MYASTHENIA GRAVIS FOUNDATION OF AMERICA

ABSTRACT LIST

MGFA 15TH INTERNATIONAL CONFERENCE

ON MYASTHENIA AND RELATED DISORDERS

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MYASTHENIA GRAVIS FOUNDATION OF AMERICA

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1

SYNCOPE AS A PRESENTING SYMPTOM OF MUSK-ASSOCIATED MYASTHENIA GRAVIS: A CASE REPORT

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INTRODUCTION: Dysautonomia in neuromuscular junction disorders is not frequently reported and is not widely recognized. It has been linked to thymoma and several novel antibodies, yet, autonomic instability can be found even when these features are absent. In MuSK-related MG, clinical autonomic signs have been found in a significant percentage.

OBJECTIVE: We present a series of cases with MuSK-related MG that present initially with orthostatic intolerance.

METHODS**:** With the assistance of a clinical librarian, two independent reviewers screen for studies relating to myasthenia gravis, MuSK, dysautonomia and autonomic dysfunction. A third reviewer achieves consensus for included papers.

RESULTS: We present a series of cases with MuSK-related MG that present initially with strong dysautonomic symptoms, primarily orthostatic intolerance. Both patients have a severe disease course due to autonomic and myasthenic crises and require intensive treatment for recovery.

SUMMARY/CONCLUSION: The patients are unique in their syncopal burden prior to MG diagnosis, and it is difficult to explain dysautonomia in Musk. However, current evidence along with these cases suggest yet unknown roles with broader systemic effect tied to the MuSK protein.

2

ALTERED B CELL SIGNALING AND RESPONSES TO T FOLLICULAR HELPER CELL-RELATED CYTOKINES IN MYASTHENIA GRAVIS

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INTRODUCTION: Myasthenia Gravis (MG) is an autoimmune disorder characterized by autoantibody production. Responses of autoreactive B cell populations to T follicular helper (Tfh) cell-related cytokines may contribute to the disease pathogenesis.

OBJECTIVE: To study spontaneous B cell responses and alterations to cytokine stimulations in MG patients compared to healthy controls (HCs).

METHODS: A total of 23 acetylcholine receptor $(AChR)^+$ MG patients and 21 HCs were recruited. Nine patients were on immunosuppressive treatment. Peripheral blood mononuclear cells (PBMCs) were isolated and stained for CD19, CD20, CD27 and IgD. Furthermore, cells were stimulated *in vitro* with IFNα2a, IFNβ, IL-21 and IL-4. B cell phenotypes and phosphorylation of STAT proteins (pSTAT-1, -3 and -6) in $CD20^+$ B cells were compared.

RESULTS: *Ex vivo* without cytokine stimulation, pSTAT-1 (both T701 and S727) and pSTAT-3 (both T705 and S727) were elevated significantly in $CD20^+$ B cells of MG patients compared to HCs, while pSTAT-6 (Y641) tended to be higher in MG compared to HCs. When the cells were stimulated with Tfh-related cytokines, attenuated phosphorylation of pSTAT-3 (both T705 and S727) in response to IL-21 and pSTAT-6 (Y641) to IL-4 were observed in $CD20^+$ B cells of MG. Both IFNα2a and IFNβ induced no significant changes in pSTAT-1 (both T701 and S727) compared to HCs. Phenotypic analysis of these MG patients showed significantly lower $CD27^+IgD^+$ unswitched memory and $CD27^+IgD^-$ switched memory B cells compared to HCs, while $CD27^-IgD^+$ naïve as well as $CD27^-IgD^-$ B cells were higher in MG.

SUMMARY/CONCLUSION: MG patients exhibit altered phosphorylation profiles of pSTAT proteins in B cells, characterized by elevated basal phosphorylation, suggesting a sustained IL-21 and possibly IFN type I response in disease pathogenesis.

3

A NOVEL INTERNATIONAL PATIENT REGISTRY IN MYASTHENIA GRAVIS LINKING CLINICAL AND PATIENT-REPORTED OUTCOMES DATA: THE VITACCESS REAL MG (VRMG) REGISTRY

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INTRODUCTION: Myasthenia Gravis (MG) is a rare, chronic, autoimmune disease characterized by debilitating and fluctuating muscular weakness. There is no robust source for MG research combining PROs and clinical data, including symptoms, daily activities and quality of life.

OBJECTIVE: To design a global patient registry ("Vitaccess Real MG") to optimally quantify the impacts of disease and treatment on patients living with MG using electronic medical record (EMR) and patient-reported outcome (PRO) data.

METHODS: Patients with a clinically-confirmed diagnosis of MG are recruited in the US and UK, with planned expansion to additional European countries in 2025/6. In all countries, recruitment can occur at clinical sites, with healthcare professionals contributing clinical data from patients' medical records. In the US only, patients can also be recruited direct-to-patient or via their treating community neurologist; in both cases, clinical data are captured retrospectively via an electronic medical record aggregator. Clinical data – including medical history, treatment history, and adverse events – are captured on a six-monthly basis. For all patients, clinical data are linked with PRO data – including: Myasthenia Gravis Activities of Daily Living; MG Symptoms PRO Fatigue Scale; NeuroQoL Fatigue Short Form; and Myasthenia Gravis Quality of Life 15-item Revised Scale. Patients contribute PRO data directly via the web-enabled VRMG platform on a monthly or bi-monthly basis, in order to track disease activity between clinic visits. Patients can opt in to receiving weekly text message prompts to capture MG symptom changes.

RESULTS: Direct-to-patient and community neurologist recruitment in the US were initiated in July 2024, and site recruitment in the US and UK were initiated on September 2024 and April 2025, respectively.

SUMMARY/CONCLUSION: By integrating digitally-captured clinical data and PROs, this novel registry aims to improve understanding of the symptoms and quality of life impact experienced by MG patients, in order to optimize future disease management.

DISCLOSURES: Fatemeh Amini, Jack Lawrence, Sally Vincent, Tsitsi Monera-Penduka, Geraldine Hall, Alasdair Fellows, and Mark Larkin are current or former employees of Vitaccess, which has received research support from UCB. Anna Scowcroft, Raphaëlle Beau-Lejdstrom, and Natasa Savic are current or former employees and shareholders of UCB. Saiju Jacob has served as an international advisory board member for Alexion, Alnylam, argenx, Immunovant, Regeneron, and UCB Pharma; is currently an expert panel member of the Myasthenia Gravis consortium for argenx and has received speaker fees from Terumo BCT and Eisai Pharmaceuticals. Ali A. Habib has received research support from Alexion Pharmaceuticals, argenx, Cabaletta Bio, Genentech/Roche, Immunovant, Regeneron Pharmaceuticals, UCB and Viela Bio (now Amgen). He has received honoraria from Alexion Pharmaceuticals, Alpine Immune Sciences, argenx, Genentech/Roche, Immunovant, Inhibrx, Regeneron Pharmaceuticals, NMD Pharma and UCB. Francesco Saccà has served as a Consultant for Alexion Pharmaceuticals, argenx, Biogen, Dianthus, Genpharm, Johnson & Johnson, Lexeo, Madison Pharma, Medpharma, Neopharm Israel, Novartis, Reata, Sandoz, UCB and Zai Lab. He has received research support paid to his institution from AIFA and FARA. Amanda Hayes has nothing to disclosure.

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4

PATIENT PREFERENCES AND EXPERIENCE WITH SELF-ADMINISTRATION OF ROZANOLIXIZUMAB IN GENERALISED MYASTHENIA GRAVIS

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INTRODUCTION: Rozanolixizumab is currently administered by healthcare professionals (HCPs) using programmable syringe drivers (SD). The Phase 3, open-label, crossover MG0020 study (NCT05681715) investigated patient self-administration of rozanolixizumab using manual push (MP) and SD methods.

OBJECTIVE: To evaluate successful self-administration, patient preferences, patient experience and safety of self-administered rozanolixizumab in MG0020.

METHODS: Adults with gMG received once-weekly rozanolixizumab (weight-tiered dosing or 7 mg/kg) for 18 weeks: training (6 weeks) followed by 1:1 randomisation to Sequence 1 (SD then MP) or Sequence 2 (MP then SD) to self-administer (6 weeks per method). The primary endpoint was successful self-administration (choosing correct infusion site, administering subcutaneously, delivering intended dose) at Weeks 12 and 18. Treatment-emergent adverse events (TEAEs), total immunoglobulin G (IgG) over time, change from baseline in MG-ADL score, patient preference for administration method, and patient experience (self-injection assessment questionnaire [SIAQ]-infusion version) were also assessed.

RESULTS: Of 62 enrolled patients, 55 were randomised. All successfully self-administered rozanolixizumab at each visit. Decreases from baseline in median total IgG and mean MG-ADL score (≥2.0 points) were observed at Week 7 and sustained during self-administration.

Regardless of treatment sequence, most patients preferred self-administration (63.6% [n=35/55]) to HCP administration (9.1% [n=5/55]) during training; no preference: 16.4% (n=9/55). More patients preferred MP (45.5% [n=25/55]) than SD (30.9% [n=17/55]); no preference: 12.7% (n=7/55). Mean pre-infusion SIAQ scores were 5.8–8.6 (on a 0–10 scale); mean post-infusion SIAQ scores were high (7.5–9.3), indicating a positive experience. TEAEs occurred in 75.8% (n=47/62) of patients, with most events (97.6% [161/165]) being mild/moderate.

SUMMARY/CONCLUSION: All patients successfully self-administered rozanolixizumab; clinical response and safety profile were consistent with the known profile of HCP-administered rozanolixizumab. Self-administration via MP was the preferred method, and a positive experience was reported with rozanolixizumab self-administration in patients with gMG.

5

LONG-TERM SAFETY AND EFFICACY OF NIPOCALIMAB IN GENERALIZED MYASTHENIA GRAVIS: VIVACITY-MG3 OPEN-LABEL EXTENSION PHASE RESULTS

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INTRODUCTION: There is an unmet need for generalized myasthenia gravis (gMG) treatments that are safe and provide sustained symptom control for patients. In autoantibody-positive patients with gMG**,** nipocalimab, a novel neonatal fragment crystallizable receptor (FcRn) blocker, demonstrated significant improvement from baseline over weeks 22, 23, and 24 with mean (standard error [SE]) change in Myasthenia Gravis-Activities of Daily Living (MG-ADL) score of –4.70 (0.329) vs. placebo (least square [LS] mean difference –1.45; p=0.002) in the phase 3 Vivacity-MG3 study (NCT04951622).

OBJECTIVE: To assess the long-term safety and efficacy of nipocalimab in patients with gMG from the Vivacity-MG3 open-label extension (OLE) phase.

METHODS: Autoantibody-positive (n=153, anti-acetylcholine receptor [AChR]/muscle-specific tyrosine kinase [MuSK]/low-density lipoprotein receptor [LRP4] positive) and triple-autoantibody-negative patients (n=43) with gMG (Myasthenia Gravis Foundation of America [MGFA] Class II-IV), inadequately controlled (MG-ADL >6) on standard-of-care (SOC) therapy, were randomized 1:1 to nipocalimab + SOC or placebo + SOC in a 24-week double-blind study, with the option to enter an ongoing OLE phase. Safety was assessed in patients receiving at least 1 dose of study drug.

RESULTS: A total of 137 autoantibody-positive patients from the double-blind phase enrolled in the OLE and received nipocalimab + SOC. The mean (SE) change in MG-ADL from the double-blind baseline was –5.73 (0.401) [n=81] at OLE week 24, and –5.97 (0.681) [n=37] at OLE week 48. Nipocalimab was generally well-tolerated and there were no new safety findings in the OLE phase. Updated results of this ongoing study will be presented.

SUMMARY/CONCLUSION: The FcRn blocker nipocalimab demonstrated sustained disease control over 72 weeks across double-blind and open-label phases, as assessed using the MG-ADL scale, in a broad population of autoantibody-positive patients with gMG in the phase 3 Vivacity-MG3 study.

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EFGARTIGIMOD CHANGES THE COURSE OF ACHR AND NON-ACHR MYASTHENIA GRAVIS

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INTRODUCTION: Inhibition of the neonatal Fc receptor (FcRn) is a new therapeutic strategy for antibody mediated diseases including generalized Myasthenia Gravis (gMG). Among available compounds, Efgartigimod (EFG) was approved for gMG with positive anti-AChR antibodies. We report our real world experience with EFG, since November 2021, on 30 patients affected with AChR+ and non-AChR gMG.

OBJECTIVE: To evaluate effectiveness of EFG in AChR+ and non-AChR MG and the impact on the course of the disease in a real world setting.

METHODS: We treated 17 patients with AChR+ and 13 with non-AChR gMG (5 MuSK, 2 LRP4 and 6 triple negative, confirmed by live CBA). EFG was administered according to the GENERATIVE protocol (consisting of a Fixed period of 2 treatment cycles of 4 infusions at weekly intervals, followed by a Flexible period during which EFG was given in case of clinical worsening) starting from November 2021. Outcomes were evaluated by means of the MG-ADL (MG Activity of Daily Living), QMG (Quantitative MG score) and MG Composite (MGC) and MG-QoL-15r questionnaire

RESULTS: Meaningful improvement was recorded at each cycle in AChR+ gMG as well as in non-AChR gMG (mean score reductions MG-ADL -5.5; MGC -8.5 and QMG -4.84). The number of cycles/year was 3.9±0.99. The mean interval between cycles was 8.9±3.8 weeks. MG-ADL improvement greater than 5 points was recorded in 49% of patients. None of our gMG patients were hospitalized or needed plasmaexchange or immunoglobulins during EFG (compared to 65% before EFG). EFG was well tolerated.

SUMMARY/CONCLUSION: EFG provided meaningful clinical improvement independently of antibody specificity; interestingly, in a subset of patients improvement lasted more than IgG half-life allowing treatment personalization. EFG had a dramatic impact on the course of MG (no need for plasmaexchange or immunoglobulins). Extension of the indication of EFG to seronegative patients should be reconsidered.

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THE ITALIAN MYASTHENIA GRAVIS REGISTRY

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INTRODUCTION: The improvement in understanding the unmet needs and clinical management of a rare disease such as MG depends on in-depth knowledge of the patient population distributed across each country, particularly in the era of targeted therapies that need large data sets from the real world. As no MG registry is currently existing in Italy, we implemented the Italian MG registry (ITA-MG) to collect relevant information, including epidemiological data and response to standard and innovative treatments.

OBJECTIVE: The aim of the ITA-MG registry is to collect epidemiological and clinical data on the Italian MG population, to better evaluate MG natural history, response to treatments and promote multicentre collaboration.

METHODS: We designed an eCRF based on the REDCap software including one-entry clinical and epidemiological data, with recurrent data collection at every patient visit. The eCRF has been designed taking into account common data elements and disease specific datasets for MG as suggested by the Myasthenia Gravis Association of America and the European Reference Network for Rare Neuromuscular Disorders. Attention has been paid to the pseudonymisation protocol, and to the identification of duplicates. Response options have been specified for each item of the eCRF to avoid variability, and ontology has been included for classification of comorbidities and side effects. A specific Data Protection Impact Assessment (DPIA) document has been drawn up.

RESULTS: 44 Italian reference centres for MG have joined the registry and started the approval process

SUMMARY/CONCLUSION: Patient registries are essential to collect standardized patient data, especially in rare diseases including MG. The ITA-MG registry was founded to collect uniform clinical and epidemiological data on the Italian MG population, allowing to collect a large pool of patient data essential for the improvement of disease knowledge, access to treatments, multicentre collaboration and clinical research.

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IDENTIFICATION OF CLINICAL VARIABLES ASSOCIATED WITH TREATMENT RESPONSE TO EFGARTIGIMOD IN GENERALIZED MYASTHENIA GRAVIS

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INTRODUCTION: Efgartigimod (EFG) is a neonatal FC receptor blocker approved for the treatment of AChR-positive gMG. Treatment cycles are administered according to clinical evaluation and frequency of retreatment can vary among patients. Our experience with EFG has demonstrated a frequency of retreatment similar to that of the ADAPT+ study and other real world experiences. However, we were able to identify two subsets of patients, with similar epidemiological and clinical features within each subset, that required either very frequent or very sparse retreatments, possibly allowing the identification of clinical biomarkers useful to predict treatment response.

OBJECTIVE: To identify clinical variables associated with early loss of response or very prolonged response to EFG as potential biomarkers.

METHODS: We treated 17 AChR+ gMG patients with EFG administered according to the Generative protocol (a Fixed period of 2 treatment cycles of 4 weekly infusions, followed by a Flexible period during which EFG was given according to clinical evaluation) starting from November 2021. Outcomes were evaluated by means of the MG-ADL, QMG and MG Composite scores at beginning and end of every treatment cycle.

RESULTS: Meaningful improvement was recorded at each treatment cycle and the number of cycles/year was 3.9±0.99. However, 42.1% of patients required retreatment every 4 weeks. This subset of patients shared common features like female sex, early disease onset, thymic involvement, refractory disease, and very rapid response to EFG. On the other hand 23.5% of patients, characterized by male sex, late onset MG and a slower response to EFG, required <2 cycles/year.

SUMMARY/CONCLUSION: We observed the existence of common features among patients that require frequent retreatment and those with sustained prolonged response to EFG, which might be considered as clinical biomarkers of treatment response. However, more data are needed to establish the possible existence of clinical biomarkers predictive of treatment response.

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UPDATED GUIDELINES ON THE PASSIVE TRANSFER MYASTHENIA GRAVIS RAT MODEL: THE ADVANTAGES OF SUBCUTANEOUS ADMINISTRATION

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INTRODUCTION: The passive transfer model of Myasthenia Gravis, reflecting the acute phase of the human condition, is commonly induced in female rats using monoclonal antibody 35 (mAb35) using intraperitoneal (I.P.) or intravenous (I.V.) administration. While offering rapid absorption, it poses challenges such as injection placement and, for of I.P., potential animal discomfort. Subcutaneous (S.C.) administration could be a more robust technique to induce the disease.

OBJECTIVE: Here we investigated the suitability of S.C. administration as an alternative to I.P. administration in the PTMG rat model.

METHODS: Forty-four 11-week-old, female Lewis rats were used divided over two experiments. Following guidelines, one group was injected I.P. with 20 pmol/100g body weight (BW) mAb35 and euthanized 48h post-immunization. Other animals were injected S.C. 20 or 40 pmol/100g BW with mAb35 and were euthanized 48h or 72h post-immunization. Control groups received 0.5 mg/kg IgG1 isotype control S.C. or I.P. and were euthanized 48h post-immunization. Blood samples were taken (24h post-immunization and at terminal time point) and muscle weakness, fatigue, weight and disease scores were daily recorded. During the terminal procedure, total AChR content was determined by electromyography and AChR-muscle content was analyzed postmortem. The experiment was repeated using a different batch of mAb35 S.C. at a dose of 40 pmol/100g BW. Control animals received saline injections.

RESULTS: MAb35 administration induced BW loss and MG symptoms comparable to I.P. administration. Circulating mAb35 levels remained stable from 24 hours to euthanasia. However, I.P. injection presented a risk of misplacement, making it potentially a less reliable administration method which could lead to false positive results in drug studies. While MG characteristics were observed regardless of mAb35 dose, route and batch, variability differed significantly between routes of administration.

SUMMARY/CONCLUSION: We demonstrated S.C. injection offers reduced discomfort and a consistent induction method for PTMG, establishing it as a refined, effective alternative to I.P. administration.

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CO-DESIGN OF DISCRETE CHOICE EXPERIMENT SURVEY WITH MYASTHENIA GRAVIS PATIENTS USING NOMINAL GROUP TECHNIQUE AND FOCUS GROUPS

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INTRODUCTION: Given the significant costs of Myasthenia Gravis (MG) treatments, understanding patient preferences is critical for guiding resource allocation. Discrete Choice Experiment (DCE) is a quantitative survey technique that elicits patient preferences for healthcare treatments. DCEs present hypothetical but real-life scenarios, and patients are asked to choose between options. The success of DCEs depends on selecting the relevant attributes (specific characteristics that depict treatments).

OBJECTIVE: This study explored the feasibility of using the Nominal Group Technique (NGT) and consumer engagement via focus groups to collaboratively design a DCE with patients with MG.

METHODS: We recruited nineteen Australian patients (12 females, 7 males) aged 35 to 82 years to participate in two 1-hour online sessions in July and August 2024. Each session included 4-6 patients facilitated by three researchers. Participants were presented with three scenarios: 'mild' exacerbation, severe exacerbation/MG crisis and maintenance. The first session employed NGT to consider treatment attributes and rank the most valued attributes for each scenario. In the second session, patients were presented with draft DCE scenarios and were asked for feedback on the attribute descriptions and levels. The final DCE was reviewed by a multidisciplinary group (clinicians, health economists and patients) to ensure its real-life applicability.

RESULTS: The use of NGT and focus groups played a pivotal role in the design of our DCE. It eliminated low-priority attributes (e.g., bone loss) and helped refine scenarios and attribute levels. However, while NGT can be highly effective for prioritising attributes, it should be complemented by additional methods. For example, upon review of our DCE by our multidisciplinary group, one lower-ranked attribute by patients (e.g., the total cost to the patient) was considered important by clinicians and health economists and was included.

CONCLUSION: This study confirms that NGT and focus group sessions are feasible and extremely useful when coupled with multidisciplinary review.

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EFGARTIGIMOD FOR TREATMENT REFRACTORY ACETYLCHOLINE RECEPTOR ANTIBODY POSITIVE MYASTHENIA GRAVIS: THE NATIONAL HOSPITAL FOR NEUROLOGY & NEUROSURGERY EXPERIENCE

Authors: Aravindhan Baheerathan[1], Narmathey Thambirajah[1], Georgiana Logou[1], Sheetal Sumaria[1], Dimitri Kullmann[1], Robin Howard[1], Jennifer Spillane[1]

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INTRODUCTION: Myasthenia gravis is a chronic auto-immune neuromuscular junction disorder that is caused by pathogenic auto-antibodies (IgG) that interfere with physiological synaptic transmission. Despite current medical treatment, approximately 15-25% of patients with generalized myasthenia gravis (gMG) remain refractory to currently available therapeutics. Efgartigimod, a neonatal Fc-receptor antagonist has recently emerged as an efficacious therapeutic agent in AcHR positive GMG but its real world clinical efficacy and safety is still being established.

OBJECTIVES: We review the efficacy, safety and tolerability in 29 patients with treatment resistant AcHR positive gMG who were treated with efgartigimod on an early access scheme at our center.

METHODS: Prospective data for all patients treated in the NHNN with Efartigimod were colllecte (Nov 22 -Nov 24) . Follow-up ranged from 1-22 months (mean 13 months). Data was collected on: • Patient demographics and details of gMG • Baseline gMG treatments • Outcome measures: Reduction in MG-ADL & prednisolone dose during course of treatment • Adverse effects and tolerability

RESULTS: • 29 patients were treated with Efgartigmod • 69% of our treated cohort was female • The mean age of our cohort was 50 (range 29-64) • Patients had a mean disease duration of 12 years prior to treatment and the average number of disease modifying therapeutics previously trialed was 4 • 66% of patients have had an overall improvement in their ADL >2 with a mean improvement of 4.8 • 57% of patients treated with efgartigimod have reduced their prednisolone dosing with a mean reduction of 7.5mg once daily • 24% of patients have stopped efgartigimod treatment during this period with the commonest reason being lack of treatment efficacy. • 13.8% noted a reduction in efficacy when switching from intravenous to subcutaneous regimens and were therefore transitioned back to intravenous administration • One patient with concurrent infection developed myasthenic crisis requiring rescue treatment with PLEX and IVIg. There were no other serious adverse events reported.

SUMMARY/CONCLUSION: Efgartigimod is an effective, well tolerated therapeutic option in patients with treatment refractory gMG.

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RITUXIMAB FOR GENERALISED MYASTHENIA GRAVIS: A SINGLE CENTRE EXPERIENCE OF SAFETY, TOLERABILITY AND EFFICACY

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INTRODUCTION: Myasthenia gravis is a chronic auto-immune neuromuscular junction disorder that is caused by pathogenic auto-antibodies (IgG) that interfere with physiological synaptic transmission. Despite current medical treatment, approximately 15-25% of patients with generalized myasthenia gravis (GMG) remain refractory to currently available therapeutics. Rituximab, a monoclonal antibody that targets the CD20 antigen

OBJECTIVES: We performed a retrospective review of patients with gMG who were treated with rituximab at NHNN between 2019-2024 to assess its efficacy, safety and tolerability.

METHODS: Records were prospectively collected for 32 patients with gMG who were treated with rituximab at NHNN. We collected data on: • Patient demographics • Details of MG diagnoses • Antibody status (AchR or MuSK antibody) • Treatments administered prior to Rituximab • MG-ADL prior to and at 6 months post rituximab • Current MG-ADL • Steroid dose pre and post rituximab • Adverse effects and tolerability Positive outcomes were recorded if, a) a reduction of at least 2 points in MG Activities of Daily Living (ADL) or 3 points in MG composite scale occurred, b) if treatment escalation was not required, or c) if either prednisolone was weaned by >75% or intravenous immunoglobulin were weaned.

RESULTS: Out of 32 patients, 26 (81.2%) were female and 6 were male. Eighteen (56.2%) patients were acetyl-choline receptor antibody positive (AchR) and thirteen were muscle-specific kinase (MuSK) antibody positive. Mean age at start of treatment was 46.8 years (range 25 – 76) and mean disease duration was 13.2 (+/-10) (range 1 to 47). An average of 4 other immunosuppressive agents had been tried previously (range 1–7). Twenty (62.5%) patients responded to RTX. 76.9% (10/13) of MuSK positive and 50% (9/18) of AchR positive patients improved. Age and thymectomy were unrelated to outcomes while less than 10 years to treatment correlated to positive outcome. One multi-morbid patient died from Covid19.

SUMMARY/CONCLUSION: Rituximab is effective in MuSK positive gMG but variably effective in AchR positive gMG.

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LONGITUDINAL OVERVIEW OF SYMPTOMATIC AND IMMUNOSUPPRESSIVE DRUGS IN LEMS

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INTRODUCTION: Lambert-Eaton Myasthenic Syndrome (LEMS) is a very rare autoimmune disorder characterized by antibodies targeting voltage-gated calcium channels at the neuromuscular junction. Amifampridine is currently the only agent approved for the treatment of LEMS, although other therapies, including immunosuppressive agents, may also be prescribed off-label. How LEMS specific therapies change per patient over a longer period of time has not been elucidated.

OBJECTIVE: To evaluate the effect of amifampridine and assess the long-term use of other LEMS specific therapies.

METHODS: Medical record data of patients diagnosed with LEMS, were retrospectively collected. Data collected included epidemiological and clinical data, LEMS specific therapy start/stop dates and reasons for discontinuation. The effect of amifampridine was assessed qualitatively and with a newly developed leg score, this score categorizes the leg symptoms in 4 groups with increasing symptoms.

RESULTS: 70 patients with LEMS were included, with visits between 1992-2024. Mean duration of follow up was 96 months (range 0-356 months). 88.6% of patients had non-tumour associated LEMS. All patients had used amifampridine at some point during their disease. The effect on the leg score as well as qualitatively was evident. 81.4% had used pyridostigmine as symptomatic treatment, of whom, 31.6% stopped mostly because of side effects. Immunosuppressive therapies consisted mainly of prednisolone (48.6%) and azathioprine (42.9%), and these drugs were discontinued in 38.2% and 50% of patients respectively, most frequent reason for stopping these drugs were also side effects. Interestingly, in some cases immunosuppressives were started multiple years after diagnosis.

