Diagnosis and Management of Myasthenia Gravis

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

PURPOSE OF REVIEW: This article reviews updated diagnostic procedures and currently available treatment modalities for myasthenia gravis (MG).

RECENT FINDINGS: Patients with MG can be classified based on antibody status and their clinical presentation; treatment responses may differ based on disease subtypes. Improved diagnostic methods and recognition of new antigenic targets such as lipoprotein-related protein 4 have led to improved diagnostic efficiencies. Corticosteroids remain the first-line immunotherapy, but there is a trend toward minimizing their use at high doses and for long durations. Oral immunosuppressants such as mycophenolate mofetil, azathioprine, and tacrolimus remain useful. An international, multicenter randomized trial comparing thymectomy plus prednisone with prednisone alone demonstrated that thymectomy improves clinical outcomes in selected patients with nonthymomatous MG. Eculizumab, efgartigimod, and ravulizumab have recently been approved by the US Food and Drug Administration (FDA) for adult patients with generalized MG who are acetylcholine receptor–antibody positive. These drugs take advantage of novel mechanisms of action and expand treatment options for patients with MG. Data on rituximab suggest that it can be a good option, especially for patients with MG who are positive for antibodies against muscle-specific tyrosine kinase (MuSK). The number of clinical trials and drugs in development for MG is steadily increasing.

SUMMARY: The diagnosis of MG can generally be made from the patient's history, a neurologic examination, and laboratory and electrodiagnostic testing. Carefully selected treatment improves outcomes in MG. Additional treatment options for MG will likely be available in the near future.

INTRODUCTION

Myasthenia gravis (MG) is the most common disorder of the neuromuscular junction. In MG, autoantibodies directed against various components of the postsynaptic muscle membrane result in characteristic fatigable weakness of ocular, bulbar, respiratory, axial, and limb muscles. Patients typically report worsening muscle dysfunction with exercise or toward the end of the day, indicative of reduced safety factor at the neuromuscular junction. About

CITE AS:
CONTINUUM (MINNEAP MINN) 2022;28(6, MUSCLE AND NEUROMUSCULAR JUNCTION DISORDERS):1615-1642.

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RELATIONSHIP DISCLOSURE:
Dr Hehir has received personal compensation in the range of $500 to $4999 for serving as a consultant for Janssen and UCB Pharma, in the range of $5000 to $9999 for serving as a consultant for argenx, and in the range of $10,000 to $49,999 for serving as a consultant for Alexion Pharmaceuticals. Dr Li has received personal compensation in the range of $500 to $4999 for serving as a consultant for Catalyst Pharmaceuticals, Immunovant, and UCB Pharma and in the range of $5000 to $9999 for serving as a consultant for argenx. The institution of Dr Li has received research support from argenx.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Hehir and Li discuss the unlabeled/investigational use of azathioprine, corticosteroids, cyclophosphamide, cyclosporine, intravenous immunoglobulin, methotrexate, mycophenolate mofetil, plasma exchange, and tacrolimus, for the treatment of myasthenia gravis.

two-thirds of patients experience isolated ptosis, diplopia, or both at disease onset.[1] Up to 75% of these patients will develop generalized weakness within 2 to 3 years of developing symptoms.[2]

EPIDEMIOLOGY

Myasthenia gravis is classified as a rare disease. However, its incidence and prevalence have increased over time, likely because of increased recognition of MG, better diagnostic testing, and an increase in the number of effective treatments. The incidence of MG is estimated to be between 5 and 30 cases per 1 million person-years.[3,4] The prevalence is estimated to be between 10 and 20 cases per 100,000 people.[5]

A bimodal age distribution in MG incidence is classically described, with a peak around age 30 years and another peak around age 50 years.[6,7] In the younger cohort, the incidence of MG is more common in females, whereas in the older cohort the incidence is more equal between the sexes. Recent data indicate that the incidence of MG may be highest after age 65 years.[8-10]

CLASSIFICATION OF MYASTHENIA GRAVIS

Patients with MG are classified according to several clinical features that can inform discussions of prognosis and treatment strategies. Ocular MG is defined as the restriction of weakness to ocular muscles, causing a combination of ptosis, diplopia, and eye closure weakness.[11] Patients with generalized MG experience weakness in other distributions, including bulbar, axial, limb, and respiratory muscles. Evaluation and management of patients with ocular and generalized MG differ, as discussed subsequently in this article.

Patients with MG are also classified based on the type of autoantibodies measured in serum, including antibodies against acetylcholine receptor (AChR), muscle-specific tyrosine kinase (MuSK), and lipoprotein-related protein 4 (LRP4).[12] Patients without measurable autoantibodies are classified as having seronegative MG when the diagnosis can be confirmed with other tests or favorable treatment responses. Antibody classification is important, as patients with anti-AChR, anti-MuSK, and anti-LRP4 antibodies and those with seronegative MG may have differing clinical courses and responses to treatment. Patients with anti-MuSK MG often have a more severe phenotype compared with other forms of MG. Patients with anti-MuSK MG can have early involvement of bulbar, respiratory, and neck muscles. Patients with anti-MuSK MG experience quicker progression of weakness, a higher incidence of myasthenic crisis, and a reduced likihood of a pure ocular MG phenotype.[13,14] Treatment differences among these subtypes will be discussed.

Finally, clinical differences between patients with late-onset MG (typically defined as onset age greater than 50 years) and early-onset MG are increasingly recognized. Patients with late-onset MG may have better overall outcomes than those with earlier onset.[8,10] Medical comorbidities and concurrent medications for other medical conditions in the older MG population may influence treatment strategies and cause an increased risk of treatment-related side effects.

HISTORY AND BEDSIDE EVALUATION

As with other conditions of the peripheral or central nervous system, the clinical history will provide sufficient information to localize a patient's condition in the

nervous system. Because of the selective vulnerability of certain muscle groups in MG, patients experience a distinctive pattern of weakness. Two-thirds of patients experience weakness in ocular muscles first. Patients with MG often describe variable double or blurry vision during periods of extended visual concentration such as driving, reading, working on a computer, and watching television. Patients may also describe eyelid droop or closure with eye use or when tired. Because of bulbar muscle weakness, patients may describe jaw muscle fatigue when chewing, loss of fluid through the nose when drinking, coughing or aspiration with eating, and fatigable slurred speech with a nasal quality. Patients may also describe a lack of facial expression. Limb muscle weakness may impair patients' ability to raise their arms overhead for activities such as washing their hair or face, to climb stairs, and to rise from a low chair without the assistance of the upper extremities.

Once the diagnosis of MG is suspected based on the clinical history, a number of simple bedside maneuvers can be performed in the clinic to begin to establish the diagnosis (CASE 3-1). The neurologic examination is used to evaluate for fixed and fluctuating weakness in muscles known to be affected in MG. Useful bedside tests include asking the patient to keep their gaze fixed in the horizontal or vertical plane to watch for the development or worsening of double vision or ptosis, checking the ability to hold air in the mouth with cheek puff to evaluate lower facial weakness, asking the patient to count out loud from 1 to 50 in a single breath to assess fatigable dysarthria, testing neck flexion and extension in the supine and prone positions, testing shoulder abduction and hip flexion, and testing the patient's ability to stand from a seated position without using their hands. Patients with MG will often show a worsening weakness with extended or repeated muscle use. The MG Core Exam adapts the in-person MG clinical examination for video telemedicine.[15] The MG Core Exam can also be used in person and is designed to be followed over time with results that are comparable in both clinical settings. An ice pack test can also be performed in the office or by telemedicine. Cooling muscle tissue increases the amount of acetylcholine present at the neuromuscular junction, improving the likelihood that AChRs will be activated. In the ice pack test, the distance from the center of the pupil to the upper lid margin is measured at baseline. Then a bag of ice is applied to the lid for 2 minutes. A 2-mm improvement in ptosis is defined as a positive test. The ice pack test carries a sensitivity of 80% to 95% and a specificity of 79% to 97%.[16,17] Performing the ice pack test after sustained upgaze may improve the sensitivity and specificity of the test in patients with more subtle ptosis.[18]

DIAGNOSTIC TESTING

A combination of serum antibody and electrodiagnostic testing can be used to confirm or refute the diagnosis of MG (FIGURE 3-1[19]). Once the diagnosis of MG has been confirmed, all patients should have chest CT or MRI with contrast to evaluate for a possible associated thymoma.

