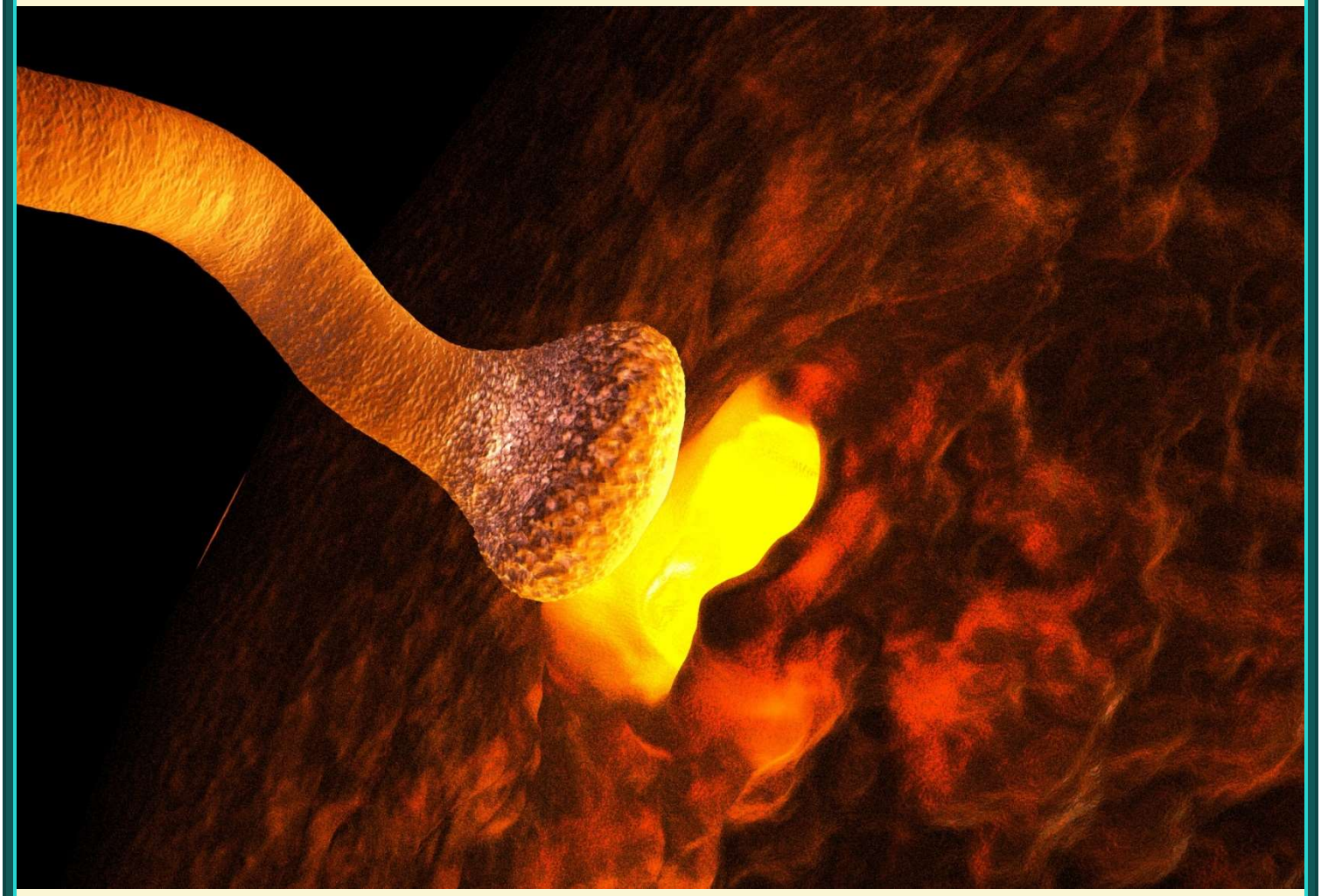
MYASTHENIA GRAVIS FOUNDATION OF AMERICA



2020 Scientific Session

of the Myasthenia Gravis Foundation of America

Saturday, October 3rd

October 3, 2020

Welcome Scientists, Clinicians and Guests,

On behalf of the Board of Directors of the Myasthenia Gravis Foundation of America, Inc., welcome to the 2020 Scientific Session of the MGFA Medical and Scientific Advisory Board. We thank you for your interest in Myasthenia Gravis (MG). This is an exciting time for our community- advances in research and innovative treatments in clinical trials bring us closer to a cure for MG. As we all deal with the COVID 19 pandemic, we are coming to you virtually this year. We hope to see you in person next year.

Our vision: A World Without MG
Our mission: Create Connections, Enhance Lives, Improve Care, Cure MG

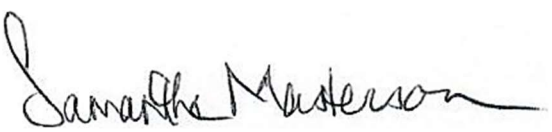
This year has looked somewhat different, but we continue to be dedicated to our vision and our mission. We cannot meet our goals without you. Beyond today, we hope that you will be a part of MGFA. There are many ways you can help: speaking at support groups (we have many virtual support groups this year reaching a wide audience), writing or reviewing an article, donating, and joining our *Partners in MG Care* program to facilitate patient referrals to your practice. You can also simply encourage your patients to enroll in the MG Patient Registry.The Registry, with more than 3,000 participants, has already produced significant findings to advance clinical trial research and advocacy.

If you would like to learn more about the Foundation and its programs, please contact us at 1-800-541-5454 or visit us at myasthenia.org, where you can find information about the MG Patient Registry, information for health professionals, patient resources, and the latest in research. Special thanks to our Session Chairs, Araya Puwanant, MD Srikanth Muppidi, MD, and Shruti Raja MD, and all of our speakers and presenters. Special thanks to our Presenting Sponsors, Alexion Pharmaceuticals, argenx, Momenta Pharmaceuticals, and UCB, and to our Silver Sponsor, Immunovant. We are grateful for their support!

We hope you find this scientific session to be informative.

Sincerely,

Samantha Masterson, CEO



Nancy Law, Board Chair

2020 MGFA Scientific Session

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Assistant Professor, Neurology
University of Pittsburgh

Srikanth Muppidi, MD
Clinical Associate Professor, Neurology & Neurological Services
Stanford Hospital

Shruti M. Raja, MD
Assistant Professor, Neurology
Duke University School of Medicine

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Agenda Scientific Session – October 3, 2020

Meeting held virtually

11:00 am ET to 5:00 pm ET

11:00 am ET (10 min) **Welcome** – Samantha Masterson (introduce the planning committee) and Dr. Araya Puwanant (welcome everyone)

11:10 am ET (5 min) **Introduction Dr. Kaminski** (Deborah Gelinas, MD - Argenx)

11:15 am ET (30 min) **Open with Dr. Henry Kaminski** - Keynote Speaker
11:45 am ET (10 min) Q & A – Moderated by Araya Puwanant, MD

11:55 am ET (20 min) **Poster Break**

12:15 pm ET (5 min) **Introduction MG Diagnostics (**Christine Rowe, MBA - Alexion)

MG Diagnostics
12:20 pm ET (20 min) **Presentations on Cell-Based Assays**

- Hans Frykman, MD, PhD
  LIVE CELL-BASED ASSAY FOR ANTIBODIES TO CLUSTERED ACETYLCHOLINE RECEPTOR IN MYASTHENIA GRAVIS, CROSS VALIDATION, INTER-ASSAY STABILITY AND UTILITY IN A PAEDIATRIC COHORT SUSPECTED FOR MG
- Jeffrey Guptill, MD
  VALIDATION OF A LIVE CLUSTERED CELL BASED ACETYLCHOLINE RECEPTOR ASSAY IN A COHORT OF DOUBLE SERONEGATIVE DEFINITE MYASTHENIA GRAVIS PATIENTS

12:40 pm ET (5 min) Q & A - Moderated by Araya Puwanant, MD

12:45 pm ET (15 min)

- Miriam Fichtner, MD
  AFFINITY MATURATION IS REQUIRED FOR PATHOGENIC MONOVALENT IGG4 AUTOANTIBODY DEVELOPMENT IN AUTOIMMUNE MYASTHENIA GRAVIS

1:00 pm ET (5 min) Q & A - Moderated by Araya Puwanant, MD
(5-minute transition)

1:10 pm ET (15 min) Data Blitz #1: **Focused on Diagnostics**

- Ki Hoon Kim, MD
  ANTI-TITIN ANTIBODIES ARE FREQUENTLY OBSERVED IN PATIENTS WITH MYASTHENIA GRAVIS WHO EXPERIENCED THE RECURRENCE OF THYMOMA
- Pritikanta Paul, MBBS
  REFLEX ALGORITHM FOR IMPROVING ACCURACY OF MYASTHENIA GRAVIS AUTOANTIBODY TESTING
- Faraz S. Hussain, PhD
  PROTEOMIC PROFILING MAY REVEAL NOVEL BIOMARKERS FOR MYASTHENIA GRAVIS

1:25 pm ET (5 min) Q & A - Moderated by Araya Puwanant, MD

1:30 pm ET (20 min) **Exhibit Hall Break**

1:50 pm ET (5 min) **Introduction – MG, COVID and MG Registries** (Omar Sinno, MD, MBA – UCB)

MG, COVID and MG Registries

1:55 pm ET (30 min) **Presentations on COVID-related Topics**

- Amanda Guidon, MD
  FEASIBILITY AND ACCEPTABILITY OF REMOTE MONITORING OF PATIENTS WITH MYASTHENIA GRAVIS USING DIGITAL TECHNOLOGY
- Srikanth Muppidi, MD
  COVID-19 ASSOCIATED RISKS AND EFFECTS IN MYASTHENIA GRAVIS (CARE-MG): AN INTERNATIONAL PHYSICIAN-REPORTED REGISTRY

2:25 pm ET (5 min) Q & A - Moderated by Shruti M. Raja, MD
(5-minute transition)