SUMMARY/CONCLUSION: Amifampridine is an effective, first-line symptomatic treatment in LEMS. Nonetheless, in more than 50% of patients during follow-up immunosuppressive treatment is started, sometimes several years after diagnosis.

DISCLOSURES: WRB is employed by the department of clinical pharmacy and toxicology which produces and supplies the 3,4-diaminopyridine base modified release tablets to 40–50 users in the Netherlands.TVG is employed by the department of clinical pharmacy and toxicology which produces and supplies the 3,4-diaminopyridine base modified release tablets to 40–50 users in the Netherlands. In the last 3 years tvg has received lecture fees and consulting fees from Roche Diagnostics, Thermo Fisher, Vitaeris, CSL Behring, Astellas, and Aurinia Pharma. JJGMV has been involved in MG research sponsored by the Princess Beatrix Fonds, Health Holland, and Consultancies for Argenx, Alexion, and NMD Pharma. Reimbursements were received by the LUMC. He is coinventor on patent applications based on Musk-related research. The LUMC receives royalties for musk antibody assays. He is a member of the target-

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DESIGN OF A PHASE 3 RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF SUBCUTANEOUS EFGARTIGIMOD PH20 ADMINISTERED BY PREFILLED SYRINGE IN ADULTS WITH OCULAR MYASTHENIA GRAVIS

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INTRODUCTION: Despite therapeutic advancements in gMG over the last 3 years, there remains a significantly unmet need for patients with oMG. Retrospective analysis of data supporting the approval of efgartigimod for treatment of adults with gMG indicated improvement in ocular symptoms in this population.

OBJECTIVE: To present the design of the ADAPT OCULUS Trial (NTC06558279), a Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of subcutaneous (SC) efgartigimod PH20 (coformulated with recombinant human hyaluronidase PH20), an immunoglobulin G (IgG)1 antibody Fc-fragment that selectively reduces IgG levels by blocking neonatal Fc receptor (FcRn)-mediated IgG recycling, in oMG.

METHODS: Adults with confirmed oMG and a Myasthenia Gravis Impairment Index (MGII) patient-reported outcome (PRO) subcomponent ocular score ≥6 who are on stable MG therapy will be randomized 1:1 to receive 4 once-weekly efgartigimod PH20 SC 1000 mg or placebo injections administered via prefilled syringe, followed by 4 weeks of follow-up. Participants may continue in the up-to-2-year open-label extension part of the study evaluating long-term efgartigimod PH20 SC efficacy and safety in oMG.

RESULTS: The primary endpoint is change from baseline to Week 4 in MGII PRO ocular score. Key secondary endpoints include changes from baseline to Week 4 in MGII ocular score (PRO plus physical examination), Myasthenia Gravis Activities of Daily Living (MG-ADL) ocular domain score, and MGII total score. Statistical analyses for efficacy endpoints will be conducted in hierarchical order at a 1-sided significance level of α=.025. Safety assessments include adverse event incidence and severity.

SUMMARY/CONCLUSION: This is the first Phase 3 clinical trial evaluating the safety and efficacy of an FcRn inhibitor, efgartigimod PH20 SC, in patients with oMG, addressing the unmet need for treatment of this disease.

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DEVELOPING A PATIENT LIVED EXPERIENCE RESEARCHER TOOLKIT FOR ENGAGING COLLABORATIVE CLINICAL ASSISTANCE: PILOT STUDY ON NEW DIAGNOSITIC EYE TESTS

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INTRODUCTION: Generalized Myasthenia Gravis (MG) is notoriously challenging to diagnose and many people suffer for years searching for a diagnosis and treatment. The eye muscles are the most susceptible muscles affected by MG, however current ocular motility testing techniques miss latent MG eye signs (MGES) in many patients. The author has developed new ocular motility tests that quickly evoke latent MGES. The tests were designed by utilizing Patient Lived Experience (PLE), knowledge of the Safety Factor, The Mary Walker Effect, and orthoptic clinical skills and knowledge.

OBJECTIVE: Researchers living with MG who are unable to work in clinical studies due to their debilitating symptoms are unable to fully contribute their unique insight. This research aims to highlight the value of the unique insight of Lived Experience, and to develop a Toolkit to connect PLE Researchers (PLERs) with research groups to perform further clinical studies on all MG antibody groups on their behalf.

METHODS: The development of a Toolkit and a Taskforce to guide the procedures for the PLER and research groups connection and collaborative engagement.

RESULTS: A PLER Toolkit for engaging collaborative clinical assistance is an essential resource for all future PLER research as it will help reduce barriers to research for PLERs and allow for accelerated innovation in MG research.

SUMMARY/CONCLUSION: Developing new disease-specific clinical methods for identifying latent fatigable eye muscle weakness such as those described by the author can improve patients' quality of life by aiding in earlier diagnosis. This research highlights the value of the unique knowledge of PLERs, and the changes required in the research community to acknowledge and accommodate the needs of the PLERs that occur due to the debilitating effects of their illness. The adoption of these recommended changes will enable PLERs to accelerate innovation in MG research through their unique insight.

DISCLOSURES: None to declare.

THIS RESEARCH INCLUDES: A brief presentation of the miscommunication of MG historical findings that are important to be aware of for earlier MG diagnosis, as well as a summary of the newly developed eyes tests designed by this author, and were published in 2024 in: Beaupark, S. (2024). Myasthenia Gravis Misunderstood – Identifying the historical misinterpretations, miscommunication, and misconceptions. RRNMF Neuromuscular Journal, 5(3). http://doi.org/10.17161/rrnmf.v5i3.21137 and, Beaupark, S. (2024). Eliciting Latent Myasthenia Gravis Eye Signs Utilizing 'The Mary Walker Effect'. RRNMF Neuromuscular Journal, 5(2). https://doi.org/10.17161/rrnmf.v5i2.21240

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CLINICAL AND SEROLOGIC CHARACTERISTICS OF SERONEGATIVE MYASTHENIA GRAVIS: AN ITALIAN MULTICENTER STUDY

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INTRODUCTION: Myasthenia gravis is an antibody-mediated autoimmune disorder affecting neuromuscular transmission. About 10-15% of patients are seronegative when tested by standard assays, of whom up to 30% harbour low-binding surface conformational autoantibodies detected by live cell-based assays (L-CBA).

OBJECTIVE: The objective of this study is to assess serologic and clinical characteristics of seronegative MG patients (SNMG) in a multicenter Italian cohort.

METHODS: MG patients who tested negative to radioimmunoassay or enzyme-linked immunosorbent assay for autoantibodies to acetylcholine receptor (AChR) or muscle-specific kinase protein (MuSK) were included; neurophysiologic findings of impaired neuromuscular transmission or a positive response to acetylcholinesterase inhibitors were required to support clinical diagnosis. Sera were tested by L-CBA for autoantibodies to clustered adult-(A)-AChR, fetal-(F)-AChR, MuSK and lipoprotein-receptor-related protein 4 (LRP4).

RESULTS: A total of 238 patients were recruited from nine Italian referral Centers: most were females (n=142) and had an early-onset phenotype (n=150). L-CBA was positive in 49/238 patients: 38/238 AChR and 11/238 MuSK. There were no LRP4 positive sera. We found no differences between SNMG patients and patients seropositive after L-CBA when considering disease severity (maximum MG Foundation of America class ≤2; p=0.72, Fisher's exact test) or outcome (post-intervention status; p=0.63, Fisher's exact test). Diagnosis of SNMG was

heterogeneous among different Centers, with several not requiring suggestive neurophysiology for diagnosis (n=66 negative test/not performed; n=6 data not available).

SUMMARY/CONCLUSION: Our study confirms that L-CBA offers a diagnostic gain compared to standard assays and supports its use as second-line screening of SNMG patients. Nonetheless, we raise the question of the clinical utility of LRP4 testing. The high proportion of triple-SNMG patients to L-CBA and the lack of an alternative biomarker underlines the importance of well-defined clinical/electromyographic diagnostic criteria. Further research is warranted to better define the clinical characteristics of SNMG and help designing specific diagnostic and management guidelines.

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ZILUCOPLAN VERSUS ECULIZUMAB AND RAVULIZUMAB FOR TREATING GENERALISED MYASTHENIA GRAVIS: MATCHING-ADJUSTED INDIRECT COMPARISONS

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INTRODUCTION: Three C5 inhibitors are approved for the treatment of generalised myasthenia gravis. Zilucoplan was assessed in the RAISE trial, eculizumab in the REGAIN trial and ravulizumab in the CHAMPION trial. Zilucoplan has not been directly compared with eculizumab nor ravulizumab. This is an indirect comparison of efficacy.

METHODS: Two unanchored matching-adjusted indirect comparisons (MAICs) were conducted using logistic propensity score weighting to align RAISE trial data with REGAIN and CHAMPION trials' baseline characteristics. This alignment allowed estimation of zilucoplan outcomes as if patients were enrolled in the comparator studies. For REGAIN, only refractory patients were considered. Expert clinicians identified key baseline factors, including MG-ADL, QMG, MGC scores and corticosteroid usage. Differences were assessed using standardized mean differences and p-values. The outcomes of interest were MG-ADL and QMG, responder proportions and change from baseline at 24 weeks in RAISE-XT, compared with comparator studies' primary endpoints of 26 weeks.

RESULTS: The estimated sample size post-matching with REGAIN and CHAMPION trials were 28 and 55 respectively. Zilucoplan demonstrated significantly higher improvement than eculizumab in MG-ADL (mean difference [95% confidence interval]: −1.99 [−3.3, −0.69]) and QMG (−3.23 [−4.63, −1.82]). The odds of achieving at least a 3-point improvement in MG-ADL (odds ratio [95% confidence interval]: 6.32 [1.70, 23.52]), a 4-point improvement in MG-ADL (3.20 [1.06, 9.66]) or a 5-point improvement in QMG (3.00 [1.03, 8.69]) were significantly better for zilucoplan. Compared with ravulizumab, zilucoplan demonstrated significantly higher improvement in MG-ADL (−2.70 [−3.74, −1.67]) and QMG (−5.72 [−7.02, −4.43]). Zilucoplan also had significantly better odds of MG-ADL 2-point improvement (8.24 [2.70, 25.15]) and 3-point improvement (5.65 [1.98, 16.10]) and of QMG 3-point improvement (21.10 [5.97, 74.50]) compared with ravulizumab.

SUMMARY/CONCLUSION: These MAICs show zilucoplan was associated with significant and clinically meaningful benefits compared with eculizumab and ravulizumab at 24/26 weeks of treatment.

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REGULATORY FEATURES OF CD8$^+$ T CELLS IN MYASTHENIA GRAVIS

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INTRODUCTION: Inhibitory killer-cell immunoglobulin-like receptors (KIR), as well as programmed cell death protein-1 (PD-1) expressing CD8$^+$T cells play regulatory roles through inhibition of T cells. This study examines CD8$^+$T cells in MG to evaluate their potential roles in controlling disease development.

OBJECTIVE: To investigate the potential regulatory role of CD8+T cells in (MG) by examining PD-1 and KIR molecules, and to compare these findings with those from a healthy control (HCs).

METHODS: AChR (+) MG patients (n= 29) and age- and sex-matched healthy controls (HCs, n= 24) were enrolled. Peripheral blood mononuclear cells (PBMCs) were stained with anti-CD3, CD8, PD-1, KIR (KIR2DL1, KIR2DL5, KIR2DL2/L3, KIR3DL2, KIR3DL1), CD28, TIGIT, CD45RA, and CCR7 antibodies and analyzed.

RESULTS: Higher proportion of CD8$^+$T cells were carrying KIR molecules in MG patients (10.3%) compared to HCs (4.7%, p= 0.01). Among the five KIR subtypes, KIR2DL2/L3 and KIR3DL1 were the most frequent variants in both groups. As shown for CD8$^+$ regulatory T cell phenotype before, KIR$^+$TIGIT$^+$ (9.1 vs. 4.4%, p= 0.01) and KIR$^+$CD28$^-$ (10.8 vs. 5.0%, p= 0.01) cells were significantly increased in MG patients compared to HCs. CD8$^+$ T cell subset expressing PD-1 did not reveal any difference between MG patients and HCs (19.3% vs. 24.2%). Among the CD8$^+$T cells, the central memory (CM) (CCR7$^+$CD45RA$^-$) population of was significantly higher in MG patients than in HCs (8.1% vs. 3.1%, p= 0.0009).

SUMMARY/CONCLUSION: The increase of recently identified regulatory KIR$^+$ CD8$^+$T cells in MG suggest a functional effect of these cells in this disease, as shown in some other autoimmune diseases. Moreover, these increased cells have also shared the KIR$^+$TIGIT$^+$ and KIR$^+$CD28$^-$ phenotype in CD8$^+$T cells in this autoimmune disease, supporting their possible inhibitory features.

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WE VALUE EVERYONE'S PLACE AT THE TABLE

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INTRODUCTION: VALUE-MG is a multifaceted health-economic study examining the cost-effectiveness of intravenous immunoglobulin (IVIg) therapy in Australian MG patients. The government-funded study is designed as a unique collaboration between clinicians, patients, researchers, stakeholders, and consumer groups.

OBJECTIVE: VALUE-MG aims to assess and justify the clinical boundaries for cost-effective and equitable use of IVIg therapy, versus comparator treatments, to improve symptom management in MG patients in Australia.

METHODS: Health economic models will be applied to a comprehensive dataset that will be generated by linking de-identified data from different sources. MGBase registry will provide clinical effectiveness data from 5 hospital sites. Quality-of-life (QoL) data will be collected prospectively from 300 participants completing quarterly electronic patient-reported outcome measures (ePROMs). Healthcare use and costs will be tracked via hospital and government administrative data. Furthermore, a partnership was established with MSBase Foundation and Myasthenia Alliance Australia (MAA) to promote the study, recruit participants for Discrete Choice Experiments (DCEs) to evaluate their treatment preferences, and disseminate key findings.

RESULTS: Applying quantitative analysis on combined data from a relatively large MG patient sample will enable the development of decision-analytic economic models to determine the cost-effectiveness of IVIg therapy strategies to improve symptom management in Australian MG patients.

SUMMARY/CONCLUSION: Given the increasing usage and expenditure on Ig products, VALUE-MG will be highly valuable in guiding practice towards more cost-effective IVIg use for MG in clinical settings. The study will provide people with MG with data on the optimal dose, frequency and duration of IVIg therapy. Clinicians will also be able to apply the study's outcomes to select the most appropriate MG treatments, thus improving their patients' overall well-being. Moreover, policymakers will rely on the study's findings to make evidence-based decisions for allocating healthcare resources to maximise the benefits for patients and the healthcare system as a whole.

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FATIGABILITY IN AUTOIMMUNE MYASTHENIA GRAVIS: FACT OR FICTION? A SCOPING REVIEW OF EXISTING LITERATURE

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INTRODUCTION: Fatigability, defined as a reduction in a muscle's ability to generate or maintain force during prolonged or repetitive tasks, is commonly considered as the hallmark symptom of myasthenia gravis (MG). It can affect any muscle group impacted by the disease, including ocular, orofacial, respiratory, trunk and limb muscles.

Despite a recent review addressing various aspects of perceived fatigue in MG, the precise cause of fatigability in MG is unclear. The ability to objectively assess or quantify pathological fatigability could refine therapeutic approaches and enhance understanding of the underlying mechanisms and consequences of this chronic condition. While several studies have explored this topic, it remains uncertain whether individuals with MG exhibit objectively measured deficits in resistance to fatigability, likely due to the heterogeneity of experimental paradigms employed. Currently, there is no consensus on a standardised or specific protocol to identify pathological fatigability in MG.

OBJECTIVES: Thus, the aim of this scoping review is to identify and synthesise existing literature evaluating fatigability in MG, in order to answer the following research questions: 1) Which experimental paradigms have been used to assess fatigability in MG? 2) Does current evidence support increased fatigability in MG? 3) What gaps or limitations exist in terms of experimental paradigms (e.g fatiguing tasks, measurement methods), study populations (e.g MG phenotype, disease duration, time of onset), or both? Identifying these gaps will help inform future research and support the development of standardised assessment protocols.

METHODS: A total of 5,165 records were identified through searches in 6 databases conducted in October 2023. After removing duplicates, 3,321 records were screened independently by two researchers. Fourteen studies met the inclusion criteria for this review.

RESULTS: Fatigability of limb muscles was assessed in seven studies, extraocular muscles in three, respiratory muscles in two, orofacial/bulbar muscles in one and global fatigability using

functional tasks in one study. The included studies demonstrated considerable heterogeneity in the muscle groups assessed, evaluation protocol employed, and characteristics of the study population, highlighting the current lack of standardised methodologies for evaluating fatigability in MG.

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"WHY AM I SHORT OF BREATH?" A PROSPECTIVE STUDY TO EVALUATE DYSPNEA IN ADULTS WITH AUTOIMMUNE MYASTHENIA GRAVIS: THE MYARESP STUDY PROTOCOL

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INTRODUCTION: Individuals with MG often experience shortness of breath that may be activity-related, occur at rest, or even arise during sleep. They commonly report sensations of air hunger, chest tightness or pressure on their chest, even during periods of disease stability. These symptoms can limit activities of daily life, social participation, exercise tolerance while also creating anxiety and negatively impacting quality of life and overall health. Possible causes include respiratory muscle dysfunction due to MG itself, secondary deconditioning, adverse effects of corticosteroids (such as excessive weight gain), anxiety, hyperventilation syndrome, sleep-disordered breathing (which may or may not be MG-related), asthma, residual effects of mechanical ventilation or a combination of these factors. Moreover, dyspnea can serve as a warning sign of impending acute respiratory muscle failure and MG crisis. Although dyspnea is a frequently reported symptom in MG – often highly debilitating and potentially life threatening - it has rarely been explored in the literature. Dyspnea is a complex, multidimensional, and multifactorial symptom involving sensory perception, cognition and emotion. Identifying the underlying cause(s) of dyspnea in MG may help guide therapeutic strategies, reduce discomfort, improve QoL and prevent respiratory deterioration and MG crises.

OBJECTIVE: The aims of the MYaRESP study are to describe the characteristics of dyspnea in MG and to understand contributing factors to dyspnea and factors associated with it, including the relationship between patient-reported dyspnea, disease severity and functional limitations. Results from this study will help to determine which tests are the most useful to identifying the causes and contributing factors and prevent or minimize MG crises by detecting respiratory impairment early and implementing an appropriate management plan. Such actions and plans will free-up resources, minimize overall health costs and improve overall quality of life, function and participation.

METHODS: Study design: Prospective, observational, cross-sectional study. Evaluations include PROs, objective respiratory function tests, polysomnography.

RESULTS: Recruitment is planned for mid-2025.

DISCLOSURES: This study is supported by a grant from ARGENX.

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REAL-WORLD TREATMENT PATTERNS AMONG PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS

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INTRODUCTION: Generalized myasthenia gravis (gMG) is a rare chronic autoimmune condition. Conventional treatments include acetylcholinesterase inhibitors (AChEI), corticosteroids, and non-steroidal immunosuppressants. Newly approved targeted therapies include neonatal Fc receptor (FcRn) and complement-5 (C5) inhibitors. Knowledge of real-world treatment patterns with currently available therapies and MG-related clinical events is limited.

OBJECTIVE: To evaluate real-world treatment patterns and MG-related clinical events among patients with gMG in the US.

METHODS: Adults with gMG were identified from the Komodo Research Database (01/2017-09/2023). Index date was the first MG diagnosis by a neurologist. Baseline (12-months pre-index) demographic characteristics, follow-up (≥12 months post-index) treatment patterns, including first 5 observed treatment episodes, MG exacerbations and crises were described.

RESULTS: 6,195 patients were included (mean age: 61.1 years; female: 49.1%; mean follow-up: 32.7 months). Among those receiving treatments, from the first episode (n=5,652) to the fifth episode (n=2,107): AChEI use declined from 81.1% to 58.5%; corticosteroid use fluctuated between 48.2-63.2%, and use of the following treatments increased: any non-steroidal immunosuppressants (11.8% to 41.8%), any immunoglobulin (6.3% to 15.6%), FcRn inhibitors (0.1% to 2.7%), and C5 inhibitors (0.2% to 2.9%). Mean time from index date to FcRn initiation was 20.7 months and to C5 inhibitors initiation 15.8 months. Post-index, 48.8% and 3.1% of patients had MG exacerbation or crisis, respectively. Exacerbations and crises were most common 1-year post-index (41.5%), but declined over time (20.3%, 18.0%, and 14.4% in the second, third, and fourth year, respectively).

SUMMARY/CONCLUSION: Conventional treatments were an initial treatment strategy for most patients in this cohort, while immunoglobulin and targeted treatments were generally used later. This, combined with the high rates of exacerbation and crisis during the first year,

highlights the unmet need for treatment strategies that provide stable and sustained disease control earlier in the disease course when managing patients with gMG.

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THE SKELETAL MUSCLE SPECIFIC CHLORIDE-1 ION CHANNEL (CLC-1) REGULATES THE MUSCLE'S ABILITY TO ACTIVATE AND THEREFORE REPRESENTS A VIABLE COMPLEMENTARY THERAPEUTIC TARGET TO IMMUNOSUPPRESSANTS AND IMMUNOMODULATORY AGENTS

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ClC-1 is a chloride ion channel specifically expressed in skeletal muscle cell membrane throughout the muscle fiber. The channel helps to stabilize the resting membrane potential during activity of skeletal muscle and regulates muscle fiber excitability. The ClC-1 channel is involved in regulating muscle fiber excitability during intense exercise, where a large amount of action potentials is required to activate sufficient calcium release from the sarcoplasmic reticulum. Such electrical activity is accompanied by movement of ions in and out of the muscle fiber, resulting in changes that affect resting membrane potential, energy status and volume. ClC-1 plays an important role in regulating the excitability of the muscle fiber membrane during such activity, ensuring that action potentials may be generated without risking the development of spontaneous action potentials due to excessive potassium efflux to the t-tubular system. During initiation of action potentials at the postsynaptic side of the neuromuscular junction, ClC-1 acts as a counter current for the activating current, and by extension it can be theorized that reducing ClC-1 activity could increase the likelihood of generating an action potential at the neuromuscular junction, yet most textbook illustrations of the NMJ do not capture the impact of this channel. Recently, it was shown that inhibition of the ClC-1 channel improves neuromuscular transmission in isolated rat muscle exposed to a neuromuscular blocking agent, and in rat models and patients with MG. Interestingly, because the ClC-1 channel is expressed along the entire length of the muscle fiber, the postsynaptic changes observed in MG does not impact ClC-1 function as much as other proteins located at the synapse. Here we give an overview of the role of the ClC-1 chloride channel in muscle fiber excitability and function in relation to MG and other diseases where the neuromuscular transmission is affected.

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FREQUENCY OF LRP4 ANTIBODIES IN A CONSECUTIVE COHORT OF SUSPECTED MYASTHENIA GRAVIS PATIENTS

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INTRODUCTION: Autoantibodies to the lipoprotein receptor-related protein-4 (anti-LRP4) have been reported in a minority of patients with Myasthenia Gravis (MG), with potential pathogenic role and uncertain clinical relevance. However, LRP4 antibodies frequency varies substantially according to the type of assay used for their detection.

OBJECTIVE: Our aim is to investigate the prevalence of anti-LRP4 in a consecutive cohort of patients with suspected MG.

METHODS: We established a live-CBA expressing full lenght LRP4, and used it to test a consecutive cohort of 333 patients with suspected MG. All samples were tested in parallel with validated ACHR and MUSK live-CBA. Seronegative MG (SNMG) diagnosis was assessed through clinical history, signs plus one among electromyography and cholinesterase response.

RESULTS: The LRP4 CBA was validated by demonstrating its surface expression by staining of the live cells with a commercial antibody targeting extracellular epitopes of LRP4. Of the samples tested, 32% (n=108) were positive for either anti-AChR or anti-MuSK, while 0 were positive for LRP4. Among 225 triple-negative patients, a diagnosis of SNMG was established in 11% (n=26). The median age of SNMG patients at sampling was 63 years (range: 32-80), and 46% (n=12) were female. Thirty percent (n=8) of SNMG patients were collected at disease onset, and 58%(n=15) had GMG.

SUMMARY/CONCLUSION: LRP4 antibodies seem to be exceedingly rare, thus questioning their clinical relevance in routine clinical practice. As technical variations of the assays used for their detection have been reported, standardization studies are warranted to understand the actual clinical impact of requesting LRP4 testing.

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OPTIMIZATION OF A SCREENING ASSAY FOR ANTIBODY-MEDIATED COMPLEMENT ACTIVATION (ACA) IN AUTOIMMUNE NEUROLOGICAL DISORDERS

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INTRODUCTION: Myasthenia gravis (MG) and neuromyelitis optica spectrum disorders (NMOSD) are neurological conditions associated respectively with Acetylcholine receptor (ACHR) and Aquaporin4 (AQP4)-antibodies. These pertain to the IgG1/3 subclass and can induce antibody-mediated-complement-activation. Other MG forms associate with MUSK-antibodies, that are IgG4 and unable to induce ACA.

OBJECTIVE: to develop a screening assay to assess ACA in the serum of MG/NMOSD patients.

METHODS: HEK293T cells transfected with either AQP4, ACHR, or MUSK were incubated for 2 hours with complement inactivated polyclonal serum from MG/NMOSD patients with or without healthy donors as complement source, or with healthy donor serum alone. Three independent raters scored the ACA by evaluating the reduction in secondary antibody labeling compared to the control group using a semiquantitative scale (0= no reduction, 4= strong reduction).

RESULTS: ACA was identified by all raters in NMOSD (13/22 patients, 59%) and ACHR-MG (6/30 patients, 20%). Interrater agreement was higher for AQP4 (Fleiss' kappa=0.804) compared to ACHR (Fleiss' kappa=0.585). Agreement became perfect (Fleiss' kappa=1) when considering scores >1 in NMOSD and >1.5 in ACHR-MG. Only 1/15 MUSK-MG showed low levels (score=1) of ACA. Results from qualitative assay were further validated with a luminescent assay of cell-viability, which showed an average 40% cell-killing in two AQP4 samples with high ACA (score=4).

SUMMARY/CONCLUSION: our assay allowed to detect ACA in IgG1/3, but not in IgG4 samples. The high interrater agreement for high scores suggests that this might be a reliable tool to stratify patients who could benefit from complement inhibitor drugs.

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EPIDEMIOLOGY OF ACHR-IGG AND MUSK-IGG SEROPOSITIVE MYASTHENIA GRAVIS IN OXFORDSHIRE, UK (2011-2023)

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INTRODUCTION: Epidemiological data on myasthenia gravis in the United Kingdom are limited, and reported prevalence and incidence rates vary due to the disease's rarity, diagnostic delays, and variation in healthcare data sources analysed.

OBJECTIVE: To describe the prevalence and incidence of acetylcholine receptor (AChR)-IgG and muscle-specific kinase (MuSK)-IgG seropositive MG in Oxfordshire, UK, between 2011 and 2023.

METHODS: Adult patients were identified from the UK Myasthenia Database (REC: 22/SS/0093) and 2023/2024 Oxford University Hospitals NHS Foundation Trust Myasthenia Service clinic lists. Prevalence was calculated for two UK census dates (27/03/2011 population: 653,798; 21/03/2021 population: 725,300) and annual incidence rates from Office of National Statistics mid-year population estimates for 2011-2023. Residency in Oxfordshire between 2011 and 2023 was verified using the NHS National Care Records Service.

