2014 Scientific Session
OF THE MYASTHENIA GRAVIS FOUNDATION
OF AMERICA, INC.

November 1, 2014 • Savannah, GA
November 1, 2014

Welcome,

On behalf of the Board of Directors of the Myasthenia Gravis Foundation of America, Inc., we are pleased to welcome you to the 2014 Scientific Session of the MGFA Medical/Scientific Advisory Board. The MGFA was founded in 1952. The mission of the Foundation is “finding a cure for myasthenia gravis and closely related disorders, improving treatment options and providing information and support to people with myasthenia gravis through research, education, community programs and advocacy”.

If you would like to learn more about the Foundation and its Medical/Scientific Advisory Board and programs, please contact the national office at 1-800-541-5454 or visit our Web site at http://www.myasthenia.org

Sincerely,

Tor Holtan
Chief Executive

Samuel A. Schulhof
Chair, MGFA
2014 MGFA Scientific Session

Program Chair

Linda Kusner, Ph.D
Assistant Professor
Department of Pharmacology and Physiology
The George Washington University

Jeff Guptill
Department of Neurology
Duke University Medical Center

MGFA Medical/Scientific Advisory Board Executive Committee

Ted M. Burns, MD, Chair
Robert Ruff, MD
Linda Kusner, PhD
Gil I. Wolfe, MD, Immediate Past Chair

MGFA Executive Committee of the Board of Directors

Samuel Schulhof, Chair
Susan Klinger, Vice Chair
Edward T. Walsh, Treasurer
Denise Rossi, Secretary
Jennifer Faucett, Chapter Liaison
Marcia Lorimer

MGFA National Staff

Tor Holtan, Chief Executive
<table>
<thead>
<tr>
<th>Time</th>
<th>Presenting Author</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00</td>
<td>Sam Schulhof, MGFA – Chair</td>
<td></td>
</tr>
<tr>
<td>8:15</td>
<td>John S Yi</td>
<td>Comparison of B10 cells in immunosuppressed and immunosuppression naïve AChR+ MG</td>
</tr>
<tr>
<td>8:35</td>
<td>Yanchen Xie</td>
<td>Plasma Interleukin-17A Level Stratifies Across Myasthenia Gravis Patient Subtypes</td>
</tr>
<tr>
<td>8:55</td>
<td>Vern C. Juel</td>
<td>Parallel clinical and jitter changes during rapid, eculizumab-induced myasthenic remission</td>
</tr>
<tr>
<td>9:15</td>
<td>Michael Rosario</td>
<td>How Robust is Remission?</td>
</tr>
<tr>
<td>9:35</td>
<td>Mamatha Pasnoor</td>
<td>Phase II Trial of Methotrexate in Myasthenia Gravis</td>
</tr>
<tr>
<td>9:55</td>
<td>BREAK</td>
<td></td>
</tr>
<tr>
<td>10:05</td>
<td>Donald B. Sanders</td>
<td>International Task Force for Treatment Guidelines in Myasthenia Gravis</td>
</tr>
<tr>
<td>10:35</td>
<td>Ted Burns</td>
<td>MGFA Patient Registry and “My MG” app: Update, Fall 2014</td>
</tr>
<tr>
<td>10:55</td>
<td>Nnamdi Dike</td>
<td>Does IVIG Administration Allow for Tapering of Steroids in Myasthenia Gravis?</td>
</tr>
<tr>
<td>11:15</td>
<td>Deeksha Agrawal</td>
<td>Steroid-Sparing Effects of Azathioprine or Mycophenolate Mofetil: A Retrospective Review</td>
</tr>
<tr>
<td>11:35</td>
<td>Kristin L. Jack</td>
<td>A Review of Azathioprine-associated Hepatotoxicity and Myelosuppression in Myasthenia Gravis</td>
</tr>
</tbody>
</table>
INTERNATIONAL TASK FORCE FOR TREATMENT GUIDELINES IN MYASTHENIA GRAVIS

DB Sanders (Durham, NC), GI Wolfe (Buffalo, NY)

Introduction: Formalized treatment guidelines for myasthenia gravis (MG) have been developed or are under development in several countries, but an international guideline has never been established. Such guidelines are increasingly used to support quality care standards and help guide public health care policy.

