2018 Scientific Session Summary

By Robert Ruff, M.D., Ph.D.

The 2018 MGFA Scientific Session was held on October 10, 2018, in conjunction with the annual meeting of the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM). The location was the Gaylord Conference Center at National Harbor, MD outside of Washington, DC. There is a large Ferris Wheel in the National Harbor, which was lit up with teal lights in honor of MG on the night the Scientific Session was held. The session was attended by about 200 people. Scientific Program Chairs were Michael Hehir (University of Vermont Medical Center), Amanda Guidon (Massachusetts General Hospital) and Araya Punwanant (University of Pittsburgh Medical Center). Before the presentations began, Edward Walsh, Chair of the MGFA Board of Directors, thanked the MGFA Content Development and Review Committee led by Dr. Yuebing Li (Cleveland Clinic Foundation, Cleveland OH) for his committee’s work reviewing and updating the MGFA’s medical information literature for patients. Nancy Law, Chief Executive Officer of the MGFA, welcomed care providers attending the session to join the Partners in MG Care program.

Below, I summarize the Speaker Presentations (platform presentations) and “Data Blitz Presentations” from the meeting. There were also 12 posters displayed.

KEYNOTE PRESENTATION

CIRCULATING MICORNA AS BIOMARKERS FOR MYASTHENIA GRAVIS

Anna Punga – Uppsala, Sweden

The purpose of biomarkers is to predict the course and perhaps what types of treatment a person with a disease such as MG will best respond to. A biomarker is a chemical or other “crystal ball” to help the patient and clinician plot the smoothest course while navigating the obstacles that will occur with MG. Micro RNAs (miRNA) are short segments of RNA that are in effect incomplete copies of the RNA that a cell uses as the template for making proteins. MiRNAs are kicked out of cells in packets called exosomes or vesicles. The packeted RNA is stable enough to measure in blood samples. RNA and DNA are made by linking small chemicals called nucleotides. The miRNAs can be analyzed based upon the sequence of nucleotides present and the length of the miRNA (number of nucleotides present). By comparing the composition of the miRNAs, Dr. Punga’s group found that a few miRNAs were present in different proportions in people with different forms of MG – early vs. late onset of disease. The compositions of miRNAs changed in response to immune treatments with medications such as prednisone and also with thymectomy. Dr. Punga’s group also found that exercise was safe for people with stable MG and that exercise altered the miRNA pattern in patients in a specific way. People with MuSK MG have clinical differences and may lack the thymus change found in people with AChR MG. Her group found that people with MuSK MG had different patterns of miRNAs compared to AChR MG. Early and late onset MG had distinct patterns of miRNAs. There were also variations in the miRNA patterns associated with people who had mild or severe MG. Can miRNAs predict which people with ocular-only MG will progress to generalized MG? Amazingly, the amount of one particular miRNA was able to predict with high accuracy which patients with ocular MG would develop

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generalized MG and which would not. Therefore, the miRNA patterns would distinguish who had early versus late onset MG, AChR vs. MuSK MG and whether a person with ocular-only MG would progress to generalized MG. Dr. Punga’s group is collaborating with researchers in other countries, including the U.S., to further study the role of miRNA in MG.

Submitted abstracts that were selected for platform presentations

ISOLATING AND INVESTIGATING RARE AUTOANTIBODY-PRODUCING B CELLS IN MYASTHENIA GRAVIS
K. Takata, P. Strathopoulos, M. Ficchner. P. Suarez, E. Bennotti, R. Nowak, K O’Connor – Yale Univ, New Haven, CT

In MuSK MG, the predominant pathogenic antibody is immunoglobulin type 4, Ig4. This group is working to identify the antibody producing B cells that underlie MuSK MG. The Ig4 antibodies bind to the same part of MuSK that agrin binds to so the anti-MuSK Ig4 antibodies may act by disrupting the normal interaction where agrin binds to MuSK to initiate AChR clustering. They directly demonstrated that the Ig4 antibodies prevented MuSK-mediated clustering of AChRs. Impaired clustering will reduce the number of AChRs present on the endplate membrane. Thus, this presentation suggested how AChR function is compromised in MuSK MG.