RESULTS: 117 seropositive MG patients were included (115 AChR-MG, 2 MuSK-MG). Prevalence of AChR-MG on 27/03/2011 was 2.60 per 100,000 (95% CI: 1.36-3.84, n=17), with 70.6% female (n=12, F:M 2.4) and 94.1% white ethnicity (n=16); no MuSK-MG patients were prevalent. On 21/03/2021, the prevalence of AChR-MG was 10.75 per 100,000 (95% CI: 8.37-13.14), with 59.0% male (n=46, F:M 0.7), and 94.9% white ethnicity (n=74). The prevalence of MuSK-MG was 0.14 per 100,000 (95% CI: 0.00 - 0.41), with one prevalent case (female, white). The average yearly incidence of MG diagnosis was 9.04 per 1,000,000 person-years (95% CI 7.08 – 10.99), showing a general increasing trend. The age distribution of incident cases was: 16.3% (n=15) aged 18-49, 43.48% (n=40) aged 50-69, 40.22% (n=37) aged over 70.

SUMMARY/CONCLUSION: Observed prevalence is lower than reports from UK primary care databases; further review of 2011-2022 clinic lists is warranted to confirm complete case ascertainment. Rising MG incidence is consistent with global trends, and future studies should investigate whether this increase reflects biological factors beyond advances in diagnostic awareness, accuracy, and monitoring.

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EFFICACY OF RAVULIZUMAB IN LONG-STANDING MYASTHENIA GRAVIS

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INTRODUCTION: A 62 years-old man was diagnosed with myasthenia gravis (MG) in 2005. He began with bulbar symptoms and the diagnosis was confirmed by positive AchR Ab and single fiber electromyography. Chest CT scan showed the presence of thymoma, which was operated with the vatet technique in 2006. He started therapy with pyridostigmine and prednisone and over the years, he made therapeutic attempts with azatioprine and ciclosporin, suspended due to side effects.

OBSERVATION: Stable patient until the end of 2019, then had two relapses in close proximity with hospitalization and cycle of IvIg. After the second relapse, the dosage of steroids was increased to a therapeutic regimen (1 mg/kg/day). In January 2020 he had a relapse, worse than the previous ones with bulbar and limb involvement. The MGFA class was IVb, the ADL score 16 and the QMG 23. After a cycle of plasmapheresis, he started Ravulizumab and immediately after the first infusion, the patient showed an improvement: the ADL score dropped to 6 and the QMG to 8 after four years of follow up the patient showed a further progressive improvement, until reaching the minimal symptomatic expression (MSE) after 2 years and he suspended all other concomitant therapies for myasthenia. The patient is currently in pharmacological remission (ADL and QMG 0) and he maintains an optimal quality of life.

CONCLUSION: This case demonstrates the efficacy of Ravulizumab even in a patient with long duration of disease (15 years), as well as rapidity of action and efficacy over time, in a four-year follow-up. In this case, Ravulizumab changed the history of the patient's disease, who no longer needed rescue therapy and was able to suspend concomitant medications.

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MIRNA-MRNA-LNCRNA NETWORKS MODULATING T AND B CELL PROLIFERATION CONTRIBUTE TO UNRESPONSIVENESS TO IMMUNOSUPPRESSIVE DRUGS IN MYASTHENIA GRAVIS

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INTRODUCTION: Non-coding RNAs (ncRNAs), including long ncRNAs (lncRNAs) and microRNAs (miRNAs), play a key role in modulating immune response, thus representing candidate biomarkers for personalized medicine in autoimmune diseases. Personalization of myasthenia gravis (MG) treatment is a crucial medical need, due to inter-individual variation in clinical response to the available drugs. A proportion (~10-15%) of MG patients is refractory to conventional immunosuppressive (IS) therapies, or become refractory over time, thus highlighting the usefulness of biomarkers to predict or monitor IS drug efficacy in individual patients.

OBJECTIVE: This study aimed at identifying miRNAs and lncRNAs as biomarkers of unresponsiveness to IS therapies in MG patients.

METHODS: We analysed whole miRNome in peripheral blood mononuclear cells (PBMCs) of MG patients stratified as responder (R, n=14) and non-responder (NR, n=16) to IS drugs by microarrays. Selected miRNAs, and their interacting mRNAs and lncRNAs, were assessed in PBMCs of an expanded cohort of patients (23 R, 21 NR) by qPCR.

RESULTS: Our results revealed specific miRNAs differentially expressed in PBMCs of NR compared to R patients. MiR-150-5p, an MG-associated immune-miR known to modulate T and B cell proliferation, and miR-423-5p, a cell growth regulator, were significantly decreased in PBMCs of NR patients, and their levels were able to discriminate between the two patients' groups. Contrariwise, MYB and EEF2, target genes of miR-150-5p and miR-423-5p respectively, were overexpressed in NR patients, who also showed overexpression of MALAT1, a lncRNA promoting cell proliferation and interacting with miR-423-5p.

SUMMARY/CONCLUSION: We identified a cell proliferation-related lncRNA-miRNA-mRNA network contributing to unresponsiveness to IS drugs in MG, which could represent a molecular tool for monitoring IS drug efficacy and early directing NR patients towards more effective targeted therapies.

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EFFECTS OF THYMECTOMY IN LATE-ONSET MYASTHENIA GRAVIS: A MULTI-CENTER LONGITUDINAL RETROSPECTIVE STUDY

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OBJECTIVE: Limited evidence has led to ongoing debate about the benefits of thymectomy for late-onset myasthenia gravis (LOMG). This study aims to compare the outcomes of LOMG patients who underwent thymectomy versus those who received medical treatment alone, and evaluate the incidence of surgical adverse events.

METHODS**:** Non-thymomatous acetylcholine-receptor antibody positive LOMG patients were selected from a multi-center longitudinal clinical database. Rates of and time to response (remission and minimal manifestations status) were compared between two groups by propensity score matching (PSM), Kaplan-Meier analysis and Cox regression models. Additionally, the incidence of adverse events about thymectomy was compared between LOMG and younger MG aged 40-50 years.

RESULTS**:** A total of 36 and 175 LOMG patients were enrolled in the thymectomy and medical treatment groups, respectively. Thymectomy group had a significantly younger onset age (56.58±6.27 vs. 62.70±7.88, $p<0.001$), and demonstrated a trend toward a better response (66.7% vs. 49.1%, $p=0.055$) compared to medical treatment. After PSM adjustment, thymectomy showed higher response rates (66.7% vs. 44.4%, $p=0.028$), greater cumulative probability ($p=0.044$), and a 1.714-fold (95%CI=1.008-2.914, $p=0.047$) higher chance of better outcomes compared to medical treatment. The incidences of adverse events were comparable between LOMG and younger MG patients (34.4% vs. 31.0%, $p=0.781$).

INTERPRETATION: Thymectomy may be an effective therapeutic option for LOMG. Our findings highlight the need for further development of a randomized trial targeting LOMG patients.

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COMBINED USE OF MAGNETIZATION TRANSFER RATIO AND T2-MAPPING TO EVALUATE EXTRAOCULAR MUSCLE PATHOPHYSIOLOGY IN MYASTHENIA GRAVIS WITH OPHTHALMOPARESIS

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BACKGROUND: Myasthenia gravis (MG) is an autoimmune neuromuscular disorder that most frequently affects the extraocular muscles (EOMs), which causes symptoms such as ptosis and restricted eye movement. The EOMs in MG patients are representative of autoimmune inflammatory changes in muscle tissue. Currently, there is no reliable, and sensitive imaging technique for monitoring EOM changes to assist in the evaluation of underlying pathological changes.

METHODS: This study included MG patients treated between March and November 2022 at the First Affiliated Hospital of Sun Yat-sen University. Healthy controls (matched by age and sex) were included. Participants underwent 3.0 T MRI with magnetization transfer imaging (MTI) and T2-mapping to measure the magnetization transfer ratio (MTR) and T2-mapping values in the superior, inferior, medial, and lateral rectus muscles. Comparisons were made between MG patients and healthy controls, and between MG subgroups with and without ophthalmoparesis.

RESULTS: The MTR and T2-mapping values successfully reflected EOM fibrosis and inflammatory edema in MG patients. MG patients showed significantly higher MTR and T2-mapping values in the EOMs compared with healthy controls. MG patients with ophthalmoparesis exhibited a lower MTR but higher T2-mapping value compared with those without ophthalmoparesis. Combined MTR and T2-mapping values effectively distinguished between MG patients and healthy controls, and between different severities of EOM involvement, with a superior diagnostic accuracy compared with each parameter alone.

CONCLUSION: The combination of MTI and T2-mapping MRI techniques can provide key

insight into the pathological changes in EOMs in MG patients. This approach enhances early diagnosis and treatment planning, and therefore may improve clinical outcomes.

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IDENTIFYING RISK FACTORS FOR EXACERBATION AND SYMPTOM WORSENING—A RETROSPECTIVE COHORT STUDY OF PATIENTS WITH MYASTHENIA GRAVIS IN THE UNITED STATES

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INTRODUCTION: The Myasthenia Gravis (MG) Foundation of America Global MG Patient Registry (MGFAPR) captures longitudinal patient-reported data that may facilitate understanding risk factors associated with MG.

OBJECTIVE: To identify baseline (enrollment) risk-factors for ≥1 self-reported exacerbation(s) in the past 6-months at first follow-up, and for an MG activities-of-daily-living (MG-ADL) score ≥2 point increase between baseline and first follow-up.

METHODS: This retrospective cohort study analyzed 1319 MGFAPR surveys completed between July 2013–June 2023 by US-based adults with self-reported MG and first follow-up data available within 12 months of enrollment. Exacerbations in the past 6-months and changes in MG-ADL scores at first follow-up were evaluated. Univariate analyses and multivariate logistic regressions were conducted.

RESULTS: Of 1319 patients assessed, 1187 (90%) reported the presence/absence of exacerbation(s); 460 (39%) reported ≥1 exacerbation. At first follow-up, identified factors positively associated ($p<0.05$) with a report of experiencing ≥1 exacerbation(s) in the previous 6-months were comorbid anxiety/depression (2x more likely), living alone (74%+), corticosteroids (36%+), and MG-ADL score point-increase (19%+ per-point) at enrollment. Factors inversely associated ($p<0.05$) with ≥1 exacerbation(s) included ocular versus generalized first MG symptoms (51%-), nonsteroidal immunosuppressants at enrollment (25%-), and each additional year post-diagnosis (2%-). Overall, 1232 (93%) patients reported MG-ADL scores at enrollment and first follow-up; 210 (17%) had ≥2 point increase in MG-ADL score. Factors positively associated ($p<0.05$) with MG-ADL score increase ≥2 included first MG-symptoms as generalized vs ocular (~138%+) and comorbid anxiety/depression (73%+). Factors inversely associated ($p<0.05$) with MG-ADL ≥2 point increase were plasma exchange (excluding rescue therapy; 83%-), physical activity at enrollment (37%-), and increased age at first follow-up (2%-/year).

SUMMARY/CONCLUSION: Findings from this MGFAPR-based analysis suggest many US individuals with MG reported uncontrolled disease despite available treatment options. Important risk factors identified for exacerbation or symptom worsening included living alone, generalized MG symptomology, and comorbid anxiety/depression.

DISCLOSURES: ZC and NC are employees and stockholders of Janssen Scientific Affairs, LLC, a Johnson & Johnson company, Titusville, NJ, USA.MP, ACM, and AZG are employed by Alira Health, Boston, MA, USA, which derives profits from interactions with pharmaceutical sponsors. PN is affiliated with Beth Israel Deaconess Medical Center/ Harvard Medical school and reports Research support: AHRQ, PCORI, Alexion/AstraZeneca Rare Disease, Momenta/Janssen, and Ra/UCB; Advisory boards/ Consultations: Alexion/Astra Zeneca Rare disease, Amgen, argenx, CVS, Dianthus, GSK, ImmuneAbs, Janssen, Merck, Novartis, Serono, UCB; Data Monitoring Committee Chair: Sanofi, argenx; Royalties: Springer Nature. RG has served on advisory boards for argenx, UCB, Janssen, Roche, and speakers' bureaus for argenx, Alexion, and UCB. MK is an employee of Cytel Inc., Cambridge, MA, USA, which derives profits from interactions with pharmaceutical sponsors. RN is affiliated with Yale University School of Medicine and reports research support from the National Institutes of Health, Genentech, Inc., Alexion Pharmaceuticals, Inc., argenx, Annexon Biosciences, Inc., Ra Pharmaceuticals, Inc. (now UCB S.A.), the Myasthenia Gravis Foundation of America, Inc., Momenta Pharmaceuticals, Inc. (now Janssen), Immunovant, Inc., Grifols, S.A., and Viela Bio, Inc. (Horizon Therapeutics, now Amgen Inc.). RN served as a consultant and advisor for Alexion Pharmaceuticals, Inc., argenx, Cabaletta Bio, Inc., Cour Pharmaceuticals, Ra Pharmaceuticals, Inc. (now UCB S.A.), Immunovant, Inc., Momenta Pharmaceuticals, Inc. (now Janssen), and Viela Bio, Inc. (Horizon Therapeutics, now Amgen Inc.).

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MAPPING OUT THE PATIENT JOURNEY OF GENERALIZED MYASTHENIA GRAVIS: INSIGHTS AND CHALLENGES

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INTRODUCTION: Generalized myasthenia gravis (gMG)—a rare, chronic autoimmune neuromuscular disease—causes muscle-weakness, fatigue, and/or ocular symptoms. Patient perspectives can help better understand symptom variety and current treatment burden.

OBJECTIVE: Characterizing the lived patient experience with gMG.

METHODS: US adults with self-reported gMG/ocular MG diagnosis or their caregivers were recruited to participate in a 13-question online survey. Survey responses guided/facilitated four 2-hour virtual Patient-Engagement Research-Council (PERC) focus group discussions, and a two-stage patient journey map was generated.

RESULTS: Of 16 participants (n=4 caregivers; n=12 patients), the highest proportion per sociodemographic-category were white (62.5%), identified female (50%), aged 50–59 years (37.5%), with bachelor's degrees (37.5%). Based on the pre-session survey, frequently reported first symptoms were vision problems (63%), extreme fatigue (50%), eyelid-drooping (44%), and muscle-weakness (44%). Although most participants (62.5%) were diagnosed within one-year of seeking healthcare for gMG-related symptoms; 25% experienced 1–4-year diagnostic-delays and 69% experienced misdiagnosis. About half had tried 4–6 gMG treatments; 44% were dissatisfied with timing to find a treatment for symptom improvement. Treatment delays due to insurance issues were reported by 69% of participants; 81% felt gMG-symptoms were dismissed as unrelated to gMG. Survey results were validated by the PERC discussions, as most participants reported emotionally-challenging gMG journeys compounded by persistent caregiver fear/anxiety. One participant cited frustration over the "trial-and-error basis" of their treatment choices. Patients suggested mapping out the patient journey of their experiences non-linearly to reflect variations in treatment-management and disease instability, and how exacerbation/myasthenic crisis may occur at any time.

SUMMARY/CONCLUSIONS: The unpredictable, emotionally-challenging patient journey of gMG highlights persisting uncertainty around treatment paradigms and the need for robust, targeted, and more consistently efficacious therapeutic options. Leveraging these insights may help improve gMG-management and patient/caregiver outcomes, as US-patients with gMG continue to experience substantial disease instability despite increased treatment options.

DISCLOSURES: ZC, LJ, NC, LS, SR, and MAT are employees and stockholders of Janssen Scientific Affairs, LLC, a Johnson & Johnson company, Horsham, PA, USA. KGG has received

consulting honoraria from Alexion, Argenx, UCB and Amgen. She has received speaking honoraria from Alexion and argenx. KG is employed by Henry Ford Hospital, Detroit, MI, USA, and reports advisory board meetings for UCB, Kyverna, Amgen, and Johnson & Johnson. BM is employed by SSM Health, MO, USA, and reports advisory board meetings for Sanofi, argenx, UCB, Johnson & Johnson, Amgen, Ultragenyx; speaker for Sanofi, UCB, Johnson & Johnson.

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PARTNERING WITH PATIENTS AND CAREGIVERS TO GUIDE THE DEVELOPMENT OF IMPACTFUL STUDY ENGAGEMENT TOOLS IN A GENERALIZED MYASTHENIA GRAVIS REAL-WORLD STUDY

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INTRODUCTION: Recent years have seen significant advances in research in generalized myasthenia gravis (gMG). Clinical trials are conducted to advance new therapies while real-world studies focus on understanding unmet needs. In rare diseases like gMG, patient recruitment and retention (R&R) are key to successful study completion. Within MGNation, a prospective real-world study, a Patient Engagement Research Council (PERC) comprising gMG patients and caregivers was formed and focus groups were conducted to advise on the study R&R plans.

METHODS: The gMG PERC is a diverse group of patients and caregivers with respect to time since diagnosis, disease severity, serostatus, treatments, age, gender, and race/ethnicity. Nine gMG patients and 5 caregivers participated in 4 virtual, 2-hour semi-structured focus groups. Sessions focused on reviewing recruitment materials, accessibility, engagement, and retention strategies.

RESULTS: Insights gathered on recruitment materials provided actionable changes such as enlarging and standardizing text fonts to support patients with ocular MG symptoms while creating concise materials with easy-to-understand language for the end-user. Feedback on retention tactics was also assessed, such as interest in receiving a newsletter for study patients and desired frequency and channel of study reminders. Additional suggestions were also collected to better understand motivation and retention of patients in an ongoing 2-year study.

SUMMARY/CONCLUSION: Including patient and caregiver perspectives in the development and review of study recruitment material is key to creating thoughtfully designed and impactful engagement tools. This work highlights how patients and caregivers can contribute to scientific advancements and help better understand MG.

DISCLOSURES: Maria Ait-Tihyaty, Brindley Rospars, Brian Sawyer, Zia Choudhry, and Lisa Shea are employees or consultants for Janssen Pharmaceuticals and may own stock or stock options in Johnson & Johnson.

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source/documents/meetings/annual-meeting-program.pdf?sfvrsn=6f77f6b0_6

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SINGLE FIBER EMG IN THE DIAGNOSTIC WORKUP OF DIPLOPIA AND PTOSIS

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INTRODUCTION: Diplopia and ptosis are common neuro-ophthalmologic signs, yet identifying their specific aetiology can be challenging owing to the broad differential diagnosis. One of this can be myasthenia gravis (MG) but repetitive nerve stimulation (RNS) is often negative when only ocular symptoms are present. Moreover, the possibility of seronegative patients creates the need for an alternative reliable diagnostic tool for ocular MG patients.

OBJECTIVE: The objective of this prospective study is to evaluate the reliability of the stimulated single fiber electromyography (SFEMG) in supporting the diagnosis of MG presenting with diplopia and ptosis.

METHODS: We included 100 patients who presented with diplopia (n=42), ptosis (n=22), or both (n=36), and underwent a comprehensive serological, radiological and electrophysiological workup, including SFEMG. Specific cut-offs for stimulated concentric needle SFEMG (MCD≥28 us and individual jitter≥38 μs) were calculated based on healthy controls at our centre.

RESULTS: SFEMG yielded positive results in 34 of 100 (34%) patients of the cohort. Among the patients diagnosed with MG (n=41), SFEMG showed a sensitivity of 68.3% (95% CI: 0.52 – 0.82) and specificity of 89.8% (95% CI: 0.79 – 0.96) with a positive predictive value of 82.4% (95% CI: 0.68 – 0.91) and a negative predictive value of 80.3% (95% CI: 0.72 – 0.87). Notably, SFEMG was positive in 7 seronegative MG cases and in 14 cases with negative RNS. In the non-MG group (59/100 patients), SFEMG was negative in the majority (53 patients, 89.8%) of cases, further supporting its value in ruling out MG. A relevant proportion (32/59) of these cases remained undiagnosed.

SUMMARY/CONCLUSION: Our findings suggest that SFEMG is a valuable tool in the diagnostic workup of diplopia and ptosis and in the differential diagnosis of MG, especially in seronegative MG cases and in those with negative RNS results.

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RAPID EFFICACY OF ECULIZUMAB IN PATIENTS WITH REFRACTORY GENERALIZED MYASTHENIA GRAVIS: A SINGLE-CENTER STUDY

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INTRODUCTION: Eculizumab is a humanized monoclonal antibody that targets C5 complement protein, inhibiting terminal complement-mediated damage at the neuromuscular junction. Recently, it has been approved in Italy for the treatment of patients with refractory generalized myasthenia gravis (gMG) associated to anti-acetylcholine receptor antibodies (AChR+).

OBJECTIVE: The main objective of our study was to evaluate the efficacy onset time of Eculizumab in the cohort of patients with refractory AChR+ gMG followed at our department.

METHODS: All patients with refractory AChR+ gMG treated with eculizumab (900 mg/week for 4 weeks, 1200 mg the fifth week and then every 2 weeks) followed at our department were included. Outcome measures were MG-ADL scores, QMG evaluations, number of exacerbations and adverse events. Data were collected before starting Eculizumab (T0), after 5 weeks (T1), then every three months (T2).

RESULTS: Data were available for 6 adult patients (4F; 2M); median age at T0 was 72.5 years. Two patients had a history of thymoma surgically treated. All patients were treated with pyridostigmine and were under stable azathioprine and/or prednisone therapy. Median MG-ADL score reduced from 9 at baseline to 2 at T1 ($p = 0.014$) and 4.5 at T2 ($p=0.014$). Median QMG score dropped from 16.5 at baseline to 7.5 at T1 ($p = 0.014$) and 4.5 at T2 ($p=0.014$). Median MG-ADL and QMG-score did not significantly differ between T1 and T2 (respectively $p=0.18$ and $p=0.65$). No meningococcal infections neither adverse drug reactions were reported. No patients required rescue therapy. One death occurred during FU, unrelated to Eculizumab.

SUMMARY/CONCLUSION: This single-center study confirms the rapid and sustained efficacy of Eculizumab in a real-world setting in patients with refractory gMG. Findings are consistent with the efficacy and safety results from the REGAIN trial and allow to hypothesize future clinical trials designed to evaluate Eculizumab use in gMG exacerbations.

DISCLOSURES: VT has received speakers' honoraria, travel grants and/or compensation for consulting service from Alexion. AT has received honoraria for acting as a consultant on advisory boards for Bial, and abbVie; has received speakers' fees from Bial, UCB, Lusofarmaco, Chiesi Farmaceutici, abbVie, and Zambon; has served on the editorial board of Parkinsonism and Related Disorders; and is associate editor for the European Journal of Neurology. AB has received speakers' honoraria, travel grants and/or compensation for consulting service from Alexion, Amgen, Biogen, Merck, Novartis, Genzyme and Roche.

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IMMUNE CHECKPOINT INHIBITOR ASSOCIATED SERONEGATIVE POST SYNAPTIC NMJ DISORDER: A CASE REPORT AND LITERATURE REVIEW

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INTRODUCTION: Immune Checkpoint Inhibitors (ICI) have revolutionized care in certain malignancies, however more data is emerging regarding ICI related neurologic immune-related adverse events (irAEs), specifically postsynaptic neuromuscular junction (NMJ) disorders with or without associated myositis. Postsynaptic NMJ disorder Myasthenia Gravis (MG) is well described ICI related irAEs, however presynaptic NMJ disorders like Lambert Eaton Mysthenic Syndrome (LEMS) are not nor their coexistence.

OBJECTIVE: To improve the diagnostic odyssey of presynaptic NMJ disorder LEMS following use of ICI in absence of seromarkers and to review available literature.

METHODS: A 67-year-old male with malignant melanoma of unknown primary with a dermal deposit suggestive of a metastatic lesion as well as marginal zone B cell lymphoma received adjuvant systemic therapy with anti-PD1 antibody pembrolizumab for planned duration of one year at 200 mg IV every 3 weeks. However, after the first infusion, patient developed pneumonitis, severe fatigue, diplopia, proximal extremity muscle weakness and autonomic symptoms of dry eyes, visual disturbance and postural dizziness.

RESULTS: The AChR Ab and PQ type VGCC Ab remained negative. CK was normal. RNS failed to show an appropriate decremental response, although SFEMG was consistent with an increased jitter in EDC and Frontalis. The patient initially was treated with pyridostigmine, but response was poor. Immunotherapy with corticosteroids followed by IVIG did not improve symptoms significantly either. Further electrophysiological testing showed post exercise increase in CMAP amplitude and facilitation at high frequency RNS which led to the treatment with 3,4 diaminopyridine with a dramatically improved clinical response.

SUMMARY/CONCLUSION: Not only Post synaptic NMJ disorders can develop following ICI therapy, but predominant presynaptic pathology can dominate ICI irAEs in spite of seronegativity of PQ type VGCC. An awareness of such a complication can reduce the diagnostic delay and appropriate treatment of patients who develop ICI related irAEs.

DISCLOSURES: Dr. Desai has served on Advisory Board for Amgen, Argenx, Astra Zanaca, Avidity, Catalyst, Edgewise, Fulcrum, Kyverna, Sarepta, Takeda, UCB

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REFRACTORY MYASTHENIA GRAVIS CHARACTERISED BY WIDESPREAD INNATE AND ADAPTIVE IMMUNE SYSTEM CHANGES

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INTRODUCTION: Despite recent advances in therapeutics for Myasthenia Gravis (MG), mechanisms driving treatment resistance, and biomarkers to predict response to therapies are lacking.

OBJECTIVE: We aimed to examine the immune profile in patients with MG of differing treatment requirements, with prospective follow-up following B cell depletion.

METHODS: Flow cytometry was used to determine cell frequencies and expression of surface markers on peripheral blood mononuclear cells (PBMCs) from 58 individuals with acetylcholine-receptor antibody positive MG of differing treatment requirements and 20 controls. 8 of the 10 refractory patients received rituximab and were followed prospectively at 1, 7 and 13 months following B cell depletion.

RESULTS: In MG the B cell compartment contains a higher proportion of highly differentiated CD27+ memory B cells, particularly in refractory disease and in those with early-onset MG. B cells in MG also display a pro-inflammatory phenotype, producing more IL-6 and TNF-α upon stimulation compared to control.

Refractory patients demonstrate reduced regulatory T cell (Treg) frequencies, which correlate negatively with disease severity and quality of life scores. Dendritic cell frequencies are also reduced in refractory cases, whereas monocytes are expanded.

Circulating levels of complement proteins C3, C5 and clusterin are highest in refractory cases. Additionally, there is higher expression of complement receptors on lymphocytes in MG, which correlate with the expression of the immune checkpoints PD-1 and CTLA-4 on T cells.

Following rituximab, Treg frequencies increase, but persistent circulating plasmablasts are identified. Those who demonstrated poor response to rituximab had low baseline B cell frequency and evidence of persistent complement activation.

CONCLUSION: Refractory MG is characterised by widespread immune changes that favour autoreactivity. Further work is required to validate these findings as biomarkers to predict treatment response, and to explore whether targeting these changes, such as promoting Treg expansion, would help treat MG resistant to current therapies.

DISCLOSURES: JKLH has done paid advisory boards for argenx and consultancy for Adivo Associates related to myasthenia. MIL has received speaker honoraria or travel grants from UCB Pharma and Horizon Therapeutics, and consultancy fees from UCB Pharma. She serves on scientific or educational advisory boards for UCB Pharma, Argenx and Horizon Therapeutics. JSp has received speakers fees from Argenx, UCB and J&J, travel support from Argenx and UCB and has served on advisory boards for UCB, Argenx and J&J. Stuart Viegas has received speaker honoraria or travel grants from UCB Pharma.

