International Consensus Guidance for the Management of Myasthenia Gravis

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Abstract:

INTRODUCTION: The rarity of myasthenia gravis (MG) makes randomized controlled trials (RCTs) logistically difficult. Most current treatments are based on uncontrolled studies, with a high risk of bias. Even good RCTs may have limited generalizability and do not address the comparative effectiveness of different treatment modalities in a disease as heterogeneous as MG. Recommendations based on the consensus opinion of experts can help to guide treatment in such situations.

OBJECTIVE: To develop formal consensus-based guidance for the management of MG.

METHODS: In October 2013, the Myasthenia Gravis Foundation of America appointed a Task Force to develop treatment guidance for MG, and a panel of 15 international experts was convened. The RAND/UCLA appropriateness methodology was used to develop consensus guidance statements. Definitions were developed for: goals of treatment, minimal manifestations, remission, ocular MG, impending crisis, crisis and refractory MG. An in-person meeting of the panel then determined 7 treatment topics to be addressed. Initial guidance statements were developed from summaries of the literature for each topic. Three rounds of anonymous e-mail votes with modifications of the guidance statements, based on panel input were used to attain consensus.

RESULTS: Guidance statements were developed for: symptomatic and immunosuppressive treatments, intravenous immunoglobulin and plasma exchange, management of impending and manifest myasthenic crisis, thymectomy, juvenile MG, MG associated with antibodies to muscle specific tyrosine kinase and MG in pregnancy.

CONCLUSION: This is an international formal consensus of MG experts intended to be a guide for clinicians caring for MG patients worldwide.

Introduction

Acquired myasthenia gravis (MG) is the most common primary disorder of neuromuscular transmission and results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the acetylcholine receptor (AChR). Estimates of incidence range from 0.3 to 2.8 per 100,000 worldwide, and the median estimated prevalence is 10 per 100,000.[1] Based on these numbers, it is estimated that MG affects more than 700,000 people worldwide. Epidemiological studies have shown an increasing prevalence over the past 50 years, due in part to an increase in the frequency of diagnosis in the elderly. As the population has aged, the average age at onset has increased correspondingly.[2-6]

Improvement in the prognosis for patients with MG in recent years is due largely to advances in intensive care medicine and the increasing use of immunomodulating agents.[7] From among the available therapeutic options, treatment must be determined for each patient based upon factors such as the distribution and severity of weakness, the predicted course of the disease, and the response to previous treatments. Successful treatment of MG requires close medical supervision and long-term follow-up.

Why do we need MG Guidance Treatment Statements?

Although there is widespread agreement on the use of many treatments for MG, there is no internationally-accepted standard of care. Because MG is heterogeneous, no one treatment approach is best for all patients. Since MG is relatively uncommon, only a few physicians treat enough patients to be familiar with all its features and to be comfortable with all available treatments. Because of the relative rarity of MG, large RCTs of MG therapies are few. Given the heterogeneity of MG, RCTs are limited in their generalizability and uncontrolled studies are

limited by their risk of bias. The absence of high-level evidence makes management of MG difficult to standardize, resulting in varying treatment approaches. Hence, an effort to develop consensus among international experts was undertaken to guide clinicians worldwide on the multifaceted approach to managing MG.

Panel Constitution and Method of Expert Consensus

In October 2013, a Task Force of the Myasthenia Gravis Foundation of America convened an international panel of 15 experts in MG to develop guidance treatment statements based on formalized consensus. The panel was chosen to represent the breadth of knowledge and experience and a wide variety of opinions from MG experts internationally. All panel members are MG experts who have participated in regional/national guidelines, or have interests and have published in specific areas of MG treatment, or both. A non-voting member (PN) facilitated and moderated the panel discussions and voting process.

Development of preliminary definitions

The panel initially voted anonymously by e-mail on the following definitions that would form the foundation for guidance treatment statements: goals of treatment, remission, ocular MG, impending crisis, myasthenic crisis and refractory MG.

The Task Force co-chairs drafted initial definitions based on available literature.[8] These were sent by e-mail to the panelists, who were asked to vote "yes" or "no" on each, and to provide modifications if they did not agree. Panelists were instructed not to discuss the definitions among themselves, and to send their votes only to the facilitator to preserve anonymity. A simple consensus was used (≥ 80% of panelists voting "yes"). Definitions that did not achieve consensus were modified based on the suggestions of the panelists and the modified definitions

and discussions were shared with the panel for a second, and if needed, third round of voting. Twelve to fourteen members of the panel voted on each definition.

Development of Guidance Treatment Statements

The following were agreed upon *a priori*:

1. Treatment costs and availability would not be considered, as it is not possible to make international consensus statements specific for all countries.
2. Clinical examination is assumed to have been performed by physicians skilled in the evaluation of neuromuscular disease.
3. "MGFA Clinical Classification," including "Remission," refers to the state of the patient at the time of evaluation.

A formal systematic review of the literature was not performed. The Task Force co-chairs and facilitator drafted guidance statements for the initial round of voting based on literature cited in recent national and regional guidelines, [9-14] supplemented by other literature.

Guidance statements were developed for the following:

1. Symptomatic and immunosuppressive (IS) treatments
2. Intravenous immunoglobulin (IVIg) and plasma exchange (PLEX)
3. Impending and manifest crisis
4. Thymectomy
5. Juvenile MG (JMG)

6. MG with antibodies to muscle specific tyrosine kinase (MuSK-MG)

7. MG in pregnancy

Voting Process for Consensus Guidance Treatment Statements

We used the RAND/UCLA Appropriateness Method (RAM)[15] for formal consensus to quantify agreement. The rationale underlying RAM is that when RCTs – the "gold standard" for evidence-based medicine - are either not available or cannot provide evidence applicable to the wide range of patients with a given condition, physicians must still make decisions regarding the benefits of treatments available for the condition. RAM attempts to combine the best available scientific evidence with the collective judgment of experts to yield a statement regarding the appropriateness of interventions for the condition. "Appropriateness" in RAM refers to the relative benefit vs. harm of the intervention. RAM uses a multi-round modified-Delphi process to obtain a quantitative assessment that reflects the judgment of a group of experts.

The formal consensus process in RAM provides a wide range of knowledge and experience, interactions to stimulate debate, and consideration of a variety of opinions, thus challenging previously held ideas, stimulating new ideas, and synthesizing judgments when uncertainty and differences of opinions exist, leading to identification of areas of agreement and establishing areas of lack of agreement. The structured process with formal rules and procedures helps minimize some disadvantages of other, less formal consensus processes, in that performance is less likely to be affected by the presence of other experts, and pressure to conform to the judgment of others is minimized.

The Task Force co-chairs and facilitator developed literature summaries and draft statements for each of the topics, which were then submitted to the panel along with the literature summaries.

We obtained anonymous votes and feedback from the panelists on each draft statement. Panelists rated each statement for appropriateness on a nine point scale (1-3: inappropriate, 4-6: uncertain, and 7-9: appropriate). Panelists sent responses by e-mail to the facilitator, who tallied the votes and collated the discussions. Following each round of voting, modified statements were developed by the Task Force co-chairs and the facilitator based on the panel feedback and votes and sent to the panelists along with the discussion for the next round of voting.[15] Statements that did not achieve consensus within three rounds were excluded.

For statements on Symptomatic and Immunosuppressive Therapies and Thymectomy, an initial round of e-mail voting was followed by a one day face-to-face meeting in Durham, NC, USA on March 1, 2014. During this meeting, statements that had undergone prior voting by e-mail were refined with panel input and a second round of voting was completed. All subsequent voting was by e-mail.