2:35 pm ET (15 min) Data Blitz #2: **Focused on COVID and Registries**

- Kevin Li, MD
  KNOWLEDGE AND PERCEPTIONS OF THE COVID-19 PANDEMIC AMONG PATIENTS WITH MYASTHENIA GRAVIS
- Megan Barra, PharmD, BCPS, BCCCP
  IMPACT OF A MYASTHENIA GRAVIS DRUG-DISEASE INTERACTION CLINICAL DECISION SUPPORT TOOL ON PROVIDER PRESCRIBING
- Donald Sanders, MD
  THE DUKE MYASTHENIA GRAVIS CLINIC REGISTRY: DESCRIPTION AND DEMOGRAPHICS

2:50 pm ET (5 min) Q & A - Moderated by Shruti M. Raja, MD

2:55 pm ET (20 min) **Poster Break**

3:15 pm ET (5 min) **Introduction MG Clinical Trials** (Tricia Gooljarsingh, PhD, CMPP - Momenta)

MG Clinical Trials

3:20 pm ET (30 min) **Presentations on Clinical Trials**

- Jeffrey Guptill, MD
  A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, EFFICACY, PK, AND PD OF NIPOCALIMAB (M281) IN ADULTS WITH GENERALIZED MYASTHENIA GRAVIS
- James Howard, MD
  TREATMENT OF PATIENTS WITH MYASTHENIA GRAVIS WITH EFGARTIGIMOD: RESULTS OF THE PHASE 3 ADAPT STUDY

3:50 pm ET (5 min) Q & A – Moderated by Srikanth Muppidi, MD
(5-minute transition)

4:00 pm ET (15 min) Data Blitz #3: **Trials/New Strategies**

- Richard J. Nowak, MD, MS
  THE MYASTHENIA GRAVIS INEBILIZUMAB TRIAL (MINT): DESIGN OF RANDOMIZED, PLACEBO-CONTROLLED PHASE 3 STUDY OF AN ANTI-CD19 MONOCLONAL ANTIBODY IN GENERALIZED MYASTHENIA GRAVIS
- Suraj Muley, MD, FAAN
  TWO-YEAR POST-MARKETING SAFETY EXPERIENCE OF ECULIZUMAB IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS IN THE UNITED STATES
- Sangwook Oh, PhD
  MUSCLE-SPECIFIC TYROSINE KINASE CHIMERIC AUTOANTIBODY RECEPTOR T CELLS (MUSK-CAART) AS A PRECISION CELLULAR IMMUNOTHERAPY FOR ANTIGEN-SPECIFIC B CELL DEPLETION IN MUSK MYASTHENIA GRAVIS (MG)

4:15 pm ET (5 min) Q & A - Moderated by Srikanth Muppidi, MD

4:20 pm ET (5 min) **Closing Remarks – Thank you(s) – Samantha Masterson**

4:25 pm ET (30 min) **Poster Break and Exhibit Break**

Agenda subject to change

Posters:

Mathieu Cuchanski, DO - OVERLAP PARANEOPLASTIC SYNDROME: THYMOMA PRESENTING AS MYASTHENIA GRAVIS AND IMMUNE MEDIATED MYOPATHY - A CASE SERIES

Constantine Farmakidis, MD - FOLLOW-UP CARE IN MYASTHENIA GRAVIS DURING COVID-19: COMPARISON OF TELEMEDICINE AND IN-PERSON ENCOUNTERS

Hans Frykman, MD, PhD - VALIDATION OF A SURFACE PLASMON RESONANCE ASSAY FOR THE DIAGNOSTIC DETECTION AND CHARACTERIZATION OF MUSCLE-SPECIFIC TYROSINE KINASE (MUSK) ANTIBODIES IN MYASTHENIA GRAVIS PATIENTS

Andre Granger, MD - CHARACTERISTICS AND OUTCOMES OF MYASTHENIA GRAVIS PATIENTS WITH COVID-19 – A CASE SERIES

Abigail Healy, BS - MYASTHENIA GRAVIS POPULATION AT UCONN HEALTH: A SINGLE CENTER PROFILE ANALYSIS COMPARING PATIENT EPIDEMIOLOGY AND IVIG TREATMENT REQUIREMENTS

Goknur Kocak, MD - A NOVEL DIAGNOSTIC METHOD FOR MYASTHENIA GRAVIS

Ikjae Lee, MD - DETERMINATION OF COMPLEMENT ACTIVATION IN MYASTHENIA GRAVIS: A PILOT STUDY

Janice Massey, MD - RAPIDLY REVERSIBLE TONGUE ATROPHY IN SERONEGATIVE MYASTHENIA GRAVIS FOLLOWING TREATMENT

Posters, Continued:

E Wayne Massey, MD - FAMILIAL MUSK MYASTHENIA GRAVIS

David Post, MD - VARIABILITY OF COMPLEMENT LEVELS IN A SPECTRUM OF MYASTHENIA GRAVIS PATIENTS

Danielle Richards, DO - ACHR ANTIBODY OVERSHOOT FOLLOWING PLASMAPHERESIS ASSOCIATED WITH CLINICAL DETERIORATION OF MYASTHENIA GRAVIS

Joome Suh, MD - REAL-WORLD EXPERIENCE OF ECULIZUMAB FOR MYASTHENIA GRAVIS

Niraja Suresh, MD - MUSK MUTATION IN AN ANTI-ACETYLCHOLINE RECEPTOR AND MUSK ANTIBODY NEGATIVE PATIENT

Christopher Tran, BMsc - PERFORMANCE OF DIFFERENT CRITERIA FOR REFRACTORY MYASTHENIA GRAVIS

Carolyn Tsai, MD - A CASE OF MUSK MYASTHENIA GRAVIS PRESENTING WITH ISOLATED RESPIRATORY INSUFFICIENCY

Uzma Usman, MD - EFFICACY OF ECULIZUMAB IN MYASTHENIA-GRAVIS-FOUNDATION-OF-AMERICA (MGFA) GRADE-V MYASTHENIA GRAVIS

PLATFORM PRESENTATIONS:

Validation of a Live Clustered Cell Based Acetylcholine Receptor Assay in a Cohort Of Double Seronegative Definite Myasthenia Gravis Patients

A Cruz (Vancouver, Canada), J Oger (Vancouver, Canada), T Aziz (Vancouver, Canada), P Kumar (Vancouver, Canada), J Yi (Durham, NC), A Hammett (Durham, NC), H Frykman (Vancouver, Canada), J Guptill (Durham, NC)

Introduction: A myasthenia gravis (MG) diagnosis is largely confirmed by laboratory testing. However, 10-15% of MG patients test negative for acetylcholine receptor antibodies (AChR Abs) by radioimmunoprecipitation assay (RIPA), the current gold standard test. We are evaluating the sensitivity of the live clustered cell based assay (CBA) for AChR Abs compared to the gold standard RIPA in an adult patient cohort.

Objective: To evaluate a live clustered AChR CBA in the diagnosis of a "seronegative" MG patient cohort.

Methods: 90 plasma samples from MG patients at Duke Medical Center, who were seronegative for AChR and MuSK Abs with commercially available RIPA assays, were tested for AChR Abs using a live clustered CBA and RIPA optimized for plasma. Positive samples by CBA and RIPA were re-assayed for verification. All patients had a clinical diagnosis of MG with abnormal neuromuscular transmission on repetitive nerve stimulation or jitter studies and/or had a response to treatment for MG. We also correlated the antibody results to the patients' clinical phenotype.

Results: 11/90 (12.2%) samples were positive on the CBA. One sample positive by CBA was also RIPA low positive (3.74 nmol/L).

Summary/Conclusion: A live clustered CBA for AChR Abs aids in the diagnosis of a cohort previously seronegative MG patients. We will provide clinical descriptions of patients who tested positive for AChR Ab. Detection of AChR Abs in previously seronegative patients may have important treatment implications in some cases.

Live Cell-Based Assay for Antibodiest Clustered Acetylcholine Receptor in Myasthenia Gravis, Cross Validation, Inter-Assay Stability and Utility in a Pediatric Cohort Suspected For MG

A Cruz (Vancouver, Canada, H Frykman (Vancouver, Canada)

Introduction: A large proportion of generalized myasthenia gravis (MG) patients have detectable acetylcholine receptor antibodies (AchR Abs) or muscle-specific tyrosine kinase antibodies (MuSK Abs) by radioimmunoprecipitation assay (RIPA). Children with mostly lower affinity antibodies have shown to test negative by RIPA. A live cell-based assay (CBA) that expresses clustered AchR Abs on the cell surface through the co-expression of rapsyn has demonstrated the ability to detect AchR Ab in 16%-60% of MG patients that do not have measurable AchR Ab or MuSK Abs by RIPA.

Objective: To validate the CBA for testing of clustered AchR Ab in the diagnosis of MG

Methods: 49 AchR Abs RIPA positive and 50 healthy control sera, were blinded and assayed three separate occasions by clustered AchR Abs CBA. Additionally, a cohort of serums from 45 Canadian children age 16 years and younger with suspect MG, that had previously tested negative for AchR Abs by RIPA, were assayed.

Results: 100% concurrence was observed with the CBA results between the three blinded assays of 99 samples. Of the 49 RIPA positive, 48 tested CBA positive or low positive in all 3 assays, and one negative. All 50 healthy controls tested negative. Of the 45 children samples that were tested, 7 were CBA positive. Follow-up of these showed that 3 have ocular MG and 4 have generalized MG.

Summary/Conclusion: The clustered AchR Abs CBA is a highly sensitive and replicable assay. It was shown to improve diagnostic sensitivity of MG in children.

