TREATMENT OF AUTOIMMUNE MYASTHENIA GRAVIS: EVIDENCE-BASED AND NEW DEVELOPMENTS

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Overview of Treatment Approach. The treatment of patients with myasthenia gravis (MG) is individualized based on several factors such as severity, distribution weakness and rate of progression, age, presence of muscle specific kinase (MuSK) antibodies, and comorbidities. However, the general treatment approach can be summarized as follows: start with acetylcholinesterase inhibitors as symptomatic therapy in nearly all patients; assess whether thymectomy is appropriate and proceed if it is; use immunosuppressive (IS) therapy in severe or refractory disease; and when rapid improvement is necessary in the setting of severe disease or rapid deterioration, treat patients with intravenous immunoglobulins (IVIg) or therapeutic plasma exchange (TPE). The goal of therapy as stated in recent international treatment guidelines is to achieve a clinical response of Minimal Manifestations or better with no side effects or minimal side effects that don't require intervention.[1] As defined by the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America (MGFA), Minimal Manifestations consists of "no symptoms or functional limitations from MG but the patient has some weakness on examination of some muscles."[2] Importantly, patients and health care providers should be educated about factors that may exacerbate myasthenic weakness particularly the use of contraindicated drugs, such as quinolone antibiotics (www.myasthenia.org). The remainder of the syllabus provides additional details on common approaches for the management of patients with MG using evidence-based practices when available.

A consensus guidance statement developed by a panel of 15 international MG experts on the treatment of MG was recently published.[1] This document covers goals of treatment and provides guidance statements on the following topics: symptomatic and IS treatments; IVIg and TPE; impending and manifest myasthenic crisis; thymectomy; juvenile MG; MuSK MG; and MG in pregnancy. Interested clinicians are encouraged to refer to this guidance document for information not covered in this syllabus.

Symptomatic therapy. Acetylcholine esterase inhibitors, usually pyridostigmine, should be used as initial therapy in all MG patients. We usually start with ½ tablet (30mg) three times daily and titrate up as needed to control symptoms. Patients will usually notice improvement approximately 30 minutes after a dose and the effects often wears off in 3-4 hours. In most circumstances the maximum dose is 1 tablet (60mg) three to four times daily. Higher doses usually do not provide additional benefit and are more likely to cause adverse effects. We do not usually prescribe the extended-release formulation of pyridostigmine because the effect is more variable, probably due to erratic absorption.

Importantly, patients with MuSK MG may become worse or develop profuse fasciculations. Low doses should be used in MuSK MG patients until they demonstrate tolerability. If fasciculations or worsening occurs, pyridostigmine, should be discontinued.

Patients should be evaluated soon after starting pyridostigmine to assess their response. If the response is inadequate after titrating to an appropriate dose, patients should be considered for immunomodulatory or immunosuppressive therapy. Patients with ocular MG may be managed with pyridostigmine as monotherapy. However, if the disease becomes generalized or ocular weakness remains disabling after optimizing pyridostigmine treatment, immunosuppressives such as prednisone or possibly thymectomy can be considered.

Thymectomy. Thymectomy has been a treatment for MG for over 70 years. Thymus tissue in patients with MG shows lymphoid follicular hyperplasia in approximately 70% of patients and 10-15% of MG patients have a thymoma.[3] Surgery is indicated in nearly all patients with thymoma, and all thymic tissue should be removed with the tumor. In elderly patients and those with significant comorbid conditions palliative radiotherapy can be considered. Incompletely resected thymomas should be treated by an interdisciplinary approach that often incorporates radiotherapy and/or chemotherapy.[4]

Based on published reports thymectomy has been recommended as an option to increase the probability of remission or improvement in patients with nonthymomatous MG,[5] and thymectomy has been thought to be the only treatment for MG that carries a realistic probability of drug-free remission. In the absence of thymoma, thymectomy has been performed to hopefully avoid or minimize chronic immunosuppressive therapy, or in situations where patients have failed or had intolerable side effects from immunotherapy.

Until recently, the most appropriate nonthymomatous MG patient populations for thymectomy were not certain. The landmark study for thymectomy in acetylcholine receptor antibody positive (AChR) MG was published in 2016.[6] In this study conducted between 2006 and 2012, 126 patients, aged 18-65, at 36 sites were randomized to extended transsternal thymectomy plus alternate-day prednisone or alternate-day prednisone alone. The primary outcomes were the time-weighted average Quantitative Myasthenia Gravis score and prednisone dose at 3 years. Compared with the prednisone arm, patients in the thymectomy group had 1) a lower Quantitative Myasthenia Gravis score, 2) a lower alternate-day prednisone dose; 3) fewer hospitalizations; and 4) a reduced requirement for additional immunosuppression in the form of azathioprine.

Although this clinical trial answered many critical questions related to the role of thymectomy in patients with AChR MG, several remained unanswered, including the optimal timing of thymectomy after disease onset and the role of thymectomy in other populations such as pediatric/adolescent MG, MuSK MG, and patients over 65 years of age. Outside of the recent trial, the best available evidence suggests thymectomy should be considered within 1 to 2 years after symptom onset in patients 15-50 years old and in peripubertal children with moderate to severe AChR MG. Many clinicians consider thymectomy in pubertal children only after failure of drug therapy. At the present time there is no compelling evidence to support thymectomy for patients with MuSK, LRP4 or agrin antibodies. Thymectomy may be considered for generalized seronegative MG patients who fail adequate immunosuppressive therapy or to avoid/minimize adverse effects expected from immunosuppressives.