The level of appropriateness and presence or absence of agreement was determined for each statement. The full 14 member panel voted on most statements; only 13 panelists voted in a few instances. Agreement was calculated for either a 14 or 13 member voting panel, as appropriate for each round. Consensus statements were classified as:

Appropriate: Median score 7-9, without disagreement

Uncertain: Median score 4-6, or any median with disagreement

Inappropriate: Median score 1-3, without disagreement

Agreement was defined as: No more than 3 panelists (for a 13 member voting panel) or 4 panelists (for a 14 member voting panel) rate the statement outside the 3 point region containing the median score.

Disagreement was defined as: At least 4 panelists (for a 13 member panel) or 5 panelists (for a 14 member voting panel) rate the statement in the 1-3 region, and at least 5 panelists rate it in the 7-9 region.

Results.

All the definitions below achieved simple consensus and all the guidance statements below were agreed upon as being appropriate by the panel.

Preliminary Definitions

1. Goals for the treatment of MG:

MGFA Task Force Post-Intervention Status (PIS) classification Minimal Manifestation Status (MMS) or better,[8] with no more than Grade 1 Common Terminology Criteria for Adverse Events (CTCAE) medication side-effects.[16]

MMS: The patient has no symptoms or functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of Remission have mild weakness.[8]

CTCAE Grade 1 medication side-effects: Asymptomatic or only mild symptoms; intervention not indicated.

Panel votes: Agree – 11/12, 91.6%

2. Definition of "Remission:"

The patient has no symptoms or signs of MG. Weakness of eyelid closure is accepted, but there is no weakness of any other muscle on careful examination. Patients taking cholinesterase inhibitors (ChEIs) every day with reasonable evidence to support symptomatic benefit are therefore excluded from this category.

Panel votes: Agree – 11/12, 91.6%

3. Definition of "Ocular MG:"*

MGFA Class I[8] - Any ocular muscle weakness. May have weakness of eye closure. Strength in all other facial, bulbar and limb muscles is normal. [#]

*Based on dysfunction due to MG at a given or specified point in time, and is not dependent upon the duration of disease.

[#]It is recognized that some patients report fatigue when strength testing is normal. The physician should use clinical judgment in attributing fatigue to generalized MG in the absence of objective non-ocular muscle weakness.

Panel votes: Agree - 12/12, 100%

4. Definition of "Impending Myasthenic Crisis":

Rapid clinical worsening of MG that, in the opinion of the treating physician, could lead to crisis in the short term (days to weeks).

Panel votes: Agree - 12/14, 87.5%;

5. Definition of "Manifest Myasthenic Crisis:"*

MGFA Class V[8] - Worsening of myasthenic weakness requiring intubation or non-invasive ventilation to avoid intubation, except when these measures are employed during routine postoperative management.[#]

*The concept of crisis focuses on the clinical implications - it represents a serious, life-threatening, rapid worsening of MG and potential airway compromise from ventilatory and/or bulbar dysfunction.

[#]The use of a feeding tube without intubation places the patient in MGFA Class IVB.[8]

Panel votes: Agree – 10/12, 83%

6. Definition of "Refractory MG:"

PIS[8] is Unchanged or Worse after corticosteroids and at least two other IS agents, used in adequate doses for an adequate duration with persistent symptoms and/or side-effects that limit functioning, as defined by patient and physician.

Panel votes: Agree – 12/12, 100%

Consensus Guidance Statements

I.A. Symptomatic and Immunosuppressive Treatment of MG: Literature Review

Symptomatic therapy of MG.

- Treatment with ChEIs represents the most important symptomatic therapy, but their use in MG is based on uncontrolled observational studies, case series and common clinical experience.[11, 17] A Cochrane review found only one RCT, in which the efficacy of neostigmine versus placebo was demonstrated in 10 generalized MG patients in a non-fully transparent cross-over design.[17]
- Patients with MuSK-MG may become worse with ChEIs, even at low doses, and require special medical attention.[18-22]
- Pyridostigmine bromide is the oral drug of choice for the symptomatic treatment of MG. Cholinergic overdose symptoms are not expected at oral doses ≤ 300 mg/d. The most common AEs with oral administration are diarrhea, abdominal cramps, hypersalivation, sweating, bradycardia, and blurred vision.[11, 17] IV administration can produce more dramatic symptoms of cholinergic intoxication (increased myasthenic weakness, excessive bronchial secretions and bronchospasm, heart block and miosis).
- Edrophonium chloride is used primarily as a diagnostic agent because of its short duration of action. It is also used to determine whether and to what extent cholinergic intoxication contributes to myasthenic weakness.
- Neostigmine can be given parenterally in patients with dysphagia who are unable to take oral pyridostigmine.

- A small placebo-controlled, randomized pilot study showed that the β2 agonist terbutaline had a positive effect on muscle strength in 5 out of 8 treated MG patients.[23]
- Some MG patients have improved after administration of 3,4-diaminopyridine,[24, 25] but a placebo-controlled study did not show benefit in children and adolescents.[26] It is not currently recommended for use in autoimmune MG.

Immunosuppressive therapy in MG. The benefit of immunosuppression in generalized MG is generally accepted, however, only a few IS agents are supported by high level evidence from RCTs. The defined treatment goal for MG is often achieved but is maintained only with continuous immunotherapy. There are few reports describing successful termination of immunosuppression.[27, 28] Abrupt withdrawal of IS agents in poorly stabilized patients should be avoided, as it may lead to recurrent symptoms, even MG crisis.[27, 29] After the treatment goal has been sustained for at least 6 months, slow withdrawal should be attempted. In some cases, immunosuppression must be maintained indefinitely. With increasing duration of immunosuppression, opportunistic infections, lymphomas and other serious AEs may occur. Monitoring and adjustment of therapy over time is important.

- **Glucocorticosteroids** such as prednisone, prednisolone and methylprednisolone are the most commonly used agents. They produce improvement in up 80% of MG patients, often beginning within 2 weeks.[11, 30, 31] A small randomized controlled trial suggests that low dose prednisone is effective in the treatment of ocular myasthenia.[32] Non-randomized and retrospective studies of patients with initially purely ocular MG have concluded that they are less likely to progress to generalized myasthenia if they receive corticosteroids or other IS agents.[33-35] Because of unacceptable AEs, corticosteroids are frequently used in combination with another IS agent, most commonly azathioprine or mycophenolate mofetil.

Corticosteroids cause early transient worsening within the first 3-7 days in about 50% of patients treated with high daily doses and worsening can occur even with lower doses.[36] These exacerbations can be severe enough to lead to crisis,[30] especially in patients with bulbar weakness.[36] Therefore, close monitoring of newly treated patients is essential. Two different dosing strategies are used for oral corticosteroid administration (e-Table 1):

Option 1. Begin with 10-20 mg/d prednisone or equivalent, increasing by 5 mg weekly until a stable remission is achieved (target dose, 1 mg/kg).[37] Advantages: less likely to induce an exacerbation, fewer steroid side-effects. Disadvantages: slower and less predictable onset of action.

Option 2. Begin with 60-80 mg/d prednisone or equivalent.[30] Change to an alternate day dosing strategy and begin slow taper after improvement begins. Advantages: quicker onset of action. Disadvantages: early exacerbation in up to 50% of patients unless preceded by IVIg or PLEX.

For maintenance therapy, the target is the minimum effective alternate day corticosteroid dose, which can only be determined empirically for each patient by reducing the dose slowly (e.g., by 10% or daily reduction equivalent of 5 mg/d every 4 weeks) while monitoring for recurrence of MG symptoms. In many patients, continuing a low dose of corticosteroids long-term can help to maintain the treatment goal.