Antibody Testing

Autoantibodies against AChRs can be detected in 75% to 90% of patients with generalized MG. In generalized MG, AChR-binding antibody testing carries a specificity of 90%.[17,20] Higher antibody titers are associated with increased specificity.[21] False-positive AChR-binding antibody testing has been described in

KEY POINTS

- Patients with myasthenia gravis (MG) develop characteristic muscle weakness that worsens with activity and fatigue. MG has a predilection to affect ocular, bulbar, neck, respiratory, and proximal limb muscles more than others.
- Two-thirds of patients with MG develop a combination of diplopia and eyelid ptosis. Up to 75% of these patients will progress to generalized MG within the first 2 to 3 years of developing symptoms.
- Classification of patients based on age, autoantibody status, and ocular versus generalized MG is essential to guide the diagnostic workup and treatment decisions.
- Evaluation of patients with suspected generalized MG relies on a combination of clinical history, clinical examination, bedside maneuvers, serum autoantibody testing, and electrodiagnostic testing.
- The MG Core Exam can be used to evaluate and follow patients in the clinic and through video telemedicine.
- In patients with ptosis, the ice pack test carries a sensitivity of 80% to 95% and a specificity of 79% to 97%.
- Anti-acetylcholine receptor–binding antibody can be elevated in about 75% to 90% of patients with generalized MG. At low titers, false positives can be observed in patients with other autoimmune disorders.

systemic lupus erythematosus, Hashimoto thyroiditis, rheumatoid arthritis, idiopathic pulmonary fibrosis, primary eosinophilia, autoimmune hepatitis, and granulomatous disease; false positives are more common with low antibody titers.[21] In patients with lower AChR-binding antibody titers, reflex testing of AChR-modulating antibody improved specificity from 89% to 94% in one study.[21] This reflex testing may be most useful in patients whose clinical presentation does not appear consistent with MG. In rare MG cases, testing for AChR-modulating antibodies is positive with negative AChR-binding antibody results.[21]

CASE 3-1

A 45-year-old woman presented with a 6-month history of intermittent eyelid drooping and double vision with reading. She reported having difficulty holding her arms overhead to wash her hair in the shower; she took regular breaks during this activity. Friends and family described her speech as slurred at times. She had experienced a few episodes of loss of fluid from her nose when drinking water. All symptoms were worse at the end of the day and when she was tired.

On neurologic examination she had moderate bilateral ptosis that worsened within 10 seconds of sustained upward gaze. She had a positive curtain sign bilaterally, with contralateral ptosis worsening upon lifting one eyelid. She had no overt ocular misalignment in primary gaze. She developed binocular diplopia, with improvement upon covering either eye, and dysconjugate gaze within 20 seconds of fixed horizontal gaze and 15 seconds of fixed upward gaze. She developed nasal dysarthria when counting out loud to 25. She had noticeable weakness in neck flexion, shoulder abduction, hip flexion, and hip abduction. She was unable to rise from a chair without the assistance of her hands. Distal limb muscles were strong.

Diagnostic testing was performed, and the bedside ice pack test showed modest improvement in the patient's ptosis. One week after presentation, tests for acetylcholine receptor (AChR)–binding and AChR-modulating antibodies returned and showed high titers. Because of confirmatory antibody testing in a patient with a clinical presentation consistent with myasthenia gravis (MG), additional electrodiagnostic testing, including single-fiber EMG and slow repetitive nerve stimulation, was not performed.

COMMENT

This case illustrates the classical clinical presentation of a patient with AChR antibody–positive generalized MG. The patient described functional deficits due to the fatigable weakness characteristic of MG. Her clinical examination demonstrated ocular, bulbar, neck flexion, and proximal arm and leg weakness that worsened with use. The combination of clinical history, bedside examination, bedside ice pack test, and serum acetylcholine receptor antibody testing confirmed the diagnosis of generalized MG.

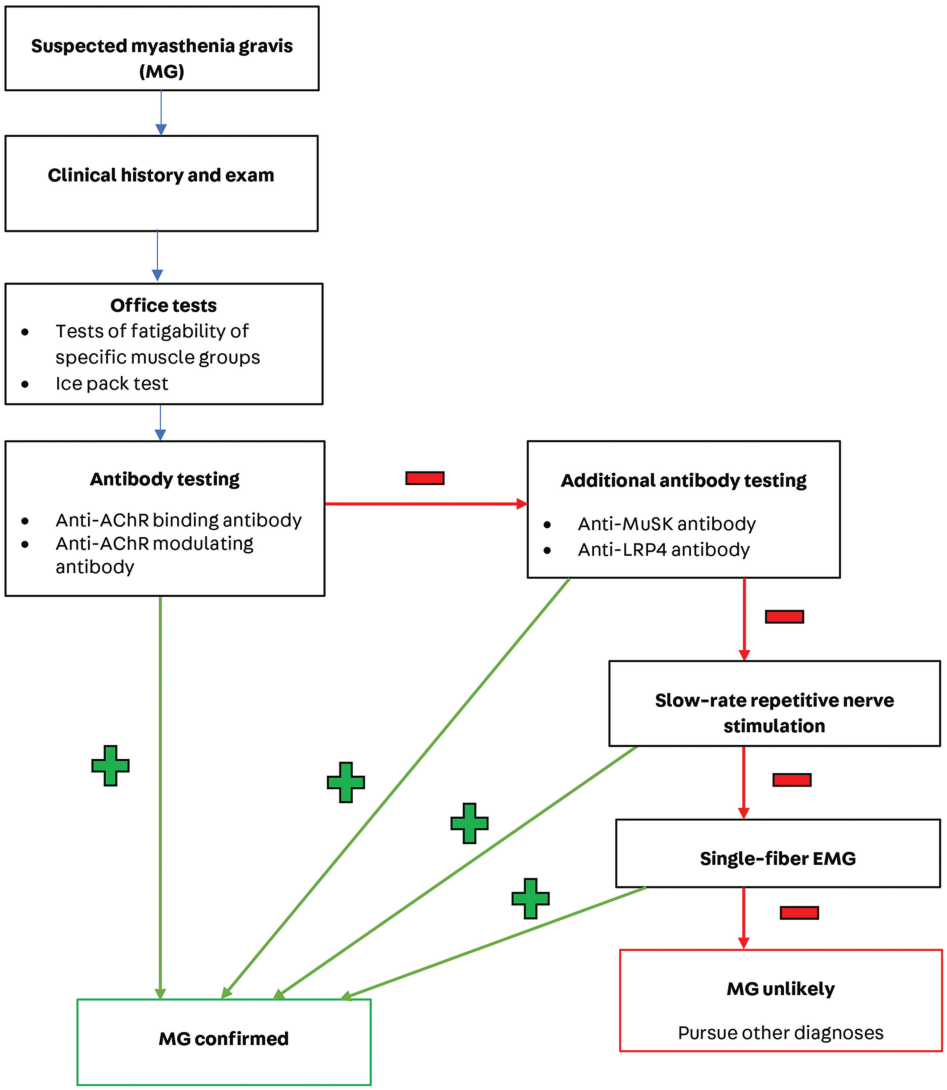

FIGURE 3-1

Diagnostic approach to myasthenia gravis.

AChR = acetylcholine receptor; LRP4 = lipoprotein-related protein 4 MuSK = muscle-specific tyrosine kinase. Modified with permission from Hehir MK, Ciafolini E, J. Wiley and Sons Inc.[19] © 2011 Blackwell Publishing Ltd.

Antibodies against MuSK are typically checked in patients in whom anti-AChR antibodies are not detected. Rare cases have been described of patients with concurrent positivity for both anti-AChR antibodies and anti-MuSK antibodies.[22,23] Anti-MuSK antibodies are detected in about one-third of patients who are negative for anti-AChR antibodies, equivalent to about 7% of all generalized patients with MG.[13] Anti-MuSK antibodies are IgG4 subclass antibodies that do not activate complement. Treatment in these patients is different from that in patients with anti-AChR antibodies and patients who are seronegative.[24,25]

In patients without measurable anti-AChR and anti-MuSK antibodies, testing of anti-LRP4 antibodies can be considered. Anti-LRP4 antibodies can be detected in up to 15% of seronegative generalized patients with MG.[26] Patients who are

KEY POINTS

- Antibodies against muscle-specific tyrosine kinase, lipoprotein-related protein 4, and clustered acetylcholine receptors can be detected in a large portion of patients with generalized MG without anti-acetylcholine receptor–binding antibodies.
- Slow-rate repetitive nerve stimulation and single-fiber EMG can be used to confirm a diagnosis of MG in those who do not have measurable autoantibodies.

positive for anti-LRP4 antibodies have a similar clinical course and response to treatment as patients with anti-AChR antibody positive MG.[26,27]

Although not clinically available in the United States at the time of publication, a cell-based immunofluorescence assay to measure antibodies to clustered AChR may be positive in up to 38% of seronegative generalized patients with MG.[28,29] Patients with measurable antibodies to clustered AChR tend to be younger than age 30 years, more likely to have a mild clinical phenotype, and likely to respond to treatment better than truly seronegative patients.[28] This assay is likely to become an important part of the diagnostic algorithm in the future.

