Myasthenia Gravis

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Abstract

Myasthenia gravis (MG) is the most common disorder of the neuromuscular junction (NMJ), with an estimated prevalence between 25 and 142 per million. It characteristically presents with fatigable weakness, often initially involving the ocular muscles and manifesting as intermittent ptosis and diplopia. Ultimately, the disease generalizes in two-thirds of patients, leading to weakness of bulbar, neck, limb, and respiratory muscles. The majority of patients with generalized MG, and roughly half of patients with purely ocular disease, harbor antibodies to skeletal muscle nicotinic acetylcholine receptors. A subset of patients with generalized disease have antibodies to muscle-specific receptor tyrosine kinase (MuSK). Acetylcholinesterase inhibitors are often the first modality of therapy for MG. As an immune-mediated disorder, MG can respond to several immunosuppressive agents, such as corticosteroids, azathioprine, mycophenolate mofetil, and cyclosporin. Thymectomy is a key component of management in appropriately chosen MG patients and those with thymoma. Newer or alternative immunotherapies including tacrolimus, rituximab, methotrexate, and complement inhibiting agents are an area of active investigation.

Keywords
- myasthenia gravis
- treatment
- anticholinesterases
- immunosuppression
- thymectomy

Myasthenia gravis (MG) is the best understood autoimmune disease of the nervous system and the most frequently encountered disorder of the neuromuscular junction (NMJ). The incidence of myasthenia gravis is around 30 per one million per year and the prevalence is estimated to be between 25 and 142 per million.[1] There is a bimodal age of onset, with a female predominance in the second and third decades and a fairly even gender distribution in later age groups (sixth and seventh decades). The main clinical features that distinguish MG from other neurologic disorders are the fluctuating nature and distribution of symptoms. Patients describe weakness that worsens with activity and as the day progresses. Ocular muscles are affected in almost all patients and are usually the first involved, producing intermittent ptosis and diplopia. In roughly two-thirds of patients, the symptoms generalize beyond the ocular muscles, leading to bulbar symptoms (dysphagia, dysphonia, dysarthria, chewing difficulty), and axial and proximally predominant limb weakness. Fifteen to 20% of MG patients will have respiratory muscle weakness severe enough to endanger life, a condition referred to as myasthenic crisis. Myasthenic crisis typically occurs in the first 2 years after disease onset and is often triggered by an intercurrent infection or other stressor.

The diagnosis of MG is based on appropriate history and examination, the latter often demonstrating fatigable weakness. Antibodies to the nicotinic skeletal muscle acetylcholine receptor (AChR) are detectable in roughly 50% of patients with ocular MG and 85% of patients with generalized MG. An additional 8 to 10% of patients with generalized disease harbor antibodies against muscle-specific receptor tyrosine kinase (MuSK), a protein involved with AChR clustering on synaptic clefts. Electrodiagnostic studies support the diagnosis of MG. Slow (2–3 Hz) repetitive nerve stimulation demonstrates a decremental response in affected muscles (►**Fig. 1**). Single fiber electromyography reveals increased jitter values or blocking, and is the most sensitive diagnostic test in MG when a cranial muscle (e.g., frontalis) is tested. All patients should undergo imaging (usually computed tomography) of the chest to evaluate for thymoma, which occurs in 10 to 15% of patients with MG and will be discussed below in more detail.

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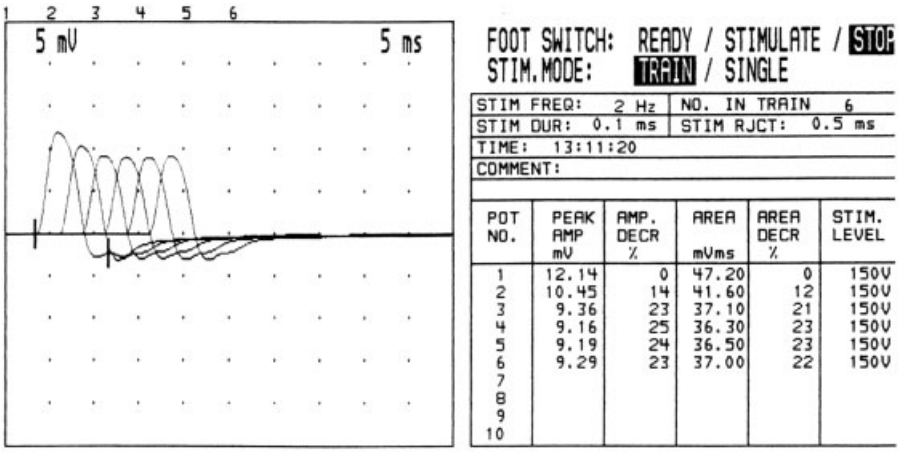

POT NO.	PEAK AMP mV	AMP. DECR %	AREA mVms	AREA DECR %	STIM. LEVEL
1	12.14	0	47.20	0	150V
2	10.45	14	41.60	12	150V
3	9.36	23	37.10	21	150V
4	9.16	25	36.30	23	150V
5	9.19	24	36.50	23	150V
6	9.29	23	37.00	22	150V
7					
8					
9					
10					

Figure 1 2 Hz repetitive nerve stimulation of the median nerve, demonstrating a significant amplitude decrement peaking at 25% on the fourth waveform of the train. Note that the greatest absolute decrement of 14% is observed between the first and second waveforms, typical for the decremental pattern seen on slow rates of repetitive nerve stimulation.

