



MYASTHENIA GRAVIS

FOUNDATION OF AMERICA, INC.

2012 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 October 3, 2012 in Orlando, FL at the JW Marriott Grande Lakes. The session was organized by Drs. Linda Kusner and Ted M. Burns and moderated by Drs. Kusner and Charlene Hafer-Macko. For the fourth 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. Sam Schulhof, Chair of the Board of Director of the MGFA, introduced the program.

There were 7 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: Gil Wolfe, MD

Co-Authors: N. J. Silvestri, G. I. Wolfe

University of Buffalo, Buffalo NY 21201

Support: NIH and MGFA grants for the International Conference on MG held in NY City, in May 2012

HIGHLIGHTS FROM 12TH INTERNATIONAL CONFERENCE ON MYASTHENIA GRAVIS AND RELATED DISORDERS

Dr. Wolfe presented the highlights of the MGFA conference that were most relevant to people with MG. He began with the progress of the International Thymectomy, which is a study to determine the effectiveness of thymectomy. This study is extremely important for people with MG to provide data to combat efforts from insurance companies to disallow payment for thymectomies because this procedure has to date been documented to be effective, even though many clinicians are convinced that it is very useful in some patients with MG. Dr. Wolfe described the efforts of members of the MGFA MSAB to develop standard measures to be used in all clinical studies so that findings can be compared across different studies. He then described a study of Monarsen an oral agent that alters the expression of the gene that produces the enzyme acetylcholinesterase, the enzyme that is inhibited by Mestinon. Monarsen, also called EN101, was more effective than Mestinon in lowering the QMG score, a marker developed by members of the MSAB that measures the severity of MG. This finding was encouraging and may serve to advance the progression of Monarsen to become available to people with MG. Dr. Wolfe then reviewed findings presented by Angela Vincent related to the assays used to determine if a person has MG, the assay for antibodies to the acetylcholine receptor (AChR). Finally, he described a new gene defect associated with a congenital form of MG. The target gene was involved with adding glucose molecules to proteins, a process referred to as glycosylation. These mutations resulted in a more diverse disorder than traditional MG. There was a pattern of proximal upper and lower extremity weakness that responded to agents such as Mestinon. As is true for other congenital myasthenias, there was no immune component to the disorder.

Dr. Silvestri summarizes specific scientific presentations. One study related to the role of a gene that is involved in the expression of a type of calcium channel that is located in the neuromuscular junction. Knocking out this gene results not only in loss of the calcium channel, but also alteration in the

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structure of the neuromuscular junction. He went on to describe a trial of the benefits of using prednisone for the eye-only form of MG, ocular MG. This study is in progress, but it promises to provide clear evidence of the benefit and side effects of prednisone when used for ocular MG. The most common form of MG that is not associated with AChR antibodies is MG associated with antibodies to MuSK, a protein at the neuromuscular junction. The study showed that animals treated with MuSK antibodies became weak, lost weight and had structural alterations at the neuromuscular junction that resembled the findings in MuSK-positive MG.

Editorial Comment: The International Conference on MG at the NY Academy of Sciences is an extremely important recurring conference (occurring about every 5 years). This conference allows researchers and clinicians from around the world to network and exchange information that may help all people with MG. The MGFA has been involved with the International Conference from the beginning. This Conference serves as a focus for both clinical and basic research in MG, related autoimmune disorders and congenital disorders of neuromuscular transmission.

Presenter: Charlene Hafer-Macko, MD

Co-Authors: M. Schmidt, R. Nadel, C. Atallah, R. Macko, A. Ryan

University of Maryland, Baltimore MD

Support: Department of Veterans Affairs Center of Excellence Pilot, MGFA Pilot

BENEFITS OF EXERCISE FOR MYASTHENIA GRAVIS

This presentation compared the exercise performance of people with MG compared with other people in the Baltimore area of similar age. The people with MG had lower exercise capacity, they exercised less during the course of a day and they had excess body fat. Overall, the people with MG were extremely sedentary and obese. Given these findings they organized an exercise program for people with MG. Along with the exercise program they provided counseling to encourage exercise and to teach people to modulate activity so that people do not get into a pitfall of exercising too much on “good days” and being too inactive on “bad days”. The program consisted of an initial training stage where people were counseled to exercise properly several days per week. They developed strategies to enable people to increase their exercise capacity and to maintain exercising over extended times. An assessment done at 3 months did not demonstrate an improvement in fitness, which was not expected during such a short period of time. What was clearly demonstrated was that the ability to exercise improved and the capacity to perform work improved. The participants became more efficient in performing activities. Perhaps most importantly, the glucose tolerance improved suggesting a reduction in the risk for Type 2 Diabetes Mellitus.

Editorial Comment: I truly hope that this work will be widely embraced widely throughout the US and Canada. The study confirmed the impression of many clinicians such as myself, that people with MG over time can become progressively less active, less fit and gain weight. This is not a criticism of people with MG. I personally have a medical condition that prevents me from walking normally. I know the difficulty that people with muscle weakness have in exercising and how that can lead to weight gain. The important message is that people with MG should not give in to their MG, rather they should continue to work in a regular fashion to maintain their levels of activity. Effective exercise programs for people with MG provide ways for people to be able to improve themselves and get some control over their disease. This program was funded by the MGFA and the VA. Sam recognizes the true value of exercise to people with MG and is encouraging the Macko’s to continue to develop successful exercise programs targeted for people with MG. Charlene Macko is a past MGFA Doctor of the Year. Both Richard and Charlene Hafer- Macko are members of the MSAB.

