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ABSTRACT

MUS MGFA Abstracts

EFFICACY OF RAVULIZUMAB TREATMENT ACCORDING TO TIME FROM DIAGNOSIS IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS: A POST HOC SUBGROUP ANALYSIS OF THE CHAMPION MG STUDY

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Introduction: The 26-week, phase 3, randomized, double-blind, placebo-controlled CHAMPION MG study (NCT03920293) demonstrated the efficacy and tolerability of the terminal complement C5 inhibitor ravulizumab, administered every 8 weeks, in patients with anti-acetylcholine receptor antibody-positive (AChR Ab+) generalized myasthenia gravis (gMG). A post hoc analysis was performed of responses according to time from MG diagnosis.

Methods: Enrolled patients with Myasthenia Gravis-Activities of Daily Living (MG-ADL) or Quantitative Myasthenia Gravis (QMG) assessments at baseline and Week 26 were included in the analyses. Mean changes from baseline to Week 26 in MG-ADL and QMG total scores were assessed in ravulizumab- and placebo-treated patient subgroups according to time from MG diagnosis to study start (date of informed consent).

Results: Analyses of MG-ADL and QMG scores included 160 and 154 patients, respectively. Mean (standard deviation) changes from baseline to Week 26 in MG-ADL total score by time from diagnosis (≤2, >2-≤5, >5-≤10, >10 years) for ravulizumab were -4.6 (3.6), -3.5 (3.0), -2.3 (3.6), -2.9 (2.8), respectively; and for placebo were -1.7 (3.4), -1.8 (3.0), -0.8 (4.0), -1.6 (2.6), respectively. Corresponding data for QMG total score in ravulizumab- and placebo-treated patient subgroups showed similar patterns of response.

Conclusion: A trend was observed toward greater reduction from baseline to Week 26 in MG-ADL and QMG total scores in patients with AChR Ab+ gMG who initiated ravulizumab earlier after MG diagnosis compared with later. The placebo group did not demonstrate a similar trend. Potential benefits of ravulizumab administration early after MG diagnosis warrant further investigation.

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CONSISTENT EFFICACY OF RAVULIZUMAB ACROSS SEX AND AGE SUBGROUPS OF PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS: A POST HOC ANALYSIS OF THE CHAMPION MG STUDY

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Introduction: The efficacy and tolerability of the long-acting terminal complement C5 inhibitor ravulizumab were demonstrated in a broad population of patients with anti-acetylcholine receptor antibody-positive (AChR Ab+) generalized myasthenia gravis (gMG) in the 26-week, phase 3, randomized, double-blind, placebo-controlled CHAMPION MG study (NCT03920293). A post hoc analysis was conducted of the efficacy of ravulizumab in patient subgroups defined by sex and age at first ravulizumab infusion (baseline).

Methods: This analysis included all enrolled patients with Myasthenia Gravis-Activities of Daily Living (MG-ADL) or Quantitative Myasthenia Gravis (QMG) assessments at Week 26. Mean changes from baseline to Week 26 in MG-ADL and QMG total scores were analyzed according to sex and age at baseline (18-65 years, >65 years) in patients receiving ravulizumab or placebo.

Results: Mean (standard deviation) changes from baseline to Week 26 in MG-ADL total score for the subgroups of males aged 18-65 years, males >65 years, females 18-65 years, and females >65 years were: ravulizumab (n=78) -3.2 (3.2), -2.9 (3.1), -3.3 (3.5), -4.2 (2.7); placebo (n=82) -0.8 (3.1), -1.8 (2.8), -1.9 (3.3), -1.4 (3.1), respectively. Corresponding data for change in QMG total score were: ravulizumab (n=76) -3.0 (4.2), -2.4 (4.2), -3.1 (4.2), -5.8 (3.5); placebo (n=78) -0.7 (4.1), -1.7 (4.1), -0.3 (2.8), -1.2 (2.9).

Conclusion: In the CHAMPION MG study population ravulizumab provided a treatment benefit as measured by MG-ADL and QMG, regardless of patient sex and age. These results support the use of ravulizumab for the treatment of a broad population of patients with AChR Ab+ gMG.

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LONG-TERM EFFICACY AND SAFETY OF RAVULIZUMAB, A LONG-ACTING TERMINAL COMPLEMENT INHIBITOR, IN ADULTS WITH ANTI-ACETYLCHOLINE RECEPTOR ANTIBODY-POSITIVE GENERALIZED MYASTHENIA GRAVIS: RESULTS FROM THE PHASE 3 CHAMPION MG OPEN-LABEL EXTENSION

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Introduction: The 26-week, double-blind, randomized, placebo-controlled phase (RCP) of the CHAMPION MG study (NCT03920293) demonstrated the efficacy and tolerability of the terminal complement C5 inhibitor ravulizumab in patients with anti-acetylcholine receptor antibody-positive (AChR Ab+) generalized myasthenia gravis (gMG). Patients who completed the RCP could receive ravulizumab in the ongoing open-label extension (OLE).

Methods: In the OLE, patients receive intravenous ravulizumab (blind induction or bridging dose for those previously receiving placebo or ravulizumab, respectively, then 3000-3600 mg according to body weight every 8 weeks) for up to 4 years. Assessments include Myasthenia Gravis-Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) total scores and safety evaluations.

Results: This interim analysis included data for 79 patients (38 received ravulizumab, 41 received placebo in the RCP) who entered the OLE at least 26 weeks before data cut-off. Improvements in MG-ADL score achieved by ravulizumab-treated patients in the RCP were maintained: least squares (LS) mean change from RCP baseline at Week 52 of -4.2 (95% confidence interval [CI] -5.7, -2.7; p<0.0001). Patients who switched from placebo in the RCP to ravulizumab in the OLE showed rapid improvement in MG-ADL score, which was maintained through 26 weeks (LS mean change from OLE baseline at Week 26 of the OLE: -2.4, 95% CI -3.8, -0.9; p<0.01). QMG scores showed a similar response. Ravulizumab was well tolerated.

Conclusion: Ravulizumab, administered every 8 weeks, demonstrated sustained improvements in symptoms and was well tolerated for up to 1 year in adults with AChR Ab+ gMG.

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ANMJ-MORPH: A SIMPLE MACRO FOR RAPID ANALYSIS OF NEUROMUSCULAR JUNCTION MORPHOLOGY

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Large-scale data analysis of synaptic morphology is becoming increasingly important to the field of neurobiological research (e.g. 'connectomics'). In particular, a detailed knowledge of neuromuscular junction (NMJ) morphology has proven to be important for understanding the form and function of synapses in both health and disease. The recent introduction of a standardized approach to the morphometric analysis of the NMJ—'NMJ-morph'—has provided the first common software platform with which to analyse and integrate NMJ data from different research laboratories. Here, we describe the design and development of a novel macro—'automated NMJ-morph' or 'aNMJ-morph'—to update and streamline the original NMJ-morph methodology. ImageJ macro language was used to encode the complete NMJ-morph workflow into seven navigation windows that generate robust data for 19 individual pre-/post-synaptic variables. The aNMJ-morph scripting was first validated against reference data generated by the parent workflow to confirm data reproducibility. aNMJ-morph was then compared with the parent workflow in large-scale data analysis of original NMJ images (240 NMJs) by multiple independent investigators. aNMJ-morph conferred a fourfold increase in data acquisition rate compared with the parent workflow, with average analysis times reduced to approximately 1 min per NMJ. Strong concordance was demonstrated between the two approaches for all 19 morphological variables, confirming the robust nature of aNMJ-morph. aNMJ-morph is a freely available and easy-to-use macro for the rapid and robust analysis of NMJ morphology and offers significant improvements in data acquisition and learning curve compared to the original NMJ-morph workflow.

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EVALUATION OF AUTONOMIC AND MOTOR CONTROL RESPONSES IN PATIENTS WITH IMMUNOLOGIC VARIANTS OF MYASTHENIA GRAVIS EXPOSED TO COGNITIVE AND EMOTIONAL ACTIVATION

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Myasthenia gravis is a neurodegenerative autoimmune disease in which cholinergic transmission at the neuromuscular plate level is compromised. Given the wide distribution of acetylcholine and its varied functions in the regulation of body systems, the evaluation of autonomic function under cognitive and emotional activities in patients with myasthenia gravis of different immunological groups was performed. From the evaluation of heart rate variability in the time domain as an indicator of parasympathetic regulation function, a decrease in the regulatory capacity was evidenced in patients belonging to each immunological variant. In addition, it was generally found that the participants presented lower levels of skin electrical conductance, lower RR intervals (elevated heart rates) and lower pulse transit times in relation to the non-myasthenic population, suggesting greater reactivity of the sympathetic nervous system in the different tests performed. The performance of the participants during the resolution of consecutive subtractions, the decrease of the FHR in the second Flicker session and the differences between the immunological groups show cognitive fatigue that would be due to a decrease of the central cholinergic transmission. Finally, the evaluation of motor control with the support test showed coherence in relation to the oscillation frequencies reported in the literature and shows that the methodology used is practical.

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THE ASSOCIATION BETWEEN ANTI-ACETYLCHOLINE RECEPTOR ANTIBODY LEVEL AND CLINICAL IMPROVEMENT IN MYASTHENIA GRAVIS

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Background Anti-AChR-antibodies in the serum are detected in most patients with generalized myasthenia gravis (MG) and used as a diagnostic tool. The aim of this study was to analyse a possible association between anti-AChR-antibody serum levels and clinical improvement of MG.

Methods The Maastricht University Medical Center is a centre of expertise for the treatment of MG. Between 1997 till 2020, more than 4.000 anti-AChR-antibodies were measured for clinical care using quantitative radioimmunoassay (RIA) technique. These results, in combination with the clinical status obtained from the patients' electronic patient files, were retrospectively analysed by a single

blinded clinician. Symptoms of MG were classified by the Myasthenia Gravis Foundation of America (MGFA).

Results In total, 90 anti-AChR-antibody positive MG-patients with 837 blood samples were included. Median follow-up time was 72 months. The majority of the included patients were female (61.1%), on immunosuppressive drug therapy (88.9%), and did undergo a thymectomy (54.4%). Multilevel logistic regression analysis showed a significantly inverse association between change in anti-AChR-antibody level and the odds of MGFA improvement (per 10 percent decrease of anti-AChR-antibody level OR: 1.21, CI: 1.12-1.31, p <0.001).

Conclusions A change in anti-AChR-antibody serum level is associated with the clinical status in patients with MG. Analyses of anti-AChR-antibody are not only useful for diagnostics but also in follow-up of adult symptomatic patients with MG. The use of repetitive anti-AChR-antibody serum levels might be valuable as a long-term monitor for clinical improvement in patients with MG, however, further research is required for specific recommendations.

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SERUM AUTOANTIBODY LOWERING BY THE ANTI-FCRN MONOCLONAL ANTIBODY, NIPOCALIMAB, CORRELATES WITH CLINICAL IMPROVEMENT IN GENERALIZED MYASTHENIA GRAVIS PATIENTS

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Objective: To evaluate the relationship between clinical improvement in Myasthenia Gravis-Activities of Daily Living (MG-ADL) scores and the pharmacodynamic effects of IgG autoantibody lowering induced by nipocalimab in the Vivacity MG Phase 2 study.

Background: Nipocalimab is a fully human, aglycosylated, effectorless IgG1 anti-FcRn monoclonal antibody that targets the neonatal Fc receptor (FcRn) with high affinity, thereby lowering IgG pathogenic antibodies in autoimmune disease.

Design/Methods: The relationship between the reduction in acetylcholine-receptor (AChR)- and Muscle-Specific-Tyrosine-Kinase (MuSK)- autoantibodies with improvement in MG-ADL scores were explored across the four nipocalimab dose arms in the Vivacity MG Phase 2 Study in generalized myasthenia gravis (gMG) patients.

Results: Of the 68 patients enrolled, 54 were randomized to one of the four nipocalimab dosing arms. 51 (94%) were seropositive for anti-AChR, 3 (6%) for anti-MuSK. Nipocalimab was well-tolerated and achieved substantial, dose-dependent and rapid reductions in serum total IgG, including all IgG subtypes and anti-AChR autoantibodies. These reductions were associated with dose-dependent, durable and rapid MG-ADL responses in all nipocalimab-treated groups. A similar trend in IgG reduction was noted in anti-MuSK-positive patients, though the sample was small.

Conclusion: The results support the rapid, dose-dependent and predictable effect of nipocalimab in lowering pathogenic autoantibodies and inducing clinical improvement in patients with gMG. In addition, the close correlation between serum IgG, anti-AChR and clinical response suggest the potential of using serial serum IgG levels as a biomarker in management of gMG patients treated with nipocalimab; this will be tested in the ongoing Vivacity Phase 3 gMG trial.

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JUVENILE MYASTHENIA GRAVIS: UTILIZING REAL WORD DATA TO EXPLORE ACCESS TO CARE AND TRIALS IN THE USA

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Background: Juvenile myasthenia gravis (MG) is a rare autoimmune disorder, with manifestations ranging from mild ocular symptoms alone to profound muscle weakness and life-threatening crises, requiring intubation and ventilation. Current standard-of care treatments are associated with significant adverse events, and up to a quarter of patients may not respond at all to existing treatments. New, safe and more effective therapies are urgently needed, as are clinical sites with juvenile MG expertise to assess these therapies via clinical trials.

Objective: To evaluate the at-need juvenile MG patient density by accessing emergent treatments for MG in the USA by zip code and their proximity to sites participating in juvenile MG trials

Results: Regions with a high density of juvenile MG patients with preselected characteristics (i.e. age, ICD-10-CM code, diagnosed between January 2015 through December 2021, and at least 1 visit for IVIG and/or Plasma exchange [PLEX] treatment) were identified using US Real World Data. Heatmaps were created for this cohort and overlaid with 27 sites currently participating in juvenile MG trials (Clinicaltrials.gov, accessed December 15, 2021). Several regions with high heat maps had no nearby trial site.

Conclusion: There is an urgent need for safer, more effective treatments for juvenile MG. Several new therapeutic agents are currently being tested in clinical trials, yet access to trial sites is limited for the majority of patients seen in the US, who are dependent on local physicians for their treatment and continue to receive hospital-based emergent treatments such as IVIG or PLEX for disease management.

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SIGNIFICANCE OF OCULAR WEAKNESS IN ACHR-POSITIVE MYASTHENIA GRAVIS PATIENTS

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Background: Even though ocular weakness is the most common symptom in myasthenia gravis (MG), it receives relatively little attention in outcome scales and in clinical trials. We investigated the importance of ocular weakness in MG patients the differences in immunosuppressive treatment between ocular (OMG) and generalized MG (GMG) patients.

Method: We investigated immunosuppressive therapy, the distribution of muscle weakness and patient-reported most disabling symptoms in 117 MG patients with acetylcholine receptor antibodies.

Results: At last follow-up, 74% of OMG and 73% of GMG patients used corticosteroids, with a mean daily dosage of 8.2 mg and 15.7 mg, respectively ($p = 0.002$). The proportion of patients that reported side effects was not-significantly different (29% and 38%; $p = 0.528$, respectively. A major part of GMG patients reported ocular weakness as the most disabling symptom (35%). Compared to patients with neck/limbs/respiratory (NLR) weakness, patients without NLR weakness more often entered into remission (60% and 40%; $p = 0.001$, respectively) and less often used azathioprine (63% and 37%; $p = 0.005$, respectively), other immunosuppressants (41% and 22%; $p = 0.032$, respectively) or had undergone IVIG treatment (21% and 4%; $p = 0.012$, respectively).

Conclusions: An almost identical proportion of OMG and GMG patients use corticosteroids suggesting a similar need for alternative therapies in both groups. In addition, initial clinical phenotype was shown to be of prognostic value. Lastly, a major group of GMG reported ocular weakness as the most disabling symptom, justifying more attention to ocular weakness in MG scales and clinical trials.

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B CELL RELATED PREDICTIVE BIOMARKERS OF TREATMENT RESPONSE IN MYASHTENIA GRAVIS

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Background and aims Myasthenia Gravis (MG) is a B cell-mediated autoimmune disease characterized by muscle weakness and fatigability, mostly associated to antibodies against the acetylcholine receptor (AChR). MG patients are chronically treated by immunosuppressants and 10-15% are treatment refractory. The purpose of our study is to identify changes in B-cell subsets that could predict treatment response in MG subgroups with different treatment-related status, with the aim of improving MG management, leading to personalized therapy.

MethodsPeripheral blood mononuclear cells were isolated from 95 AChR-MG patients and 16 healthy-controls for the characterisation of transitional (CD19+CD20+CD24+CD38+), naïve (CD19+CD20+IgD+CD27-), double negative (CD19+CD20+IgD-CD27-), unswitched memory (CD19+CD20+IgD+IgM+CD27+), switched memory (CD19+CD20+IgD-CD27+IgG+), plasmablasts (CD19+CD27++CD38+) by multicolour flow cytometry.

ResultsForty-seven/95(49%) patients were males and median age at onset was 46 years. At sampling, 30/95(32%) patients were immunotherapy-naïve, 49/79(52%) were immunotherapy-responders, 18/95(19%) were refractory to standard immunotherapy and 15/95 (16%) were in clinical stable remission (CSR). The frequency of total B-cells did not differ among the clinical subgroups. Naïve B-cells were significantly reduced in immunotherapy-responders and refractory patients compared to healthy-controls($p<0.001$) immunotherapy-naïve($p=0.002$), CSR patients($p=0.05$). Transitional B-cells were increased in refractory MG compared to immunotherapy-naïve ($p=0.003$) and responders($p=0.006$). Transitional B cells were also increased in patients with thymoma compared to patients with thymic hyperplasia($p=0.037$) both before/after thymectomy.

DiscussionThe persistence of transitional B-cells, rather than antigen experienced B-cells, might predict unresponsiveness to immunotherapy in a subgroup of patients. In these cases, early B cell-directed therapies could restore the balance between regulatory and inflammatory B-cells in the pre-germinal compartment.

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PROGNOSTIC BIOMARKER FOR TREATMENT-RESISTANT OPHTHALMOPARESIS IN MYASTHENIA GRAVIS: PILOT STUDY

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Background: Extraocular muscles are frequently affected when patients with myasthenia gravis (MG) manifest, but their treatment responsivity is not uniform. Up to 20% of MG patients show treatment-resistant ophthalmoparesis/plegia. Aim: A biomarker, e.g. microRNA, to predict myasthenic-ophthalmoplegic treatment resistance, will impact management.

Methods: We collected and stored plasma (according to a standardized protocol) on new MG patients who had not received immune treatment. Ocular involvement was scored at baseline and at follow-up visits when patients were categorised as responders vs non-responders (persistent ophthalmoplegia) at ±12 months. Immune treatments were started if ocular symptoms did not respond to cholinesterase inhibitors. Thirty-one candidate microRNAs were profiled using a microRNA qPCR-array (Qiagen); these were selected based on; differential expression in extraocular muscle compared to limb muscle (literature curation); involvement in key genes/pathways found to be dysregulated in orbital muscles of treatment-resistant myasthenic ophthalmoparesis MG patients vs controls. Four potential reference microRNAs were included for normalisation.

Results: Relative expression levels of baseline plasma microRNA from 9 non-responders vs 21 responders were analysed using GeneGlobe Data Analysis web modules (Qiagen). Analysis of candidate reference microRNAs showed that some were unstable, therefore Normfinder was used to select 10 microRNAs with stability across responder and non-responder samples to normalise the expression levels. MicroRNA-125b-5p and 199a-3p were significantly different ($p<0.025$) between responders and non-responders, and 5 further microRNA showed trends towards differences ($p<0.1$). A parallel cohort is undergoing analysis. Conclusions: Preliminary results show possible prognostic microRNA biomarkers to predict individuals at risk of developing treatment-resistant ophthalmoplegia in MG.

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QUALITATIVE INTERVIEWS TO UNDERSTAND THE EXPERIENCE OF ADULTS WITH GENERALIZED MYASTHENIA GRAVIS IN EVERYDAY LIFE

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Background: Generalized myasthenia gravis (gMG) is a rare autoimmune disease, hallmarked by muscle weakness, fatigability, and in severe cases hospitalization. Prior to this study, knowledge of symptoms and impacts relevant to patients was sparse. This reports an in-depth qualitative exploration of patients' daily experience of gMG.

Methods: Published qualitative studies (i.e., reporting patients' exploratory interviews; September 2020) were reviewed to identify symptoms and functional impacts of gMG which were subsequently organized into a preliminary conceptual model. Patients were interviewed about their gMG (i.e., signs, symptoms, impacts on daily activities and quality of life) using open-ended questions from semi-structured guides. Transcribed verbatim interviews were analyzed using thematic analysis. Symptoms and impacts were reviewed to determine saturation and to understand which were most salient (i.e., reported by ≥50% patients, with disturbance rating of ≥5 [on a 10-point numeric rating scale]).

Results: Twelve patients were interviewed, and conceptual saturation was reached. Thirteen symptoms (stiffness, blurry vision, trouble swallowing liquids, choking, trouble aspirating saliva, general fatigue, sleep apnea, cognitive impairment, brain fog/mental fatigue, balance, gastrointestinal issues, incontinence, and heat sensitivity) and one impact (self-care) were newly identified in interviews and added to the preliminary conceptual model. Most salient symptoms were shortness of breath, general fatigue, muscle weakness (arms, legs, & neck), poor voice quality, difficulty speaking, choking, and heat sensitivity. All impacts were salient.

Conclusions: This research highlights unmet needs and aspects most relevant to patients with gMG. Future trials and clinical practice should aim to improve these experiences.

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DYSGAMMAGLOBULINEMIA IN MUSK MYASTHENIA GRAVIS PATIENTS

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A subset of myasthenia gravis (MG) is caused by Muscle-Specific Kinase (MuSK) binding IgG4 antibodies. A dominant role for IgG4 in autoimmune disease is surprising due to its anti-inflammatory characteristics. Therefore, we hypothesized that MuSK MG patients might have a general disbalance of IgG subclasses. We investigated serum Ig(G) subclasses and isotypes using nephelometric assays in immunosuppressive treatment naïve MuSK MG (n=28) and AChR MG patients (n=51). Absolute serum IgG1 and total IgG were elevated in both MuSK (14 and 12%) and AChR (25 and 16%) MG patients compared to healthy donors. MuSK MG patients showed elevated serum IgG4, both on absolute levels (67%) and as a percentage of total IgG (50% increase), compared to healthy donors and AChR MG patients. These elevations cannot be explained only by the contribution of antigen-specific antibodies. Taken together, this suggests MuSK MG patients have a general dysregulation of especially the IgG4 humoral response.

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A PROSPECTIVE NATURAL HISTORY STUDY AND BIOREPOSITORY FOR PATIENTS WITH MYASTHENIA GRAVIS (EXPLORE-MG2)

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Background: The myasthenia gravis (MG) Rare Disease Clinical Research Network (MGNet) was funded by the National Institutes of Health to better understand the clinical course of MG and develop improved approaches to diagnosis and treatment. As part of this initiative a multicenter prospective natural history study and biorepository was developed: Exploring Outcomes and Characteristics of Myasthenia Gravis 2 (EXPLORE-MG2).

Methods: EXPLORE-MG2 is a web-based observational registry that incorporates NIH recommended common data elements for MG. Key eligibility criteria include: ≥18 years old and diagnosed with MG within 2-years of study enrollment based on clinical presentation. Biospecimen collection focuses on immunosuppressive naïve patients and rare MG subgroups. Participants will be followed for at least 2-years with study visits approximately every 6 months in the context of usual clinical care. The study opened to enrollment in January 2021 with 6 sites currently activated/participating.

Results: 82 patients have been enrolled and 226 biospecimens were collected as of 12/20/2021. The mean age was 61.5 years (range 20-84); 48% were female, 67% were acetylcholine receptor antibody-positive, 20% were MuSK-antibody positive, and 13% were seronegative. New enrollment and follow-up of existing participants are ongoing to reach our goal of 400 enrolled participants. We will present updated enrollment data and demographics at the meeting.

Conclusion: The EXPLORE-MG2 study is active after a COVID-19 pandemic related delay. Samples and clinical data will be available to researchers for current and future investigation. Data from EXPLORE-MG2 will improve clinical trial readiness for future studies and facilitate development of treatment-responsive biomarkers.