Intravenous high-dose corticosteroid-pulse therapy has been used to treat severe exacerbations.[38, 39] 500 to 2000 mg methylprednisolone is given IV, followed by oral maintenance therapy. Pulse therapy may be repeated at intervals of 5 days. This high-dose therapy can lead to a rapid, temporary worsening in patients with bulbar symptoms; acute steroid myopathy has also been described. Therefore, corticosteroid-pulse therapy is

recommended only in impending or myasthenic crisis, together with PLEX or IVIg. The number and severity of AEs are related to the cumulative corticosteroid dose. At particular risk are patients with medical comorbidity, especially diabetes mellitus. Pregnant women require extra caution (see below). With duration of therapy longer than 3 months and a daily dose >7.5 mg prednisone equivalent, patients should receive prophylaxis with calcium 1000 -1500 mg/d and vitamin D 400-800 IU/d.[40] In postmenopausal women, bisphosphonates (e.g., zeledronic acid, risedronate, etidronate) and teriparatide (a synthetic parathyroid hormone) are used to treat or prevent corticosteroid -induced osteoporosis. Data regarding prevention of fractures in men with corticosteroid -induced osteoporosis are limited. The best prophylaxis against AEs is to limit the duration of treatment and avoid higher-dose long-term therapy.

- **Azathioprine** is the most widely used non-steroidal immunosuppressant in MG.[41-44] The initial maintenance dose is 2-3 mg/kg/day. A therapeutic response is not expected with monotherapy for at least several months and may take up to a year.[45] After the optimal response has been achieved, the dose can be slowly tapered to the minimum effective dose while closely monitoring the clinical response; some patients can be maintained on as little as 50 mg/d. (See Statement I.B:2, 3, 5, below). About 80% of patients treated with azathioprine have an increase in mean corpuscular volume. Azathioprine is also used as a steroid-sparing agent, which is especially beneficial in older patients.[44, 46, 47] Combination therapy with corticosteroids is more effective than corticosteroids alone, with longer remissions and fewer side-effects.[45] A satisfactory response is not achieved with azathioprine plus corticosteroid in 10-20% of patients, in which case other agents are used. Abrupt withdrawal of azathioprine may lead to recurrent MG symptoms, even myasthenic

crisis.[27, 48] The most common AE from azathioprine is hepatotoxicity, which usually occurs within 6 weeks and is almost always reversible if the dose is reduced or discontinued. Liver enzymes should be monitored (e-Table 1). If taken with drugs such as allopurinol, which interfere with xanthine oxidase and inhibit the breakdown of azathioprine, only 25% of the standard dose (0.5-0.75 mg/kg/d) should be taken to avoid myelotoxic side-effects. From 2 to 15% of patients have a hypersensitivity reaction within days after beginning azathioprine, which prevents its further use[49, 50] and may be sufficiently severe to induce crisis.[51] A single oral 50 mg test dose prior to beginning azathioprine detects such AEs. Severe myelosuppression occurs rapidly after initiation of azathioprine in patients with insufficient or absent thiopurine methyltransferase (TPMT) activity. Patients with absent TPMT activity or homozygosity for known TPMT mutations should not be treated with azathioprine. This phenotype is very rare (about 0.5%). Determination of TPMT activity or the TPMT genotype is advisable before beginning azathioprine, if available. Patients with low normal TPMT values may be treated but a test dose and slow titration are advised. Reports indicate a significantly increased incidence of cutaneous hyperkeratosis and skin cancer,[52] which is attributed to increased UVA photosensitivity.[53] Regular dermatological examinations are recommended in patients taking azathioprine chronically. There does not appear to be an increased risk of other cancer when azathioprine is given for less than 10 years.[54-56] Lymphoma, myelodysplastic syndromes and serious opportunistic infections were rarely observed in MG patients on azathioprine.[49, 57] Azathioprine is the non-steroidal IS of choice for MG in pregnancy in Europe but is considered high risk in the USA (See MG in Pregnancy, below).

- **Cyclosporin A (CYA).** A placebo-controlled study provided evidence that CYA is effective as monotherapy in MG,[58, 59] and retrospective analyses have reported improvement in most patients taking CYA, with or without corticosteroids.[60] The recommended target dose is 5-6 mg/kg/d, in two divided doses 12 hours apart, alone or in combination with corticosteroids. The serum trough level is checked after one month and the dose adjusted to produce a serum level of 75 to 150 ng/ml. Blood pressure and serum creatinine should be monitored monthly and the dose adjusted to keep the creatinine below 150% of pretreatment values. Serum creatinine should be followed at least every 2 to 3 months while on CYA. Prednisone may be started simultaneously with CYA, and the dose tapered or discontinued altogether after CYA has become effective. CYA can then be tapered to the minimum effective dose, which may be as little as 50 mg/d. Onset of action is relatively rapid, usually within 4-6 weeks. AEs are usually dose-related, and are less with the use of microencapsulated formulations. AEs include opportunistic infections, myelosuppression, hirsutism, gingival hyperplasia, gastrointestinal symptoms, nephrotoxicity with hyperkalemia and arterial hypertension. Tremor, headache, convulsions, paresthesias and rare reversible posterior leukoencephalopathy are also seen. Many medications interact with CYA and should be avoided or used with caution. Serum CYA levels rise after administration of macrolide antibiotics, calcium channel blockers, opiates, grapefruit juice and corticosteroids.
- **Mycophenolate mofetil** (MMF) selectively inhibits *de novo* purine synthesis in T and B cells. It is widely used in MG as monotherapy or as a steroid-sparing agent, and was approved as an off-label treatment for MG in Germany in 2012. Several cohort studies reported clinical improvement and a steroid-sparing effect in MG,[61, 62] however, two phase

III studies showed no advantage of MMF over prednisone monotherapy as initial treatment at 3 months[63]or as a steroid-sparing agent over 9 months.[64] Several factors may explain these negative results, including the generally mild disease of study subjects, the better-than-expected response to relatively low corticosteroid doses, and the relatively short duration of the trials.[65] An uncontrolled cohort study suggested that a beneficial effect of MMF as monotherapy or in combination with prednisone may be detected after 6 months.[66] The typical MMF dose is 1000 mg twice daily, but doses up to 3000 mg/d can be used. AEs are usually mild, the most common being diarrhea, nausea, and abdominal pain. MMF is contraindicated during pregnancy because of a high rate of malformations and spontaneous abortions[67] and should be discontinued at least 4 months before planned pregnancies. Progressive multifocal leukoencephalopathy (PML) has been reported in rare heavily immunosuppressed patients receiving MMF, and isolated cases of primary CNS lymphoma and a T-cell proliferative disorder have also been reported in MG patients treated with MMF.[68, 69]

- **Tacrolimus**, like CYA, is a calcineurin inhibitor that selectively inhibits the transcription of proinflammatory cytokines and IL-2 in T-lymphocytes. Several uncontrolled studies and small case series have reported successful treatment of refractory MG[70] and a single center open-label study reported favorable responses.[71] A recent critical review concluded that there is limited yet promising information to suggest a beneficial role for tacrolimus in patients with refractory or new-onset MG.[72] Tacrolimus is approved for MG in Japan.[73, 74] AEs with tacrolimus are similar to those of CYA, and there are interactions with many drugs by induction or blockade of CYP3A4 metabolism. Increased potassium levels often occur.