Affinity Maturation is Required for Pathogenic Monovalent Igg4 Autoantibody Development in Autoimmune Myasthenia Gravis

M Fichtner (New Haven, CT), C Vieni (NY, NY), R. Redler (NY, NY), L Kolich (NY, NY)
R Jiang (New Haven, CT), K Takata (New Haven, CT), P Stathopoulos (New Haven, CT),
P Suarez (New Haven, CT), R Nowak (New Haven, CT), S Burden (NY, NY), D Ekiert (NY, NY)
K O'Connor (New Haven, CT)

Introduction: Pathogenic autoantibodies in muscle-specific tyrosine kinase (MuSK) myasthenia gravis (MG) are predominantly of the IgG4 subclass. A unique feature of human IgG4 antibodies is their exclusive ability to participate in Fab-arm exchange (FAE). In FAE IgG4, molecules can dissociate into two halves and recombine with other half IgG4 molecules resulting in bispecific antibodies. Consequently, MuSK MG autoantibodies are functionally monovalent. The recent generation of human-derived MuSK monoclonal autoantibodies (mAbs) provides a novel opportunity to advance the understanding of MuSK-specific autoantibody development.

Objective: To gain insight into the details of MuSK MG autoantibody development.

Methods: We examined MG patient-derived monoclonal autoantibodies (mAbs), their corresponding germline-encoded unmutated common ancestors (UCA) and monovalent antigen-binding fragments (Fabs) to investigate how antigen-driven affinity maturation contributes to both binding and immunopathology. Fabs were used to emulate FAE.

Results: Mature mAbs, their UCA counterparts and Fabs derived from the mature mAbs bound to the autoantigen and demonstrated pathogenic capacity. The mature Fabs were characterized by very high affinity (sub-nanomolar), driven by a rapid on-rate and slow off-rate. Monovalent UCA Fabs bound to MuSK with approximately 100-fold lower affinity and did not have measurable pathogenic capacity. Crystal structures of two Fabs shed light on how mutations acquired during affinity maturation may contribute to increased MuSK binding affinity.

Summary/Conclusion: These collective findings indicate that the autoantigen drives autoimmunity in MuSK MG through the accumulation of somatic mutations such that monovalent IgG4 FAE autoantibodies reach a high affinity threshold required for pathogenic capacity.

Feasibility and Acceptability of Remote Monitoring of Patients with Myasthenia Gravis Using Digital Technology

A Guidon (Boston, MA), J Ouillon (Boston, MA), L Burton (Boston, MA), A Gupta (Boston, MA)

Introduction: Remote assessments of myasthenic weakness are needed for telemedicine and performance of clinical trials when face-to-face assessment is limited.

Objective: This study's objective was to determine if computer-based, remote assessments were feasible and acceptable in patients with MG.

Methods: A protocol evaluating automated techniques for decoding movement and speech abnormalities in MG was modified, when in person assessments were suspended during the COVID-19 pandemic. Adult patients with MG were recruited from Massachusetts General Hospital during telemedicine visits. Informed consent was obtained virtually. Patients completed a health questionnaire remotely plus MGADL, and other health related surveys (EQ-5D-5L, Rand SF-36, Neuro QoL Fatigue Scale) at baseline. MGADL was repeated at study conclusion. Participants received email reminders to complete weekly tasks including a speech survey (via SurveyLex Web interface) and computer mouse task (Hevelius) designed to measure dominant upper extremity movement. Speech tasks included counting to 50 and a single breath count test. Total study time was 2-2.5 hours divided over 4 weeks. Patients completed a study feedback survey at the final visit.

Results: Pilot data from 11 participants completing a computer mouse task demonstrated preliminary evidence of the task's correlation with MG severity scores and prompted this further study. In the first month of remote study activity, 4 patients have enrolled. Data collection is ongoing and will be presented.

Summary/Conclusion: A weekly, remote, digital technology-based monitoring protocol can be implemented for patients with MG. The feasibility and acceptability of the data will inform remote clinical and natural history trial development.

Covid-19 Associated Risks and Effects in Myasthenia Gravis (Care-Mg): An International Physician-Reported Registry

S Muppidi (Palo Alto, CA), R Nowak (New Haven, CT), ,S Jacob (Birmingham, United Kingdom) H Kaminski (Washington, DC), J Howard (Chapel Hill, NC), G Cutter (Birmingham, AL), H Wiendl (Münster, Germany), J Guptill (Durham, NC)

Introduction: Patients with myasthenia gravis (MG) are possibly at high risk of poor outcomes with Covid-19 due to chronic immunosuppression, respiratory muscle weakness and potential adverse events related to Covid-19 therapies.

Objective: To investigate the risks and outcomes in MG patients who develop Covid-19.

Methods: We launched a physician-reported, web-based, international database to collect information on outcomes in myasthenics with serologically confirmed or clinically determined Covid-19. We collected clinical features of MG and its treatment before Covid-19, severity of Covid-19 manifestations, specific therapies used for Covid-19, any MG exacerbation or treatment changes during Covid-19 and outcomes.

Results: A total of 36 MG patients were included at the time of interim analysis (31May2020), 88% with serologically confirmed Covid-19. Of the 36 patients (mean age 58 years), 53% were female, 86% had generalized MG, and 78% were on prior immunosuppressive therapy. Well-controlled or mild MG was reported in 83% of patients prior to Covid-19. MG worsening/crisis requiring rescue therapy (IVIG or PLEX or steroids) in the setting of Covid-19 was reported in 47% of patients. Complete recovery was reported in 17% of patients while 28% of patients died due to Covid-19. The remaining patients were either still recovering, or outcome was unknown.

Conclusion: A physician-reported database was successfully established with ongoing accrual. Firm conclusions are not yet possible from these early observations due to small sample size to date and sampling bias. This registry will provide insight into the impact of Covid-19 on MG and help mitigate and improve outcomes in future.

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Efficacy, Pk, and Pd of Nipocalimab (M281) in Adults with Generalized Myasthenia Gravis

J Guptill (Durham, NC), C Antozzi (Milano, Italy), V Bril (Toronto, Canada), J Gamez (Barecelona, Spain), S Meuth (Münster, Germany), J Muñoz Blanco (Madrid, Spain), R Nowak (New Haven, CT), D Quan (Aurora, CO), T Sevilla (Valencia, Spain), A Szczudlik (Kraków, Poland), B Hegarty (Cambridge, MA), M Jouvin (Cambridge, MA), J Jin (Cambridge, MA), S Arroyo (Cambridge, MA)

Introduction: Nipocalimab (M281) is a fully human, aglycosylated immunoglobulin (IgG1) antibody that targets neonatal Fc receptor (FcRn) IgG binding site with high affinity, thereby interfering with the binding of native IgG. Interference with FcRn function leads to IgG catabolism. In patients with generalized myasthenia gravis (gMG), nipocalimab is expected to reduce circulating IgG levels, including pathogenic autoantibodies, and ameliorate disease activity.

Methods: This is a multicenter, randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity of nipocalimab in patients with gMG who had an insufficient response to ongoing, standard of care therapy (NCT03772587). Eligible subjects were ≥18 years with gMG (MGFA Class II-IVa), positive for anti-AChR or anti-MuSK autoantibodies, and with QMG score ≥12 at baseline.
Subjects were randomized 1:1:1:1:1 to one of these groups (~12 subjects/group): Placebo once every 2 weeks or nipocalimab 5mg/kg once every 4 weeks; 30mg/kg once every 4 weeks; 60mg/kg as a single dose; or 60mg/kg every 2 weeks. Using a dose-responsive test with the doses sorted in ascending order, the study will have >80% power and experiment-wise one-sided type I error of 5% to detect a difference from placebo in MG-ADL at Day 57. Safety was assessed by adverse events and serious adverse events. Key efficacy endpoints included MG-ADL and QMG scores.
Results: 68 subjects completed the 8-week treatment period and are in follow-up. We will present key safety and efficacy results at the meeting.

Summary: Results from this study will inform optimal nipocalimab dosing regimens for future phase 3 study planning.

Treatment of Patients with Myasthenia Gravis with Efgartigimod: Results of the Phase 3 Adapt Study

J Howard (Chapel Hill, NC), T Vu (Tampa, FL), V Bril (Toronto, Canada), S Peric (Belgrade, Serbia), J Verschuuren (Leiden, Netherlands), R Mantegazza (Milan, Italy), H Murai (Narita, Japan, P Ulrichts (Boston, MA), A Guglietta (GHENT, Belgium), H de Haard (Boston, MA)
W Parys (Boston, MA), S Beydoun (Los Angeles, CA), M Pasnoor (Kansas City, KS), C Karam (Portland, OR), Sr Muppidi (Palo Alto, CA), T Bertorini (Cordova, TN), R Bhavaraju-Sanka (San Antonio, TX), Y Li (Cleveland, OH)

Introduction: Myasthenia gravis (MG) is a rare, chronic, and debilitating antibody mediated disease that lessens patients' quality of life. Current treatments are either inefficient, burdensome and/or carry frequent side effects. Efgartigimod, a human IgG1 antibody Fc-fragment, blocks FcRn which decreases recycling of IgG; thereby reducing IgG autoantibody levels.

Methods: Phase 3, randomized, double-blind, placebo controlled, global multicenter 26-week study evaluated the safety and efficacy of efgartigimod in patients with generalized MG (MG-ADL ≥ 5: ≥50% non-ocular symptoms). Participants were randomized 1:1 to receive an initial four weekly 10 mg/kg infusions of efgartigimod or placebo with subsequent treatment cycles initiated per according to clinical response, assessed by MG-ADL score. The primary endpoint was percentage of AChR-Ab + patients who were MG-ADL Responders (≥2 points improvement sustained for ≥ 4 weeks) after first treatment cycle.

Results: N = 167 patients were randomized with n=129 AChR-Ab+ and n = 38 AChR-Ab-. The primary endpoint was achieved in 67.7% AChR-Ab+ treated patients compared to 29.7% placebo patients ($p<0.0001$). When including AChR-Ab – treated patients, 67.9% were MG-ADL responders, 37.3% placebo ($p<0.0001$). Furthermore, 63.1% of AChR-Ab+ treated patients compared with 14.1% placebo patients were Quantitative Myasthenia Gravis (QMG) responders (≥3 points improvement sustained for ≥ 4 weeks) with first treatment cycle. Minimal symptom expression (MG-ADL score 0-1) was achieved in 40% AChR-Ab+ treated patients compared to 11% placebo patients. The majority of adverse events were mild and moderate with few ≥ grade 3.

