

Development of a Consensus Statement for Treatment Guidance in Myasthenia Gravis

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The treatment of MG is complex and no one treatment approach works best for all patients. One approach is to use medications such as pyridostigmine to control symptoms temporarily by improving the signaling between the nerve and muscle. This alone is not usually sufficient to improve symptoms adequately except in the mildest of cases. Most patients require some form of “immunomodulation,” or treatment that suppresses the immune system. Several medications are used for this in MG. Corticosteroids, such as prednisone, are often used as the initial form of immunomodulation. Several other immunomodulating medications are also used, including as azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, etc. Sometimes patients require quick relief of serious symptoms such as breathing or swallowing difficulty. Treatments such as plasma exchange or intravenous immunoglobulin are used in these instances. Removal of the thymus gland (thymectomy) has long been used in the treatment of selected MG patients, and a clinical trial of thymectomy has just been completed and will soon be reported.

The choice of MG treatment is complicated by other issues that must be considered. For example, mycophenolate mofetil and methotrexate can cause birth defects and should not be used in women who are likely to get pregnant. Some patients develop intolerable side effects to medications. Therefore MG has to be thoughtfully and carefully treated in each patient, taking into effect the age, gender, presence of other illnesses, the muscles affected and how severely they are affected, and response to any previous treatments that have been used. Also, because MG is a rare disease, few clinicians see enough patients to be comfortable with all available treatments and to use them appropriately.

What information is available to guide physicians and MG patients in the treatment of MG? We usually rely on reports of clinical trials in the medical literature for this. But clinical trials in MG are complicated because it is difficult to find a large number of patients to participate, and because treatments may take a long time to have effect and long studies are expensive and patients may drop out. Also, MG affects different patients in different ways and

the response to treatments varies among patients. Thus, it would be virtually impossible to perform a clinical trial that would compare all the available treatment options. So the data in the literature is difficult to use for clear guidance. But we must still treat people with MG, and MG patients must make decisions based on the benefits and risks of the treatment options that are available.

In order to provide guidance to the clinicians who treat MG and to MG patients, Dr. Donald Sanders, a neurologist who has conducted numerous studies on MG, and who has treated MG for several decades, approached the MGFA with a plan to develop guidance statements for MG treatment based on the consensus opinion of an international group of experts in MG. Consensus of expert opinions is used to develop guidance statements when the available studies do not provide strong information about the treatment of a condition. In October 2013, the MGFA appointed a Task Force for this purpose, led by Drs. Sanders and Gil Wolfe, and an international panel of 15 physicians from 9 countries was convened.

The Task Force used the RAND-UCLA Appropriateness Method (RAM) of formal consensus, which was developed in the 1980s by the Research and Development (RAND) Corporation in collaboration with the University of California, Los Angeles (UCLA) School of Medicine. This formal consensus process uses an anonymous process of voting to measure the degree to which panel members agree that a given treatment recommendation is appropriate. “Appropriateness” in RAM is a judgment of the benefits and harms of each treatment being considered. A number voting system is used to determine if each treatment recommendation is appropriate, inappropriate or uncertain. Recommendations that the panel agrees are appropriate are accepted.

A one day meeting of the panel members was held in Durham, NC on March 1, 2014, supported by the MGFA. Drs. Sanders and Wolfe chaired the Task Force and Dr. Pushpa Narayanaswami provided the methodological expertise and led the RAM process. First, using the scientific literature available, we developed preliminary guidance statements on seven important topics in the treatment of MG, including: symptomatic and immunosuppressive treatments, intravenous immunoglobulin (IVIg) and plasma exchange, management of impending and manifest crisis, thymectomy, juvenile MG, MG with antibodies to muscle specific tyrosine

kinase (MuSK-MG) and MG in pregnancy. We obtained anonymous votes and feedback from the expert panel on each statement. The initial statements on the first three topics were discussed and voted upon anonymously at the initial meeting. All other voting rounds were done by e-mail. Panelists sent responses to the Dr. Narayanaswami, who tallied the votes and collated the discussions. Following each round of voting, statements were revised based on panel input and we sent the final vote tally and revised statement back to the panelists for the next round of anonymous voting, along with the group discussion comments. This was repeated once if needed. The whole process took about two years to complete.

The International Consensus Guidance for the Management of Myasthenia Gravis has just been published in the journal *Neurology*[®], the official journal of the American Academy of Neurology. With the support of the MGFA, this paper is an open access article, which means that anyone can download it from the website and use it for information. The article is available at the following link:

<http://www.neurology.org/content/early/2016/06/29/WNL.0000000000002790.short>

The intent of this undertaking is to provide guidance to clinicians who treat people with MG and for people with MG and their families to help steer decisions regarding treatment. We urge patients and families to read the guidance statements and discuss them with their doctors. However, it is important to realize that none of these statements are absolute recommendations intended to supersede the clinician's judgment or to be used by insurance companies to deny specific treatments. As new scientific evidence becomes available, these statements will require revision. It is our hope that this guidance statement is a start in the effort to optimize treatment and improve the quality of life of all people with MG. We are grateful to the MGFA for recognizing the importance of this project and supporting it at every step, including helping to make the final paper available as open access to patients and clinicians and thus widely disseminate this information.