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MOLECULAR AND METABOLIC ANALYSES OF ACHR^{+} MG SKELETAL MUSCLES

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INTRODUCTION: Myasthenia gravis (MG) is a rare chronic neuromuscular disease due to pathogenic autoantibodies directed against acetyl choline receptors, in 80% of patients. These antibodies are produced in the thymus and target the neuromuscular junction. Therefore, patients suffer of muscle weakness aggravated by exercise.

So far, we and others have demonstrated that in autoimmune MG patients, defective inflammatory processes indu [1] ced by thymic epithelial cells and T-cells are responsible the pathophysiologic events occurring in the thymus such as the production of autoantibodies.

However, few is understood for the skeletal muscle. It has been demonstrated that autoantibodies mediate disruption of the neuromuscular-junction leading to compromised neuromuscular transmission. In addition, we have also shown that MG skeletal muscles have disturbed tissue regeneration repair processes characterized by an altered differentiation of muscle stem cells, the satellite cells.

OBJECTIVE: To understand and identify the molecular events supporting the skeletal muscle regeneration defects observed in autoimmune MG patients.

METHODS: we performed a transcriptomic analysis of muscle biopsies that lead us to investigate, with in vitro methods, metabolic pathway of MG myoblasts.

RESULTS: Transcriptomic analysis with bulk RNA-seq allows us to identify dysregulated transduction pathway concomitantly to a chronic inflammatory environment in MG muscle. We have confirmed the differential gene expressions by using a second cohort of patients.

In order to confirm that dysregulated pathways identified by transcriptomic analysis reflect dysregulated functions, we performed metabolic functional assay *in vitro* on primary cultured MG myoblasts. compared to non-MG myoblasts, we observed a significant alteration of metabolic processes in MG muscle cells.

CONCLUSION*:* These data reveal for the first-time that MG muscles display concomitantly a chronic inflammatory environment and a dysregulated metabolic pathway that may contribute to the muscle regeneration impairment. This project may support a potential impact a pro-inflammatory environment on skeletal muscle homeostasis in autoimmune MG condition.

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REFINING THE METHODOLOGY TO STUDY ANTIBODY-INDUCED ACETYLCHOLINE RECEPTOR MODULATION IN MYASTHENIA GRAVIS

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INTRODUCTION: Myasthenia gravis (MG) is a chronic autoimmune disorder in which autoantibodies against the acetylcholine receptors (AChR) are present in most patients and disrupt neuromuscular transmission, leading to muscle weakness and fatigue. AChR modulation is a well-characterized pathogenic mechanism, where antibodies drive the internalization and degradation of AChRs causing functional impairment in muscle contraction, and worsening disease symptoms. However, this pathogenic mechanism is variable deOral in patient specific anti-AChR characteristics.

OBJECTIVE: We aim to develop and refine the methodology to quantitatively assess AChR internalization induced by AChR autoantibodies, enhancing our understanding of how these antibodies contribute to receptor depletion and disease progression as well as to therapy response.

METHODS: Using CN21 cells, we induced AChR internalization with mAb 637 and patient sera. Residual surface AChRs were then labeled with a-bungarotoxin radiolabeled with I125 (I125-aBTX), and gamma counting was used to measure the remaining radioactivity. Data were normalized to quantify modulation, using the no anti-AChR condition as a baseline to measure antibody-driven receptor loss.

RESULTS: Our approach demonstrates measurable differences in AChR autoantibodies modulation capacity across samples from MG patients. The method’s sensitivity enables a clear quantitative assessment of antibody-induced receptor.

SUMMARY/CONCLUSION: This methodology provides a reliable tool to study AChR modulation in MG, offering potential as a biomarker of disease severity and treatment response. Furthermore, quantifying individual patients' antibody effects on AChR modulation may support the development of targeted therapeutic strategies that prevent receptor loss, potentially leading to improved clinical outcomes for AChR-MG patients.

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ECULIZUMAB AS A RESCUE THERAPY IN MYASTHENIC CRISIS IN ICU

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INTRODUCTION: In anti-acetylcholine receptor antibody-positive (AChR+) generalized MG (gMG), terminal complement activation leads to AChR antibody-mediated destruction of the motor endplate, disrupting neuromuscular transmission. Myasthenic crises (MC) are potentially life-threatening, most severe presentation of MG characterized by profound muscle weakness, bulbar symptoms, and potential for respiratory failure (MGFAV). Intravenous immunoglobulins and plasma exchange are conventional treatments for myasthenic exacerbations. Eculizumab (ECU) is a humanized monoclonal antibody that binds to complement protein C5 and inhibits the activation of terminal complement, thus protecting the neuromuscular junction from these destructive effects.

OBJECTIVE: The open-label extension phase of REGAIN, as well as observational studies and case series/reports have suggested favorable outcomes and safety with ECU in refractory MG but ECU has not been studied in severe myasthenic exacerbation or myasthenic crisis (MGFA V).

METHODS: Three patients with AChR+ gMG who had MGFA-V and treated with conventional rescue therapies in ICU without any clinically meaningful response for at least a month, received ECU. After obtaining written patient consent, data were collected retrospectively from medical records.

RESULTS: Three female patients with MGFA-V treated with ECU in intensive care unit (ICU) included in the study. Mean age at the MC was 51.3 (ranges 31-62) years. The eldest was a newly diagnosed patient presented with respiratory problems and entered ICU. One had history of recurrent thymoma and worsened possibly due to viral infection. The third patient had a long term well-controlled MG, but exacerbated after a major surgery. All received prompt administration of IVIg (2 g/Kg over five days) after the presentation and maintained with high dose oral corticosteroids. Mean time in ICU prior to ECU treatment was 49.3 (ranges 33-62) days. All had tracheostomy due to prolong intubation. Mean MG-ADL score prior to the ECU was 17 (ranges 13-21), 2.3 (ranges 0-6) after a month and 2 (0-5) after 12 months. All patients extubated successfully and discharged from ICU within 2 weeks of the treatment with ECU. No significant side effects were reported.

SUMMARY/CONCLUSION: Our data provide real-world evidence supporting the use of ECU as a rescue treatment for the patients with myasthenic crisis in ICU. Further studies are needed to evaluate the efficacy and safety of eculizumab in myasthenic crises.

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ECULIZUMAB VERSUS RITUXIMAB FOR REFRACTORY ANTI-ACETYLCHOLINE RECEPTOR ANTIBODY-POSITIVE GENERALIZED MYASTHENIA GRAVIS: A SINGLE-CENTER EXPERIENCE

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BACKGROUND: Rituximab (RTX) and eculizumab (ECU) are treatment options for refractory myasthenia gravis (MG), but comparative clinical data derived from real-world experience are limited. Here we describe the baseline characteristics, and treatment and safety outcomes of patients with anti-acetylcholine receptor antibody-positive (AChR+) generalized myasthenia gravis (gMG) treated with ECU and/or RTX in our clinic.

METHODS: Patients with refractory AChR+ gMG who received ECU or/and RTX treatment for more than one year at the Department of Neurology, Istanbul Faculty of Medicine were included in this observational study. After obtaining written patient consent, data were collected retrospectively from medical records.

RESULTS: Twelve patients treated with ECU and 25 patients treated with RTX were included in the analysis. Groups were comparable with regard to demographic and clinical characteristics, including age at onset of MG, disease duration and history of thymoma. ECU was associated with significantly better outcomes compared with RTX, as measured by decreases in the mean MG activities of daily living score at 1 ($p = 0024$), 3 ($p < 0.001$), 6 ($p < 0.001$), and 12 ($p < 0.001$) months of treatment; steroid-sparing effect after 1 year of treatment (decrease in mean [standard deviation] daily prednisolone dose of -21.8 [13.5] mg vs -6.6 [9.4] mg with RTX; $p < 0.001$); need for rescue treatment and number of myasthenic crisis episodes during treatment ($p < 0.001$). No new safety signals were observed with either treatment.

CONCLUSION: Our data provide real-world evidence supporting ECU over RTX to treat patients with refractory AChR+ gMG.

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DEVELOPMENT OF THE MYASTHENIA GRAVIS-HEALTH INDEX (MG-HI), A REGUALTORY-GRADE PATIENT-REPORTED OUTCOME MEASURE

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INTRODUCTION: There is a need for a reliable, sensitive, myasthenia gravis (MG)-specific, patient-reported outcome (PRO) measure capable of detecting clinically-relevant changes in disease status in response to therapeutic interventions. The MG-ADL is widely used, however, there are several limitations regarding this scale related to its linear weighting of items and its inability to capture the full MG patient experience. Therefore, there is a need for a fully validated PRO that contains symptoms that are most impactful to the patient population

OBJECTIVE: To develop and validate a disease-specific PRO that measures the symptoms most important and prevalent among patients with MG.

METHODS: We conducted qualitative interviews with individuals with ocular and generalized MG to identify symptoms of potential importance. Next, we conducted a national cross-sectional study to determine the most common and important symptoms and symptomatic themes. Questions were selected for the first version of the Myasthenia Gravis-Health Index (MG-HI) based upon their relevance, impact, and potential to respond to therapeutic intervention. Subsequently, we utilized factor analysis to group together instrument subscales representing the most important areas of MG symptomatic health. We then performed beta testing to assess the comprehensibility of the instrument by asking patients their understanding of the questions. Test-retest reliability and known groups analysis were conducted to optimize the reliability and responsiveness of the MG-HI.

RESULTS: Fifteen individuals with ocular or generalized MG participated in qualitative interviews and 222 individuals completed the online cross-sectional study. We conducted beta testing and test-retest reliability with 17 and 20 participants with MG, respectively. Beta testing and test-retest reliability indicated that the MG-HI is reliable (ICC = 0.854), comprehensive, easy to use, and relevant to the patient population.

SUMMARY/CONCLUSION: The MG-HI is a regulatory-grade, valid, disease-specific PRO measuring 14 areas of granular MG health designed to support FDA drug-labeling claims.

DISCLOSURES: Author Michael Benatar reports consulting for Alector, Alexion, Annexon, Arrowhead, Biogen, Cartesian, Denali, Eli Lilly, Horizon, Immunovant, Janssen, Novartis, Roche, Sanofi, Takeda, UCB, and uniQure. Author Chad Heatwole receives royalties for the use of multiple disease specific instruments. He has provided consultation to Biogen Idec, Ionis Pharmaceuticals, aTyr Pharma, AMO Pharma, Acceleron Pharma, Cytokinetics, Expansion Therapeutics, Harmony Biosciences, Regeneron Pharmaceuticals, Astellas Pharmaceuticals,

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INTERLEUKIN-6 INHIBITION IN MYASTHENIA GRAVIS; A CASE SERIES EXPOSED TO TOCILIZUMAB

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INTRODUCTION: Inhibition of interleukin-6 (IL6) has recently been suggested as an add-on in refractory MG and Satralizumab is currently in clinical trials for myasthenia gravis (MG).

OBJECTIVE: We here aim to present clinical data from a case series in Sweden examining possible clinical utility in MG.

METHODS: Single center retrospective case series including patients exposed to ≥1 dose of subcutaneous/ intravenous Tocilizumab. Clinical outcome was assessed by Quantitatve Myasthenia Gravis (QMG) score, prednisolone dose, rescue treatment and/or additional immunosuppressive drugs. Safety was assessed.

RESULTS: We identified 24 MG patients treated with Tocilizumab. Treatment indication was refractory disease (n=15), severe new onset disease (n=6), increased susceptibility to infections (n=1), or non-MG related cause (n=2). Mean age at first treatment was 59.4 years (standard deviation, SD 18.2), 41.7% were females, 50% EOMG, 95.8 % generalized MG, and 70.8 % AChR+. Average disease duration was 10 years (SD 10.4), QMG score 6.9 (SD 5.6), and 83.3% were previously exposed to or had ongoing treatment with Rituximab. Mean treatment duration was 0.8 years (SD 0.8), with a somewhat longer duration in the refractory group (1.2 years, SD 0.9), 20.8 % had ongoing treatment at data withdrawal. The majority of refractory patients (60%) experienced increased disease activity, needed rescue treatment and/or switch to other immunomodulatory treatments within a year of treatment start. One severe adverse event was reported, a suspected Stevens-Johnson syndrome, and seven additional adverse events were reported.

SUMMARY/CONCLUSION: IL6 inhibition represents a novel approach to treat MG and benefits from robust safety data obtained from rheumatic conditions. While firm conclusions on clinical effectiveness in MG awaits ongoing trials, our data provide an initial indication of potential clinical utility in certain clinical scenarios.

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A SINGLE CENTER EXPERIENCE IN THE USE OF RITUXIMAB IN MYASTHENIA GRAVIS WITH LONG-TERM FOLLOW UP

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INTRODUCTION: Myasthenia gravis (MG) is a B cells mediated disease. Rituximab, an anti-CD20 monoclonal antibody, is the main B cell-depleting therapy used to this day in MG. CD20 is expressed throughout B cell maturation from the pre-B cell stage through the other maturation stages including short-lived plasma cells (plasmablasts), which are the main cells responsible for anti-Musk IgG4 production and B regulatory cells (Breg). However, rituximab does not affect long-lived CD20-negative plasma cells, which are responsible for producing IgG1/IgG3 anti-AChR antibodies. Rituximab has proved effective in treatment of anti-Achr and anti-Musk MG, both in MG and refractory MG.

OBJECTIVE: This study aims to describe our single-center experience in the use of Rituximab in anti-AchR and anti-Musk MG with standard dose and low dose regimens.

METHODS: A retrospective evaluation of MG patients treated with rituximab at our MG center was conducted. Clinical outcome through standardized clinical scales (MGADL, MGFA, MGFA-PIS) at 6 months, 1, 2 and 5 years follow up was recorded. Steroid spearing effect was also recorded.

RESULTS: 38 patients were included in the evaluation (23 Anti-Achr MG patients and 15 anti-Musk MG patients). Both groups showed a significant clinical improvement and steroid sparing effect, both more significant in the anti-Musk MG group with an high rate of clinical remission. Five patients (anti-AhcR MG) were non-responders or had a very low clinical response. One of these patients showed an elevated anti-rituximab antibody titre. No differences were detected in response in antiMusk patients treated with 1000 mg protocol compare to those treated with low does protocol (500 mg).

SUMMARY/CONCLUSION: Rituximab is a useful therapeutic tool in MG, especially in anti-musk patients, with a high rate of clinical remission.

THIS IS AN ENCORE PRESENTATION OF: Erra, C. et.al. (2024, Jun 29-Jul 2). *A Single Center Experience in the Use of Rituximab in Myasthenia Gravis with Long-Term Follow Up.* [Conference presentation abstract] 10th Congress of the European Academy of Neurology, Helsinki, FI https://www.ean.org/congress2024

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MYASTHENIA GRAVIS MISDIAGNOSIS: UNCOVERING THE PITFALLS AND PATTERNS

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INTRODUCTION: MG diagnosis is challenging, particularly in seronegative cases. While increased disease awareness and advanced serological tests have led to a rise in MG diagnosis, the risk of overdiagnosis remains. Accurate diagnosis is crucial especially with the availability of novel targeted therapies.

OBJECTIVE: To evaluate the rate and underlying causes of MG misdiagnosis in a tertiary MG clinic.

METHODS: We retrospectively analyzed medical records from patients diagnosed with MG who were referred to our tertiary clinic for a second opinion between January 2019 and December 2024.

RESULTS: We included 144 patients, of whom 26 (18.1%) were found to have been misdiagnosed. Among these, 13 (50%) were seronegative. AChR antibodies (Abs) were identified in 12 of the misdiagnosed patients (6 by radioimmunoassay and 6 by ELISA), while MuSK-Abs were detected in only one case. None of these 26 patients had clinical symptoms consistent with MG. Fixed cell-based assay was negative in all cases. Of the 13 previously seropositive patients, nine were retested using radioimmunoassay at our center, with seven yielding negative results. Six patients had prior positive electrodiagnostic studies: four with abnormal repetitive nerve stimulation (RNS) and two with minimal abnormalities on single-fiber electromyography. When repeated at our center, RNS did not confirm the previous results in any of these four cases. The median duration of misdiagnosis was 36 months [1–99 months]. Twenty misdiagnosed patients had received anticholinesterase treatment, immunosuppressants were prescribed for 14 (53.8%), two patients underwent thymectomy.

CONCLUSIONS: MG misdiagnosis is not uncommon and often leads to prolonged, unnecessary treatment. The main causes of MG misdiagnosis include atypical clinical presentation, false-positive antibody results, and technical artifacts or equivocal findings on neurophysiological tests. These findings underscore the importance of a thorough clinical evaluation for MG, proper antibody testing protocols, and specialized expertise in neurophysiological testing.

DISCLOSURES: R. Iorio – has received consultancy fees and speaker honoraria from Alexion, Argenx, UCB and Dianthus Therapeutics. A.Evoli – has received consultancy fees and speaker honoraria from Grifols, UCB, Alexion, Argenx. None of the other authors has any conflict of interest to disclose.

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THE EVOLVING LANDSCAPE OF MUSK-MG EPIDEMIOLOGY AND TREATMENT

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INTRODUCTION: The striking prevalence of young women is a well-recognized MuSK-MG characteristic. In contrast to AChR-MG, a bimodal pattern of onset and very-late presentation are uncommon. MuSK-MG epidemiological data remain scarce due to the disease rarity. Rozanolixizumab was recently approved for this MG subtype, though real-world data are lacking.

OBJECTIVE: To analyze demographic changes and clinical characteristics in a MuSK-MG cohort seen in our center over the last four decades, and to report the response to rozanolixizumab in these patients.

METHODS: Patients with onset between January 1980 and December 2024 were included. MuSK antibodies were tested by radioimmunoassay. We analyzed demographic characteristics and disease severity according to MGFA classification. The response to rozanolixizumab was assessed through MG-ADL, QMG scores at baseline and at the end of treatment cycle. Steroid dose changes were also evaluated.

RESULTS: Epidemiologic study included 111 (76% females) patients with onset between January 1980 and December 2024. Median age at onset steadily increased from 36 years [range: 20-66] in the 80s to 51 years [16-80] in the last decade; patients with age at onset ≥50 years increased from 12.5% to 53.1% ($p=0.007$). In the last decade, 9/32 patients (28%) were ≥65-year-old at presentation. The proportion of male patients increased from 18.8% in the first decade to 37.5% in the most recent decade. Maximum disease severity decreased over time, with a remarkable decline in respiratory crises and four ocular cases were observed. Thirteen patients were treated with rozanolixizumab, seven (63.6%) reached minimal manifestation at week 6; MG-ADL score was significantly reduced from baseline after first cycle ($p=0.03$) whereas both MG-ADL and QMG improved significantly after second cycle ($p=0.02$).

CONCLUSION: Epidemiological changes similar to those reported in AChR-MG were seen to a lesser extent in MuSK-MG population. Further studies are needed to confirm these observations and rozanolixizumab therapeutic role.

DISCLOSURES: R. Iorio – has received consultancy fees and speaker honoraria from Alexion, Argenx, UCB and Dianthus Therapeutics. A.Evoli – has received consultancy fees and speaker honoraria from Grifols, UCB, Alexion, Argenx. None of the other authors has any conflict of interest to disclose.

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EVALUATING THE EVIDENCE BEHIND THE MYASTHENIA GRAVIS MEDICATION OF CAUTION LIST

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INTRODUCTION: Certain classes of medications are avoided in Myasthenia Gravis (MG) patients due to the reported risk of MG exacerbation. Given multiple medical comorbidities in MG patients, our goal is to evaluate the quality of evidence behind the MG medication of caution list.

OBJECTIVE: To conduct a review of the literature on medications and vaccines that have historically been avoided or used cautiously in patients with MG.

METHODS: Ovid MEDLINE searches were conducted; a study was included if it met the following criteria: peer-reviewed source, published after 1984, and the study described outcomes in MG patients who received a cautionary drug or vaccine. Search categories were cardiac medications, antibiotics, immunosuppressants, minerals, anesthetics, statins, miscellaneous, and vaccines. The Adverse Drug Reaction (ADR) probability scale was applied to individual patients in each study by two reviewers to characterize MG exacerbation following administration of a cautionary drug as doubtful, possible, probable, or definite. For studies without individual patient data, the ADR probability scale was applied to the statistical metrics and methodology of the pooled data to estimate a score. Discrepancies in ADR probability scores were resolved by a third-party adjudicator.

RESULTS: At the time of this abstract, the cardiac medication search was analyzed and included antiarrhythmics, beta-blockers, and calcium channel blockers. Ninety studies were identified, 11 were included. Six were case reports, two were case-control studies, two were non-randomized, non-controlled clinical studies, and one was a single blinded placebo-controlled crossover study. With application of the ADR probability scale, 9 drug reactions were deemed doubtful (52.9%), 6 possible (35.3%), 2 probable (11.8%), and 0 (0%) definite.

SUMMARY/CONCLUSION: Our preliminary analysis suggests certain drugs of caution may be safer in MG than previously thought and may have important implications for use in clinical practice. We will present final results.

DISCLOSURES: Author Michael Hehir discloses he has been a consultant to Argenx, Alexion, UCB, and Janssen. Author Yuebing Li discloses he has been a consultant for Alexion, Argenx, Amgen, and received a research grant from Argenx.

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COMPLEMENT INHIBITION FOR THE TREATMENT OF GENERALIZED MYASTHENIA GRAVIS: A REAL WORLD EXPERIENCE WITH RAVULIZUMAB

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INTRODUCTION: Complement activation plays a key role in the pathogenesis of Myasthenia Gravis (MG). Ravulizumab, a complement inhibitor derived from Eculizumab, was found to be safe and effective in the CHAMPION MG randomized controlled study.

OBJECTIVE: To evaluate effectiveness and safety of Ravulizumab in a real-world setting.

METHODS: 14 patients were treated with Ravulizumab i.v., according to the Early Access Program, from May 2023 to November 2024 (follow-up 10±3,5 months). At baseline 3 patients (21,4%) were classified as MGFA IVB. Ravulizumab was administered i.v. every 8 weeks as add on to ongoing therapy with anticholinesterase inhibitors, immunosuppressive drugs and/or corticosteroids (the mean steroid dose at baseline was 20.1 mg ± 14.5). Clinical outcomes were measured by means of the MG-ADL, QMG and MGQoL-15 rating scales.

RESULTS: A clinically meaningful improvement was recorded by all rating scales from the second week in 12/14 patients (85.7%). At baseline the MG-ADL was 8.4 ± 2.3 (mean and SD), QMG 14.4±5.7 and MG-QOL-15r 16±4.6. After two weeks, MG-ADL was 3.9± 3.5 (- 4,5), QMG was 7.9 ± 4.3 (- 6,5) and MG-QOL-15r 8.4± 6.2 (- 7.6). 7 patients (50%) achieved Minimal Symptom Expression (MSE) within two weeks and the MSE condition was maintained for the entire duration of follow-up. Ravulizumab was discontinued in 3 patients (21.4%) due to loss of response. 7/14 patients (50%) reduced the corticosteroid dose (percentage reduction: 41%). During treatment with Ravulizumab no patients were hospitalized or needed treatment with Plex/IVIG, compared with the year before treatment. Ravulizumab was well tolerated.

SUMMARY/CONCLUSION: Ravulizumab provided rapid, meaningful and sustained improvement to our gMG patients, as well as a steroid- and immunomodulatory-sparing effect. Ravulizumab modified dramatically the course of the disease compared with the year before treatment.

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SWITCHING TO SUBCUTANEOUS ZILUCOPLAN FROM INTRAVENOUS COMPLEMENT INHIBITORS IN GMG: PATIENT PREFERENCE AND SATISFACTION FROM A PHASE 3B STUDY

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INTRODUCTION: Zilucoplan, a macrocyclic peptide complement component 5 (C5) inhibitor, is self-administered as a subcutaneous injection, offering an alternative to intravenous infusion of antibody-based complement C5 inhibitors.

OBJECTIVE: To evaluate safety, efficacy, patient preference and satisfaction with zilucoplan in adults with acetylcholine receptor autoantibody–positive generalised myasthenia gravis (MG) switching from their current intravenous complement C5 inhibitors to subcutaneous zilucoplan.

METHODS: MG0017 (NCT05514873) was a Phase 3b, open-label, single-arm study with a 12-week main treatment period of daily subcutaneous zilucoplan. Patients were required to have stable disease on an intravenous complement C5 inhibitor and be willing to switch to zilucoplan.

Incidence of treatment-emergent adverse events (TEAEs; primary endpoint), change from baseline in Myasthenia Gravis Activities of Daily Living score at Week 12 (secondary endpoint) and preference for intravenous or subcutaneous complement C5 inhibitors at Week 12 (exploratory endpoint) were assessed. Treatment satisfaction was measured using the 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9; scored 0–100; exploratory endpoint).

RESULTS: Twenty-six patients enrolled and received zilucoplan; 16 switched from eculizumab and 10 from ravulizumab. Of these, 23 patients completed the main treatment period and three discontinued (two due to TEAEs). TEAEs occurred in 19/26 (73.1%) patients and were mostly mild in severity. At Week 12, MG symptoms were improved or unchanged in approximately 75% of patients. Subcutaneous treatment was preferred by 20/26 (76.9%) patients; 4/26 (15.4%) preferred intravenous treatment and 2/26 (7.7%) had no preference. At Week 12, mean (standard deviation) changes from baseline in the TSQM-9 global satisfaction, effectiveness and convenience sub-scores were +19.410 (27.429), +13.889 (21.534) and +21.739 (19.955), respectively.

SUMMARY/CONCLUSION: Zilucoplan demonstrated a favourable safety profile. More patients preferred subcutaneous to intravenous treatment, and overall treatment satisfaction increased after switching from intravenous complement C5 inhibitors to subcutaneous zilucoplan.

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Jos Bloemers is an employee and shareholder of UCB. Babak Boroojerdi and Andreea Lavrov are employees and shareholders of UCB. Eumorphia Maria Delicha is an employee of UCB. Puneet Singh is an employee and shareholder of UCB, and is a shareholder and previous employee of GSK. James F. Howard Jr. has received research support (paid to his institution) from Ad Scientiam, Alexion/AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, the Centers for Disease Control and Prevention, the Muscular Dystrophy Association, the Myasthenia Gravis Foundation of America, the National Institutes of Health, NMD Pharma, and UCB; has received honoraria/consulting fees from AcademicCME, Alexion/AstraZeneca Rare Disease, Amgen, argenx, Biohaven Ltd, Biologix Pharma, CheckRare CME, CorEvitas, Curie.Bio, Hansa Biopharma, Medscape CME, Merck EMD Serono, Novartis, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics, Toleranzia AB and UCB; and has received non-financial support from Alexion/AstraZeneca Rare Disease, argenx, Biohaven Ltd, Cartesian Therapeutics, Toleranzia AB and UCB.

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A PHASE I/IIA FIRST-IN-HUMAN STUDY OF TOL2, AN IMMUNE TOLERISING AGENT, IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS

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INTRODUCTION: TOL2 is a chimeric recombinant protein comprising the extracellular domain of the alpha-1 chain of the human skeletal muscle AChR. Repeated intravenous administration of TOL2 has confirmed its potential to induce antigen-specific tolerance in the rat EAMG disease model.

OBJECTIVE: To determine the safety profile of TOL2 as a treatment in patients with AChR antibody seropositive autoimmune generalized MG and to assess its ability to induce antigen-specific immune tolerance.