J.T. Guptill: *Consultant*; JTG has received consulting fees/honoraria from Immunovant, Alexion, Apellis, Momenta, Ra Pharma, Cabaletta, Regeneron, Argenx, Janssen, UCB, and Toleranzia.. *Other*; JTG receives industry grant support from UCB pharma for a fellowship training grant; is a site investigator for Alexion, Janssen, UCB Pharma, Argenx, Takeda and grant/research support from: NIH (NIAID. **R.J. Nowak:** *Consultant*; RJN has no specific conflicts with this abstract. He has served as consultant/advisor for Alexion Pharmaceuticals, Inc, argenx, Cabaletta Bio, Inc, CSL Behring, Grifols, S.A., Ra Pharmaceuticals, Inc. *Other*; RJN received research support from NIH, Genentech, Inc, Alexion Pharmaceuticals, Inc, argenx, Annexon Biosciences, Inc, Ra Pharmaceuticals, Inc (now UCB S.A.), the MGFA, Inc, Momenta Pharmaceuticals,. **A.C. Guidon:** *Consultant*; ACG has no conflicts specific to this abstract. ACG received consulting fees/honoraria from Argenx, Alexion, Ra Pharma/UCB, Momenta/Janssen and royalties from Oakstone publishing. *Other*; ACG has received prior or current research support from Project Data Sphere, the MGFA, MGNet Rare Disease Network, PCORI and Biosensics. **J.F. Howard, Jr:** *Consultant*; JFH Alexion Pharmaceuticals, argenx BVBA, Immunovant Inc., Ra Pharmaceuticals (now UCB Biosciences), Regeneron Pharmaceuticals, Sanofi US and Viela Bio Inc. (now Horizon Therapeutics). *Other*; JFH

non-financial support from Alexion Pharmaceuticals, argenx BVBA, Ra Pharmaceuticals (now UCB Biosciences), Toleranzia AB. Clinical Trial Support (paid to my institution): Alexion Pharmaceuticals,. **B. Soliven:** None. **A. Hammett:** None. **B. Munro Sheldon:** None. **Y. Li:** *Other*; YL receives research support from the MGFA and MGNet (U54 NS115054). **T. Muir:** None. **I. Aban:** *Other*; research grants to UAB OSP from MGFA; Ra/UCB Pharmaceutical Alexion, Argenx, and Catalyst through MGFA. Verona Pharmaceutical. **G. Cutter:** *Consultant*; Data and Safety Monitoring Boards: AMO Pharma, Astra-Zeneca, Avexis Pharmaceuticals, Biolinerx, Brainstorm Cell Therapeutics, Bristol Meyers Squibb/Celgene, CSL Behring, Galmed Pharmaceuticals, Green. *Other*; GC is employed by the University of Alabama at Birmingham and President of Pythagoras, Inc. **H.J. Kaminski:** *Consultant*; HJK is a consultant for Roche, Cabeletta Bio, Lincoln Therapeutics, Takeda and UCB Pharmaceuticals.. *Other*; HK is CEO and CMO of ARC Biotechnology, LLC based on US Patent 8,961,98. He is PI of the Rare Disease Network for Myasthenia Gravis (MGNet) NINDS, U54 NS115054 and Targeted Therapy for MG R41 NS110331. **E. Study Team:** None.

RESULTS OF THE RARE DISEASE NETWORK COVID-19 EPIDEMIC SURVEY OF PATIENTS WITH MYASTHENIA GRAVIS

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The Covid-19 pandemic has brought to light the inadequacy of the health care system in the United States. The NIH Rare Disease Clinical Research Network conducted a cross-sectional web-based survey to target the rare disease community in the USA and are under the age of 90 years. The survey requested demographic, disease- specific, drug treatment, symptom information, and the perceived impact of the Covid-19 pandemic on them. The survey opened in May 2020 and closed in December 2020. The largest number of respondents (594) identified as having MG with a large majority of responses submitted in June, which is MG awareness month. Eighty-nine percent identified as White. Sixty percent of respondents were women with a mean age of 60 years. Respondents did not appreciate a worsening of symptoms after the pandemic. Only seven respondents reported the diagnosis of Covid-19. Eleven percent indicated they had difficulty accessing care at the time of the survey and an increase in telemedicine use. Despite advocacy for use of hydroxychloroquine and azithromycin, which are contraindicated as treatments for Covid-19, none of the MG patients reported their use. A major limitation of the survey is its inability to access minority populations. Nevertheless, the results of the RCDRN survey of patients with MG provide clear evidence that the pandemic has demonstrated the deficiencies in US healthcare.

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A DECENTRALIZED, PROSPECTIVE OBSERVATIONAL STUDY TO COLLECT REAL-WORLD DATA FROM PATIENTS WITH MYASTHENIA GRAVIS USING SMARTPHONES

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We report results from a 3-month prospective observational study in adults with myasthenia gravis (MG) using fully decentralized methods, to assess the feasibility of real-world data collection from smartphones for patients with this rare disease. Using an app designed for the study (available on iOS and Android), participants reported their daily symptoms, symptom severity, exacerbation status, and health-related quality of life using digital versions of the MG-Activities of Daily Living (MG-ADL) and MG-Quality of Life (MG-QoL) assessments. Participants could also make optional connections to contribute secondary, passive data streams (e.g. daily step count). The study enrolled and onboarded 113 participants across 37 US states. Participants' mean age was 53.6 years (SD 14.0), 60% were female, and 73% (N=82) completed the study. Participants were representative of clinically-observed age and gender distributions for MG. During the study, 45 participants (39.8%) reported MG exacerbations, with an average of 6.3 exacerbation days per participant over the 90-day study period. Median MG-ADL scores during self-reported exacerbation and non-exacerbation periods were 5 (interquartile range 2-8, range 0-24) and 0 (interquartile range 0-0, range 0-15), respectively, with association between MG-ADL scores and exacerbation status. Machine learning methods were applied to the data to examine symptom signatures and clustering during exacerbation and non-exacerbation periods. Overall, the study demonstrated that it is feasible to collect real-world data from patients with MG, which may provide enhanced visibility into the natural history of the disease to guide clinical management and future therapeutic development. Funded by UCB Pharma, in collaboration with Sharecare.

S. Steyaert: *Employee*; Sharecare. **M. Lootus:** *Employee*; Sharecare. **C. Sarabu:** *Employee*; Sharecare. **Z. Framroze:** *Employee*; Sharecare. **H. Dickinson:** *Employee*; UCB. **E. Kunka:** *Employee*; UCB. **J. Steels:** *Employee*; UCB. **N.R. Shah:** *Employee*; Sharecare. **F. Rinaldo:** *Employee*; Sharecare.

INVESTIGATION OF 3 TRAINING METHODS ON THE EFFECT OF INTER-RATER VARIABILITY IN CLINICAL OUTCOME ASSESSMENT TESTING

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Introduction: Rater training is paramount in decreasing testing inconsistencies and variability in clinical outcome assessment (COA) testing. This study evaluated 3 different training methods: asynchronous video training, synchronous remote training, and synchronous in-person training, to ascertain which training method yielded the lowest inter-rater variability and the least errors in testing Patient Reported Outcomes (PRO) and Clinician Reported Outcomes (ClinRo).

Methods: Physical therapy doctoral students were randomly divided into three training groups: in-person, remote, and video. Each group was trained on a customized clinical assessment tool comprised of elements from validated performance tests used in Myasthenia Gravis clinical trials, namely the MG-ADL and MGC. All groups were video recorded assessing a scripted mock patient. Video of assessments were evaluated by a blinded expert reviewer for protocol adherence and testing discrepancy.

Results: Across all tests, the video group scored substantially lower (more errors) with higher variability than the remote group and the in-person group. The mean scores (± SD) for the video group on the PRO and ClinRO were 31% (± 40%) and 55% (±14%) the remote group 80% (± 21%) and 90% (± 9%), and the in-person group 88% (± 13 and 91% (± 4%), respectively.

Conclusion: Results illustrate that the raters who participated in synchronous in-person and synchronous remote training, demonstrated significantly lower inter-rater variability and decreased testing error rates when compared to the asynchronous video training group. Synchronous in-person and synchronous remote training should be highly considered as part of a CE training program for clinical trials to ensure data integrity.

M. Calcagni: *Consultant*; Rater Trainer Consultant. **B. Lum:** *Consultant*; rater training consultant.

LONG-TERM SAFETY, TOLERABILITY, AND EFFICACY OF EFGARTIGIMOD IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS: INTERIM RESULTS OF THE ADAPT+ STUDY

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Introduction: Treatment with efgartigimod, a human IgG1 antibody Fc-fragment that blocks neonatal Fc receptor, resulted in clinically meaningful improvement in generalized myasthenia gravis (gMG)-specific outcome measures in the ADAPT study. Patients who completed ADAPT were eligible to enroll in its ongoing open-label, extension study, ADAPT+.

Objective: To evaluate the safety, tolerability, and efficacy of efgartigimod in patients with gMG enrolled in ADAPT+.

Methods: Efgartigimod 10 mg/kg was administered intravenously in cycles of 4-weekly infusions, with subsequent cycles initiated based on predefined criteria. Efficacy was assessed during each cycle using Myasthenia Gravis Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) scales.

Results: Ninety percent (151/167) of ADAPT patients entered ADAPT+. As of February 2021, 106 AChR-Ab+ and 33 AChR-Ab- patients received ≥1 dose of efgartigimod (including 66 ADAPT placebo patients). The mean(SD) study duration was 363(114) days, resulting in 138 patient-years of observation. The most common adverse events in the efgartigimod-efgartigimod and placebo-efgartigimod arms were: headache (15.1%/30.3%), nasopharyngitis (8.2%/13.6%), and diarrhea (6.8%/10.6%). Adverse events were predominantly mild or moderate. Clinically meaningful improvement occurred in AChR-Ab+ patients during each cycle for up to 10 cycles (mean[SE] improvements in cycle 1: MG-ADL, -5.1[0.34]; QMG, -4.7 [0.41]). Clinical improvements mirrored maximal reductions in total IgG and AChR-Ab levels. Similar results were observed in AChR-Ab- patients (cycle 1: MG-ADL, -5.4[0.76]; QMG, -5.2[0.74]).

Summary/Conclusion: This analysis supports that long-term treatment with efgartigimod is well tolerated and efficacious in gMG. No new safety signals were identified, despite occurring during the COVID-19 pandemic before vaccine availability.

J.F. Howard: *Other*; Alexion Pharmaceuticals, Inc, argenx, Myasthenia Gravis Foundation of America, Muscular Dystrophy Association, National Institutes of Health (including the National Institute of Neurological Disorders and Stroke and the National Institute of Arthritis and Musculoskeletal and Skin Diseases), Patient-Centered Outcomes Research Institute, Ra Pharmaceuticals Inc (now UCB), Regeneron Pharmaceuticals Inc, Takeda Pharmaceuticals, Immunovant, Inc, Sanofi US, Viela Bio, Inc (now Horizon Therapeutics plc). **V. Bril:** *Other*; CSL, Grifols, SA, UCB, Bionevia, Shire, Octapharma. **T. Vu:** *Consultant*; Alexion Pharmaceuticals, Inc, argenx, UCB. *Other*; Alexion Pharmaceuticals, Inc, argenx, National Institutes of Health, Ra Pharmaceuticals Inc/UCB, Viela Bio, Inc (now Horizon Therapeutics plc), Regeneron, Sanofi, Cartesian Therapeutics, Grifols, SA. **C. Karam:** *Consultant*; Acceleron Pharma Inc, Akcea Therapeutics, Alnylam Pharmaceuticals, Inc, argenx, Biogen, CSL Behring, Sanofi Genzyme. *Other*; Neurology,

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FUNCTIONAL MONOVALENCY AMPLIFIES THE PATHOGENICITY OF ANTI-MUSK IGG4 IN MYASTHENIA GRAVIS

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MuSK myasthenia gravis (MG) is characterized by pathogenic IgG4 autoantibodies and a hallmark IgG4 autoimmune disease. IgG4 is the only human antibody able to undergo Fab-arm exchange; a process where IgG4 half-molecules exchange with unrelated IgG4s in the circulation in a stochastic and continuous manner. This renders the great majority of IgG4 functionally monovalent for its antigen. We investigated whether functional monovalency of anti-MuSK IgG4 contributes to the pathophysiology of MuSK MG. MuSK-specific B-cell receptor sequences were isolated from MuSK MG patients and produced recombinantly as monoclonal bivalent MuSK antibodies. The controlled Fab-arm exchange method was adapted to IgG4 to yield "pure" functionally monovalent MuSK antibodies. In mice, functionally monovalent anti-MuSK IgG4s rapidly caused progressive and severe myasthenic muscle weakness, whereas the bivalent equivalents did not cause overt muscle weakness or were less potent. Therefore, the functional monovalency of anti-MuSK IgG4 amplified the pathogenicity *in vivo*. This may be explained by the opposing effects of bivalent and monovalent MuSK antibodies on MuSK signaling (i.e. activating vs inhibiting) in the NMJ, as demonstrated in cultured myotubes. These findings suggest that isotype switching to IgG4 autoantibodies is a critical step in the development of MuSK MG and establishes functional monovalency as a novel pathogenic determinant in IgG4-mediated autoimmunity.

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IGG4-MEDIATED AUTOIMMUNE DISEASES HAVE A NORMAL B CELL COMPARTMENT

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MuSK myasthenia gravis (MG) was recently classified into a new niche of autoimmune diseases hallmarked by dominant pathogenic IgG4 autoantibodies (IgG4-AIDS). Other members of this niche include several neuropathies, skin blistering disorders, nephropathies and a hemolytic disorder. Why IgG4 predominates these disorders is unknown. We hypothesized that dysregulated B cell maturation or aberrant isotype switching causes overrepresentation of IgG4 B cells and plasma cells. Therefore, we evaluated the B cell landscape of 11 MuSK MG and 10 pemphigus patients (two archetypical IgG4-AIDs) in comparison to AChR MG patients, Lambert-Eaton Myasthenic Syndrome (LEMS) patients and age-matched healthy donors, using a validated EuroFlow B cell marker panel by flow cytometry. B cell subset counts at all maturation stages were normal in two IgG4-AIDs, except for a reduction in immature and naïve CD5+ cells likely related to azathioprine treatment. IgG4 B cell and plasma cell counts were normal in IgG4-AID patients. However, in both IgG4-AID groups we found increased CD20-CD138+ plasma cells (8.5-fold over all other groups). These cells precede long-lived bone marrow-residing plasma cells and are linked to other (non-IgG4 mediated) autoimmune diseases, including AChR

MG. Notably, this increase was observed for most isotypes. In conclusion, patients with IgG4-AID do not show impaired B cell maturation or increased levels of IgG4-expressing cells. These results argue against aberrant B cell biology in these patients. Instead, the IgG4 predominance in autoantibodies may be antigen-driven or induced by altered T cell help. The increase in mature plasma cell counts is striking and warrants further research.

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PREGNANCY COURSE AND MUSK-POSITIVE MYASTHENIA GRAVIS: A SINGLE CENTER CASE SERIES

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Introduction Although myasthenia gravis with muscle specific tyrosine kinase (MuSK) antibodies (MMG) is predominantly seen in women of childbearing age, the disease course during pregnancy and postpartum has not been well described.

Methods A retrospective review of the medical records of patients with MMG in the Duke MG Clinic after 2003.

Results Ten identified patients who were pregnant after onset of MMG had a total of 14 pregnancies. Initial MG symptoms developed during pregnancy or within 6 months postpartum in 6 patients. Four patients had 2 pregnancies, 3 of whom developed MG during the first pregnancy. In the patients diagnosed prior to pregnancy, MG symptoms increased in 5 of 8 pregnancies. Four patients required rescue therapy with plasma exchange or intravenous immunoglobulin during pregnancy or postpartum. One patient had a C-section after prolonged labor due to failure of delivery progression. There were no other complications of pregnancy or delivery, and all the babies were healthy at delivery. Four of 8 patients who underwent thymectomy before or after pregnancy had thymic hyperplasia.

Discussion/Conclusion As in non-MuSK MG, women with MMG may also have disease improvement or worsening or develop initial MG symptoms during pregnancy or within 6 months postpartum. Among our MMG patients, 4 required rescue therapy; pregnancy and delivery were not otherwise complicated by MG exacerbation or complication except for 1 patient who required C-section due to failure of delivery progression. Further study is needed to understand the mechanism and risk of worsening of MMG during pregnancy or postpartum.

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ADDRESSING OUTCOME MEASURE VARIABILITY IN MYASTHENIA GRAVIS CLINICAL TRIALS

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Introduction: An increasing number of clinical trials are enrolling patients with myasthenia gravis (MG). Lack of standardization in outcome measure performance generates confusion amongst site research teams and is a source of variability in clinical trial data. MGNet views standardization of MG outcome measures as a critical need.

Methods: Experts summarized key outcome measures used in MG clinical trials and a virtual symposium was convened to address issues contributing to outcome measure variability. Consensus recommendations resulted in changes to outcome measure instructions, and in some cases, modifications to specific instruments. Part of the process is to post proposed changes for public comments prior to finalization.

Results: Changes to the MG-Activities of Daily Living, MG-Quality of Life-15r, and MG-Impairment Index were limited to adding details to the administration instructions. Recommendations for proper positioning of subjects and how to score items that could not be performed due to non-MG reasons were provided for the MG Composite. The Quantitative MG Score (QMG) required the most attention, and changes were made both to the instructions and methods for evaluating certain items (e.g., ptosis assessment). The Post-Intervention Status was felt to have a limited role in clinical trials, except for the concept of minimal manifestation status.

Discussion: Training materials and source documents will be developed and posted on the MGNet website. These materials, which will be freely available to study teams, will reduce resources needed for study start-up and improve MG outcome measure

standardization. Further studies will need to validate changes made to the QMG.

J.T. Guptill: *Consultant*; JTG has received consulting fees/honoraria from Immunovant, Alexion, Apellis, Momenta, Ra Pharma, Cabaletta, Regeneron, Argenx, Janssen, UCB, and Toleranzia.. *Other*; JTG receives industry grant support from UCB pharma for a fellowship training grant; is a site investigator for Alexion, Janssen, UCB Pharma, Argenx, Takeda and grant/research support from: NIH (NIAID. **V. Granit:** *Consultant*; VG has no COI relevant to this abstract. He received honoraria as a consultant/advisory board member from Alexion Phermaceuticals, Argenx, Immunovant Inc, and Amylyx Pharmaceuticals Inc. **A. Habib:** *Consultant*; AH has received consulting fees/honoraria from argenx, Alexion, UCB.. *Other*; AH has received research support from argenx, Alexion, VielaBio, UCB Pharma, Genentech, Regeneron and Sanofi. **I. Lee:** *Other*; IL has no relevant disclosures directly related to this work. He has received research support from the Myasthenia Gravis Foundation of America. **K. Ruzhansky:** *Consultant*; KR serves as a consultant for Alexion, Argenx, Immunovant, UCB/Ra.. *Other*; KR receives grant funding from the MGFA. **J.F. Howard:** *Consultant*; JFH has no specific conflicts as it pertains to this abstract, and has received non-financial support from Alexion Pharmaceuticals, argenx BVBA, Ra Pharmaceuticals (now UCB Biosciences) and Toleranzia. *Other*; JFH has received research support from Alexion, argenx BVBA, the CDC, MGFA, MDA, NIH, PCORI. **C. Barnett-Tapia:** *Consultant*; CBT has received honoraria from Alexion Pharmaceutical, Sanofi, Argenx and CSL.. *Other*; CBT is the primary developer of the MGII and may receive royalties. She has received research support from the US DoD, NIH, MGNet, Muscular Dystrophy Canada, the Ontario Ministry of Health, Octapharma. **M.M. Dimachkie:** *Consultant*; MMD serves/served as a consultant for ArgenX, Catalyst, CSL-Behring, Janssen, Momenta, NuFactor, Octapharma, RaPharma/UCB, RMS Medical, Shire Takeda, and UCB Biopharma.. *Other*; MMD received research grants or contracts or educational grants from Alexion, Catalyst, CSL-Behring, Grifols, NIH, Octapharma, Ra Pharma/UCB, Shire Takeda, & UCB Biopharma / RaPharma. **R.J. Nowak:** *Consultant*; RJN has no specific conflicts with this abstract. He has served as consultant/advisor for Alexion Pharmaceuticals, Inc, argenx, Cabaletta Bio, Inc, CSL Behring, Grifols, S.A., Ra Pharmaceuticals, Inc. *Other*; RJN received research support from NIH, Genentech, Inc, Alexion Pharmaceuticals, Inc, argenx, Annexon Biosciences, Inc, Ra Pharmaceuticals, Inc (now UCB S.A.), the MGFA, Inc, Momenta Pharmaceuticals,. **H.J. Kaminski:** *Consultant*; HJK is a consultant for Roche, Cabeletta Bio, Lincoln Therapeutics, Takeda and UCB Pharmaceuticals.. *Other*; HK is CEO and CMO of ARC Biotechnology, LLC based on US Patent 8,961,98. He is PI of the Rare Disease Network for Myasthenia Gravis (MGNet) NINDS, U54 NS115054 and Targeted Therapy for MG R41 NS110331. **M. Benatar:** *Consultant*; MB received compensation for consultative services provided to Alexion, Immunovant, Sanofi, UCB, and Cartesian.. *Other*; MB has served as a site investigator in MG clinical trials funded by Alexion UCB, NIH. **O. the MGNet Outcome Measures Working Group:** None.

INTRODUCING THE PEDIATRIC MYASTHENIA GRAVIS CONSORTIUM

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Limited data and consensus exist regarding the natural history, evaluation, and management of children with myasthenia gravis, congenital and acquired. An anonymous gift to UCSF allowed the creation of the Pediatric Myasthenia Gravis Consortium. The primary investigator (PI) from the coordinating center chose an additional five centers based on their experience and caseload. On September 22, 2019, with the support of the MGFA, the six PIs met, established a mission statement, protocol, and agreed on an initial data set. The following day an advisory board comprised of patients and their families, representatives from pharmaceutical companies with drugs in development for MG, and representatives of MGFA, reviewed the work and provided feedback which enhanced the final collection set. Following this meeting, the PI researched options for software support. A decision was made to work with FigMD, who also designed the registry for the American Academy of Neurology and is well versed in data collection direct from Electronic Medical Record systems. IRB approval was obtained at the primary site. Supporting documents were created for each site to obtain local IRB approval. Contract discussion was initiated with each site; however, work progress has slowed due to institutional focus diverted to Covid-19 management. Also, MRO Corporation acquired FigMD, so contracts needed to be renegotiated. We plan to complete all contracts in early 2022 with data collection to start in the second quarter of the year. The consortium remains committed to developing a robust natural history of myasthenia gravis in children in the United States.

J.B. Strober: *Consultant*; Jansen Pharmaceuticals, UCB Pharma. **D. Castro:** *Consultant*; Jansen Pharmaceuticals. **N. Kuntz:** None. **J. Brandsema:** *Consultant*; Jansen Pharmaceuticals. **E. Ciafaloni:** *Consultant*; Alexion, Momenta. **R. Maselli:** *Consultant*; Argenx Pharmaceuticals, AMPLO Biotechnology.

STUDY DESIGN OF INTRAVENOUS EFGARTIGIMOD IN JUVENILE GENERALIZED MYASTHENIA GRAVIS

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Introduction: Efgartigimod is a human IgG1 antibody Fc-fragment that blocks neonatal Fc receptor (FcRn), thereby reducing pathogenic IgG autoantibody levels. ADAPT, a phase 3 trial in adults with generalized myasthenia gravis (gMG), showed that efgartigimod is efficacious and well tolerated. The incidence of juvenile gMG (1-5:1,000,000) is considerably lower than that of adult gMG; however, the medical need for effective and safe treatments remains high. Here, we present the study design evaluating efgartigimod in pediatric patients with juvenile gMG (NCT04833894).

Objective: The primary aim of this study is to confirm the age-appropriate dose of intravenous efgartigimod and provide (model-predicted) evidence for the treatment response.

Methods: The study will recruit 12 patients, aged 2-17 years, starting with the older age group (12-17 years). Patients must have a confirmed diagnosis of gMG class II, III, or IVa, the presence of anti-AChR antibodies, and be on a stable background therapy. In Part A, patients receive 1 infusion of efgartigimod, followed by a 8-week treatment-free follow up period. In Part B, patients receive 4 weekly infusions of efgartigimod.

Results: Pharmacokinetics (PK), pharmacodynamics (PD), safety, and clinical response are assessed. In children >6 years of age, the MG-ADL and modified QMG scales are used as clinical scores, while a detailed neurological assessment is used to measure clinical response in children aged ≤6 years.

Summary/Conclusion: The unique design of this study will provide data to support PK/PD modelling during the study to confirm age-appropriate dose and evaluate efficacy and safety of efgartigimod in pediatric gMG patients.

N.L. Kuntz: *Other*; Alexion Pharmaceuticals, Inc, argenx, Astellas Therapeutics, Novartis, Reveragen, Roche, Sarepta Therapeutics, Biogen, Sarepta. **A. Bogatyreva:** *Employee*; argenx. **J. Podhorna:** *Employee*; argenx. **S. Steeland:** *Employee*; argenx. **T. Van Bragt:** *Consultant*; argenx. *Employee*; Partner Curare Consulting BV. **B. Van Hoorick:** *Employee*; argenx. **A. Guglietta:** *Employee*; argenx. **J.F. Howard:** *Other*; Alexion Pharmaceuticals, Inc, argenx, Myasthenia Gravis Foundation of America, Muscular Dystrophy Association, National Institutes of Health (including the National Institute of Neurological Disorders and Stroke and the National Institute of Arthritis and Musculoskeletal and Skin Diseases), Patient-Centered Outcomes Research Institute, Ra Pharmaceuticals Inc (now UCB), Regeneron Pharmaceuticals Inc, Takeda Pharmaceuticals, Immunovant, Inc, Sanofi US, Viela Bio, Inc (now Horizon Therapeutics plc).

