

Treating myasthenia on consensus guide: Helpful and challenging but still unfinished business

Marinos C. Dalakas, MD

Correspondence to
Dr. Dalakas:
marinos.dalakas@jefferson.edu

Neurology® 2016;87:350–351

Myasthenia gravis (MG) is the prototypic autoimmune disease and the most gratifying because it is treatable in most cases. Although in successful clinics it is no longer considered “gravis,” it does require high doses of corticosteroids to induce remission, and immunosuppressants, such as azathioprine, mycophenolate, cyclosporine, methotrexate, or tacrolimus, for steroid-sparing treatment, even though their efficacy is variable and based on small-scale underpowered trials.^{1–3} IV immunoglobulin (IVIg) and plasmapheresis provide life-saving short-term benefit for crises or difficult cases and probably account for the reduced mortality witnessed over the last 20 years.¹

Like other autoimmune diseases, MG requires chronic maintenance therapy but the aforementioned agents are variably applied, even among MG experts, depending on mentorship, immunotherapy background, and the way we assess existing trials. Convening an experienced panel to provide consensus guidance on how best to treat MG is therefore helpful. The effort poses difficulties from the outset on how to exclude the possibility of using predominantly like-minded experts, use updated definitions, construct key treatment guidance statements, select the right methodology, and ensure transparency of the electronic voting process. Sanders and Wolf, the lead authors, have managed a highly commendable effort in tackling several of these issues to offer treatment guidance for the novice.⁴ They have acknowledged that other experts may have opposing views and assured readers that their goal was to offer guidance and not to dictate formal legally binding guidelines or to influence payment and insurance decisions. Accordingly, the consensus is an overall helpful guide for the practicing neurologist. Several of the non-evidence-based consensus opinions are not necessarily shared by other experts and some opinions need highlighting, while some old or untested views merit revisiting.

First, the panel relied on old definitions based on the 2000 Myasthenia Gravis Foundation of America Task Force to define treatment goals, such as minimal manifestation state or remission (defined as asymptomatic for 1 year). With better immunotherapies applied since then, these criteria require revision. The same applies

for refractory MG, defined as being unchanged or worse after corticosteroids and at least 2 other immunosuppressants, not accounting benefits from plasmapheresis, IVIg, or rituximab. Second, a number of conclusions, based on the panel’s experience but not necessarily on evidence, are not universally followed. For example, the statement that nonsteroidal immunosuppressants, like azathioprine, mycophenolate, or cyclosporine, “should be used alone when corticosteroids are contraindicated or refused” lacks evidence. IVIg may be considered first in these circumstances, but the efficacy of immunosuppressants (which are also slow-acting) has not been established as first-line therapy in steroid-naïve patients, although the authors cited a few old references and reviews. Similarly, that IVIg can be considered as maintenance therapy lacks support⁵ and may lead to overuse of this expensive drug; the benefit of IVIg as chronic therapy is being tested in ongoing trials (ClinicalTrials.gov NCT 02473952, 02473965). Further, the old concept that MG may worsen after corticosteroids needs revisiting; initially observed more than 30 years ago when corticosteroids were initiated at high doses, today, with the commonly used escalation therapy, this worsening is uncommon, mild, and transient. The consensus’ suggestion that plasmapheresis and IVIg may be used if deemed necessary, even prior to beginning corticosteroids, seems exaggerated and may lead to overuse of these expensive treatments or alarm patients. IVIg and plasmapheresis are generally used first for short-term benefit in patients with severe generalized disease from any cause.

Some views, referring to avoiding drugs that worsen MG, go back to our predecessors who only had anticholinesterases in their armamentarium. Except for botulinum toxin, curare-based drugs, and D-penicillamine, the litany of drugs listed in table e-2, even some with black box warnings, needs reassessment. For example, there has not been objective evidence that β -blockers or statins, in spite of rare unverified reports, worsen MG, so patients should not be deprived a priori of their benefits. Regarding antibiotics (a common concern), it is unproven if any associated worsening is caused by the antibiotics themselves or more likely by

See page 419

From the Department of Neurology, Thomas Jefferson University, Philadelphia, PA; and Neuroimmunology Unit, University of Athens Medical School, Greece.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the author, if any, are provided at the end of the editorial.

the underlying infection/inflammation for which they were given.

The panel has not explicitly addressed chronic management, which generates the most common questions by patients: “How long should I take steroids, and at what doses? Am I going to be on azathioprine or mycophenolate forever? When should I stop?” Although these are highly individualized decisions, a more concrete stand by the experts on drug tapering and maintenance would have been welcome. The panel concludes that once treatment goals are achieved, the immunosuppressant should be tapered to a minimal effective amount after 6–24 months. But is there such a thing? Does maintaining the patient on subtherapeutic doses (i.e., 50–75 mg azathioprine, or 500–1,000 mg mycophenolate) ensure sustainable remission not only in MG but any other autoimmune disease? Such doses are probably akin to discontinuation, which can lead to relapse, as we have witnessed and recently confirmed.⁶ For refractory MG, the chronic use of IVIg, plasmapheresis, and cyclophosphamide (the least preferable because of toxicity) reached consensus based on experience; rituximab, however, which seems quite promising,^{7–9} with even more studies than cyclophosphamide, did not. The statement that “the ability to discontinue pyridostigmine can be an indicator that the patient has met treatment goals and may guide the tapering of other therapies” may have reversed the causality: the benefit from pyridostigmine in most patients is mild, even early on, and an indicator to initiate better therapies.

Finally, the cost, availability, or long-term adverse effects of IVIg, mycophenolate, or rituximab were not considered. This was a conscious decision because guidance would differ for each country; even if irrelevant for some countries, consideration of these concerns would be welcome.

In spite of these limitations, this is a helpful guide to neurologists treating MG and a stimulus to reexamine unsettled issues, especially regarding chronic

management and remission maintenance. As the authors indicated, this is a living document; it should be improving with frequent updates, including results from upcoming trials—most importantly, the just completed thymectomy trial. Consensus on MG treatment remains an unfinished business and so diversity of opinion may continue for some time.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The author reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

1. Dalakas MC. Future perspectives in target-specific immunotherapies of myasthenia gravis. *Therap Adv Neurol Disord* 2015;8:316–327.
2. Guptil JT, Soni M, Meriggioli MN. Current treatment, emerging translational therapies, and new therapeutic targets for autoimmune myasthenia gravis. *Neurotherapeutics* 2016;13:118–131.
3. Dalakas MC. Novel future therapeutic options in myasthenia gravis. *Autoimmun Rev* 2013;12:936–941.
4. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: executive summary. *Neurology* 2016;87:419–425.
5. Dalakas MC. IVIg in the chronic management of myasthenia gravis: is it enough for your money? *J Neurol Sci* 2014; 338:1–2.
6. Oskarsson B, Rocke DM, Dengel K, Richman DP. Myasthenia gravis exacerbation after discontinuing mycophenolate: a single-center cohort study. *Neurology* 2016;86: 1159–1163.
7. Díaz-Manera JL, Martínez-Hernández E, Querol L, et al. Long-lasting treatment effect of rituximab in MuSK myasthenia. *Neurology* 2012;78:189–193.
8. Nowak RJ1, Dicapua DB, Zebardast N, Goldstein JM. Response of patients with refractory myasthenia gravis to rituximab: a retrospective study. *Ther Adv Neurol Disord* 2011;4:259–266.
9. Iorio R, Damato V, Alboini PE, Evoli A. Efficacy and safety of rituximab for myasthenia gravis: a systematic review and meta-analysis. *J Neurol* 2015;262:1115–1119.