Electrodiagnostic Testing

In patients suspected to have MG with negative antibody testing or patients with suspected false-positive antibody testing, electrodiagnostic testing of neuromuscular junction function can be helpful. Two-Hz to three-Hz slow repetitive nerve stimulation testing carries a sensitivity of 40% to 50% and a specificity of 95% to 100% in patients with generalized MG.[30] (FIGURE 3-2[31]) As a general rule, it is important to perform repetitive nerve stimulation on a weak muscle or a muscle in proximity to a weak muscle; for example, repetitive nerve stimulation of the facial nerve should be performed over stimulation of the median nerve in a patient with primarily ocular weakness. A description of this technique is beyond the scope of this article.

At specialized neuromuscular centers, single-fiber EMG can also be performed to evaluate the neuromuscular junction. Because of the specialized nature of single-fiber EMG, it is best to have the test performed at a center that routinely administers it. In generalized MG, sensitivity ranges from 75% to 90% and specificity from 60% to 90%.[17,32] Many centers have switched from a specialized single-fiber needle electrode to the standard concentric needle electrode used for routine EMG.[32,33] Single-fiber EMG evaluates for asynchronous firing of muscle fibers from the same motor unit. In MG, these fibers fire asynchronously, resulting in the electrical finding of increased jitter. (FIGURE 3-2) Normal values for absolute jitter and mean jitter are available for both the specialized

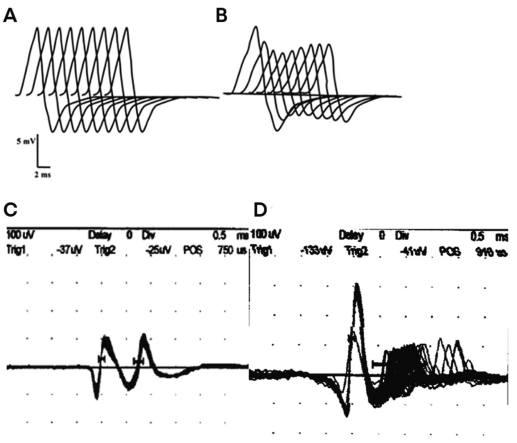

FIGURE 3-2

Slow repetitive nerve stimulation and single-fiber EMG. *A*, Normal 3-Hz slow repetitive nerve conduction study. *B*, Abnormal 3-Hz slow repetitive nerve conduction study demonstrating a decremental compound motor action potential (CMAP) amplitude with successive stimulations. The largest drop in amplitude occurs between the first and second stimulations and the maximal decrement occurs at the fourth stimulation, producing the classic "U-shaped" curve. *C*, Normal single-fiber EMG of the frontalis. *D*, Abnormal single fiber EMG of the frontalis. This study demonstrates asynchronous firing of two muscle fibers, recorded 100 times simultaneously, from the same motor unit. This finding is termed *increased jitter*.

Panels A and B reprinted with permission from Meriggioli MN, Marcel Dekker, Inc.[31] © 2004, Marcel Dekker, Inc.

single-fiber EMG needle and the standard concentric needle.[34,35] These values also change with age and muscles being studied.[36] False-positive results can be seen in other neuromuscular disorders such as neuropathies, myopathies, and motor neuron disease. Correlation between the single-fiber EMG and clinical presentation is essential.

OCULAR MYASTHENIA GRAVIS

Patients with ocular MG tend to be older than patients with generalized MG and less likely to have measurable serum MG-specific autoantibodies[37] (CASE 3-2).

CASE 3-2

A 65-year-old man presented with a 9-month history of intermittent eyelid drooping and intermittent double vision when watching television and with reading. The double vision always improved upon covering either eye. His symptoms were most prominent when he was tired and at the end of the day; the symptoms improved with rest and sleep. He had no difficulty with chewing or swallowing, shortness of breath, or weakness of his arms or legs.

Neurologic examination revealed moderate bilateral ptosis that worsened within 20 seconds of sustained upward gaze. The patient had a positive curtain sign bilaterally, with contralateral ptosis worsening upon lifting one eyelid. The ptosis improved upon cooling the eyes with an ice pack for 2 minutes. The patient had conjugate primary gaze. He developed diplopia and dysconjugate gaze within 20 seconds of fixed horizontal gaze and 15 seconds of fixed upward gaze. The remainder of the neurologic examination was normal.

Diagnostic testing was performed. As noted previously, the bedside ice pack test showed modest improvement in the patient's ptosis. Acetylcholine receptor–binding antibodies, acetylcholine receptor–modulating antibodies, and anti–muscle-specific tyrosine kinase (MuSK) antibodies were not detected in serum. Slow repetitive nerve stimulation of the facial nerve was normal without detection of an electrical decrement. Voluntary single-fiber EMG of the frontalis muscle demonstrated abnormal jitter in 6 of 20 recorded muscle fiber pairs, consistent with pathology at the neuromuscular junction.

COMMENT

This case illustrates the classical clinical presentation of a patient with seronegative ocular myasthenia gravis (MG). The neurologic examination demonstrated weakness in extraocular and eyelid levator muscles. Bulbar, neck muscle, and proximal arm and leg strength was normal. The combination of clinical history, bedside examination, and bedside ice pack test supported a clinical diagnosis of ocular MG. Negative antibody results and normal slow repetitive nerve stimulation testing demonstrate the low sensitivity of these tests in patients with pure ocular MG. Confirmatory testing with single-fiber EMG in a muscle adjacent to the affected ocular muscles is often useful to support the diagnosis of seronegative ocular MG.

Between 40% and 70% of patients with ocular MG will progress to generalized MG within 2 years of developing symptoms.[37] Patients with ocular MG with measurable titers of anti-AChR antibodies are more likely to transition to generalized MG.[37,38]

The diagnostic algorithm is similar between patients with suspected ocular MG and those with suspected generalized MG. However, the sensitivity and specificity of diagnostic tests are different. Despite a specificity of 98% in ocular MG, the sensitivity of testing for AChR-binding antibodies is only between 45% and 65%.[17] Therefore, in many patients with ocular MG, the diagnosis relies on a combination of the clinical history, clinical examination, provocative bedside maneuvers, and electrodiagnostic testing.

Bedside Tests

Bedside maneuvers such as the ice pack test are useful in evaluating a patient with suspected ocular MG. The ice pack test carries a sensitivity of 80% to 95% and a specificity of 79% to 97%.[16,17] In patients with mild ptosis, the sensitivity of the ice pack test can be as low as 25%; the sensitivity can be increased to 70% by fatiguing muscles with sustained upgaze before performing the test.[18] The combination of the ice pack test with a single-fiber EMG can increase both sensitivity and specificity.[16]

Electrodiagnostic Testing

Similar principles apply for electrodiagnostic testing of the patient with suspected ocular MG; targeting a weak muscle or a muscle in proximity to a weak muscle necessitates testing the facial nerve with slow-rate repetitive nerve stimulation and testing the frontalis or orbicularis oculi with single-fiber EMG. In ocular MG, repetitive nerve stimulation of the facial nerve or spinal accessory nerve carries a sensitivity of 15% to 35% and a specificity of 95% to 99%.[30] Because of the low sensitivity, it is often necessary to progress to a single-fiber EMG in patients with suspected ocular MG. The sensitivity and specificity of single-fiber EMG vary among patients exhibiting isolated ptosis, isolated diplopia, or a combination of ptosis and diplopia. In patients with isolated ptosis or ptosis and diplopia, the sensitivity of single-fiber EMG ranges from 80% to 98% and the specificity ranges from 75% to 85%.[32,39] Although the specificity remains high in patients with isolated diplopia, the sensitivity drops to 30%.[39] In patients with isolated diplopia, if the single-fiber EMG is repeated after ptosis develops several months later, the sensitivity increases to about 90% to 95%.[39] When there is a high suspicion of ocular MG, serial single-fiber EMG may be useful to confirm the diagnosis in patients with an initially normal single-fiber EMG. A drawback to single-fiber EMG is its low specificity. As with all electrodiagnostic testing, results must be interpreted within the context of a patient's clinical history and examination. The specificity of the single-fiber EMG can increase to 85% to 92% if combined with a positive ice pack test.[16]

TREATMENT OF MYASTHENIA GRAVIS

Treatment strategies for patients with MG are influenced by age at onset, disease severity, rate of progression, duration of illness, antibody status, childbearing potential, comorbidity, and desired time course of improvement. The treatment goal is to achieve a status of disease remission, which is defined as being free of symptoms or signs of weakness, or a status of minimal manifestation, which is

defined as having no functionally limiting symptoms or signs of weakness, with no or minimal treatment-related side effects.[11]

Rather than providing a comprehensive discussion of all aspects of MG treatment, this review is intended to highlight some of the important aspects based on literature review and the authors' personal experience. Several treatment guidelines are available.[11,40-42]

General Care

The very first step of management is patient education. Both the Myasthenia Gravis Foundation of America and the Muscular Dystrophy Association offer educational documents for patients (see "Useful Websites" at the end of this article). Patients should be advised on the typical natural course of MG. The risk of exacerbation is generally highest within the first 3 years of symptom onset. Patients with MG have a normal life expectancy, and the overall prognosis with treatment is excellent. It is often necessary to review MG-specific symptoms for the purposes of quick recognition and avoidance of excessive treatment. If medications are to be given, a prior discussion of planned dosages and commonly encountered side effects usually increases compliance.