EFFICACY, SAFETY, AND TOLERABILITY OF EFGARTIGIMOD IN ACETYLCHOLINE RECEPTOR AUTOANTIBODY SERONEGATIVE PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS: INTEGRATED INTERIM ANALYSIS OF THE ADAPT AND ADAPT+ STUDIES

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Introduction: Efgartigimod is a human IgG1 antibody Fc-fragment that reduces pathogenic IgG autoantibody levels through blockade of the neonatal Fc receptor. Patients with AChR antibody-negative generalized myasthenia gravis (gMG) comprise 15%-20% of the gMG population and have limited treatment options due to historical exclusion from clinical trials.

Objective: To evaluate long-term safety and efficacy of efgartigimod in AChR antibody-negative patients with gMG using data pooled from the phase 3 ADAPT study and its ongoing long-term extension, ADAPT+.

Methods: ADAPT evaluated the safety and efficacy of efgartigimod in both AChR antibody-positive (n=129) and -negative (n=38) gMG patients. Patients who completed ADAPT, including 33 AChR antibody-negative patients, were eligible to enroll in ADAPT+. An integrated analysis included data from 37 AChR antibody-negative patients who received efgartigimod in ADAPT/ADAPT+ through October 2020.

Results: Among AChR antibody-negative patients in ADAPT, 68.4% (13/19) of efgartigimod-treated vs 63.2% (12/19) of placebo patients were MG-ADL responders, and 52.6% (10/19) of efgartigimod vs 36.8% (7/19) of placebo patients were QMG responders. In cycle 1 of the integrated analysis, AChR antibody-negative patients improved from cycle baseline in both MG-ADL (≥3-, ≥5-, and ≥7-point improvements of 81.1%, 54.1%, and 35.1%, respectively) and QMG (≥3- to ≥9-point improvements of 86.5%-27.0%, respectively). Similar improvements in both efficacy scales occurred across all cycles. There were no clinically meaningful differences in safety or efficacy outcomes between AChR antibody-positive and -negative patients.

Summary/Conclusion: Long-term treatment with efgartigimod was associated with repeated clinically meaningful improvements in MG-ADL and QMG scores in AChR antibody-negative patients in ADAPT/ADAPT+.

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CONTINUOUS AND FIXED-CYCLE DOSING OF INTRAVENOUS EFGARTIGIMOD FOR GENERALIZED MYASTHENIA GRAVIS: STUDY DESIGN OF ADAPT NXT

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Introduction: Individualized cyclic administration of efgartigimod, a human IgG1 antibody Fc-fragment that blocks the neonatal Fc receptor, was effective and well tolerated in the ADAPT phase 3 trial of patients with generalized myasthenia gravis (gMG). The phase 3b ADAPT NXT study (NCT04980495) will investigate the efficacy and safety of efgartigimod in both continuous and fixed-cycle regimens.

Objective: To evaluate the efficacy, safety, and tolerability of 10 mg/kg intravenous efgartigimod administered in a continuous dosing regimen (every 2-3 weeks) or a fixed cyclic regimen (4 infusions at weekly intervals with a 4-week intertreatment period).

Methods: Adult patients with gMG who are AChR antibody positive, have an MG-ADL total score of ≥5 (with >50% of the score due to nonocular symptoms), and on a stable dose of ≥1 concomitant gMG treatment will be recruited (N=72 estimated enrollment). Patients will be randomized 3:1 to either continuous or fixed cyclic dosing regimens. After the initial 21-week period of the study, all patients will be enrolled in a continuous regimen every 2 weeks, with the option to switch to every 3 weeks as tolerated.

Results: The primary endpoint will be the mean average change in MG-ADL total score from study baseline to week 21 for each regimen. Safety, tolerability, additional measures of clinical efficacy (including patient satisfaction), and pharmacokinetic/pharmacodynamic effects will also be assessed.

Summary/Conclusion: The results of ADAPT NXT will provide important data to inform alternative treatment regimens which may be more convenient for individual patients. The estimated study completion date is April 2024.

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MGFA TASK FORCE FOR STANDARDIZATION OF MG OUTCOME MEASURES IN CLINICAL PRACTICE

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Introduction: Myasthenia gravis (MG) studies and clinical trials utilize validated MG-specific outcome measures as study end points. It is important to use these outcome measures as evaluation tools in clinical practice to monitor effectiveness of treatments and disease progression. Common clinical outcome measures include MG-ADL, MG-MMT, MGC, MGFA-CC, MG-PIS, MG-QOL15r, and QMG. There is considerable variation and confusion regarding the use of these metrics. The MGFA appointed a task force in 2019 to address ambiguities and eliminate inconsistencies in applying these outcome measures in clinical practice.

Methods: A survey among MG clinicians gathered insights regarding the use of outcome measures in clinical practice. The survey explored ease of use of the measures, accuracy of capturing overall clinical status, minimally important clinical difference, and preferred personnel to administer them. Based on survey results, a focus group script was developed. An online clinician focus group was conducted by MindSpot Research.

Results: Ninety-eight responses were obtained from the survey, and the focus group (N=10) was assembled. Major themes included classification and timeframes for remission, minimum duration for minimal manifestation status, timeframe for scoring the measures, scoring in the presence of co-morbidities, and assigning severity to muscle weakness. Following the focus group voting statements were drafted for consensus.

Discussion: The final step (ongoing) is to develop consensus statements from focus group results using the RAND/UCLA appropriateness method. Consensus statements will be available for clinicians to help standardize and improve clinical applications of outcome measures.

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MUSK ANTIBODY TITER AND MYASTHENIA GRAVIS SEVERITY

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Antibodies against muscle-specific tyrosine kinase (MuSK) has been identified in approximately 5% of myasthenia gravis (MG) patients. MuSK is necessary for the development and maintenance of acetylcholine receptor clustering. Previously, it has been shown that the MuSK antibody titer was significantly associated with MG severity according to the Myasthenia Gravis Foundation of America (MGFA) classification and quantitative clinical score. We collected serum samples in patients with known MuSK positive MG and used Luminex assays to measure MuSK antibody levels. A total of 33 samples were collected in 21 patients. Two to four samples were collected at different times in eight different patients. There was no significant relationship between MuSK antibody titers of all 33 samples and the MG severity score, MG composite scale, quantitative MG score and MG activities of daily living scale (MGADL). However, we could observe a close intrapatient relationship between MuSK antibody titer and MGADL when comparing the eight patients with more than one collected serum sample. MuSK antibody titers fluctuated in each patient and the titer had a tendency to increase when MGADL scores were higher. Our results suggest that MuSK antibody titers may not correlate with MG clinical severity on an interpatient level. On an intrapatient level, however, MuSK antibody titers had a close relationship with MG clinical severity.

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DISEASE DURATION AND THYMECTOMY IN NON-THYMOMATOUS MYASTHENIA GRAVIS

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Thymectomy is known to be effective treatment for anti-acetylcholine receptor antibody positive MG. Few studies have investigated whether disease duration has an effect on thymectomy. It is also uncertain whether late thymectomy has a potential benefit compared to non-thymectomy status. This study evaluated whether disease duration is associated with outcome in non-thymomatous MG after thymectomy and whether late thymectomy is beneficial.

Records of non-thymomatous, acetylcholine receptor antibody positive MG patients between 2005 and 2020 were reviewed retrospectively. MG patients with thymectomy were matched to those without thymectomy using propensity score matching. We also compared the outcomes between MG with thymectomy within two years (early) and over two years (late) after disease onset.Among 443 MG patients, 155 (35.0%) had undergone thymectomy while 288 (65.0%) had not. Thymectomized patients were younger and had a female predominance compared to controls ($p<0.001$). Using propensity score matching to attenuate the impact of age and sex, 139 patients with thymectomy and 139 controls were selected. Thymectomized patients had a higher remission rate ($p<0.001$), lower myasthenic functional score ($p<0.001$) and lower pyridostigmine dose at last follow-up ($p=0.008$) compared to controls. Early thymectomy group had a higher remission rate ($p=0.035$) and lower myasthenic functional score ($p=0.028$) than late thymectomy group. Late thymectomy group had a higher remission rate ($p<0.001$), lower myasthenic functional score ($p=0.001$) and lower pyridostigmine dose at last follow-up ($p=0.016$) compared to the control group.

Thymectomy has a beneficial effect in MG. Early thymectomy is favorable but late thymectomy is beneficial as well.

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CHARACTERIZATION OF NOVEL MUSCLE ACETYLCHOLINE RECEPTOR MODIFIER, ITS ACTION ON CHANNEL KINETICS AND POTENTIAL FOR TREATMENT OF FAST CHANNEL CONGENITAL MYASTHENIC SYNDROME

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Congenital myasthenic syndromes (CMS) are genetic disorders of the NMJ. Fast channel CMS, which results from mutations in the muscle acetylcholine receptor (AChR) that abbreviate ion channel activity, can be particularly difficult to treat. DC-98-LC74, a novel compound, was studied by single channel electrophysiology and two-electrode voltage clamp. In adult wildtype (WT) AChR, DC-98-LC74 (30 uM) increased the duration of the longest population of channel bursts (τau) at 100 nM [ACh] from 5.02 ± 0.52 ms ($n=5$) to 30.0 ± 4.23 ms ($n=7$). In two fast channel CMS mutant channels (εP121L & βI285S) τau was increased from 0.81 ± 0.27 ($n=3$) to 6.34 ± 0.85 ms ($n=3$) and 0.84 ± 0.1 ($n=3$) to 7.50 ± 0.90 ms ($n=5$), respectively. Furthermore, DC-98-LC74 (30 uM) increased the open probability of AChR cluster activity at 10 uM [ACh] in WT AChR (45 % vs 79 %) and of εP121L clusters at saturating [ACh] 3 mM (21 % vs 67 %). DC-98-LC74 (30 uM) alone did not elicit any channel activity. DC-98-LC74 is likely acting as a positive allosteric modulator. In WT mouse diaphragm, miniature endplate currents (mEPC) were prolonged, decay τ increased from 1.19 ± 0.11 to 1.94 ± 0.11 ms ($n=8$ & 12 fibres, respectively). In our transgenic mouse model of AChR deficiency in which mEPC is carried exclusively by fetal AChR, mEPC decay τ was largely unaffected (3.00 ± 0.11 vs 3.27 ± 0.15 ms; $n=19$ & 23 fibres, respectively). Thus, the binding site for DC-98-LC74 is adult-AChR specific.

R.G. Webster: None. **S. Alabaf:** None. **A. Li:** None. **R. Beerli:** *Employee*; Novartis Pharma AG. **N. Gerwin:** *Employee*; Novartis Pharma AG. **Y. Dong:** None. **D. Beeson:** None.

THE EFFECT, SIDE EFFECTS AND NET CLINICAL BENEFIT OF PYRIDOSTIGMINE IN A LARGE COHORT OF MYASTHENIA GRAVIS PATIENTS

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Introduction: Since its introduction in 1940, pyridostigmine is the only symptomatic treatment that is registered for clinical use in myasthenia gravis (MG). Remarkably, no randomized controlled trials on its efficacy have ever been completed and its effect, the severity of its side effects and its net benefit is unknown. Most guidelines recommend the initiation of immune suppressant medication when the effect of pyridostigmine is deemed "insufficient", without further specification. Treatment decisions are therefore based on incomplete data, which may lead to suboptimal treatment, as the use of chronic immune suppressant medication carries major health risks and has serious long term adverse effects. We aimed to study the effect, side effects and net benefit of pyridostigmine amongst participants of the Dutch-Belgian registry for neuromuscular junction disorders. A previous study showed that 74% of participants in this registry use pyridostigmine.

Methods: a link to an online questionnaire was sent out to 645 MG patients. We queried the dose and duration of current and past pyridostigmine use. Patients were asked to quantify the perceived effect of pyridostigmine (both current and previous doses) on twelve typical MG symptoms and thirty potential side effects on a three point scale. In case of previous changes in their dosing regimen, patients were asked about the reason for this change. Finally, patients were asked to indicate on a visual analog scale whether the benefits of their current pyridostigmine outweigh the side effects.

Results: 408 participants (63%) completed all questionnaires. Results will be presented at the conference.

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IMMUNE RESPONSE AND SAFETY OF SARS-COV2 MRNA 1273 VACCINE IN PATIENTS WITH MYASTHENIA GRAVIS

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Introduction and objectives: Evidence on mRNA vaccines safety and efficacy in MG patients is scarce. Our aim is to determine whether mRNA-1273 vaccine is safe and able to induce humoral and cellular response in MG patients.

Methods: An observational, prospective, cross-sectional study from April 2021 to November 2021, including 100 MG patients from our referral centre for MG in Barcelona, Spain. The mRNA-1273 vaccine was scheduled for all participants. Blood samples were collected before vaccination and 3 months after the second dose. Clinical changes in MG were measured using the MG-ADL score at baseline and after both doses. Humoral and cellular immune response after vaccination was assessed using a spike-antibody ELISA and interferon gamma release assay in plasma.

Results: Ninety-nine patients completed the full vaccination schedule and ninety-eight had the two blood samples taken. A statistically significant, but not clinically relevant, worsening of symptoms was identified after both dose of the mRNA-1273 vaccine. Mild adverse events occurred in 14 patients after the first dose and in 21 patients after the second dose. Eighty-seven patients developed a humoral response and seventy-two patients showed a T-cell response. Combined therapy with prednisone and other immunosuppressive drugs correlated with a lower seroconversion ratio (OR = 5.97 (CI 95% 1.46 - 24.09), p=0.015) and a lower T-cell response ratio (OR=2.83 (CI 95% 1.13 -7.13), p=0.024).

Conclusions: mRNA vaccination against COVID19 is safe in MG patients and showed no negative impact on the disease course. Patients achieved high humoral and cellular immune response levels.

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THE UNMET CLINICAL NEED FOR CLUSTERED ACETYLCHOLINE RECEPTOR CELL-BASED ASSAY TESTING IN PATIENTS WITH SERONEGATIVE MYASTHENIA GRAVIS

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Background and objectives: Eligibility for clinical trials in myasthenia gravis (MG) remains largely dependent on a positive autoantibody serostatus. Therefore, a lack of detectable autoantibodies in patients with seronegative MG (SNMG) not only hampers a prompt diagnosis, but it also restricts their access to new treatments and payers' reimbursement. In a variable proportion of SNMG patients, autoantibodies binding to the acetylcholine receptor (AChR) can be detected by a clustered AChR cell-based assay (CBA). However, data on the frequency of CBA-positive SNMG patients in the United States are lacking. Our aim was to report and validate the results of a clustered AChR CBA in a large cohort of SNMG patients evaluated by two major U.S. centers.

Methods: Serum or plasma samples from SNMG patients in the Yale and Duke MG Clinics' biorepositories were tested through clustered AChR CBA using flow cytometry. Immunoglobulin G purification and serial sample dilutions were performed to validate the CBA results. A novel B-cell culturing approach that allows for in vitro differentiation of B cells into antibody-producing cells was employed to identify circulating AChR-specific B cells in SNMG patients.

Results: Of 99 SNMG patients, 18 (18.2%) tested positive by clustered AChR CBA. In 17/18 patients, AChR autoantibodies were detected by both validation methods. In a complementary experiment, circulating AChR-specific B cells were identified in a CBA-positive SNMG patient, but not in 3 patients with a negative CBA result.

Discussion: These findings support the clinical need to implement clustered AChR CBA testing in the evaluation of SNMG patients.

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MOVING TOWARD PERSONALIZED MEDICINE: MIR-30E-5P AS A PREDICTIVE BIOMARKER IN MYASTHENIA GRAVIS

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Background: Myasthenia Gravis (MG) is a very heterogenous disease and progression may differ greatly among patients over time. In order to obtain personalized medicine for MG patients, we would need an objective biomarker that is able to predict the disease course and treatment response. MicroRNAs emerged in the last years as potential biomarkers in several diseases, and studies performed in MG subgroups have highlighted specific circulating miRNAs serum profiles which correlate with clinical response upon treatment and thymectomy. One study suggested that serum microRNA miR-30e-5p levels could predict generalization in ocular MG.

Methods: The aim of our study was to further characterize the role of miR-30e-5p as a prognostic biomarker over time in different MG subgroups. Serum levels of miR-30e-5p were analyzed in 27 patients with clinical follow-up data over time and divided into two groups: 1) "high miR-30e-5p" and 2) "low miR-30e-5p". We performed a survival analysis in these two groups, considering a change in MCG score > 3 or MGFA class > 1 as clinical relapse.

Results: 15 patients had high miR-30e-5p levels, and 12 patients had low miR-30e-5p levels. A significant correlation was found between miR-30e-5p levels and risk of relapse (p=0.0495), with a hazard ratio of 2.81 (95% CI 1.002-7.876).

Discussion: Although the number of patients was limited, we believe that our findings support the role of miR-30e-5p as a predictive biomarker in MG patients, regardless of disease subgroup.

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CONDITIONED MESENCHYMAL STROMAL CELLS AS TOOLS FOR IMMUNOMODULATION IN MYASTHENIA GRAVIS

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MG treatments are limited by adverse effects mandating the set-up of novel therapies. Mesenchymal Stromal Cells (MSC) are multipotent progenitors presenting immunomodulatory capacities that can be enhanced by a co-culture step with peripheral blood mononucleated cells (PBMC). Here, we characterized and compared phenotypes, gene expression profiles and functional capacities *in vitro* and *in vivo* of resting and conditioned cells. MSC derived from adipose tissue were conditioned by PBMC (cMSC), left untreated (rMSC), or activated by IFN-γ (γ-MSC). Flow cytometry analysis showed that in cMSC, the expression of CD54, CD273 and CD49a were increased and HLA-DR decreased. In contrast, major changes in MSC phenotype were induced by IFNγ activation (increased CD54, HLA molecules, CD47, reduced CD59). Single cell clustering by mass cytometry suggested cMSC and rMSC proximity and underlined the phenotypic alterations induced by IFNγ. Gene expression study by RNA-Seq showed differential expression of 244 genes between rMSC and cMSC, while 2089 and 3614 genes were differentially expressed when comparing γ-MSC with rMSC and cMSC, respectively. *In vitro* immunomodulating capacities were evaluated by PBMC proliferation inhibition assays and showed that cMSC supernatants were the only ones able to reduce proliferation by at least 50%. Finally, cMSC were challenged in a humanized MG mouse model, and cMSC-treated mice presented MG scores lowered by 50% compared to untreated mice from 2 weeks post-injection. To sum-up, this work unveiled treatment-dependent phenotypic and transcriptomic markers of MSC and demonstrated that immunomodulation capacities *in vitro* and *in vivo* are enhanced by cellular conditioning.

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REAL WORLD EXPERIENCE ON USE OF RITUXIMAB AT A NATIONAL HEALTH SERVICE REGIONAL REFRACTORY MYASTHENIA GRAVIS CLINIC IN BIRMINGHAM, UNITED KINGDOM

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Myasthenia gravis (MG) is a T-cell dependent B-cell mediated autoimmune disease targeting neuromuscular junction. Rituximab is a chimeric CD20 monoclonal antibody which gives consistently high response rates in anti-Muscle Specific Kinase antibody positive MG.[1,2,3]It is likely due to the fact that anti-MuSK abs are of IgG4 subclass, produced from CD20 abundant mature B cells.[4] In contrast, the response rates were observed to be variable for anti-Acetylcholine Receptor antibody positive MG.[1,2,5] Further clinical trials are undergoing to clarify. In the UK, the National Health Service (NHS) approved use of rituximab in specific circumstances in Myasthenia patients since 2019.[6] Our NHS regional refractory MG clinic reviewed 15 patients who received Rituximab from 2019 to 2021. 14 were anti-AchR positive and 1 was anti-LRP4 positive. 7 had severe disease (MGFA Class IV/V). Mean duration of disease at time of Rituximab was 9.4 years. 12 had had prednisolone and at least 2 other immunosuppressants. 9 received standard Rituximab regime of 2 doses of 1 Gram 2-weeks apart. 6 received more than 2 doses due to unsatisfactory clinical improvement or relapse. From an average of 10% before treatment, peripheral CD19+ B cell depletion to 0% was achieved in all although 3 had reappearance with one needing retreatment due to an accompanying clinical relapse. Outcome:A. Efficacy in MGFA Post-Intervention Status: 2 achieved Minimal Manifestations-3, 2 >50% Improved, 5 <50% Improved, 5 Unchanged and 1 Worse. B. Safety:

None experienced side effects. Further analysis of steroid dose reduction and long-term outcome is currently being undertaken.

P. San: None. **S. Jacob:** *Other*; Has served as international advisory board member for Alexion, ArgenX, Regeneron, Immunovant and UCB pharmaceuticals; is currently an expert panel member of Myasthenia Gravis consortium for ArgenX, Has received speaker fees from Terumo BCT and Eisai pharmaceuticals. **G. Sadalage:** None. **A. Roe:** None.

CD8 T CELL IMMUNE SIGNATURES IN AUTOIMMUNE MYASTHENIA GRAVIS

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Background: Myasthenia gravis (MG) is a chronic autoimmune disease mediated by T cells. Previous studies have predominantly focused on CD4 T cells, and the role of CD8 T cells in MG pathogenesis is uncertain.

Methods: Multi-color flow cytometry was performed on CD8 T cells among MG patients (N=42) with no immunosuppressive treatment (No-IS), with steroids and health controls (HC) (N=20). IsoPlexis single-cell platform was applied to a subset of patients to detect cytokine production prior to and post steroid treatment (N=12). NanoString RNA sequencing of 752 autoimmune related genes was performed on CD8 T cells to validate the cytokine changes (N=26).

Results: Memory (CD27+) and Exhausted (CTLA4+, PD-1+, EMOES +) CD8 T cell were increased in No-IS MG patients. In unbiased Self-Organizing Maps (FlowSOM), central memory and CXCR5+ CD8 T cells were increased in No-IS compared to HC and decreased post treatment. Single-cell analysis detected elevated frequencies of effector and inflammatory cytokines, including granzyme B, IFN-g, IL-9, MIP-1b, TNF-a, IL-17A, GM-CSF, IL-12, and MIP-1a in the No-IS group. Effector and inflammatory cytokines and frequencies of polyfunctional CD8 T cells significantly decreased with steroid treatment. RNA sequencing assays are in process and results will be presented at the conference.

Conclusion: Analysis of CD8 T cells demonstrates an effector phenotype with prominent polyfunctional inflammatory cytokine function in MG patients. Steroid treatment reduces the CD8 T cell proinflammatory phenotype. These data suggest that CD8 T cells play a role in MG pathogenesis and could have potential as a biomarker for monitoring response to treatment.

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EXTRAPYRAMIDAL MOTOR SIGNS IN A COHORT OF LATE ONSET MYASTHENIA GRAVIS

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Objectives. The aim of this study was to investigate the presence of extrapyramidal signs (EPS) and to evaluate striatal dopamine transporter binding in a cohort of Late-Onset Myasthenia Gravis (LOMG).

Methods. Rating and assessment of 19 LOMG patients were performed using the MGFA clinical research recommendations. EPS were evaluated on the MDS-UPDRS-III Scale. DaTSCAN was performed to evaluate the degree of striatal uptake loss.

Results. The mean age at MG clinical onset was 69.5 years (range 52-86). Clear Parkinson's-type features were found in 17 patients (14 male/3 female), with bradykinesia, rigidity, tremor, postural instability, and camptocormia the most frequent EPS. DAT images confirmed a reduced striatal uptake, which was bilateral in 10 patients and unilateral in 5. Among the LOMG patients with EPS, the clinical diagnosis was Parkinson's disease (11 patients), progressive supranuclear palsy (1), vascular parkinsonism (1), and essential tremor/essential tremor plus (6). No correlation was found between presynaptic nigrostriatal dopamine pathways and the severity/functional involvement of MG (MG class, QMG, and ADL-MG).

Discussion: EPS may be common in LOMG, and increase disability in MG patients. The role of pyridostigmine and other drugs in triggering the onset of these movement disorders is subject to debate. Health professionals must be alert to this possible comorbidity to be able to treat these specific symptoms. Acknowledgments: PI 16/01673 FIS-FEDER.

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PATIENT-REPORTED AND QUALITY OF LIFE OUTCOMES FROM MYCARING, A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, PHASE 3 TRIAL OF ROZANOLIXIZUMAB IN GENERALISED MYASTHENIA GRAVIS

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INTRODUCTION: Several validated patient-reported outcome measures (PROs) are used to measure the impact of generalized myasthenia gravis (gMG) on patients' daily lives.

OBJECTIVE: Assess the effect of rozanolixizumab, a fully humanized IgG4 monoclonal antibody inhibiting the neonatal Fc receptor, on change from baseline (CFB) in PROs and health-related quality of life (QOL) in patients with gMG.