The immune-mediated nature of MG was suspected as early as 1960 when Simpson speculated that it was an autoimmune disease with antibodies directed against the nicotinic skeletal muscle AChR.[2] This hypothesis was confirmed in the 1970s when Lindstrom and colleagues developed an animal model of experimental autoimmune myasthenia gravis (EAMG) by immunizing rabbits and rats with highly purified AChR from the electric organ of the eel.[3] AChR antibodies have been shown to reduce the number of functional AChRs by several mechanisms: accelerated turnover by cross-linking, complement-dependent lysis of the postsynaptic membrane, and direct blockade of acetylcholine-binding sites. In light of the relatively well-characterized immune-mediated nature of MG, it is not surprising that immunotherapy plays a key role in its effective management.

Overview of Treatment

The treatment of MG has improved dramatically over the last few decades, with introduction of an increasing number of immunotherapies. In general, the objective of therapy is to return patients to normal function as expeditiously as possible, while limiting side effects and costs. With optimal therapy, most patients can return to productive lives, and there is essentially no mortality.[4] Treatment focuses on anticholinesterases, immunosuppressive agents, thymectomy, and short-term interventions—plasma exchange (PEx) and intravenous immunoglobulin (IVIg). Treatment should be individualized, and there is no single regimen that is appropriate for all patients.[5] The aggressiveness of management should be weighed relative to several factors including disease severity, distribution of involvement, rate of progression, degree of functional impairment, lifestyle and career choices, coexisting disease, and patient age and gender. The prognosis with treatment is generally favorable. In a recent survey, only 4% of patients followed for at least 12 months had moderate or severe disability, although a mild degree of ocular or generalized weakness persisted in the majority.[6]

Anticholinesterase Agents

Rational therapeutic use of cholinesterase inhibitors dates back to the second half of the 19th century, when Calabar bean extract was given as an antidote for atropine poisoning[7] and physostigmine was first used to treat glaucoma.[8] In 1934, Walker[9] introduced the use of anticholinesterases in MG when she reported that physostigmine salicylate injections produced dramatic, though temporary, improvement in a 56-year-old woman. Today, the synthetic quaternary ammonium compound pyridostigmine is the mainstay of anticholinesterase therapy in MG because of limited central nervous system (CNS) toxicity. Cholinesterase inhibitors are often the initial intervention in MG. These agents inhibit the enzymatic hydrolysis of ACh by acetylcholinesterase at the synapse, allowing the neurotransmitter to accumulate at the NMJ, prolonging its activity, and increasing the number of neurotransmitter-receptor interactions. A clinical response to pyridostigmine generally begins in 15 to 30 minutes and lasts up to 3 to 4 hours, although a "wearing-off" effect may occur before then. Initial doses of 30 to 60 mg every 4 to 6 hours are typical.[10] Doses can be titrated upward to 90–120 mg to maximize the clinical response, but regimens exceeding 120 mg every 3 hours are unlikely to have added benefit and will likely produce cholinergic side effects.[11] Dosing equivalents for other cholinesterase inhibitors and pediatric doses are shown in ►**Table 1**. A 60 mg/5 ml elixir of pyridostigmine and 2 mg injection (equivalent to 60 mg administered orally)[12] are also available. Mestinon Timespan® (Valeant Pharmaceuticals International, Montreal Quebec, Canada), a timed-release 180 mg pyridostigmine tablet, is occasionally prescribed at bedtime for patients who awaken in the middle of the night or in the morning with myasthenic symptoms.[13] However, absorption of the timed-release preparation is unpredictable, and many MG experts do not recommend it.

Proper dosing of pyridostigmine requires individualization. Patients often learn to self-adjust the dose for optimal

Table 1 Equivalent Dosing of Acetylcholinesterase (AChE) Inhibitors

AChE Inhibitor	Oral Dose	IM Dose	IV Dose	Pediatric Oral Dose
Pyridostigmine bromide (Mestinon)	60 mg	2.0 mg	0.7 mg	1.0 mg/kg; up to 7.0 mg/kg/d in divided doses
Neostigmine (Prostigmin)	15 mg (bromide)	1.5 mg (methylsulfate)	0.5 mg (methylsulfate)	0.3 mg/kg; up to 2 mg/kg/d in divided doses
Ambenonium chloride (Mytelase)	7.5 mg			0.15–0.3 mg/kg; up to 1.5 mg/kg/d in divided doses

IM, Intramuscular; IV, intravenous.

benefit. For patients with purely ocular disease, ptosis often improves, but diplopia may not resolve completely. In settings of severe, unilateral ptosis, anticholinesterase agents may unmask double vision by raising the lowered lid, and this may prove to be even more disabling.[14] Overall, 20 to 40% of ocular MG patients respond satisfactorily to anticholinesterases. MuSK MG patients tend to respond poorly to them.[15,16] The most common adverse effects of the cholinesterase inhibitors are muscarinic in nature, including gastrointestinal cramps; diarrhea; nausea and vomiting; increased lacrimal, salivary, and bronchial secretions; and sweating.[10] Oral glycopyrrolate (1 mg), hyoscyamine sulfate (0.125 mg), atropine (0.4 mg), or over-the-counter loperamide can be prescribed on an as-needed basis or prophylactically with each pyridostigmine dose to limit these side effects. Nicotinic toxicity includes muscle cramping, fasciculations, and weakness.