Summary/Conclusion: Efgartigimod demonstrated significant efficacy in treating patients with MG with no significant safety issues.

DATA BLITZ PRESENTATIONS:

Anti-Titin Antibodies are Frequently Observed in Patients with Myasthenia Gravis who Experienced the Recurrence of Thymoma

K Kim (Seoul, Korea, South), S W Kim (Seoul, Korea, South), H Shin (Seoul, Korea, South)
S M Kim (Seoul, Korea, South)

Introduction: Myasthenia gravis (MG) is an autoimmune disease of neuromuscular junction characterized by fatigability and weakness of striated muscles. Titin is a giant filamentous striatal muscle protein and commercial test for anti-titin antibodies has become available a few years ago. Anti-titin antibody was found to be associated with thymoma and disease severity. However, not much has been elucidated regarding the clinical significance of anti-titin antibodies.

Objective: We evaluated the clinical characteristics of the patients with MG having positive result for anti-titin antibodies.

Methods: We retrospectively reviewed the medical records of the patients with MG in Severance Hospital from July 2017 to May 2020. The diagnosis of MG was based on clinical features, titer of anti-AChR antibody, and the result of repetitive nerve stimulation test. Patients were divided into the anti-titin antibody-positive group (titin + group) and anti-titin antibody-negative group (titin - group).

Results: Total 118 anti-AChR Ab-positive patients with MG were tested for anti-titin antibody during the study period:44(37.3%) patients were titin+ and 74(62.7%) patients were titin-. anti-AChR antibody titer($p<0.001$), age($p=0.003$), MGFA clinical classification($p=0.015$) and thymus finding on chest CT($p=0.002$) were significantly different between two groups. Thymoma recurrence was more frequent in the titin + group than titin – group($p=0.016$). After adjusting for the sex, age and AChR titer, positive anti-titin antibody was significantly associated with thymoma recurrence(OR=11.06,95% confidence interval,1.15-106.78,$p=0.038$).

Summary/Conclusion: The current result reveals that anti-titin autoantibodies are associated with thymoma recurrence in patients with MG. Further prospective study is required to elucidate whether anti-titin antibodies are the risk factor of the recurrence of thymoma.

Reflex Algorithm for Improving Accuracy of Myasthenia Gravis Autoantibody Testing

P Paul (Rochester, MN), S Shelly (Rochester, MN), H Bi (Rochester, MN), D Dubey (Rochester, MN), M Milone (Rochester, MN), B Crum (Rochester, MN), R Laughlin (Rochester, MN), T Liewluck (Rochester, MN), J Mandrekar (Rochester, MN), S Pittock (Rochester, MN), A Zekeridou (Rochester, MN), A McKeon (Rochester, MN), M Harper (Rochester, MN), John Mills (Rochester, MN), C Klein (Rochester, MN)

Introduction: Serologic autoantibody testing in myasthenia gravis (MG) is very helpful especially when diagnostic uncertainty remains after clinical or electrodiagnostic assessement.

Objective: To improve MG autoantibody testing

Methods: MG serological tests with confirmatory or refuting clinical-electrodiagnostic (EDX) testing and cancer evaluations were reviewed over 4-years (2012-2015). All patients had acetylcholine-receptor-binding (AChR-Bi), modulating (AChR-Mo) and striational (STR) autoantibody testing, and negatives reflexed to muscle-specific-kinase (MuSK). Thymoma and cancer occurrences were correlated with STR and reflexed glutamic-acid-decarboxylase-65 (GAD65), ganglionic-acetylcholine-receptor (alpha-3), collapsin-response-mediating-protein-5 (CRMP5), and voltage-gated-potassium-channel-complex (VGKC) autoantibodies.

Results: Of 433 tested, 133 (31%) met clinical-EDX criteria for MG. Best sensitivity (90%) occurred at AChR-Bi>0.02nmol/L, leaving 14 negative (6-ocular-MG, 7-generalized-MG, 1-MuSK-MG) with specificity 90% (31 false-positives). Using AChR-Mo antibodies (>20% loss) specificity was better (92%, 24 false-positives), however sensitivity dropped (85%). Specificity improved (95%) by testing AChR-Mo when AChR-Bi are positives, resulting in 45% reduction of false-positives (31 to 17), maintaining AChR-Bi 90% sensitivity. Cut-off values recommended by area-under-curve analysis did not outperform this approach. AChR-Bi and AChR-Mo values were significantly higher in true-positives. CT images in 121 MG revealed 16 thymomas. Historical or subsequent cancers occurred in 22. STR and reflexed autoantibodies were not more common in MG with thymoma or other cancers. Full-body CT (n=34) was performed in those with STR and reflex autoantibody positivity, but without additional cancers found.

Summary/Conclusion: Accuracy of MG serological testing is improved by reflexing AChR-Bi positive cases to AChR-Mo. STR and other reflexed cancer evaluation autoantibodies did not provide value beyond standard CT-chest imaging at the time of MG diagnosis.

Proteomic Profiling May Reveal Novel Biomarkers for Myasthenia Gravis

F Hussain (Edmonton, Canada), R Piragasam (Edmonton, Canada), H Sarkar (Edmonton, Canada), E Yacyshyn (Edmonton, Canada), C Fernandez-Patron (Edmonton, Canada), R Fahlman (Edmonton, Canada), Z Siddiqi (Edmonton, Canada)

Introduction: Myasthenia Gravis (MG) is a chronic autoimmune disorder characterized by autoantibody-mediated attack on the neuromuscular junction in voluntary muscles causing fatigable weakness. Currently, a timely diagnosis of MG is challenging, and no robust biological marker are available to follow the disease course. The discovery of such a biomarker is a major priority as it will have an enormous impact in improving MG diagnosis as well disease outcomes.

Objective: The current study is aimed to identify specific proteomic biomarkers in the sera of MG patients with diverse disease serotypes and severity.

Methods: Global proteomic profiling was adopted, and serum samples were obtained from MG (n = 31; anti-AChR+ = 27, anti-MuSk+ =1, seronegative=3) and rheumatoid arthritis (RA; n = 20) patients and healthy controls (n = 30). RA was used as a reference disease to eliminate any common humoral component primarily associated with autoimmune response.

Results: Based on ANOVA, we identified three proteins as potential biomarkers for MG with a statistical significance of $p<0.01$, were targeted for further validation. A new set of blinded samples resulted in a 100% identification rate. A cohort analysis by targeted proteomics showed that the median values for the three proteins in MG samples were at 28 to 54-fold higher than the RA samples and 250 to 4000-fold higher than the control samples.

Summary/Conclusion: Serum proteomics may potentially distinguish MG patients with a significant dynamic range. Our findings may be an important advance in disease diagnosis as identified proteins may provide a universal standard, shared among all MG serological types.

Knowledge and Perceptions of the Covid-19 Pandemic Among Patients with Myasthenia Gravis

Y Li (Durham, NC), C Emmett (Durham, NC), M Cobbaert (Durham, NC), D. Sanders (Durham, NC), V Juel (Durham, NC), L Hobson-Webb (Durham, NC), J Massey (Durham, NC), K. Gable (Hillsborough, NC), S. Raja (Durham, NC), N Gonzalez (Durham, NC), J Guptill (Durham, NC)

Introduction: Patients with myasthenia gravis (MG) may be particularly vulnerable during the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic due to risk of worsening disease during infection, potential adverse impacts of coronavirus disease 2019 (COVID-19) treatments on neuromuscular transmission, and a limited ability to fight off infection related to immunosuppressive treatments.

Objective: To understand how patients with MG are experiencing the pandemic, including where they receive relevant information, how it has affected medical care, and the measures being used to protect themselves.

Methods: This is a prospective online survey study at a large academic practice.

Results: A total of 1,413 patients with a diagnosis code for MG in the Duke Health System were approached to participate in the Research Electronic Data Capture (REDCap) survey; 75 patients completed the survey. The most frequently used sources of information were non-presidential federal government (75%), state government (57%), local healthcare provider (37%), and television news (36%). Non-presidential federal government sources (80%), local healthcare providers (55%), state government (33%) and patient organizations (29%) were considered the most trusted information sources. Thirty-three of survey responders (44%) had attended a telemedicine visit. Patients were taking recommended precautions during the pandemic and remained very concerned (69%) about COVID-19. Generalized Anxiety Disorder-7 scores were moderate-severe in 20% of responders.

Summary/Conclusion: Health care providers, the government, and patient organizations play a critical role in communicating with the MG patient community. Increased use of targeted messaging strategies by these groups may be an efficient way to convey accurate information and reduce anxiety in this patient population.

Impact of a Myasthenia Gravis Drug-Disease Interaction Clinical Decision Support Tool on Provider Prescribing

M Barra (Boston, MA), R Roberts (Boston, MA), M Ross (Newton Lower Falls, MA), R Hallisey (Boston, MA), S Hung-Anh Le (Boston, MA), P Szumita (Boston, MA), A Guidon (Boston, MA)

Introduction: Patients with myasthenia gravis are at high-risk of increased weakness when exposed to medications known to affect the neuromuscular junction.

Objective: We evaluated the success of a drug-disease electronic decision support tool on reducing prescribing of high-risk interacting medications over a 6-month period at Massachusetts General Hospital.

Methods: In 2019, real-time electronic decision support was implemented for patients ordered for a medication associated with a myasthenic exacerbation using an inherent drug-disease module. An expert panel reviewed the available drug-disease pairing and associated levels of severity to activate the alerts.

Results: In total, 395 alerts occurred in 34 unique patients over 6-months. Approximately 94.2% of alerts occurred in the inpatient setting, with 54.7% alerts during provider order entry and 45.3% during pharmacist order-verification. The most common alert occurred for beta-blockers (61.0%, of which 14.9% were for intravenous administration), followed by intravenous magnesium (22.5%), non-depolarizing neuromuscular blocking agents (9.1%), and macrolide antibiotics (4.1%). Fourteen of 47 (29.8%) unique high-risk medications patient-exposures were prevented in 34 patients. Drug-disease interactions were prevented in 100% (1/1) of patients ordered for an aminoglycoside, 100% (1/1) quinine, 75% (3/4) macrolide, 50% (1/2) fluoroquinolone, 38.5% (5/13) intravenous magnesium, and 8.7% (2/23) beta-blocker. All patients ordered for a calcium channel blocker (n=1) and non-depolarizing neuromuscular blocker (n=2) received therapy.