METHODS: The MycarinG study (MG0003/NCT03971422) was a randomized, double-blind, placebo-controlled, Phase 3 trial that evaluated rozanolixizumab in adults with MGFA Class II-IVa, AChR or MuSK antibody-positive gMG. Patients were randomized 1:1:1 to weekly subcutaneous rozanolixizumab 7mg/kg, 10mg/kg or placebo for 6 weeks. Primary outcome was CFB in MG Activities of Daily Living (MG-ADL) at Day 43. PROs included MG Symptoms PRO scales, MG Impairment Index (MGII), and MG-QOL15r.

RESULTS: In total 200 patients were randomized. At Day 43, rozanolixizumab improved CFB in MG-ADL vs placebo (7mg/kg -3.370, 10mg/kg -3.403 and placebo -0.784; p<0.001 for both doses). MG Symptoms PRO scales improved from baseline: Muscle Weakness Fatigability (-23.029 [7mg/kg], -25.751 [10mg/kg] vs -10.588 [placebo]; both p<0.001), Physical Fatigue (-19.287, -25.459 vs -10.637; p=0.012 and p<0.001) and Bulbar Muscle Weakness (-14.839, -14.224 vs -3.519; both p<0.001). CFBs in overall MGII were -12.4, -16.1 and -3.4 and in MG-QOL15r were -4.0, -5.3 and -1.3, respectively.

SUMMARY/CONCLUSION: Compared to placebo, both doses of rozanolixizumab statistically and/or clinically meaningfully improved patients' symptoms and their ability to undertake daily activities as demonstrated by multiple MG PROs used in MycarinG, including the new MG Symptoms PRO. Funded by UCB Pharma.

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EVALUATION OF MRNA COVID-19 VACCINE REACTOGENICITY AND SAFETY IN MYASTHENIA GRAVIS PATIENTS.

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Introduction/Aims. Data on the safety and tolerability of vaccines against SARS-CoV-2 (COVID-19) among MG patients are at present scarce. Our study investigated the safety of mRNA-based 2-dose vaccination in a cohort of MG patients.

Methods: A prospective observational study evaluated the safety of mRNA-based vaccines administered to 91 MG patients with stable disease. Local and systemic reactogenicity post-injection was monitored for each dose administered. The patients were categorized and clinically assessed according to the MGFA recommendations.

Results: 36 males and 55 females received vaccines (mean age at first vaccine dose was 58.84 years, SD 17.05). Seventy-two (79.1%) patients were taking one or more immunosuppressants. The most common adverse effects were injection site pain, fatigue, myalgia, chills, fever, and headache. Local and systemic reactions were transient. 58.2% of the patients had one or more reactions. No anaphylactic reaction was observed. No patient experienced a myasthenic crisis, and two experienced a slight deterioration from their QMG baseline score.

Discussion: Our results suggest that COVID-19 vaccination does not cause clinical exacerbation in stable MG patients, regardless of their age, gender, history of myasthenic crisis, or whether they are taking immunosuppressants. Acknowledgments: PI 16/01673 FIS-FEDER.

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A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2 STUDY OF SUBCUTANEOUS BATOCLIMAB IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS

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Batoclimab (IMVT-1401), a human anti-neonatal Fc receptor monoclonal antibody, reduces circulating IgG antibodies and may improve generalized myasthenia gravis (gMG) symptoms by reducing pathogenic anti-acetylcholine receptor antibody (AChRAb) levels. This study (NCT03863080) consisted of 3 periods. Double-blind Period-1: AChRAb+ gMG subjects (MGFA Class II-IVa) randomized to receive subcutaneous (SC) batoclimab injection (680mg or 340mg) or placebo QW x 6 doses; Open label Period-2: subjects received SC batoclimab 340mg Q2W x 3 doses; Period-3: 6-week follow-up. Primary objectives were safety and pharmacodynamics. Clinical efficacy was a secondary objective although the current study was not powered to detect statistical differences between groups. Seventeen subjects (680mg [n=6], 340mg [n=5], placebo [n=6]) were enrolled. During Period-1, adverse events (AEs) occurred in 83%, 80%, and 83% of subjects for 680mg, 340mg, and placebo groups, respectively. Injection site erythema was more common with batoclimab (3/11) than placebo (1/6). One subject (680mg) experienced a serious AE (not treatment-related). Four subjects (680mg) experienced reductions from normal albumin levels to low post-baseline values (26-31 g/dL). At Week 6, IgG and AChRAb levels were respectively reduced from baseline by 76% and 86% (680mg), 59% and 54% (340mg), and 2.5% and 1.1% (placebo), ($p<0.05$ for each dose vs. placebo). Batoclimab-treated subjects (pooled) compared to placebo showed numerical improvements in MG-Activities of Daily Living (-3.8 vs. -0.2), Quantitative MG (-3.9 vs. -1.8), and MG-Composite (-8.0 vs. -0.8) scores. The safety profile and preliminary clinical findings observed with batoclimab induction therapy support its further investigation as a potential patient-administered therapy for gMG.

R.J. Nowak: *Consultant*; Alexion, Argenx, Calbetta Bio, CSL Behring, Grifols, Sanofi, UCB, Immunovant, Momenta, Viela Bio. **M. Benatar:** *Consultant*; Alexion, Immunovant, Sanofi, UCB, Cartesian. *Other*; Alexion, UCB. **A. Breiner:** None. **D.J. Isaacman:** *Employee*; Immunovant, Inc. **V. Bril:** None.

COMPARISON OF FIXED AND LIVE CELL BASED ASSAY FOR THE SEROLOGICAL DIAGNOSIS OF MYASTHENIA GRAVIS

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Introduction: Aim of this study was to analyse the performance of live and fixed cell-based assay (CBA) in the serological diagnosis of myasthenia gravis (MG).

Methods: MG serum samples pre-selected according to radioimmunoassay (RIA) results and stored at -20°C until use were tested with both live CBA (L-CBA) employing HEK293 cells transfected with adult/foetal AChR or MuSK and the commercial fixed CBA (F-CBA) (Euroimmun, Lubeck). Two blinded independent raters assessed the assays. The results of F-CBA and L-CBA were compared with McNemar's test. Interrater agreement was evaluated with Cohen's kappa.

Results: Eighty-six samples from MG patients were tested (21 AChR-RIA-positive, 21 MuSK-RIA-positive and 44 RIA-negative). L-CBA was positive in all RIA-positive cases, while F-CBA was positive in all RIA-positive sera but one MuSK-RIA-positive sample. Of the 44 RIA-negative sera, 14 (31.8%) were positive on L-CBA (9 for AChR antibodies, 5 for MuSK antibodies) and 9 (20.5%) resulted positive on F-CBA (8 for AChR antibodies, 1 for MuSK antibodies). All F-CBA positive samples were also positive on L-CBA. Although both assays were effective in detecting antibodies in RIA-negative MG patients, L-CBA was more sensitive than F-CBA ($p=0.0313$). Interrater agreement was 98.9% for L-CBA (Cohen's kappa: 0.975, 95%C.I.=0.926-1.000) and 97.5% for F-CBA (Cohen's kappa: 0.955, 95%C.I.=0.893-1.000).

Conclusions: L-CBA was more sensitive than F-CBA in the detection of both AChR and MuSK antibodies. Interrater agreement was excellent for both assays. While F-CBA may be a valuable alternative to RIA, L-CBA could be reserved to the diagnostic workup of RIA and F-CBA negative samples.

G. Spagni: None. **G. Monte:** None. **Z. Chemkhi:** None. **S. Falso:** None. **A. Evoli:** None. **V. Damato:** None.

INCREASED SERUM IL-2, IL-4, IL-5 AND IL-12P70 LEVELS IN ACHR SUBTYPE GENERALIZED MYASTHENIA GRAVIS

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Background: Myasthenia gravis (MG) is an autoimmune disorder affecting neuromuscular junction. Cytokines play important roles in facilitating the immune response and augmenting the pathogenic antibody production. The current study aims to sensitively characterize the serum levels of cytokines with very low concentration in generalized MG (gMG).

Methods: Using ultrasensitive single-molecule arrays (SIMOA), we measured serum IL-2, IL-4, IL-5 and IL-12p70 in 228 participants including 152 immunotherapy-naïve anti-acetylcholine receptor (AChR) subtype gMG from Huashan MG registry and 76 healthy controls. Subgroup analysis was then performed by stratifying patients according to the onset ages (early-onset MG versus late-onset MG), MGFA classification (mild group with MGFA II versus moderate to severe group with MGFA III/IV), disease duration at baseline (short

duration with less than 6 months versus long duration with longer than 6 months).

Results: Serum IL-2, IL-4, IL-5 and IL-12p70 levels were significantly elevated in gMG compared to controls. Subgroup analysis revealed that IL-2 levels were slightly elevated in gMG with MGFA II compared to MGFA III/IV as well as elevated levels of IL-2 and IL-5 in late-onset gMG compared with the early-onset gMG. gMG patients with a long duration had a significant increased serum IL-12p70 than those with a short duration.

Conclusion: Serum cytokines with very low concentrations may provide as potential biomarkers in stratifying gMG patients in future prospective cohort studies.

X. Huan: None. **R. Zhao:** None. **J. Song:** None. **H. Zhong:** None. **M. Su:** None. **Y. Wang:** None. **C. Yan:** None. **S. Chen:** None. **Z. Zhou:** None. **J. Lu:** None. **J. Xi:** None. **S. Luo:** None. **C. Zhao:** None.

RAT T CELL CULTURE FOR THE DEVELOPMENT OF MYASTHENIA TREATMENTS

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We have developed a protocol to purify and culture rat T cells with the purpose of developing and testing T cell mediated treatments such as chimeric autoantibody receptor (CAAR) T cells in rat models of AChR and MuSK myasthenia. Spleen mononuclear cells were first separated by centrifugation in density gradient media followed by T cell purification by positive selection with anti-CD3 magnetic microbeads column. Purified T cells were grown on plates coated with T cell activating antibodies (anti-CD3 and anti-CD28) and in media supplemented with IL-2. Initial cell proliferation was assayed by flow cytometry of CFSE loaded cells. We found that cells start to proliferate after 24 hours in culture, initially with proliferation of CD8+ T cells, with a doubling time of 24 hours. We optimized media formulation and plating density to achieve robust cell proliferation for more than 10 days in culture. Cultured T cells could be transduced with human lentivirus, with an efficiency of around 20%, allowing for in vitro genetic manipulation. Autoreactive T cells are found in myasthenia gravis and this protocol can be used to study their role in this disease and other antibody mediated autoimmune diseases.

L.S. Borges: *Other*; Research funding from Cabaletta Bio. **H. Mir:** *Other*; Research funding from Cabaletta Bio. **O.C. Tong:** *Other*; Research funding from Cabaletta Bio. **D.P. Richman:** *Other*; Research funding from Cabaletta Bio.

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

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

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

Summary/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 analysis is ongoing.

C. Farmakidis: *Consultant*; UCB, Argenx, Momenta. **S. Hunt:** None. **M. Pasnoor:** *Consultant*; Terumo BCT, Alexion, Argenx, Catalyst, CS Behring, Momenta, Takeda. **D. Jabari:** None. **S. Chandrashekhar:** None. **O. Jawdat:** None. **M.M. Dimachkie:** *Consultant*; ArgenX, Catalyst, CSL-Behring, Janssen, Momenta, NuFactor, Octapharma, RaPharma/UCB, RMS Medical, Shire, Takeda, UCB Biopharma. *Other*; Alexion, Catalyst, CSL-Behring, Grifols, NIH, Octapharma, Ra Pharma/UCB, Shire Takeda, UCB Biopharma / RaPharma.

AAV9-MEDIATED GENE THERAPY OF CHOLINE ACETYLTRANSFERASE DEFICIENT MICE

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The enzyme choline acetyltransferase (ChAT) synthesizes acetylcholine from acetyl-CoA and choline at the neuromuscular junction and at the nerve terminals of cholinergic neurons of the central and autonomic nervous systems. Mutations in the ChAT gene (*CHAT*) result in a presynaptic variant of congenital myasthenic syndrome (CMS) that associates with life threatening episodes of apnea. Knockout mice for *Chat* (*Chat* $^{-/-}$) are immobile and die at birth. To circumvent the perinatal mortality of *Chat* $^{-/-}$ we crossed mutant mice that possess loxP sites

flanking *Chat* exons 4 and 5 with mice that express *Cre-ER^{T2}*. Injection of tamoxifen (Tx) into double homozygous *Chat$^{flox/flox}$-Cre-ER^{T2}* mice at postnatal day 11 induced downregulation of Chat, arrest of growth, weakness, and death. However, a proportion of *Chat$^{flox/flox}$-Cre-ER^{T2}* mice perinatally injected in the cerebral ventricles with 2e13 vg/Kg adeno-associated virus type 9 (AAV9) carrying human *CHAT* (AAV9-*CHAT*) survived a subsequent Tx injection and lived to adulthood without showing any obvious signs of weakness. The expression of Chat in spinal cord motor neurons in *Chat$^{flox/flox}$-Cre-ER^{T2}* mice injected with Tx was about a third of that of wild-type mice, and about half of *Chat$^{flox/flox}$-Cre-ER^{T2}* mice injected with AAV9-*CHAT* and Tx. Viral genome quantification by real time PCR revealed persistent expression of AAV9 in the brain of injected mice.

AAV9-mediated gene therapy may provide an effective treatment for children severely affected with CMS caused by *CHAT* mutations.

C.A. Thomas: None. **C.C. Lin:** None. **T.L. Huynh:** None. **D.T. Wei:** None. **J. Vazquez:** None. **R.A. Maselli:** *Consultant*; AMPLO Biotechnology, ARGENX Biotechnology, Guidepoint Global.

IMPROVING PATIENT OUTCOMES THROUGH STANDARDIZED PROTOCOLS WHEN PRESCRIBING GLUCOCORTICOIDS

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Background: Glucocorticoids are prescribed in the (iNMD) clinic. Currently, there is lack of uniformity and evidence-based practice regarding counseling, monitoring parameters, and prophylactic medications when prescribing glucocorticoids. Glucocorticoids are linked to many short and long term, reversible and irreversible side effects. These side effects have impact on morbidity and mortality for our patients. Following evidence-based guidelines on monitoring and prescribing prophylactic medications can mitigate these side effects.

Design/Methods: Our initial step included a literature review to create guidelines around glucocorticoid monitoring. We identified four areas of intervention: (1) Bone health, (2) baseline blood work including evaluation for infectious disorders, (3) GI prophylaxis and (4) PCP prophylaxis. Our second step was to present our data to the iNMD clinic providers and prospectively monitor for recommendation compliance. We identified one primary recommendation (vitamin D and Calcium initiation), which we would monitor for compliance, as well as secondary recommendations.

Results: We worked with our institution to explore efficient tools for data collection, and used the edge reporting system. ~55% of patients on glucocorticoids therapy were recommended vitamin D and calcium at baseline. This increased to 85% at seven months post intervention.

Conclusions: Moving forward, we will continue to follow the data and review outliers, including root cause analysis. We will expand to include our secondary recommendations, review data for other immunomodulatory treatments, and expand outside the iNMD clinic within neuromuscular, neurology, and eventually to other divisions.

N. Goyal: None. **T. Chang:** None.

THE DUKE MYASTHENIA GRAVIS CLINIC REGISTRY: SINGLE FIBER EMG FINDINGS

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Introduction. The Duke Myasthenia Gravis (MG) Clinic Registry contains physician-derived information on patients seen in the Duke MG Clinic since 1980.

Objective: To report single-fiber EMG (SFEMG) findings in Registry patients.

Methods: We reviewed Registry data from patients with MG initially seen in the Duke MG Clinic between 1980 and 2017. Jitter was measured with SFEMG electrodes during voluntary activation using conventional techniques. The extensor digitorum (ED) or frontalis muscles were usually examined first.

Results: Data from the initial SFEMG studies on 1,081 patients were included in the following analyses: Jitter was increased in at least one muscle in 990 patients (92%): 84% of 228 with purely ocular muscle weakness and 94% of 853 with generalized MG; 95% of 684 with AChR-antibodies and 86% of 348 without these antibodies. ED and a facial muscle were both tested in 393 patients: both were abnormal in 60%; the facial muscle alone was abnormal in 26% and the ED alone in 5%. Frontalis and orbicularis oculi (OO) were both tested in 73 patients: both were abnormal in 20%, OO alone in 42% and frontalis alone in 11%. Follow-up SFEMG studies were performed in 90 patients whose initial studies were negative, and were abnormal in 23 (26%).

Summary/Conclusions: Jitter was increased in 92% of initial SFEMG studies in 1,081 patients with MG, and in follow-up studies in an additional 2%. Facial muscles were more often abnormal than limb muscles, but no one muscle was more abnormal or more often abnormal in every patient.

D.B. Sanders: *Consultant*; Accordant Health Services, Alexion, Cabaletta, Immunovant. *Other*; Edshagen Publishing House, Roche, VielaBio, Janssen. **S.M. Raja:** *Consultant*; Regeneron, Signant Health. **V.C. Juel:** *Other*; Alexion. **J.T. Guptill:** *Consultant*; Alexion, Apellis, Argenx, Immunovant, Cabaletta, Janssen, Momenta, Ra Pharma, Regeneron, UCB, Toleranza. **L.D. Hobson-Webb:** None. **J.M. Massey:** *Consultant*; Argenx, Momenta. *Other*; Revance.

THE DUKE MYASTHENIA GRAVIS CLINIC REGISTRY: ANALYSIS OF OUTCOMES

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INTRODUCTION: The Duke Myasthenia Gravis (MG) Clinic Registry is a disease-specific database that contains comprehensive physician-derived data on Duke MG Clinic patients seen since 1980.

OBJECTIVE: To report outcomes to treatment in patients initially seen in the Duke MG Clinic from 1980 to 2008.

METHODS: Data from 1,458 patients with MG were reviewed. Treatment was determined by the treating neurologist and evolved over the years, generally in accordance with the Consensus 2016/2021 Guidance statements. MGFA Post-Intervention Status (PIS) was determined at each clinic visit by the treating neurologist. Treatment Goal (TG) was defined as achieving Minimal Manifestations or better. Kaplan-Meier analysis was performed to investigate the effect of sex, onset age, disease distribution (ocular vs generalized) and AChR antibody presence on the time to achieve TG. The initial visit date defined the time origin, events were defined as the earliest date that TG was achieved, and censoring was defined by the date of the last visit with PIS data.

RESULTS: PIS data were available for 969 patients. TG was achieved by 58% at 2 years, 70% at 5 years and 73% at 10 years after their initial visit. TG was achieved by more males (p=0.0005) and patients with AChR-Abs (p=0.05), onset ≥ 50 (p=0.0003) and ocular MG (p=0.0006).

SUMMARY/CONCLUSION: Among patients treated in the Duke MG Clinic from 1980 to 2008, 73% of those followed for ≥10 years achieved Minimal Manifestations or better, and were more likely to be male, have AChR antibodies, onset after age 50 and ocular MG.

D.B. Sanders: *Consultant*; Accordant Health Services, Alexion, Cabaletta, Immunovant. *Other*; JanssenRnD, Roche, VielaBio, Edshagen Publishing House. **M.W. Lutz:** None. **S.M. Raja:** *Consultant*; Regeneron, Signant Health. **V.C. Juel:** *Other*; Alexion. **J.T. Guptill:** *Consultant*; Alexion, Apellis, Cabaletta, Argenx, Immunovant, Janssen, Momenta, Ra Pharma, Regeneron, UCB, Toleranza. **L.D. Hobson-Webb:** None. **J.M. Massey:** *Consultant*; Argenx, Momenta. *Other*; Revance.

MEASURING ADVERSE EVENT BURDEN IN MYASTHENIA GRAVIS: SINGLE CENTER PROSPECTIVE EVALUATION OF THE ADVERSE EVENT UNIT (AEU)

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Background: The Adverse Event Unit (AEU) is a physician and patient derived consensus metric to measure treatment adverse event (AE) burden. Unlike previous measures, the AEU quantifies AE burden, independent of any disease or treatment, to facilitate treatment comparisons over time. We anticipate that AEU scores will provide novel information to better inform patient treatment decisions and MG population treatment paradigms.

Design/Methods: In this study, AEU scores are also being obtained alongside the routinely administered MG-ADL, MG-QOL15r, and MG-Composite at in person and telemedicine clinic visits. AEU administration will be considered feasible if completion rate is equal to or better than MG-ADL completion rate during a 6 month period. Participating physicians and patients are also being surveyed about satisfaction with and utility of the AEU. We are also comparing the time to administer the AEU and other MG metrics, and evaluating if AEU scores are associated with decisions to change treatment.

Results: 46 patients are currently enrolled. Baseline characteristics: Mean age 65 years, 48% female, 60% generalized MG, 69% visits in person. Treatments: pyridostigmine 78%, prednisone 41%, mycophenolate 33%, azathioprine 7%, eculizumab 15%, IVIG 13%, plasma pheresis 6%, tacrolimus 2%. AEs reported at 30% clinic visits. Mean time to complete the MG-ADL and QOL-15r is 6.5 minutes. Mean time to complete the AEU was 4.2 minutes.

Conclusions: Administration of the AEU appears feasible at MG clinic visits. AEU influences on treatment decisions, patient/physician satisfaction with the AEU, and differences in AEU scores among different treatments is currently being evaluated.

M.K. Hehir: *Consultant*; Alexion Pharma, Argenx Pharma. **M. Conaway:** None. **A.B. St. Sauveur:** None. **N. Kolb:** None. **W. Waheed:** None. **B.L. McNeish:** None. **N. Tweedy:** None. **D. Sanders:** None. **P. Narayanaswami:** None. **T.M. Burnd:** None.

MEASURING ADVERSE EVENT BURDEN IN MYASTHENIA GRAVIS: RETROSPECTIVE VALIDATION OF THE ADVERSE EVENT UNIT (AEU)

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Objective: In collaboration with the PROMISE-MG trial (NCT03490539), the goal of this project is to evaluate the validity and utility of the Adverse Event Unit (AEU) as a tool to measure treatment adverse event (AE) burden in myasthenia gravis (MG).

Background: The AEU is a physician and patient derived consensus metric to measure treatment AE burden. Unlike previous measures, the AEU quantifies AE burden, independent of any disease or treatment, to facilitate treatment comparisons over time. We anticipate that AEU scores will provide novel information to better inform patient treatment decisions and MG population treatment paradigms.

Design/Methods: In the PROMISE-MG trial, 167 treatment naïve adult MG patients recruited from 19 centers in the US and Canada, were followed prospectively for 24-36 months at routine clinical visits. CTCAE AE values from each trial visit will be converted into AEU scores. To assess AEU construct and concurrent validity, correlations between AEU scores, CTCAE, MG-Composite, and MG-QOL15r will be computed. We are also measuring differences in the AEU yearly burden among the medications used to treat patients in PROMISE-MG. AEU score will also be tested as a predictor of medication discontinuation.

Results: PROMISE-MG trial data are currently being analyzed for this study.

Conclusions: This study will present validation data for the AEU as a novel tool to measure AE burden in an MG trial population. We will also present data about differences in AE burden among MG treatments. Final study results will be presented.

M.K. Hehir: *Consultant*; Alexion Pharma, Argenx Pharma. **M. Conaway:** None. **A.B. St. Sauveur:** None. **D. Sanders:** None. **P. Narayanaswami:** None. **N. Kolb:** None. **W. Waheed:** None. **B. McNeish:** None. **N. Tweedy:** None. **T.M. Burns:** None.

CHARACTERISATION OF A NOVEL MOUSE MODEL FOR CONGENITAL MYASTHENIC SYNDROME DUE TO DEFECTIVE ACHR CLUSTERING CAUSED BY MUTATIONS IN CHRND

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Congenital Myasthenic Syndromes (CMS) are a group of genetic disorders of the neuromuscular junction (NMJ) characterised by fatigable muscle weakness. In some CMS, the disease is caused by mutations impairing acetylcholine receptor (AChR) clustering at the motor endplate, often due to mutations in RAPSN. A CMS patient with a RAPSN like CMS phenotype instead had compound heterozygous mutations in the AChR delta subunit. One was a null mutation and the other was p.R396H in the cytoplasmic loop of the delta subunit. We showed that clustering in myotubes is impaired if AChR harbours this mutation, but AChR kinetics or surface expression are not altered. Much of what we know about CMS derives from mouse models replicating pathophysiology of the human disease. We designed a mouse model harbouring δR399H (corresponding to p.R396H in humans), which was generated using the MRC GEMM programme. Mice were genotyped and phenotypically characterised up to postnatal week 20. Wildtype (WT), heterozygous and homozygous mice were compared separately for males and females. In model mice, up to 50% compound muscle action potential amplitude decrement was detectable on repetitive nerve stimulation (RNS) at postnatal week 6. In contrast, muscle fatigability as measured using an inverted screen became apparent later, at 11 weeks of age. Despite worsening muscle weakness with age, the amount of decrement did not increase at postnatal week 12. WT mice showed no electrophysiological evidence of NMJ defect while heterozygous mice may show mild weakness along with mild decrement on RNS. Further studies are ongoing.

