2011 Scientific Session of the Myasthenia Gravis Foundation
Robert L. Ruff, MD, PhD

The annual scientific session of the Myasthenia Gravis Foundation of America (MGFA) was held on September 14, 2011 in San Francisco, CA at the Union Square Hilton. The session was organized by Drs. Ted M. Burns and Linda Kusner and moderated by Dr. Kusner. For the third time the scientific session was held in conjunction with the annual meeting of AANEM – a professional society of physicians who focus on neuromuscular medicine and electromyography (EMG). Again, the session had an audience of more than 100 clinicians. Members of the National Board of the MGFA also attended.

There were seven platform presentations (where a person speaks to the audience) and four poster presentations from around the world. Many of the presentations were related to clinical treatment studies and programs to improve the fitness of patients with MG.

Presenter: Richard Macko, MD
Co-Authors: Charlene Hafer-Macko, Alice Ryan, Chalita Atallah,
University of Maryland, Baltimore MD 21201
Support: Department of Veterans Affairs Center of Excellence Pilot, MGFA Pilot
Fitness, Functional Performance, and Exercise in Myasthenia.
This presentation described and exercise program utilizing treadmill training. Note that treadmills come in many different designs. One design, a partial weight support treadmill, enables people who are too weak to stand without support to exercise on a treadmill. This is a very exciting approach to improving the lives of people with MG that is targeted toward improving physical conditioning. Unfortunately, the weakness associated with MG can lead to deconditioning, weight gain and cardiovascular compromise with hypertension, reduced ability of the heart to effective pump blood and susceptibility to heart failure, heart attacks and stroke. The reality is that MG often has its greatest adverse impact on older people with MG through impaired cardiovascular health rather than MG-induced weakness. The important findings were that an organized program of exercise was well tolerated, that the program resulted in improved ability to exercise with less fatigue and development of more efficient muscle activity. The improvement in muscle functioning over time lead to a the muscle becoming more efficient in utilizing energy so that activity is associated with a reduced sense of tiredness.
Editorial Comment: This is a pilot program that I am hoping will be embraced widely throughout the US and Canada. Developing effective exercise programs for people with MG provides a way for people to be able to improve themselves. This program was funded by the MGFA. Sam recognized the true value of exercise to people with MG and encouraged the Macko's to develop successful exercise programs targeted for people with MG. Charlene Macko is a past MGFA Doctor of the Year. Both Richard and Charlene are members of the MSAB.

Presenter: Charlene Hafer-Macko, MD
Co-Authors: Alice Ryan, Chalita Atallah, Richard Macko
University of Maryland, Baltimore MD
Support: Department of Veterans Affairs Center of Excellence Pilot, MGFA Pilot
Body composition abnormalities in stable myasthenia.

This presentation showed that a cohort of people with stable MG who volunteered to participate in an exercise program. At baseline the people with stable MG were physically deconditioned with reduced muscle mass and increased percent of body fat. The baseline findings in this group are likely representative of others with MG who have over time become sedentary, using motorized scooters instead of walking etc. and other life style changes will overtime alter an individual's make up so that muscle is replaced by fat and it becomes increasingly harder for an individual to exercise. This is the beginning of a series of presentations that will lead to a more refined view of how to enable people with MG to regain the ability to live more active lives.

JFHoward1; R Barohn2; G Cutter3; M Freimer4; V Juel5; T Mozaffar6; M Mellion7; M Benatar8; M Farragia9; M Pulley10; K Gorson11; V Chaudry12; R Pascuzzi13; Z Siddiqi14; JT Kissell4; and the MG Study Group
1University of North Carolina, Chapel Hill, North Carolina; 2University of Kansas, Lawrence, Kansas; 3University of Alabama at Birmingham School of Public Health, Birmingham, Alabama; 4The Ohio State University, Columbus, Ohio; 5Duke University, Durham, North Carolina; 6University of California, Irvine, California; 7TheWarren Alpert Medical School of Brown University, Providence, Rhode Island; 8University of Miami, Miami, Florida; 9Institute of Neurological Sciences, Glasgow, United Kingdom; 10University of Florida and Shands Neuroscience Institute, Jacksonville, Florida; 11Caritas St. Elizabeth's Medical Center, Brighton, Massachusetts; 12The Johns Hopkins University School of Medicine, Baltimore, Maryland; 13Wishard Memorial Hospital, Indianapolis, Indiana; 14University of Alberta Hospital, Alberta, Canada
Support: Alexion Pharmaceuticals, Inc.