Thymectomy should always be considered elective and the perioperative mortality is very low if the surgery is performed when the patient is stable. In an effort to minimize post-operative complications, patients can be treated with IVIg or TPE prior to surgery if weakness is severe, or particularly when there is any oropharyngeal or respiratory muscle involvement.

Minimally invasive endoscopic thymectomy techniques have become common in most academic centers. There is currently no data to suggest that either transsternal or minimally invasive techniques are superior to the other. Due to the faster recovery and lower expected complication rate, endoscopic thymectomy is a reasonable approach when performed at experienced centers with a good safety record. Open surgery is still preferred for removal of most thymomas.

Immunomodulatory agents. For patients with rapidly progressive or severe generalized weakness, IVIg or TPE should be considered. Both treatments are considered equivalent in most situations,[7] though TPE may show improvement more rapidly and it may be better for patients with MuSK MG.[8] The choice of IVIg or TPE in most clinical settings is usually determined by practical considerations, such as availability and patient comorbidities. When possible TPE should be performed using peripheral venous access to minimize the risks posed by indwelling central lines.[9] In rare circumstances, IVIg can be considered as a maintenance therapy for patients with MG refractory to multiple oral immunotherapies or for those in whom these agents may be contraindicated. The efficacy of chronic IVIg therapy is currently being investigated in clinical trials (ClinicalTrials.gov Identifier: NCT02473952; NCT02473965).

Oral immunosuppressives. Corticosteroids are the most commonly used IS in the United States and worldwide.[10] In patients without an adequate response to pyridostigmine, we commonly start patients with generalized disease on prednisone 60mg daily and those with ocular findings on 20mg daily. After patients achieve a maximal response, the dose is slowly tapered over the course of several months to the lowest effective dose. Nearly all neurologists are well aware of the adverse effects of chronic high dose steroid use. These adverse effects can be minimized by tapering to the lowest effective dose, and daily doses of 7.5mg or less have been associated with better tolerability. In some cases, reaching this dose while also achieving the goals of therapy is not possible and additional or alternative therapy is necessary.

Oral IS therapies other than corticosteroids can be used as mono- or combination therapy in situations where 1) corticosteroids are contraindicated; 2) patients cannot achieve the goals of therapy with steroids alone; or 3) steroid side effects are limiting. Several IS have been used as steroid sparing drugs, though the evidence is strongest for azathioprine and cyclosporine.[11] Commonly used IS and their dosing are shown in Table 1. Each oral IS has monitoring requirements that clinicians should be aware of.[12] As with corticosteroids, the lowest dose of medication should be used that controls the disease. We will reevaluate the IS drug dose used in each patient at least annually and determine whether an attempt to taper to a lower dose is warranted.

Table. Commonly used oral immunosuppressives and dosing for MG

Drug	Common dosing
Prednisone	0.75–1.00 mg/kg/day (generalized MG) 20 mg/day (mild or ocular MG)
Azathioprine	2–3 mg/kg/day
Mycophenolate mofetil	2.0–2.5 g/day in divided twice daily doses
Tacrolimus	3–5 mg/day
Cyclosporine	4–6 mg/kg/day in divided twice-daily doses
Cyclophosphamide	500 mg/m^2 or 50 mg/kg×4
Methotrexate	7.5–25.0 mg weekly

Biologic therapies. Rituximab, a monoclonal antibody directed against CD20+ B cells, is currently the biologic therapy with the most use in MG, and published reports indicate that MuSK MG responds extremely well with long lasting remissions.[8, 13] A randomized clinical trial is underway to further evaluate the efficacy of rituximab in AChR MG and should report results within the next year (NCT02110706). Currently, rituximab should be considered as an early therapeutic option for MuSK MG.

Two clinical trials have been completed in refractory generalized AChR MG with the humanized murine monoclonal antibody eculizumab.[14, 15] Eculizumab binds to C5 and inhibits cleavage of C5 to C5a and C5b, resulting in blockade of terminal complement activation. After the phase 2 study demonstrated promising efficacy results, a pivotal phase 3 study was initiated. The larger phase 3 study, which enrolled 125 patients, did not meet the primary efficacy endpoint, which was the change from baseline in MG-Activity of Daily Living total score. However, the majority of the secondary endpoints were met. The full study results have not been published yet and the role of eculizumab in the future of MG treatment is uncertain.

Conclusions. With proper management >65% of AChR MG patients will achieve the treatment goals defined at the beginning of the syllabus, making MG a rewarding neurologic disease to treat.[16] Treatment outcomes for MuSK MG patients with oral IS therapy is likely not as favorable, but the experience to date with rituximab strongly suggests that similar results are possible when this therapy is available to manage these patients. In many cases, it will take 1-2 years for patients to achieve minimal manifestations of disease and get patients on the lowest effective dose of medication. Patients should be counseled about before starting therapy in an effort to manage expectations. Novel biologic therapies are expected to change the treatment landscape in the coming years, offering more therapeutic options and hopefully improved clinical outcomes.

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