Objective: The MG Foundation of America has established and funded an international task force to develop guidelines for treating acquired autoimmune MG based on consensus of experts from North America, Europe and Asia.

Method: The International MG Treatment Task Force, co-chaired by Don Sanders and Gil Wolfe, is comprised of 15 physicians with expertise in treating adult and childhood MG. A "modified Delphi" process is being used to obtain consensus, and Pushpa Narayanaswami is serving as the consensus process facilitator.

Results/Discussion: The Task Force met on March 1, 2014, in Durham, NC, to establish the consensus process and began deliberations, which are ongoing and should be complete by the end of 2014. The conclusions of the Task Force will be submitted for publication in a major medical journal, and will be the first MG treatment guidelines based on international opinion.

COMPARISON OF B10 CELLS IN IMMUNOSUPPRESSED AND IMMUNOSUPPRESSION NAÏVE ACHR+ MG

JS Yi, DB Sanders, JM Massey, VC Juel, KJ Weinhold, JT Guptill (Durham, NC)

Introduction: B10 cells are a rare subset of B cells that contribute to the regulation of the immune response through the production of IL-10. B10 cells inhibit T cell responses, and elimination of these cells exacerbates autoimmune diseases. Very little is known about B10 cells in myasthenia gravis (MG). We investigated B10 cell frequencies in acetylcholine receptor positive (AChR+) MG patients with generalized disease.

Methods: To determine B10 cell frequencies, peripheral blood mononuclear cells from 8 non-immunosuppressed and 11 immunosuppressed AChR+ generalized MG patients were cultured for 48 hours in the presence of lipopolysaccharide or cytosine-phosphate-guanosine DNA and recombinant CD40L. For the last 5 hours phorbol-12-myristate 13-acetate, ionomycin, and brefeldin A were added to the cultures. Following intracellular cytokine staining for IL-10, we assessed B10 cell frequencies by polychromatic flow cytometry analysis. The effect of IL-21 on B10 cell proliferation was also examined.

Results: Comparison of B10 cells between immunosuppressed and non-immunosuppressed patients revealed lower B10 cell frequencies in immunosuppressed patients (p=0.04). Addition of IL-21 to B10 cultures in vitro enhanced B10 cell frequencies.

Discussion: These results suggest that immunosuppression affects the generation of regulatory B cells. Further studies, including functional assays, are necessary to determine the full effect of immunosuppressive medication on these regulatory cells. Since B10 cell frequencies in MG
patients can be enhanced through IL-21 stimulation, this approach could be investigated as a novel therapy to ameliorate the disease.

Support: This study was supported by a clinician-scientist development award sponsored by the American Brain Foundation and the Myasthenia Gravis Foundation of America (JT Guptill), a MGFA High Impact Pilot Projects on Myasthenia Gravis award (JT Guptill), and a pilot grant from the Duke Translational Research Institute (CTSA grant UL1RR024128). This abstract was made possible with the help from the Duke University Center for AIDS Research (CFAR), an NIH funded program (P30 AI 64518).

PLASMA INTERLEUKIN-17A LEVEL STRATIFIES ACROSS MYASTHENIA GRAVIS PATIENT SUBTYPES

Y Xie (Washington, DC), H Li (Qingdao, China), B Jiang, Y Li (Beijing, China), HJ Kaminski, LL Kusner (Washington, DC)

Introduction: Myasthenia gravis (MG) is an autoimmune disease. Interleukin (IL)-17A is a proinflammatory cytokine produced by activated Th17 and other cells of the immune system. There is evidence that IL-17 is involved in the pathogenesis of MG. We determined IL-17A levels prior to immunotherapy initiation are associated with clinical subtypes of MG.