Thymectomy

Thymectomy has been a component of MG management for over 70 years. In 1939, Blalock et al[17] reported improvement of generalized MG in a 21-year-old woman following removal of a cystic thymic tumor. In his subsequent report[18] of six MG patients without thymoma who underwent thymectomy, one became symptom-free, two significantly improved, two had mild benefit, and one expired. The presence of thymoma provides a clear indication for thymectomy. There is a general consensus that generalized nonthymomatous MG patients between puberty and 60 years of age will also benefit from thymectomy.[19] However, randomized studies of thymectomy that control for medical therapy have never been performed. In a 1977 analysis,[20] remission rates compiled from a larger series did not portray a significant difference between the surgical and nonsurgical treatment groups. In 2000, an evidence-based practice parameter from the American Academy of Neurology (AAN) analyzed retrospective, controlled, nonrandomized studies of thymectomy in nonthymomatous MG.[21] A total of 28 studies published between 1953 and 1998 were identified. The effect of surgery was broadly favorable in most series. However, the benefit of surgery was generally small. For example, the median relative rate favoring surgery over nonsurgical treatment for achieving remission was 2.1, a modest gain when considering that the median remission rate in the nonthymectomized groups was 10%. Other median relative rates were 1.6 for asymptomatic status, 1.7 for improvement, and 1.1 for survival. Patient subgroup analysis indicated that only those patients with moderate weakness (Osserman 2b)[22] or greater showed a significant improvement following thymectomy compared with controls. Importantly, the modest benefits ascribed to thymectomy were confounded by baseline differences between the surgical and nonsurgical groups. No study included blinded assessments. In those few studies that employed a matched design with an attempt to control for multiple confounding variables, a consistent benefit from thymectomy was not observed. The AAN practice parameter concluded that thymectomy should be considered a treatment *option* in patients without thymoma.[21] To address this uncertainty, an international, NIH-supported, prospective, single-blinded, randomized trial controlling for medical therapy has been organized in nonthymomatous MG and began enrolling patients in late 2006.[23]

In terms of extent of resection, transsternal thymectomy approaches are still routinely performed because they permit greater thymic tissue removal. Recent evidence, however, suggests that transcervical and infraaxillary video-assisted approaches allow a similar extent of removal with quicker recovery times and shorter postoperative hospital stays.[24,25] Robotic-assisted surgery has proven to be a safe and effective technique and is associated with shorter recovery times and similar rates of improvement compared with transsternal approaches.[26,27] Nevertheless, there remains evidence to support the view that the greater the resection, the better the long-term results.[28] Using a "maximal" thymectomy approach that includes both transcervical and transsternal incisions, life-table analyses demonstrated an 81% remission rate at 7.5 years.[29] Comparative remission rates for transcervical approaches have been in the 30 to 45% range at 7 years,[30] and ~50% at 6 years using either an extended transsternal or a video-assisted thoracoscopic procedure that includes a transverse cervical incision.[31] In a retrospective review of 54 patients who underwent transsternal thymectomy, Takanami[32] found that 67% of patients demonstrated improvement (including 9% in complete remission), and 33% of patients had no change in symptoms. Shorter disease duration prior to surgery (<24 months) and more advanced Myasthenia Gravis Foundation of America (MGFA) classifications status[22] before surgery were the best predictors of favorable outcome. It should be noted that remission rates in surgical series often are unexpectedly high. Definitions of remission as well as their duration vary between studies, and

the retrospective determination of these outcomes is certainly open to bias.[21,28] No matter the approach, thymectomy should not be performed as an emergent procedure. PEx or IVIg can be used to stabilize patients with more severe disease prior to surgery.

Because most patients with MG have no thymoma, how can the practicing neurologist come to terms with uncertainties surrounding the role of thymectomy and communicate effectively with patients? At this point, it is reasonable to advise patients that more likely than not they will improve after thymectomy. However, such statements should be balanced by informing them that potential benefits have not been established in rigorous clinical studies, and that remission and improvement are known to occur without thymectomy. Furthermore, it would be misleading to guarantee improvement after thymectomy or give a fixed timetable for clinical benefit.

Thymectomy is generally not a first- or second-line approach in patients with pure ocular MG. One retrospective review of 110 patients with ocular myasthenia who underwent extended transsternal thymectomy, however, demonstrated that 84.6% patients experienced symptomatic improvement after median follow-up of 33.5 months.[33] Thymectomy is probably less effective in the elderly, and most MG experts do not advocate its use in this group, with cutoff ages ranging between 50 and 70 years (median 60 years).[19] Thymectomy has been performed with favorable results in childhood[34]—even in patients less than 5 years of age.[35,36] Its use, however, remains controversial in the youngest children, with recommended lower age limits ranging from 1 year to puberty.[19]

Corticosteroids

Corticosteroids, the first immunosuppressants to be widely used in MG, produce marked improvement in 80% or more of patients.[37,38] Despite the absence of controlled, randomized studies, corticosteroids are considered by many MG experts as the most effective oral immunosuppressive agent.[39] In a study of 116 patients, prednisone produced remission in 28%, marked improvement in 53%, moderate improvement in 15%, and no improvement in only 5%.[38] The clinical response is relatively rapid, observed within the first 2 to 4 weeks on dosing of ~1 to 1.5 mg/kg/d (►**Table 2**). If a positive response is apparent in this timeframe, patients can be switched to an alternate day regimen of 1 to 1.5 mg/kg/d after 4 weeks.[40] More refractory patients require daily dosing for 2 to 3 months before a slower alternate-day taper can commence. The mean response to maximum benefit is 5 to 6 months.

A recent study of 35 MG patients demonstrated that prednisone was superior to pyridostigmine in improving ocular symptoms and signs.[41] Complete resolution of ocular symptoms was seen in only 29% of patients on anticholinesterase agents alone versus 70% of those taking prednisone. It is noteworthy that a recent retrospective analysis suggests that prednisone reduces the incidence of disease generalization at 2 years in patients presenting with pure ocular MG.[42] Only 7% of ocular MG patients receiving prednisone developed generalized disease, compared with 36% receiving only pyridostigmine or no medication. Notably, an American Academy of Neurology Quality Standards Subcommittee evidence-based review failed to uncover high-quality study data on which to base recommendations for the pharmacologic treatment of ocular MG.[43] The report also concluded that corticosteroids and azathioprine are of uncertain benefit in reducing the risk of progression to generalized MG. A large multicenter trial is planned to address this question.