- **Methotrexate (MTX).** A recent small phase II RCT failed to demonstrate a steroid-sparing benefit of MTX in MG.[75] MTX has been used as a reserve treatment in MG in the way it is used in rheumatoid arthritis.[76, 77] A dose of 7.5-25 mg is administered orally or subcutaneously once a week. Some experts prefer MTX over CYA in the elderly.[78]
- **Cyclophosphamide,** an alkylating cytotoxic agent, has been used after failure of standard therapy in severe MG. Different regimens of cyclophosphamide have been used in small, uncontrolled studies: orally at an initial dose of 2 mg/kg;[79, 80] pulse dosing of 500 mg/m^2 every 4 weeks until stabilization;[81] and as myeloablative therapy, 50 mg/kg x4d.[82] Dose-related myelosuppression and hemorrhagic cystitis may occur. Late complications of cyclophosphamide include malignancies, pulmonary fibrosis, myocardial injury and dermatofibromas.
- **Monoclonal antibodies.** Rituximab is a chimeric monoclonal antibody directed against the B-cell surface marker CD20. Several case reports and small case series suggest that MG patients, especially those with MuSK-MG, improve after treatment with rituximab.[83-94] The usual dosage is based on experience from treating B-cell lymphoma: 4 doses of 375 mg/m^2 at weekly intervals or 1,000 mg repeated again 14 days after the first dose. B-cell depletion persists for 6-9 months. Given recent reports of severe AEs, including PML, rituximab is considered a treatment option for severe generalized MG in which traditional treatment options have failed, and is recommended as second-line therapy in MuSK-MG. A phase II RCT of rituximab in MG is underway.
- **Complement inhibition** has been effective in experimental MG, [95] and a phase II RCT of the C5 inhibitor, eculizumab, showed promise in severe refractory MG; [96] a phase III study of this agent is in progress.

Readers are referred to e-Table 1 for guidance regarding medication dosing and monitoring and e-Table 2 for medication cautions in MG.

I.B. Guidance Statements for Symptomatic and Immunosuppressive Treatment of MG

1. Pyridostigmine should be part of the initial treatment in most MG patients. Pyridostigmine dose should be adjusted as needed based on symptoms. The ability to discontinue pyridostigmine can be an indicator that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids and/or other IS therapy should be used in all MG patients who have not met treatment goals after an adequate trial of pyridostigmine.

   Panel votes: Median 8, range 4-9

2. A non-steroidal IS agent should be used alone when steroids are contraindicated or refused. A non-steroidal IS agent should be used initially in conjunction with corticosteroids when the risk of steroid side-effects is high based on medical co-morbidities. A non-steroidal IS agent should be added to steroids when:

   a. Steroid side-effects, deemed significant by the patient or the treating physician, develop;

   b. Response to an adequate trial (e-Table 1) of corticosteroids is inadequate; or

   c. The corticosteroid dose cannot be reduced due to symptom relapse.

   Panel votes: Median 9, range 8-9

3. Non-steroidal IS agents that can be used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate and tacrolimus. The following factors should be considered in selecting among these agents:

   a. There is widespread variation in practice with respect to choice of IS agent since there is little literature comparing them.

b. Expert consensus and some RCT evidence support the use of azathioprine as a first line IS agent in MG.

c. Evidence from RCTs supports the use of cyclosporine in MG, but potential serious adverse effects and drug interactions limit its use.

d. Although available RCT evidence does not support the use of mycophenolate mofetil and tacrolimus in MG, both are widely used, and one or both are recommended in several national MG treatment guidelines.[9-12]

Panel votes: Median 8, range 6-9

4. Patients with refractory MG should be referred to a physician or a center with expertise in management of MG. In addition to the previously mentioned IS agents, the following therapies may also be used in refractory MG:

   a. Chronic IVIg and chronic PLEX (see Section II B: 6).

   b. Cyclophosphamide

   c. Rituximab, for which evidence of efficacy is building, but for which formal consensus could not be reached.

Panel votes: Median 9, range 7-9

5. IS agent dosage and duration of treatment

   a. Once patients achieve treatment goals, the corticosteroid dose should be gradually tapered. In many patients, continuing a low dose of corticosteroids long-term can help to maintain the treatment goal.

b. For non-steroidal IS agents, once treatment goals have been achieved and maintained for 6 months to 2 years, the IS dose should be tapered slowly to the minimal effective amount. Dosage adjustments should be made no more frequently than every 3-6 months. (e-Table 1)

c. Tapering of IS drugs is associated with risk of relapse, which may necessitate upward adjustments in dose. The risk of relapse is higher in patients who are symptomatic, or after rapid taper.

d. It is usually necessary to maintain some immunosuppression for many years, sometimes for life.

Panel votes: Median: 8, range 7-9

6. Patients must be monitored for potential AEs and complications from IS drugs. Changing to an alternative IS agent should be considered if AEs and complications are medically significant or create undue hardship for the patient.

Panel votes Median: 9, range: 8-9

II.A: Intravenous Immunoglobulin (IVIg) and Plasma Exchange (PLEX): Literature Review

Intravenous immunoglobulin (IVIg) is produced by extraction of Ig fractions from blood from at least 1,000 donors. IVIg affects humoral and cell-based immunity through multiple pathways, without a single dominant mechanism. IVIg suppresses antibody production, has anti-idiotype activity, interferes with co-stimulatory molecules including cytokines and chemokines, and inhibits activation of complement and formation of the membrane attack complex. IVIg also modulates the expression and function of Fc receptors on macrophages and alters the activation, differentiation, and effector functions of T-cells. In MG, IVIg is thought to inhibit the complement cascade and compete with autoantibodies for binding sites on the postsynaptic membrane.[97]

The use of IVIg in MG was first reported in 1984,[98, 99] and it has subsequently been shown to be effective in reducing the time of mechanical ventilation in myasthenic crisis[100, 101] and in management of severe generalized MG.[102] It has also been used to stabilize MG before surgery, including thymectomy, and prior to high-dose corticosteroid therapy to minimize or prevent steroid-induced exacerbations. IVIg has been used in the short term instead of corticosteroids or PLEX in moderate to severe MG in childhood and adolescence.[103]

There are no data from RCTs regarding the value of IVIg as maintenance therapy in MG, either alone or as add-on therapy to IS agents. IVIg has been used chronically as maintenance therapy in individual cases.[104-107]

Based largely on the early successful experience of IVIg in idiopathic thrombocytopenic purpura,[108] IVIg is usually given initially at a daily dose of 0.4 gm/kg/d x 5days or 1 gm/kg/d x 2days, depending on local preferences, patient tolerance and IVIg formulations.

Different IVIg products vary in pH, IgA content, osmolarity, and sodium content; liquid and lyophilized forms are available. Common AEs of IVIg include headaches, chills and fever, which usually improve if the infusion rate is slowed. Serious side-effects are rare, but include renal toxicity, thromboembolism, leukopenia and aseptic meningitis. Lyophilized forms of IVIg may be associated with more frequent AEs in patients with neuromuscular diseases.[109] Sucrose-free formulations are associated with a lower risk of renal toxicity. Trials of subcutaneous Ig in MG are currently in progress.

Therapeutic plasma exchange (PLEX) removes the non-cellular blood components by blood centrifugation or plasma separation via vascular access provided by large peripheral or central venous catheters. PLEX is labor-intensive and is usually performed in intensive care units, renal or hematological departments.

PLEX has been used since 1976 in autoimmune MG.[110, 111] A typical schedule is 6-8 treatments, usually every other day, each exchanging from 1-1.5 times the plasma volume, and continued until clinical stability is achieved. The clinical effects last only a few weeks unless concomitant IS agents are given, and may be followed by worsening due to increased new antibody production.[112] Studies indicate that there is no long-term immunosuppressive effect of PLEX.[113, 114] Temporary depletion of clotting factors limits the exchange rate. Multimorbid, elderly patients, particularly with heart disease, are at risk for volume shifts during fluid replacement.