Methods: The clinical course of 69 patients with MG who had not received immunotherapy was prospectively monitored for a minimum 2 years in a standardized fashion with assessment of quantitative MG score (QMGS) and Osserman classification. IL-17A concentration was determined from plasma obtained at time of study entrance.

Results: IL-17A levels prior to initiation of treatment were associated with more severe disease as assessed by Osserman classification and greater elevation of the QMGS. IL-17A concentration was greater among patients positive for acetylcholine receptor (AChR) antibody. IL-17A levels were higher among patients with ocular MG who within 6 months of study entrance developed generalized MG. Higher levels of IL-17A differentiated women with early onset MG without thymoma.

Discussion: IL-17A elevation is associated with greater clinical severity and appears to be associated with generalization of disease from OMG to diffuse muscle weakness. The results further support the role of IL-17A in the pathogenesis of MG and in particular in the subgroup of patients with early onset MG who are likely to have thymic hyperplasia.
DOES IVIG ADMINISTRATION ALLOW FOR TAPERING OF STEROIDS IN MYASTHENIA GRAVIS?

G Small, N Dike (Pittsburgh, PA)

Introduction: Myasthenia gravis (MG) treatment choices have included corticosteroids, cell-mediated immune suppressants, plasma exchange (Plex) and intravenous immunoglobulin (IVIG). Steroid- sparing agents are commonly used including IVIG, although lacking class I evidence of steroid-sparing capability. Our objective is to determine whether IVIG administration allowed for tapering of steroid therapy to 10mg or less in a myasthenia gravis population.

Methods: 46 adult patients with clinically and serologically diagnosed myasthenia gravis treated at our dedicated MG clinic were retrospectively reviewed. Inclusion criteria included those aged 18 - 89, evidence of steroids as maintenance therapy above 15 mgs/day and addition of IVIG as secondary therapy. 33 patients were excluded due to addition of other immunosuppressants. MGFA classification was recorded during 4 different patient encounters (1: Initial presentation, 2: Initiation of steroids, 3: Initiation of IVIG, 4: After 6 months of IVIG).

Results: In 9/13 (69.2%) patients, we observed that steroids were able to be tapered to 10mg or less. In 8/13 (61.53%) patients, there was evidence of clinical improvement based on MGFA classification 6 months after IVIG was added to patients’ medication regimen. Mean duration to wean steroids was 2.75 months. 1/13 (7.6%) patient relapsed after steroids were weaned, requiring hospitalization.

Discussion: In this retrospective case review, we observed that IVIG addition to a steroid maintenance regimen in a population of MG patients allowed for weaning of steroids down to 10 mg or less. We observed that only a small number had a significant adverse reactions or relapse. Future prospective evaluation is necessary to determine whether IVIG use in this population may spare steroid side-effects.

HOW ROBUST IS REMISSION?

M Rosario, JM Massey (Durham, NC)

Introduction: Complete Stable Remission (CSR) is defined as no sign or symptom of Myasthenia Gravis (MG) for at least 1 year on no therapy. We present a patient with seronegative generalized MG whose symptoms relapsed 22 years after reaching CSR

Methods: A previously normal 4 year old female presented with ptosis, dysarthria, drooling, and difficulty climbing stairs without autonomic signs. Examination revealed asymmetric bilateral fatigable ptosis, moderate eye closure, cheek puff, tongue and proximal extremity weakness. Sensory examination and reflexes were normal. Her twin sister was unaffected. Hand muscle 3 Hz repetitive nerve stimulation studies demonstrated a 71% maximum decrement without facilitation. EMG was normal. Tensilon improved ptosis and neck flexor strength. Acetylcholine receptor antibodies (AChR) were negative. Plasmapheresis produced improvement. Thymectomy via median sternotomy was without complications. Mild ocular and generalized weakness improved and after 3 years she reached CSR. She remained asymptomatic and participated in competitive collegiate cheerleading. At age 28 she developed fluctuating
ptosis. She denied exacerbating factors. Examination showed bilateral asymmetric ptosis and eye closure weakness similar to that seen at age 4. AChR and MuSK antibodies and thyroid profile were normal. Pregnancy testing was positive.