Summary/Conclusion: Implementation of a myasthenia gravis drug-disease interaction alert reduced overall patient exposure to potentially-harmful medications by approximately 30%. Future optimization includes enhanced provider and pharmacist education. Further refinement of alert logic criteria to optimize medication risk reduction and reduce alert fatigue is warranted.

The Duke Myasthenia Gravis Clinic Registry: Description and Demographics

D Sanders (Durham, NC), S Raja (Durham, NC), V Juel (Durham, NC), J Guptill (Durham, NC), L Hobson-Webb (Durham, NC), J Massey (Durham, NC)

Introduction: The Duke Myasthenia Gravis (MG) Clinic Registry is a disease-specific, physician-derived database containing comprehensive clinical information about patients seen in the Duke MG Clinic since 1980.

Objective: To report demographic and clinical features of Registry patients.

Methods: Data from 1,103 patients with confirmed MG who were initially seen in the Duke MG Clinic between 1980 and 2008 were reviewed. Demographics were determined for 1,060 patients who did not have MuSK antibodies (n=38) or d-penicillamine-induced MG (n=5). Not all data were available for all patients.

Results: 573 (54%) were male; 379 (66.1%) of males and 204 (41.9%) of females had symptom onset after age 50, Late-Onset MG (LOMG). Onset incidence in males peaked in the 7th decade; overall, females had no predominant onset age. Mean onset age, proportion of males and proportion with LOMG increased during the study period. 819 of 1046 (78.3%) patients had AChR-antibodies. 90 of 1060 (8.5%) had thymoma. 689 of 1049 (65.7%) had only ocular symptoms at onset; 132 remained purely ocular for at least 2 years after onset (Ocular MG - OMG) and 12 of these (9.1%) became generalized >2 years after onset.

Summary/conclusion: Data from patients seen between 1980 and 2008 in the Duke MG Clinic demonstrate the frequency of AChR antibodies, LOMG, OMG and thymoma. The median onset age, proportion of males and proportion with LOMG increased over the study period. Future reports will analyze disease subgroups, e.g., OMG, thymomatous MG, MuSK-MG, juvenile MG and seronegative MG, and the responses of these subgroups to treatment.

The Myasthenia Gravis Inebilizumab Trial (Mint): Design of Randomized, Placebo-Controlled Phase 3 Study of an Anti-Cd19 Monoclonal Antibody in Generalized Myasthenia Gravis

R Nowak (New Haven, CT), M Benatar (Miami, FL),E Ciafaloni (Rochester, NY), J Howard, (Chapel Hill, NC), M Leite (Oxford, United Kingdom), K Utsugisawa (Hanamaki, Japan), J Vissing (Copenhagen, Denmark), Y Wu (Gaithersburg, Maryland), L Abuhatzira (Gaithersburg, MD), E Katz (Gaithersburg, MD), J Ratchford (Gaithersburg, MD)

Introduction: B-cell depletion is a biologically rational therapeutic approach in myasthenia gravis (MG). Inebilizumab is a humanized monoclonal antibody that depletes CD19+ B cells. CD19 is expressed on a wider range of B cells than CD20, including on CD20-negative antibody-secreting cells (plasmablasts and some plasma cells). Targeting CD19+ B cells may be beneficial in autoantibody-mediated diseases like MG.

Objective: To determine whether depletion of CD19+ B cells with inebilizumab reduces disability and improves outcomes in patients with generalized MG.

Methods: This randomized, double-blind, placebo-controlled, parallel-group study will enroll 172 acetylcholine receptor antibody-positive (AChR-Ab+) and 80 muscle specific kinase antibody-positive (MuSK-Ab+) generalized MG patients. Patients on selected standard-of-care therapy with inadequate symptom control will be included. Participants will be randomized 1:1 to add-on inebilizumab or placebo. Patients entering the study on corticosteroids will undergo a protocol-specified corticosteroid taper. The randomized-controlled period is 12 months for AChR-Ab+ MG and 6 months for MuSK-Ab+ MG, followed by an optional, 18-month, open-label period. The primary endpoint is change in MG Activities of Daily Living score between baseline and end of the randomized-controlled period. Secondary endpoints include safety, time to first exacerbation, Patient Global Impression of Change, and changes in Quantitative MG, MG Composite, and MG Quality of Life-15r scores.

Results: Study background, rationale, and design will be presented.

Summary/Conclusion: This study (MINT) will determine whether anti-CD19 directed therapy with inebilizumab, targeting a broad population of B cells including those producing autoantibodies, is beneficial and safe in AChR-Ab+ and MuSK-Ab+ MG. Enrollment will begin in 2020.

Two-Year Post-Marketing Safety Experience of Eculizumab in Patients with Generalized Myasthenia Gravis in the United States

S Muley (Phoenix, AZ), S Muppidi (Palo Alto, CA), T Levine (Phoenix, AZ), E Rodrigues (Boston, MA), C Carrillo-Infante (Boston, MA), J Howard (Chapel Hill, NC)

Introduction: Eculizumab was approved in 2017 by the US FDA for the treatment of acetylcholine receptor antibody-positive generalized myasthenia gravis (gMG), based on data from the phase 3 REGAIN trial.

Objective/methods: This analysis of post-marketing pharmacovigilance surveillance data describes the most common healthcare provider (HCP)-confirmed adverse events (AEs) and HCP-confirmed infection events in patients with gMG receiving eculizumab in the US following eculizumab approval (October 23, 2017) through February 29, 2020.

Results: As of February 29, 2020, cumulative exposure to eculizumab in patients with gMG in the US was 1933 patient-years. Of 8188 AEs reported, 1404 (17.1%) were confirmed by healthcare providers, comprising 485 (34.5%) serious and 919 (65.4%) non-serious AEs. The most common AEs reported included drug ineffectiveness (3.5%), hospitalization unspecified (2.9%), fatigue (2.8%), condition aggravated (unspecified worsening of an underlying condition) (2.5%), headache (2.2%) and dyspnea (2.1%). Of 130 infections that were reported, 80 (61.5%) were serious (e.g. requiring hospitalization), at a rate of 4.4 serious infections per 100 patient-years. The most common serious infections were urinary tract infections (12.5%), pneumonia (11.3%), sepsis (10.0%), cellulitis (8.8%), osteomyelitis (6.3%) and unspecified infections (6.3%). There was one report of meningococcal meningitis (cumulative reporting rate, 0.05 per 100 patient-years), from which the patient recovered with antibiotic treatment.

Summary/conclusion: Based on 2 years of post-marketing pharmacovigilance surveillance data, the observed safety profile of eculizumab in patients with gMG was consistent with that reported in clinical trials, and with the established long-term safety profile of eculizumab in other indications.

Muscle-Specific Tyrosine Kinase Chimeric Autoantibody Receptor T Cells (Musk-Caart) As A Precision Cellular Immunotherapy for Antigen-Specific B Cell Depletion in Musk Myasthenia Gravis (Mg)

S Oh (Philadelphia, PA), K O'Connor (New Haven, CT), A Payne (Philadelphia, Pennsylvania)

Introduction: Myasthenia gravis (MG) is a potentially life-threatening autoimmune disease caused by autoantibody-producing B cells that target neuromuscular junction proteins. Standard of care for MuSK MG, a subset representing 6-7.5% of total MG patients, involves chronic broad immunosuppression, highlighting the need for more targeted therapies that avoid risk of serious infections while inducing durable disease remissions. Recently, we developed a novel gene-engineered cellular immunotherapy for antigen-specific B cell depletion using MuSK chimeric autoantibody receptor T cells (MuSK-CAART). MuSK CAAR, consisting of MuSK extracellular domain and CD137/CD3-zeta cytoplasmic domains, directs human T cells to specifically lyse autoreactive B cells expressing anti-MuSK B cell receptors.

Objective: To investigate the preclinical efficacy and safety of MuSK CAAR T cells.

Methods: Specific cytolysis of anti-MuSK B cells was investigated using luciferase cytotoxicity assays and anti-MuSK Nalm6 xenograft models. Potential off-target toxicity was evaluated by high-throughput membrane proteome array and in vitro cytotoxicity and cytokine assays.

Results: MuSK-CAART demonstrated specific lysis of B cells targeting different MuSK epitopes with varying affinities. Bioluminescence imaging confirmed cytotoxicity toward anti-MuSK B cells in vivo. Specific toxicity was not observed against U87MG cells expressing LRP4, a MuSK cis-interacting protein. Furthermore, screening arrays of 5300+ human membrane proteins with soluble MuSK-CAAR ectodomain did not identify productive off-target interactions.

Summary/Conclusion: These studies establish the preclinical feasibility of MuSK-CAART for precision cellular immunotherapy of MuSK MG. Given the remarkable remissions of B cell-mediated cancers with chimeric antigen receptor T cells, MuSK CAAR T cells offer the potential for durable remissions of B cell-mediated autoimmunity in MuSK MG.

POSTER PRESENTATIONS:

Overlap Paraneoplastic Syndrome: Thymoma Presenting as Myasthenia Gravis and Immune Mediated Myopathy - A Case Series

M Cuchanski (Fairport, NY), M Band (Danville, PA), J Avila (Danville, PA)

Introduction: Concurrent immune mediated myopathy (IMM) and myasthenia gravis (MG) associated with thymoma is rare. We report two cases and propose a treatment approach.

Objective: To describe two patients with thymoma presenting as IMM and MG.

Methods: Case series and review of the literature.