IVIg vs PLEX in MG

Recent Cochrane reviews comparing the use of PLEX and IVIg in MG emphasize the small number of RCTs.[101, 114] Comparison studies indicate that PLEX and IVIg are probably equivalent in the treatment of MG exacerbations.[11, 100, 102, 115, 116]

A recent structured review of the literature concluded that "IVIg and PLEX are equally effective in worsening MG. Treatment decisions may depend on several variables, including presence of respiratory distress, medical comorbidities, access to medication, and cost. PLEX will likely remain the treatment of choice in true myasthenic crisis."[117]

IVIg and PLEX in Impending and Manifest crisis

In the treatment of MG exacerbations, PLEX and IVIg are probably equivalent despite a controversial review of PLEX studies from 1995 to 2009[118-120] and both can be used.[11, 101, 102, 117] One observational study showed no significant difference between these two treatment modalities.[100] A controlled cross-over study, in which the recruitment goal was not met,[116] and a retrospective cohort study[115] both showed no evidence for the superiority of either treatment over the other. Although the latter study showed that the duration of mechanical ventilation in the PLEX group was always shorter, neither study was stratified or balanced in terms of prior duration of mechanical ventilation or crucial predictors (age, comorbidity, initial pCO_2).

II.B: Guidance Statements for Intravenous Immunoglobulin (IVIg) & Plasma Exchange (PLEX)

1. PLEX and IVIg are appropriately used as short-term treatments in MG patients with life-threatening signs such as respiratory insufficiency or dysphagia; in preparation for surgery in patients with significant bulbar dysfunction; when a rapid response to treatment is needed; when other treatments are insufficiently effective; and prior to beginning corticosteroids if deemed necessary to prevent or minimize disease exacerbation.

   Panel votes: Median 9 range 7-9.

2. The choice between PLEX and IVIg depends on individual patient factors (e.g. PLEX cannot be used in patients with sepsis and IVIg cannot be used in renal failure) and on the availability of each.

   Panel votes: Median 9, range 8-9

3. IVIg and PLEX are probably equally effective in the treatment of severe generalized MG.

   Panel votes: Median 9, range 7-9

4. The efficacy of IVIg is less certain in milder MG or in ocular MG.

   Panel votes: Median 9, range 4-9

5. PLEX may be more effective than IVIg in MuSK-MG

   Panel votes: Median 9, range 4-9

6. The use of IVIg as maintenance therapy can be considered for patients with refractory MG or for those in whom IS agents are relatively contraindicated.

   Panel votes: Median 9, range 6-9

III.A: Impending and Manifest Myasthenic Crisis: Literature Review

Although cholinergic crises are now rare with the introduction of various immunotherapies, excessive ChEI cannot be completely excluded as a cause of clinical worsening. Also, ChEIs increase airway secretions, which may exacerbate breathing difficulties. Thus, it is essential that the ChEI dosing be reduced to the minimal amount that produces clinical improvement. This is best achieved by using a dose that produces observable improvement after most administrations.

PLEX and IVIg are the mainstay of management in myasthenic crisis. The literature regarding the role of these agents in myasthenic crisis is summarized in section II.A.

III.B Guidance Statements for the Management of Impending and Manifest Myasthenic Crisis

Impending and manifest myasthenic crisis are emergent situations requiring aggressive management of MG and supportive care.

1. Impending crisis requires hospital admission and close observation of respiratory and bulbar function, with the ability to transfer to an intensive care unit if it progresses to manifest crisis. Myasthenic crisis requires admission to an intensive care or step-down unit to monitor for or manage respiratory failure and bulbar dysfunction.

   Panel votes Median: 9, range: 8-9

2. PLEX and IVIg are used as short-term treatment for impending and manifest myasthenic crisis and in patients with significant respiratory and/or bulbar dysfunction. Corticosteroids* or other IS agents are often started at the same time to achieve a sustained clinical response.

   *Because corticosteroids may cause transient worsening of myasthenic weakness it may be appropriate to wait several days for PLEX or IVIg to have a beneficial effect before starting corticosteroids.

   Panel votes Median: 9, range: 4-9

3. Although clinical trials suggest that IVIg and PLEX are equally effective in the treatment of impending or manifest myasthenic crisis, expert consensus suggests that PLEX is more effective and works more quickly. The choice between the two therapies depends on patient co-morbidity* and other factors, including availability and cost. A greater risk of

hemodynamic and venous access complications with PLEX should also be considered in the decision. [#]

*E.g., PLEX cannot be used in sepsis and IVIg is contraindicated in patients with known hypercoagulable states, renal failure or hypersensitivity to immunoglobulin.

[#]Many complications of PLEX are related to route of access and may be minimized by using peripheral rather than central venous access.

Panel votes Median: 8, range: 1-9

IV.A: Thymectomy in MG: Literature Review

The clinical use of thymectomy in MG is based on empiric observations and numerous reports of improvement after thymic resection over the past 75 years. There is no Class I evidence of efficacy of thymectomy in MG, either for its overall effect or its relative effect in different patient subgroups. The most convincing retrospective review matched thymectomized and medically-treated MG patients before 1965 and showed a significantly higher incidence of remission in the former group.[121] According to Grob et al., patients undergoing thymectomy between 1940–1957 had a higher remission rate than those who did not, but there was no difference between the two groups in 1958–1965 and 1966–1985.[122] This may result from the inability to detect the efficacy of thymectomy due to the widespread use of immunotherapy in later time periods.

It has been reported that thymectomy is more effective in MG when performed early and in younger patients with generalized disease who have not been treated with IS therapy; a less favorable response is seen in those with thymoma.[123] An evidence-based review of Class II thymectomy studies[124] suggested that effectiveness was better in those with generalized rather than ocular MG, in severe rather than mild disease, and in females versus males.

A Cochrane Review concluded that "observational studies suggest that thymectomy could be beneficial in MG," and concluded that an RCT is needed.[125] The first RCT of thymectomy in MG is nearing completion in late 2015. This study is only assessing patients with AChR antibodies without thymoma between ages 18-65.[126]

Thymic histology: Evidence for the role of the thymus in AChR-antibody positive MG comes from histological findings of thymic hyperplasia and studies showing that in these thymuses

muscle-like myoid cells in the thymic medulla expressing AChR could be driving the antibody mediated response.[127]

Overall, the relationship between thymic histology and response to thymectomy is not clear. In an extensive review published in 1974 before antibody status was documented, Vetters & Simpson found no uniform opinion about the relationship between thymic histology and response to thymectomy in previous reports, and concluded from review of their own experience that, "There is a tendency for patients with relatively unreactive thymus glands to obtain a better result from thymectomy but this is not statistically significant."[128] Castro noted that juvenile MG patients may benefit from thymectomy even when thymic histology is normal, [129] although it should be noted that an unusually small proportion of their patients had thymic hyperplasia despite having elevated AChR-antibodies.

In contrast, Spillane [130] recently confirmed previous reports that complete stable remission was most likely in patients with thymic hyperplasia, but their results were exclusively from AChR-antibody positive patients.