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A NEW REPETITIVE NERVE STIMULATION PROTOCOL FOR EVALUATION OF THE FACIAL NERVE IN MYASTHENIC RATS

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INTRODUCTION: Repetitive nerve stimulation (RNS) is a commonly utilized diagnostic test for myasthenia gravis (MG) and disorders of the neuromuscular junction (NMJ). In humans, RNS is typically performed in both the limb and axial muscles. Axial muscles have greater sensitivity compared to the limb muscles. Rodent protocols for RNS of the median nerve/brachial plexus or sciatic nerve are well described, but not for axial muscles.

METHODS: Facial nerve RNS was performed in anesthetized, healthy Lewis rats. Stimulating and recording electrodes were created by arranging subdermal, monopolar needle electrodes at a fixed distance of 5 mm. The recording electrode was inserted in the lower lip of the rat, approximately 2 mm distal to the labial commissure. Electrical stimulus was applied approximately 20 mm proximal from the recording electrodes, in the mandibular branch of the facial nerve, visualized through shaved skin. The conventional sciatic nerve RNS protocol was also performed in the same session.

RESULTS: The facial nerve RNS protocol yielded consistent, reproducible results in healthy rats with minimal technical artifact that was comparable or superior to the conventional sciatic nerve protocol.

CONCLUSION: This rat facial nerve RNS protocol represents a sensitive electrodiagnostic method for demonstrating dysfunction of the NMJ. It may be particularly useful for models of MuSK-MG, which exhibit significant bulbar and axial weakness. We plan to utilize this protocol in future experiments with MuSK-MG rat models.

O.C. Tong: *Other*; Received research funding from the California Institute for Regenerative Medicine. **D.P. Richman:** *Other*; Received research funding from NIH, Myasthenia Gravis Foundation of America, and Cabaletta Biopharma.

CRYPTOCOCCAL MENINGITIS IN A GENERALIZED MYASTHENIA GRAVIS PATIENT ON ECULIZUMAB (SOLARIS) THERAPY-A SURVIVAL STORY GEORGE A. SMALL, MD, SUKHMANI SANDHU, MD ALLEGHENY GENERAL HOSPITAL, ALLEGHENY HEALTH NETWORK, PITTSBURGH, PENNSYLVANIA, USA

George Alan Small, Sukhmani Sandhu

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Background: Myasthenia Gravis pathophysiology involves AchR blocking and binding antibodies, which result in neuromuscular junction dysfunction. Recently, the importance of complement-mediated post-junctional membrane destruction was recognized in MG pathogenesis, resulting in FDA approval of complement blocking therapy, eculizumab, that improves generalized MG, but exposes patients to life-threatening, encapsulated pathogens. We report the first case of cryptococcal meningitis in an eculizumab-treated patient.

Case Report: 55 year old HIV- male farmer with Type-2 diabetes and hypertension developed AchR binding +, MGFA stage 3 myasthenia gravis in 2014. No thymoma. Treated with pyridostigmine, 20 mg prednisone daily, requiring intermittent plasmapheresis or IVIG administration for dyspnea and dysphagia. Azathioprine 1.5mg/kg/day instituted in 2018 as well as a video-assisted thymectomy performed to prevent

exacerbations requiring hospitalization, IVIG, and PLEX. Eculizumab therapy instituted in January, 2019 after two Bexsero and Menactra vaccinations, according to ACIP and package insert timing guidelines. Prednisone dose weaned to 10mg/day and azathioprine weaned off over 4 months. MG-related exacerbation frequency decreased. In December, 2019, the subject developed headache, fever, and neck pain. CT head normal. Lumbar puncture: WBC 53, protein 65, glucose 23, cryptococcal antigen +. Negative viral antigen panel. Eculizumab discontinued. Amphotericin/flucytosine induction therapy initiated, severe skin rash prompted fluconazole substitution for flucytosine. Consolidation phase antifungal therapy completed, lifetime oral fluconazole continues due to subject's need for immunosuppressants for bulbar weakness.

Conclusion: Cryptococcal meningitis affects one million victims worldwide- Mortality 60%. We propose our subject's rural occupation involving soil-turning activity placed him at risk for this infection while on eculizumab.

G.A. Small: *Consultant*; Alexion. *Other*; Speakers Bureau. **S. Sandhu:** None.

PHASE 1B/2A STUDY OF AUTOLOGOUS MRNA-ENGINEERED ANTI- B-CELL MATURATION ANTIGEN CHIMERIC ANTIGEN RECEPTOR T-CELLS FOR TREATMENT OF SEVERE GENERALIZED MYASTHENIA GRAVIS

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Introduction: Descartes-08 is the first chimeric antigen receptor (CAR) T-cell therapy for treatment of generalized myasthenia gravis (gMG). Descartes-08 is an autologous mRNA-engineered CAR T-cell that targets B-cell maturation antigen (BCMA). BCMA expression is limited to plasma cells, the primary cell type that secretes antibodies including those pathogenetically associated with MG.

Methods: Three patients with severe gMG (median baseline MG-ADL score 11) requiring immunosuppression were treated in an outpatient setting in the open-label dose escalation portion of this phase 1b/2a study, with increasing weekly doses of 3.5 x 10^6 cells/kg on Day-1, 17.5 x 10^6 cells/kg on Day-8, and 52.5 x 10^6 cells/kg on Day-15. No lymphodepleting preconditioning therapy was administered.

Results: There were no serious adverse events or grade ≥2 treatment-related adverse events. Mild, self-limited grade 1 headache, was the only recurring adverse event. All patients experienced reductions in disease severity measures. Most notably, changes in MG Composite Score in patients 1, 2, and 3 respectively were -11/-6/-2 [median -6] from Baseline to Week 4, -5/-10/+1 [-5] from Baseline to Week 8, and -7/-10/0 [-6] from Baseline to Week 12, with similar changes in other indices.

Discussion: Descartes-08 treatment was safe and well tolerated, with preliminary evidence suggesting a possible clinical benefit in patients with gMG. Enrollment to the open-label Dose Expansion portion of the study is ongoing.

V. Granit: *Consultant*; Alexioan Pharmaceuticals, Argenx, Immunovant Inc., Amylyx Pharmaceuticals Inc. **T. Mozaffar:** *Consultant*; Alexion, Amicus, Argenx, Arvinas, Audentes, AvroBio, Maze Therapeutics, Momenta (now Janssen), Sanofi-Genzyme, Sarepta, Spark Therapeutics, UCB/Ra Pharmaceuticals, Modis/Zogenix. *Other*; Alexion, Amicus, Argenx, Arvinas, Audentes/Astellas Gene Therapy, Bristol-Myers-Squib, Cartesian Therapeutics, Grifols, Momenta, Ra Pharmaceuticals, Sanofi-Genzyme, Spark Therapeutics, UCB, Valerion. **M. Benatar:** *Consultant*; Ra Pharmaceuticals, UCB, Alnylam, Viela Bio, Immunovant. *Other*; Alexion, UCB. **J.F. Howard:** *Other*; Alexion Pharmaceuticals, argenx BVBA, Cartesian Therapeutics, Ra Pharmaceuticals (now UCB Biosciences), Regeneron Pharmaceuticals, Takeda Pharmaceuticals, Immunovant Inc., Sanofi US, Viela Bio Inc. (now Horizon Therapeutics), Toleranzia AB. **D.L. Pereira:** None. **J. Steele:** None. **J.K. Fong:** None. **M. Chopra:** None. **A. Chowdhury:** *Employee*; Cartesian Therapeutics. *Other*; Cartesian Therapeutics. **M.D. Miljkovic:** *Employee*; Cartesian Therapeutics. **M. Kurtoglu:** *Employee*; Cartesian Therapeutics. *Other*; Cartesian Therapeutics.

A QUALITATIVE STUDY OF SYMPTOM AND TREATMENT IMPACT IN MG

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Background: The patient burden of MG is often underestimated. New MG treatments, such as biologics, may increase the proportion of patient symptom-free patients. However, these new treatments have potential side effects and associated costs. Understanding the treatment preferences of people with MG will help inform patients, clinician and policy makers. We are studying how people with MG make decisions regarding new interventions--considering trade-offs between potential side effects and efficacy.

Methods: Fifteen patients with a wide range of MG severity participated in semi-structured interviews. Interviews were recorded and transcripts were analyzed using line-by-line open coding, to generate themes. We used these themes to identify treatment characteristics to develop a discrete choice experiment.

Results: Four themes were identified: MG symptoms and burdens, patient experience with treatment side effects, patient treatment preferences and patient treatment goals. Double vision was the most bothersome symptom for 40% of patients, Prednisone-related adverse events were the most frequently described, with weight gain reported as the most bothersome in 33%. Most patients preferred treatments in the form of pills (67%). The most frequently reported

treatment goals were returning to normal or zero symptoms (40%), discontinuation of prednisone (40%), and a preference to take less pills (33%).

Conclusion: We identified relevant characteristics for potential MG treatments. These will be incorporated into an ongoing discrete choice experiment to understand how people with MG make treatment decision. Potential attributes are: efficacy in controlling ocular, bulbar and limb symptoms, ability to reduce prednisone, risk of infections and administration route.

M. MEndoza: None. **E. Wolff:** None. **M. Chou:** None. **A. BAyoumi:** None. **C. Barnett-Tapia:** *Consultant*; ALEXION, SANOFI, ARGENX. *Other*; Reserach support Grifols and Octapharma.

NOVEL BIOMARKERS ASSOCIATED WITH AUTOIMMUNE MYASTHENIA GRAVIS: A PILOT STUDY USING TWO DIFFERENT PROTEOMIC APPROACHES

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Autoimmune MG is characterized by antibodies directed against molecules of the neuromuscular junction and more generally against the acetylcholine receptor (AChR). These antibodies are crucial for the diagnosis. Biological markers could be important for clinical follow-up and prediction of severe cases. Here we used the Somascan and Olink technologies, both of which target specific proteins in biological fluids. We analyzed a pilot cohort of 15 patients with non-steroidal MG and nine controls and focused on the 171 molecules common to both proteomic approaches. Analysis of differentially expressed proteins revealed 65 significant proteins with SomaScan and 28 with Olink, with 18 proteins being common. Most of the downregulated proteins were upregulated in MG patients (17 upregulated, one downregulated). These results were identical in both techniques. Furthermore, comparing p values between the two methods revealed a very good correlation, showing that the changes observed in this study are reproducible. Our data confirmed previous studies and revealed several new biomarkers associated with MG. Among the deregulated proteins were two metalloproteases (MMP9, MMP10), CXCL11, CD40L, S100A12. In addition, the levels of CXCL16 and IL17RA were correlated with the clinical score. Reactome pathway analysis revealed the potential involvement of the innate immune system. In conclusion, this work shows that proteomic analyses may reveal new insights into MG disease and potential biomarkers with clinical relevance. However, the size of the cohort was small, and validation on a larger number of patients would be necessary.

F. Truffault: None. **J. Vanwassenhove:** None. **E. Fadel:** None. **F. Bolgert:** None. **S. Demeret:** None. **R. Le Panse:** None. **S. Berrih-Aknin:** *Consultant*; Vitaccess. *Other*; CSO, Naki Health.

HUMAN NEUROMUSCULAR JUNCTION ON A CHIP: PATHOPHYSIOLOGICAL MODEL OF MYASTHENIA GRAVIS

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Background: Therapeutic strategies for myasthenia gravis (MG) currently focus mainly on targeting the immune system and less on improving the neuromuscular junction (NMJ) function. Considering that the β-adrenergic agonist salbutamol has the ability to stabilize acetylcholine receptors (AChRs) in mouse muscle cells, strengthening NMJ structure through stabilization of human AChR clustering could be an approach to develop additional MG treatment.

Methods: In order to investigate the molecular mechanisms that govern NMJ stabilization and examine how various molecular mechanisms in MG affect NMJ transmission, we are establishing an *in vitro* NMJ model using induced pluripotent stem cells (iPSCs). Further, we are studying the optimal conditions for iPSC-derived NMJ tissue grown on microelectrode array (MEA) for detailed study of extracellular electrophysiological signals both pre-and postsynaptically.

Results: The connectivity of muscle cells, motorneurons, and Schwann cells was observed, as well as AChR clustering, indicating successful NMJ formation. The combination of poly-L-ornithine and Matrigel as MEA surface treatment had the best effect on cell attachment.

Conclusions: This iPSC derived model could recapitulate human NMJ function; allowing for both morphological and electrophysiological studies in a humanized model of MG.

Y. Huang: None. **M. Radivojevic:** None. **A. Rostedt Punga:** None.

WHOLE MIRNOME SEQUENCING IN MYASTHENIA GRAVIS THYMUS REVEALS MIRNA/TARGET GENE NETWORKS IMPLICATED IN IMMUNE DYSREGULATION

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MicroRNAs (miRNAs) are key regulators of innate and adaptive immune response. They have been implicated in many autoimmune diseases, but their contribution to the intra-thymic pathogenesis of myasthenia gravis (MG) is not completely known. We performed whole miRNome next generation sequencing in 32 thymuses (discovery cohort), including 8 hyperplastic MG thymuses, 8 MG thymomas, 8 non-MG thymomas, and 8 normal thymuses. Validation of differentially expressed miRNAs, followed by miRNA target gene expression

analysis, was performed by qPCR in the same thymic tissues, and in additional 51 thymuses (validation cohort), including 14 hyperplastic MG thymuses, 11 MG thymomas, 19 non-MG thymomas, and 7 normal thymuses. MiRNome sequencing identified 45 differentially expressed (27 up- and 18 down-regulated) miRNAs in hyperplastic MG compared to control thymuses, and 163 differentially expressed (102 up- and 61 down-regulated) miRNAs in MG compared to non-MG thymomas. Gene Ontology terms associated with altered miRNAs were enriched in TGF-β signaling-related biological processes. Validation of selected miRNAs and analysis of their target genes revealed dysregulated expression of miR-150-5p/STAT1, miR-486-5p/PTEN, and miR-450/CREB1 pairs in hyperplastic MG thymuses, and of the miR-20b-5p/SMAD2/PTEN molecular axis in MG thymomas. Since STAT1, PTEN, CREB1 and SMAD2 genes are critically involved in T cell differentiation and function, we suggested a contribution of the altered miRNAs to immune dysregulation in pathological MG thymuses. Our findings unveil miRNA/target gene networks relevant for MG pathogenesis, that could be tested in further investigations for their potential as targets of innovative miRNA-based therapies to counteract autoimmunity.

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CONGENITAL MYASTHENIC SYNDROME DUE TO A MUTATION IN A NUCLEAR MEMBRANE PROTEIN

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Next generation sequencing has led to the identification of unexpected gene mutations affecting neuromuscular signalling. Here we have identified a family with a novel congenital myasthenic syndrome (CMS) with a mutation in a nuclear envelope protein.

The index case and his brother have mild fatiguable muscle weakness in shoulder abductors, finger extensors and ankle dorsiflexors, and mild wasting of deltoid and medial gastrocnemius. They showed decrement of 40% and 26% on repetitive nerve stimulation (RNS) at 3Hz respectively. Whole exome sequencing identified a homozygous single nucleotide deletion c.127delC; p.P43fs in *TOR1AIP1*. This gene encodes inner nuclear envelope protein LAP1 (lamin-associated protein 1), of which at least two isoforms (LAP1B and shorter LAP1C) exist. The variant is predicted to ablate the expression of LAP1B but not LAP1C and segregates with disease. Trapezius biopsy showed mild variation in muscle fibre size, and no detectable expression of LAP1 in abnormal, herniated muscle nuclei.

Mice in which LAP1 is ablated in striated muscle were initially strong, with normal electromyography and diaphragm spontaneous and evoked endplate potentials. They became weak from 6 weeks of age and by 12 weeks of age showed up to 15% decrement at 20Hz RNS. Diaphragm spontaneous and evoked endplate potentials became prolonged, and EDL and soleus endplates were fragmented. Electron microscopy showed abnormal endplate structure.

Mutations in TOR1AIP1 are rare and have been reported to cause cardiac failure and muscular dystrophy. Our findings reveal the potential for nuclear membrane proteins to disrupt NMJ function and cause CMS.

J.A. Cossins: None. **P. Rodriguez Cruz:** None. **R. Webster:** None. **S. Maxwell:** None. **J. Shin:** None. **W. Dauer:** None. **D. Beeson:** None.

MYASTHENIA GRAVIS AND MRNA VACCINATION FOR COVID

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Exposure to infections in MG may be deleterious with clinical worsening, possibly leading to myasthenic crises. Sars-Cov2, responsible of COVID 19 pandemia, is particularly fearsome in MG for respiratory involvement. Vaccination with mRNA vaccines was a strong indication for frail patients such as myasthenics: we participated to a study, denominated VAX4FRAIL (ClinicalTrials.gov NCT04848493), to evaluate immunological protection and safety of mRNA vaccines. 104 MG patients were recruited and injected with Comirnaty or Spikevax: 87 were followed-up with clinical and immunological evaluations. Anti spike and neutralizing antibodies, and spike T cell responses were performed: 93% of patients become seropositive and no differences were noted in the anti Spike antibody levels using Comirnaty or Spikevax. Only 6 (7%) patients were seronegative patients and, importantly, 5 of them were treated with Mycophenolate. Most of anti-spike seropositive positive has neutralizing antibodies and a correlation between anti Spike and neutralizing antibodies was found (p 0.001). Only 13.4% of patients had a production of IFNγ less than 10 pg/ml on a cell-mediated immune response after a full course of vaccination.Twenty-one (24.3%) of patients did not report any adverse event and in the remaining patients a variety of adverse events were reported, mostly in the site of injection; they were transient and no worsening of MG was noted, at least in the time-frame of the study. Overall mRNA vaccination was safe in MG and provided both humoral and T cell mediated protection to SarsCov2 virus.

R. Mantegazza: *Other*; I have received funding for Travel, Meeting attendance or Advisory Board participation from Alexion, Argenx, Biomarin, Catalyst, SANOFI, Regeneron and UCB.. **A. Consonni:** None. **E. Rinaldi:** None. **E. Ciusani:** None. **E. Corsini:** None. **C. Antozzi:** None. **L. Maggi:** None. **R. Frangiamore:** None. **S. Bonanno:** None. **F. Andreetta:** None. **C. Agrati:** None. **F. Baggi:** None.

INFECTION-RELATED HOSPITALIZATION IN PATIENTS WITH MYASTHENIA GRAVIS: A RETROSPECTIVE STUDY ON LIFE-THREATENING EVENTS

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Introduction: Infection is the most common cause of the life-threatening events (LTEs) in myasthenia gravis (MG) patients. No representative study of hospitalized MG patients with infections has examined the rates of LTE and related clinical factors. **Methods:** We performed a retrospective analysis of hospitalized MG patients who were also diagnosed with infections between 2013 and 2021. Participants were identified from the hospital system of Huashan Hospital that includes 152 cases.

Results: There was 92 cases (60.52%) with LTEs in 152 infection-related hospitalizations. The LTE group had a higher chance of infection-related hospitalization frequencies ($p=0.03$) and longer duration of hospitalization ($p<0.01$). Patients with LTEs during hospitalization had more emerging infections ($p=0.02$) and pneumonia ($p<0.01$), while patients without LTEs had more antecedent infections ($p<0.01$) and hepatitis ($p<0.01$). Less inpatients in LTE group received IS treatment before ($p<0.01$) or within one year before infection-related hospitalizations ($p<0.01$). Among the patients without LTEs, the use of oral methylprednisolone ($p=0.02$) and rituximab ($p<0.01$) were higher, and time length for steroids were longer ($p=0.02$). **Discussion:** Infection types differed significantly between patients with and without LTEs

M. Su: None. **S. Jin:** None. **J. Zheng:** None. **S. Luo:** None. **C. Zhao:** None.

COVID SPIKE ANTIBODIES IN PATIENTS WITH MYASTHENIA GRAVIS: A KU EXPERIENCE

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Background: There is limited literature on immune response to COVID vaccination in immune suppressed myasthenia gravis (MG) patients. **Objective:** To assess the effect of immunosuppressive therapies on COVID spike antibody level in MG patients after immunization. **Methods:** We performed a retrospective chart review of immunized MG patients who had COVID antibody testing. We collected demographic, clinical, diagnostic and treatment data. COVID spike antibody levels were also abstracted. We performed descriptive statistical analysis. **Results:** 60 patient charts were reviewed to date. These were 31 males and 29 females with mean age of 67±15.5 and mean time interval between antibody acquisition and date of last vaccination of 170±38.7 days. High antibody titer (>250) was seen in 32 patients (none 8, PRED 19, MTX 4, MMF 1, AZA 4, IVIG 7, ECU 2), intermediate titers (0.40 - 250) in 24 patients (none 3, PRED 16, MTX 5, MMF 2, AZA 5, IVIG 5, ECU 3, EFG 1) and undetectable antibody titer (<0.40) in 4 cases (none 1, MMF 2, RTX 1, PRED 1). In our MG population, 8/12 (75%) patients not receiving immunosuppressants had a high antibody titer whereas only 50% (24/48) of those on receiving these therapies had high antibody titers. **Conclusion:** Our study reveals modest impact of immunosuppression on COVID spike antibody titers following MG patient immunization. While this finding is limited by small number of patients and heterogeneity in therapies, age and interval between vaccination and antibody testing, our finding supports the importance of booster vaccine in this patient population.

M. Pasnoor: *Consultant*; Argenx, Terumo BCT, CSL Behring, Takeda, Catalyst, Momenta, Alexion. **A. Tajuddin:** None. **O. Jawdat:** None. **D. Jabari:** None. **C. Farmikidis:** *Consultant*; UCB, Momenta. **S. Chandrashekhar:** None. **A. Heim:** None. **K. Higgs:** None. **M.M. Dimachkie:** *Consultant*; Argenx, catalyst, CSL Behring, Janssen, Momenta, Nufactor, Octapharma, Ra Pharma, UCB, RMS medical, Takeda, UCB-Biopharma.

IN VITRO MG MODEL TO STUDY COMPLEMENT SYSTEM INDUCTION IN HUMAN SKELETAL MUSCLE CELLS

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In vitro myasthenia gravis (MG) models have the potential to reduce the suffering and sacrifice of experimental animals and allow for detailed pathophysiological studies in a more human-like setting. However, there is no established *in vitro* model that allows for induced complement system and formation of membrane attack complex (MAC) in human skeletal muscle cells (hSkMCs).

Here, we propose a novel method of complement system activation in human skeletal muscle cells cultured *in vitro*. We confirmed the formation of MAC upon the addition of MG patient serum on the muscle cell surface by immunostaining and confocal microscopy. We also quantified the number of MAC-formed cells of the total cell population from administered healthy control serum and serum of MG patients to cultured human skeletal muscle cells, respectively. In addition, we confirmed the time and dose-dependent change in MAC formation from 30 minutes to 24 hours after serum administration. No difference in MAC formation with and without cobra venom factor (CVF) was observed.

We successfully established a novel *in vitro* MG model that allows in-depth studies of the effects of complement system activation at the skeletal muscle membrane. This *in vitro* disease model could be important in future mechanistic and therapeutic studies in MG and presents an alternative to rodent models.

J. Lee: None. **Y. Huang:** None. **A. Punga:** None.

PRECLINICAL SAFETY AND ACTIVITY STUDIES SUPPORTING PRECISION ENGINEERED T-CELL THERAPY FOR MUSK MYASTHENIA GRAVIS

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MuSK MG is an autoimmune disease where MuSK-specific autoantibodies disrupt neuromuscular junction (NMJ) signaling. MuSK chimeric autoantibody receptor T-cells (MuSK-CAARTs) are autologous T-cells engineered with a chimeric immunoreceptor containing the MuSK extracellular domain, designed to direct MuSK-CAART cytotoxicity toward B-cells expressing anti-MuSK B-cell receptors (BCRs), with the goal of long-term remission after a single infusion without systemic or chronic immunosuppression. Preclinical studies were conducted to explore the safety and efficacy of MuSK-CAART prior to Phase I clinical studies.

MuSK-CAART cytotoxic activity was evaluated in the presence or absence of soluble autoantibody using anti-MuSK BCR^{+} Nalm6 cells in vitro and in vivo, and in exploratory experimental autoimmune MG (EAMG) models. MuSK-CAART demonstrated anti-MuSK BCR-specific cytotoxicity in all models and restored AChR clustering—visualized by bungarotoxin staining—in the EAMG model. Coagulation and cytokines were evaluated in mice with anti-MuSK antibodies and no adverse findings were identified. No evidence of off-target binding or cytotoxic activity of MuSK-CAART was identified using high-throughput membrane proteome arrays and cytotoxicity assays against primary human cells and human myotube cultures. Reverse antibody-dependent cellular cytotoxicity of Fcγ-receptor-expressing cells was not observed in assays using monocytes, natural killer cells, and CD16/CD64-expressing K562 cells. AChR clustering was preserved in co-cultures of MuSK-CAART, anti-MuSK autoantibody, and C2C12 cells, indicating no evidence of NMJ disruption through CAART interactions by antibody crosslinking. Together, these data support the specificity and activity of MuSK-CAART providing rationale for further clinical development of MuSK-CAART, a novel precision cellular immunotherapy for the treatment of MuSK autoantibody-positive MG.