MUSK MYASTHENIA GRAVIS IS ASSOCIATED WITH AN IMBALANCE IN TFH17 CELL SUBSETS
Y. Li, J. Guptill, M. Russo, J. Massey, Vern Juel. L. Hobson-Webb, S. Raja, J. Howard, M. Chapra, J Li (Duke, Durham NC; Univ of North Carolina, Chapel Hill, NC) and W Liu Sun Yat Sun Univ, Guangzhou, Guangdong China

TFH (follicular helper T cells) are a class of T cells that activate B cells so that B cells produce antibodies. The TFH class 17 cells are dramatically increased (upregulated) in people with MuSK MG and regulatory T cells (which would reduce B cell activation) are downregulated in people with MuSK MG. Another class of TFH cells that were upregulated was TFH21 cells. CD4+ T cells may be the ones that upregulate the TFH17 cells thru cytokines secreted by the CD4+ T cells.

HIGHLY PURIFIED STAPHYLOCOCCAL PROTEIN DECREASES DISEASE ACTIVITY IN THE MOUSE MODEL OF MYASTHENIA GRAVIS
L. Kusner (Wash DC GW Univ) M. Catalina (Florham Park NJ)

PRTX-100 is a peptide produced by staph type A bacteria. PRTX-100 is used by the staph bacteria to suppress the immune system of the being that the staph is attacking. PRTX decreases the activity of the immune system by binding to immunoglobulins and attacking immune cells. This study compared the beneficial action of PRTX-100 relative to IVIG in a mouse model of MG. MG was induced by sensitizing mice to AChR protein. Both PRTX and IVIG comparably reduced disease severity including reducing weakness in mice with induced AChR MG. Both treatments reduced IgG class 1 (IgG1) and class 2 (IgG2) antibody levels. The treatments reduced the amount of complement deposition and membrane attack complex deposited at the nerve-muscle junction (NMJ). Both treatments also preserved the AChR content at the NMJ. This study suggests that PRTX could have clinical benefits for MG treatment, but the study needs to be followed up with additional studies followed by clinical trials.
MYASTERIX A PHASE 1B CLINICAL TRIAL OF CV-MG01, ACETYLCHOLINE RECEPTOR MIMETIC PEPTIDES, THERAPEUTIC VACCINE CANDIDATE FOR MYASTHENIA GRAVIS.

R. Mercelis (Antwerp), S. Huberty, N. Havelange – Netherlands

CV-MG01 is a complement of a segment of the AChR (peptides 67-76) that is designed to induce antibodies that bind to and inactivate pathogenic immune cells that are making antibodies against the AChR region containing peptides 67-76. The current report is of 24 patients with MG treated with high or low doses of CV-MG01. The vaccine was safe with only local site reactions. Only one patient was removed from the study due to episodic weakness which was unrelated to MG. In this small pilot study, there was no clear improvement in the vaccine treated vs. untreated groups of people with MG. The investigators are working to make a more potent vaccine. In effect the mechanism of action of the vaccine seems to be valid. The vaccine worked in animals, but so far not in humans. The problem may be that the vaccine would only be active against those B-cells producing antibodies against one specific region of the AChR and in human AChR MG antibodies are directed toward many regions of the AChR. An additional challenge is that the targeted regions of the AChR vary among people with MG. The vaccine is very effective in the animal model, because the animal MG is induced by sensitizing an animal to the specific region of the AChR that the vaccine targets. It is not known how many peptides need to be represented in a vaccine for it to be effective in clinical AChR MG.

RESULTS FROM THE MGTKX EXTENSION STUDY OF THYMECTOMY IN MYASTHENIA GRAVIS.