Exercise for Myasthenia Gravis Patients

Most patients with MG tolerate physical exercise and experience the benefits of exercise without deterioration. This is particularly true for patients with mild or stable MG.[43] Benefits of exercise include strengthening muscles, counteracting muscle atrophy, increasing endurance, and improving psychological well-being. Aerobic exercise intermixed with periods of rest should be encouraged, with prolonged endurance exercise being less preferred, and exercise should be performed in a comfortable environment with high temperatures avoided. A reasonable starting program could be 150 minutes of medium-intensity exercise per week. If an exercise program is not feasible for patients with severe illness, simply standing and minimizing sedentary time are equally important. Therapy incorporating stretching and balance training such as tai chi and yoga are also suitable. Patients with MG should be encouraged to find activities for which they can adjust intensity and duration based on tolerability.

Fatigue

Fatigue is seen in up to 80% of patients with MG at various stages of their disease. Fatigue in MG is multifactorial. It surely occurs when fluctuating muscle weakness is present, but it can also be indicative of cognitive fogginess, poor sleep hygiene, sleep-disordered breathing, weight gain, physical and cardiovascular deconditioning, depression, or medication side effects. Perception of fatigue can still be present after MG symptoms have been largely controlled, and management of isolated fatigue without MG-specific symptoms or signs may not involve escalation of MG treatment. Cognitive-behavioral therapy, aerobic exercise, weight reduction, sleep evaluation, pain control, and mood stabilization treatment may help alleviate fatigue in some patients with MG.[44,45]

Dyspnea

Although shortness of breath can be a sign of respiratory insufficiency due to muscle weakness in MG, isolated subjective dyspnea without other bulbar manifestations is rarely an indication of impending myasthenic crisis. When

KEY POINTS

- Confirming the diagnosis of ocular MG relies on bedside testing and electrodiagnostics in many patients because of the low sensitivity of antibody testing when symptoms are restricted to ocular muscles.
- Slow-rate repetitive nerve stimulation has high specificity but low sensitivity in ocular MG.
- Single-fiber EMG has a high sensitivity in ocular MG. However, single-fiber EMG has the possibility of false-positive testing in ocular MG due to lower specificity (75% to 90%).
- The specificity of single-fiber EMG can be improved by combining it with an ice pack test for patients with ocular symptoms.
- Treatment of MG varies according to many patient characteristics and practical considerations and should be individualized.
- Patient education on typical MG symptoms, course, prognosis, and treatment is important for treatment success.
- Physical exercise is beneficial to patients with MG and can be modified based on tolerability.
- Fatigue in MG is multifactorial, and isolated perception of fatigue may not require medication escalation.
- Isolated perception of dyspnea at rest or with exertion does not indicate myasthenic crisis and rarely needs treatment escalation.

working with patients with MG who report exertional dyspnea, it is necessary to evaluate coexisting bulbar or neck muscle weakness and possibly perform pulmonary function testing. Isolated subjective dyspnea rarely indicates a need for treatment escalation. A sensation of breathlessness may be reported by patients with MG who have no objective evidence of respiratory muscle weakness or noticeable weakness of other skeletal muscle groups. Patients with MG may exhibit shallow breathing with a tendency to hyperventilate at rest or with minimal exertion. Contributory factors include deconditioning, weight gain, obstructive sleep apnea, and corticosteroid-related anxiety. Physical exercise or

TABLE 3-1 **Medications to Avoid or Use With Caution in Myasthenia Gravis**[a]

Medication	Risk of worsening myasthenia gravis (MG)	Comments
Aminoglycoside antibiotics (eg, gentamycin, amikacin, tobramycin)	Moderate	US Food and Drug Administration (FDA) issued a boxed warning for muscle paralysis; use with caution if no alternative is available
Beta-blockers	Low	May worsen MG; use with caution, especially in myasthenic crisis or postoperative setting
Botulinum toxin	High	Local use of small dose could worsen MG; avoid
Chloroquine and hydroxychloroquine	Low	Rare reports of worsening MG; use with caution
Fluoroquinolones (eg, ciprofloxacin, levofloxacin, ofloxacin)	Probably moderate	FDA issued a boxed warning for use in MG; use with caution
Immune checkpoint inhibitors (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, cemiplimab, durvalumab, avelumab, dostarlimab, relatlimab)	High	Can cause de novo MG or worsen preexisting MG; use with extreme caution if no alternative, but discontinue if MG worsens
Interferon alfa	Low	May worsen or cause MG; use with caution
Iodinated contrast agent	Low	Rare reports of worsening MG; use with caution
Macrolide antibiotics (eg, azithromycin, clarithromycin, erythromycin)	Probably moderate	May worsen MG; use with caution
Magnesium, IV	High	May worsen MG because of its action on neuromuscular junction; avoid
Penicillamine	High	Can cause MG; avoid
Quinine	Low	Rare reports of worsening MG; use with caution
Statins (eg, atorvastatin, pravastatin, simvastatin)	Low	Rare reports of worsening MG; use with caution
Telethromycin	High	Can cause MG; FDA issued a boxed warning for its use in MG; avoid
Anti–tumor necrosis factor (eg, etanercept, infliximab, adalimumab)	Unclear	Risks of causing or worsening MG are likely low; some patients with MG improve; use with caution

[a] Data from Narayanaswami P, et al, Neurology.[40]

respiratory muscle training such as diaphragmatic or pursed-lip breathing may help to improve respiratory muscle endurance and reduce perception of dyspnea.[43]

Medications That May Trigger Exacerbation

Factors that may worsen myasthenic symptoms include systemic illness, infection, postpartum status, heat, emotional upset, and medication.[46] TABLE 3-1[42] provides a list of medications that may exacerbate MG. Medications classified as "use with caution" can be tolerated by most patients with MG with mild disease or in stable remission. These medications can still be given to patients with MG with more significant weakness when no alternative is available if the patient is monitored regularly. Evidence supporting inclusion of some medications (eg, beta-blockers, chloroquine, iodinated contrast, quinine, statins) is limited to anecdotal case reports or case series; the possibility of these medications inducing MG exacerbation is likely low. Several classes of antibiotics (ie, aminoglycosides, macrolides, and fluoroquinolones) are probably best avoided if possible, but many stable patients with MG have been administered macrolides or fluoroquinolones without ill effects.[47,48] In the setting of treating an infection, it is sometimes difficult to attribute a worsening of MG symptoms to the underlying infection or the use of antibiotics.

Immune checkpoint inhibitors are increasingly used in the treatment of a variety of malignancies (TABLE 3-1). Several immune checkpoint inhibitors may induce or aggravate a variety of immune-mediated neurologic conditions, and severe complications occur in approximately 1% of patients using such therapies.[49] MG, necrotizing myositis, myocarditis, or motor-predominant polyneuropathy may occur in combination or in isolation. Symptoms typically occur within the first six cycles of immune checkpoint inhibitor treatment.[49] The presentation may be variable, as some cases are mild and indolent, but others are rapidly progressive or even fulminant. Prompt recognition is critical because the condition can evolve rapidly. Diagnosis of MG or coexisting neuromuscular disorders in these patients can be challenging. Many patients with immune checkpoint inhibitor–induced de novo MG do not have measurable MG-specific autoantibodies. In addition to neuromuscular junction dysfunction, electrodiagnostic studies may show findings of concurrent irritative myopathy and inflammatory polyradiculoneuropathies.[49] The mainstay of treatment is to stop immune checkpoint inhibitor therapy and start immunotherapy, especially corticosteroids. Although many patients with MG are responsive to corticosteroids, patients with concurrent myositis or myocarditis may have a more aggressive course of immune-related MG, requiring multiple modalities of immunotherapy.[49] It is essential to work with the patient's oncologist in addressing complications of immune checkpoint inhibitors. Many patients receiving these therapies have advanced-stage, aggressive malignancies without other treatment options. In the authors' experience, patients with known MG under good control can be cautiously treated with immune checkpoint inhibitors. We typically follow these patients at frequent intervals and encourage them to call if they experience any symptoms of worsening MG.