METHODS: A clinical trial application has been submitted to the European Medicines Agency's Clinical Trials Information System, CTIS. Herein, key aspects of the study are described. Patients with generalized MG, Grade II – IVa, positive for anti-AChR antibodies, are eligible. This double-blind, randomized, placebo-controlled clinical trial consists of a single ascending dose (SAD) part, in which single doses of TOL2 or placebo will be administered by IV infusion in 5 sequential cohorts, followed by a multiple ascending dose part (MAD), where participants in 3 sequential cohorts will receive a total of 10 daily IV doses of TOL2 over 12 days. A Bayesian logistic regression model based on the continual reassessment method utilizing the overdose control (EWOC) criterion will be applied for dose escalation. The primary objective of the study is to evaluate the safety and tolerability of TOL2. Secondary objectives include determining the pharmacokinetic profile of TOL2 after single and multiple dosing, evaluating the tolerance induction/immune modulation upon administration of TOL2, and evaluating the preliminary efficacy of TOL2 treatment by assessment of MG scales. Immunological biomarkers will also be analyzed.

SUMMARY/CONCLUSION: TOL2 has the potential to produce long-lasting improvement in patients with gMG through immune tolerance. Additional details of the study design will be presented.

DISCLOSURES: Authors Vidar Wendel-Hansen, Cecilia Kemi, Björn Löwenadler and Charlotte Fribert are employees or consultants for Toleranzia AB and may be shareholders of Toleranzia AB. Author Jan D. Lünemann has received speaker fees, research support, travel support, and/or

served on advisory boards by Abbvie, Alexion, Adivo, Argenx, Biogen, CSL Behring, Janssen, Merck, Moderna, Novartis, Roche, Sanofi, Takeda and UCB Pharma and he is member of the medical advisory board of the German Myasthenia Gravis Society. Author Anna Rostedt Punga is a consultant on advisory boards/speaker honoraria of Argenx, UCB, Alexion, Toleranzia AB, Dianthus Therapeutics, and Amgen. Author John Vissing is a consultant on advisory boards/speaker honoraria of Roche, Regeneron, Argenx BVBA, UCB Biopharma SPRL, Amgen, Dianthus Therapeutics, NMD Pharma, Alexion Pharmaceuticals, Johnson & Johnson, Toleranzia AB. He has been principal investigator in MG clinical trials by Roche, Amgen, Argenx BVBA, Novartis Pharma AG, Alexion Pharmaceuticals, UCB Biopharma SPRL, Regeneron, Johnson & Johnson, Dianthus Therapeutics. Author James F. Howard, Jr has received research funding (paid to his institution) from Ad Scientiam, Alexion AstraZeneca Rare Disease, Argenx, Cartesian Therapeutics, Centers for Disease Control and Prevention, MGFA, Muscular Dystrophy Association, NIH, NMD Pharma, PCORI, and UCB Pharma; Honoraria/consulting fees from AcademicCME, Alexion AstraZeneca Rare Disease, Amgen, Biohaven Ltd, Biologix Pharma, CheckRare CME, CoreEvitas, Curie.bio, Medscape CME, Merck EMB Serono, Novartis Pharma, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics, Toleranzia AB, UCB Pharma, and Zai Labs; non-financial support from Alexion AstraZeneca Rare Disease, argenx, Biohaven Ltd., Cartesian Therapeutics, Toleranzia AB, UCB Pharma and Zai Labs.

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INVESTIGATING THE BIOEQUIVALENCE, INJECTION SPEED, AND USABILITY OF SUBCUTANEOUS EFGARTIGIMOD PH20 ADMINISTRATION USING A PREFILLED SYRINGE

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INTRODUCTION: Efgartigimod is a human immunoglobulin G1 (IgG1) antibody Fc-fragment that reduces IgG levels, including pathogenic IgG autoantibodies, through neonatal Fc receptor blockade. Efgartigimod administered subcutaneously (SC, coformulated with recombinant human hyaluronidase) was well tolerated and efficacious in phase 3 trials in participants with gMG and chronic inflammatory demyelinating polyneuropathy (CIDP). The 1000-mg fixed-dose formulation of efgartigimod PH20 SC is provided in a vial administered via a separate syringe (V+S). To increase patient convenience, a prefilled syringe (PFS) has been developed to ease the injection procedure.

OBJECTIVE: To investigate bioequivalence, safety, and tolerability of efgartigimod PH20 SC via PFS vs a V+S in healthy participants.

METHODS: Bioequivalence of efgartigimod PH20 SC administered via PFS vs V+S was assessed in a phase 1, open-label, randomized, 2-period cross-over study. Healthy participants (n=72) were randomized to receive a single injection of efgartigimod PH20 SC via PFS or V+S in a cross-over design. Bioequivalence was determined based on predefined criteria. Separate studies were conducted to determine the feasibility of different injection speeds and the usability of the PFS.

RESULTS: Bioequivalence between efgartigimod PH20 SC administered via PFS or V+S was established, as the 90% CI around the GMR of Cmax and AUC0-inf was within the predefined criteria of 80.00% to 125.00%. The majority of adverse events were mild to moderate, and there were no observed differences in incidence of reported injection site reactions. No serious adverse events and no deaths were seen in the study. Rapid (20-second) administration was feasible, and human factor validation studies determined that the PFS could be safely prepared and administered by participants/caregivers.

SUMMARY/CONCLUSION: This study demonstrated efgartigimod PH20 SC administered via PFS is bioequivalent to efgartigimod PH20 SC administered via V+S, which may provide an additional convenient treatment option for patients with gMG and CIDP.

DISCLOSURES: Authors Filip Borgions, Koen Allosery, and Cassandra De Muynck disclose that they are employees of argenx. Author Jan Noukens discloses that he is a consultant for argenx.

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States. index.mirasmart.com/AAN2025/

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MYASTHENIA GRAVIS CONCURRENT WITH PARKINSON'S DISEASE. A REPORT OF 18 CASES

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INTRODUCTION: Recent epidemiological studies suggest an increase in cases of late-onset myasthenia gravis (LOMG). Aging MG patients usually present other concurrent diseases.

OBJECTIVE: To investigate the concurrence of MG and Parkinson's disease (PD) in a large cohort of Spanish MG patients.

MATERIAL/ METHODS: We classified patients with concurrent MG and PD in a cohort of 631 MG patients by gender, age, MGFA class, quantitative MG score at diagnosis, UPDRS score at diagnosis, and the DaTSCAN uptake pattern, the interval between the onset of the two diseases, and medication administered. Our study included a review of the cases in the literature.

RESULTS: We identified eighteen patients (sixteen men) with concurrent MG and PD. The mean age at MG diagnosis was 68.2 years. The interval between the diagnosis of the first and second disease was 8.1 years. It was 8.7 years when MG was the first diagnosis and fell to 4.6 years when PD was the first. The MG phenotype included dropped head in 8 cases. DaTSCAN showed a bilateral reduced uptake pattern in eleven cases and unilateral in the remainder.

CONCLUSIONS: To our knowledge, this is the largest reported series of concurrent MG and PD. This concurrence is more common than expected (2.8%). Either MG or PD may appear first. We found no iatrogenic relationship for the order of appearance. The overlapping symptoms sometimes lead physicians to overlook the second disease, instead viewing it as a deterioration of the first. This study describes patients with well-documented diagnoses of both MG and PD, thus providing further indications of a shared aetiology of these two diseases. Prospective studies including genetic, immunological, and environmental analysis are necessary to identify possible common pathogenic mechanisms. Health professionals must be alert to this possible comorbidity to be able to treat these specific symptoms appropriately.

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DISEASE BURDEN IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS

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INTRODUCTION: Despite newer treatments for generalized myasthenia gravis (gMG), many patients continue to experience inadequately controlled symptoms.

OBJECTIVE: To investigate the burden of gMG using recent United States medical claims data.

METHODS: Adult patients diagnosed with gMG (International Classification of Diseases [ICD]-10 codes G70.00/G70.01), from 01/01/2022-12/31/2023 were identified from the Optum Clinformatics database. Data on patient demographics, treatment characteristics, and clinical events were collected for a 12-month baseline period and a 24-month follow-up period. Disease burden was assessed through the incidence of MG-related hospitalizations and emergency room (ER) visits, acute respiratory failure, mechanical ventilation, gastrostomy tube insertion, intensive care unit (ICU) stay, any use of corticosteroids, and rescue treatments (immunoglobulin or plasma exchange).

RESULTS: A total of 6480 patients with gMG were identified and followed for up to 24 months (median: 556 days). The proportion of patients with at least one event and, among them, the frequency of all events per patient-year, respectively, were 26.9%/3.65 for exacerbations; 39.2%/1.53 for MG-related hospitalizations; 12.2%/1.55 for acute respiratory failure; 5.2%/1.16 for mechanical ventilation; 1.0%/1.29 for gastrostomy tube insertion; 22.0%/1.30 for MG-related ICU stay; 23.4%/1.15 for MG-related ER visits; and 7.8%/2.77 for the use of rescue treatments. Corticosteroid use was recorded in 50.2% of patients, with 50.5% of these receiving prednisone equivalent doses >10 mg/day. Among 482 patients who received targeted immunotherapy, the disease burden remained high.

SUMMARY/CONCLUSION: Despite recent therapeutic advancements, a significant disease burden persists in patients with gMG, highlighting an ongoing unmet medical need.

DISCLOSURES: Nicholas Silvestri: Consultant/advisor for Alexion, Amgen, Annexon, argenx, Immunovant, Janssen, and UCB. Speaker for Alexion, argenx, Takeda, and UCB. Kavita Gandhi, Ibrahim Turkoz, Mehmet Daskiran, Bonnie Chen Shaddinger, Maria Ait-Tihyaty, and Ewa Lindenstrom: are or were employees, contractors, or consultants for Janssen Pharmaceuticals and may hold stock or stock options in Johnson & Johnson.

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source/documents/nmfoundation/media/about/aanem-abstracts-guide.pdf?sfvrsn=cab7028f_11

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COMPOSITE RESPONSE TO NIPOCALIMAB, A NOVEL FcRn BLOCKER, BASED ON MG-ADL AND QUANTITATIVE MG SCORES IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS

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INTRODUCTION: Nipocalimab demonstrated statistically significant efficacy with the Myasthenia Gravis-Activities of Daily Living (MG-ADL) and Quantitative MG (QMG) scales in the 24-week double-blind Phase-3 Vivacity-MG3 study (NCT04951622). A meaningful treatment response incorporating both patient and clinician perspectives reflects clinical improvement and functional impact on patient quality of life.

OBJECTIVE: To evaluate the likelihood of composite treatment response using the MG-ADL and QMG scales, representing patient's and clinician's perspectives, respectively, in patients with generalized MG (gMG) receiving nipocalimab+standard-of-care [SoC] (nipocalimab) or placebo+SoC (placebo).

METHODS: Composite response (CR) was defined as having MG-ADL total score improvement of >=2 points and QMG total score improvement of >=3 points from baseline. The proportion of patients achieving CR was assessed at each visit. Proportion of patients with sustained composite response (SCR) for >=4, 6, 8, 12, 16, 20 weeks was examined. Patients with missing change in MG-ADL and/or QMG were considered as not having met improvement criteria. Generalized estimating equations evaluated differences in CR rates over 24-weeks.

RESULTS: In the primary efficacy analysis set (N=153 patients), a greater proportion of nipocalimab-treated patients achieved CR from week-2 through week-24 than placebo-treated patients. At week-2, 36.8% in nipocalimab group versus 11.8% in placebo group achieved CR. By week-24, the proportion of CR increased to 42.9% for nipocalimab versus 19.7% for placebo. Nipocalimab-treated patients were 4-times more likely to achieve CR (odds ratio: 4.02 [95% CI]: 2.33, 6.97) over 24-weeks and >4-times more likely to achieve SCR for >=4,6, 8, 12, 16, 20 weeks versus the placebo group. For >8-weeks, nipocalimab-treated patients were >6 times more likely to attain SCR (odds ratio [95% CI]: 6.34 [2.85, 14.07]) than placebo.

SUMMARY/CONCLUSION: Patients with gMG demonstrated significantly higher likelihood of achieving CR and SCR based on both patient-reported MG-ADL and clinician-reported QMG assessments when treated with nipocalimab+SoC versus placebo+SoC.

DISCLOSURES: Said R. Beydoun has been a consultant for Alexion, Alnylam, Amylyx, Argenx, Biogen, Catalyst, CSL, Janssen, Octapharma, Mitsubishi Tanabe, Takeda, UCB; has served on a Speakers Bureau for Alexion, Alnylam, Amylyx, Argenx, CSL, Grifols, Takeda; has

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EFFICACY OF NIPOCALIMAB, A NOVEL FcRn BLOCKER, AS MEASURED USING QUANTITATIVE MYASTHENIA GRAVIS ASSESSMENT: FINDINGS FROM PHASE 3 VIVACITY-MG3 STUDY

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INTRODUCTION: There remains an unmet need for effective treatments providing meaningful symptom control in generalized myasthenia gravis (gMG). Patients treated with nipocalimab+standard-of-care (SoC) achieved significant improvement in mean MG-Activities of Daily Living score from baseline over weeks 22 to 24 compared with placebo+SoC in the 24-week double-blind, phase-3 Vivacity-MG3 study (NCT04951622).

OBJECTIVE: To assess nipocalimab efficacy using Quantitative Myasthenia Gravis (QMG) in patients with gMG.

METHODS: Mean changes in QMG total score were compared between nipocalimab+SoC (nipocalimab) and placebo+SoC (placebo). A negative change in score indicates improvement. The proportion of patients achieving improvement of QMG >=3 points (QMG-3), and sustaining QMG-3 improvement, and the proportion of time spent with QMG-3 improvement were examined for nipocalimab and placebo groups.

RESULTS: Nipocalimab demonstrated statistically significant improvement in QMG total score vs placebo over weeks 22 and 24; least-square (LS) mean change (SE): –4.9(0.50) vs –2.0(0.50); difference = –2.81(0.710); p<.001. Mean differences between groups were observed as early as the first post-baseline assessment (week 2): LS-mean change (SE): –3.6(0.36) vs –0.6(0.355); difference of –3.1(0.51); p<.001 favored nipocalimab. Earliest week (mean [SD]) QMG-3 improvements were 3.8(3.88) for nipocalimab vs 7.5(6.33) weeks for placebo. Within 8 weeks of treatment initiation, 89 (nipocalimab:71.4%[55/77]; placebo:44.7%[34/76]) patients achieved QMG-3 improvement (p<.001). Of 63 patients with sustained QMG-3 improvement for >=8 weeks, significantly greater proportion were from the nipocalimab (55.8%[43/77] vs 26.3%[20/76]; p<.001) placebo group. Patients receiving nipocalimab were over four times more likely to sustain QMG-3 improvement for >=16 weeks (Odds Ratio [95%CI]: 4.31[1.93, 9.66]) and for >=20 weeks (Odds Ratio [95%CI]: 4.53[1.93, 10.62]). Significantly more patients from nipocalimab vs placebo (36.4% vs 10.5%; p<0.001) group spent >75% of study duration with QMG-3 improvement.

SUMMARY/CONCLUSION: Nipocalimab, a novel FcRn blocker, demonstrated disease control in patients with gMG, as evidenced by significant improvements in QMG scores.

DISCLOSURES: Richard Nowak: Research support: National Institutes of Health, Genentech, Inc., Alexion Pharmaceuticals, Inc., argenx, Annexon Biosciences, Inc., Ra Pharmaceuticals, Inc.

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Maria Ait-Tihyaty, Ibrahim Turkoz, Kavita Gandhi, and Sindhu Ramchandren: are/were employees, contractors or consultants for Janssen Pharmaceuticals and may hold stock or stock options in Johnson & Johnson.

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ECONOMIC BURDEN OF MYASTHENIA GRAVIS EXACERBATION AND CRISIS FROM US PAYER PERSPECTIVE

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INTRODUCTION: Myasthenia gravis (MG) is a rare autoimmune neuromuscular disease characterized by muscle weakness and fatigability. Little is known about the changes in healthcare costs before and after MG diagnosis, as well as the impact of clinical deterioration events on the healthcare costs among MG patients.

OBJECTIVE: To evaluate the impact of MG diagnosis, exacerbation, and crisis on healthcare costs.

METHODS: Adults who had >=1 inpatient or >=2 outpatient claims (>=30 days apart) with MG diagnosis from 2017-2022, with >=1 diagnosis provided by neurologist, and >=12 months pre- and post-index (i.e., initial MG diagnosis) continuous enrollment were selected from the MarketScan® commercial and Medicare Supplemental databases. Patients with MG diagnosis during 12 months pre-index were excluded. MG exacerbation was defined as having a medical claim associated with MG acute exacerbation, the use of immunoglobulin or plasma exchange or MG-related hospitalization. MG crisis was defined as MG-related hospitalization associated with respiratory failure and endotracheal intubation/ventilation. Monthly all-cause healthcare costs before and after MG diagnosis were analyzed using restricted maximum likelihood controlling for age, gender, Charlson comorbidity index and payer type.

RESULTS: A total of 891 newly diagnosed MG patients were identified [mean (±SD) age: 55.7 (±15.3) years; female: 52.7%; mean (±SD) Charlson comorbidity index: 1.2 (±1.6)]. All-cause costs increased by $1,163 per patient per month after MG diagnosis (P<0.0001) compared with pre-diagnosis. MG exacerbation and crisis further increased all-cause costs in the month that the event occurred by $13,283 and $81,840 per patient, respectively (both P<0.0001). On average, monthly all-cause costs continued to increase by $17 and $147 per patient for each additional month following MG exacerbation (P=0.011) and crisis (P<0.0001), respectively.

SUMMARY/CONCLUSION: MG exacerbation and crisis were costly clinical events. Effective treatment reducing the risk of crisis/exacerbation can mitigate the economic burden of MG to the healthcare system.

DISCLOSURES: Authors Daniel Labson, Qian Cai, Kavita Gandhi, Maria Ait-Tihyaty, Andreas Nikolaou, and Winghan Jacqueline Kwong are/were employees of Janssen; may hold stock or stock options in Johnson & Johnson.

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LONG-TERM USE OF ORAL CORTICOSTEROIDS AND OVERALL SURVIVAL AMONG PATIENTS WITH MYASTHENIA GRAVIS: A NATIONWIDE POPULATION-BASED STUDY

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INTRODUCTION: Myasthenia gravis (MG) is a rare autoimmune neuromuscular disease characterized by muscle weakness and fatigability. Oral corticosteroids (OCS) are widely used to treat MG; however, the impact of long-term OCS use on overall survival (OS) in patients with MG is unclear.

OBJECTIVE: To assess the association between long-term OCS exposure and OS among patients with MG.

METHODS: Data for adult patients with >=1 primary diagnosis of MG (ICD-10-SE G70.0) provided by neurologist from 01-Jan-2006 to 30-Dec-2020 were extracted from four linkable, longitudinal, nationwide population-based Swedish registries. Patients having >=1 OCS prescription on or after the MG diagnosis and >=12-month follow-up period were included. Long-term OCS use was defined as continuous OCS use for >=3 consecutive months and without gaps of >60 days between prescriptions or end of data availability during the 12 months after MG diagnosis (landmark period); patients not meeting these criteria were defined as short-term users. OS was assessed from the end of landmark period to end of follow-up. OS rates were adjusted for age, gender and other differences in Cox-regression models.

RESULTS: A total of 1,942 patients were included; 272 (22%) were long-term OCS users (mean [SD] age: 65.2 [17.1] years; female, 48.5%); 964 (78%) were short-term OCS users (age, 63.4 [17.0] years; female, 47.4%]). Median OS in long-term OCS users was 10.9 years versus 13.5 years among short-term users (log-rank test: P<0.01). After covariate adjustment, long-term OCS users had a significantly higher risk (42%) of death versus short-term users (adjusted HR: 1.42; 95% CI: 1.10–1.83).

SUMMARY/CONCLUSION: Long-term OCS use was associated with lower OS among patients with MG in Sweden highlighting potential limitations of OCS use and unmet need for safe and effective treatments in this population.

DISCLOSURES: Authors Qian Cai, Kavita Gandhi, Maria Ait-Tihyaty, and Winghan Jacqueline Kwong are/were employees of Janssen; may hold stock or stock options in Johnson & Johnson. Authors Nurgul Batyrbekova and Gabriel Isheden are employees of SDS Life Science- a Cytel company, Uppsala, Sweden.

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SAFETY PROFILE OF NIPOCALIMAB, A NEW NEONATAL FRAGMENT CRYSTALLIZABLE RECEPTOR BLOCKER IN THE PHASE 3 VIVACITY STUDY

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INTRODUCTION: Nipocalimab demonstrated efficacy and a tolerable safety profile in the phase 2 VIVACITY-MG study; it was further evaluated in phase 3 VIVACITY, a randomized, double-blind (DB), placebo-controlled study (NCT04951622).

OBJECTIVE: To report the safety profile of nipocalimab, a novel neonatal fragment crystallizable receptor (FcRn) blocker, from the phase 3 VIVACITY study.

METHODS: Adult patients with generalized myasthenia gravis (gMG) were randomized (1:1) to receive either nipocalimab (30 mg/kg for first infusion, 15 mg/kg, thereafter) or placebo once every 2 weeks in addition to standard-of-care therapy for 24 weeks. The safety analysis set included all patients receiving >=1 dose (partial or complete) of any study treatment. Adverse events (AEs), treatment-emergent AEs (TEAEs) and serious AEs (SAEs) were summarized.

RESULTS: A total of 198 patients were included in safety analysis set (nipocalimab: 98 and placebo: 98, median follow-up: 24 weeks). Overall, 11 (11.2%) nipocalimab-treated patients and 16 (16.3%) placebo-treated patients discontinued study treatment; the most common reason being AEs (7 [7.1%], placebo-treated; 4 [4.1%], nipocalimab-treated). The proportion of patients experiencing >=1 TEAEs in DB phase was similar between the nipocalimab-treated (81.6%) and placebo-treated (82.7%) treatment groups except for urinary tract infection (5.1% vs 0), dizziness (5.1% vs 1.0%), diarrhea (7.1% vs 3.1%), nausea (5.1% vs 2.0%), muscle spasms (12.2% vs 3.1%), peripheral edema (10.2% vs 0), pyrexia (7.1% vs 1.0%), cough (7.1% vs 3.1%), and insomnia (5.1% vs 2.0%), which were higher (>5% and >2X as frequently as placebo) in the nipocalimab group versus placebo group. Arthralgia was reported more frequently in the placebo group (2.0% vs 5.1%). Most TEAEs were mild-to-moderate in severity. In DB phase, 9.2% of nipocalimab-treated patients and 14.3% of placebo-treated patients experienced >=1 SAE.

SUMMARY/CONCLUSION: Nipocalimab was generally well-tolerated in adult patients with gMG, with no new safety concerns identified.

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COMPLEMENT INHIBITION IN SEVERE MYASTHENIC CRISIS – A RETROSPECTIVE MULTICENTER ANALYSIS OF 17 CASES IN GERMANY

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INTRODUCTION: Generalized myasthenia gravis (gMG) can lead to life-threatening myasthenic crises requiring mechanical ventilation. Therapy for myasthenic crises includes intravenous immunoglobulins (IVIg), plasmapheresis and high-dose corticosteroids.

OBJECTIVE: To determine the potential beneficial effects of complement inhibitors for the treatment of therapy-resistant myasthenic crises.

METHODS: This is a retrospective, non-interventional, multicenter analysis of cases in Germany between 2017 and 2024. Inclusion criteria were a myasthenic crisis or a severe exacerbation involving bulbar symptoms (MGFA IVb/V) in patients with AChR-antibody positive gMG who started eculizumab or ravulizumab in the intensive (ICU) or intermediate care unit (IMC). The primary outcome was the proportion of patients leaving ICU/IMC within six

weeks after initiation of complement inhibitor therapy (German Clinical Trials Registry; DRKS00032104).

RESULTS: We identified 17 cases across six centers: 12 had received eculizumab and five ravulizumab. Seven (41%) were females, median age was 77 years (range 23-88 years). Median time from diagnosis to index crisis was 0.6 years. A total of seven (41%) had undergone thymectomy; of those six (35%) had been diagnosed with thymoma. One further thymoma was diagnosed with biopsy only.

The most frequent cause of crisis were infections. Non-invasive ventilation was sufficient for five patients, while 12 necessitated invasive ventilation with nine receiving tracheotomy. During the crisis, all patients received prednisolone (range 15-1000mg); 12 received intravenous pyridostigmine. IVIg were applied in six cases, plasmapheresis in two cases and both IVIg and plasmapheresis/immunoadsorption in nine cases. In two cases, rituximab was started during the crisis. The primary outcome was reached for 14 (82%) patients. There was no case of meningococcal infection. Two patients died following bacterial sepsis.

CONCLUSION: In severe therapy-refractory myasthenic crisis where standard treatment including IVIg and plasmapheresis is not sufficient, add-on complement inhibition with C5-inhibitors may be an effective strategy.

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TREATMENTS FOR GENERALIZED MYASTHENIA GRAVIS: RAPID IMPROVEMENT IN TWO ACHR-AB POSITIVE PATIENTS TREATED WITH SUBCUTANEOUS ZILUCOPLAN IN A REAL-WORLD SETTING.

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INTRODUCTION: Zilucoplan is a subcutaneous, self-administered macrocyclic peptide that inhibits complement C5, a new treatment option for generalized myasthenia gravis (gMG).

OBJECTIVE: We report two gMG AChR-Ab positive patients with severe symptoms who experienced a rapid improvement of their bulbar dysfuntion with Zilucoplan.

METHODS: two female patients received Zilucoplan during their hospitalization according to Early Access Program (EAP). Zilucoplan was administered as add-on to ongoing treatment with anticholinesterase inhibitors, immunosuppressive agents and corticosteroids. Clinical outcomes were evaluated by means of the MG Activities of Daily Living (MG-ADL), Quantitative Myasthenia Gravis (QMG) and MG Quality of Life-15 (MGQoL-15) scores. Both patients were classified as MGFA Class IVB, with poor response to prior immunomodulatory therapies.

RESULTS: A clinically meaningful improvement was recorded by all rating scales from the first week after Zilucoplan introduction, with further improvement during the subsequent follow-up. For patient 1, baseline scores were: MG-ADL 6/24, QMG 19/39, and MGQoL-15 22/30. After one week of treatment, the MG-ADL decreased by 3 points, the QMG by 4 points and the MGQoL-15 by 2 points. For patient 2, baseline scores were MG-ADL 11/24, QMG 18/39, and MGQoL-15 19/30. The MG-ADL decreased by 2 points after one week, the QMG of 4 points and the MGQoL-15 decreased from 19 points to 5. Both patients were classified as MGFA Class IIB at discharge from hospital two weeks from Zilucoplan introduction. No major side effects were observed during follow-up, and both patients started tapering corticosteroid therapy.

SUMMARY/CONCLUSION: Zilucoplan provided rapid improvement of bulbar symptoms of our gMG patients, allowing for their earlier discharge from hospital. The observed improvement was sustained over time and further increased during the follow-up. Zilucoplan can be considered as a valid self-administered treatment option for gMG patients with bulbar dysfunction

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UNDERSTANDING NEUROLOGISTS' PREFERENCES FOR TREATMENT ATTRIBUTES IN MANAGING GENERALIZED MYASTHENIA GRAVIS

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INTRODUCTION: Generalized myasthenia gravis (gMG) treatment landscape has changed in recent years with the approval of different therapies. However, there is limited understanding of neurologists' preferences when selecting a therapy for this debilitating condition.

OBJECTIVE: This study aimed to assess neurologists' preferences for hypothetical gMG treatments.

METHODS: An online, cross-sectional study was conducted in collaboration with the Spanish Society of Neurology in April-July, 2024. Neurologists completed a survey that included demographic information, professional background, behavioral traits, and preferences for hypothetical treatments. A comprehensive literature review was performed to select the most important gMG treatment attributes: improvement in MG-ADL scale, onset of action, effect duration, adverse events, and route/frequency of administration. Participants were presented with 8 hypothetical treatment scenarios created through orthogonal design to rank them based on their preferences from the most to the least preferred. A conjoint analysis was then applied to assess attributes preferences.