The thymic histology of patients who have neither AChR nor MuSK antibodies shows findings that are similar to, but less marked than those in AChR-antibody positive patients, whereas most reports indicate that thymus histology is essentially normal in MuSK-MG patients.[131-134] However, others have reported hyperplasia, as well as clinical improvement after thymectomy, in some MuSK-MG patients.[135, 136] Of note, expression of MuSK on human myoid cells has been reported.[137]

AChR-antibody status: Common practice is to limit thymectomy to AChR-antibody positive patients. The benefit of thymectomy in patients without detectable AChR antibodies is not clear,

although reports suggest that some of these patients do benefit.[90, 136, 138] For example, one report found no difference in response to thymectomy between AChR-antibody positive and negative patients in a Taiwanese cohort except that those with antibodies had more preoperative PLEX or IVIg.[138] Another study reported a 21% complete remission rate in both AChR-antibody negative and AChR-antibody positive patients after thymectomy.[135] In contrast, a third report found no clear clinical benefit after thymectomy in 37 AChR-antibody negative patients.[139]

MuSK-MG: There is insufficient evidence regarding the efficacy of thymectomy in MuSK-MG patients, with conflicting results and experience from experts. Although some reports showed improvement, definite benefit from thymectomy could not be concluded, as many patients continued to receive IS therapy after thymectomy.[90, 140, 141] Also, when MuSK-antibody titers were measured before and after thymectomy, no changes were found.[142] However, complete stable remission after thymectomy was reported in 3/7 MuSK-MG patients in one study,[143] 2/10 in another[144] and 2/9 in a third.[136] Given these discrepant studies, it cannot be concluded that thymectomy is of no value in MuSK-MG. Further studies are needed to assess the value of thymectomy in other groups besides AChR-antibody positive MG.

In summary, thymectomy is considered a treatment option for patients with generalized MG without thymoma, based on Class II evidence from a meta-analysis.[124] Some experts consider thymectomy as an option also in patients with purely ocular myasthenia if drug therapy is inadequate.[145-147] The benefits of thymectomy appear to be greatest for AChR-antibody positive patients, followed by double seronegative patents, then followed by those with MuSK antibodies.

Thymectomy is always an elective procedure, and the surgical risk is low if performed when the disease is stable, usually after effective pretreatment, e.g., with PLEX, IVIg or corticosteroids.

Benefit from thymectomy is usually delayed and is often only identified retrospectively after several years.

Patients aged 15-50 years with generalized MG appear to benefit most clearly from thymectomy if it is carried out within 1-2 years after diagnosis. However these age limits for thymectomy are arbitrary and are less closely held by some experts.[148] In children and adolescents aged 5-14 years with AChR-antibody positive generalized MG, thymectomy is usually considered after unsatisfactory response to ChEIs and corticosteroids. (See Thymectomy in JMG, below)

Thymoma: The presence of thymoma is always a surgical indication, regardless of the severity of MG. In elderly and multi-morbid patients, palliative radiation therapy may be adequate when there is little tumor spread and slow tumor progression. The most important prognostic factors are the intraoperative tumor staging[149] and the histology. Thymomas that are stage II and WHO type B2 and B3, and all III and IV stage tumors should be treated with of an interdisciplinary approach after standard radiation therapy. The association of MuSK-MG with thymoma occurs rarely: 2 patients have been reported in the English literature[18, 150] and a third case has recently been published in a Japanese journal.[151] Thus, mediastinal imaging appears to be appropriate for all MG patients.

Surgical technique: The traditional thymectomy technique uses a trans-sternal approach, with removal of the entire thymus and retrosternal fat tissue.[152] The maximal thymectomy requiring both transsternal and transcervical incisions is rarely performed today.[152] In MG patients without thymoma, the transcervical (with direct visualization of thymus) approach has been used. Although the latter appears to be cosmetically preferred to a trans-sternal incision, there is no evidence to prove efficacy equal to the open trans-sternal approach. Open thymectomy is

performed far less often now that video-assisted thoracoscopic thymectomy (VAT-T) techniques are widely available. [153-158] Large case series of VAT-T report therapeutic results similar to the trans-sternal procedure.[159, 160] The trans-sternal approach is usually performed in thymoma to assure complete tumor removal.

Thymectomy in JMG

As with adult MG, there is no RCT evidence to support thymectomy in JMG. Most reports involve a small number of children and all are retrospective.[129, 161-170] Studies that include seronegative children bear the risk that some had a congenital myasthenic syndrome (CMS) and not immune-mediated JMG.[171-174] Thymectomy should not be performed in neonatal MG or in CMS: neonatal MG is a transient disorder, and CMS are not immune mediated.

With the same caveats that apply in adults, thymectomy should be considered as part of the management of post-pubertal AChR-antibody positive generalized JMG and preferably performed within 1-2 years of disease onset.[129, 161-166, 169, 175-177] The consensus from published reports is that the rate of remission in this subgroup of JMG is higher than for medical therapy alone or for spontaneous remissions. It is possible that benefits of thymectomy are underestimated as JMG children who undergo thymectomy are often more severe and refractory to medical therapy.[129, 166] Despite concerns, there is no good evidence that long-term immunocompetence is compromised when thymectomy is performed after one year of age.[166, 173, 178-180]

IV.B: Guidance Statements for Thymectomy in MG

1. In non-thymomatous MG, thymectomy is performed as an option to potentially avoid or minimize the dose or duration of immunotherapy, or if patients fail to respond to an initial trial of immunotherapy or have intolerable side-effects from that therapy*.

   Because of the long delay in onset of effect, thymectomy for MG is an elective procedure. It should be performed when the patient is stable and deemed safe to undergo a procedure where postoperative pain and mechanical factors can limit respiratory function.

   Panel votes: Median 8, range 2-9

2. The value of thymectomy in the treatment of pre-pubertal MG patients is unclear, but thymectomy should be considered in children with generalized AChR-antibody positive MG either:

   a) If the response to pyridostigmine and IS therapy is unsatisfactory, or

   b) In order to avoid potential complications of IS therapy.

   For children diagnosed as seronegative generalized MG, the possibility of a congenital myasthenic syndrome or other neuromuscular condition should be entertained, and evaluation at a center specializing in neuromuscular diseases is of value prior to thymectomy.

   Panel votes: Median: 8, range: 7-9

3. With rare exceptions, all MG patients with thymoma should undergo surgery to remove the tumor. Removal of the thymoma is performed to rid the patient of the tumor and may not produce improvement in MG. All thymus tissue should be removed along with the tumor.

Further treatment of the thymoma will be dictated by histologic classification and degree of surgical excision. Incompletely resected thymomas should be managed after surgery with an interdisciplinary treatment approach (radiotherapy, chemotherapy).

Panel votes: Median: 9, range: 7-9

4. In elderly or multi-morbid patients with thymoma, palliative radiation therapy can be considered in the appropriate clinical setting. Small thymomas may be followed without treatment unless they are enlarging or become symptomatic.

   Panel votes: Median: 9, range: 8-9

5. Endoscopic and robotic approaches to thymectomy are increasingly performed and have a good track record for safety in experienced centers. Data from randomized, controlled comparison studies are not available. Based on comparisons across studies, less invasive thymectomy approaches appear to yield similar results to more aggressive approaches.

   Panel votes: Median: 9, range: 4-9

6. Thymectomy may be considered in generalized MG patients without detectable AChR-antibodies if they fail to respond adequately to IS therapy, or to avoid/minimize intolerable AEs from IS therapy. Current evidence does not support an indication for thymectomy in patients with MuSK, LRP4 or agrin antibodies.