Results: Case 1: A 79-year old woman presented with dysphagia and generalized weakness. Exam demonstrated distal greater than proximal arm weakness and proximal leg weakness. Chest CT revealed a thymoma. Creatine Kinase (CK) was elevated at 1127 U/L. Acetylcholine receptor (AChR) antibody was positive. Muscle biopsy showed an inflammatory myopathy. She was treated with a 5-day course of high dose steroids followed by an oral taper and monthly intravenous immunoglobulin (IVIG) infusions with improvement.
Case 2: A 56-year old woman developed generalized weakness and proximal limb myalgias. Exam demonstrated left Horner syndrome and proximal greater than distal limb weakness. Chest CT revealed an invasive thymoma. Muscle MRI demonstrated diffuse edema in the bilateral thighs. CK was elevated at 3434 U/L. Myositis antibody panel was negative. AChR antibody was positive. Muscle biopsy revealed necrotic fibers and lymphocytic infiltrates. She was treated with a 3-day course of high dose steroids with an oral taper and IVIG infusions twice monthly with improvement.

Summary/Conclusion: Immunosuppression strategies are complicated in the setting of malignancy. No standardized guidelines for management exist at this time. The combination of steroids and IVIG may be a reasonable approach in patients with MG and co-existing paraneoplastic myositis, particularly when tumor resection needs to be delayed.

Follow-Up Care in Myasthenia Gravis During Covid-19: Comparison of Telemedicine and In-Person Encounters

C Farmakidis (Prairie Village, KS), S Hunt (Kansas City, Kansas), M Pasnoor (Kansas City, KS), O Jawdat (Lenexa, KS), D Jabari (Overland Park, KS), R Barohn (Kansas City, KS), M Dimachkie (Kansas City, KS)

Introduction: While more studied in amyotrophic lateral sclerosis, telemedicine may also have a role in myasthenia gravis (MG) care.

Objective: Compare videoconferencing (ZM), telephone (TEL) and in-person (PER) MG follow-up encounters for patient characteristics, MG examination and clinical decision-making.

Methods: This is a retrospective study of MG follow-up encounters conducted between March 16 and June 2, 2020 at a tertiary neuromuscular clinic.

Results: Ninety-four encounters were evaluated (46% ZM, 30% TEL and 24% PER). A Kruskal Wallis test was used to determine if differences between groups were statistically significant. Differences in patient age and distance from clinic do not appear to be significant. However MG-ADL scores appear to be statistically different [ZM median 3.6 IQR=(1,3), TEL median 2.8 IQR=(1,4), PER median 5 IQR=(3,9) p=0.02]. Both encounter duration in minutes [ZM mean 24.3, TEL mean 22.8, PER mean 31.5 p<0.01] and MG-specific physical exam content regions [ZM mean 2.4, TEL mean 1.1, PER mean 3 p<0.01] differences appeared to be statistically significant. However, the number of medical actions at the conclusion of each encounter type did not appear to be significantly different [ZM median 3 IQR=(2,3), TEL median 2.5 IQR=(2,3), PER median 3 IQR=(2,4) p=0.34].

Conclusion: MG telehealth follow-up encounters appeared feasible and occurred without respect to age and distance from clinic, while patients with higher MG-ADL scores appeared more likely to be evaluated in person. While duration and exam content appear to differ between ZM, TEL and PER encounters, quantity of clinical decision-making remained similar. Encounter review is ongoing.

Validation of a Surface Plasmon Resonance Assay for the Diagnostic Detection and Characterization of Muscle-Specific Tyrosine Kinase (MuSK) Antibodies in Myasthenia Gravis Patients

E Gibbs (Vancouver, Canada), H Frykman (Vancouver, Canada)

Introduction: MuSK MG is diagnosed by the detection of serum MuSK antibodies using a radioimmunoprecipitation assay (RIPA). Due to the use of radioactive labels in RIPA, novel label-free assays are attractive alternatives in clinical laboratory diagnoses. SPR is a biosensor platform that detects real-time biomolecular interactions without radio- or enzyme- labels. The resultant sensorgrams provide information on active concentration, affinity, equilibrium constants, stoichiometry and binding specificity. As it does not involve washing steps, Biacore™ is an optimal analytical platform for detecting both high and low affinity antibodies, although the clinical relevance of low affinity antibodies is not well understood.

Objective: To validate a surface plasmon resonance-based (SPR) assay for detecting anti-MuSK Ab in serum in the diagnosis of myasthenia gravis (MG)

Methods: The SPR assay was validated with 41 samples to establish sensitivity, specificity, accuracy, recovery and interference. We cross-validated and verified the assay using 80 blinded samples from Oxford University assayed by RIPA.

Results: Analytical sensitivity, specificity and accuracy were determined to be 100%, 94% and 95%, respectively. No interference in positive serum samples spiked with hemoglobulin and lipid emulsion (1 – 6mg/ml) was observed while there was dose-dependent interference with high concentrations of bilirubin (> 5mg/ml). Among the 80 blinded samples, 20 tested positive and 50 negative for both SPR and RIPA. Ten samples tested SPR positive but RIPA negative. Further SPR inhibition and antibody isotyping analyses of discrepant samples demonstrated that they are true positives.

Summary/Conclusion: The SPR assay has attractive diagnostic attributes for detection and characterization of anti-MuSK antibodies in MG.

Characteristics and Outcomes of Myasthenia Gravis Patients with Covid-19 – A Case Series

P Kwon (Brooklyn, NY), A Granger (Brooklyn, NY), E Zakin (New York, NY)

Introduction: Myasthenic crisis is most commonly precipitated by infection and carries a mortality rate of about 4%. In patients with respiratory failure secondary to infection with the novel coronavirus, the mortality rate is estimated to be between 10-24%. The effect that COVID-19 has on patients with myasthenia gravis and the characteristics that affect outcome require further investigation.

Objective: To investigate the effect of SARS-CoV-2 infection in patients with myasthenia gravis.

Methods: Retrospective analysis of seven patients with Myasthenia Gravis infected with SARS-CoV-2.

Results: Of the seven patients, baseline neurologic exam, comorbidities and medication regimen prior to infection with SARS-CoV-2 did not appear to affect the probability of requiring admission or mortality. Five of the seven patients required hospitalization. Two of the five hospitalized patients expired, and both had the longest disease duration of the group (mean=9 years). Respiratory failure was the cause of clinical decompensation. Higher inflammatory markers and lower absolute lymphocyte counts were found on serologic studies of those two patients. Two of the five hospitalized patients received a dose of a monoclonal antibody against interleukin-6 (i.e. tocilizumab) and had marked improvement in their clinical course, ultimately discharged at their baseline neurologic status.

Summary/Conclusion: Though our case series is limited to only seven patients, it provides insight into the clinical characteristics and outcomes of patients with myasthenia gravis who were infected with SARS-CoV-2. The management of immunosuppression in this patient population is challenging. It merits larger scale investigations to delineate specific guidelines and establish factors that affect clinical outcome in this specific patient population.

Myasthenia Gravis Population at Uconn Health: A Single Center Profile Analysis Comparing Patient Epidemiology and IVIg Treatment Requirements

A Healy (Farmington, CT), M Imperioli (Southbury, CT)

Introduction: Myasthenia Gravis (MG) is an immune mediated disorder of the neuromuscular junction and classically thought to be a disease of young females and older males. IVIg is used as both rescue and maintenance therapy.

Objective: We aim to study the epidemiology of our patients and correlate these trends with IVIg usage.

Methods: Single site profile analysis, retrospective chart review of patients age 18 and older diagnosed with MG, seen at UConn Health between 2005-2019.

Results: UConn Health treated 209 MG patients between 2005-2019. 55.5% were female, 82.5% white, and 71.0% non-Hispanic or Latino. Average age of onset was 59 years old. Early onset MG (<50 years old) consisted of 78.95% female, late onset MG (>50 years old) consisted of 35.71% female and very late onset MG (>65 years old) consisted of 54.54% female. Of our patient population, 37 (17.7%) patients required IVIg; 56.7% for acute exacerbations only, while 18.9% required maintenance therapy only. The IVIg treatment group consisted of a greater proportion of patients with very late onset MG, 51.4% versus the general MG population, which consisted of 36.8%. Similarly, the IVIg treatment group also consisted of a higher percentage of antibody positive status patients, 67.57% AchR+ versus 62.21% respectively.

Summary/Conclusion: In our patient population, early onset MG was predominantly female, late onset MG was slightly male predominant and very late onset MG was female predominant. Approximately 20% of our patients required maintenance IVIg. This group was comprised largely of very late onset and acetylcholine receptor antibody positive patients.

A Novel Diagnostic Method for Myasthenia Gravis

G Kocak (Istanbul, Turkey), B Dolek (Istanbul, Turkey), M Tutuncu (Istanbul, Turkey), M Oren (Istanbul, Turkey), E Kara (Istanbul, Turkey), M Yener (Istanbul, Turkey), A Atas (Istanbul, Turkey), N Adatepe (Istanbul, Turkey)

Introduction: Videonystagmography (VNG) which directly records eye movements using infrared video goggles with mini-cameras, is used to measure involuntary eye movements called nystagmus.

Objective: To explore whether VNG can be used to detect a decrement in the extraocular muscle (EOM) activity of patients with myasthenia gravis (MG).

Methods: Thirty-four patients with MG, including 13 with ocular and 21 with generalized MG and 23 healthy controls participated. Using VNG we recorded the velocity of the eye movements of the patients as they followed a moving target. We then calculated the gain by dividing the eye movement velocity (degrees/second) by the target velocity (degrees/second).

Results: In MG subjects, the mean initial gain (maximum gain) was 1,23 ± 0,31d/s(range:0,63-2,15) for the right eye and 1,22 ± 0,37d/s(range;0,60-2,28) for the left eye. The mean minimum gain was 0,11 ± 0,12d/s(0,01-0,58) for the right and 0,14 ± 0,5d/s(0,02-0,55) for the left. Due to fatigue, the movement gain was reduced by 91.7% in the right and 88.2% in the left. The decrement begun to improve within 1,08± 0,52(0,3-2,4) seconds for the right and 1,49± 0,85(0,4-3,6) seconds for the left. After the decrement, the minimum gain peak is obtained once again. There was no decrement in fatigue in healthy subjects.