The main concern when initiating prednisone at higher doses is the transient worsening that may occur. Pascuzzi et al[38] observed transient worsening in 8.6% of patients who required intubation. Thus, an advised practice is to admit MG patients to the hospital for 5 to 7 days when initiating high-dose prednisone. A common regimen used to avoid these transient exacerbations is to begin with low-dose prednisone on alternate days, starting at 10 to 25 mg, increasing the dose by 10 mg every few days to a peak dose of 1.5 mg/kg on alternate days.[44] This is a useful strategy in patients with milder disability or pure ocular MG where a slower response is acceptable.

After patients have achieved significant improvement, there should not be a rush to taper off corticosteroids.[45] Premature or rapid tapering are common management errors. It is best to taper slowly, reducing the dose no faster than 5 mg every 2 weeks. Once a dose of 20 mg every other day has been reached, tapering at even slower rates is advisable. Other immunosuppressants to be discussed later can be added to prednisone as "steroid sparers" to assist with tapering efforts.[46] Prior thymectomy does not appear to influence the likelihood of a successful prednisone taper.[47]

Side effects of corticosteroids are common and significant (►**Table 2**), occurring in two-thirds of patients.[38] Side effects can subside at doses below 20 mg every other day. The American College of Rheumatology guidelines suggest that calcium and vitamin D supplementation, along with a weight-bearing exercise program that maintains adequate muscle mass are suitable therapies for all patients on long-term corticosteroids.[48] In those patients who have established osteoporosis before initiation of steroid therapy or who have declining bone mineral density values on serial DEXA scans, bisphosphonates or zoledronic acid should be started. The side-effects burden has led some to question whether corticosteroids are overutilized in MG.[49] Still, the low cost and efficacy of steroids provide a strong argument for their continued use.[50] A multicenter Japanese survey indicates that the proportion of MG patients treated with corticosteroids actually increased from 50% in 1987 to 64% in 1999–2000.[6]

Other Immunotherapies

Azathioprine

Azathioprine inhibits purine metabolism and blocks cell proliferation, thereby affecting rapidly dividing cell populations including lymphocytes. It remains the most established "steroid-sparing" agent in MG. In addition to its use in patients who have had a relapse during a corticosteroid taper

Table 2 Summary of immunotherapies for Myasthenia Gravis

Agent (Trade Names)	Initial Dose	Maintenance Dose	Onset of Action	Major Adverse Events	Laboratory monitoring	Comments
Prednisone	15–20 mg daily, increasing by 5–10 mg every 2–3 d	1.5 mg/kg/d, followed by slow alternate-day taper (taper by 5–10 mg/mo)	2–4 wk	HTN, diabetes, weight gain, bone loss, cataracts, GI ulcers, psychologic disorders	K +, glucose every few months; bone density monitoring	Administer in single AM dose; if starting with high doses (1.5 mg/kg) watch for early worsening seen in up to ½ of patients
Azathioprine	50 mg daily	Increase by 50 mg increments every 2–4 weeks to target of 2–3 mg/kg	2–10 mo for initial response. Up to 24 mo for peak	Fever, abdominal pain, n/v, anorexia, leukopenia, hepatotoxic, skin rash	CBC, LFTs 2–4 times in first month, then monthly	10% of patients cannot tolerate because of flulike reaction; major drug interaction with allopurinol
Cyclosporin	100 mg twice daily	Increase slowly as needed to 3–6 mg/kg on twice daily schedule	1–3 mo	Hirsutism, tremor, gum hyperplasia, HTN, hepatotoxic, nephrotoxic	CBC, LFTs, BUN/Cr monthly. Follow trough drug levels	Bioequivalence differs between preparations; avoid brand switching when possible
Mycophenolate mofetil	500 mg twice daily	1000–1500 mg twice daily	2–12 mo	Diarrhea, vomiting, leukopenia	CBC weekly for 4 wk, every 2 wk for 4 wk, then monthly	Diarrhea may resolve by switch to three times a day dosing
Cyclophos-phamide	3–5 mg/kg/d Can be preceded by IV pulse	2–3 mg/kg/d	2–6 mo	Alopecia, leukopenia, nausea and vomiting, skin discolor-ation, anorexia hemorrh-agic cystitis, malignancy	CBC, chemistry panel, urinalysis every 2–4 wk	IV pulse therapy may be less toxic
Tacrolimus	3–5 mg/d or 0.1 mg/kg/d	Increase up to 5 mg/d following trough levels (see last column)	1–3 mo	Hypergly-cemia, hypertension, headache, hyperkalemia, nephrotoxicity, diarrhea, nausea and vomiting	BUN/Cr, glucose, potassium, trough levels every few weeks initially, then less regularly	Insulin-dependent diabetes mellitus developed in 20% of postrenal transplant patients. Trough levels of 8–9 ng/ml have been effective in MG
Rituximab	375 mg/m^2 IV every 1–2 wk for 4 wk	None or 375 mg/m^2 every 4–10 wk for a few months	1–3 mo	Pruritus, nausea, vomiting, dizziness, headache, angina, cardiac dysrhythmia, anemia, leukopenia, thrombocytopenia	CBC regularly in first month of therapy, cardiac monitoring in patients with pre-existing disease	Tumor lysis syndrome should not be an issue in the MG population; premedicate with acetaminophen and diphenhydra-mine
Etanercept	25 mg SQ twice weekly	25 mg SQ twice weekly	2–6 mo	Injection site reactions, vomiting, rhinitis, upper respiratory tract infection, anemia, pancytopenia, vasculitis, central demyelination	CBC	Reactivation of hepatitis B and granulomatous disease (TB) is of concern; avoid in patients with heart failure
Intravenous immunoglobulin (IVIg)	2 g/kg over 2–5 d	0.4–1 g/kg every 4 wk; can attempt to decrease frequency over time	1–2 wk	Headache, aseptic meningitis, nephrotoxic, ischemic events, fluid overload	BUN/Cr	Avoid in patients with recent ischemia