   Panel votes: Median: 9, range: 6-9

V.A: Juvenile MG (JMG): Literature review:

JMG is arbitrarily defined as onset before age 15-20 years and can be further divided into pre-, peri- and post-pubertal onset. (In most series puberty is arbitrarily defined as occurring at age 12.) JMG accounts for 10-15% of MG in Caucasians and as many as 50% of MG in Asians.[163, 181-186] Treatment options are similar to those in adult MG. Several factors, including gender, age at onset and race are associated with differences in clinical manifestations and distribution (ocular vs. generalized), sensitivity of AChR antibody testing, response to treatments including thymectomy and the likelihood of spontaneous remission.[169, 176]

Pre-pubertal JMG is more likely to be seronegative, ocular or mild generalized, with a higher rate of spontaneous remissions.[129, 165, 166, 169, 173, 176, 187-189] Post-pubertal JMG is similar to adult MG in several regards, including a greater proportion of generalized MG, female predominance (F:M 2-4:1), frequency of AChR antibodies, and a higher remission rate after thymectomy.[129, 161-165, 167, 168, 176, 190] Most thymectomy series in post-pubertal JMG show that most have a hyperplastic thymus.[161, 162, 164, 191]

JMG in Asians is more likely to be seronegative, ocular and of pre-pubertal onset (often between 2-4 years of age) and is more benign with a higher rate of spontaneous remissions.[161, 165, 186, 189, 192] On the other hand, African-Americans with JMG have a poorer outlook with a lower spontaneous remission rate and poorer response to thymectomy.[129, 176, 193]

Given the greater likelihood that pre-pubertal onset JMG will be seronegative and difficult to differentiate from CMS or a non-myasthenic disorder, it is critical to make an accurate diagnosis. Although response to immunomodulation (with IVIg or PLEX) or immunosuppression is sometimes taken as evidence supporting the diagnosis of JMG, biases on the part of patient,

family and physician may hamper objectivity in assessing improvement. Clues that may favor CMS over JMG include onset *in utero* (with arthrogryposis multiplex when the mother does not have MG), at birth or within the first year; a positive family history or consanguinity.

V.B. Guidance Statements for Juvenile MG (JMG)*

1. Children with acquired autoimmune ocular MG are more likely than adults to go into spontaneous remission. Thus, young children with only ocular symptoms of MG can be treated initially with pyridostigmine. Immunotherapy can be initiated if goals of therapy are not met.

   Panel votes Median: 8.5, range: 8-9

2. Children are at particular risk of steroid side-effects, including growth failure, poor bone mineralization and susceptibility to infection, in part due to a delay in live vaccinations. Long-term treatment with corticosteroids should use the lowest effective dose to minimize side-effects.

   Panel votes Median: 9, range: 1-9

3. Maintenance PLEX or IVIg are alternatives to immunosuppression in JMG.

   Panel votes: Median: 8, range: 6-9

*See Guidance Statement IV. B: 2 for thymectomy in JMG

VI.A: MG with MuSK Antibodies: Literature Review

Observational studies[17] show that many MuSK-MG patients respond poorly to ChEIs, and that conventional pyridostigmine doses frequently induce side-effects of cholinergic hyperactivity,[22] evident both clinically (fasciculations and cramps)[136, 194-196] and on motor nerve stimulation (repetitive discharges).[21] Moreover, a few MuSK-MG patients have severe ChEI hypersensitivity and experience worsening weakness leading to cholinergic crisis.[197, 198] On the other hand, from 13% to 32% of MuSK-MG patients in different reports respond to and tolerate therapeutic doses of pyridostigmine.[22, 194]

There are no reports on parenteral ChEI treatment in MuSK-MG patients. On the basis of clinical experience with neostigmine injection for diagnostic purposes, [197, 198] it should not be used in MuSK-MG.

Pyridostigmine has been shown to worsen postsynaptic AChR depletion in a mouse model of MuSK-MG, [196] and recent observations provide a rationale for the unresponsiveness or deterioration of MuSK-MG with ChEIs.[195, 199] These clinical and experimental reports suggest that chronic treatment with ChEIs may be deleterious in MuSK-MG.

3,4-diaminopyridine (3,4-DAP) may be better tolerated in MuSK-MG as it enhances quantal release, and unlike pyridostigmine, does not increase ACh half-life at the NMJ.[195] Results from experimental studies support the use of 3, 4-DAP as symptomatic treatment in MuSK-MG.[196, 200] A partial response to 3, 4-DAP has been reported in two pediatric MuSK-MG cases.[201]

Improvement with both ephedrine and salbutamol has been reported in a patient with severe MuSK-MG.[202] The use of salbutamol as a symptomatic agent in MuSK-MG is supported by its effectiveness in CMS due to a MuSK mutation[203] and in a MuSK-MG animal model.[204]

Immunosuppression is the mainstay of therapy for MuSK-MG and is required in 95-100% of these patients.[22, 194] The clinical response to IS agents in MuSK-MG has only been evaluated in retrospective studies and, for some drugs, mainly in single-case reports. There is general consensus that patients with MuSK-MG respond well to corticosteroids[22, 90, 136, 140, 194, 205] and tend to remain dependent on them despite concomitant treatment with steroid-sparing agents.[22, 141, 206]

High-dose prednisone (1.5 mg/kg/d) given with PLEX (5-6 exchanges on alternate days) has been effective in treating respiratory crises in MuSK-MG.[90] There is general agreement that MuSK-MG responds very well to PLEX, while IVIg seems to be less effective, with response rates ranging from 11% to 46%.[198, 207] The response to PLEX is often rapid and dramatic[90] and, on the basis of small series and single-case reports, appears to be more consistent than that to IVIg.[22, 206] Some MuSK-MG patients with respiratory crisis have been successfully treated with high-dose cyclophosphamide[208] or rituximab.[88, 92, 93, 209] Exacerbations after beginning corticosteroids have not been reported in MuSK-MG.[22]

The response to azathioprine is mostly unsatisfactory in MuSK-MG[90, 205] and tacrolimus was ineffective in two patients with refractory disease.[210, 211] On the other hand, good responses have been reported to both cyclosporine and mycophenolate.[90]

To date, more than 70 MuSK-MG patients treated with rituximab have been reported in the English literature; most had refractory disease. Treatment was performed according to different protocols: four to six infusions of 375 mg/m^2 weekly in 63 patients,[22, 86, 88, 92-94, 209, 212-221] two infusions of 1,000 mg 2-4 weeks apart in four patients[222-225] and a low-dose regimen of 1,000 mg in two divided doses in three patients.[91] The number of rituximab cycles ranged between 1 and

6, and the reasons for repeating treatment are not always clear. Only 3 of 70 reported patients (4.3%) failed to improve after receiving rituximab.[212, 221, 225] No severe side-effects were reported. In several reports rituximab appeared to induce a more sustained response in MuSK-MG than in AChR-antibody MG.[93, 215, 220] Rituximab has therefore been proposed as an early therapeutic option in MuSK-MG patients who had an unsatisfactory response to corticosteroids.[93]

Overall, long-term outcomes in MuSK-MG are generally favorable and comparable to those of patients with AChR-antibody positive MG, although MuSK-MG patients often require long term administration of multiple IS agents.[22] Some MuSK-MG patients are left with persistent, non-disabling facial and tongue muscle weakness and atrophy despite long term IS therapy.[22]

VI.B: Guidance Statements for MG with MuSK Antibodies

1. Many MuSK-MG patients respond poorly to ChEIs, and conventional pyridostigmine doses frequently induce side-effects.

   Panel Votes: Median 9, range 6-9

2. MuSK-MG patients appear to respond well to corticosteroids and to many steroid-sparing IS agents. They tend to remain dependent on prednisone despite concomitant treatment with steroid-sparing agents.

   Panel votes: Median 8, range 5-9

3. MuSK-MG responds well to PLEX, while IVIg seems to be less effective.

Panel votes: Median 8, range 5-9

4. Rituximab should be considered as an early therapeutic option in MuSK-MG patients who have an unsatisfactory response to initial immunotherapy.