RESULTS: A total of 149 neurologists were included (mean age [SD]: 39.0±9.4 years, 54.4% male, median experience managing gMG [IQR]: 7 [3-15] years; 32.2% fully dedicated to gMG). Median gMG patients attended per month was 10 (IQR: 5-20). A proportion of 34.9% participants reported using minimum symptom expression to guide treatment decisions.

Neurologists placed the greatest importance on intensity of improvement (38.6%), followed by onset of action (21.5%) and effect duration (17.4%). In contrast, route and frequency of administration was the least important (8.1%). Importance percentages varied according to sex, having a gMG specific consultation, degree of empathy, and personality traits

(conscientiousness). However, intensity of improvement remained the most preferred attribute in all cases.

SUMMARY/CONCLUSION: Neurologists showed a preference towards treatments that are effective, fast, and long-acting when improving gMG symptoms. These findings provide valuable insights into the complex decision-making process that neurologists face when prescribing gMG treatments and may help scientific societies when designing clinical management guidelines.

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IMPORTANCE OF BODILY FUNCTIONS IN GENERALIZED MYASTHENIA GRAVIS FROM NEUROLOGISTS' PERSPECTIVE

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INTRODUCTION: Generalized myasthenia gravis (gMG) can lead to multiple impairments due to weakness in several functional systems. Some might be under-recognized by physicians and of high value for patients.

OBJECTIVE: This study aimed to assess the importance given by neurologists to the bodily functions of gMG patients.

METHODS: An online, cross-sectional study was conducted in collaboration with the Spanish Society of Neurology in April-July, 2024. Neurologists completed a survey that included demographic information, professional background, and behavioral traits. Importance was assessed through the Values of Bodily Functions Questionnaire (VABOF) adapted to gMG, covering 15 functions. A bivariate and a stepwise multivariate linear regression analyses were used to determine the association between neurologists' characteristics and given importance.

RESULTS: A total of 149 neurologists were included (mean age [SD]: 39.0±9.4 years, 54.4% male, median experience managing gMG [IQR]: 7 [3-15] years; 32.2% fully dedicated to gMG). Median gMG patients attended per month was 10 (IQR: 5-20).

Neurologists placed the greatest importance on Respiratory involvement [mean (SD): 2.1 (3.3)], followed by Dysphagia [2.9 (2.8)], and Difficulty chewing [5.5 (2.9)]. The least prioritized functions were Impact on sleep [11.9 (2.9)], and Impact on sexuality [12.5 (2.9)].

Importance of functions varied according to age, sex, number of patients treated, number of neurologists in the unit, type of hospital, clinical trial participation, last congresses attendance, tools used for decision-making, mechanism of action preference, resistance to change behavior, attitude against work, burnout, personality traits and empathy, although general ranking positions were similar. Participation in gMG clinical trials and giving importance to mechanism of action

were predictors of placing Respiratory involvement as a prioritized function ($p<0.05$). Being male was a predictor of giving higher importance to Impact on sexuality ($p<0.01$).

SUMMARY/CONCLUSION: These results highlight the importance given by neurologists to bulbar symptoms and may help when reaching an agreement towards a patient-centred care.

DISCLOSURES: Author Adrián Ares has received speaking honoraria, consultation services compensation, or travel support for congress and scientific meetings attendance from Almirall, Bayer, Biogen, BMS, Janssen, Merck, Novartis, Roche, Sanofi, and Teva. Authors Rocío Gómez-Ballesteros, Elisa Salas, Paola Díaz-Abós, and Jorge Maurino are employees of Roche Pharma Spain. Author Luis Querol received speaker honoraria from Merck, Sanofi, Roche, Biogen, Grifols and CSL Behring; provided expert testimony for Grifols, Johnson & Johnson, Annexon Pharmaceuticals, Sanofi, Novartis, Takeda, and CSL-Behring; and received research funds from Roche, UCB, and Grifols. Author Gerardo Gutiérrez-Gutiérrez has received compensation for consulting services from CSL Behring, Biogen, Alter, Takeda, Akcea, Lupin Neuroscience, Roche, Alexion, and Argenx; congresses support from Alter, Esteve, Sanofi-Genzyme, Pfizer, and UCB Pharma; has scientific relation with Lilly, Alexion, Genzyme, Takeda, Biogen, Pfizer, and Alter; books with Exeltis, Alter, Esteve, Andrómaco, and Bristol-Myers; and has received grants and awards from Lilly, UCB Pharma, and CSL Behring. Author Javier Sotoca has received travel/congress support and compensation for consulting services from Roche, Biogen, UCB, and Argenx. Author Elena Cortés-Vicente has received speaking and advisory boards honoraria from UCB Pharma, Alexion, Argenx, and J&J.

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ASSESSING GLUCOCORTICOID ASSOCIATED TOXICITY IN MYASTHENIA GRAVIS USING THE GLUCOCORTICOID TOXICITY INDEX

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INTRODUCTION: Glucocorticoids (GC) are mainstay therapy for treatment of Myasthenia Gravis (MG), but quantitative data measuring GC-associated toxicity is lacking.

OBJECTIVE**:** This study aims to quantify GC-related toxicity in MG patients using Glucocorticoid toxicity index (GTI), an assessment tool designed to measure and quantify GC related toxicity.

METHODS: This is a monocentric, prospective, observational, non-interventional study. Enrolled patients were assessed during 3 visits over a year, with measurement of GTI, medication dosage, measures of disease severity, and adverse event unit (AEU). The GTI aggregate improvement score (GTI-AIS) measures change in GC toxicity between two time points, while the cumulative worsening score (GTI-CWS) measures cumulative GC toxicity.

RESULTS: At the time of analysis, enrollment goal of 50 patients was reached and full GTI data for visits 1 (V1) and 2 (V2) was available for 25 patients for analysis. At V1, patients received a mean daily dose of Prednisone 19.6 mg (SD 10.2 mg). Between V1 and V2, there was a mean reduction in daily prednisone dosage of -6.9 mg/day (SD 7.0; range -25 to 0). No linear correlation was noted between (1) daily Prednisone dosage at V2 and the GTI-AIS (p-value 0.34) or GTI-CWS (p-value 0.18), (2) change in daily Prednisone dosage and the GTI-AIS (p-value 0.46) or the GTI-CWS (p-value 0.33), or (3) GTI scores and cumulative Prednisone dosage since 12 months before enrollment, age, or AEU. A moderate positive linear relationship was seen between the GTI-CWS and MGADL (Pearson r 0.58; p-value 0.002) and GTI-CWS and MGQOL (Pearson r 0.55; p-value 0.004).

CONCLUSION: At the time of preliminary analysis, GTI scores did not correlate with daily or cumulative Prednisone dosage, but it did correlate with measures of disease activity. The degree of glucocorticoid toxicity may depend on other factors than the steroid dosage, and future analysis of the full dataset will bring additional information.

DISCLOSURES: Author Neelam Goyal has been an advisor and consultants for Alexion, Argenx, UCB/Ra Pharma, Janssen, Amgen, EMD Sereno, Novartis and has grant funding from Argenx. Author Srikanth Muppidi has attended advisory board meetings for Alexion, argenx, UCB/Ra, and Amgen Pharma

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REAL-WORLD REDUCTION IN ORAL CORTICOSTEROID UTILIZATION AT 1-YEAR FOLLOWING EFGARTIGIMOD INITIATION

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INTRODUCTION: Oral corticosteroids (OCS) are a mainstay therapy in the management of many autoimmune conditions, including generalized myasthenia gravis (gMG), but are known to be associated with dose- and duration-dependent toxicities. There is clinical interest in investigating whether novel gMG treatments, such as efgartigimod (EFG), can be used as steroid-sparing agents.

OBJECTIVE: To evaluate OCS usage at 1-year following EFG initiation.

METHODS: Patients with gMG using OCS pre-EFG initiation were identified from a United States medical and pharmacy claims database (based on information licensed from IQVIA: Longitudinal Access and Adjudication Data [LAAD] for the period April 2016−December 2023, reflecting estimates of real-world activity [all rights reserved]). Mean (SD) average daily dose (ADD) of OCS was evaluated during the 3-months prior to, and at 6- and 12-months post-EFG initiation. To assess outcomes, de-identified Myasthenia Gravis Activities of Daily Living (MG-ADL) data collected in the "My VYVGART Path" patient support program was tokenized and integrated into the primary dataset.

RESULTS: A total of 169 adults (aged ≥18 years) who were using chronic OCS pre-EFG initiation, initiated EFG by December 31, 2022, and continued EFG for at least 12 months were included in the analysis. At 6- and 12-months post-EFG, respectively, 31 (18%) and 45 (27%) patients had no OCS usage. Overall mean (SD) OCS ADD was significantly reduced at 6-months (13.2 [13.9] mg/day, $P<0.001$), and at 12-months (10.2 [12.1] mg/day, $P<0.001$) post-EFG initiation compared with baseline (17.2 [13.7] mg/day). Among a subset of 72 patients (43%) who had both pre- and post-EFG MG-ADL scores available, best-follow up mean (SD) MG-ADL was significantly reduced (from 8.3 [3.7] to 3.4 [2.8], $P<0.001$).

SUMMARY/CONCLUSION: The significant reduction of OCS usage observed at 6-months post-EFG initiation was retained at 12-months, while demonstrating MG-ADL response expected from EFG treatment.

DISCLOSURES: Author Neelam Goyal discloses she has participated in advisory and consulting engagements with Alexion, argenx, UCB/Ra Pharma, Janssen, Amgen, EMD Sereno, Novartis and received grant funding from argenx. Authors Cynthia Qi, Deborah Gelinas, Edward Brauer, Matthew Jefferson, and Glenn Phillips are employees of argenx. Author John Stone discloses he has consulted for argenx on glucocorticoid toxicity. Author Tobias Ruck discloses he has received honoraria for speaking and advice as well as travel support from argenx, Alexion, Celgene/BMS, Biogen, Johnson&Johnson, UCB, Roche, Sanofi Genzyme, Merck, Novartis, and Teva and received research funding from Alexion, argenx, Biogen, Novartis, Merck, Roche, Sanofi Genzyme, and SERB Pharmaceuticals. Authors Tharun Balaji Suthagar, Rohit R Menon, and Mai Sato are employees of ZS Associates (Evanston, IL, USA) and serve as paid consultants for argenx.

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EXPLORING THE CORRELATIONS BETWEEN FATIGUE, DEPRESSION, SLEEP DISORDERS AND CLINICAL SEVERITY IN MG PATIENTS

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INTRODUCTION: According to recent evidence, MG has a wide spectrum of manifestations not only limited to the neuromuscular junction. Fatigue, the subjective sensation of exhaustion, differs from the fatigability determined by MG, but is frequently complaint by patients. Sleep disorders and depression are also reported, though their correlation with clinical manifestations still needs to be clarified.

OBJECTIVE: Aim of this study was to explore the possible correlations between fatigue, depression, sleep disorders and clinical severity in a cohort of MG patients

METHODS: Twenty-seven consecutive, unselected MG patients (18 females and 9 males), referring to our Unit, underwent administration of scales for the assessment of MG symptoms (QMG, MG-ADL, MGC), quality of life (MGQol15), fatigue (Fatigue Severity Scale, FSS, and Multidimensional Fatigue Severity index short form, MFSI-SF), sleep disorders (Pittsburgh Sleep Quality Index, PSQI) and depression (Beck Depression Inventory-II, BDI-II). Demographic and clinical data were collected, and patients were stratified according to presence or absence of fatigue, depression and sleep disorders, according to FSS, BDI-II and PSQI total scores. Chi-square test and Student's t test, for qualitative and quantitative variables respectively, and correlation analysis were performed.

RESULTS: Positive correlation emerged between clinical scores and fatigue, with particular significance for general and physical sub-scores according to MFSI-SF. Depression showed positive correlation with MG-ADL and MGQoL15, and correlation with general, emotional and mental fatigue sub-scores. Direct correlation was also found between clinical severity and sleep disorders. No relation emerged between fatigue, sleep disorders, depression and corticosteroid therapy.

SUMMARY/CONCLUSION: These results show a strict relation between fatigue and both MG physical and non-physical manifestations. Depression is mainly associated with patients' symptoms perception, due to its correlation with patients' reported outcomes; on the other hand, sleep disorders seem to have a more specific association with clinical severity, though their actual causality relation needs further investigation.

DISCLOSURES: Author Roberto Massa discloses he has been a consultant for Akcea Therapeutics, UCB, Alexion, Merck and Spark Therapeutics and currently receives clinical trial support from Novartis Pharma, Akcea Therapeutics and Lupin. Author Giulia Greco has taken part to events sponsored by Alexion, UCB, Argenx and Novartis as both speaker and attendant.

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THE SAFETY AND EFFICACY OF CHRONIC WEEKLY ROZANOLIXIZUMAB TREATMENT IN PATIENTS WITH GENERALISED MYASTHENIA GRAVIS (MG0004)

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INTRODUCTION: In the Phase 3 MycarinG study (MG0003/NCT03971422), six once-weekly subcutaneous infusions of rozanolixizumab 7mg/kg or 10mg/kg significantly improved MG-specific outcomes versus placebo. After MycarinG, patients could enrol in open-label extension MG0004 (NCT04124965).

OBJECTIVE: To evaluate the safety, tolerability and efficacy of chronic, weekly rozanolixizumab in patients with gMG.

METHODS: In MG0004, patients were randomised (1:1) to once-weekly subcutaneous rozanolixizumab 7 mg/kg or 10 mg/kg for 52 weeks, followed by an 8-week observation period. Patients could switch dose at the investigators' discretion. After ≥6 visits, patients could roll over into MG0007 (NCT04650854), which replaced MG0004. Analyses are presented by first dose received unless specified otherwise. Efficacy data are presented to Week 33.

RESULTS: In MG0004, 70 patients received rozanolixizumab 7 mg/kg (n=35) or 10 mg/kg (n=35). Mean duration of rozanolixizumab was 22.9 (7mg/kg) and 23.7 (10mg/kg) weeks.

Patient numbers after Week 33 (17/70 [24.3%]) were low, primarily due to rollover into MG0007. Eight (11.3%) patients completed 52 weeks in MG0004. Treatment-emergent adverse events by most recent dose were reported in 76.0% (38/50; 7mg/kg) and 78.6% (33/42; 10mg/kg) of patients; most mild or moderate. Headache occurred in 30.0% (15/50; 7mg/kg) and 28.6% (12/42; 10mg/kg) of patients and infections in 26.0% (13/50; 7mg/kg) and 21.4% (9/42; 10mg/kg) of patients. Clinically relevant improvements in MG-ADL score were observed; mean reduction from baseline between Weeks 7–33 ranged from −2.7 to −3.1 (7mg/kg) and −3.4 to −4.1 points (10mg/kg). Mean QMG score improvements ranged from −2.6 to −5.4 (7mg/kg) and −4.2 to −6.2 points (10mg/kg). Mean maximum reduction from baseline in total serum immunoglobulin G was 74.7% (7mg/kg) and 78.4% (10mg/kg). No clinically relevant reductions in albumin were observed.

SUMMARY/CONCLUSION: Chronic, weekly rozanolixizumab was well tolerated, with a safety profile similar to repeated cycles of rozanolixizumab treatment. Clinically relevant mean improvements were maintained across MG-specific outcomes.

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EVALUATION OF THE INDIRECT AND NONMEDICAL IMPACTS OF GMG ON PATIENTS AND CAREGIVERS

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INTRODUCTION: gMG is a rare, chronic autoimmune disorder. Indirect gMG-associated economic impacts on patients and caregivers are not well studied.

OBJECTIVE: Assess indirect and nonmedical costs for US patients with gMG and caregivers.

METHODS: Data from independently recruited patients and caregivers were collected for 2022 via web-based survey (Aug-Dec 2023). Total indirect costs using survey data and nationally representative earnings data were stratified by age/sex/payer and weighted by gMG prevalence yielding weighted averages.

RESULTS: Respondents included 239 patients with gMG and 81 caregivers (63% and 58% aged 18-49 years, respectively; 69% and 42% female). Time since gMG diagnosis/caring began was <10 years for most (83%/91%). Most patients (61%) had commercial insurance. Many caregivers were parents (26%) or spouses/partners (37%). On average, patients received formal/paid (9 hours/week) and informal (75 hours/week) care. The primary nonmedical gMG-related patient cost was equipment ($1201/year). The primary out-of-pocket caregiver cost was non-gMG household member care ($3103/year). Lost social productivity was 46% of patient productivity costs ($11,949/year). Caregiver productivity costs were lost earnings from early retirement (30%; $6414/year), absenteeism (26%; $5544/year), lost social productivity (26%; $5532/year), and reduced work productivity (18%; $3973/year). Indirect costs for patients ($33,388/year [weighted]) were driven by lost productivity and for caregivers ($92,101/year) by informal caregiving. Indirect patient costs increased with Myasthenia Gravis Activities of Daily Living score (0-6 [n=68], $30,698/year; 7-12 [n=115], $51,300/year; 13-18 [n=51], $71,534/year; 19-24 [n=5], $93,253/year).

SUMMARY/CONCLUSION: Patients with gMG and caregivers report high annual indirect and nonmedical costs. Along with excess direct medical costs, these indirect and nonmedical costs contribute substantially to the total economic impact of gMG.

DISCLOSURES: Author Kelly G. Gwathmey has received honoraria from AcademicCME, Alexion, AstraZeneca Rare Disease, Amgen, argenx, and UCB. Author Pushpa Narayanaswami has received research support from Alexion/AstraZeneca Rare Disease and Momenta/Janssen; served on advisory boards and/or consulted for Alexion/AstraZeneca Rare Disease, Amgen, argenx, CVS, Dianthus, GSK, ImmuneAbs, Janssen, Novartis, and UCB; serves as Data Monitoring Committee Chair for argenx and Sanofi; and receives royalties from Springer Nature. Author Allison Foss is an employee of the Myasthenia Gravis Association, a member of the argenx Leadership Council, Rare Disease Connect in Neurology Steering Committee for UCB and has received consulting honoraria. Author Christina Ramirez is cofounder and board treasurer for Own MG. Author Jamie Sullivan is an employee of EveryLife Foundation, which receives funding from the research sponsor for work unrelated to this research. Author Susan dosReis received grant funding from GSK, the National Institute of Mental Health (NIMH), the Patient Centered Outcomes Research Institute (PCORI), and the Pharmaceutical Research Manufacturers of America (PhRMA) Foundation. Author Taylor T. Schwartz is an employee of Avalere, which received funding to conduct this research and consults with life sciences organizations. Author Nicole Betor is an employee of Avalere, which received funding to conduct this research and consults with life sciences organizations. Author Olivia Hunt is an employee of Avalere, which received funding to conduct this research and consults with life sciences organizations. Author Karen S. Yee is an employee of Alexion, AstraZeneca Rare Disease, and holds stock or stock options in AstraZeneca and Takeda. Author Mayvis Rebeira is an employee of Alexion, AstraZeneca Rare Disease, and holds stock or stock options in AstraZeneca.

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HUMAN FACTORS VALIDATION STUDY OF GEFURULIMAB PREFILLED SYRINGE AND AUTOINJECTOR DEVICES

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INTRODUCTION: Gefurulimab, a new investigational complement inhibitor, is in clinical development for treatment of AChR antibody-positive gMG. Gefurulimab was developed with low molecular weight, making it suitable for subcutaneous self-administration by prefilled syringe (PFS) or autoinjector (AI). Human factors (HF) studies ensure user interfaces (eg, devices, instructions for use [IFU], packaging) can be used safely and effectively and are conducted with end users (patients, caregivers, healthcare providers [HCPs]) to incorporate user feedback into product development.

OBJECTIVE: To describe the design of a US-based HF validation study of gefurulimab PFS and AI and to highlight these interfaces were optimized with end-user input.

METHODS: Study participants included 30 patients with gMG, 30 caregivers to patients with gMG, and 15 injection-experienced HCPs in relevant specialties. Patients and caregivers were untrained prior to injection simulation and randomly assigned to a device type (PFS or AI with mock solution) and dosage (1 or 2 injections). HCPs were assigned to the AI cohort. In a simulated use scenario, participants performed use tasks to simulate preparation, administration, and disposal. Participants were then asked knowledge-based questions about product label and IFU (eg, number of times a device can be used, storage information, and dosing procedures) to confirm understanding of usage. After the simulated use scenario and the knowledge task, a moderator probed participants about their experience and asked about difficult/incorrect actions to determine if modifications to the user interface could mitigate misuse.

RESULTS: This trial has enrolled the target end-user population across 8 states.

SUMMARY/CONCLUSION: HF studies facilitate the administration process for end users by optimizing the user interface. This HF validation study was designed to confirm if the gefurulimab PFS and AI user interfaces can be used safely and effectively.

DISCLOSURES: Author Kelly G. Gwathmey has received honoraria from AcademicCME, Alexion, AstraZeneca Rare Disease, Amgen, argenx, and UCB. Author Joe Koo is an employee of Alexion, AstraZeneca Rare Disease, and holds stock or stock options in AstraZeneca. Author Scott Laorr is an employee of Insight by Nemera and was compensated for conduct of the study by Alexion, AstraZeneca Rare Disease. Author Panru Jing is an employee of Insight by Nemera and was compensated for conduct of the study by Alexion, AstraZeneca Rare Disease. Author

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THE MYASTHENIA GRAVIS REGISTRY:CHARACTERISTICS, INSIGHTS, AND LEARNINGS AFTER A DECADE (2013-2023)

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INTRODUCTION: The Myasthenia Gravis Foundation of America (MGFA) Patient Registry was initiated with the purpose of assessing disease progression, management, clinical trial recruitment, and to provide an educational platform. The registry is funded by the MGFA and previously the Coordinating Center located at the University of Alabama at Birmingham. In 2022, the next iteration of the registry, the MGFA Global MG Patient Registry (MGFAPR), was developed in partnership with Alira Health.

OBJECTIVE: To report the baseline demographics and disease characteristics of the MGFAPR, including insights/learnings from a patient-reported registry.

METHODS: The MGFAPR is an online longitudinal registry with information collected at enrollment and then at 6-month intervals. Subjects are ³18 years at enrollment, with self-reported MG. Descriptive analyses were conducted on key clinical features/variables. Enrolled subjects are contacted biannually to provide updates.

RESULTS: 3556 subjects (95% Non-Hispanic; 87% White; 61% female) were enrolled from July 2013 through June 2023. The mean age at enrollment was 55.8 years and at diagnosis was 49.4 years. Of the 1814 reporting serostatus: 62.8% AChR antibody-positive, 5.2% MuSK antibody-positive, 0.4% LRP4 antibody-positive, and 31.6% seronegative. Enrollment and follow-up remain ongoing.

SUMMARY/CONCLUSION: The MGFAPR represents the largest existing MG-specific registry which has captured data on over thirty-five hundred individuals. The advantages of this registry include the volume of the data collected, the completeness of the dataset, and the unique perspective into the MG disease impact with patient-reported outcomes and healthcare resource utilization. While there are clear limitations, unique insights and learnings over the past decade support its ongoing utility and value.

DISCLOSURES: Author Kelly Gwathmey discloses consulting for Alexion, argenx, UCB, Amgen and speaking for Alexion and argenx. Authors Oshin Sangha, Minjee Park, & Renee Willmon are or were employees at Alira Health. Author Richard J. Nowak discloses research support from NIH, Alexion (Astra Zeneca), argenx, Ra Pharmaceuticals (now UCB), MGFA, Momenta (now Janssen), Immunovant, Grifols, and Viela Bio (Horizon Therapeutics, now Amgen); consultant/advisor for Alexion (Astra Zeneca), argenx, Cabaletta Bio, Ra

Pharmaceuticals (now UCB Pharma), Immunovant, Momenta (now Janssen), Viela Bio (Horizon Therapeutics, now Amgen). The remaining author has no conflict of interest.

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RESET-MG: A PHASE 1/2, OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND EFFICACY OF AUTOLOGOUS CD19-SPECIFIC CHIMERIC ANTIGEN RECEPTOR T CELLS (CABA 201) IN PARTICIPANTS WITH GENERALIZED MYASTHENIA GRAVIS

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MG is a classic example of a B-cell-mediated autoimmune disease, with the majority of patients having autoantibodies directed to molecular elements of the neuromuscular junction. Available therapeutic options for MG often require chronic administration and/or intermittent dosing, have a modest effect, focus on specific symptoms, and may be associated with serious long-term side effects. There is a need for therapies that provide durable clinical responses without chronic immunosuppression, and Chimeric Antigen Receptor (CAR) T therapies have recently demonstrated this potential in autoimmune disease (AD). CABA-201 is a fully human, autologous 4-1BB anti-CD19-CAR T cell therapy being investigated in multiple ADs, designed to deeply and transiently deplete CD19 positive cells following a one-time infusion. This approach may cause an immune system reset with the potential for a drug-free, durable response. RESET-MGTM (NCT06359041) is a Phase 1/2 trial evaluating the safety and efficacy of CABA-201 in 2 independent MG cohorts of anti-AChR Antibody-Positive and anti-AChR-Antibody Negative participants. Eligible participants are =18 to =70 years with a generalized MG diagnosis, MGFA Clinical Classification II, III, or IV disease, and a total MG-ADL score of =6 despite prior or current treatment with at least 2 MG treatments. A single infusion of 1x106 CAR T cells/kg is administered following a preconditioning regimen (fludarabine 25 mg/m2/d on Days -5, -4 and -3, and cyclophosphamide 1,000 mg/m2 on Day -3). All non-corticosteroid immunosuppression is stopped before preconditioning. Participants require a minimum of 4 days inpatient monitoring post-CABA-201 infusion. The primary endpoint is safety and tolerability within 28 days of infusion, focusing on events such as cytokine release syndrome and neurotoxicity. Secondary endpoints include translational assessments (including CAR T cell pharmacokinetics and impact on peripheral B-cell populations) and efficacy outcomes (including changes in MG-ADL and QMG). RESET-MG clinical trial updates will be shared at the meeting.

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EFFICACY AND SAFETY OF ROZANOLIXIZUMAB TREATMENT CYCLES IN PATIENTS WITH GENERALISED MYASTHENIA GRAVIS: FINAL POOLED ANALYSIS OF PHASE 3 STUDIES

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INTRODUCTION: In the Phase 3 MycarinG study (MG0003/NCT03971422), one 6-week cycle of subcutaneous rozanolixizumab significantly improved MG-specific outcomes versus placebo. After MycarinG, patients could enrol in open-label extension studies (MG0004 then MG0007, or MG0007 directly) which are now complete.

OBJECTIVE: To assess the efficacy and safety of rozanolixizumab over multiple symptom-driven cycles in patients with generalised MG.

METHODS: In MG0004 (NCT04124965), patients received chronic, once-weekly rozanolixizumab 7 mg/kg or 10 mg/kg for ≤ 52 weeks. In MG0007 (NCT04650854), after an initial cycle of rozanolixizumab 7 mg/kg or 10 mg/kg, subsequent cycles were based on symptom worsening at the investigator's discretion. Pooled data are reported across MycarinG,

MG0004 (first 6 weeks) and MG0007 (final data) for patients receiving ≥2 symptom-driven cycles for efficacy outcomes (up to 13 cycles) or ≥1 cycle for safety.