G. Wolfe (Univ of Buffalo, Buffalo NY) H. Kaminski (GW Univ, Wash DC), I Aban (Univ Alabama, Birmingham AL) G Cutter (Univ Alabama, Birmingham AL) and MGTKX Study Group (Buffalo, NY)

MGTKX study end points were clinical state and reduction in prednisone dosing. The study had 67 sites around the world including N. America, S. America, Europe and Asia. The original report of the MGTKX showed that thymectomy improved QMG scores by about 3 and reduced prednisone dosing by about 22 mg QOD (every other day). The extension study extended the finding by following a subset of the initial study group (68 patients) out to 60 months after thymectomy. The improvement in QMG score persisted as did the reduction of prednisone dosing. By the end of the extension study the prednisone dose in the Thymectomy group was reduced by about 60 mg QOD compared with the onset of the study. This report indicated that thymectomy produced prolonged benefits for people with AChR MG.

LONG TERM EFFECTIVENESS AND SAFETY OF ECULIZUMAB IN GENERALIZED MYASTHENIA GRAVIS: BEYOND MG-ADL AND QMG

S Muppidi (Stanford Univ, Stanford CA), F O’Brien (Yale, New Haven CT), J Wang (Yale, New Haven CT), K Fujita (Yale, New Haven CT), J Howard Jr. (Univ of North Carolina, Chapel Hill, NC)

This is a report of the open-labeled extension (patients able to get Eculizumab if they were on placebo or continue on Eculizumab if they had been receiving that treatment). Total of 42 prior placebo and 43 Eculizumab patients completed this extension study. The patients who were initially on placebo received Eculizumab and caught up to those who had been treated from onset with Eculizumab. Benefits continued for the 3 year duration of study. So far 60% of subjects reached minimal manifestation status.

OVERLAP SYNDROME OF MYASTHENIA GRAVIS AND MYOSITIS IS A COMMON ETIOLOGY OF NEUROMUSCULAR WEAKNESS ASSOCIATED WITH IMMUNE CHECKPOINT INHIBITORS IN A MULTICENTER RETROSPECTIVE STUDY OF 15 PATIENTS.

A Guidon (Boston MA) S Raja (Durham, NCA) D Dubey (Boston MA) N Clement (Boston MA) K Reynolds (Boston MA) J Guptill (Durham NC) W David (Boston MA)

Checkpoint inhibitors are used in patients with advanced cancers to rev up the immune system and encourage a patient’s immune system to mount an immune attack against the cancer. A side effect of therapy is to activate or initiate an autoimmune disorder such as MG. Autoimmune disorders involving the nervous system occur in about 1-2% of patients who receive checkpoint...
inhibitor Rx. This study of 15 patients who developed MG and/or myositis as a consequence of checkpoint inhibitor treatment demonstrated that 6/15 developed both myositis and MG. Myositis refers to immune attack directed against the entire length of a muscle fiber as opposed to being limited to the NMJ (neuromuscular junction). People with both myositis and MG frequently had muscle pain (myalgia), difficulty breathing, eye movement weakness (diplopia), difficulty swallowing and impaired walking. Only 4/15 had detectable AChR antibodies. Diagnosis was usually made by EMG and other supporting testing. The weakness did improve with treatment in most patients but a subset had severe and fatal disease. Fortunately, only 1-2% of people who are given immune checkpoint inhibitors develop autoimmune disorders involving the nervous system including the NMJ.

