiAChR-positive nonthymomatous MG.^{14,15} Current evidence does not indicate that thymectomy is beneficial in antiMuSK- or antiLRP4-positive MG, possibly due to different thymic pathology from antiAChR-positive MG.^{16,17}

Rituximab

Rituximab is a chimeric, monoclonal antibody that selectively targets CD20 epitopes on normal and malignant B cells, leading to effective depletion of circulating B cells as well as interfering with B-cell proliferation and activation. A meta-analysis of 169 people with MG who were treated with rituximab showed that 72% of individuals who had antiMUSK-positive MG achieved postintervention status of MMS compared to 30% of those who had antiAChR-positive MG.¹⁸ In another study, a cohort of 16 people with refractory antiAChR-positive MG who were treated with rituximab were followed for 18 to 84 months. All participants achieved MMS, complete remission, or pharmacologic remission, and 13 of the 16 participants were able to discontinue all other immunotherapies 8 months after the last infusion of rituximab. Mean time to relapse was 36 months.¹⁹ A prospective multicenter blinded review evaluated a total of 77 people with antiMuSK-positive MG and found 58% of those treated with rituximab achieved MMS or better compared with only 16% of control patients; the number needed to treat was 2.^{4,20}

In a randomized double-blind multicenter futility-design trial,^a participants with refractory antiAChR-positive MG treated with rituximab did not have more than a 30% reduction in prednisone dose compared with those treated with placebo. The safety arm of this study revealed no major AEs. A major limitation of this study was that it did not include individuals with antiMuSK-positive MG. Rituximab is a promising option for people with antiMuSK-positive MG, given the nature of immune-mediated IgG4 disease,

A major limitation of the MG rituximab literature is the heterogeneous doses used. Future studies should focus on the most effective initiation and maintenance dosing while limiting toxicity and exposure. The most commonly identified rituximab dose was 375 mg per body surface area weekly for

4 weeks. Although rituximab is generally considered safe, infusion side effects can occur (eg, hypotension). A single case of rituximab-associated progressive multifocal leukoencephalopathy in a person with antiAChR-positive MG was reported.¹⁸

Intravenous Immunoglobulin and Myasthenia Gravis

Intravenous immunoglobulin (IVIG) is widely used as a neurologic treatment in other autoimmune diseases and has pleiotropic effects including binding pathologic antibodies, clearing IgG, and altering complement-mediated inflammatory reactions. For myasthenia exacerbations, IVIG is well-accepted as a treatment that will provide rapid symptomatic improvement. Generally, IVIG is given as 2 g per kg over 2 to 5 days. Headache, infusion reactions, thrombotic events, renal disease and hemolytic anemia may occur.

Because of the long treatment effect latency in steroid-sparing immunomodulators, many clinicians use IVIG for maintenance treatment of persistent symptoms despite high-dose corticosteroid therapy, refusal, or intolerance to steroid AEs, and can also be used in lieu of potentially teratogenic immunosuppressive medications in women of childbearing age. In uncontrolled trials, IVIG has been reported to improve MG symptoms.²² An ongoing, randomized, clinical trial of IVIG maintenance therapy has been completed with QMG as a primary outcome, but the results are not yet published.

Subcutaneous Immunoglobulin

Subcutaneous immunoglobulin (SCIG) has many proposed advantages over IVIG. It can be administered at home and IgG levels can be more consistently maintained with less of a wearing-off effect or boost in energy shortly after IVIG infusion, reducing the risk of being dependent on IVIG for this energy boost. There are fewer systemic AEs, such as headache and flu-like reactions. In participants with MG in open-label prospective studies SCIG treatment has shown benefit in QMG scores at 6 weeks.²¹

Belimumab

The B-cell activation factor (BAFF) and a proliferation inducing ligand (APRIL) are cytokines that promote B-cell survival and differentiation. Belimumab and atacicept are 2 humanized monoclonal antibodies that target these antigens. Belimumab has been studied in persons with MG in a phase 2, randomized double-blind placebo-controlled trial. The primary outcomes in this trial were safety and QMG score improvement. The trial ran for a 24-week treatment phase and a 12-week extension phase. Belimumab was dosed at 10 mg per kg IV at weeks 0, 2, 4, 8, 12, 16, and 20. The treatment arm had a higher proportion of patients with more than a 3-point improvement on the QMG scale but was not statistically significant. Limitations of the study design included lack of enrollment of individuals with antiMuSK-positive MG in the treatment arm. Belimumab

^a BeatMG; phase II trial of rituximab in myasthenia gravis (NCT02110706).

was safe; the only serious AE was influenza.²² Despite the negative outcomes, BAFF remains a promising area to explore. There are no current trials of atacicept in MG patients. Consideration should be given to patients with refractory disease, similar to the design of the eculizumab trial.¹²

Neonatal Fc Receptors

The IgG subclass of immunoglobulins appears to play a significant role in autoimmune disease, partly because of the longer half-life of IgG compared with other proteins and Ig subclasses. Neonatal Fc receptors bind IgGs with high affinity in an acidic environment, thereby saving them from lysosomal degradation. The IgGs are subsequently released in neutral pH and recycled, prolonging their half-life. A few neonatal Fc receptor blockers are available. Efgartigimod has been studied in MG in a small phase 2 trial with 24 participants with generalized antiAChR-positive MG who underwent daily infusions with efgartigimod or placebo.²³ Those treated with efgartigimod had statistically significant improvements in the QMG and MG-ADL scales compared with those who received placebo.

Ruxolitinib and Tocilizumab

One factor leading to autoimmune disease is the proliferation of CD4 cells to Th1 and Th17 subtypes. This differentiation is activated by the JAK/STAT pathway (janus kinase/signal transducer and activation of transcription pathway). Interleukin 6 is a cytokine that plays a role in stimulating the production of autoantibodies from plasma cells. Ruxolitinib is a JAK1 and JAK2 pathway inhibitor. Tocilizumab is a humanized, monoclonal antibody directed against interleukin 6. There are rare case reports of persons with refractory MG achieved significant improvement in QMG scores. These medications can cause significant side effects.²⁴

Conclusion

Discovered and recognized as a disease in the 1930s, MG was initially coined *myasthenia gravis* because of the significant mortality rate of 40% to 60%. After recognition of this entity as a neuromuscular and autoimmune disease, mortality in MG was reduced to less than 5%. This is primarily due to respiratory care in intensive care units and prevention of complications.¹ Currently, there are many novel treatments and trials underway for MG. In the near future, it is hoped that clinicians can tailor and personalize treatment for MG, selecting from a wide armamentarium of treatment options. ■

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