BUN, blood urea nitrogen; CBC, complete blood count; Cr, creatinine; HTN, hypertension; IV, intravenous; LFT, liver function tests; MG, myasthenia gravis; n/v, nausea/vomiting; SQ, subcutaneous; TB, tuberculosis.

or who are experiencing adverse events from chronic steroid use, azathioprine also is used as a first-line agent.[51] Retrospective studies demonstrate that 70 to 90% of MG patients improve on azathioprine.[51,52] However, its role is hampered by a delayed onset of action; benefit may begin as early as 2 months,[51] but may not be seen for 10 months,[52] and a maximal effect may not be reached for 12 to 24 months.[46]

A randomized double-blind trial compared the use of oral prednisolone plus azathioprine 2.5 mg/kg/d versus prednisolone alone, providing useful insight into its role in MG.[53] Once patients reached remission, prednisolone was tapered by blinded personnel to the minimal dose that maintained remission. Median prednisolone dosing did not differ between the two arms at 12 months, but was significantly lower in the combined therapy group at 24 and 36 months, with a steroid-sparing effect first discernible at 15 months. Patients receiving azathioprine had fewer relapses, longer remissions, and fewer side effects with less weight gain. At 3 years, 63% of patients receiving azathioprine had been completely tapered off of prednisolone, compared with 20% who had received prednisolone alone.[53] In another study, relapses occurred in the majority of patients who discontinued azathioprine.[54] These patients did respond as favorably upon reinitiation of azathioprine as they did with initial treatment, although the time course was not provided. Initial responses to azathioprine were seen within the first year, with continued improvement through 3 years of therapy.

Prior to initiating treatment with azathioprine, all patients should be screened for thiomethyl purine transferase (TPMT) deficiency. Patients that are heterozygotes for mutations in the TPMT gene have difficulty metabolizing the drug and should be placed on low doses with close monitoring for bone marrow suppression. Those that are homozygotes for the mutation should not receive the drug at all. Initial and maintenance dosing and adverse events for azathioprine are listed in ►**Table 2**.

Mycophenolate Mofetil

Mycophenolate mofetil entered common use in MG after showing promise in uncontrolled open series demonstrating favorable responses in two-thirds of patients.[55,56] The most common dosing regimen is 1 g twice daily. Mycophenolate blocks inosine monophosphate dehydrogenase, resulting in selective inhibition of B- and T-lymphocyte proliferation by impairing purine synthesis. Main side effects are diarrhea, vomiting, increased risk for infection, and rarely leukopenia. Long-term safety for mycophenolate is still in question. Malignancy rates do not appear higher in the transplant population; however, there are rare reports of lymphoma or lymphoproliferative disorders developing in MG patients.[57,58] Resolution is generally observed with cessation of mycophenolate and appropriate therapy. Also of concern are recent reports from the Food and Drug Administration of progressive multifocal encephalopathy in solid organ transplant recipients and in patients with systemic lupus erythematosus who were receiving mycophenolic acid.

In a retrospective analysis of 85 patients that employed MGFA postintervention classifications, 73% achieved pharmacologic remission, minimal manifestation status, or improvement with mycophenolate.[59] Mycophenolate had a relatively rapid onset of action, with improvement observed at a mean of 9 to 11 weeks and maximal improvement by ~6 months.[60] However, in some patients the initial response lagged up to 40 weeks. Only 6% of patients discontinued therapy because of side effects.

Unfortunately, two randomized controlled trials failed to demonstrate that mycophenolate plus prednisone was more successful than prednisone alone in reducing QMG scores,[60] attaining minimal manifestation status,[61] or improving various secondary outcome measures. Several explanations have been forwarded for these negative results: the generally mild disease status of patients, the better-than-expected response to relatively low doses of prednisone, and the duration of the studies. A recent retrospective review of 102 AChR antibody-positive patients treated with mycophenolate (either monotherapy or in conjunction with prednisone) demonstrated that MGFA minimal manifestation status or better was generally reached after 6 months of treatment.[62] A clear steroid-sparing effect was seen after 12 months in the majority of patients.

Cyclosporin

Cyclosporin potently inhibits T-cell-dependent immune responses via disruption of calcineurin signaling, reduced production and secretion of cytokines such as interleukin-2, and impaired T-helper-cell activation. Cyclosporin has been subjected to randomized double-blinded, placebo-controlled trials in MG.[63–65] Thirty-nine patients were randomized in the larger study, 20 to cyclosporin (5 mg/kg/d) and 19 to placebo.[64] An unblinded investigator adjusted dosing to achieve morning trough levels of 300 to 500 nm/mL without impairing renal function. By 6 months, patients receiving cyclosporin demonstrated significantly improved strength, reduced symptoms, and greater reduction in AChR antibodies than patients on placebo. A trend toward more successful steroid tapering in patients receiving the active drug was also observed. Clinical improvement with cyclosporin usually occurs between 4 and 12 weeks after initiation.[65] A preliminary report of a double-blind trial suggested that azathioprine 2.5 mg/kg/d and cyclosporin 5 mg/kg/d were equally effective.[66]