Medical Treatment for Myasthenia Gravis

Myasthenia gravis is treated with a combination of symptomatic treatment (acetylcholinesterase inhibitors), immunosuppressive medications, plasma exchange, and thymectomy. The most frequently used immunosuppressive

KEY POINTS

- **Medications listed as "use with caution" in MG can be tolerated by patients with mild disease and may be given to patients with significant weakness under careful monitoring if no alternatives exist.**
- **Immune checkpoint inhibitors may cause a combination of MG, myositis, and myocarditis, and an aggressive treatment strategy for these complications is needed.**

therapies include corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus, cyclophosphamide, rituximab, eculizumab, ravulizumab, efgartigimod, IV immunoglobulin (IVIg), and subcutaneous immunoglobulin.[50] TABLE 3-2 contains detailed information on each of the above-mentioned nonsurgical treatments.

At the time of publication, the number of treatments available for patients with MG is rapidly growing.[51] Three newer treatments that take advantage of novel mechanisms of action have recently been approved to treat adult patients with anti-AChR generalized MG. Eculizumab and ravulizumab act as IV complement inhibitors, and efgartigimod is an IV neonatal Fc receptor (FcRn) inhibitor. Additional complement inhibitors and FcRn inhibitors are currently being studied in phase 2 and 3 clinical trials. Other disease-specific agents are also being evaluated in clinical trials. As more treatments are approved for patients with MG, decisions about which treatments to employ will likely be driven by patients and their physicians who will weigh differences in efficacy, time to achieve good clinical status, comparative efficacy, burden of therapy (eg, frequency of infusions), adverse event profiles, and cost.

NONIMMUNOSUPPRESSIVE AGENTS. Pyridostigmine is the most commonly used acetylcholinesterase inhibitor. It is typically effective in alleviating the symptoms of ptosis and dysarthria. The regular-release form of pyridostigmine is preferred, as the slow-release formulation exhibits erratic absorption and is reserved for the small group of patients with morning weakness who may benefit from a dosage of the slow-release form at bedtime. Pyridostigmine is used alone in purely ocular and mild generalized MG or in combination with immunotherapy in more severe cases. In practice, the need for a pyridostigmine dose of more than 180 mg to 240 mg daily, intolerable side effects, and worsening weakness are indications for initiating immunotherapy. Pyridostigmine should be administered with caution in impending MG respiratory crisis, as it can increase secretions and complicate airway management. Once MG is controlled with immunotherapy, pyridostigmine becomes less useful. Most patients can stop it, use it only when necessary, or take it infrequently, mostly out of habit or a sense of security.

Pyridostigmine is generally safe and without long-term complications. However, excessive pyridostigmine can lead to skeletal muscle weakness. One fact that is less well known is that pyridostigmine (and at times corticosteroids) may modify the splicing of acetylcholinesterase, limiting its own efficacy. This alteration at the RNA level may explain the waning efficacy of pyridostigmine with time and in the context of immunotherapy.[52]

Other symptomatic treatment options include albuterol, 3,4-diaminopyridine, and ephedrine. However, the role of these agents in MG treatment requires further confirmation.

IMMUNOTHERAPY. Immunotherapy should be considered for patients with MG with significant symptoms or those with mild symptoms that do not respond to nonimmunosuppressive agents.

CORTICOSTEROIDS. Corticosteroid treatment has a broad effect on the immune system and is rapidly effective in all subtypes of MG. Some patients experience a transient worsening of weakness from MG for the first 5 to 7 days after initiating corticosteroid therapy or with large dosage increases in patients already taking

them. After this initial period, improved strength in patients with MG is typical. Some experts have argued that starting with a lower dose of corticosteroid followed by a slow increase in medication rather than starting with a higher dose is associated with a lower risk of developing the transient worsening. However, it remains unclear whether the "start low" approach reduces the risk of corticosteroid-induced exacerbation.[50] Although side effects pose significant challenges, corticosteroids are widely recommended as first-line therapy for patients with MG who require more treatment than pyridostigmine alone. The side effects associated with corticosteroids typically track with higher doses and longer duration of corticosteroid treatment.

Prednisone is the most commonly used corticosteroid for treatment of MG and can be started at the target dose of 20 to 60 mg/d. Because of the risk of worsening weakness upon initiating corticosteroids, in patients with severe weakness, especially those with bulbar or respiratory weakness, corticosteroid initiation should be delayed until patients undergo a course of either IVIg or plasma exchange with observed improvement in strength. For patients with mild to moderate weakness who are frequently encountered in the outpatient setting, an initial dose of 20 to 30 mg/d could be considered with subsequent dosage adjustment based on treatment response. Results from the Muscle Study Group trial on mycophenolate mofetil suggested that 77% of patients with MG with mild to moderate disease (Myasthenia Gravis Foundation of America class II or III) responded well to prednisone at a dosage of 20 mg/d.[53] Starting at this moderate dose of prednisone may reduce the risk of developing side effects. Once significant clinical improvement has occurred, a taper of prednisone should be started; use of a concurrent noncorticosteroid immunosuppressant may be needed to maintain a good clinical outcome at lower doses of prednisone.[54] An alternating-day schedule of using prednisone is historical, and its benefit over daily dosing has never been firmly proven in clinical practice. The goal should be to achieve a prednisone dose of less than or equal to 7.5 mg/d or its every-other-day equivalent by 1 year. Patients taking 7.5 mg/d of prednisone with minimal disease manifestations are more likely to report a good quality of life and less likely to report side effects than patients receiving higher doses.[55] When prednisone reaches such a low dosage while the disease is well controlled, there is often a need to discuss the pros and cons of further dose reduction with patients. A successful discontinuation of prednisone often depends on a multitude of factors, including disease severity, comorbidity, usage of other noncorticosteroid immunotherapy, and whether a patient had a thymectomy.

NONCORTICOSTEROID IMMUNOSUPPRESSANT MEDICATIONS. Traditionally, noncorticosteroid immunosuppressant medications have included azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus, and cyclophosphamide. Evidence of the efficacy of azathioprine and cyclosporine as add-on treatments to corticosteroids is based on data from prospective randomized controlled trials.[56,57] Randomized trials of mycophenolate mofetil, methotrexate, and tacrolimus did not meet the primary endpoints to demonstrate efficacy or steroid-sparing properties.[53,58,59] Retrospective data, however, suggest that mycophenolate mofetil is an effective treatment for MG both in combination with prednisone and as monotherapy, especially in the time period after which the primary endpoint was adjudicated in the randomized controlled trials.[60] The efficacy of methotrexate, tacrolimus, and

KEY POINTS

- **Pyridostigmine is used alone in ocular and mild MG or in combination with immunosuppressants in severe cases and can be minimized or stopped after patients improve on immunotherapy.**
- **Prednisone remains the first-line immunotherapy for MG, and the starting dosage may vary depending on disease severity. A higher dosage may not be necessary for mild disease.**
- **Prednisone tapering should be slow, with a target goal of 5.0 to 7.5 mg/d at approximately 1 year.**

TABLE 3-2 Summary of Medical Treatment for Myasthenia Gravis

Medication	Starting dosage	Maintenance dosage	Onset of action
Pyridostigmine	30-60 mg 3 times a day	60-120 mg 4 times a day while awake	30-60 min
Prednisone	20-60 mg/d	20-60 mg/d with slow tapering	10-20 days
Azathioprine	50 mg/d	150 mg/d or 2-3 mg/kg/d	6-18 months
Mycophenolate mofetil	500 mg/d	500-1500 mg 2 times a day	3-12 months
Cyclosporine	100 mg 2 times a day	3-5 mg/kg/d, divided into 2 doses	1-3 months
Tacrolimus	1 mg/d	3 mg/d divided into 2 doses	1-6 months
Methotrexate	2.5 mg/wk	15-25 mg/wk	6-12 months
Cyclophosphamide	0.5-1.5 g/m^2 body surface area (BSA) or 50-100 mg/d orally	0.5-1 g/m^2 BSA monthly or 50-100 mg/d orally	1-6 months