Summary/Conclusion: Our study documents a decrement in EOM activity recorded by VNG in patients with MG which begins to improve within one to two seconds, analogous to traditional low-frequency repetitive nerve stimulation testing and its U-shaped pattern. Thus, VNG can be a promising diagnostic tool for MG.

Determination of Complement Activation in Myasthenia Gravis: A Pilot Study

I Lee (Birmingham, AL), W Cao (Kansas City, KS), B Guillory (Birmingham, AL), C Schwartzlow (Birmingham, AL), X Zheng (Kansas City, KS)

Objective: Complement plays major role in pathogenesis of acetylcholine receptor antibody positive (AChR-Ab+) myasthenia gravis (MG). We explored whether measurement of soluble complement products would serve as a biomarker for disease severity and treatment response.

Methods: Adult AChR-Ab+ MG patients were recruited. Demographics and disease related history were reviewed. Blood samples were obtained, and disease severity was documented at enrollment and follow up. Plasma sC5b-9, iC3b and C4d in these patients were measured by using commercial ELISA kits and compared to those in the healthy controls.

Results: Seven total MG patients were recruited thus far. The mean age was 63 and 57% male. MGFA class at enrollment was I (14%), IIa (28%), IIIa (28%) and V (28%). Current treatments at enrollment included pyridostigmine (71%), prednisone (43%), mycophenolate mofetil (14%), eculizumab (14%), and IVIG (14%). Ten blood samples were obtained, two patients had three and two samples respectively during plasma exchange treatment. The mean levels (standard deviation) of plasma sC5b-9, iC3b and C4d levels were 396.3ng/mL (272.3), 7.8ng/mL (4.2), and 1.4ng/mL (0.7) respectively. Only one patient who was in MG crisis and prednisone naïve had elevated sC5b-9 level. Details of the patient who had elevated sC5b-9 level will be presented. iC3b and C4d measurements were all within normal reference range.

Conclusion: Further study is needed to determine the utility of plasma sC5b-9. This pilot study, however, did not provide a signal that iC3b and C4d might serve as useful biomarkers in MG.

Rapidly reversible tongue atrophy in Seronegative Myasthenia Gravis following treatment

J Massey (Durham. NC)

Introduction: Tongue atrophy in MuSK+ and ACHR+ myasthenia gravis is known (photos). However, rapid resolution has not been reported and is documented in this patient after 5 weeks of therapy.

Objective: describe seronegative myasthenia gravis patient with rapidly reversible tongue atrophy.

Results: A 61-year old male developed a subacute progressive respiratory difficulty leading to a hypercapneic respiratory failure requiring intubation. By history at presentation he had experienced gradual loss of stamina, difficulty chewing, dysarthria, episodes of dysphagia and progressive weakness in all extremities over the previous year. He remained ambulatory. Presumptive diagnosis at presentation was amyotrophic lateral sclerosis. On examination after extubation, he was diffusely weak, normal reflexic with normal tone and sensory exam was intact. There was mild bilateral ptosis and extraocular muscle weakness. There was marked dysarthria and severe tongue atrophy. (Photo). Electromyography demonstrated widespread fibrillations but normal motor unit potential morphology including the tongue. SFEMG of his tongue demonstrated increased jitter with blocking. AChR antibodies and MuSK antibodies were negative. He underwent treatment with plasmapheresis (PLEX) and high dose daily prednisone with improvement of his weakness, dysarthria, and dysphagia. At 5 weeks following PLEX along with daily prednisone, his tongue was markedly improved with bulk, strength, and function (photo).

CONCLUSION: Tongue atrophy often suggests motor neuron disease. In this case, clinical profile suggested myasthenia gravis. Rapid reversal of tongue atrophy with treatment in Myasthenia Gravis is unique and promising for selected individuals.

Familial Musk Myasthenia Gravis

J Massey (Durham, NC), E W Massey (Durham, NC)

Introduction: There are several reports of AChR + Familial Myasthenia Gravis (Honeybourne at al.1982; Chin et al.1985 and Evoli et al. 1995) Two patients with myasthenia gravis or autoimmune conditions. No MuSK+ cases have been reported.

Objective: Describe two siblings with MuSK+ Myasthenia Gravis

Results: Case-1: A 34-year old right-handed African American female developed intermittent horizontal diplopia followed by weekly recurrent gasping for air and choking while eating. Episodes resolved after 1-2 minutes. Initial diagnosis was asthma, but inhaler gave no relief. About 16 months later, AChR antibody panel was negative. With continued episodes, MuSK antibody panel was positive at 1:2560. Over 6 months, she further noted dysphagia, facial weakness, and persistent diplopia. Occasionally, when drinking liquids, fluid came out her nose. She developed neck and extremity weakness worse at end of day. Trapezius 3 HZ repetitive nerve stimulation (RNS) demonstrated a 14% decrement. Chest CT was negative for thymoma but showed a small thyroid nodule. She improved with initiation of prednisone 30 mg daily and Mestinon 60 mg daily. After several months, trapezius RNS demonstrated a 13.4% decrement and post activation exhaustion of 18.6%. MMT was 26 and plasmapheresis produced resolution of symptoms at 1-month follow-up. CellCept 1000 mg BID was added and prednisone 60 daily continued with stable improvement. Case-2: A year prior to symptom onset of Case 1, her brother, a 31-year old right-handed male, developed similar episodic weakness including symptoms of fatigue late in the day. Workup yielded a negative AChR antibody panel; however, MuSK antibody panel was positive. His diagnosis and response to therapy led to the evaluation and treatment for his sister later that year. He is stable by history and medical record review from another location.

Conclusion: We describe two siblings with AChR antibody negative but MuSK+ myasthenia gravis, which has not previously been reported.

Variability of Complement Levels in a Spectrum of Myasthenia Gravis Patients

D Post (Stanford, CA), A Habib (Irvine, CA), N Goyal (Irvine, CA), P Shieh (Los Angeles, CA), S Muppidi (Palo Alto, CA)

Introduction: Complement mediated destruction at the neuromuscular junction is seen in myasthenia gravis (MG) and prevention of terminal complement formation has been shown to improve MG symptom burden. This raises the important question of whether terminal complement levels could serve as a biomarker of MG disease activity.

Objective: To measure serum terminal complement levels in a wide spectrum of MG patients.

Methods: We measured C5a and C5b-C9 levels in a wide range of acetylcholine receptor antibody positive MG patients. We also obtained MG specific data including MG-ADL, MG COMPOSITE, MGFA status, and current immunotherapy.

Results: To date, we collected serum C5a and C5b-C9 in 10 patients. Mean age was 57.6 years (SD 18). MGFA status was 2a/b in 8 patients and class 3a/b in 2 patients. Duration of MG ranged from 1 to 40 years. Three patients had thymectomy and one patient has thymoma. Six patients were on prednisone at the time of evaluation and 5 were on additional oral immunosuppressive agents. Mean MG-ADL was 3.9 (SD 2.8) and MG composite 6.2 (SD 4.7). C5a level was high in 1 patient, and C5b-C9 level was elevated in 3 patients. At the time of testing 3 patients were on eculizumab; 2 of these patients had elevated complement levels.

Conclusions: Complement levels were highly variable in our cohort and did not appear to be a reliable marker of MG disease activity. Larger prospective studies are needed to evaluate whether complement levels can be useful in the management of MG patients.

Acetylcholine Receptor (AChR) Antibody Overshoot Following Plasmapheresis Associated with Clinical Deterioration of Myasthenia Gravis

D Richards (Cleveland, OH), J Ching (Los Angeles, CA), R Lewis (Los Angeles, CA), Y Li (Cleveland, OH)

Introduction: Plasma exchange is effective in the treatment of severe generalized myasthenia gravis (MG), presumably by removing AChR antibodies from the circulation. However, rebounding antibody synthesis, which may occur due to removal of regulators of antibody production, has not been well characterized.

Objective: To report rebound/overshoot of serum AChR antibody titers following plasmapheresis treatment in five MG patients and describe corresponding exacerbations of clinical symptoms.

Methods: Retrospective chart review.

Results: Five patients with generalized MG were included. Three were males. Two had thymoma. The median age at time of MG diagnosis was 64 (38-74) years old and the median duration of MG was 1 (1-7) year. Baseline median AChR antibody titers prior to plasmapheresis was 30.8 (9.2-39.5) nM, and the median maximal AChR antibody titer following plasmapheresis was 158 (133.1-272) nM. AChR antibody overshoot occurred within 1 to 6 months following plasmapheresis. In 4 patients, antibody overshoot was not preceded by a reduction of immunotherapy. In 4 patients, AChR antibody overshoot was associated with the occurrence of myasthenic crisis or impending crisis.

Summary/conclusion: Plasmapheresis may cause clinically relevant AChR antibody overshoot in MG patients; thus, the use of other immunotherapy is essential in preventing a rebound of MG symptoms.

Real-World Experience of Eculizumab for Myasthenia Gravis

J Suh (Boston, MA), V Clarke (Boston, MA), A Guidon (Boston, MA)

Introduction: Clinical trials demonstrated efficacy and tolerability of eculizumab for myasthenia gravis (MG). Published real-world experience is limited.

Objective: To review characteristics and outcomes of patients receiving eculizumab for acetylcholine receptor antibody-positive generalized MG since January 2019 at a single institution's MG clinic.

Methods: Retrospective chart-review.

Results: 5/9 patients were female. At eculizumab initiation, mean age was 52 years (range 21-77). Mean disease duration was 7 years (range 0.16-18). MGFA severity class was IIa/b (3 patients), IIIa/b (4) and IVa/b (2). Three patients had undergone thymectomy for thymoma. A mean of 3.2 immunomodulatory therapies (including steroids, maintenance IVIG, and maintenance therapeutic plasma exchange (TPE)) had been used per patient. Six patients were receiving maintenance IVIG or TPE at eculizumab initiation. 8/9 had refractory MG.