Side effects of hypertension and nephrotoxicity are common with cyclosporin; clinical experience suggests the drug is less well tolerated than either azathioprine or mycophenolate mofetil. Over one-quarter of patients will have serum creatinine levels increase between 30 to 70% above baseline levels.[65] In the randomized trial, at 36-month follow-up of 18 patients initially randomized to cyclosporin, 55% had discontinued the medication due to side effects.[63] Dosing, adverse event, and laboratory monitoring information for cyclosporin are listed in ►**Table 2**. Current dosing recommendations for ongoing therapy are lower than the 5 to 6 mg/kg/d used in earlier studies. Long-term disease control is possible in many patients with dosing at 3 mg/kg/d or less.[65] Trough blood levels of 100 to 150 µg/L tend to correlate with clinical improvement.[65] It is important not to mix

different cyclosporin preparations as the different brands are not bioequivalent. Cyclosporin has numerous problematic drug interactions, including aminoglycosides, vancomycin, amphotericin B, ketoconazole, trimethoprim/sulfamethoxazole H_2 blockers, colchicine, and several nonsteroidal antiinflammatory drugs.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIg) is frequently used for immune-mediated neuromuscular diseases including MG. In an analysis of eight published retrospective studies in MG, a 73% favorable response rate to IVIg was calculated, with clinical responses seen in 4 to 5 days.[67] The effect can persist for several weeks to several months. A randomized double-blinded, placebo-controlled trial of IVIg in generalized MG was initiated, but was terminated before an adequate number of patients could be enrolled.[68] In the open-label IVIg extension, favorable trends in quantitative strength and electrophysiologic outcome measures were seen in patients who had initially received placebo, in line with qualitative improvement seen in prior reports.[68]

A more recent randomized double-blinded, placebo-controlled trial enrolled 51 patients and found significant improvement on the QMG score at 14 days after IVIg 2 g/kg versus placebo.[69] The treatment effect persisted through day 28, although the change in QMG barely missed statistical significance. When stratifying patients, it was determined that only those with more severe disease at entry (QMG score $\geq$ 11) benefited from IVIg. The authors concluded that patients with minor symptoms or with pure ocular disease are unlikely to benefit from IVIg. No serious adverse events were observed, although 75% of subjects randomized to IVIg reported headache.

Indications for IVIG are similar to PEx: reducing perioperative morbidity prior to thymectomy, inducing rapid improvement in settings of crisis or severe disease, and chronic management in selected refractory patients. IVIg demonstrated similar efficacy to plasmapheresis in MG exacerbations,[70] although some reports suggest it is less effective than PEx in true crisis scenarios. In a recent study of 84 patients with moderate or severe MG (QMG >10.5), patients were randomized to IVIg (1 g/kg/d $\times$ 2 days) and plasmapheresis (total of five exchanges every other day).[71] The postintervention status at 14 days was similar in the two groups: 69% of patients who received IVIg and 65% who received PEx demonstrated improvement on the QMG. However, 17.5% patients who received IVIg worsened compared with only 2% who underwent plasmapheresis. In general, complication rates tend to be lower for IVIg than for PEx. IVIg is a particularly attractive alternative to PEx in patients with poor venous access, hemodynamic instability, or other contraindications to plasmapheresis. Average cost for a course of IVIg tends to be less than that for PEx in MG exacerbation.[72] Standard IVIg regimens and adverse events are listed in ►**Table 2**.

Plasma Exchange

Plasma exchange was first used in MG in 1976,[73] and is routinely employed in the short-term, acute management of severe disease including crisis and in preparing weak patients for thymectomy.[74] A recent AAN practice parameter, however, determined that there is insufficient evidence to support or refute the use of plasmapheresis in MG based on the absence of rigorous, controlled data.[75] Nevertheless, most MG experts agree that plasmapheresis is effective therapy for patients in myasthenic crisis. Improvement is often seen within 48 hours after the first or second exchange. Treatments can be performed daily or every other day in the acute setting. Evidence suggests that the benefit of plasmapheresis is greater if it is started within 2 days following hospital admission.[76] Because the response to PEx is short-lived, high-dose corticosteroids are routinely administered in crisis settings. Long-term bimonthly or monthly exchanges are used in selected refractory patients as part of a chronic treatment program.

Plasma exchange has several limitations. Many are related to the need for large-bore dual lumen central dialysis catheters, including pneumothorax, hypotension, line infection and sepsis, and pulmonary embolism. Plasmapheresis is expensive and unavailable in many community hospital settings. The clinical response is relatively brief when not combined with immunosuppressive agents.[77]

Cyclophosphamide

The use of cyclophosphamide, a nitrogen mustard alkylating agent that blocks cell proliferation, is mainly reserved for refractory MG patients. Studies are limited. Perez et al[78] reported 42 patients treated with cyclophosphamide; 33 were also receiving corticosteroids. At the time of retrospective analysis, 25 (60%) were asymptomatic and 12 were in complete remission off all medications. In a randomized double-blinded, placebo-controlled study, monthly intravenous (IV) pulses of cyclophosphamide 500 mg/m^2 were given to 23 MG patients with severe, refractory disease or steroid-related side effects.[79] At month 12, the cyclophosphamide arm had significantly improved muscle strength on quantitative MG scoring. At both 6 and 12 months, steroid doses were significantly lower in the cyclophosphamide group. Similarly, impressive therapy responses were seen in three refractory MG patients who received high-dose (50 mg/kg) IV cyclophosphamide for 4 days followed by "rescue" with granulocyte colony stimulating factor. Marked improvement in strength without disease recurrence over several years was observed.[80] Of note, one of these patients was MuSK antibody-positive.