Randomized, Double-Blind, Placebo-Controlled, Crossover, Multicenter, Phase II Study of Eculizumab in Patients with Refractory Generalized Myasthenia Gravis (gMG)

Refractory generalized MG is fortunately a rare variant of MG. This version of MG is associated with extreme complement attack of the NMJ. Eculizumab is a monoclonal antibody that is directed to block the final steps in complement activation. This was a very carefully designed multisite study that had very strict enrollment criteria to ensure that the subjects were as uniform as possible. The study design was a double blind crossover design so that all the subjects received the active agent, yet neither the subjects nor their caregivers knew what agent a subject was receiving at any point of the study. The subjects had stable MG, but with appreciable muscle and functional manifestations. What was found was that patients showed appreciable improvements in their QMG scores during the time that they received Eculizamab with strong statistical support for the beneficial effects of Eculizamab. In response to Eculizamab, 86% of subjects achieved a 3 point improvement in QMG score. The frequency of adverse events, primarily worsening of MG, was similar for Eculizmab and placebo treatment phases. There was a carryover effect so that after Eculizmab treatment the improvement in QMG scores persisted for several weeks after the agent was completely washed out and the impact on complement activation was gone. The carryover period may have been due in part to the following: during Eculizmab treatment the neuromuscular junctions were able to repair by reforming secondary synaptic folds and repopulation of the neuromuscular junction (NMJ) with acetylcholine receptors (AChRs) and sodium (Na) channels. The repairs made during the period of Eculizamab treatment may have endured for a period of time after the complement system was reactivated.

Editorial Comment: This was a very exciting presentation of a clinical trial that was specific for MG. The findings were impressive. The truly impressive aspect of this presentation was that the treatment focused on a specific aspect of complement activation that is highly relevant to MG and not a generalized immune suppression. The risk of suppressing complement is increased susceptibility to some infections such as *Listeria*-induced meningitis.

Presenter: Linda L. Kusner, (actual present was Dr. Satija)

Co-Authors: Namita Satija, Michael J. Richards, Henry J. Kaminski,
Saint Louis University, St. Louis, MO

Feasibility of Specific Targeting of Treatment to the Junction

One of the mechanisms for MG attack of the NMJ is complement-mediated attack of the NMJ leading to destruction of AChRs, synaptic folds and important components in the NMJ including Na channels. This presentation was a test of the impact of inhibiting complement on NMJ damage. The specific mechanism of inhibition was to use an antibody, mAb35, that binds to the AChR, but does not inhibit AChR action. The authors linked DAF an agent that inhibits complement to mAB35. The mAb35-DAF combination does bind to the NMJ and did not inhibit AChR action. The combination agent, scFv-DAF, did not cause complement to aggregate at the NMJ. Most importantly, in an animal model of MG, the combination agent was able to suppress development of MG. The scFV-DAF treatment clearly preserved AChRs at NMJs, as shown by treated animals having higher concentrations of AChR at the NMJ. A great potential advantage of this treatment is that it targets just the NMJ and is not a global suppressor of complement or other immune systems.

Editorial Comment: While this line of treating MG was still in the animal study stage, compared to the Eculizmab clinical study, this approach has great promise because it specifically targets complement activation at the NMJ. Consequently, this treatment strategy has the potential to develop into a specific cure for MG without systemic side effects.

Presenter: Emily Choi DeCroos, MD
Co-Authors: Lisa Hobson-Webb, MD, Vern C. Juel, MD, Janice M. Massey, M.D., Donald B. Sanders, MD, Duke University Medical Center, Durham, NC

Increased occurrence of late onset myasthenia gravis

This is study of the age and gender distribution of MG utilizing data from the Duke MG Data Registry. Older studies indicated that MG occurred in the 20's for women and in the 60's for men. Newer studies, such as presented at the MG Annual meeting in 2010 by Drs. Brealy and Auger, suggest that there may be more individuals developing MG in older individuals. In this study the peak for men was 60-69 years. Women also showed an increase in the incidence of MG in their 20's and another larger peak at 60-79 years of age. For North Carolina, there did not seem to be a change in the distribution of MG between late and early onset MG for the periods between 1980 and 2009. Going back to the 1970's there appears to be an increase in the recognition of MG between 1970 and 1980 that probably represents improved techniques for diagnosing MG, including both antibody tests and EMG test and an increased recognition of MG by clinicians. The main finding was that late onset MG is more common than early onset MG for both men and women.