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Notable adverse events	Monitoring	Comment
Abdominal cramping, diarrhea, nausea, excessive lacrimation or salivation, fasciculations, cramps	Watch for excessive secretions in patients with bulbar symptoms	Given 30 min before meals if dysphagia is present; adjustment needed with renal impairment; glycopyrrolate, hyoscyamine, or loperamide can be used for muscarinic side effects
Weight gain, hyperglycemia, hypertension, eye disease, bone density loss, gastric ulcer, insomnia, mood disorder	Hemoglobin A_{1c} every few months, annual dual-energy x-ray absorptiometry (DEXA) scan, blood pressure checks	Steroid-induced exacerbation may occur in one-third of patients; greater risk in elderly patients with bulbar weakness; side effect management includes diet control, calcium and vitamin D supplementation, and annual eye examination
Idiosyncratic flulike reaction, hepatotoxicity, pancreatitis, bone marrow suppression, risk of skin cancer and lymphoma	Complete blood cell count (CBC), liver enzymes 1-4 times in the first month, then monthly for 6 months, then every 3 months	Once-daily dosing is appropriate. Dosage adjustment based on thiopurine S-methyltransferase level; dose reduction with coadministration of allopurinol or sulfasalazine; avoid rechallenging in patients with idiosyncratic reaction (fever, skin rash, abnormal liver function, pancreatitis), significant hepatotoxicity, or bone marrow suppression
Teratogenicity, diverticulosis, bone marrow suppression, risk of skin cancer and rare lymphoma	CBC every 2 weeks for first month, then monthly for 6 months, then every 3 months; Risk Evaluation and Mitigation Strategy (REMS) program for women of childbearing age	Contraception needed when used in women of childbearing age; should be taken 1 hour before or 2 hours after meal; dose adjustment with coadministration of cholestyramine
Hypertension, nephrotoxicity, hepatotoxicity, neuropathy, tremor, cancer risk, drug interaction	CBC, liver enzymes, blood urea nitrogen/creatinine monthly for 3 months, then every 3 months	Fast onset of action is advantageous, but side effects may limit its use; target trough level of 100-150 ng/mL, monitoring of creatinine level to not exceed 1.5 times baseline, dosage adjustment needed when given parenterally
Hyperglycemia, hypomagnesemia, nephrotoxicity, tremor, bone marrow suppression, rare cancer risk	Metabolic profile monthly for 3 months, then intermittently	Target trough level of 2-9 ng/mL; taken on empty stomach; dosage adjustment needed when given parenterally; fewer side effects than cyclosporine
Hepatotoxicity, stomatitis, nausea, vomiting, pulmonary toxicity, teratogenicity	CBC, liver enzymes monthly, then every 3 months; intermittent screening for interstitial lung disease	Contraindicated in pregnancy; can be given orally or parenterally; folate or folinic acid supplement may be beneficial in avoiding side effects
Teratogenicity, infertility, nausea, alopecia, bone marrow suppression, cystitis, cancer risk	CBC, metabolic profile, liver enzymes, urinalysis monthly	Contraception recommended for patients; pretreatment hydration and antiemetics are needed; monitoring needed for hematuria; efficacy is short-lived; may be indicated for rare cases of refractory myasthenia gravis

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Medication	Starting dosage	Maintenance dosage	Onset of action
Rituximab	1 g every 2 weeks for 2 doses, or 375 mg/m^2 BSA weekly for 4 doses	Cycle repeated at 6-month interval if needed	1-3 months
Eculizumab	900 mg/wk for 4 weeks	1200 mg every 2 weeks	2-12 weeks
Ravulizumab	2400-3000 mg once based on weight	3000-3600 mg once, based on weight, 2 weeks following loading, then every 8 weeks	1 week or later
Efgartigimod	10 mg/kg/wk up to 1200 mg/wk for 4 weeks	Cycle repeated as early as 4 weeks after if necessary	1-2 weeks
IV immunoglobulin (IVIg)	2 g/kg divided over 2-5 days	0.4-1 g/kg every 1-6 months	3-10 days
Subcutaneous immunoglobulin	0.5 g/kg weekly	Adjust based on response	Approximately 2 weeks
Plasma exchange	1-1.5 blood volume, 3-5 procedures	1-4 procedures monthly for maintenance	2-5 days

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Notable adverse events	Monitoring	Comment
Bone marrow suppression, infusion reaction, rarely progressive multifocal leukoencephalopathy	CBC, metabolic profile, possibly CD19 lymphocyte count	A minimum of two treatment cycles is usually required; effectively removed by plasma exchange; mechanism of action is complement dependent and thus should not be combined with complement inhibitor therapy
Myalgia, headache, nasopharyngitis, meningococcal infection	None	Must administer meningococcal vaccination 2 weeks before initiation or cover with antibiotics; maintenance meningococcal vaccination needed for prolonged use; dosage adjustment needed with plasma exchange
Headache, diarrhea, nausea, tendonitis, infections	None	Same vaccination schedule as eculizumab; dosage adjustment needed for plasma exchange and IVIg
Headache, urinary or respiratory infections	CBC	Duration of efficacy may vary among patients; long-term side effects not established
Headache, aseptic meningitis, nephrotoxicity, thrombosis	Blood urea nitrogen/creatinine every month with decrease to every 3 months over time.	Screening for IgA deficiency is virtually unnecessary before use due to extremely low incidence of anaphylaxis; avoid in patients with recent thrombotic event
Injection site tenderness, bruising, or pruritus; rarely systemic reactions similar to IVIg	Blood urea nitrogen/creatinine every month with decrease to every 3 months over time	Serum immunoglobulin level peaks around week 4; data on its use in acute exacerbation are lacking
Hypotension, cardiac arrhythmia, anemia, hemorrhage, line-associated infection and thrombosis	CBC and electrolytes at times of plasma exchange	Contraindicated in sepsis and persistent hypotension; fewer side effects with peripheral line access; other immunotherapy needed to avoid myasthenia gravis rebound

cyclophosphamide is based on data from non–placebo-controlled studies.[61-63] Opinions often differ regarding the "ranking order" of these agents, and their selection often depends on a multitude of factors, including desired time course of improvement, burden of therapy, potential side effects, cost, patient preference, and providers' familiarity. In the United States, azathioprine and mycophenolate mofetil are the most commonly used noncorticosteroid immunosuppressants.[64]

A few important points are in order regarding the use of the above-mentioned agents. First, these oral noncorticosteroid immunosuppressive agents are not typically effective until 1 to 14 months after initiating therapy (TABLE 3-2).[56,57,60] Second, azathioprine, mycophenolate mofetil, methotrexate, and tacrolimus can also be given as the initial monotherapy for patients with relatively mild disease or having contraindications to corticosteroids (eg, poorly controlled diabetes, osteoporosis, or patient's choice). In more severely affected patients in whom corticosteroids are contraindicated, a course of IVIg, plasma exchange, eculizumab, efgartigimod, or ravulizumab may be considered to bridge patients until noncorticosteroid oral agents become effective. Third, many noncorticosteroid immunosuppressant drugs require intermittent laboratory monitoring (TABLE 3-2). Medication dosage adjustment is usually required when white blood cell count is less than 3000/mm^3, neutrophil count is less than 1000/mm^3, or levels of aspartate aminotransferase or alanine aminotransferase exceed 3 times the upper limit of normal. Some lymphopenia in the range of 500/mm^3 to 1000/mm^3 is allowable following the use of some of these medications. Fourth, in patients whose MG has been in stable remission for a minimum of 3 to 5 years, dosage reduction of these agents can be considered.[11] The tapering process should be slow to reduce the risk of relapse. For example, the daily dosage should not be reduced by more than 50 mg for azathioprine and 500 mg for mycophenolate mofetil on a yearly basis.[65,66] A quicker dosage reduction may risk MG relapse.[50,67] Patients who experience a relapse will typically improve if the dosage of the noncorticosteroid immunosuppressant is increased.[65]

Long-term use of these drugs may increase the risk of skin, lymphoproliferative, and solid organ malignancies.[68-72] These medications should be reserved for those who have not responded well to prednisone, who relapse on prednisone tapering, or who have clear contraindications to corticosteroid use. There may not be a definite need to switch to this class of medications if MG is controlled with a prednisone dosage of 7.5 mg/d or less, which may be seen in approximately 50% of patients with generalized MG.[73] It remains debatable which of the following two options is associated with more severe long-term adverse effects: low-dose prednisone versus full-dose, noncorticosteroid immunosuppressant medications. At the time of publication, research is under way to address this question.

In some cases, it is possible to wean corticosteroids completely while leaving noncorticosteroid immunosuppressants in place. In other cases, both prednisone and the noncorticosteroid immunosuppressant agent are kept at low dosages to achieve stable control, due to possible synergistic effects. Complete stable remission without the continuing need for immunotherapy can only be achieved in approximately 10% to 20% of patients with generalized MG, and about 30% of patients following thymectomy. In view of the low rate of complete stable remission, it is advisable to consult with patients and balance the risk of relapse with the use of low-dose maintenance immunotherapy for the long term.

RITUXIMAB. Rituximab has been used as a treatment for MG. Compelling data from retrospective studies suggest that rituximab is effective in anti-MuSK antibody positive MG and should be considered as an early therapy in these patients.[24,74] Negative results from one randomized trial in patients positive for AChR antibodies and data from a systematic review suggest that rituximab may be less effective but still useful in some patients with antibodies against AChRs.[74,75] Although it is often reserved for refractory MG, more recent results suggest that rituximab may be effective in new-onset anti-AChR MG and in patients with onset of anti-AChR MG after age 60.[76-78] Rituximab is easily given in cycles (TABLE 3-2). Patients can be redosed every 4 to 6 months based on clinical relapse or CD20-positive B-cell counts. Rituximab showed no or minimal side effects in most patients. Progressive multifocal leukoencephalopathy (PML) is a feared complication that occurs after reactivation of the JC virus. To date, only one case of PML has been reported in the setting of rituximab therapy for MG, following the use of several other immunosuppressants for long durations; thus, the risk of rituximab-associated PML in the MG population appears low. The COVID-19 pandemic has also revealed that patients treated with B-cell inhibition are less likely to mount effective antibody responses to vaccination.[79] In clinical practice, the authors recommend rituximab early in the treatment course for patients with anti-MuSK MG. Weighing potential risks of infection, rituximab may also be useful earlier in the treatment paradiagm for patients with anti-AChR MG.