Presenter: Raghav Govindaraja

Co-Authors: D. Reyes, J. Morren, N. Galvez

Cleveland Clinic, Florida

RETROSPECTIVE ANALYSIS OF INCIDENCE OF INFECTIONS IN GENERALIZED MYASTHENIA GRAVIS (MG)

People with MG are more susceptible to infections due to often being on treatments that attenuate their immune systems, and treatments such as plasmapheresis and IVIG that may introduce infection via intravenous catheters. Infections were commonly noted in this population of people who likely had at least moderately severe MG. Overall the chart review disclosed that about 65% of the people had some episode of care involving an infection. Infections that could be attributed to impaired immunity were more common in people who were treated with glucocorticoid medications such as prednisone. Infections were associated with 44% of MG exacerbations. The most common infections were upper respiratory infections, as might occur with "flu". Infection due to *Candida*, also commonly referred to as yeast, were the most frequent identified infectious agents. The author suggested that some people who are on long term immune suppression treatments may be candidates for prophylactic antibiotic protocols

Editorial Comment:

Present: Donald Sanders

Co-Authors: J. M. Massey, V. C. Juel, L. Hobson-Webb

Duke University; Durham, North Carolina

Do Antibody Levels Predict the Course of Myasthenia Gravis?

AChR antibodies are used to diagnose MG. Can they also be used to predict the future for a person with MG? The initial question is whether AChR antibodies can be used to determine which people who present with Ocular-MG will progress to generalized MG? While having AChR antibodies (remember that only about 80% of people with ocular MG have AChR antibodies) does not predict who will go on to develop generalized MG. People who developed generalized MG had higher AChR antibody levels. However, the scatter in the antibody levels was sufficiently large that the antibody level (also called titre) cannot be used to predict who will go on to develop generalized MG. In addition, antibody levels could not be used to predict who would go on to improve, go into remission or worsen. Drops in antibody levels also did not effectively correlate with clinical improvement. The studies were done in people with MG who did not have thymomas.

Editorial Comment: AChR antibody levels are useful for detecting MG, but are not useful for predicting future course or likelihood to respond to improvement to therapy.

Presenter: Charles Kassardjian

Co-Authors: S. Kokokyi, D. Jewell, V. Bril, B. Murray, H. D. Katzberg

University of Toronto; Toronto, Ontario Canada

ASSESSMENT OF SLEEP, SLEEPINESS AND NEUROMUSCULAR FATIGUE IN MYASTHENIA GRAVIS

Prior studies suggested that more than half of people with MG have some type of sleep disorder. This study of 8 patients looked at how well they slept and how sleepy they were. All of the subjects had some disorder of sleep and half had evidence of obstructive sleep apnea. Measures of muscular fatigue increased over the course of the day. Episodes of actual sleep can reduce fatigue.

Editorial Comment: This was a small study of a very important and understudied issue. Sleep can be important not just for reducing fatigue as this study suggested, but also because sleep can reduce the likelihood of weight gain that can compromise exercise ability. An issue is that this type of research is not likely to be funded by drug companies other than the few companies that have agents to combat daytime fatigue. At its early stage of development, sleep research in specific disease states has not advanced to the stage of involving molecular biology; hence, sleep research may not be very interesting to national funding agencies such as NIH. My personal bias is that impaired sleep is an underappreciated complication of MG and one that will accelerate progression of MG.

Presenter: Nancy Kuntz
Chicago IL

MYASTHENIA IN INFANTS, CHILDREN AND ADOLESCENTS

Myasthenia in children is a mix of congenital MG and autoimmune MG. Autoimmune MG consisted of both AChR and MuSK antibody MG. Dr. Kuntz indicated that it is currently difficult to determine the incidence or prevalence of MG in children and adolescents. There is misunderstanding among many clinicians that autoimmune MG does not exist in children or adolescents. Because of this and likely other misunderstandings, MG is underdiagnosed in young people. The diagnosis of congenital MG is highest in Europe, the United States and South America. Because congenital myasthenic disorders are not immune related, antibody levels are not useful in diagnosis and the most useful testing is sophisticated EMG testing.

Editorial Comment: This presentation pointed out that world-wide, MG in children is probably under diagnosed.

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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 Eculizumab with strong statistical support for the beneficial effects of Eculizumab. In response to Eculizumab, 86% of subjects achieved a 3 point improvement in QMG score. The frequency of adverse events, primarily worsening of MG, was similar for Eculizumab and placebo treatment phases. There was a carryover effect so that after Eculizumab 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 Eculizumab 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 Eculizumab 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: Ted Burns
University of Virginia

My MG – A Smart Phone APP

for people with MG to record their disease severity scores and activities measures.

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 Eculizumab 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. Due to the complex interactions between antibodies and the NMJ, including activation of complement; the antibody levels do not predict disease severity.