THE RISK OF SERIOUS INFECTIONS AND FRACTURES IN MYASTHENIA GRAVIS

C Kassarakdjian (Univ of Toronto, Toronto, ON), J Widdifield (Toronto, ON), M. Paterson, C. Barnett (Toronto, ON), C. Nagamuthu, A. Kopp, A Breiner (Toronto, ON)

The presentation started with case reports. Questions that emerged were: how common do these adverse consequences occur and what should be done. Two groups MG vs. Control. The MG group at baseline had more disease burden such as diabetes. During the follow-up period, the Infection rate was doubled for MG patients and infections occurred sooner. Infections were often respiratory. Fracture rates were similar for MG and controls. I was surprised that people with MG did not have increased risk of fractures compared to the control group. One person commented that perhaps people treating MG, usually neurologists, are well aware of the side effects of prednisone or other glucocorticoid steroids (note glucocorticoids are very different from anabolic steroids, androgens, estrogens and progesterone) and prescribe vitamin D and calcium supplements for people receiving prednisone to reduce the risk of dangerous bone thinning caused by prednisone.

SUBCUTANEOUS IMMUNOGLOBULIN IN MYASTHENIA GRAVIS: A NORTH AMERICAN OPEN LABEL STUDY

M. Dimachkie (Univ of Kansas, Kansas City, KS), V. Bril (Toronto ON), T. Levine (Phoenix AZ), J. Trivedi (Dallas TX), N. Silvestri (Buffalo NY), M. Phadnis (Kansas City KS), D. Saperstein (Phoenix AZ), S. Nations (Dallas TX)

This was a seven year duration study to see if patients on IVIG can be safely converted to Sub Cutaneous (Sub-Q) IG. This study is ongoing. Agent used is Hizentra. 23 subjects, all AChR positive. Drop-out rate was about 5%. 86% had appreciable improvement while on the SubQ IG. So far the Sub-Q IG has been successful. People learn how to administer the SubQ IG to themselves or to have a family member/friend trained to administer the Sub-Q IG. This program is particularly useful for people who live in remote areas where it may be very difficult to obtain IVIG or may have difficulty with IV access.

THYMECTOMY MAY NOT BE ASSOCIATED WITH CLINICAL IMPROVEMENT IN A MULTICENTER COHORT OF PATIENTS WITH MUSK MYASTHENIA GRAVIS

K. Clifford (Burlington VT – AANEM trainee award winner), I. Hobson-Webb (Durham, NC), M. Benetar (Miami FL), T Burns (Charlottesville, VA), C. Bennett (Toronto, ON), N Silvestri (Amherst, NY), J Howard (Chapel Hill, NC), A Visser (Portland, OR), B Crum (Rochester, MN), R Nowak (New Haven, CT), R Beekman (New Haven, CT), A Kumar (New Haven, CT), K Ruzhansky (Charleston, SC), I Chen (Charleston, SC), M Pulley (Jacksonville, FL), S Laboy (Jacksonville, FL), M. Fellman (Miami, FL), N Kolb (Burlington, VT), S Greene (Providence, RI), M Pasnook (Kansas City KS), M Dimachki (Kansas City KS), R Barohn (Kansas City KS), M Hehir (Burlington, VT)

This was a retrospective analysis of a study or patients who were in a randomized controlled trial of Rituximab. From that study the investigators identified 26 subjects who had a thymectomy and 29 subjects who did not. MGFA Post-Intervention Score (PIS) of minimal manifestations (MM) or better was the primary outcome measure.
Whether or not a subject previously had a thymectomy did not improve the likelihood that a subject would improve in response to Rituximab. Rituximab increased the likelihood of appreciable improvement by 7-fold for the group of subjects with MuSK MG. Note, that a repeat of the International Thymectomy Clinical Trial is unlikely to occur; therefore, this study gave some useful information on the decision of doing thymectomy or not for patients with MuSK MG. My take on this study is that whether or not a subject had a thymectomy did not alter the likelihood that a subject achieved improvement to MM status. One attendee raised concern that the patient sample may not be a representative sample to determine if thymectomy is beneficial for people who have MuSK MG.