Mean follow-up was 6.9 months. MGFA severity class improved compared to eculizumab initiation in 44% at 1 month and in 67% by last follow-up. Mean prednisone dose was 17.8mg/day at initiation, 15.9mg/day at 3 months and 13.6mg/day at 6 months. 6/6 discontinued maintenance IVIG/TPE and 3/9 partially weaned nonsteroidal oral immunotherapy during follow-up.

Six patients reported ≥1 of these possibly related adverse event(s): musculoskeletal, gastrointestinal symptoms, headache. One reported mild pruritus during an infusion. No meningococcal infections or eculizumab discontinuations occurred.

Summary/Conclusion:
Eculizumab was reasonably tolerated and resulted in improved MGFA class in two-thirds of patients. All patients on maintenance IVIG/TPE were able to discontinue these therapies. Prednisone wean was modest, and oral immunotherapy taper occurred in one-third of patients. Longer follow-up of a larger cohort is needed.

MuSK Mutation in an Anti-Acetylcholine Receptor and Musk Antibody Negative Patient

N Suresh (Riverview, FL), J Farias (Tampa, FL), C Gooch (Tampa, FL), T Vu (Tampa, FL)

Introduction: We report a patient diagnosed with double seronegative MG whose subsequent testing revealed a MuSK genetic mutation.

Case Report: A 38-year old man presented with 5 years of progressive weakness in proximal limb muscles, intermittent heaviness of eyelids, chronic respiratory insufficiency, and severe exercise intolerance. Anti-acetylcholine receptor and MuSK antibodies were absent. Repetitive stimulation and single-fiber EMG showed no neuromuscular transmission defect. Myopathic units in the deltoids were noted on EMG. Nevertheless, he had a good response to pyridostigmine and was symptomatically palliated with plasma exchange, prednisone 15 mg daily, and azathioprine 50 mg daily. Withdrawal of immunotherapy resulted in severe exacerbation of symptoms. Subsequent genetic sequencing identified variants of unclear significance in the ATP2A1 and TRAPPC11 genes and a pathogenic mutation associated with 3 tandem repeats of exons 4-8 within the MuSK gene, likely resulting in absent or disrupted protein. This specific variant, though not reported in the literature, was thought to be pathogenic.

Summary/Conclusion: MuSK gene mutations have been reported in fewer than 40 patients and 8 families worldwide. In seronegative MG, it is important to recognize that mutations in genes encoding proteins involving in neuromuscular transmission may cause symptoms similar to autoimmune MG.

Performance of Different Criteria for Refractory Myasthenia Gravis

C Tran (Scarborough, Canada), A Biswas (Toronto, Canada), M Mendoza (Toronto, Canada) H Katzberg (Toronto, Canada), H Katzberg (Toronto, Canada), V Bril (Toronto, Canada), C Barnett-Tapia (Toronto, Canada)

Introduction: Defining refractory myasthenia gravis is important, as this can drive clinical decision-making, for example, by escalating treatments in refractory individuals. There are several definitions of refractory myasthenia and their performance has not been compared. Having valid and reliable criteria can help select patients in whom more aggressive treatments may be needed.

Objective: To compare the different criteria for refractory MG and compare measures of disease severity and quality of life(QoL) across these patients.

Methods: We applied 5 different refractory myasthenia criteria (Drachman, Mantegazza, Suh, the International Consensus Guideline (ICG), and the REGAIN study) to a cohort of 237 patients. We compared the proportion of refractory patients among different criteria, and the scores on disease severity, fatigue, and QoL scales.

Results: The ICG and REGAIN criteria were more conservative, with a refractory diagnosis in 9.7% and 3.0% of patients, respectively. The Drachman, Mantegazza, and Suh criteria resulted in high proportions of refractory individuals (40.1%, 39.2% and 38.8%, respectively). Refractory patients by the ICG and REGAIN criteria had worse disease severity, QoL and fatigue scores, compared to patients classified as refractory by other criteria. All criteria had high agreement between raters (between 70% and 100%).

Summary/Conclusion: The proportion of refractory MG patients depends on the criteria used. The ICG and REGAIN criteria are more stringent and also reflect patients with worse disease severity and QoL, compared with more lenient criteria. Therefore, we recommend using either the ICG or REGAIN criteria in future studies, with the ICG criteria perhaps being the most robust.

A Case of Musk Myasthenia Gravis Presenting with Isolated Respiratory Insufficiency

C Tsai (Chapel Hill, NC, A Mehrabyan (Chapel Hill, NC)

Introduction: MuSK antibody positivity is seen in 1-4% of patients with myasthenia gravis (MG). 40% of patients report bulbar weakness as the manifesting symptom, commonly associated with neck and respiratory muscle involvement.

Objective: We present a case of a MuSK-MG with the only presenting symptom of progressive respiratory insufficiency.

Methods: A 40 year old female developed dyspnea on exertion and orthopnea, which progressed over a year necessitating BiPAP use for 16-24 hours daily. She was extensively evaluated and treated for cardiac and pulmonary conditions, but unresponsive to treatments and thus referred to neurology.

Results: Neurological exam revealed mild weakness of the neck and proximal arm muscles. Initial work up was directed toward evaluation of myopathies, autoimmune and genetic. Laboratory testing was negative for facioscapulohumeral dystrophy 1 and 2, with normal CK, myositis panel, and comprehensive neuromuscular panel. EMG was unrevealing for neuropathic or myopathic findings. Muscle biopsy demonstrated type 2 fiber atrophy. Acetylcholine receptor binding and modulating antibodies were in a normal range. At this point MuSK antibodies were obtained and were positive. Single fiber EMG was consistent with postsynaptic neuromuscular junction dysfunction. She was treated with prednisone and plasma exchange with resolution of neck and proximal arm muscle weakness and requiring BiPAP only at night.

Summary/Conclusion: MuSK antibody positive MG can present with isolated progressive respiratory muscle weakness and can be easily misdiagnosed with primary respiratory or cardiac disease. High index of suspicion should be maintained when these patients are referred for evaluation of neurological causes of dyspnea.

Efficacy of Eculizumab in Myasthenia-Gravis-Foundation-of-America (MGFA) Grade-V Myasthenia Gravis

U Usman (New Haven, CT), C Chrisman (Phoenix, AZ), D Houston (Phoenix, AZ), C Chow (Phoenix, AZ), N Reddy (Columbus, Ohio), S Muley (Phoenix, AZ)

Introduction: Eculizumab has been shown to be efficacious in Acetylcholine-receptor (AChR)-antibody positive, Myasthenia-gravis-foundation-of-America-(MGFA) grade-II-IV myasthenia-gravis (MG) patients. However, it has not been studied in MGFA grade-V MG patients.

Objective/Method: We present 3-seropositive, generalized-MG(gMG) patients with myasthenic-crisis, refractory to multiple immunotherapies, including Rituximab (in one-case),who were treated with Eculizumab, demonstrating its role in MGFA(Grade-V) MG.

Results: Case-1: 21-year-old post-partum woman with poorly-controlled gMG, who was intubated 4-days after delivery for worsening myasthenic-symptoms. She remained refractory to prednisone, plasmapheresis (PLEX), IVIG and Rituximab. Eculizumab was started 2-months after Rituximab, displaying sustained improvement. She was extubated 3 days after Eculizumab. MGC (MG Composite)-score improved from 21 to 0 after 4-weeks of Eculizumab. Case-2: 77-year-old man, with 2-week history of worsening myasthenic-symptoms, requiring ventilator support. He remained refractory to prednisone, PLEX, IVIg, requiring tracheostomy and feeding tubes. He received Eculizumab on day 23, showing marked improvement and was transitioned to trach collar the next day and subsequently extubated. MGC-score improved from 36 to 9 after 6-weeks of receiving Eculizumab. Case-3: 56-year-old man, who presented with 2-week history of myasthenic-crises after pneumonia, requiring ventilatory support. He didn't tolerate steroids and CellCept and remained refractory to IVIg, PLEX, showing partial response to Eculizumab and was able to be weaned off to trach collar, requiring positive pressure ventilatory support. MGC-score improved from 48 to 32, 3-weeks after eculizumab.

Conclusion: Overall, these cases suggest spectrum of Eculizumab effectiveness in variety of myasthenic patients with its potential benefit in advanced refractory cases. Further studies are necessary in order to obtain evidence-based guidelines in clinical practice.

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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 Registry is managed by the Coordinating Center of the University of Alabama at Birmingham (UAB) with oversight by the MGFA Patient Registry Committee.

The MG Patient Registry is:

- For myasthenia gravis research
- Participant-driven
- Free to enroll
- Confidential
- Open to Adults 18+ in the U.S.

What types of questions are in the enrollment survey?

- General contact information
- Demographic information, for example, education, employment status, income, insurance
- Year, month, and place of birth of parents and grandparents
- Information on places where 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

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Partners in MG Care is a program that recognizes and supports quality MG care.

The *Partners in MG Care* program is designed to:

- Create a network of quality MG healthcare providers for patients
- Strengthen healthcare provider connections through information, services and support for MG patients and caregivers
- Empower MG patients with a robust resource of healthcare providers and support
- Enhance knowledge-sharing, professional education and networking opportunities about MG for healthcare providers

***Partners in MG Care* Approach:**

- *Partners in MG Care* have interest in treating MG patients, experience treating MG, involvement in MG community, ability to refer patients to MGFA as well as promote and support MGFA activities.
- A *Partner in MG Care* receives a recognition certificate and is publicly acknowledged on the MGFA website. Information about their practice will be shared with local MG patients seeking referrals. MGFA will provide literature, information about educational opportunities, research and advocacy updates, clinical trial notifications, and other important information to participants of the program. *Partners* are also invited to be a part of the MG Clinical Network.

How to Get Started:

- The *Partners in MG Care* program launched in fall 2017. Current M/SAB members who are U.S.-based and seeking patients will be invited to become a *Partner in MG Care* and asked to complete an agreement and information form.

To learn more about how to become a *Partner in MG Care*, please contact us at: MGFA@myasthenia.org

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