J. Lee: *Employee*; Cabaletta Bio. **S. Oh:** *Other*; Inventor on patents licensed by Cabaletta Bio. **S. Basu:** *Employee*; Cabaletta Bio. **U. Herzberg:** *Employee*; Cabaletta Bio. **S. Manfredo-Vieira:** None. **D. Patel:** *Employee*; Cabaletta Bio. **G.K. Binder:** *Employee*; Cabaletta Bio. **M.C. Milone:** *Other*; Co-founder and member of the Scientific Advisory Board of Cabaletta Bio, Inventor on patents licensed by Cabaletta Bio. **K.C. O'Connor:** *Other*; Consultant for Cabaletta Bio, Receives grant funding from Cabaletta Bio. **F.D. Arditti:** *Employee*; Pharmaseed Ltd. **R. Nazan-Eraslan:** *Employee*; Invivotek LLC. *Other*; Member of Genesis Drug Discovery and Development (GD3). **R. Fong:** *Employee*; Integral Molecular. **S. de Munnik:** *Employee*; Charles River Laboratories. **D.J. Chang:** *Employee*; Cabaletta Bio. **A.S. Payne:** *Other*; Co-founder and member of the Scientific Advisory Board of Cabaletta Bio, Inventor on patents licensed by Cabaletta Bio.

DOK7-AAV IMPROVED ACETYLCHOLINE DEFICIENCY CMS IN A MOUSE MODEL AND ENHANCED THE EFFECTIVENESS OF PYRIDOSTIGMINE TREATMENT

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Mutations in *CHRNE* that lead to deficient acetylcholine receptor (AChR) expression at the NMJ is the most common cause of congenital myasthenia (CMS). The best current front line treatment for this is the cholinesterase inhibitor pyridostigmine. However, nearly half of these patients remain moderately disabled after optimised treatment, with nearly a third still needing a wheelchair at some point. Muscle AChR is highly antigenic, thus a direct gene replacement therapy that induces CHRNE expression in naïve patients could lead to myasthenia gravis. We tested a DOK7-AAV gene therapy on our established mouse model of AChR deficiency CMS, and found that it increased AChR localisation at the NMJ, creating enlarged endplates. This significantly improved neurotransmission, and performance on inverted screen tests in the mice. Remarkably, DOK7-AAV treatment also markedly improved the response of mice to pyridostigmine treatment compared to SHAM treated mice, nearly doubling the improvement in hang time on inverted screen tests.

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HETEROGENEITY OF ACETYLCHOLINE RECEPTOR AUTOANTIBODY-MEDIATED COMPLEMENT ACTIVITY IN PATIENTS WITH MYASTHENIA GRAVIS.

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Background Autoantibodies targeting the acetylcholine receptor (AChR) are found in patients with myasthenia gravis (MG). AChR autoantibodies mediate pathology through three mechanisms: complement-directed tissue damage, blocking of the acetylcholine binding site, and internalization of the AChR. Clinical assays, used to diagnose and monitor patients, measure only AChR autoantibody binding. As such, they provide no information regarding which mechanism(s) are functioning within and among patients.

Objective To develop a live cell-based assay that measures AChR autoantibody-mediated complement membrane attack complex (MAC) formation.

Methods An HEK293T cell line, which was modified using CRISPR/Cas9 genome editing such that expression of the complement regulator genes (CD46, CD55 and CD59) was disrupted, was used to measure AChR autoantibody-mediated MAC formation via FACS.

Results Serum samples (n=155) from 97 clinically confirmed AChR MG patients, representing a wide range of disease burden and autoantibody titer, were tested along with 32 healthy donor (HD) samples. AChR autoantibody-mediated MAC formation positively associated with autoantibody binding in most —but not all—patient samples (*rho*=0.8968, p<0.0001), and was not detected in the HD group. Correlation between MAC formation and clinical disease scores suggested a modest positive association (*rho*=0.34, p=0.0023), which also included a subset of outliers.

Conclusions We developed a novel assay for evaluating AChR autoantibody-mediated complement activity that identified a subset of patients that lack association between MAC formation and autoantibody binding or disease burden. This assay may provide a better understanding of the heterogeneous molecular pathology and identify patients expected to benefit from complement inhibitor therapy.

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COVID-19 VACCINE SAFETY IN PATIENTS WITH MYASTHENIA GRAVIS

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Background: The views, experience, and outcomes of COVID-19 vaccination in the myasthenia gravis (MG) population are unknown. We conducted a longitudinal survey to understand COVID-19 vaccination status, vaccine-related adverse events, and post-vaccination COVID-19 infection outcomes among MG patients.

Methods: An initial REDCap survey was deployed 9/21/2021 and a follow-up survey 1/11/2022. Adults with MG were recruited through Myasthenia Gravis Foundation of American social media platforms. Data collected included demographics, MG status, experience with COVID-19 infection and vaccination, and infection mitigation strategies.

Results: 1,405 individuals participated in the initial survey. 67% were female, the median age was 62, (IQR 49-72), and most were white/Caucasian (88%). Most survey responders were taking immunosuppressive treatments (37% prednisone, 58% nonsteroidal immunosuppressives). The vaccination rate was 91%, and 52% had received a third COVID vaccine dose. 62% experienced an adverse effect from the vaccine; most were mild - 8% of patients saw a physician for a side effect. 20% reported MG exacerbation from the vaccine (vs 57% from a COVID infection), but only 7% of vaccinated patients reported any treatment change due to vaccination associated exacerbation. Follow-up survey data are still being collected.

Conclusions: This survey demonstrated high acceptance of COVID vaccines in MG patients. Vaccine safety was similar to non-MG populations and risk of exacerbations and hospitalization are higher in unvaccinated patients. Data on vaccine safety and disease worsening in the MG population are needed to address the concerns of unvaccinated patients and additional data from our ongoing analysis will be presented at the meeting.

Y. Li: *Other*; YL receives research support from the MGFA and MGNet (U54 NS115054). **S. Muppidi:** None. **S.M. Raja:** *Consultant*; SMR is a consultant for SignantHealth and Regeneron. *Other*; SMR receives research support from a clinician scientist development award co-sponsored by the MGFA, American Academy of Neurology and American Brain Foundation. **S. Masterson:** *Employee*; SM is an employees of the MGFA. **W. Huff:** *Employee*; WH is an employee of the MGFA. **T. Karatz:** None. **J.T. Guptill:** *Consultant*; JTG has received consulting fees/honoraria from Immunovant, Alexion, Apellis, Momenta, Ra Pharma, Cabaletta, Regeneron, Argenx, Janssen, UCB, and Toleranzia.. *Other*; JTG receives industry grant support from UCB pharma for a fellowship training grant; is a site investigator for Alexion, Janssen, UCB Pharma, Argenx, Takeda and grant/research support from: NIH (NIAID.

TOWARDS ANTIGEN-SPECIFIC THERAPY FOR MYASTHENIA GRAVIS BY INDUCTION OF TOLERANCE

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In the majority of MG patients, the autoimmune response is targeted mainly against the muscle AChR. Currently, MG is usually treated with

non-specific immunomodulatory agents, which may have several side effects. Therefore, there is a need for the development of novel, more specific therapies. Reprogramming the autoreactive immune cells in order to restore immune tolerance is a compelling approach. We aim towards an antigen-specific therapy, based on administration of domains of the AChR. We have previously described the expression of a mutated form of the human AChR α1 subunit ECD (α1-ECD) in yeast with increased solubility. *In vivo* studies were performed in a rat experimental autoimmune MG animal model, induced by immunization with the α1-ECD. We assessed the therapeutic efficacy and antigen specificity of α1-ECD administration by different routes, after disease induction. The most profound effect resulted from intravenous treatment with α1-ECD, resulting in significantly reduced EAMG symptoms. The effect was long-lasting, in contrast to drugs used in current standard of care for MG. Serum samples taken at various time points after induction were used for autoantibody characterization and cytokine level measurements. Due to the short protein serum half-life, strategies to extend its half-life could increase the treatment potency. Further investigations are underway to elucidate the immune mechanisms involved. Restoring the immunological tolerance against specific autoantigens by intravenous administration is, therefore, a promising therapeutic approach for MG.

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MAY IL-17 PLAY A ROLE IN MUSCLE PATHOPHYSIOLOGICAL MECHANISMS INVOLVED IN AUTOIMMUNE MG

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Autoimmune myasthenia gravis (MG) is due to auto-antibodies that target acetylcholine receptors (AChRs) located at the neuromuscular junction. The $AChR^{+}$ MG patients are affected by muscle weakness and fatigability. Previous data showed that the pro-inflammatory cytokine, IL-17, contributes to the chronic inflammation found in the thymus (the disease effector organ) and in the blood of MG patients. We investigated whether IL-17 participated to the pathogenic events occurring in the muscle. We found a significant increased expression of IL-17A in $AChR^{+}$ MG muscles compared to healthy controls. A similar observation was obtained in tibialis anterior of mice challenged with the EAMG/$AChR^{+}$ model compared to controls. Surprisingly, the immunohistochemistry analysis of skeletal muscles revealed that IL-17 staining is not due to T cell infiltrates but due to muscle fibers. In addition, we found a significant increased number of IL-17 positive fibers in myasthenic individuals compared to controls in human as well as in EAMG mice. Finally, IL-17 expression level correlates with the disease clinical score in mice. These observations may suggest an active implication of IL-17 in skeletal muscle in the pathophysiological events occurring in MG individuals. Deeper investigations are required to define the roles and mechanisms of action of IL-17 in MG skeletal muscle.

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A MULTICENTER PILOT TRIAL ADAPTING DISEASE-SPECIFIC OUTCOME MEASURES FOR TELEHEALTH IN MYASTHENIA GRAVIS (ADAPT TELE-MG)

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Background: The Myasthenia Gravis (MG) Rare Disease Clinical Research Network (MGNet) is funded by the National Institutes of Health to better understand the clinical course of MG and develop improved approaches to diagnosis and treatment. As part of MGNet, the Adapting Disease-Specific Outcome Measures Pilot Trial for Telehealth in MG (ADAPT teleMG) study aims to validate 2 MG outcome measures adapted for telemedicine.

Methods: The study assesses inter and intra-rater reliability of a virtual version of the previously validated MG Composite score and newly developed MG Core Exam. Included are adults with confirmed diagnosis of MG, recent face-to-face clinic visit, and ability to perform two telemedicine visits via tablet or laptop. Recorded videos of scales are rated by two independent MG specialists and an adjudicator if required. Quality of life and fatigue scales are included. Encounter-specific satisfaction with telehealth is evaluated. The study began enrolling in September 2021 among 4 MGNet sites.

Results: Fifteen participants have completed the study as of 12/30/2021. Mean age was 56.4 years (range 23-88) and 47% were female. Baseline MGFA clinical classification was: Class 0 or 1 (N=3); Class 2 or 3 (N=12). Mean MG ADL at visit 1 was 4.2 (range 0-16). Enrollment is ongoing to reach 50 participants. We will present updated enrollment data and demographics at the meeting.

Conclusion: The ADAPT teleMG study is ongoing and evaluates objective MG outcome measures in the telehealth environment. Results will facilitate development and utilization of telehealth-adapted, MG-specific outcome measures to augment clinical care and trials.

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NOVEL MUSK SPLICING VARIANT HIGHLY EXPRESSED IN ADULT MUSCLE

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Muscle-Specific Kinase (MuSK) is required for neuromuscular synapse formation and maintenance. Disruption of its function during embryonic development and adult life either by mutation or autoantibodies causes congenital myasthenic syndrome and myasthenia gravis, respectively. We identified two MuSK isoforms expressed in adult mouse muscle containing an extra 30 and 60 base pairs. These reflect splice inserts in the coding region between Ig-like domains 2 and 3 of the MuSK extracellular domain. One splice variant is encoded by exon 5b (MuSK 30), the other is encoded by both a novel exon 5a and exon 5b (MuSK 60). Equivalent exons are present in human and rat MuSK genes, and we found that human muscle also express mRNA for these isoforms. In adult mouse muscle, MuSK 60 mRNA makes up 50% of the total MuSK mRNA. To characterize MuSK 60 expression during muscle differentiation we extracted mRNA from C2C12 cell line myoblasts and myotubes. We found that Musk 60 mRNA is highly expressed in myotubes but not in myoblasts. To further determine the expression pattern and function of Musk 60 protein, we developed isoform specific monoclonal antibodies. Musk 60 specific antibody stains the adult mouse neuromuscular junction and colocalizes with AChR clusters in C2C12 myotubes in culture. In contrast, a pan-Musk antibody stains both C2C12 myoblasts and myotubes. In conclusion, we identified novel MuSK variants expressed at the adult NMJ, whose splice inserts could impact MuSK signaling and maintenance of the adult NMJ.

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FIVE DECADES OF EPIDEMIOLOGY IN MYASTHENIA GRAVIS: DATA FROM TWO ITALIAN MG REFERRAL CENTERS

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Background and aims: We investigated the epidemiological changes occurred over five decades in the patient populations of two Italian MG Centers, Università Cattolica del Sacro Cuore (UCSC), Rome and Istituto Neurologico Carlo Besta (INNCB), Milan.

Methods: Adult patients with MG onset from 1970 through 2019 were included. AChR and MuSK antibodies (Abs) were tested by radioimmunoassay, LRP4 Abs were detected by cell-based assay. We recorded onset age and gender over the whole observation period, together with Ab status and thymus pathology. In patients with onset in the last two decades outcome at last visit and treatment were recorded.

Results: The study included 2429 patients, 1193 from UCSC and 1236 from INNCB; 1324/2429 (55%) were females. Of these patients, 1930 (80%) were AChR-positive, 135 (6%) MuSK-positive, 5 (0.2%) LRP4-positive, and 312 (13%) seronegative; 457 (19%) had thymoma-associated MG. The median onset age steadily increased from 31.3 years (IQR: 24-43.5) in the 70s to 61 years (IQR: 44.5-71) in the last decade ($p<0.0001$) and the rate of very late-onset MG (VLOMG, onset ≥65 years) increased from 3% to 41% ($p<0.0001$), paralleled by a decrease of the early-onset population. In the last decade, there was a significant increase in the proportion of males ($p<0.0001$). Most patients with onset in the last two decades achieved a status of minimal manifestations-or-better.

Conclusions: VLOMG is currently the predominant disease subtype in our Centers, confirming previous observations. These data may be related to the general population aging, although the contribution of environmental factors cannot be excluded.

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OUTCOMES FROM RAISE: A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, PHASE 3 TRIAL OF ZILUCOPLAN IN GENERALIZED MYASTHENIA GRAVIS

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INTRODUCTION: Generalized myasthenia gravis (gMG) is a heterogeneous chronic neuromuscular disease, characterized by fluctuating fatigable muscle weakness. In AChR autoantibody-positive (AChR+) gMG, some pathogenic autoantibodies activate the complement cascade, thereby damaging the neuromuscular junction and impairing muscle contraction. Zilucoplan (ZLP) is a subcutaneous self-administered macrocyclic peptide that binds to complement protein 5 and inhibits its cleavage. Following positive Phase 2 results, this Phase 3 clinical trial studied ZLP in patients with AChR+ gMG.

OBJECTIVE: To determine the efficacy, safety, and tolerability of ZLP in patients with gMG, including in subgroups defined by demographic and clinical characteristics.

METHODS: RAISE (NCT04115293) was a Phase 3, multicenter, randomized (1:1), double-blind, placebo-controlled study of ZLP in participants with gMG. The primary efficacy outcome was change from baseline at Week 12 in MG Activities of Daily Living (MG-ADL) score. Secondary endpoints included CFB to Week 12 in Quantitative Myasthenia Gravis (QMG) score, MG Composite score, and MG Quality of Life 15-Item Scale and safety/tolerability outcomes. Subjects had MGFA Class II-IV gMG, confirmed AChR autoantibodies, MG-ADL score of ≥6 and QMG score of ≥12. Daily subcutaneous doses of 0.3mg/kg ZLP or placebo were self-injected over a 12-week treatment period.

RESULTS: In total, 174 adult patients were randomized. At the time of submission, data are being analyzed. Results will be available for presentation, including prespecified analyses of subgroups defined by demographic and baseline clinical characteristics.

SUMMARY/CONCLUSION: These data from RAISE will provide information on the efficacy and safety of ZLP in patients with AChR+ gMG.

J.F. Howard: *Consultant*; Alexion Pharmaceuticals, argenx BVBA, the Centers for Disease Control and Prevention (Atlanta, GA, USA), the Myasthenia Gravis Foundation of America, , the Muscular Dystrophy Association, the National Institutes of Health (including the National Institute of Neurological Disorders and Stroke and the National Institute of Arthritis and Musculoskeletal and Skin Diseases), PCORI, Ra Pharmaceuticals (now UCB Biosciences), Regeneron Pharmaceuticals, Takeda Pharamaceuticals, Immunovant Inc., Sanofi US, Viela Bio Inc. (now Horizon Therapeutics). *Other*; Alexion Pharmaceuticals, argenx BVBA, Ra Pharmaceuticals (now UCB Biosciences), Toleranzia AB. **A. Genge:** *Consultant*; Medtronic, Atlantic Research Group, Calico, Apellis, Anexon, Als-Pharma, QurAlis, Orion, Sanofi Genzyme, Ionis, Wave Life Therapies, Anelixis, Roche, Cytokinetics, Mitsubishi Tanabe Pharma, Amylyx, Alexion, UCB, RA Pharma, Biogen, Eli Lilly, Amicus Therapeutics. **Y. Hussain:** None. **H.J. Kaminski:** *Consultant*; Roche, Cabeletta Bio, Lincoln Therapeutics, Takeda, UCB Pharmaceuticals, Rare Disease Network for Myasthenia Gravis (MGNet). *Employee*; ARC Biotechnology. **R. Mantegazza:** *Consultant*; Alexion, Argenx, Biomarin, Catalyst, SANOFI, Regeneron, UCB. **K. Utsugisawa:** *Consultant*; UCB Pharma,

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EFFICACY AND SAFETY OF ROZANOLIXIZUMAB IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS: A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY (MYCARING)

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INTRODUCTION: gMG is a rare autoimmune neuromuscular disease caused by pathogenic IgG autoantibodies. Rozanolixizumab is a fully humanized, IgG4 monoclonal antibody inhibiting the neonatal Fc receptor, reducing serum IgG levels, including levels of pathogenic IgG autoantibodies.

OBJECTIVE: Evaluate efficacy and safety of subcutaneous rozanolixizumab in patients with gMG.

METHODS: The randomized, multicenter, double-blind, placebo-controlled, Phase 3 MycarinG study (MG0003/NCT03971422) recruited patients aged ≥18 years with MGFA Class II-IVa gMG and positive for AChR or MusK autoantibodies. Patients were randomized 1:1:1 to weekly subcutaneous rozanolixizumab 7mg/kg, 10mg/kg or placebo for 6 weeks, followed by 8 weeks of observation. The primary endpoint was change from baseline (CFB) to Day 43 (one week after final dose) in Myasthenia Gravis Activities of Daily Living (MG-ADL) score; safety and tolerability were also assessed.

RESULTS: Patients were randomized to rozanolixizumab 7mg/kg (n=66), 10mg/kg (n=67), or placebo (n=67). At Day 43, mean MG-ADL CFB was −3.370, −3.403 and −0.784, respectively (p<0.001 for both doses vs placebo). Mean CFB at Day 43 was −5.930, −7.554, and −2.029 for MG Composite score and −5.398, −6.672, and −1.915 for Quantitative MG score (all p<0.001 vs placebo). Rozanolixizumab treatment reduced total IgG by >70% from baseline. Treatment-emergent adverse events (TEAEs) occurred in 81.3%, 82.6%, and 67.2% of patients receiving 7mg, 10mg, and placebo; 3.1%, 7.2%, and 3.0% of patients withdrew due to TEAEs SUMMARY/CONCLUSION:

Rozanolixizumab statistically and clinically meaningfully improved multiple MG-specific outcome measures vs placebo and was well tolerated with no new safety signals. Study funded by UCB Pharma.

V. Bril: *Consultant*; Grifols, CSL, UCB Biopharma, Takeda, Alnylam Octapharma, Pfizer, Powell Mansfield Inc, Akcea, Ionis, Immunovant, Sanofi, Momenta (now J&J), Roche, Janssen, Alexion, NovoNordisk. *Other*; Alexion, Grifols, CSL, UCB biopharma, Argenx, Takeda, Octapharma, Akcea, Momenta (now J&J), Immunovant, Ionis, Vielo Bio (now Horizon). **A. Druzdz:** None. **J. Grosskreutz:** None. **A.A. Habib:** *Consultant*; Argenx, Alexion, UCB Pharma. *Other*; Argenx, Alexion, VielaBio, UCB Pharma, Genentech, Regeneron, Sanofi. **R. Mantegazza:** *Other*; Alexion, Argenx, Catalyst, Biomarin, Sanofi, Regeneron, UCB. **S. Sacconi:** *Consultant*; Biomarin, Sanofi Genzyme, Alnylam Pharmaceuticals, Spark Therapeutic, Biotechspert, BIOGEN France. **K. Utsugisawa:** *Consultant*; UCB Pharma, Argenx, Janssen Pharma, VielaBio, Chugai Pharma, Mitsubishi Tanabe Pharma. *Other*; Argenx, Alexion Pharmaceuticals, Japan Blood Products Organization. **J. Vissing:** *Consultant*; Sanofi Genzyme, Sarepta Therapeutics, Viela Bio, Novartis Pharma AG, Fulcrum Therapeutics, Stealth Biotherapeutics, Roche, Biogen, Lupin Limited, Genethon, Amicus Therapeutics, Zogenix, Regeneron, UCB Biopharma SPRL, Arvinas, ML Biopharma, Horizon Therapeutics, Lundbeck Pharma. *Other*; Sanofi Genzyme, Argenx BVBA, Alexion Pharmaceuticals, Biogen, Lupin Limited, Edgewise Therapeutics, Fulcrum Therapeutics, UCB Biopharma SPRL, Roche, Horizon Therapeutics, Novartis Pharma AG, Stealth Biotherapeutics, Genethon, ML Biopharma, Reneo Pharma, Pharnext, Janssen Pharmaceutical, Khondrion, Regeneron, Dynacure SAS. **T. Vu:** *Other*; Alexion, Argenx, Ra/UCB, Horizon/Viela Bio, Janssen/Momenta, Regeneron, Sanofi, Cartesian Therapeutics. **M. Boehnlein:** *Employee*; UCB Pharma. **F. Woltering:** *Employee*; UCB Pharma. **A. Bozorg:** *Employee*; UCB Pharma. **M. Gayfieva:** *Employee*; UCB Pharma. **H. Kaminski:** *Consultant*; Roche, Cabeletta Bio, Lincoln Therapeutics, Takeda, UCB Pharmaceuticals. *Employee*; ARC Biotechnology. *Other*; Rare Disease Network for Myasthenia GravisRare Disease Network for Myasthenia Gravis (MGNet).

DECREASE IN NON-CLASSICAL MONOCYTES IN MYASTHENIA GRAVIS PATIENTS

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Circulating monocytes are mononuclear cells which are highly specialized in phagocytosis and antigen presentation, secrete a large range of

different cytokines, and migrate to the tissues in response to infection and injury. Monocytes can be subdivided into three major subsets: the classical monocytes ($CD14^{++}CD16^{-}$), the intermediate monocytes ($CD14^{+}CD16^{+}$) and the non-classical monocytes ($CD14^{-}CD16^{+}$). It is suggested that classical monocytes differentiate successively into intermediate and non-classical monocytes. We investigated by flow cytometry the proportion and function of circulating monocytes in MG patients (8 $AChR^{+}$ MG patients and 12 controls). Gating on the monocyte population, we clearly observed in MG patients a significant decrease of non-classical monocytes defined as $CD14^{-}CD16^{+}$. This decrease of non-conventional monocytes was further confirmed by gating on $CD14^{-/low}CD16^{+}$ $CCR2^{-}$ $CD116^{-}$ to exclude a potential bias due to $CD16^{+}$ dendritic cells. We also analyzed serum levels in 24 $AChR^{+}$ MG patients and 16 controls for cytokines known to reflect monocyte activation (sCD14 and sCD163) or cytokines involved in monocyte differentiation, such as GM-CSF, M-CSF, IL-13, IFN-γ. We did not observe any variation in serum levels of sCD14 and sCD163 in MG patients but we observed an imbalance in cytokine cocktail that might influence monocyte differentiation. Altogether, we showed a decrease of non-classical monocytes in $AChR^{+}$ MG patients. This decrease might be associated with the pathophysiology of MG and need to be further investigated.

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A REAL-WORLD DATA APPROACH TO ADVANCE RESEARCH IN MYASTHENIA GRAVIS

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Longitudinal studies of myasthenia gravis (MG) are essential for improving clinical care and informing future drug development. Yet the rarity of MG and broad geographic distribution of patients complicate site-based prospective or retrospective studies. Here we describe the development of a siteless, longitudinal database from people living with MG. This model combines patient-reported data with clinical insights from medical records, allowing for a comprehensive understanding of disease progression.