VALIDATION OF THE TRIPLE-TIMED-UP-AND-GO TEST FOR CLINICAL ASSESSMENT IN LAMBERT-EATON SYNDROME PATIENTS

S. Raja (Durham, NC) D. Sanders (Durham, NC), V Juel (Durham NC), Y Harati (Houston, TX), A Smith (Richmond VA), A Pettier (Nashville TN), J Lau (Fargo ND), D Richmond

This described a physical test where a person rises from sitting in a chair without assistance of their arms and then walked in a short loop. The process is repeated three times for one measurement. The test measures lower extremity weakness and mobility. The investigators reported that results using this test did not depend upon who did the measurement (inter-rater reliability was good) and the values were consistent when repeatedly studied (values were consistent). The measure is influenced by lower extremity weakness and walking ability, thus the value of this instrument should be sensitive to what it intends to measure – lower extremity strength and walking ability. At present this instrument appears to be a good measure of physical performance for people who have Lambert Eaton Syndrome. Further studies may show that this instrument is a useful clinical tool for determining the status and response to interventions for Lambert Eaton patients.

DISEASE BURDEN AND TREATMENT HISTORY IN THE MYASTHENIA GRAVIS FOUNDATION OF AMERICA PATIENT REGISTRY

G. Cutter (Birmingham AL), H Xin (Birmingham AL), I Aban (Birmingham AL), T Burns (Charlottesville, VA), R Far (Cambridge MA), P Duda (Cambridge MA), H. Kaminski (Washington DC)

There are currently 2,800 entrants in the MG Patient Registry. The registry is comprised of patient reported data and data are not compared to medical records. This study evaluated the data in the registry in July 2017 when there were 1,140 entries. Only about 30% of patients indicated that they knew their antibody status – AchR+ or MuSK+ or seronegative. Patients in the registry tend to have moderate to severe disease burden. Surprisingly, many were not receiving immunotherapy other than prednisone. About 30% had received IVIG or PLEX (plasma exchange). Fewer participants indicated that they received agents such as mycophenolate mofetil or Imuran (azathioprine). It is not clear whether the participants were not receiving non-steroid immunosuppressant medications other than IVIG or plasma exchange or perhaps participants were not able to correctly enter their medications.

BASELINE DECREMENT IN PATIENTS WITH MILD MG PREDICTS IMMUNOMODULATION TREATMENT.

A Abraham (Tel Aviv. Israel) the following were from Univ of Toronto, Toronto ON – A Ali, C Barnett, H Katzberg, L Lavblom and V. Bril

134 patients classified by clinical status and EMG findings of Repetitive Nerve Stimulation (RNS) and Single Fiber EMG jitter. Patients with higher levels of jitter had worse clinical status and generalized MG. Patients with higher levels of jitter or abnormal RNS were more likely to receive IVIG and PLEX. Future studies may look at whether abnormal EMG findings may be an indicator of more rapid disease progression and indicate that more aggressive treatment is needed early in the course of MG.
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RETROSPECTIVE ANALYSIS OF OUTCOMES AND SAFETY AFTER RITUXIMAB USE FOR MYASTHENIA GRAVIS IN PATIENTS > 65 YEARS OLD.

C Doughty (Boston MA), A Amato (Boston MA)
W David (Boston MA) A Guidon (Boston MA)

There were 40 patients in the study. Compared older (> 65 years old) and younger patient responses. Older patients did about the same as younger patients. About 1/3 of all patients developed an infusion reaction that was mild in most cases. Older patients did as well as younger and tolerated the treatments including rituximab well.

IMBALANCE OF TWO MAIN CIRCULATING DENDRITIC CELL SUBSETS IN PATIENTS WITH MYASTHENIA GRAVIS

W Liu, P Chen, Y Li, H Huang (Nanning China), Y Li, Z Chen, X Liu, C Ou, L Ou, Z Huang, Z Lin and H Ron (researchers were from Sun Yat Sen Univ. Guangzhou China unless otherwise indicated)

This study examined MG patients who had not yet been treated (at start of treatment). MG patients had more B cells that were antibody producing cells compared to controls or patient with MG in remission. Immune treatments such as tacrolimus reduced the population of antibody producing B cells.