The high rate and severity of toxicity are the drawbacks for cyclophosphamide: Alopecia can occur in 75%, leukopenia in 35%, and nausea and vomiting in 25%. The increased risk of bladder and lymphoreticular malignancy with prolonged administration of cyclophosphamide should be of particular concern. Intravenous, pulsed cyclophosphamide may be safer than daily oral delivery, as a result of lower total cumulative doses (►**Table 2**).[79,80]

Newer Immunotherapies

Tacrolimus

Case reports[81] and open trials[82–86] have demonstrated efficacy for tacrolimus as monotherapy or when added to

immunosuppressive agents. A favorable response to tacrolimus was recently confirmed in a randomized, but unblinded prednisolone-controlled study (maximum dose 20 mg/d) in 36 de novo MG patients.[87] Plasma exchange and high-dose IV methylprednisolone were added as needed for disease control. Patients in both arms of the study improved significantly. The number of PEx and methylprednisolone treatments was significantly less in patients treated with tacrolimus both in early phases of therapy and through 1 year of follow-up ($p < 0.05$). Likewise, prednisolone doses were significantly lower for patients who were on tacrolimus at 1 year ($p < 0.05$). Four patients maintained minimal manifestation status on tacrolimus alone. Tacrolimus was well tolerated, with increased serum creatinine levels observed in only one patient who also had hypertension.

In the largest report of 212 patients, tacrolimus was given at a dosage of 0.1 mg/kg per day in two divided doses, later adjusted for plasma drug concentrations between 7 and 8 mg/mL.[88] Approximately half of the patients were on prednisone or were cyclosporin dependent. The mean follow-up time was nearly 50 months. With the addition of tacrolimus, prednisone could be withdrawn in 95% of patients. QMG scores fell significantly from 20.5 at baseline to less than 1.0 at the final visit, and muscle strength improvement was evident as early as 1 month after treatment initiation. More than 85% of patients achieved complete stable remission or pharmacologic remission at the end of follow-up. Another 5% reached minimal manifestation status. Impressive remission results were observed irrespective of whether patients had undergone thymectomy or had thymoma, although complete stable remission was less likely in thymomatous MG. Yoshikawa et al[89] recently performed a 28-week double-blind placebo-controlled study to evaluate the steroid-sparing effect and tolerability of tacrolimus in patients in minimal manifestations status on maintenance doses of prednisone (10–20 mg/d). There was no significant difference between groups in the primary endpoint (mean daily steroid dose), although tacrolimus was well-tolerated with few adverse events. Possible explanations for the lack of efficacy seen in this study include the selection of relatively stable patients, the short duration, and the modest dose of tacrolimus.

Tacrolimus doses of 3 to 5 mg a day or 0.1 mg/kg/d have been used in the various studies. Tacrolimus is a calcineurin inhibitor, the same immunosuppressant class as cyclosporin, has a similar onset of action, but may be less nephrotoxic. Hyperglycemia is a well-recognized complication (►**Table 2**).

Rituximab

Rituximab, a chimeric monoclonal antibody directed against the B-cell-surface membrane antigen CD20 that induces depletion of B lymphocytes, has produced clinical improvement within 4 weeks in case reports of adults and children.[90–93] No complications or side effects were observed. Sustained improvement for at least 1 year was demonstrated in 14 patients with severe, treatment-refractory MG.[94] In another study, 11 of 14 patients with severe, treatment-refractory disease showed significant improvement lasting an average of 12 months.[95] Recovery of B-lymphocyte counts was correlated with clinical worsening in this study, suggesting that monitoring these levels is useful in guiding the need for repeat infusions. Effectiveness in anti-MuSK MG has been seen in several series.[96,97] In addition to adverse events listed in ►**Table 2**, rituximab has been associated with the development of progressive multifocal encephalopathy in the non–Hodgkin's lymphoma population for which it is indicated.

Etanercept

This soluble, recombinant tumor necrosis factor-α (TNFα) receptor blocker, was studied in a prospective pilot trial in 11 patients with corticosteroid-dependent MG.[98] Eight patients completed the 6-month trial, receiving 25 mg subcutaneously twice a week. Prednisone was tapered according to a standardized protocol. Of the three patients who did not complete the study, one withdrew due to a generalized rash and two others because of disease worsening. Of the remaining eight patients, five improved on QMG by at least 3 points, the primary measure of efficacy. It took between 2 to 6 months to see significant improvement. At study exit, prednisone had been reduced by a mean of 80.4%.

In a satellite study, etanercept treatment raised the levels of most plasma complement and cytokine levels, including C3, interleukins (IL), and IFN-γ.[99] Patients who responded best to etanercept had either small increases or actual decreases in cytokine levels during the pilot study. The investigators surmised that in some patients etanercept might worsen disease control, especially in subjects with high baseline IL-6 and IFN-γ levels. A recent case report described a patient who developed MG while taking etanercept for rheumatoid arthritis.[100] Symptoms resolved after etanercept was discontinued.

Methotrexate

Although methotrexate is often used in the treatment of other neuromuscular disorders, most notably inflammatory myopathies, its use in MG is less common. In a single-blinded study of 24 patients with recently diagnosed generalized MG, Heckmann[101] demonstrated similar steroid-sparing efficacy for methotrexate (17.5 mg/wk) and azathioprine (2.5 mg/kg/d). The steroid-sparing effect was seen as early as 10 months after initiation. Methotrexate was generally well-tolerated. A large, multicenter double-blinded placebo-controlled trial of methotrexate in MG is underway.

Novel Approaches

Terbutaline

Although adrenergic agonists, such as ephedrine, were used in the past to treat MG, they are rarely used today. Catecholamines may have direct effects on neuromuscular transmission and may also regulate lymphocyte proliferation and antibody synthesis. A pilot, double-blinded placebo-controlled crossover study (2-week treatment periods) demonstrated that terbutaline, a β2 agonist, produced at least a 3-point improvement on the QMG in five of eight patients (63%).[102] Decrements to repetitive nerve stimulation also

improved. No such benefit was seen with placebo. The terbutaline dose of 2.5 mg three times daily was well tolerated. This study was small and brief; further investigation is warranted before sympathomimetic compounds are routinely used in MG.