Results: MG recurred after 22 years of CSR.

Discussion: Non-randomized studies suggest thymectomy is associated with CSR or pharmacological remission in two thirds of patients. Late relapse is rarely reported although follow-up of 20 years is uncommon. Autoimmune MG can relapse years after CSR has been achieved. The rate of late recurrence may be underestimated.

PHASE II TRIAL OF METHOTREXATE IN MYASTHENIA GRAVIS

M Pasnoor, L Herbelin, J He, MM Dimachkie (Kansas City, KS), S Nations (Dallas, TX), V Bril (Toronto, Canada), A Wang (Orange, CA), J Kissel (Columbus, OH), T Burns (Charlottesville, VA), D Saperstein (Phoenix, AZ), J Rosenfeld (San Francisco, CA), A Shaibani (Houston, TX), C Jackson (San Antonio, TX), A Swenson (Des Moines, IA), J Howard (Chapel Hill, NC), N Goyal, W David (Boston, MA), M Wicklund (Hershey, PA), M Pulley (Jacksonville, FL), M Benatar (Miami, FL), R Pascauzzi (Indianapolis, IN), A Genge (Quebec, Canada), E Simpson (Houston, TX), J Miller, RJ Barohn (Kansas City, MO), and the MSG Methotrexate Study MG Group

Introduction: Current effective medications for Myasthenia Gravis (MG) are azathioprine, cyclosporine and IVIG. Oral methotrexate (MTX) is an inexpensive immunosuppressive agent that deserves to be studied in MG.

Objective: To determine if oral methotrexate is an effective therapy for MG patients on prednisone.

Methods: Randomized, double-blind, placebo-controlled multi-center trial of methotrexate versus placebo in MG patients requiring at least 10mg/day of prednisone or more prior to enrollment. Prednisone dose was adjusted during the study based on clinical response. Treatment allocation was to methotrexate 20 mg/week versus placebo in a 1:1 ratio. Clinical and laboratory evaluations were performed monthly for 12 months. The primary efficacy measure is 9 month prednisone area under the curve (AUC). Secondary outcome measures include MGADL, MG Composite and QMG.

Results: Fourteen US and 1 Canadian site participated in this study. Fifty-eight patients were screened, 50 enrolled, 8 withdrew. Mean age in the MTX group was 65±10 years and placebo was 66±16. QMG score at baseline for MTX 10.5±4.1, placebo 10.4±4.2. Analysis of MTX vs. placebo AUC using rank sum test did not show significant difference (p=0.12). Comparing the mean change in secondary outcomes between the two groups from baseline to visit 15, QMG, MGADL and MG composite showed significant differences (p=0.03, 0.02, 0.01 respectively). MG MMT and MGQOL changes between baseline and visit 15 were not significantly different (p=0.09, 0.23).

Discussion: While we did not meet the primary endpoint, analysis of secondary endpoints suggests that methotrexate is safe and effective.

Support: CTSA Grant No: 8UL1TR000001-02; Fund Funded by FDA-OPD RO1 FD003538
PARALLEL CLINICAL AND JITTER CHANGES DURING RAPID, ECULIZUMAB-INDUCED MYASTHENIC REMISSION

VC Juel, DB Sanders, LD Hobson-Webb, JM Massey, JT Guptill (Durham, NC), F O’Brien, JJ Wang (Cheshire, CT), JF Howard (Chapel Hill, NC)

Introduction: Changes in clinical measures, jitter and AChR antibody levels were examined in a man with refractory generalized myasthenia gravis (MG) before, during and after temporary remission following treatment with eculizumab.