   Panel votes: Median 9, range 4-9

VII.A: MG in Pregnancy: Literature Review

MG is not prohibitive to having children. MG may improve, worsen, or remain unchanged during pregnancy.[226-229] The effect of pregnancy on MG varies substantially from woman to woman and from pregnancy to pregnancy in the same woman; the clinical status at onset of pregnancy does not reliably predict the subsequent course during pregnancy.[230] It is common for the first symptoms of MG to begin during pregnancy or postpartum.[231] Complete remission may occur late in pregnancy.[228, 232] Improvement after thymectomy before pregnancy seems to correlate with a better course during pregnancy.[233, 234]

Women with MG have an increased risk of pregnancy complications. Pregnancy is more difficult to manage at the beginning of MG, and women with MG should delay pregnancy until the disease is stable.[235, 236] Most women with MG benefit from being examined by a neurologist during pregnancy, to minimize risks and to select the best delivery mode in collaboration with obstetricians.[237] Therapeutic abortion is rarely, if ever, needed because of MG, and the frequency of spontaneous abortion is not increased.[238]

Oral ChEIs are the first-line treatment during pregnancy.[14] Intravenous ChEIs may produce uterine contractions and are contraindicated. Prednisone is the IS agent of choice. The use of IS drugs during pregnancy has theoretical potential mutagenic effects, although some feel that azathioprine and cyclosporine can be used safely.[239-245] Azathioprine is the non-steroidal IS of choice for MG in pregnancy in Europe but is considered high risk in the USA. This difference is based on a small number of animal studies and case reports.[12] Increased risk of fetal malformation has been reported when men used azathioprine prior to conception.[246] Mycophenolate and methotrexate can cause birth defects and are contraindicated during

pregnancy.[67] PLEX or IVIg are useful when an immediate, albeit temporary improvement is required during pregnancy. The FDA pregnancy categories are strongest for avoidance of mycophenolate mofetil (category D), azathioprine (category D) and methotrexate (Category X). Pyridostigmine, prednisone, IVIg and cyclosporine are category C. The FDA has recently discontinued this rating system and replaced it with a summary of the risks of using a drug during pregnancy and breastfeeding, along with supporting data and "relevant information to help health care providers make prescribing and counseling decisions."[247] Little data are available about the use rituximab during pregnancy.

A number of medications commonly used in obstetric practice can exacerbate MG. [248] Magnesium sulfate has neuromuscular blocking effects and is not recommended to manage pre-eclampsia in MG;[249]barbiturates or phenytoin usually provide adequate treatment.[250]

Labor and delivery are usually normal.[229] Cesarean section is indicated only for obstetrical indications. Regional anesthesia is preferred for delivery or cesarean section. MG does not affect uterine smooth muscle and therefore does not compromise the first stage of labor. In the second stage, voluntary muscles are at risk for easy fatigue and outlet forceps or vacuum extraction may be necessary.

Neonatal MG can cause fetal distress during delivery. Thymectomy prior to pregnancy may have a protective effect against neonatal MG. Breast-feeding is not a problem for myasthenic mothers, despite the theoretical risk of passing maternal AChR-antibodies in breast milk to the newborn.[14]

VII.B: Guidance Statements for MG in Pregnancy

1. Planning for pregnancy should be instituted well in advance to allow time for optimization of myasthenic clinical status and to minimize risks to the fetus.

   Panel votes: Median 9, range 8-9

2. Multidisciplinary communication among relevant specialists should occur throughout pregnancy, during delivery and in the postpartum period.

   Panel votes: Median 9, range 8-9

3. Provided that their myasthenia is under good control before pregnancy, the majority of women can be reassured that they will remain stable throughout pregnancy. If worsening occurs, it may be more likely during the first few months after delivery.

   Panel votes: Median 9, range 7-9

4. Oral pyridostigmine is the first-line treatment during pregnancy. Intravenous ChEIs may produce uterine contractions and should not be used during pregnancy.

   Panel votes: Median 9, range 7-9

5. Thymectomy should be postponed until after pregnancy as benefit is unlikely to occur during pregnancy.

   Panel votes: Median 9, range 8-9

6. Chest computerized tomography (CT) without contrast can be performed safely during pregnancy although the risks of radiation to the fetus need to be carefully considered. Unless

there is a compelling indication, postponement of diagnostic CT until after delivery is preferable.

Panel votes: Median 9, range 6-9

7. Prednisone is the IS agent of choice during pregnancy.

Panel votes: Median 9, range 5-9

8. Current information indicates that azathioprine and cyclosporine are relatively safe in expectant mothers who are not satisfactorily controlled with or cannot tolerate corticosteroids. Current evidence indicates that mycophenolate mofetil and methotrexate increase the risk of teratogenicity and are contraindicated during pregnancy.*

*These agents previously carried FDA Category C (cyclosporine), D (azathioprine and mycophenolate mofetil) and X (methotrexate) ratings. The FDA has recently discontinued this rating system and replaced it with a summary of the risks of using a drug during pregnancy and breastfeeding, along with supporting data and "relevant information to help health care providers make prescribing and counseling decisions."[247]

Panel votes: Median 8 range 1-9.

Although this statement achieved consensus, there was a strong minority opinion against the use of azathioprine in pregnancy. Azathioprine is the non-steroidal IS of choice for MG in pregnancy in Europe but is considered high risk in the USA. This difference is based on a small number of animal studies and case reports.

9. PLEX or IVIg are useful when a prompt, although temporary, response is required during pregnancy. Careful consideration of both maternal and fetal issues, weighing the risks of

these treatments against the requirement for use during pregnancy and their potential benefits, is required.

Panel votes: Median 9, range 6-9

10. Spontaneous vaginal delivery should be the objective and is actively encouraged.

Panel votes: Median 9, range 8-9

11. Magnesium sulfate is not recommended for the management of eclampsia in MG because of its neuromuscular blocking effects; barbiturates or phenytoin usually provide adequate treatment.

Panel votes: Median 9, range 7-9

12. All babies born to myasthenic mothers should be examined for evidence of transient myasthenic weakness, even if the mother's myasthenia is well-controlled, and should have rapid access to neonatal critical care support.

Panel votes: Median 9, range 8-9

Discussion:

We have developed international guidance statements for management of juvenile and adult MG. We utilized recent national guidelines crafted in Germany,[9,13] Japan,[10] and Great Britain,[12,14] and a regional European guideline[11] to assemble a foundation of literature, supplementing their comprehensive literature reviews with additional papers identified by panelists. After reaching agreement on the treatment goal, a three-round anonymous modified-Delphi voting process was used to obtain consensus on guidance statements. A limitation of consensus-based processes is that sub-conscious or conscious selection of like-minded panel members may result in opinions that are not representative of MG experts. This limitation was addressed by selecting an international panel with considerable variations in practice and by using a formal consensus process.

Recognizing the variability of practice patterns and availability of treatment modalities, these statements are not absolute recommendations for management, but are intended as a guide for the clinician. They are also not intended for establishing payment policies or drug tiering by payers.

This is a living document that will require updates as the MG treatment theatre continues to evolve. Any future trial of treatment that provides relevant information will merit review of these guidance statements.

Despite the limitations of consensus-based methods, given the challenges of developing treatment recommendations internationally in an evolving therapeutic environment, we believe these guidance statements will provide an up-to-date expert consensus to guide clinicians worldwide who strive to optimize function and quality of life for their MG patients, especially

for clinicians who practice in parts of the world that do not have the resources to develop local treatment guidelines.

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