ECULIZUMAB AND RAVULIZUMAB. Eculizumab is the first complement inhibitor that has been approved by the FDA for the management of anti-AChR positive generalized MG (TABLE 3-2). In addition, it is accepted in many countries as an add-on therapy for refractory MG. Clinical improvement tends to appear within 2 weeks following the first infusion, becomes maximal at 3 months for most patients, and remains stable for at least 3 years.[80,81] Complement inhibition by eculizumab renders patients prone to meningococcal infection, but so far the incidence of such infection appears rare in the MG population. Patients need to be vaccinated with both the quadrivalent and group B *Neisseria meningitidis* vaccines before initiating eculizumab treatment and require boosters of these vaccines at regular intervals. Eculizumab is rather expensive; unnecessary costly administrations can be avoided if no apparent benefit is seen within the first 3 to 6 months.[82]

Ravulizumab is an engineered form of eculizumab with improved pharmacokinetics resulting in a long half-life that permits a maintenance dosing interval of 1 infusion every 8 weeks. Its efficacy and safety were demonstrated in a pivotal phase 3 trial that led to the FDA's recent approval of its usage in adult anti-AChR positive generalized MG.[83] Its side effects and cautions follow those of eculizumab.

At this time, the authors are recommending that eculizumab and ravulizumab be used in patients who are taking prednisone and have tried one or more additional immunosuppressive drugs with incomplete disease control, patients with more rapidly progressive MG, or patients requiring repeated use of IVIg or plasma exchange.

EFGARTIGIMOD. Efgartigimod is the first FcRn inhibitor that has been approved by the FDA for the treatment of anti-AChR positive generalized MG (TABLE 3-2). In the ADAPT trial (NCT03669588), patients with MG were treated with cycles of four weekly efgartigimod infusions.[84] Following the first efgartigimod infusion, clinical improvement appeared at 1 week, became maximal at 4 to

KEY POINTS

- Selection of corticosteroid-sparing agents depends on many factors, including patient preference and providers' familiarity.
- The tapering of corticosteroid-sparing agents in MG should be slow to avoid a relapse.
- For maintenance therapy of MG, patients can be kept on a stable low-dose corticosteroid, a low-dose corticosteroid-sparing agent, or a combination of both.
- Rituximab can be an option for refractory and new-onset MG, and the incidence of progressive multifocal leukoencephalopathy appears rare.
- Eculizumab and ravulizumab have a quick onset of action, and their efficacy is long lasting, but cost is a limiting factor.

5 weeks, and gradually declined in the following 4 weeks. In the ADAPT trial, subsequent cycles were started once patients lost clinical benefits; the dose interval varied from 6 weeks to 12 weeks or longer among treated patients. At the time of this publication, there remains uncertainty about how efgartigimod dosing should be optimally managed in real-world clinical practice. Efgartigimod is an option for patients with MG who have an exacerbation or whose MG remains poorly controlled. However, it is somewhat unclear when the second treatment cycle should be given or whether efgartigimod administration at regular intervals is a persistently effective option. The FDA has advised that subsequent treatment cycles of efgartigimod be administered based on clinical evaluation and no sooner than 50 days from the start of the previous treatment cycle.

Efgartigimod is well tolerated, being associated with slightly increased risks of respiratory and urinary tract infections. There is a slight risk of neutropenia and leukopenia, so regular monitoring of complete blood cell count is beneficial. However, data on long-term safety of efgartigimod are unavailable, and it is necessary to watch for the development of neutralizing antibody with repeated efgartigimod use.

Plasma Exchange and IV Immunoglobulin

Plasma exchange and IVIg can be used in the following scenarios in the management of MG: (1) short-term therapy for moderate to severe MG, with a goal of providing rapid improvement and serving as a bridge treatment to prednisone or other immunosuppressants with slow onset of action; (2) maintenance treatment in patients who show poor response to or intolerance of multiple immunosuppressants; (3) preoperative therapy to optimize patient strength; (4) MG impending crisis and crisis.

Although no evidence from prospective, controlled, double-blind studies has been reported, there is substantial anecdotal and retrospective literature support for the use of IVIg as a maintenance therapy in selected cases. Compared with IVIg, subcutaneous immunoglobulin may provide more consistent serum IgG levels; subcutaneous immunoglobulin may be preferable in patients with poor venous access, patients without access to an infusion center or home infusion services, and patients who desire additional autonomy.[50] However, subcutaneous immunoglobulin requires self-administration with subcutaneous needles. Maintenance plasma exchange has been used infrequently in patients with refractory MG. Preoperative administration of IVIg or plasma exchange is not necessary for patients with well-controlled MG.[85]

The efficacies of plasma exchange and IVIg are comparable in patients with moderate to severe disease. Plasma exchange may be preferable in myasthenic crisis or impending crisis because of its faster onset of action.[11] The choice between plasma exchange and IVIg is mostly influenced by practical issues such as availability, institutional preference, comorbidity, or venous access. In rare cases, these two treatment modalities can be given in sequence, as patients may respond to one but not the other. To secure long-term improvement, immunosuppressive drugs should be added on or given at higher doses than before the MG exacerbation.

Treatment of Myasthenic Crisis

Myasthenic crisis is defined as the occurrence of MG-related respiratory and/or bulbar muscle weakness that is severe enough to necessitate intubation or

noninvasive positive pressure ventilation. Patients in myasthenic crisis require intensive care management, concomitant evaluation for possible triggers, and aggressive immunotherapies such as plasmapheresis or IVIg. Severe MG with noticeable dyspnea or dysphagia should be managed similarly to crisis. For patients who experience impending crisis, it is necessary to closely monitor for signs of paradoxical breathing, orthopnea, accessory muscle use, and decline in vital capacity or negative inspiratory force. Noninvasive ventilation can be a short-term management strategy prior to intubation.

Both plasma exchange and IVIg may begin to produce clinical improvements within several days. Augmentation of baseline immunotherapy is needed before their efficacy decreases. Anticholinesterase medications are generally held to reduce oropharyngeal secretions.

Once patients are started on mechanical ventilation, it typically needs to be continued for 5 to 7 days. A conservative approach to extubation is recommended. Weaning from the ventilator should be considered only when substantial improvement is observed in vital capacity, inspiratory force, and neck flexion. Weak cough, difficulty in clearing secretions, and neck muscle weakness are possible predictors of extubation failure. Patience is paramount with these patients, as most will recover with appropriate treatment and time.[86]

Thymectomy

The landmark MGTX trial (Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy) compared treatment modalities of prednisone and thymectomy versus prednisone alone. Results showed clinically meaningful and long-lasting efficacy of thymectomy in nonthymomatous patients with anti-AChR positive generalized MG up to age 65. Ideal candidates for thymectomy are young (age 50 years or younger) female patients with a short disease duration of 1 to 2 years.[87] Thymectomy may be considered in patients who are seronegative but is not recommended for patients with anti-MuSK or ocular MG.[25]

When thymectomy is indicated, it should be planned as soon as the patient's condition allows a safe surgery. Ideally, prednisone is kept at a low dose (eg, <30 mg/d) before thymectomy to allow quick wound healing. Preoperative use of IVIg or plasma exchange should be restricted to those patients with severe generalized MG and those with noticeable respiratory or bulbar weakness. In general, such preoperative treatment is not necessary for patients with a forced vital capacity of greater than or equal to 70% of predicted value.[85]

Endoscopic surgery has become the preferred approach to sternal splitting in many centers and is associated with high rates of clinical improvement, low rates of complications, shorter hospital stays, improved cosmetic appearance, and more preserved postoperative function than open surgery.[88,89] Endoscopic surgery has been applied to the treatment of nonthymomatous MG and noninvasive thymoma, whereas open thymectomy remains the preferred technique for invasive thymoma. In the presence of a thymoma, surgery is aimed at removing the tumor and all surrounding thymic tissue, irrespective of MG subtype. Postoperative radiation therapy or adjuvant chemotherapy could be considered in thymoma with extracapsular extension or when complete resection is not feasible. Long-term monitoring is needed for possible thymoma recurrence, which is usually intrathoracic.