We recruited 60 patients with a confirmed diagnosis of MG. Patients reported a mean age at diagnosis of 42 (females) and 55 years (males). 24 participants completed a survey on symptom onset and symptom impact on quality of life. The most common initial MG symptoms included double vision (21%), muscle weakness (21%), and droopy eyelids (17%). Muscle weakness was most commonly reported to have the greatest impact on patients' quality of life (50%).

The medical record of each MG patient contains a rich variety of document types from pre-diagnosis through to current management. Participant medical records (total = 8,953 documents) were collected from an average of 3 facilities per patient. We collected an average of 149 medical records per patient, spanning 10 years on average. Records included, on average, 17 general lab reports and 14 neurology notes per patient. 30% of patients had >1 electromyography record. Future work will evaluate structured clinical data on disease progression from patient medical records, and, together with patient-reported data, will result in the development of a robust real-world data resource that will power future MG research.

L.N. Lopez: *Employee*; AllStripes Research. **C. Nichols:** *Employee*; AllStripes Research. **K. Cotter:** *Employee*; AllStripes Research.

CHARACTERIZATION OF CIRCULATING IMMUNE CELLS IN MYASTHENIA GRAVIS BY MASS CYTOMETRY REVEALED DYSREGULATION ON INNATE IMMUNE CELLS

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Autoimmune Myasthenia Gravis (MG) is characterized by invalidating muscle weaknesses due especially to anti-acetylcholine receptor autoantibodies. As for other autoimmune diseases, immune dysregulations are well known for adaptive immune cells, such as B and T cells. However, to further gain insight into immune dysregulation underlying MG, we performed an in-depth analysis on peripheral mononuclear blood cells using mass cytometry. Cells from 24 AChR+ MG patients and 16 age- and sex- matched controls were stained with 37 antibodies and acquired on a Helios™ mass cytometer. Using both unsupervised and supervised approaches, we identified several circulating cell subpopulations whom expression was affected in MG, and that had not been previously associated with this disease. MG was associated with a reduction of circulating monocytes, for all subpopulations: classical (CD14++ CD16-), intermediate (CD14+/++ CD16+) and non-classical (CD14low CD16+) monocytes. In contrast, an increase in innate lymphoid cells 2 (ILC-2: CD161+ CRTH2+) and of γδ T17 cells (γδ+ CD27-) was observed in MG patients. This increase in γδ T17 cells was not detected in periphery by classical flow cytometry that might be less discriminative than mass cytometry but was clearly detected in thymic cells of MG patients. These analyses have unraveled unexpected dysregulations on innate immune cells and further investigations are ongoing to better understand their implication in MG. Innate immunity is crucial for host defense, but its improper activation could also be involved in autoimmunity.

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LONGITUDINAL MGFA-PIS EVALUATION IN A LARGE ITALIAN COHORT OF PATIENTS WITH MYASTHENIA GRAVIS

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Background: Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) is the most frequently used outcome measure in myasthenia gravis (MG) to define response to treatment. However, data from literature focused on the MGFA-PIS at the last follow-up, without considering modifications over the years. Aim of this study is to evaluate MGFA-PIS changes and related predictive factors during the disease course.

Methods: We included 754 ocular and generalized MG patients from 2 Italian Neuromuscular Centers, with MG onset between 2000 and 2018 and at least one year of follow-up. MGFA-PIS was determined by a database algorithm comparing INCB-MG and Mingazzini Scores at each timepoint with the previous one.

Results: Mean age at onset was 48.7 ±18.6 years and mean disease duration 9.1 ± 5 years. Overall, 348 out of 754 patients had generalised AChR-MG without thymoma (46.2%), 72 MuSK-MG (9.5%), 5 LRP4-MG (0.7%), 103 seronegative MG (13.7%), 123 thymoma-MG (16.3%), 103 ocular-MG (13.7%). Complete stable remission (CSR) was reached in 77/754 (10.2%) patients, including 60 (77.9%) patients achieving and maintaining the CSR until the last follow-up and 17 (22.1%) losing CSR after its achievement, usually in first disease stages. In the latter subgroup 4 out of 17 patients then returned to CSR. Among clinical, immunological and thymus parameters, female sex was the only factor associated with the chance of losing the CSR status.

Conclusions: Chance to achieve the CSR did not vary significantly from literature, but our data showed that its modification over time may change in specific MG-subgroups.

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PREVALANCE OF SLEEP RELATED BREATHING DISORDERS AND INSOMNIA COMPLAINTS IN MUSCLE SPECIFIC TYROSINE KINASE ANTIBODY POSTIVE AND NEGATIVE MYASTHENIA GRAVIS

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Introduction Myasthenia Gravis (MG) is associated with both insomnia and obstructive sleep apnea. While MuSK antibody positive (MuSK+) patients often have more bulbar weakness than MuSK antibody negative (MuSK-) patients, no study has compared sleep related breathing in these two populations.

Objective Evaluate sleep and insomnia characteristics and therapies in MuSK+ and MuSK- patients with MG.

Methods Twenty-three MuSK+ patients and 46 age and sex matched MuSK- patients were retrospectively identified utilizing the UNC MG Database. Features of sleep diagnosis, polysomnogram findings, need for positive airway pressure (PAP), and supplemental oxygen were analyzed. Statistical significance was determined using Student T-test and Chi square test ($p<0.05$).

Results MuSK+ patients (19 female, 4 male) had an average age of 47 years (8-73 yrs). Documented insomnia complaints were similar between the two groups (17% MuSK+ and 22% MuSK-). Obstructive sleep apnea was found in 35% of MuSK+ vs. 26% of Musk- patients ($p=0.45$). However, MuSK+ patients were more likely to have hypoventilation ($p<0.005$). While the frequency of PAP therapy was similar, MUSK+ patients more frequently require bilevel PAP (30% of total group) and supplemental oxygen (30% of total group) ($p<0.005$) than the MUSK- group.

Conclusion Our cohort suggests that MuSK+ and Musk- patients have a similar frequency of insomnia and obstructive sleep apnea, but MuSK+ patients are more likely to have hypoventilation and require bilevel PAP therapy and supplemental oxygen. Further investigation is needed to delineate if this is related to the pattern of muscle weakness, or hallmarks of other pulmonary impairment

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CHIMERIC AUTOANTIBODY RECEPTOR T CELLS: ANTIGEN-SPECIFIC TREATMENT OF EXPERIMENTAL MYASTHENIA GRAVIS

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We have produced rat syngeneic chimeric autoantibody receptor (CAAR) T cells targeting the autoimmune B cells underlying rat experimental autoimmune muscle-specific kinase (MuSK) myasthenia (EAMM) for use as antigen-specific treatment of this model disease. MuSK CAARs express a targeting moiety, in this case the MuSK ectodomain, directed at the anti-MuSK B cell antigen receptors, fused to T cell receptor signaling domains. EAMM closely mimics human MuSK myasthenia including the targeted MuSK domains, presence of muscle wasting and histologic findings of involvement of both pre- and post-synaptic portions of the neuromuscular junction in the absence of inflammation or necrosis. To assess efficacy of these cells in vitro, we developed hybridomas to act as surrogates for pathogenic anti-MuSK B cells. 97 hybridoma lines secreting anti-MuSK monoclonal antibodies (mAbs) were produced by electrofusion of Sp2/0-Ag14 cells with spleen mononuclear cells from rats immunized with purified mouse MuSK ectodomain. Effective activation of MuSK CAAR T cells has been demonstrated by their proliferation and gamma interferon secretion in response to both anti-MuSK mAbs and anti-MuSK hybridomas. The results of the in vitro experiments, and ongoing studies of the injection of the MuSK CAAR T cells into (immunocompetent) EAMM rats, provide preclinical data to permit development of such treatments in patients with myasthenia. In contrast to presently available treatments that nonspecifically reduce the activity of the immune system, both the abnormal (autoimmune) portions and the normally functioning portions, antigen-specific treatments potentially target the autoimmune process without off-target effects.

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B CELLS FROM MUSCLE-SPECIFIC TYROSINE KINASE ANTIBODY POSITIVE MYASTHENIA GRAVIS PATIENTS SHOW INCREASED FREQUENCIES OF CD20 LOW AND CXCR5 NEGATIVE POPULATIONS

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MuSK+ MG patients exhibit immunopathology and clinical manifestations distinct from AChR+ MG. The cellular mechanisms underlying differential treatment responses in MuSK+ MG are poorly understood; however current evidence suggests CD20+ precursor B cells to pathogenic short-lived plasma cells are effectively depleted by anti-CD20 treatment. We investigated CD20 expression on peripheral B cells isolated from MuSK+ subjects (N=7) using negative selection for B cells followed by spectral flow cytometry and compared them to non-autoimmune controls (N=9) and AChR+ subjects (N=11). Our study reveals an increased frequency of B cells with low CD20 expression ($CD20^{low}$) in MuSK+ subjects compared to AChR+ and control subjects. Interestingly, we also observed less CD20 expression on $CD20^{high}$ B cells in MuSK+ subjects. $CD20^{low}$ B cells were further characterized by low CD27 and increased CD86 expression, a phenotype that may be associated with previously reported pre-plasmablast populations. An overall increase in the frequency of B cells lacking expression of the lymphoid homing receptor CXCR5 ($CXCR5^-$) in naïve and memory B cell subsets was also observed in MuSK+ subjects compared to AChR+ subjects and controls, suggesting MuSK+ B cells may have distinct homing properties. The highest frequencies of the $CD20^{low}$ population and $CD20^+CXCR5^-$ population of B cell subsets were associated with MuSK+ subjects experiencing greater disease activity. Further molecular and functional investigations into these B cell subsets in MuSK+ MG are required to determine their pathogenic potential and provide insight into MuSK+ immunopathology.

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ANTIGEN PRESENTATION OF ACETYLCHOLINE RECEPTORS FROM DAMAGED MUSCLE TRIGGERS A SELF-SUSTAINING AUTOIMMUNE RESPONSE - A NOVEL RODENT MODEL FOR MYASTHENIA GRAVIS

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Myasthenia gravis (MG) is a chronic autoimmune disease caused by antibodies targeting muscle nicotinic acetylcholine receptors (AChRs) and impairing neuromuscular transmission. What initiates and sustains MG is largely unknown. Translation of therapeutic approaches developed in experimental autoimmune MG (EMAG) into positive results in humans faces difficulties, partly because conventional EAMG models fail to recapitulate several key aspects of MG. We developed a self-sustaining EAMG model in rats by immunizing with a chimeric acetylcholine binding protein (AChBP) containing the main immunogenic region (MIR), a group of tightly-overlapping B cell epitopes targeted by more than half of autoantibodies in MG. Both the chimeras containing the human MIR and the syngeneic MIR were potent in inducing EAMG, though the latter was less potent. Immunizing with either chimera induced large amounts of antibodies to the immunogen, of which only trace amounts of self-reactive antibodies caused complement-mediated focal lysis of the postsynaptic membrane. This resulted in shedding of membrane

fragments containing AChRs, which, in turn, initiated a secondary immune response to endogenous AChRs, as reflected by the production of autoantibodies to the AChR cytoplasmic domains that the immunogens lack. This feedforward loop of autoimmune stimulation sustained the autoimmune response. Fourteen months after immunization, these rats remained abnormally fatigable and their muscle AChR content decreased to about 38% of normal. This novel EAMG model enables us to rigorously evaluate the effectiveness of immunosuppressive therapies in suppressing the self-sustaining autoimmune response rather than a transient immune response to exogenous immunogens.

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THE DUKE MYASTHENIA GRAVIS CLINIC REGISTRY: THYMECTOMY IN MUSK MYASTHENIA

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INTRODUCTION: The Duke Myasthenia Gravis (MG) Clinic Registry is a comprehensive database of clinician-derived data on patients seen in the Duke MG Clinic.

OBJECTIVE: To describe the demographics, clinical characteristics and post-thymectomy outcomes of Registry patients with MuSK antibodies.

METHODS: 157 patients with AChR (ARMG) or MuSK antibodies (MMG) who underwent thymectomy and had at least 2 years of post-thymectomy follow-up were reviewed. RESULTS: 14 patients, all female, had MMG. Median onset age was 25 years (range 10-54); 93% had onset <age 50. Median disease duration at thymectomy was 1 year (range 0.05-21). All were generalized; 5 (36%) had MG crisis before thymectomy. 4 (29%) had thymic hyperplasia. Median follow-up was 13.6 years (2.6-33.4) At their last visit, 8 (57%) had achieved MGFA Post-Intervention Status Minimal Manifestations or better (MM+); 11 (79%) were taking an oral immunosuppressant and 1 was taking an oral immunosuppressant plus rituximab. 143 patients had ARMG; 79 (55%) were female. Median onset age was 31 years (range 2-83); 79% had onset <age 50. Median disease duration at thymectomy was 1.3 years (range 0.1-37). 98% were generalized; 11 (8%) had MG crisis before thymectomy. 78 (55%) had thymic hyperplasia. Median follow-up was 8.2 years (range 2.2-35.5). At their last visit, 98 (69%) had achieved MM+; 120 (84%) were taking an oral immunosuppressant and 1 was on rituximab.

SUMMARY/CONCLUSIONS: MMG patients had more crises before thymectomy and 29% of MMG patients had thymic hyperplasia. Long-term outcomes were favorable in both MMG and ARMG patients following thymectomy.

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MUSK CYSTEIN RICH DOMAIN IN AUTOIMMUNE MYASTHENIC SYNDROME

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Disruption of the precise trans-synaptic coordination between the different cellular compartments of the neuromuscular junction (NMJ) causes neuromuscular disorders, including Myasthenia Gravis (MG). MG is a life-threatening auto-immune disease caused by antibodies targeting key actors of the NMJ. At the vertebrate NMJ, the receptor complex formed by MuSK and its co-receptor Lrp4 constitutes the central organizer of NMJ formation and maintenance. Lrp4 and MuSK act as scaffolds for multiple binding partners including Agrin and Wnt glycoproteins. Our team demonstrated that mouse deleted from the Wnt-binding site (Cystein Rich Domain, CRD) of MuSK exhibits significant NMJ formation defects. Importantly, distinct studies have reported cases of MG patients with immunoreactivity against MuSK CRD. The goal of our study is to demonstrate whether autoantibodies targeting MuSK CRD are pathogenic. To this end, we developed a passive transfer experimental mouse model of MG harboring antibodies against MuSK CRD (anti-MuSK^{CRD}). Extensive analysis of NMJs indicated that these antibodies are responsible for severe structural and functional NMJ defects. In addition, an active transfer model is currently under development. We are also currently running *in-vitro* experiments in order to unveil the signaling pathways affected following anti-MuSK^{CRD} treatment. Preliminary results showed that anti-MuSK^{CRD} antibodies strongly affects Agrin/Lrp4/MuSK signaling in primary muscle cultures. Other experiments are necessary in order to completely decipher how anti-MuSK^{CRD} antibodies inhibit MuSK signaling upon ligand exposure. Altogether, this set of experiments will demonstrate the putative pathogenicity of anti-MuSK^{CRD} in Myasthenia Gravis.

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REAL-LIFE EXPERIENCE WITH THE DIAGNOSIS OF DOUBLE SERONEGATIVE MYASTHENIA GRAVIS: EXPERIENCE WITH MORE THAN 3000 REFERRED SEROLOGICAL TESTS

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Background MG is a disease of the neuromuscular junction and most of the acquired forms are of an autoimmune nature. In adults, acetylcholine receptor (AchR Ab) are found in 80 to 85% and muscle-specific tyrosine kinase (MuSK Ab) in 5-10%. The remaining 10 to 15% are "double seronegative" (dSN-MG). We report the experience of our laboratory based on 3678 tests referred over 1 year.

Methods Between June 2019 and August 2020, we assayed 3678 sera for AchR Ab. Using the RIPA assay 387 sera were positive. Among the 3299 negatives, 987 have been assayed for MuSK Ab using RIPA and a small numbers re-assayed for AchR Ab with a live cell based assay (CBA).

Results Among the 987 AchR Ab negative by RIPA, we found 598 MuSK Ab negative and sent a questionnaire to referring physicians. 177 of 598 (29%) responded, with the final diagnosis of 9 "not yet diagnosed", 143 "not MG" and 25 "clinical MG". Among those 25, 8 had GMG, 11 had ocular MG, 3 had congenital MG and 2 were not specified. We re-assayed 17 sera of the 25 from the double seronegative clinical MG group and found 4 positive (23%) to AchR Ab by CBA.

Conclusions As a retrospective study our findings would have to be verified in a prospective study. By questionnaire we found only 25 probable clinical MG with initial MG query. We were surprised that a relatively large proportion dSN-MG probable clinical MG patients were positive for AchR Ab MG by CBA.

H. Frykman: *Consultant*; Alexion, Cassava, Neurocode labs, Janssen Pharma, ProMIS Neuroscience. **P. Kumar:** None. **A. Mousavi:** None. **T. aziz:** None. **E. Gibbs:** None. **A. cruz:** None. **J. Oger:** None.

AUTOIMMUNE MYASTHENIA GRAVIS TREATMENT SELECTION IN THE HOMELESS

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Autoimmune Myasthenia Gravis management commonly requires immune modulation. Consensus criteria suggests oral immune modulators should be considered first line therapeutic interventions. In housing insecure patients, an increased predisposition to communicable illness including cellulitis, pneumonia and tuberculosis is observed. Immune modulation in this population must be cautiously balanced against risk of infectious illness. Treatment modality must balance the logistics of care and the security of the therapy against theft, spoilage, and loss. We present a case of a housing insecure middle-aged man with autoimmune myasthenia gravis for which Eculizumab was prescribed. Despite significant psycho-social barriers to wellness, his myasthenia gravis was well-controlled. In the United States, Medicaid state sponsored health insurance is available to the economically disadvantaged. Medicaid is required to provide access to most therapeutics approved by the Food and Drug Administration. Foundation support is often available to subsidize out of pocket patient costs. Most branded products are supported by well-organized patient care coordinator programs. Curiously, owing to patient support, branded therapeutics may be easier to access when complex decision making is required. Therapeutic selection must be individualized. Despite calamitous cost of therapy, the cost differential between a well-controlled myasthenic on Eculizumab infusions and a poorly controlled myasthenic with frequent exacerbations requiring hospitalization may be relatively narrow. The success of therapy in this case is attributed to a well-tolerated therapeutic with relatively narrow spectrum of immune modulation delivered by a trusted team in a sheltered environment.

A. Sachdev: *Consultant*; Alexion Pharmaceuticals, Catalyst Pharmaceuticals, argenx, UCB Pharma. **N. VanElls:** None. **A. Alexander:** None. **J. Reed:** None.

EFFICACY AND SAFETY OF ECULIZUMAB IN REFRACTORY GENERALIZED MYASTHENIA GRAVIS - A PROSPECTIVE CASE SERIES

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A recent clinical trial showed that Eculizumab is effective in patients with seropositive refractory generalized MG (gMG). **Objective**: We report our center's experience with Eculizumab in patients with refractory gMG. **Methods**: We prospectively followed six gMG patients with refractory disease (5 males, 1 female; mean age: 56 years) with a mean disease duration of 10 years (range: 3 - 17 years). Five patients are seropositive, and one had thymoma, which was resected. The mean baseline MG Activities of Daily Living (ADL) score was 8.8 (range 3 - 14). All patients were taking at least two immunosuppressants at the time of initiation of Eculizumab infused intravenously as per standard protocols i.e. 900 mg weekly for 4 weeks, 1200 mg in fifth week and 1200 mg every 2 weeks thereafter. The median treatment duration was 11 months (range 11 - 56 months). Overall, 5/6 patients showed significant improvement in MG ADL scores (mean: 3.2 ± 2.1 points; $p<.01$) but none achieved pharmacologic remission status. Of the 5/6 patients taking prednisone, the dose was reduced in three, increased in one and remained unchanged in one patient. Of the 2/6 patient on maintenance intravenous/subcutaneous immunoglobulin infusions, one was able to reduce the frequency of infusions. None of our patients have reported any major adverse effects with Eculizumab. **Conclusion**: Eculizumab is safe and effective in refractory gMG in most patients though none are able to achieve remission after first year of therapy. Further studies are needed to determine the long-term benefits of Eculizumab in this patient population.

Z.A. Siddiqi: *Consultant*; Alexion, Takeda, Alnylam. **D. Blackmore:** None. **M. Alvi:** None. **F. Hussain:** None.

IMPROVING DIAGNOSIS OF MYASTHENIA GRAVIS BY DETECTING LOW-DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN 4 (LRP4) AUTOANTIBODIES WITH A MODIFIED CELL- BASED ASSAY (CBA) METHOD

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Background MG is a disease of the neuromuscular junction (NMJ) of skeletal muscles which is clinically characterized by weakness on exercise, and fatigability. In adults, antibodies to the acetylcholine receptor (AchRAb) are found in 80 to 90% of patients with generalized disease and antibody to muscle-specific tyrosine kinase (MuskAb) in another 5 to 10%. The remaining 10 to 15% of MG cases are nicknamed double seronegative (dSN-MG). Autoantibodies against the LRP4 have been reported in dSN-MG with a wide range of frequency (2 to 46%). We will discuss a modifiedLPR4 CBA assay for the accurate and efficient measurement and clinical correlation of seropositive cases.
Methods Between August 2021 and January 2022, we have screened a total of 228 sera of AchRAb negative for detecting LRP4 antibodies by using fixed CBA. We used both RIPA and clustered CBA methods to analyze AchRAb. 150 of these AchRAb negative sera were also negative for Musk antibodies that measured by both RIPA and SPR methods.
Results Of 150 double seronegative MG (AchRAb negative by RIPA and clustered CBA and Musk negative by RIPA and SRP) 3 cases were positive for LPR4 antibodies (2%). They were a 29-year-male, 85-year- female and 47-year-old female. The most prominent symptoms were ptosis and double vision.
Conclusion The CBA method is a new gold standard for detecting autoantibodies in NMJ diseases that could improve clinical diagnosis and management of MG patients. Despite LRP4 antibodies are more common in female, one of our three cases was male.
P. Kumar: None. **E. Kihara:** None. **N. Kaur:** None. **A. Mousavi:** None. **T. aziz:** None. **A. cruz:** None. **H. Frykman:** *Consultant*; Alexion, Cassava, Neurocode labs, Janssen Pharma, ProMIS Neuroscience.

PATIENT CENTERED CONTENT DELIVERY IN THE PANDEMIC, THE MYASTHENIA GRAVIS FOUNDATION OF MICHIGAN EXPERIENCE

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The Myasthenia Gravis Foundation of Michigan (Mg-MI) is a patient support organization based in Grand Rapids, Michigan. Mg-MI supports 500 patients and providers through patient support groups, an annual conference, a patient support hotline, Myasthenia Gravis patient clinic staffing, provider referral services, a newsletter and community building activities. In the COVID19 pandemic, MG-MI has observed an increase in interest in patient support services and a change in audience preferences regarding content delivery, with a strong bias against face-to-face interactions. In response, Mg-MI formulated 9-day pre-recorded (2020) and 2-day live broadcast (2021) annual meeting structures with post-event surveys collected. Responses largely reflected patient feedback. The most popular talks were focused on neuro-ophthalmology and clinical research. A basic overview of available treatments was well received. The most important segment of each talk was the question-and-answer session. Total engagement exceeded previous years face-to-face events in terms of RSVP and attendance. Cost was lower and logistics was easier in the virtual environment. Donations to the organization grew. Managing electronically delivered content more effectively has become a new organization priority, with the addition of a contractor with technical expertise in this area.
A. Sachdev: *Consultant*; Alexion pharmaceuticals, Catalyst pharmaceuticals, UCB pharmaceuticals, argenx. **S. Woolner:** None.

THE MYASTHENIA GRAVIS FOUNDATION OF AMERICA: THE EARLY YEARS

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The origins of the Myasthenia Gravis Foundation of America (MGFA) and the International Symposium are anchored in the compelling story of one patient. In 1947, at age 16, Patricia Ellsworth developed generalized weakness, eventually diagnosed as myasthenia gravis, severe enough to limit her activities and aspirations. Patricia's parents were concerned and consumed with their daughter's illness and used their connections and resources to create a dedicated organization (established in 1952) for the purpose of understanding the disease and promoting research and optimal patient care. This review of the MGFA early years and the establishment of the International Symposium is based on direct discussions with Patricia Ellsworth, access to files belonging to her Mother, Jane Ellsworth Whitney, and archival files of minutes from the early MGFA meetings (from the MGFA and those from one of the charter members of the Medical Advisory Board). Serving as the original physician champion for the MGFA, Dr. Henry Viets was central to the creation of Medical Advisory Board and the establishment of the International Symposium, which first took place in 1954 and has continued every five years since. The conduct and highlights of the early International Symposia are herein reviewed.
R.M. Pascuzzi: None.

IS COMPOUND MUSCLE ACTION POTENTIAL (CMAP) AREA DECREMENT IN REPETITIVE NERVE STIMULATION STUDIES MORE SENSITIVE THAN CMAP AMPLITUDE DECREMENT FOR DIAGNOSING MYASTHENIA GRAVIS?