Methods: Bulbar symptoms began at age 25 and became generalized within 2 months. Thymectomy later revealed thymic hyperplasia. There was no significant improvement with prednisone, IVIg, azathioprine or mycophenolate mofetil. Intermittent plasma exchange (PE) produced marked, transient improvement. Prior to eculizumab treatment at age 55, there was mild generalized weakness (MGFA Class 2A) and maintenance therapy included cyclosporine, pyridostigmine and periodic PE. MG Manual Muscle Testing (MG-MMT), QMG, and MG-Composite scores, jitter in the extensor digitorum muscle and AChR antibody levels were assessed periodically for 18 years before and 4 years after receiving eculizumab for 16 weeks during a phase 2, placebo-controlled, crossover trial.

Results: One week after receiving 600 mg eculizumab, there was virtually-complete myasthenic remission, and clinical outcome measures and jitter dramatically improved. AChR antibody levels were unchanged. Diplopia and limb weakness recurred 5 weeks after the last eculizumab infusion, and rituximab (1000mg/m² x2) produced modest improvement. He relapsed 4 years later with a parallel increase in jitter.

Discussion: Eculizumab administration in a man with chronic, stable generalized MG was followed by rapid, marked parallel changes in clinical assessments and jitter, but not in antibody levels. These observations demonstrate the potential for rapid and robust improvement in MG with complement inhibition and suggest that jitter, MG-MMT, MG-Composite and QMG are valid biomarkers for MG trials.

Disclosures: Drs. Juel, Sanders, Hobson-Webb, Massey, Guptill and Howard have been investigators or consultants for clinical trials in myasthenia gravis sponsored by Alexion Pharmaceuticals. Drs. O’Brien and Wang are employees of Alexion Pharmaceuticals.

A REVIEW OF AZATHIOPRINE-ASSOCIATED HEPATOTOXICITY AND MYELOSUPPRESSION IN MYASTHENIA GRAVIS

KL Jack, WJ Koopman, D Hulley, MW Nicolle (London, Ontario, Canada)

Introduction: Myasthenia gravis (MG) is an autoimmune disorder in which antibodies, including anti-acetylcholine receptor, anti-muscle specific tyrosine kinase, anti-low density lipoprotein related receptor protein 4, and anti-agrin, interfere with neuromuscular transmission. Azathioprine (AZA) is an immunosuppressive agent frequently used for treatment of various autoimmune conditions, including MG. The literature suggests that the incidence of AZA-associated myelosuppression in MG is highly variable, ranging from ~5 to 25%. The rate of hepatotoxicity is also decidedly variable and published studies have not formally analyzed its pattern, severity, timing, and/or recovery.
Methods and Results: We identified 113 MG patients with AZA-associated toxicity amongst 571 managed with the immunosuppressant. The overall prevalence of hepatotoxicity, and/or myelosuppression was 15.2% and 9.1%. The most common pattern of hepatotoxicity seen was gamma glutamyl transpeptidase (GGT) enzyme elevation in 67.8% patients. The mean average treatment duration at the onset of hepatotoxicity was 6.0 weeks with a mean recovery of 5.8 weeks following medication tapering or discontinuation. Mild lymphopenia and an increase in mean corpuscular volume (MCV) were common trends seen in patients. 21.2% of patients with myelosuppression had normocytic anemia followed by 17.3% with pancytopenia and another 17.3% with macrocytic anemia. Mean onset of myelosuppression was 5.3 weeks with a mean recovery of 5.0 weeks.

Discussion: AZA-associated hepatotoxicity, and/or myelosuppression in MG are not uncommon and may be under-recognized depending on the timing, frequency, and specific tests ordered for blood work monitoring. Based on these results, patients initiating AZA warrant weekly liver enzymes, especially GGT and CBC, and differential monitoring for at least the first eight weeks followed by monthly observation. The pathogenesis of these toxicities is unknown and thiopurine methyltransferase (TPMT) enzyme activity assessment in this patient population planned.