RESULTS: Overall, 196 patients received ≥1 dose of rozanolixizumab, of whom 1 29 received ≥2 symptom-driven cycles of rozanolixizumab (7 mg/kg: n=7 0; 10 mg/kg: n=5 9). Treatment response was maintained from Cycles 1 to 13; mean change from baseline to Day 43 in MG-ADL score ranged from −3.2 (in Cycle 3) to −4.9 (in Cycle 12) with 7 mg/kg and −3.2 (in Cycle 3) to −6.7 (in Cycle 12) with 10 mg/kg. Similar improvements from baseline were observed for QMG and MGC scores. The incidence of treatment-emergent adverse events (TEAEs) did not increase with repeated cyclic treatment. The most common TEAE was headache, reported in 94/188 (50%) patients who received ≥1 symptom-driven cycle of rozanolixizumab, and most events were mild or moderate.

SUMMARY/CONCLUSION: Rozanolixizumab showed consistent improvements across multiple MG-specific outcomes up to 13 cycles and was generally well tolerated following repeated cyclic treatment.

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ROZANOLIXIZUMAB TREATMENT PATTERNS IN PATIENTS WITH GENERALISED MYASTHENIA GRAVIS: *POST HOC* ANALYSIS

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INTRODUCTION: In MycarinG (NCT03971422; Phase 3), adults with gMG received one 6-week rozanolixizumab treatment cycle. All patients who enrolled in the open-label extension, MG0007 (NCT04650854), received one further treatment cycle with subsequent need-based cycles initiated at the investigator's discretion. This led to variability in treatment-free intervals and number of cycles received per patient.

OBJECTIVE: To describe the range of rozanolixizumab treatment patterns and assess their associations with baseline patient characteristics.

METHODS: In MG0004 (NCT04124965), patients received chronic, once-weekly rozanolixizumab 7 mg/kg or 10 mg/kg for ≤ 52 weeks. In MG0007 (NCT04650854), after an initial cycle of rozanolixizumab 7 mg/kg or 10 mg/kg, subsequent cycles were based on symptom worsening at the investigator's discretion. Pooled data are reported across MycarinG, MG0004 (first 6 weeks) and MG0007 (final data) for patients receiving ≥2 symptom-driven cycles for efficacy outcomes (up to 13 cycles) or ≥1 cycle for safety.

RESULTS: The most balanced clustering and optimal goodness-of-fit was achieved using three clusters to describe number of cycles per year (low: <2.59; medium: 2.59–4.64; high: >4.64).

Mean (standard deviation) number of cycles per year in each cluster was 1.50 (0.53, n=74), 3.59 (0.60, n=64) and 5.82 (0.72, n=50), respectively. Overall, baseline characteristics were balanced between the clusters and did not predict in which cluster a patient would be. Rozanolixizumab was generally well tolerated across the three clusters.

SUMMARY/CONCLUSION: These three treatment clusters demonstrate that rozanolixizumab cycle cadence varies between patients, from 1–7 cycles per year. This suggests that each patient takes an individualised approach to rozanolixizumab treatment based on their own gMG experience, as the study included a broad, adult gMG population.

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DEVELOPMENT OF THE QUANTITATIVE MYASTHENIA GRAVIS-REVISED SCORE (QMG-R) TRAINING VIDEOS: IMPROVING CONSISTENCY THROUGH STANDARDIZED INSTRUCTIONS FOR CLINICAL TRIALS

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INTRODUCTION: Lack of standardization in the performance of clinical outcome measures is a potential source of variability in data collection and outcomes in clinical trials. The MGNet Clinical Trial Outcome Measure Working Group extensively reviewed key outcomes measures and published consensus recommendations for further standardizing and improving the administration of these measures. Several key changes to the instructions and performance were recommended for the Quantitative Myasthenia Gravis (QMG) score, warranting its designation as the Quantitative Myasthenia Gravis -Revised (QMG-R) score. The next step was to develop training materials for the QMG-R score.

OBJECTIVE: To demonstrate the newly developed video training materials for the QMG-R.

METHODS: Animated videos for each domain of the QMG-R were developed by a professional animation studio (Kindea Labs). Multiple rounds of review were done and revisions made to improve the quality and precision of the training videos. The latest version of the videos will be shared with the Working Group for further feedback and revisions. Thereafter, the final version will be made available for use in clinical trials.

RESULTS: The animated video approach offers several major advantages over traditional live-action videos. The animations can be readily modified without needing to re-record a completely new video. Voice-over instructions can also be easily translated into any language to facilitate training in learners' preferred languages; this, in turn, may help improve consistency in QMG-R administration across clinical trial sites globally. Videos can be conveniently split into modules, which can then be tailored individually. Sociocultural and linguistic diversity issues can also be more easily addressed with animated videos.

SUMMARY/CONCLUSION: The development of the QMG-R animated training videos will significantly aid in standardizing training for clinical trial administration. This should improve uniformity and consistency across trial sites globally and reduce variability between different clinical trials. Validation of the QMG-R is required.

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Pharmaceuticals, Canopy Immunotherapeutics, Curie.bio, Samsung, EcoR1, and EMD Serono. Argenx provides an unrestricted educational grant to George Washington University. He is an unpaid consultant for Care Constitution, holds equity interest in Mimivax, LLC, and serves as principal investigator for the Rare Disease Network, MGNet, supported by NIH grant U54NS115054. He is also a consultant for R43NS12432. MGNet Clinical Trial Outcome Measure Working Group is supported by NIH grant U54NS115054.

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FIXED CYCLE AND EVERY-OTHER-WEEK DOSING OF INTRAVENOUS EFGARTIGIMOD FOR GENERALIZED MYASTHENIA GRAVIS: PART B OF ADAPT NXT

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INTRODUCTION: Individualized fixed-cycle dosing of efgartigimod, a human immunoglobulin G1 (IgG1) Fc-fragment that blocks the neonatal Fc receptor, was well tolerated and efficacious in the ADAPT/ADAPT+ phase 3 trials in gMG.

OBJECTIVE: The phase 3b ADAPT NXT study (NCT04980495) investigated the efficacy, safety, and tolerability of efgartigimod administered either every other week (Q2W) or in fixed cycle (4 once-weekly infusions, 4 weeks between cycles) dosing regimens.

METHODS: Adult participants with anti-acetylcholine receptor antibody positive gMG were randomized 3:1 to Q2W or fixed cycle dosing of 10 mg/kg efgartigimod for a 21-week period in Part A. In Part B, participants in the fixed cycle arm received one additional cycle of 4 once-weekly infusions of efgartigimod before switching to a Q2W regimen. All participants had an option to switch to every-three-weeks (Q3W) dosing in Part B, depending on clinical assessment.

RESULTS: Sixty-nine participants were treated (fixed cycle, n=17; Q2W, n=52) in Part A. Least squares mean (95% CI) of the change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) total score from Week 1-21 (primary endpoint) was -5.1 (-6.5 to -3.8) in the fixed cycle arm and -4.6 (-5.4 to -3.8) in the Q2W arm; changes remained similar through Week 21. Achievement of minimal symptom expression (MG-ADL score 0-1) was observed in 47.1% (n=8/17) and 44.2% (n=23/52) of participants in the fixed cycle and Q2W arms, respectively. Efgartigimod was well tolerated; COVID-19, upper respiratory tract infection, and headache were the most common treatment-emergent adverse events. Sixty-five patients completed Part A and rolled over to Part B. Clinical data analysis for Part B will be presented at the congress.

SUMMARY/CONCLUSION: These interim results of ADAPT NXT build upon previous studies and provide additional efgartigimod dosing approaches (fixed cycle and Q2W) to maintain clinical efficacy in participants with gMG.

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PREVALENCE AND SEVERITY OF DYSPHAGIA IN PATIENTS WITH MYASTHENIA GRAVIS ASSESSED BY FLEXIBLE ENDOSCOPIC EVALUATION OF SWALLOWING (FEES)

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INTRODUCTION: Neurogenic dysphagia (ND) is a known symptom of myasthenia gravis (MG). However, data on the frequency and severity of ND, and its association with clinical parameters is poorly understood.

OBJECTIVE: The aim of our study was to investigate the prevalence and severity of FEES confirmed neurogenic dysphagia in MG patients with clinically suspected swallowing dysfunction. Furthermore, we tried to evaluate the association between dysphagic findings and disease-related parameters.

METHODS: The local database of all FEES examinations performed from 2010-2024 was screened for patients diagnosed with MG. Age, sex, Bogenhauser Dysphagia Score and antibody status were obtained from the medical file. Statistical tests were computed: Chi-squared and Fisher-Exact-Tests and Mann-Whitney-Tests for non-normally distributed data; Fisher's exact test for contingency tables.

RESULTS: We identified 206 patients (34% females) with confirmed MG who presented to our centre. So far, the analysis of 99 datasets has been completed. Dysphagia was present in 69 patients (64,5%). Forty-nine (49,5%) of the cases were AchR-antibody positive (AchR+), while 19 (19,2%) of the patients were positive for both AchR and titin antibodies (AchR+T+). Dysphagia was the leading symptom in 22,4% (n=11) of the AchR+ patients. Remarkably, dysphagia was even more often the leading symptom in AchR+T+ patients (57,9%, n=11, $p<0.05$). More AchR+T+ patients (68.4%) were ranked by the FEES examination as moderate and severe dysphagic, while only 26,5% of the AchR+ patients exhibited the same degree of dysphagia ($p=0.005$). While 38,8% of the AchR+ patients had no dysphagia, only 21,1% of the AchR+T+ patients exhibited no dysphagic symptoms. The two groups did not differ regarding age, sex and other epidemiologic variables ($p>0.05$).

SUMMARY/CONCLUSION: ND is a common symptom in patients with MG and seems to occur more than twice as often as the leading symptom in patients with both AChR- and titin antibody positivity when compared to AChR-positive patient group. In addition, the presence of moderate to severe ND appears to be associated with AChRand titin-positive MG.

DISCLOSURES: Author Yavor Yalachkov discloses he has received travel grants and speaking honoraria by Alexion.

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RESPONSE OF REFRACTORY RESIDUAL OCULAR SYMPTOMS TO EFGARTIGIMOD IN GENERALIZED MYASTHENIA GRAVIS: A REAL-WORLD CASE SERIES

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INTRODUCTION: Myasthenia gravis (MG) is a rare autoimmune disorder characterized by fluctuating skeletal muscle weakness, with ocular myasthenia gravis (OMG) presenting as isolated ocular symptoms in a subset of patients. Although various immunotherapies exist, including acetylcholinesterase inhibitors, corticosteroids, and nonsteroidal immunosuppressants, there is no consensus or evidence-based guideline for the management of OMG, especially for patients with persistent ocular symptoms. Efgartigimod (EFG), a novel FcRn antagonist, has demonstrated efficacy in generalized MG, but its effectiveness in treating pure OMG remains unknown. Here, we present a case series evaluating the clinical outcomes of EFG in MG patients with residual ocular symptoms.

OBJECTIVE: To evaluate the efficacy of EFG in treating residual ocular symptoms in MG patients with acetylcholine receptor antibodies (AChR-Ab).

METHODS: Five MG patients with refractory residual ocular symptoms treated with EFG at Huashan Hospital were included. The demographic and clinical information was collected, and MG Activities of Daily Living (MG-ADL) scores and Quantitative Myasthenia Gravis (QMG) scores was elevated weekly during the 8-week follow up period. The time to reach minimal symptom expression (MSE) was also recorded.

RESULTS: After a single cycle of EFG infusion, all five patients showed response in MG-ADL (≥2 points reduction), and three patients in QMG score (≥3 points reduction). The mean ± SD MG-ADL scores decreased significantly from 5.0±1.0 at baseline to 1.8±1.1 at weak 4 ($p=0.0027$) and 1.8±0.5 at weak 6 ($p=0.0027$). The mean ± SD QMG score decreased from 5.8±0.5 at baseline to 2.4±1.7 at week 4 ($p=0.1357$) and 1.0±0.7 at week 6 ($p=0.0076$). The proportions of patients reaching MSE at week 4, 6 and 8 were 20% (1/5), 20% (1/5), and 60% (3/5), respectively.

SUMMARY/CONCLUSION: AChR-Ab+ MG patients with residual and refractory ocular symptoms could benefit from EFG treatment, while the duration of efficacy varied in individuals.

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CONCOMITANT INTRAVENOUS IMMUNOGLOBULIN OR PLASMA EXCHANGE HAS NO EFFECT ON COMPLEMENT INHIBITION BY ZILUCOPLAN

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INTRODUCTION: Macrocyclic peptide complement component 5 inhibitor, zilucoplan, significantly improved myasthenia gravis (MG)-specific outcomes in the Phase 3 RAISE study (NCT04115293). An open-label extension, RAISE-XT (NCT04225871), is ongoing.

OBJECTIVE: To evaluate the impact of rescue therapy (intravenous immunoglobulin [IVIg] or plasma exchange [PLEX]) on zilucoplan concentration and complement inhibition in RAISE and RAISE-XT.

METHODS: In RAISE, adults with acetylcholine receptor autoantibody-positive generalised MG were randomised 1:1 to daily subcutaneous zilucoplan 0.3 mg/kg or placebo for 12 weeks. Patients completing qualifying double-blind studies (NCT03315130/NCT04115293) could enter RAISE-XT to self-administer daily subcutaneous zilucoplan 0.3 mg/kg. The primary outcome of RAISE-XT was the incidence of treatment-emergent adverse events (TEAEs). Zilucoplan plasma concentration was measured pre- and post-administration on the day of rescue therapy by liquid chromatography–tandem mass spectrometry. Complement activity was measured by sheep red blood cell lysis assay, with post-measurement taken ≤1 day after rescue.

RESULTS: In patients with ≥1 week of zilucoplan 0.3 mg/kg exposure during RAISE and RAISE-XT (N=200), 21 (10.5%) received IVIg and 10 (5.0%) received PLEX. Where available, zilucoplan steady-state concentrations were comparable between patients with and without rescue therapy. Mean (standard deviation) complement inhibition remained complete (>95%) pre- and post-rescue: 97.1% (0.80) and 97.4% (0.63) for IVIg (10 events with data), respectively. Pre- and post-rescue complement inhibition was 96.3% and 95.9% for PLEX (1 event with data), respectively. TEAEs occurred in 188 (94.0%) patients (data cut-off: 08 September 2022).

SUMMARY/CONCLUSION: Complete complement inhibition was maintained with rescue therapy during zilucoplan treatment, confirming that zilucoplan can be used concomitantly with IVIg and PLEX without the need for supplemental dosing.

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COMBINED ANALYSES OF PARTICIPANTS TREATED WITH EFGARTIGIMOD EARLY IN THE COURSE OF GENERALIZED MYASTHENIA GRAVIS ACROSS CLINICAL STUDIES

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INTRODUCTION: Efgartigimod is a human immunoglobulin G1 (IgG1) antibody Fc-fragment that blocks the neonatal Fc receptor (FcRn). Efgartigimod has been investigated in the treatment of gMG through intravenous (IV) and subcutaneous (SC, coformulated with recombinant human hyaluronidase PH20) administration in the ADAPT/ADAPT+, ADAPT-SC/ADAPT-SC+, and ADAPT NXT Phase 3 studies. The impact of early intervention with efgartigimod in the disease course of gMG warrants further research.

OBJECTIVE: To describe the efficacy of efgartigimod in AChR-Ab+ participants receiving either efgartigimod (IV or SC) early in the disease course of gMG based on time from diagnosis and treatment history.

METHODS: Post hoc analyses examined the efficacy of efgartigimod IV or SC within the first 21 weeks of initial treatment in AChR-Ab+ participants who were less than 3 years from gMG diagnosis and had only received treatment with pyridostigmine.

RESULTS: A total of 20 participants with AChR-Ab+ gMG were included in the pooled analysis with 17 being treated with either efgartigimod IV or SC and 3 being treated with placebo. The mean (SE) time since diagnosis for all pooled participants was 1.35 (0.99) years. The mean (SE) change from baseline at week 4 in MG-ADL total score among participants treated with efgartigimod (n=15 with evaluable data at week 4) or placebo (n=2 with evaluable data at week 4) was -4.9 (0.87) and -2.5 (0.50), respectively. The percentage of participants treated with efgartigimod who achieved minimal symptom expression (MG-ADL total score of 0 or 1) was 23.5% (n=4/17 [n=3 cyclic, n=1 every 2 week dosing]) at any timepoint in the 21 weeks assessed.

SUMMARY/CONCLUSION: Preliminary data in a limited number of participants suggest that treatment with either efgartigimod IV or SC early in the disease course of gMG led to improvements in MG-ADL total score among participants with AChR-Ab+ gMG.

DISCLOSURES: Authors Kristin Heerlein, Sophie Steeland, and Li Liu are employees of argenx. Author Ali A. Habib discloses he has received research support and honoraria from Alexion/AstraZeneca, argenx, UCB, Immunovant, Regeneron, Cabaletta Bio, Horizon/Amgen, Genentech/Roche, Alpine Immune Sciences, Inhibrx, NMDpharma, Grifols, and Arcellx. Author Neelam Goyal discloses she has participated in advisory and consulting engagements with Alexion, argenx, UCB/Ra Pharma, Janssen, Amgen, EMD Sereno, Novartis and received grant

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DECIPHERING THE ROLE OF MONONUCLEAR PHAGOCYTES IN THYMIC INFLAMMATION IN MYASTHENIA GRAVIS

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Myasthenia Gravis (MG) is an autoimmune disease characterized by autoantibodies targeting the neuromuscular junction, mainly the acetylcholine receptor (AChR). In AChR-MG, the thymus is highly inflammatory and characterized by the development of ectopic germinal centers. We have observed a decrease in thymic macrophages in AChR-MG which may contribute to the initiation and persistence of local inflammation. Macrophages correspond to mononuclear phagocytes (MNPs), as monocytes and dendritic cells. MNPs are innate immune cells essential for maintaining tissue homeostasis but also involved in tissue inflammation. To elucidate the role of MNPs in AChR-MG-associated thymic inflammation, a combination of omics approaches has been performed: single-cell RNA sequencing and imaging mass cytometry on thymic tissue from AChR-MG patients and healthy adult controls. Our results indicate an increased diversity of MNPs associated with the inflammatory microenvironment in AChR-MG, with distinct populations varying based on their localization within the thymus. We are now exploring whether these alterations are the cause or the consequence of thymic inflammation, as MNPs may play a role in both the onset and maintenance of AChR-MG-associated thymic inflammation.

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RECURRENT SUBCONJUNCTIVAL HEMORRHAGE FOLLOWING EFGARTIGIMOD TREATMENT IN OCULAR MYASTHENIA GRAVIS: A UNIQUE CASE REPORT

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INTRODUCTION: Efgartigimod is generally well-tolerated, treatment for refractory myasthenia, with most adverse events being mild to moderate. The ADAPT MG trial reported headaches and urinary or respiratory infections as common side effects, with no ophthalmological side effects. We report a unique case of a 75-year-old female with ocular MG who developed recurrent subconjunctival hemorrhage (SCH) after efgartigimod infusion, an undocumented event.

RESULTS: A 75-year-old female with ocular MG, idiopathic SCH, osteoporosis, and recurrent diplopia on prolonged steroids was started on Efgartigimod therapy due to intolerance to other immunosuppressants. Shortly after each infusion she developed subconjunctival hemorrhage (SCH) at varying intervals—within an hour, 2 days, and 3 days following the first, second, and third infusions, respectively. The SCH presented both bilaterally and unilaterally, which resolved after discontinuing the treatment. SCH can be linked to factors like age, diabetes, blood disorders, anticoagulation therapy, ocular malignancies, ocular inflammation, and Valsalva maneuver; none of which she had. Transient blood pressure elevation during the first infusion may have contributed to hemorrhagic episodes. However, normal pressure during subsequent infusions with persistent SCH ruled out elevated blood pressure as the cause. Her long-term prednisone (10 mg) use was also considered, however in her 5 years on prednisone no SCH was noted. With presence of FcRn in the cornea, retina, conjunctiva and other ocular neurovascular structures, we hypothesize that FcRn inhibition may impact vascular integrity in these areas, although the mechanism still remains unclear.

SUMMARY/CONCLUSION: While the mechanism remains unelucidated, this case highlights the first instance SCH has been reported as an adverse event following efgartigimod infusion, warranting further investigation into the long-term effects of FcRn inhibitors on blood vessel integrity. It highlights the potential need to include SCH alongside other hemorrhagic events including hemodynamic instability as exclusion criteria in the administration of efgartigimod.

DISCLOSURES: Amanda Hernandez has acted in a consultant and advisory capacity for Alexion, Argenx, Genentech, TG Therapeutics, and EMD Serono; and received personal compensation from Genentech, TG Therapeutics, EMD Serono, UCB, Janssen, Alexion, and Argenx.

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Ophthalmology Society Meeting in Waikiki, HI, United States.
https://www.nanosweb.org/i4a/pages/index.cfm?pageid=4356

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CASE REPORT: CLINICAL IMPROVEMENT IN NON-THYMOMATOUS ANTI-RYANODINE RECEPTOR (ANTI-RYR) POSITIVE GENERALIZED MYASTHENIA GRAVIS WITH EFGARTIGIMOD INTRAVENOUS INFUSIONS

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INTRODUCTION: The ryanodine receptor (RyR) antibody is an IgG antibody that targets the muscle protein RyR antigen found in the sarcoplasmic reticulum of striated muscle. It is part of the anti-striational antibodies and is typically associated with thymoma, leading to a more severe course. Efgartigimod is a monoclonal antibody that targets the Fc receptor and promotes degradation of IgG autoantibodies. It has been FDA approved for the treatment of acetylcholine receptor (AchR) positive generalized MG.

OBJECTIVE: We report a case of anti-RyR positive MG that responded positively to infusions of efgartigimod.

METHODS: Case Report

RESULTS: A 35-year-old female with a history of obstetric anti-phospholipid syndrome and psoriatic arthritis was diagnosed at 34 with non-thymomatous generalized MG, testing negative for anti-AchR, anti-MuSK, and anti-LRP-4 antibodies, but positive for anti-RyR (titer 1:40,000). She was on mestinon 60 mg four times daily and reported daily diplopia, bilateral ptosis, mild difficulty rising from a chair, eating solid food fatigue, and rare choking (MG-ADL score 7). Her MGC score was 9. Grip strength was 30 kg in the right hand and 16 kg in the left. After previous intolerance to prednisone given mood changes, she started intravenous efgartigimod at 10 mg/kg weekly for four weeks with breaks of 4 weeks, then switched to continuous weekly treatment due to worsening symptoms when off the medication after fifth cycle. She experienced no side effects, and initial benefits were noted six weeks post initial infusion. Currently, her MG-ADL score is 4, MGC score is 5, with improved grip strength of 35 kg in the right hand and 20 kg in the left, following 10 months of treatment.

SUMMARY/CONCLUSION: Real-world data regarding the use of efgartigimod is still limited, especially in cases of AchR-negative MG. We report a case of clinical improvement and response in the context of positive anti-RyR antibodies.

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CASE REPORT: CLINICAL BENEFIT OF FIRST CYCLE OF ROZANOLIXIZUMAB INFUSIONS IN NON-THYMOMATOUS ANTI-TITIN POSITIVE GENERALIZED MYASTHENIA GRAVIS

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INTRODUCTION: Anti-TITIN is an IgG antibody that is part of the anti-striational antibodies. In the context of myasthenia gravis (MG), it is associated with thymoma and a more severe disease course. Rozanolixizumab is a monoclonal antibody that targets the Fc receptor and induces lysosomal degradation of IgG autoantibodies. It was FDA-approved in 2023 for the treatment of anti-acetylcholine receptor (anti-AChR) and anti-muscle-specific kinase (anti-MuSK) MG.

OBJECTIVE: We report a case of anti-TITIN positive MG that responded to the first infusion cycle of rozanolixizumab.

METHODS: Case report

RESULTS: A 48-year-old female with a history of pulmonary hypertension secondary to obstructive sleep apnea was diagnosed with non-thymomatous generalized MG at age 46. She tested negative for anti-AChR, anti-MuSK, and anti-LRP4 antibodies, and positive for a low titer of anti-TITIN antibody (0.3 NU). She did not tolerate mestinon and mycophenolate mofetil in the past, and was on intravenous immunoglobulin (IVIg) at a dose of 0.75 g every two weeks. She was started on rozanolixizumab at a dose of 560 mg weekly for six weeks and IvIG was discontinued. Before starting infusions, she experienced daily ptosis, occasional diplopia, fatigue when eating solid food, intermittent slurred speech, and frequent choking, resulting MG-ADL 8). Her MGC score was 13, with grip strength measured at 14 kg in the right hand and 16 kg in the left. After five weeks following her first infusion, her MGC score decreased to 9, and her MG-ADL score improved to 7, and grip strength increased to 20 kg in both hands. She experienced no side effects from the infusions.

SUMMARY/CONCLUSION: Life experience data on rozanolixizumab is scarce, especially outside of cases involving positive anti-AChR and anti-MuSK MG. We report a case of initial clinical improvement in an anti-TITIN positive MG following the first cycle of rozanolixizumab infusions. Given this benefit, medication will be continued.

DISCLOSURES: Amanda Hernandez has acted in a consultant and advisory capacity for Alexion, Argenx, Genentech, TG Therapeutics, and EMD Serono; and received personal compensation from Genentech, TG Therapeutics, EMD Serono, UCB, Janssen, Alexion, and Argenx.

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EARLY AND SUSTAINED RESPONSE OVER TIME WITH ZILUCOPLAN IN GENERALISED MYASTHENIA GRAVIS: 120-WEEK POST HOC ANALYSIS OF RAISE-XT

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INTRODUCTION: RAISE-XT (NCT04225871), a Phase 3, ongoing, open-label extension study in patients with AChR Ab+ gMG, showed clinically meaningful and sustained improvements in MG-specific outcomes with zilucoplan, a macrocyclic peptide complement component 5 inhibitor.

OBJECTIVE: This *post hoc* analysis assessed the durability of response up to Week 120 of treatment in MG-ADL and QMG early zilucoplan responders at Week 1 of two double-blind studies (Phase 2, NCT03315130; Phase 3, NCT04115293).

METHODS: In RAISE-XT, adults with AChR Ab+ gMG self-administered once-daily subcutaneous zilucoplan 0.3 mg/kg. MG-ADL and QMG responders were defined as having ≥3-point and ≥5-point improvements, respectively, from double-blind baseline scores without rescue therapy. MG-ADL and QMG were assessed up to Week 120. The percentage of follow-up time patients spent in response was calculated up to Week 120 (interim data cut: 11 November 2023).

RESULTS: Overall, 93 patients were randomised to zilucoplan 0.3 mg/kg in the double-blind studies; 43.0% (n=40/93) were MG-ADL responders and 33.3% (n=31/93) were QMG responders at Week 1. Week 1 responders spent a median (range) of 98.9% (5.8–99.2) and

99.0% (2.5–99.2) of their time in response during follow-up to Week 120 for MG-ADL and QMG, respectively. Week 1 non-responders spent a median (range) of 84.6% (0.0–98.3) and 66.7% (0.0–98.9) of their time in response during follow-up to Week 120 for MG-ADL and QMG, respectively, with most responding later in the study.

SUMMARY/CONCLUSION: Among patients who were early (Week 1) zilucoplan responders, their time in response remained high (99%) up to Week 120. Among Week 1 non-responders, over two-thirds of their time was spent in response through to Week 120, showing that most patients became responders with continued use of zilucoplan. These data demonstrate rapid and sustained efficacy with long-term zilucoplan treatment. Funding: UCB.