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RNS testing is considered one of the useful tests for diagnosing MG. A positive study requires demonstration of a decremental(>10%) response in compound muscle action potential(CMAP) amplitude or area. Because of technical difficulties in the past, very few studies of RNS measuring CMAP area decrement were done. This study was done to compare the sensitivities of RNS decremental response in area versus amplitude in diagnosing MG and to determine the increase in diagnostic yield. **Methods:** In this retrospective study, RNS data of MG patients who underwent testing from 2017-2020 at a large tertiary center were reviewed. After screening 505 studies, 93 adult patients who were diagnosed with MG during follow-up were included. The maximum RNS amplitude and area decrement from each nerve-muscle pair were recorded. The sensitivities of the studies were compared by McNemar's test. **Results:** Out of 93 patients, 82.8%(n=77) had generalized MG, 50.5% were female, 86% were seropositive(AchR 77.4%, MuSK 7.5%, LRP 1.1%). A total of 274 unique RNS studies were analyzed. The sensitivity of RNS using amplitude for decrement measurement was 53.8%(55.8% for generalized-MG, 45.8% for ocular-MG). Using area as a decrement measurement, the sensitivity was 69.9% (71.5% for generalize-MG, 62.5% for ocular-MG) and increase in overall diagnostic yield was 16.1% (p=0.00015). The increased sensitivity with area decrement as compared to amplitude was present in all nerve-muscle pairs tested(Facial-nasalis, 57.45%vs 51.5%; Spinal accessory-trapezius, 48.2%vs 33.7%; median-abductor pollicis brevis, 54.9%vs 44.2%; ulnar-abductor digiti minimi, 48.3%vs 42.9%). **Conclusion:** We propose that area decrement should be routinely included in RNS study interpretation.

N. Sanghani: None. **J. Morren:** None.

NEUROMUSCULAR TRANSMISSION AND THE SAFETY FACTOR FOR MUSCLE CONTROL

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The neuromuscular junction has evolved to ensure reliable neural control of muscle contraction. When a presynaptic action potential depolarizes the motor nerve terminal it opens voltage-gated calcium channels, allowing influx of calcium ions. This triggers the exocytosis of acetylcholine, which diffuses across the synaptic cleft to activate the acetylcholine receptor cation channels in the muscle membrane. Many vesicles of acetylcholine are released simultaneously by each nerve action potential. The tiny postsynaptic depolarisations produced by each of these 'quanta' of acetylcholine sum together to produce the endplate potential that triggers the muscle fiber action potential, and initiates contraction. Trains of nerve impulses at frequencies ranging from 10-200 per second are required to produce graded contractions of a muscle. During such trains, the number of quanta of acetylcholine released by the nerve terminal declines somewhat with successive nerve impulses. In a healthy person the endplate potential greatly exceeds the threshold for triggering the muscle action potential so the natural decline in quantal content is not a problem. The extent to which endplate potential depolarization exceeds the threshold for the action potential is described as the safety factor for neuromuscular transmission. In myasthenic disorders a reduction in the safety factor, in combination with the natural decay in quantal content, results in the progressive failure of neuromuscular transmission during tetanic contractions.

W.D. Phillips: None.

A POPULATION-BASED COHORT STUDY OF PREGNANCY OUTCOMES IN WOMEN WITH MYASTHENIA GRAVIS

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MG exhibits a peak of incidence in women of childbearing age, making the relationship between pregnancy and MG a significant concern. There is conflicting data regarding the prevalence of pregnancy-related complications in MG, with few population-based studies to guide clinical management. We used large administrative health databases to estimate the incidence of pregnancy, peripartum, and neonatal complications in a cohort of pregnant MG patients, compared with matched controls. During the years 1996-2018 in Ontario, Canada, we identified 785 females between 15-50 years old living with MG. There were no significant differences between cases and controls in socioeconomic status, rates of diabetes, hypertension, or parity at index date. In the MG group, 223 had live births, 1 still birth, 33 miscarriages/ectopic pregnancies, and 55 induced abortions. The rates were similar among matched controls. There were no differences in gestational complications, apart from a higher rate of peripartum hemorrhage (6.3 vs 2.5%, p=0.003) in MG patients. There were no differences in rates of labor induction, cesarean section, or operative vaginal delivery. A higher proportion of MG patients required ICU admission (1.4 vs 0.1%, p=0.006), with slightly longer hospital stays in the MG group (4.73 v 3.28 days, p<0.001), and higher incidence of low birthweight infants (13.6 vs 6.7%, p<0.001). There were no differences in incidence of neonatal sepsis or congenital malformations. The rate of neonatal MG was 5%. Overall, we report similar parity rates in MG patients and controls, and few differences in maternal or fetal complications.

A. Breiner: None. **R. Talarico:** None. **S. Hawken:** None. **C. Barnett:** None.

COMPLEMENT AND HUMORAL IMMUNITY: DIFFERENCES BETWEEN ASYMPTOMATIC, OCULAR AND GENERALIZED ACHR-POSITIVE MYASTHENIA GRAVIS PATIENTS

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Background: MG patients with autoantibodies against AChR (AChR MG) show a wide variation in clinical phenotype. We investigated clinical and serological characteristics, and performed an ex vivo functional test to identify factors that contribute to this variation.

Method: We included sera from 6 asymptomatic patients, 5 with ocular MG (OMG) and 7 with generalized MG (GMG). Overall AChR autoantibody concentration was determined by a radioimmunoassay. Reactivity against the adult or fetal AChR was determined in a cell-based assay using HEK293 transfected cell lines and scored from 0 (no labeling) to 4 (strong labeling). Serum complement factors were investigated by routine clinical lab analysis. Mouse hemi-diaphragms were pre-incubated with humanized rat AChR monoclonal and exposed to patient serum to study the complement-mediated damage quantified in a muscle contraction experiment.

Results: Median (± SD) AChR autoantibody titers, AChR fetal/adult labeling ratios, C1q concentrations and time to 50% inhibition of tetanic contraction (T50%(min)) were 6.0 ± 20.0, 2.3 ± 0.8, 123.0 ± 37.0 and 63.1 ± 9.4, respectively, for asymptomatic patients. For OMG: 1.8 ± 11.2, 0.0 ± 0.7, 105.0 ± 13.2 and 85.3 ± 32.0, respectively. For GMG: 20.0 ± 100.0, 1.0 ± 0.7, 119.0 ± 9.7 and 75.8 ± 20.9. There was a significant inverse correlation between C1q concentration and T50%(min) ($B = -0.569$; $p = 0.014$).

Conclusions: Preliminary data suggests that AChR antibody subspecificity, complement serum factors, and functional complement activation tests can help to identify the factors that determine clinical differences in AChR MG.

R.H. de Meel: None. **J.J. Plomp:** *Other*; Co-inventor on two patent applications on MuSK-related research and receive license income from these patents.. **V. Damato:** None. **M.R. Tannemaat:** None. **M.G. Huijbers:** *Other*; Co-inventor on two patent applications on MuSK-related research and receive license income from these patents. **J.J. Verschuuren:** *Other*; Co-inventor on two patent applications on MuSK-related research and receive license income from these patents.. **A. Evoli:** None.

MRI OF THE EXTRA-OCULAR MUSCLES IN MYASTHENIA GRAVIS SHOW SMALL VOLUME AND FAT FRACTION INCREASES

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MRI of extra-ocular muscles (EOM) could provide more insight in the pathophysiology of therapy-resistant ophthalmoplegia in myasthenia gravis (MG) and might provide clues for the diagnosis of MG in seronegative patients. We used MRI to explore structural differences of the EOM between MG, chronic progressive external ophthalmoplegia (CPEO), or healthy controls. 18 recently diagnosed MG (58±20yrs), 18 chronic MG (51±17yrs), 11 healthy controls (58±13yrs) and 5 CPEO patients (52±12yrs) were scanned at a 7-Tesla-MRI-scanner. A Dixon-scan was used to quantify the fat fraction and volume of the EOM using semi-automatic 3D-segmentation. Measurements were compared between the four groups using ANOVA.

Volume differences between healthy controls, CPEO and MG patients were observed (e.g. for medial rectus, 569±129mm^3, 603±106mm^3, 635±140mm^3 and 442±114mm^3, healthy controls, recent MG, chronic MG and CPEO, $p<0.01$). The volume increase was present in the inferior, medial and lateral rectus in MG. Fat fraction was slightly elevated in CPEO and MG (e.g. for the lateral rectus, 12±2%, 15±4%, 15±5% and 20±10%, $p<0.05$), and was observed in the superior, inferior and lateral rectus for MG.

EOM fat fraction and volume can be quantified using quantitative MRI at 7T. We anticipated to find muscle atrophy, but instead observed small increases in volume and fat fractions of EOM in MG, most pronounced in chronic MG and less pronounced in seronegative MG. The absence of MG-specific or gross structural changes make this test less useful for diagnostic purposes, but could imply that EOM weakness might be reversible, even in patients with residual ophthalmoplegia.

K.R. Keene: None. **J.J. Verschuuren:** None. **I.C. Notting:** None. **M.R. Tannemaat:** None. **J.M. Beenakker:** None. **H.E. Kan:** None.

ORTHOPTIC MEASUREMENTS IN MYASTHENIA GRAVIS: ADDING PERSISTENT GAZE AS A MEASURE OF EXTRA-OCULAR MUSCLE FATIGABILITY

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Distinguishing ocular MG from mimics, such as Graves' orbitopathy (GO), chronic progressive external ophthalmoplegia (CPEO) or ocular pharyngeal muscular dystrophy (OPMD) can be challenging. We explored whether orthoptic measurements can aid in diagnosis. Nine recently diagnosed(56±19yrs), 17 chronic(51±17yrs) and 10 seronegative(59±8yrs) MG patients were included. In addition, 9 healthy controls(58±14yrs) and 6 MG mimics(57±19yrs; 1 OPMD, 4 CPEO, 1 GO) were included. Limitations in eye ductions were measured using synoptophore. Per extra-ocular muscle (EOM), relative deviations and drift over one minute in gaze were measured using a modified Hess chart. The Hess chart showed a high variability in EOM involvement pattern between all MG patients, with the medial and lateral rectus most often affected (44% and 42%), followed by the superior oblique, inferior and superior rectus and the inferior oblique muscle (respectively 27%, 27%, 25% and 17%). A drift in deviation was observed in 30/36 MG patients (83%), with 70% in recent, 88% in chronic and 90% in seronegative MG. No drift was observed in healthy controls and MG mimics. The synoptophore showed limited ductions in 16/36 MG. In the 20 MG patients without limited ductions, the Hess chart showed deviation in 11 patients. Orthoptic measurements are valuable to identify involved

EOM in MG. As drift was only present in MG, measuring persistent gaze using a Hess chart may be a highly specific diagnostic test for MG-related EOM fatigability. In MG, relative deviations occurred more than absolute duction limitations, suggesting that contraction asymmetry is more pronounced than absolute EOM weakness.

K.R. Keene: None. **J.M. Beenakker:** None. **I.C. Notting:** None. **J.M. de Nie:** None. **J.J. Verschuuren:** None. **H.E. Kan:** None. **M.R. Tannemaat:** None.

COVID-19 OUTCOMES IN PEOPLE WITH MG IN ONTARIO, CANADA

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We studied COVID-19-related outcomes in adults with a history of MG compared to matched controls, including rates of ER visits, hospital and ICU admissions and death. We also assessed COVID-19 vaccine uptake and MG-related hospitalization after vaccination. Among 11,365,233 eligible Ontario residents, we identified 4,411 MG cases, who were matched to 22,055 controls on age, sex and residential area. The mean age was 67.7 ±15.6 years, 51.6% were women and 88.0% were urban residents. The MG group had higher Charlson comorbidity index compared matched controls (0.77 ±1.42 vs 0.45 ±1.11). Between January 2020 and May 2021, 173 (3.9%) individuals with MG and 708 (3.2%) controls contracted COVID-19. Compared to controls, COVID-19 positive MG cases had higher rates of ER visits (35% vs. 23%), hospital admissions (29% vs. 15%), and ICU admissions (6% vs. 3%). MG cases were more likely to die within 30 days of positive COVID-19 test (14%) compared to controls (8%). Regarding COVID-19 vaccines, by August 2021 80.3% of MG cases and 81.2% controls had received 2 doses; 3.1% cases and 2.8% of controls one dose; 16.4% of MG cases and 15.8% of controls were unvaccinated. Among 3461 first doses in MG cases, <6 were hospitalized with an MG-related diagnosis within 30 days of vaccination. In summary, we found that individuals with a history of MG who contracted COVID-19 had approximately twice the risk of hospitalization, ICU admission and death compared to matched controls. Vaccine uptake was high, with negligible risk of severe MG exacerbations after vaccination.

M. Alcantara: None. **A. Park:** None. **M. Koh:** None. **C. Barnett-Tapia:** *Consultant*; ALEXION, SANOFI, ARGENX. *Other*; Reserach support Grifols and Octapharma.

CONGENITAL MYASTHENIA WITH JOINT CONTRACTURES AND DEVELOPMENTAL DELAY LINKED TO COMPOUND HETEROZYGOUS MUTATIONS IN *LAMA5*

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We report a 12-year-old girl with long life history of muscle weakness, ptosis, mental developmental delay, and seizures associated with dysmorphic features, high arch palate, scoliosis, and multiple joint contractures. Failure of neuromuscular transmission was confirmed by single fiber EMG in the orbicularis oculi muscle, which revealed increased jitter and blocking. Brain MRI and an extensive panel of genetic tests, including a genomic hybridization microarray were unremarkable, except for a whole exome sequencing, which showed a pathogenic variant c.1520G>A, p.Arg507Gln and a rare polymorphism c.3031G>T, p.Val1011Phe (MAF: 0.00008) in the laminin alpha-5 subunit gene (*LAMA5*). Lack of clinical response to pyridostigmine suggested presynaptic impairment of neuromuscular transmission. Laminin alpha-5 is an extracellular matrix protein present in multiple tissues including brain and the neuromuscular junction. Thus, the broad pattern of *LAMA5* expression may explain the complex phenotype of our patient. However, more research is needed to clarify the pathogenesis of neuromuscular disorders associated with mutations in *LAMA5*.

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THROMBOTIC AND HAEMORRHAGIC COMPLICATIONS ASSOCIATED WITH PLASMAPHERESIS IN MYASTHENIA GRAVIS, REDUCING THE RISKS

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Plasmapheresis has a critical role to play in myasthenic crisis and can also be used as a chronic treatment in a small number of patients with refractory MG. There are, however, risks of thrombosis and haemorrhage but no specific guidelines to mitigate these risks and practices vary significantly. To identify thrombotic and haemorrhagic complications, a retrospective audit of the records of patients receiving plasmapheresis in the National Hospital for Neurology and Neurosurgery was performed from May 2019 - October 2020. A multi-disciplinary working group set guidelines for all aspects of the plasmapheresis procedure, including mode of vascular access, use of prophylactic heparin and type of replacement fluid. The service was

subsequently re-audited. Between April 2019 and October 2020, 46 patients, including 10 with MG, were treated with plasmapheresis. 11% developed a thrombus requiring anticoagulation and 41% developed a haemorrhage, with one haemorrhage-related death in a patient with refractory MG. A protocol change was introduced which included reduced used of vascaths, replaced by implantable vascular access devices (port- a-caths), routine use of prophylactic heparin and increased use of pooled human plasma as a replacement fluid. A subsequent review of 32 patients, 4 with MG, between November 2020 to October 2021 showed a reduction of 27% and 17% in the incidence of thrombus and haemorrhage respectively. Plasmapheresis is integral to the treatment of many immune-mediated neurological diseases. Careful consideration of all aspects of the process, and changes in protocol, reduces risks and improves patient safety.

JS has served on advisory boards for Argenx and UCB Pharma. The other authors report no conflicts.

EFFECTS OF IGG1-MUSK ANTIBODIES ON THE AGRIN-INDUCED ACHR CLUSTERING PATHWAY

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The agrin/LRP4/MuSK/DOK7 pathway is essential for maintenance of the AChR at the neuromuscular junction. In MG with MuSK-antibodies, predominant monovalent IgG4 antibodies inhibit LRP4 binding to MuSK, leading to reduced MuSK phosphorylation and reduced AChR clusters on the surface of C2C12 myotubes. Interestingly, divalent IgG1,2 or 3 MuSK antibodies also reduce agrin-induced AChR clusters but do not appear to inhibit LRP4-MuSK interaction. To understand better the pathogenic mechanisms of IgG1-3 MuSK antibodies, C2C12 myotubes were incubated with IgG1-3 or IgG4 antibodies purified from five MuSK-MG patients. 12-20% of the MuSK antibodies were IgG1-3. Expression and phosphorylation of MuSK, DOK7 and AChR-beta subunit were measured by immunoprecipitation and western blotting. AChR clusters were described as fully-formed, ≥3 μm, or microclusters, <3 μm. IgG1-3, in contrast to IgG4, did not reduce MuSK or DOK7 phosphorylation. Independent application of IgG1-3 or agrin stimulated the phosphorylation of MuSK, DOK7 and AChR-beta subunit with a similar time-course peaking at around 1-2 hours and partially decreasing thereafter; thus, failing to explain the inhibitory effect of IgG1-3 on AChR clusters. With MuSK IgG4, however, microclusters were increased but failed to form full clusters, whereas with MuSK IgG1-3 both types of clusters were reduced suggesting an effect on microcluster formation. Intriguingly, with IgG1-3 AChR clusters were restored by NSC-87877, a SRC homology 2 domain-containing phosphotyrosine phosphatase 2 inhibitor (as previously reported for IgG4 MuSK antibodies). Results are consistent with a pathogenic effect of IgG1-3 in MuSK-MG but the molecular mechanisms, and how NSC-87877 restores the clusters, remain unexplained.

AV and University of Oxford held a patent for MuSK-antibodies, licensed to Athena Diagnostics, expired in 2021. AV received a proportion of royalties. None of the other authors report conflicts of interest

NSC-87877, INHIBITOR OF SRC HOMOLOGY 2 DOMAIN-CONTAINING PHOSPHOTYROSINE PHOSPHATASE 2, AMELIORATES EXPERIMENTAL AUTOIMMUNE MYASTHENIA GRAVIS INDUCED BY MUSK IMMUNIZATION

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Muscle-specific kinase antibodies (MuSK-Abs) in myasthenia gravis (MG) reduce neuromuscular transmission through inhibition of MuSK phosphorylation and acetylcholine receptor (AChR) clustering. The SRC homology 2 domain-containing phosphotyrosine phosphatase 2 is an enzyme that reduces MuSK phosphorylation. In cultured C2C12 myotubes, the specific inhibitor NSC-87877 protected against the effects of MuSK-Abs on AChR clustering, and might represent a novel therapeutic approach for MuSK-MG. Eight-week-old female Balb/C mice were immunized twice (weeks 0 and 3) with 40 micrograms of MuSK emulsified in complete Freund's adjuvant, clinically scored (0 – 4) daily, monitored for muscle weakness, and weighed twice a week. When mice exhibited Grade 2 weakness (around 6 weeks), they received daily intraperitoneal injections of NSC-87877 (100mg/kg, n=10) or PBS (n=10) for 3 weeks and were culled 2 weeks later (around week 11). The NSC-87877-treated mice had lower clinical scores by week 7 and at week 9 the mean score was under 1 ($p<0.001$ compared with PBS treated mice (2-4). The clinical benefits were maintained through to termination. The treated mice showed modest reductions in muscle weakness, increased average grip strength and higher body weights than PBS-treated mice. SHP-2 inhibitor-treated mice had reduced IgG and complement factor C3 at the neuromuscular junctions compared to PBS-treated mice. **These results show that the SHP2 inhibitor NSC-87877 ameliorates clinical and pathological findings of MuSK-induced experimental MG; the mechanisms by which it acts are now being explored.**

AV and University of Oxford held a patent for MuSK-antibodies, licensed to Athena Diagnostics, expired in 2021. AV received a proportion of royalties. None of the other authors report conflicts of interest

ACETYLCHOLINE RECEPTOR ANTIBODY CHARACTERISTICS IN MOTHERS OF CHILDREN WITH FETAL ACETYLCHOLINE RECEPTOR INACTIVATION SYNDROME

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In offspring of pregnant mothers with myasthenia gravis, the risk of neonatal myasthenia is low. Very rarely, arthrogryposis multiplex congenital occurs and can be lethal due to lack of fetal movement in utero. In these cases, the maternal antibodies bind preferentially to the fetal isoform of the AChR and block its function, paralyzing the baby. It has become clear that some of the preceding or subsequent offspring of these AChR-antibody positive mothers, including some mothers without evidence of MG, can have neonatal difficulties with a persistent, particularly facial, myopathy and other developmental abnormalities, termed fetal acetylcholine receptor inactivation syndrome. Causative antibodies and their pathogenic mechanisms have not yet been explored. We examined the maternal serum AChR antibodies from five mothers including two with no diagnosis of MG. Routine maternal AChR antibody titers ranged from 31 to 87 nM. Using adult or fetal AChR expressing cell-based assays, adult AChR titers ranged from 50 to 400 and fetal AChR titers from 200 to 3200. In each case, reactivity with fetal AChR was greater but the ratios of fetal:adult varied widely from 2 to 128. Antibodies binding to fetal AChR were of the IgG1 subclass and induced complement factor C3b deposition on the fetal AChR-expressing cells. Fetal acetylcholine receptor inactivation syndrome is part of the spectrum of maternal antibody-mediated developmental conditions associated with AChR antibodies, but not all mothers have MG. Pathogenic mechanisms may include complement-mediated damage to the developing neuromuscular junctions rather than direct block of AChR function.

AV and LJ declare involvement in a UCB funded experimental study of anti-FcRn to prevent transfer of fetal AChR antibodies to the fetus. None of the other authors have relevant conflicts of interest.

THE CLINICAL AND MOLECULAR LANDSCAPE OF CONGENITAL MYASTHENIC SYNDROMES IN AUSTRIA: A NATIONWIDE STUDY

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Congenital myasthenic syndromes (CMS) encompass a heterogeneous group of disorders due to various genetic defects resulting in impaired neuromuscular transmission. Given the availability of effective treatments, an early and correct genetic diagnosis becomes increasingly relevant. In this study, we used a nationwide approach to collect Austrian patients with genetically confirmed CMS. We provide an in-depth clinical and molecular characterisation and further aimed to estimate the current prevalence of CMS in Austria.

32 cases with genetically confirmed CMS were collected, corresponding to a prevalence of around 0.4 in 100,000. Median age at onset was 0.3 years (IQR 0-5.6) and 63.5 % of included patients were female. Median time from symptom onset to diagnosis was 6.0 years (IQR 1.8-15.5). The most frequently identified genetic aetiology was *CHRNE* (40.6%), followed by *DOK7* (15.6%) and *COLQ* (9.3%). Ptosis was reported in 89.7%, while ophthalmoparesis was found in 55.6% of the whole cohort. One patient with a pathogenic variant in *MUSK* required percutaneous endoscopic gastrostomy and invasive ventilation. Treatment comprised pyridostigmine in 21 patients (65.6%) and salbutamol/ephedrine in 14 patients (43.8%). This study represents the first detailed clinico-genetic characterisation of an Austrian cohort with CMS. In the long-run, systematic data on very rare diseases like CMS may help to optimise the clinical management of patients, especially if targeted treatments are available.

The authors declare no conflicts of interest related to this work

A LOW DOSE RITUXIMAB REGIME (USING 100MG ST) SHOWS SIMILAR EFFICACY FOR B CELL DEPLETION AS STANDARD REGIMES (1000MG OR 375MG/M2 DOSES)

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Rituximab is an anti-CD20 monoclonal antibody used in the treatment of Myasthenia Gravis and other auto-immune diseases. It's therapeutic effect is mediated through B cell depletion. The treatment regimes for Rituximab that were developed for the treatment of clonal B cell disorders were largely adopted for the treatment of autoimmune disorders. Because low dose regimes using 100mg doses in lieu of 375mg/m^2 or

1000mg doses have been reported as efficacious in the treatment of immune thrombocytopenia, we historically defaulted to a low dose regime for the treatment of non-vasculitic neurological autoimmune disease.

Patients treated with either low doses of 100mg (n=11) or standard regimen 375mg/m^2 (n=2) had lymphocyte subset profiles taken at clinical follow up. Rituximab 100mg was effective at causing complete B lymphocyte depletion (CD19) for a mean of 217 days (95% CI 109-533). The time to B cell recovery (B cell count >0.02*10^{-9} /L) was similar in those managed with 100mg to those treated with 375mg/m^2. Immediate T cell lymphopenia (CD4 and CD8) was common following rituximab administration. One patient received only 50mg rituximab due to infusion-related symptoms. In this case B lymphocyte counts were detectable after infusion.

In summary we provide evidence that low a dose Rituximab regime typically induces equivalent depletion of CD19/ CD20-expressing lymphocytes to standard regimes. This has implications for cost-effective and appropriate dosing in auto-immune disease.