STEROID-SPARING EFFECTS OF AZATHIOPRINE OR MYCOPHENOLATE MOFETIL: A RETROSPECTIVE REVIEW

D Agrawal, G Small (Pittsburgh, PA)

Introduction: Proved as successful therapy for patients with myasthenia gravis (MG), long-term steroid treatment is associated with increased morbidity and mortality. Other therapies are accepted as well, but their steroid-sparing effect is unclear. We tested the hypothesis that addition of azathioprine (AZA) or mycophenolate mofetil (MMF) to corticosteroid therapy allows steroid tapering (≤10mg) in the management of patients with ocular or generalized MG.

Methods: Patients, aged 18-89 years at diagnosis, with positive acetylcholine receptor antibody (AchR) or muscle-specific kinase antibody (MuSK) were included in this retrospective chart review. 76 patient charts were reviewed, of which 28 met inclusion criteria (N = 28). Highest prednisone doses prior to addition, at addition, and 6 months after addition of AZA or MMF were recorded. MGFA Clinical Classification was used to classify disease severity at diagnosis, at addition of immunosuppressive agent, and at 6 months post addition of AZA or MMF.

Results: Of 28 patients, 20 received azathioprine (N = 20) and 8 MMF (N = 8). Corticosteroid dose was tapered to ≤10mg in 22 patients (78.6%). MGFA stage at 6 months after treatment was worse in 2 patients, did not change in 7 patients, and improved in 16 patients.

Discussion: This study demonstrated a possible benefit of AZA or MMF addition, allowing corticosteroid dose taper. Ongoing data collection of controls is occurring, and required to further delineate the steroid-sparing effects of these immunosuppressive agents.
The MGFA Patient-reported Registry was created in 2013. Three objectives of the MGFA Registry are to: 1) help investigators learn more about MG; 2) inform the pharmaceutical industry of unmet needs; and 3) develop a large, central database of patients for MGFA. A Registry Governance committee has been established to consider what questions and surveys should be part of the Registry and to consider research requests for data analysis. Over 700 patients have completed the first survey or are in various phases of completion. Preliminary analyses have found correlations with patient-reported MG-QOL and MG-ADL, fatigue scores and depression, among others. The MGFA and the MSAB of the MGFA need to continue to promote the MGFA Patient Registry to optimize the validity of the clinical data collected.

The MGFA’s “My MG” app was created in 2012. It is a free app available for use on one’s smartphone or tablet. It is comprised of educational material (e.g. drugs to avoid; educational podcasts) and surveys (MG-ADL and MG-QOL15). The app is primarily for patients and families. It has been downloaded ~ 3000 times. English and Japanese language versions exist, with other language translations in progress.
The Myasthenia Gravis Patient Registry is an active database of persons with Myasthenia Gravis (MG), developed for the purposes of research, treatment, and patient information. The MG Patient Registry is a confidential and patient-driven research project, funded by the Myasthenia Gravis Foundation of America (MGFA), managed by the MGFA and the Coordinating Center of the University of Alabama at Birmingham (UAB) with oversight by the MGFA Patient Registry Committee.

**MG Patient Registry is:**
- For Myasthenia Gravis Research
- Participant Driven
- Free to Enroll
- Confidential
- Open to Adults 18 and Older
- Open to Residents of the United States

**What types of questions are in the enrollment survey?**
- General contact information
- Demographic information, for example, education, employment, income, insurance
- Year, month, and place of birth of parents and grandparents
- Information on places you lived when you were under 25 years old
- MG medical history, including tests and diagnoses; treatments; other conditions; family's MG history
- Information on quality of life and lifestyle
- Future, follow-up surveys will contain a subset of the enrollment questions as well as one new section of questions.

**TOGETHER WE ARE STRONGER – PLEASE JOIN US!**

http://www.soph.uab.edu/mgregistry/

Email: MGR@MGregistry.org || Phone: (855) 337-8633 toll free