KEY POINTS

- Efgartigimod has a quick onset of action and is well tolerated, but data on optimal long-term treatment are lacking.
- Plasma exchange and IV immunoglobulin can be used for acute exacerbation or as a maintenance therapy. Subcutaneous immunoglobulin has potential as maintenance immunotherapy in MG.
- Patients with impending myasthenic crisis should be monitored closely. The decision on extubation of intubated patients with MG should be made conservatively.
- Thymectomy should be considered for early-onset acetylcholine receptor antibody–positive MG, and endoscopic approaches can be used for most patients with MG.

Treatment of Ocular Myasthenia Gravis

When symptoms are mild and infrequent in ocular MG, it may be best to defer treatment until they become troublesome. Pyridostigmine should be the initial treatment for patients with mild ocular MG. Low-dose prednisone can be fairly effective for ocular symptoms, and its early use in ocular MG may reduce the risk of secondary generalization.[90] Given the negative impact of poor vision on quality of life, nonsteroid immunosuppressants or infusion-based immunosuppressive therapies (eg, IVIg, rituximab) may be indicated in patients whose vision symptoms are refractory to corticosteroids and pyridostigmine. If ptosis or extraocular dysmotility does not reverse in spite of maximal treatment over a 2-year period, the chance of recovery is probably low. In selected patients, ptosis repair and strabismus surgeries may be of benefit. Other effective

CASE 3-3

A 56-year-old man initially presented with alternating ptosis and vertical diplopia of 1 month's duration. Acetylcholine receptor antibody testing was positive at 7.7 nM/L, and chest CT did not show a thymoma. A diagnosis of ocular myasthenia gravis (MG) was made. Pyridostigmine, 60 mg 3 times a day, eliminated all symptoms and was discontinued after 2 months by the patient.

Three years later, ocular symptoms recurred, together with new symptoms of significant head drop, flaccid dysarthria, chewing and swallowing difficulty, and proximal limb weakness. The patient's serum glucose level was 321 mg/dL and his hemoglobin A_{1c} level was 12.0%. Diagnoses of generalized MG and new-onset diabetes were made. He was treated with intravenous immunoglobulin (IVIg) at 0.4 g/kg of body weight per day for 5 days, and azathioprine with a target total dose of 200 mg/d (approximately 2 mg/kg/d) was initiated simultaneously. His symptoms resolved within a week of IVIg infusion, and another course of IVIg treatment at 1.0 g/kg was given 6 weeks later owing to recurrence of lesser symptoms.

For the subsequent 5 years, his MG was well controlled with a combination of pyridostigmine and azathioprine. Pyridostigmine was discontinued after 3 years of use, and the azathioprine dosage was reduced to 150 mg/d. Near the end of this 5-year period, he experienced COVID-19 pneumonia requiring intubation for 7 days, but no signs of MG exacerbation were observed, and no MG treatment adjustment was necessary.

COMMENT

This case illustrates the use of short-course IVIg treatment as a fast-acting therapy leading to a quick improvement of significant MG symptoms. In this patient, IVIg also served as a bridge therapy to azathioprine, bypassing the need for corticosteroids, which were contraindicated owing to poorly controlled diabetes. Only short-course IVIg was administered given the patient's improved MG status, and the high cost associated with long-term maintenance IVIg therapy was avoided.

treatment modalities include crutches or tape for ptosis and an eye patch, an opaque contact lens, or prisms for diplopia.

Treatment of Patients With Severe Weakness and Refractory Myasthenia Gravis

When treating patients with new-onset MG with severe weakness, it is preferable to start with IVIg, efgartigimod, or plasma exchange, followed by maintenance immunosuppressants. Such a strategy of early fast-acting treatment was successfully applied previously, sometimes bypassing the use of high-dose corticosteroids.[55] CASE 3-3 illustrates a typical patient who received such fast-acting treatment without the use of prednisone, which was contraindicated because of his poorly controlled type 2 diabetes.

Refractory MG is defined as either (1) failure to respond to or intolerance of corticosteroids and at least one immunosuppressive medication at an adequate dose and duration, or (2) inability to reduce immunotherapy without clinical relapse or a need for ongoing rescue therapy with IVIg or plasma exchange. Refractory MG occurs in 10% to 15% of all patients with generalized MG. Treatment for refractory MG may include the use of eculizumab, ravulizumab, efgartigimod, rituximab, cyclophosphamide, and possibly investigational therapy. When evaluating such patients, it is necessary to verify that their functional limitations are MG specific, rather than being reflective of chronic comorbidities or side effects from immunotherapy. Rarely, patients with long-standing MG develop fixed weakness that no longer responds to immunotherapy. Such "burned-out weakness" needs to be recognized to avoid unnecessary tests and intervention.

Treatment of Anti–Muscle-Specific Tyrosine Kinase Myasthenia Gravis

In many patients, anti-MuSK MG is associated with more significant involvement of bulbar and respiratory muscles and a more rapid progression of weakness than anti-AChR MG.[13] Early treatment with immunosuppression is typically necessary for patients with anti-MuSK MG. The three effective treatment options for anti-MuSK MG are corticosteroids, rituximab, and plasma exchange.[24,50,74] Pyridostigmine may not be as effective as in anti-AChR MG, and significant side effects may be encountered. Use of rituximab often results in dramatic improvement for anti-MuSK MG, and rituximab has been advocated as an important treatment to use early in patients with anti-MuSK MG. The efficacy of IVIg in anti-MuSK MG appears to be lower than that of plasma exchange. Traditional immunosuppressants (ie, azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide, and tacrolimus) have been administered with success in patients with anti-MuSK MG as corticosteroid-sparing agents.

Trends and New Therapies

Owing to ongoing rapid developments, the treatment strategy for MG is rapidly evolving. It is also evident that corticosteroid therapy with a higher dose (>60 mg/d) for a long duration is associated with reduced quality of life. Thus, the trend is to minimize such therapy in the treatment of MG. The success of eculizumab, ravulizumab, and efgartigimod opened doors for other complement and FcRn inhibitors, and many other therapies targeting selective immunologic components are being actively developed and

KEY POINTS

- If ptosis or extraocular dysmotility in MG does not reverse with maximal treatment after 2 years, surgical options could be considered in selected cases.
- Fast-acting treatment of MG symptoms using plasma exchange or IV immunoglobulin may spare the use of high-dose corticosteroid therapy.
- Rituximab is particularly effective for anti–muscle-specific tyrosine kinase MG.
- Newer agents to treat MG are being developed and investigated at a rapid pace.

investigated at a rapid pace, as outlined in TABLE 3-3. Most of these newer agents have advantages over conventional immunosuppressive treatment in terms of faster onset of action and favorable side effect profile. First analyses of the cost effectiveness of the new treatments eculizumab and efgartigimod are complete; determining the cost effectiveness of not-yet-approved new treatments will be important.[82]

CONCLUSION

The incidence of MG is increasing.[91] Although many newer diagnostic methods are available, improved diagnostic accuracy is needed, especially for the group of patients who are seronegative for anti-AChR and anti-MuSK antibodies. More sensitive and specific biological markers are greatly needed to reflect disease activity and residual myasthenic symptoms, including fatigue. Currently, many treatment options exist for MG, and most patients with MG achieve favorable outcomes with treatment. However, many unresolved issues remain, including when and how to discontinue immunosuppressant therapy to avoid a relapse. The role of thymectomy in late-onset, seronegative, and pediatric MG needs to be explored. Better strategies for fatigue are needed. The development of new therapies for MG is truly exciting, but for most patients with MG, cost-utility analysis is required to enable physicians to justify the use of these costly drugs.

TABLE 3-3 **Partial List of Treatments Being Investigated or Considered in Myasthenia Gravis**

Complement inhibitor

- Zilucoplan

Neonatal Fc receptor inhibitor

- Batoclimab, nipocalimab, rozanolixizumab

B-lymphocyte depletion therapy

- Obinutuzumab, ofatumumab, ublituximab, blinatumomab, inebilizumab

Cytokine inhibitor

- Satralizumab, tocilizumab

Janus kinase inhibitor

- Ruxolitinib, baricitinib, tofacitinib

Proteosome inhibitor

- Bortezomib

Antisense oligonucleotide against acetylcholinesterase

- Monarsen

Hematopoetic stem cell transplantation

Chimeric antigen receptor T-cell (CAR-T) therapy

USEFUL WEBSITES

MUSCULAR DYSTROPHY ASSOCIATION
The Muscular Dystrophy Association provides resources to learn more about MG, MG treatments, and ongoing research trials in MG.

mda.org

MYASTHENIA GRAVIS FOUNDATION OF AMERICA
The Myasthenia Gravis Foundation of America provides access to a smartphone app that includes a list of the "medications of caution" in MG among other resources that can be provided by a patient to other medical professionals who may be treating them for conditions other than MG.

myasthenia.org

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