Complement Inhibitors

A recent study utilizing passive and active rodent models of experimental autoimmune MG demonstrated efficacy of a complement inhibitor, rEV576.[103] Treated rats demonstrated a significant reduction in weakness. Trials of complement inhibitors are underway in human subjects.

Management of Myasthenic Crisis

Myasthenic crisis refers to an exacerbation severe enough to endanger life, generally related to respiratory failure from either diaphragmatic or intercostal muscle weakness or airway compromise related to bulbar dysfunction. It occurs in ~15 to 20% of all patients with MG, primarily in the first 2 years after disease onset. Management of MG crisis should take place in an intensive care setting to allow for close monitoring. Intercurrent infections, a common trigger, should be managed aggressively. Patients with marked bulbar weakness or low baseline vital capacities of < 20 to 25 ml/kg are especially at risk for respiratory failure. Paradoxical breathing or dyspnea in a supine position are other warning signs.

Because of its rapid onset of action within days, PEx is a favored treatment for MG crisis. A course of plasmapheresis consists of 4 to 6 exchanges in which ~50 ml/kg of plasma are removed at each treatment. However, it should be stressed that there is no exact science to the number of exchanges or the amount removed. The treatments can be done daily or every other day in the hospital so that the full course is completed in 7 to 10 days. Because the response to PEx is short-lived, high-dose corticosteroids are routinely administered in crisis settings. Although IV pyridostigmine is available (2 mg IV = 60 mg orally), it is generally withheld while patients are intubated because it can complicate management of airway secretions and is unlikely to play a contributing role in successful weaning from the ventilator. IVIg has demonstrated similar efficacy to plasmapheresis in MG exacerbations, although some reports suggest it is less effective than PEx in true crisis scenarios.[70,71] Complication rates tend to be lower for IVIg than for PEx.

Treatment Algorithm

Taking into account the caveat that MG treatment must be individualized, ►**Figure 2** depicts a management approach suitable for many patients with nonthymomatous generalized MG. In general, patients with ocular disease should be started on pyridostigmine initially. If this is not successful in treating symptoms, escalating doses of prednisone may be

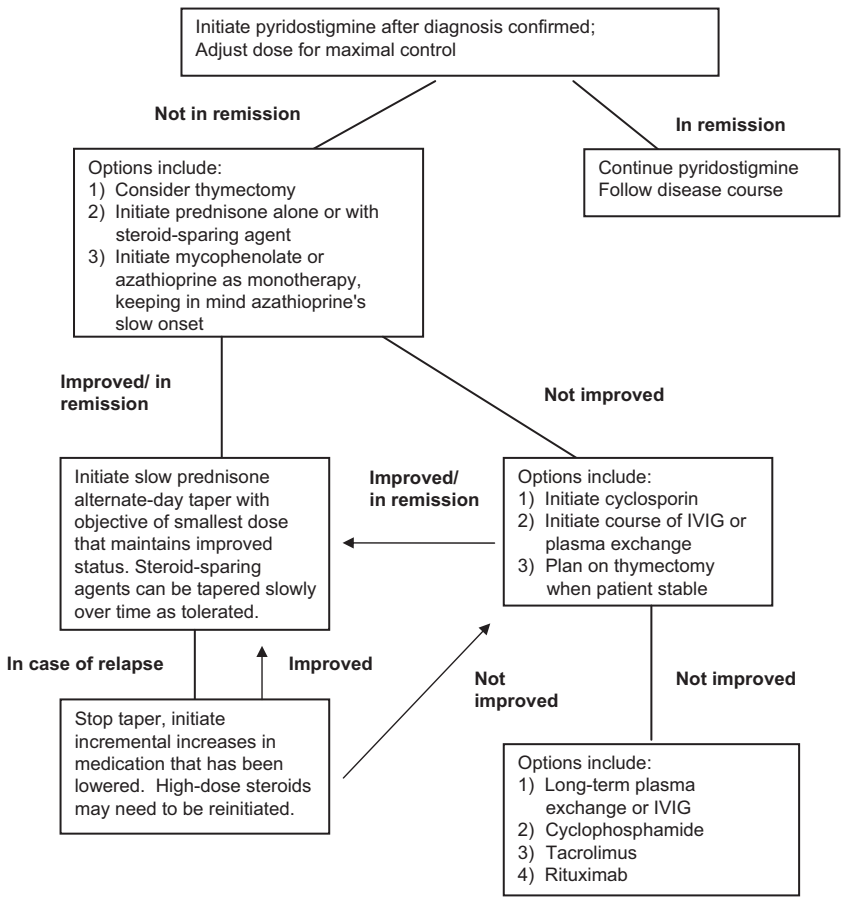

Figure 2 Algorithm for treatment of nonthymomatous generalized myasthenia gravis.

used, slowly tapering once symptoms are stabilized. Patients with generalized disease typically require both pyridostigmine and prednisone at the time of presentation. In patients with severe disease at onset, or in those that worsen once a prednisone taper has commenced, initiation of a steroid-sparing agent such as azathioprine or mycophenolate mofetil is standard. There are no evidence-based guidelines as to when it is appropriate to begin to taper pyridostigmine or steroid-sparing agents; however, it is reasonable to attempt a wean of these medications if patients are asymptomatic or minimally symptomatic on these medications for at least 1 year. In general, tapering of steroid-sparing agents should proceed no faster than a dose change every 6 months to reduce the risk of disease recurrences. In cases of thymomatous MG, thymectomy would be a requisite component of early intervention.

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