Presenter: Henry J. Kaminski,- Dr. Kaminski could not attend, Dr. Guptill presented
Saint Louis, MO
Co-Authors: Gary Cutter, Birmingham, AL; Michael Benatar, Miami, FL; Ted Burns, Charlottesville, VA; Donald Sanders, Durham, NC; Gil Wolfe, Dallas, TX

Establishment of the MGFA Patient Registry

There has been a request by patients with MG to establish a registry. This paper addresses how to construct a registry that is dependable and can be used to advance research to improve treatment and find a cure for MG. The registry that is being developed is modeled upon a successful registry model developed for Multiple Sclerosis. Establishing a reliable registry will allow researchers to be able to interact with patients who have specific types of MG and facilitate clinical advancements. The registry is modeled around the following principles:1) individuals in the registry truly have MG, 2) participants in the registry receive periodic updates of clinical studies that are ongoing or starting, 3) people with MG can decide which studies they are interested in participating in, 4) the MG patient contacts the study of interest. Such a registry would also facilitate population studies of the course of MG and impact of MG that could be done with complete protection of the identity of individuals with MG. When portions of

the registry are analyzed the patient data is de-identified to protect people with MG. The registry will not be available for commercial exploitation. How patients would access the registry needs to be worked out. At the MSAB meeting after this session, it was suggested that there be multiple portals of entry into the registry including the MGFA website.

Update of the Thymectomy Trial – Presented by Dr. Gil Wolfe

There are 67 sites involved with 8 new sites coming on soon. A total of 6575 patients were screened. The eligibility criteria are very strict, with most of screened patients being ineligible. About half of the patients who are eligible refuse to enter the study. The most common reason for refusal is that a patient does not want to undergo thymectomy. The current number of patients enrolled is 115. The target number is 150. Interested patients can find more information by looking for MGTX on the internet.

Posters

Presenter: Emily Choi DeCroos, MD,
Co-Authors: Lisa Hobson-Webb, MD, Vern C. Juel, MD, Janice M. Massey, M.D., Donald B. Sanders, MD; Duke University Medical Center, Durham, NC

Do antibodies predict the presence or absence of thymoma in myasthenia gravis?

Among the patients studied, if an individual with acquired MG did not have elevated amounts AChR binding antibodies (BND) nor elevated titers of striated muscle antibodies (STR) antibodies, that individual had less than a 1% chance of having a thymoma. The presence of both BND and STR antibodies in patients under 40 years of age was associated with a 50% chance of having a thymoma. This poster was important in establishing the value of blood tests in determining if a person might have a thymoma at the time that the MG is recognized. The major clinical implication is that if an individual does not have elevated levels of BND and STR, they are at very low risk to have a thymoma and it may not be necessary to do imaging of the chest.

Presenter: Jeffrey T. Guptill M.D., recipient of Clinician-Scientist Development Award provided by the American Academy of Neurology Foundation and Myasthenia Gravis Foundation of America
Co-Authors: Darlene Oakley R.N., Maragatha Kuchibhatla, Ph.D, Amanda Guidon M.D., Lisa D.Hobson-Webb M.D., Janice M. Massey M.D., Donald B. Sanders M.D., Vern C. Juel M.D. Duke University Medical Center, Durham, NC

Plasma Exchange Complications are Related to the Venous Access Route

Plasma exchange complications were increased significantly when central venous catheters were used for venous access.

Presenter: Samantha XY Wang
Co-Authors: Jennifer B. Rosen, Richard J. Nowak, Catherine M. Viscoli, Jonathan M. Goldstein, New Haven, CT

Does Acetylcholine Receptor Antibody Titer Predict Muscle Weakness in Myasthenia Gravis

In generalized MG, AChR antibody levels (titer is a measure of the amount of antibody present) did not correlate well with the extent of clinical weakness. The antibodies are markers of an immune attack at the NMJ. Do to the complex interactions between antibodies and the NMJ, including activation of complement, the antibody levels do not predict disease severity.