DISCLOSURES: Channa Hewamadduma has received funding for consultancy on scientific or educational advisory boards for argenx, Biogen, Lupin, Roche and UCB, and has received an investigator-led research grant from UCB. His study activities were supported by a Sheffield NIHR BRC UK centre grant. He is a trustee of the myasthenia gravis patient organisation Myaware. Saskia Bresch has served as a paid Consultant for Alexion Pharmaceuticals, argenx, Biogen, Bristol Myers Squibb, Merck, Roche, Sandoz, Sanofi Genzyme (now Sanofi) and UCB. Miriam Freimer has served as a paid Consultant for Alexion Pharmaceuticals, argenx and UCB. She receives research support from Alnylam Pharmaceuticals, Avidity Biosciences, Fulcrum Therapeutics, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), the NIH and UCB. M. Isabel Leite is funded by the NHS (Myasthenia and Related Disorders Service and National Specialised Commissioning Group for Neuromyelitis Optica, UK) and by the University of Oxford, UK. She has been awarded research grants from UK associations for patients with myasthenia and with muscular disorders (Myaware and Muscular Dystrophy UK, respectively) and the University of Oxford. She has received speaker honoraria or travel grants from Biogen, the Guthy-Jackson Charitable Foundation, Novartis and UCB. She serves on scientific or educational advisory boards for argenx, Horizon Therapeutics (now Amgen) and UCB. Angelina Maniaol has received payment for travel, meeting attendance, consulting honoraria or advisory board participation from Alexion Pharmaceuticals, argenx, Biogen, CSL Behring, Novartis and UCB. Kimiaki Utsugisawa has served as a paid Consultant for argenx, Chugai Pharmaceutical, HanAll Biopharma, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), Merck, Mitsubishi Tanabe Pharma, UCB and Viela Bio (now Amgen); he has received speaker honoraria from Alexion Pharmaceuticals, argenx, the Japan Blood Products Organization and UCB. Raphaëlle Beau Lejdstrom, Babak Boroojerdi, Fiona Grimson and Natasa Savic are employees and shareholders of UCB. James F. Howard Jr. has received research support (paid to his institution) from Ad Scientiam, Alexion AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, 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), NMD Pharma, PCORI and UCB; has received honoraria/consulting fees from AcademicCME, Alexion AstraZeneca Rare Disease, Amgen, argenx, Biohaven Ltd, Biologix Pharma, CheckRare CME, Curio.Bio, F. Hoffmann-La Roche, Medscape CME, Merck EMD Serono, NMD Pharma, Novartis, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics, UCB and Zai Labs; and has received non-financial support from Alexion AstraZeneca Rare Disease, argenx, Biohaven Ltd, Toleranzia AB and UCB.

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CORTICOSTEROID DOSE TAPERING DURING TREATMENT WITH ZILUCOPLAN IN PATIENTS WITH GENERALISED MYASTHENIA GRAVIS: 120-WEEK FOLLOW-UP OF RAISE-XT

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INTRODUCTION: The efficacy and safety of zilucoplan in patients with AChR Ab+ gMG were assessed in two double-blind studies (NCT03315130/NCT04115293). During these studies, and the first 12 weeks of the ongoing, open-label extension study, RAISE-XT (NCT04225871), the corticosteroid dose was kept stable. Thereafter, the corticosteroid dose could be changed at the investigator's discretion.

OBJECTIVE: To evaluate corticosteroid dose changes in patients with gMG during zilucoplan treatment in RAISE-XT.

METHODS: In RAISE-XT, adults who completed a qualifying double-blind study self-administered once-daily subcutaneous zilucoplan 0.3 mg/kg. The primary outcome was incidence of treatment-emergent adverse events (TEAEs). This post hoc interim analysis (data cut-off: 11 November 2023) assessed the proportion of patients who reduced, discontinued, or increased their corticosteroid dose relative to double-blind baseline and change from baseline (CFB) in MG-ADL score after 120 weeks.

RESULTS: Overall, 200 patients enrolled. Of patients on corticosteroids at double-blind baseline with Week 120 data, 61.1% (n=33/54) had reduced or discontinued corticosteroids (mean 15.5 mg dose reduction from 23.0 mg at baseline); mean CFB in MG-ADL score: −6.6 (standard

deviation [SD] 3.6). Amongst all patients with Week 120 data, 9.3% (n=8/86) increased or started corticosteroids relative to double-blind baseline (mean dose increase: 11.6 mg); mean CFB in MG-ADL score: −7.4 (SD 4.6). At Week 120, 32% of patients with a ≥7.5 mg dose at double-blind baseline had reduced their dose to a dose <7.5 mg. TEAEs occurred in 97.0% (n=194/200) of patients.

SUMMARY/CONCLUSION: Treatment with zilucoplan allowed for reduction or discontinuation of corticosteroids in the majority of patients, while demonstrating sustained efficacy.

DISCLOSURES: Channa Hewamadduma has received funding for consultancy on scientific or educational advisory boards for argenx, Biogen, Lupin, Roche and UCB, and has received an investigator-led research grant from UCB. His study activities were supported by a Sheffield NIHR BRC UK centre grant. He is a trustee of the myasthenia gravis patient organisation Myaware. Miriam Freimer has served as a paid Consultant for Arcellx, argenx and UCB. She receives research support from Abcuro, Alnylam Pharmaceuticals, argenx, Avidity Biosciences, COUR Pharmaceuticals, Dianthus Therapeutics, Fulcrum Therapeutics, Johnson & Johnson Innovative Medicine, the NIH, RemeGen Biosciences and UCB. Angela Genge has served as a paid Consultant for Alexion Pharmaceuticals, ALS Pharmaceuticals, Amicus Therapeutics, Amylyx Pharmaceuticals, Anelixis Pharmaceuticals, Annexon Biosciences, Apellis Pharmaceuticals, Atlantic Research Group, Biogen, Calico, Cytokinetics, Eli Lilly, Ionis Pharmaceuticals, Medtronic, Mitsubishi Tanabe Pharma, Orion, QurAlis, Ra Pharmaceuticals (now UCB), Roche, Sanofi Genzyme (now Sanofi), UCB and Wave Life Sciences. M. Isabel Leite is funded by the NHS (Myasthenia and Related Disorders Service and National Specialised Commissioning Group for Neuromyelitis Optica, UK) and by the University of Oxford, UK. She has been awarded research grants from UK associations for patients with myasthenia and with muscular disorders (Myaware and Muscular Dystrophy UK, respectively) and the University of Oxford. She has received speaker honoraria or travel grants from Biogen, the Guthy-Jackson Charitable Foundation, Novartis and UCB. She serves on scientific or educational advisory boards for argenx, Horizon Therapeutics (now Amgen) and UCB. Kimiaki Utsugisawa has served as a paid Consultant for argenx, Chugai Pharmaceutical, HanAll Biopharma, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), Merck, Mitsubishi Tanabe Pharma, UCB and Viela Bio (now Amgen); he has received speaker honoraria from Alexion Pharmaceuticals, argenx, the Japan Blood Products Organization and UCB. Tuan Vu is the USF Site Principal Investigator for MG clinical trials sponsored by Alexion/AstraZeneca Rare Disease, Amgen, argenx, Cartesian Therapeutics, COUR Pharmaceuticals, Dianthus Therapeutics, Immunovant, Johnson & Johnson, NMD Pharma, Regeneron Pharmaceuticals and UCB, and has served as a speaker for Alexion/AstraZeneca Rare Disease, argenx, and CSL Behring. He has performed consulting work for Alexion/AstraZeneca Rare Disease, argenx, Dianthus Therapeutics, ImmunAbs and UCB. Babak Boroojerdi, Fiona Grimson, Natasa Savic and Mark Vanderkelen are employees and shareholders of UCB. James F. Howard Jr. has received research support (paid to his institution) from Ad Scientiam, Alexion/AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, the Centers for Disease Control and Prevention, the Muscular Dystrophy Association, the Myasthenia Gravis Foundation of America, the National Institutes of Health, NMD Pharma, and UCB; has received honoraria/consulting fees from AcademicCME, Alexion/AstraZeneca Rare Disease, Amgen, argenx, Biohaven Ltd, Biologix Pharma, CheckRare CME, CorEvitas, Curie.Bio, Hansa Biopharma, Medscape CME, Merck

EMD Serono, Novartis, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics, Toleranzia AB and UCB and has received non-financial support from Alexion/AstraZeneca Rare Disease, argenx, Biohaven Ltd, Cartesian Therapeutics, Toleranzia AB and UCB.

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IDENTIFICATION GENDER DIFFERENCES IN AUTOIMMUNE MYASTHENIA GRAVIS USING MACHINE LEARNING MODELS

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INTRODUCTION: Despite numerous epidemiological and clinical factors pointing at a relevant role of gender in autoimmune myasthenia gravis (MG) literature on this subject is scarce.

OBJECTIVE: To comprehensively assess gender differences in MG and the ability of machine-learning models to estimate gender using two large registry-based MG populations.

METHODS: Cross-sectional analysis of data from the German Myasthenia Gravis Registry (MyaReg) with application of unsupervised and supervised machine learning models. Analysis included descriptive and comparative (female vs. male) statistical analysis. For unsupervised clustering analysis linear as well as non-linear dimensionality reduction techniques were applied including principal component analysis (PCA), t-distributed Stochastic Neighbor Embedding (t-SNE) and Uniform Manifold Approximation and Projection (UMAP). For gender estimation, we developed a Random Forest Classifier, implementing a robust internal validation strategy through a bootstrapped double cross-validation (DCV) procedure. SHapley Additive exPlanations (SHAP) values were used to assess relative contribution of variables to gender estimation. For external validation, the generalization performance of models trained on the development cohort was evaluated by applying a bootstrapping method to the validation cohort.

RESULTS: Machine learning models identified a subset of seven variables that can accurately estimate gender (age at disease onset, time to diagnosis, MG-ADL, Hospital Anxiety and Depression Scale, autoimmune diseases, fatigue and thymectomy) with good discriminatory power, achieving a ROC-AUC of 0.736 (95% CI: 0.705, 0.773). Results were reproduced in the external validation cohort of the Dutch MG registry. Examination of the decision-making process of machine learning models enabled us to delineate the dominant clinical manifestation in male and female MG patients.

SUMMARY/CONCLUSION: Our study demonstrates relevant gender differences in MG patients spanning, both, clinical and paraclinical aspects. This may contribute to increased awareness of gender-related factors in MG and contribute to a gender-stratified approach in clinical practice.

DISCLOSURES: Sarah Hoffmann has received support from Argenx, Alexion, Roche, UCB

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EARLY AND HIGH-DOSE MATERNAL-FETAL THERAPY TO PREVENT REPEATED FETAL ACETYLCHOLINE RECEPTOR ANTIBODY-RELATED DISORDER (FARAD)

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ABSTRACT: Fetal acetylcholine receptor antibody-related disorder (FARAD) is a rare condition caused by in utero exposure of infants to maternal antibodies targeting the fetal acetylcholine receptor isoform (fAChR)**.** The clinical picture ranges from arthrogryposis multiplex congenita to bulbar/respiratory and CNS involvement. Offspring mortality is high with approximately 25%. Immunotherapy can mitigate syndrome severity and data suggests that earlier treatment is more effective. However, to date, no prophylactic maternal-fetal treatment is known. We report an asymptomatic mother with dominant fAChR-antibodies in cell-based assay testing. The patient had a history of three pregnancies with fetal demise due to FARAD. She gave birth to a healthy life-born infant with no FARAD-stigmata after establishing a treatment regimen known from fetal and neonatal alloimmune thrombocytopenia including initial plasma exchange followed by weekly IVIg infusions at a doses of 1g/kg body weight. The case report presentation will include illustrative ultrasound videos of intrauterine FARAD stigmata, along with a positive outcome following the administered therapy.

DISCLOSURES: Sarah Hoffmann has received support from Argenx, Alexion, Roche, UCB

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IMMUNE CHECKPOINT DOWNREGULATION AND NEGATIVE CORRELATION OF TIGIT EXPRESSION WITH ADL SCORES IN MYASTHENIA GRAVIS

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INTRODUCTION: Myasthenia Gravis (MG) is an autoimmune neurological disorder characterized by impaired transmission at the neuromuscular junction leading to muscle weakness and fatigue. Recent studies indicate that immune checkpoint inhibitors play a significant role in MG, as their use has been associated with the worsening or onset of the condition.

OBJECTIVE: Our study aimed to evaluate the expression of immune checkpoints in MG patients and to correlate their level to disease activity and outcome.

METHODS: We analyzed the mRNA expression levels of immune checkpoints (CTLA-4, PD-1, LAG-3, and TIGIT) in peripheral blood mononuclear cells (PBMC) of 28 untreated MG patients and 33 healthy controls (HCs) using RT-PCR. We correlated these findings with the annualized ADL-MG score, clinical and demographic information.

RESULTS: The expression of LAG-3, PD-1, TIGIT, and CTLA-4 were significantly decreased in MG patients compared to HCs. We found a significant negative correlation between TIGIT expression and their MG-ADL score. No correlation was found between the mRNA expression of immune checkpoint receptors and age, gender, disease duration, and seropositivity.

SUMMARY/CONCLUSION: Our findings of significant downregulation of LAG-3, TIGIT, PD-1 and CTLA-4 in MG patients compared to HCs suggest that these pathways might be involved in MG pathogenesis. The negative correlation between TIGIT expression and MG-ADL scores emphasizing its potential as a biomarker. In conclusion, these findings open avenues for targeted therapies aimed at restoring immune checkpoint function to modulate the autoimmune response in MG.

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GALACTOSE SUPPLEMENTATION RESCUSES PROTEIN GLYCOSYLATION AND NEUROMUSCULAR PHENOTYPE IN GLUTAMINE-FRUCTOSE-6-PHOSPHATE TRANSAMINASE 1 CONGENTIAL MYASTHENIC SYNDROME (GFPT1-CMS)

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INTRODUCTION: Congenital myasthenic syndromes (CMS) are inheritable, early-onset neuromuscular disorders caused by mutations in proteins involved in the development, maintenance, and function of the neuromuscular junction (NMJ). To date, approximately 35 genes have been associated with the development of CMS. A subset of five of these CMS-causing genes impair protein glycosylation. Glutamine-fructose-6-phosphate transaminase 1 (GFPT1) encodes the rate-limiting enzyme of the hexosamine biosynthetic pathway (HBP), a metabolic signaling pathway that produces the necessary precursors for the formation of N- and O-linked glycans. Biallelic mutations in GFPT1 result in reduced protein expression and enzymatic activity. Previously, we demonstrated that both *in vitro* and *in vivo* Gfpt1-deficient models exhibit reduced protein O-GlcNAcylation, leading to the hypoglycosylation of key NMJ-associated proteins, such as the acetylcholine receptor delta subunit (AChRδ). Previously, monosaccharide therapies, which have been used to treat patients with congenital disorders of glycosylation (CDGs). Galactose is readily metabolized by muscle through the Leloir pathway

into UDP-GalNAc. UDP-galactose-4-epimerase (GALE) can convert UDP-GalNAc into UDP-GlcNAc, which is necessary for protein O-GlcNAcylation and is a by-product of the HBP.

OBJECTIVE: To assess whether galactose treatment would be of benefit in cell and animal models of GFPT1 deficiency.

METHODS: We treated a skeletal-muscle specific knockout mouse model, termed *Gfpt1*$^{tm1d/tm1d}$, with a 10% (w/v) solution of galactose via the drinking water. We performed behavioural techniques to examine muscle fatigue. NMJs were stained in whole muscle and captured using confocal microscopy. NMJ-morph, was then used to examine NMJ morphology. Western blot was used to assess protein glycosylation and AChRδ protein levels in *Gfpt1*$^{tm1d/tm1d}$ quadriceps.

RESULTS: Treatment of Gfpt1-deficient C2C12 myoblasts with 10 mM galactose revealed activation of Leloir pathway gene expression and downstream protein O-GlcNAcylation. Galactose therapy in *Gfpt1*$^{tm1d/tm1d}$ mice significantly rescued impaired muscle fatigability, as measured through repetitive grip strength and hanging impulse tests. In addition, galactose supplementation improved NMJ morphology in *Gfpt1*$^{tm1d/tm1d}$ mice. Finally, we determined that galactose treatment activated Leloir pathway galactose metabolism, rescued protein O-GlcNAcylation, and restored the hypoglycosylation of AChRδ in skeletal muscle.

SUMMARY/CONCLUSION: Galactose supplementation improved the glycosylation status of proteins within skeletal muscle and the NMJ and may be a suitable treatment strategy for Gfpt1-CMS patients.

DISCLOSURES: Authors have no disclosures

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THE PHASE 3 PREVAIL STUDY ASSESSING THE EFFICACY AND SAFETY OF GEFURULIMAB IN GMG: TRIAL IN PROGRESS

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INTRODUCTION: Complement component 5 (C5) inhibitors are effective treatments for anti-acetylcholine receptor antibody-positive (AChR-Ab+) generalized myasthenia gravis (gMG). Gefurulimab is a new investigational complement inhibitor that binds C5, blocks its enzymatic cleavage, and thus, inhibits the terminal complement pathway. Gefurulimab is suitable for subcutaneous (SC) self-administration. Its extended half-life allows for once-weekly injection. Gefurulimab is currently under investigation for treatment of AChR-Ab+ gMG in a phase 3, multicenter, randomized, double-blind, placebo-controlled study (PREVAIL; NCT05556096).

OBJECTIVE: Provide an overview of PREVAIL, which is evaluating the efficacy and safety of gefurulimab in adults with AChR-Ab+ gMG.

METHODS: PREVAIL will enroll up to 254 adults with AChR-Ab+ gMG, including those with mild disease. Patients may continue taking previously prescribed therapies, including immunoglobulins. Patients are randomized 1:1 to weekly SC self-injection of gefurulimab or placebo. The primary endpoint is change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) total score at week 26. Secondary endpoints include change from baseline in Quantitative Myasthenia Gravis (QMG) total score and Myasthenia Gravis Composite (MGC) total score. Safety, pharmacokinetics, pharmacodynamics, immunogenicity, and quality of life will also be assessed. PREVAIL includes an open-label extension.

RESULTS: PREVAIL is recruiting patients at ~160 sites across 22 countries in North America, South America, Europe, Asia, and the Pacific region.

SUMMARY/CONCLUSION: This study examines the potential of the C5 inhibitor gefurulimab as a new treatment for patients with AChR-Ab+ gMG that can conveniently be self-administered at home through once-weekly SC injection. Results from PREVAIL will inform the clinical development program of gefurulimab.

DISCLOSURES: Author James F. Howard has received research support (paid to institution) from Ad Scientiam, Alexion, AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, the Centers for Disease Control and Prevention (Atlanta, GA, USA), the Muscular Dystrophy Association, the Myasthenia Gravis Foundation of America, the National Institutes of Health (including the National Institute of Neurological Disorders and Stroke and the National Institute

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DEVELOPING NEEDS-DRIVEN MEDICAL EDUCATION FOR HEALTHCARE PROFESSIONALS IN MYASTHENIA GRAVIS

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INTRODUCTION: An analysis of the global MG educational landscape highlighted a lack of robustly designed ongoing education for the MG medical community.

OBJECTIVE: To cultivate an international MG community and provide a forum for knowledge translation, providing needs-based, outcomes-focused learning.

METHODS: Physician learning needs were identified through literature searches, expert insights and a comprehensive needs assessment. A backward-planning logic model was used to establish educational programme goals with a 10-year ambition and validated metrics for success at the outset. Touchpoints across the first 24 months were overseen by a Steering Committee and mapped to priority learning outcomes based on identified learning needs. Educational content was designed to meet learning objectives, laddering up to the overarching learning outcomes. Learning transfer was sought by applying proven instructional design models and active learning techniques. To foster continued learning throughout the year, educational content was made available online.

RESULTS: The resulting product-agnostic educational programme, Rare Disease Connect in Neurology, was initiated in 2021 with a 3-day virtual meeting attended by 127 healthcare professionals (HCPs) globally. Across all 3 days, the average HCP Impact Score was 8.6 (scores ≥7 indicated that HCPs found the education valuable). Overall, 91% of evaluation form respondents indicated intent to change their clinical practice (score of ≥3 on a 4-point scale). Now in its fifth year, over 500 global HCPs are registered members of this MG community.

SUMMARY/CONCLUSION: A robust approach to the programme design ensured a high impact on the MG community. Impact on HCPs is being assessed through commitment to change by implementing learnings from the programme. This successful programme is being expanded to offer education to different regions, multidisciplinary team members and therapy areas beyond MG.

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PHASE 3 TRIAL INVESTIGATING IMPACT OF INTRAVENOUS EFGARTIGIMOD IN ANTI-ACETYLCHOLINE RECEPTOR ANTIBODY NEGATIVE GENERALIZED MYASTHENIA GRAVIS

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INTRODUCTION: Antibodies directed against AChR are absent in approximately 15% of patients with gMG. Lack of approved treatment options for patients with AChR-Ab- gMG represents an unmet need in the gMG treatment landscape. Efgartigimod is an immunoglobulin G (IgG)1 antibody Fc-fragment that selectively reduces IgG levels by blocking neonatal Fc receptor (FcRn)-mediated IgG recycling. It is approved in the US and EU for the treatment of patients with AChR-Ab+ gMG, and in Japan for the treatment of patients with AChR-Ab+ and AChR-Ab- gMG. Data from previous clinical trials examining efgartigimod have demonstrated efficacy in participants with both AChR-Ab+ and AChR-Ab- gMG. This Phase 3 trial, ADAPT SERON (NCT06298552) will investigate the efficacy and safety of efgartigimod specifically in participants that are AChR-Ab- and have a confirmed diagnosis of gMG.

OBJECTIVE: To determine the efficacy and safety of 10 mg/kg intravenous (IV) efgartigimod compared with placebo in AChR-Ab- participants with gMG.

METHODS: Adults with AChR-Ab- gMG who have an MG-ADL total score of ≥5 (with >50% of the score due to nonocular symptoms) and are on a stable dose of ≥1 concomitant gMG treatment will be included. One-hundred-ten adjudicated participants will be randomized 1:1 to either receive 10 mg/kg IV efgartigimod or placebo. The study has 2 stages: the double-blinded placebo-controlled Part A, consisting of 4 once-weekly infusions and 5 weeks of follow-up, and the open-label extension Part B, consisting of varying number and frequency of cycles, and weekly infusions for ≤2 years.

RESULTS: The primary endpoint is the change in MG-ADL total score from study baseline to Day 29 in Part A. Additional efficacy outcomes (QMG, MG-QoL15r, EQ-5D-5L), safety/tolerability, and pharmacokinetic/pharmacodynamic effects are also being assessed.

SUMMARY/CONCLUSION: This Phase 3 trial will provide further data on the efficacy and safety of efgartigimod IV in the treatment of AChR-Ab- gMG.

DISCLOSURES: Author James F. Howard Jr discloses he has received research support (paid to his institution) from Ad Scientiam, Alexion AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, Centers for Disease Control and Prevention, MGFA, Muscular Dystrophy Association, NIH, NMD Pharma, PCORI, and UCB Pharma; honoraria/consulting fees from AcademicCME, Alexion AstraZeneca Rare Disease, Amgen, argenx, Biohaven, Ltd., Biologix Pharma, CheckRare CME, Curie.bio, F. Hoffmann-LaRoche Ltd, Medscape CME, Merck EMB Serono, Novartis Pharma, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics, UCB Pharma, and Zai Labs; nonfinancial support from Alexion AstraZeneca Rare Disease, argenx, Biohaven, Ltd.,

Cartesian Therapeutics, Toleranzia AB, UCB Pharma, and Zai Labs. Authors Jeffrey Guptill, Rosa H. Jimenez, Fien Gistelinck, and Sophie Steeland are employees of argenx.

THIS IS AN ENCORE PRESENTATION OF: McPhail, J., et.al. (2024, September 14-17). *Phase 3 Trial Investigating Impact of Intravenous Efgartigimod in Anti-Acetylcholine Receptor Antibody Negative Generalized Myasthenia Gravis* [Conference presentation abstract]. 2024 annual meeting of the American Neurological Association (ANA) in Orlando, FL, United States. myana.org/meetings/ana-final-programs/

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PHARMACOLOGICAL ANALYSIS OF ACETYLCHOLINE RECEPTORS IN A HUMAN MUSCLE CELL MODEL OF MYASTHENIA GRAVIS USING LIVE-CELL CALCIUM IMAGING

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INTRODUCTION: A recent study of in vitro modeling of myasthenia gravis (MG) using a human muscle cell model visualized deposition of the membrane attack complex (MAC) and the acetylcholine receptor (AChR) reduction as a result of AChR antibody-mediated attacks. Further studies are required to fully understand the functionality of the model, which could serve as a platform to evaluate the effect of AChR antibody-mediated neuromuscular transmission failure.

OBJECTIVE: To examine the functionality of the human muscle cell model for myasthenia gravis.

METHODS: Real-time live-cell calcium ($Ca2^{+}$) imaging was used to evaluate whether activation of AChRs could lead to $Ca2^{+}$ influx in human muscle cells and if this is mediated through voltage-dependent calcium channels (VDCCs). Cells were cultured on µ-slides, treated with or without agrin, and loaded with $Ca2^{+}$ indicator Fluo-8H. The AChR agonist, carbamoylcholine, was applied with or without the nicotinic AChR-specific antagonist, tubocurarine, to access pharmacological blockage of the receptors. Further, in vitro disease modeling using serum from MG patients containing AChR antibodies was performed, along with pharmacological modulation of nicotinic AChRs and VGCCs to investigate the functionality of the model.

RESULTS: AChR activation with carbamoylcholine (0.5mM) induced a solid increase in intracellular levels of $Ca2^{+}$, whereas tubocurarine abolished this $Ca2^{+}$ influx.

SUMMARY/CONCLUSION: This pharmacological study validated the model's functionality, providing an approach to investigate the pathophysiological mechanisms of MG using a human muscle cell model.

DISCLOSURES: A.R.P. has received consultancy/speaker honoraria from Argenx, UCB, Dianthus, Alexion, and Toleranzia, all unrelated to this study.

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COMPARISON OF C5 COMPLEMENT INHIBITION VERSUS FCRN ANTAGONISM IN GENERALIZED MYASTHENIA GRAVIS

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INTRODUCTION: Although conventional immunosuppression effectively controls disease activity in many gMG patients, the management of refractory MG remains a significant challenge given the increased risk of myasthenic crises. For therapy intensification, two innovative treatment strategies have emerged: Inhibitors of complement factor C5 (C5IT) target complement-mediated damage at the neuromuscular junction, while blockade of the neonatal Fc receptor (FcRn) disrupts IgG recycling. However, a direct comparison between these treatments is lacking.

OBJECTIVE: The aim of this study was therefore to compare the efficacy and safety of C5IT and FcRn inhibition based on real-world data to support evidence-based therapy recommendations.

METHODS: In this retrospective analysis, we included 153 gMG patients from specialized centers in Germany. Patients received either C5IT (26 eculizumab, 80 ravulizumab) or efgartigimod (47 patients). Following clinical characterization of these cohorts, a comparison of MG-specific scores and safety aspects within the first six months after treatment initiation was performed.

RESULTS: Both treatment strategies led to rapid clinical improvements and reductions in concomitant medications. However, deOral on the parameters analyzed, 24–49.1% of patients

experienced an insufficient response. After applying a propensity score matching based on different baseline characteristics including disease activity, 40 patients remained in each cohort. Regarding the predefined primary endpoint, there was no significant difference in the maximum improvement in MG-ADL (C5IT: -4.7±3.7 vs efgartigimod: -4.3±4.2; p=0.637). Analysis of secondary endpoints including reductions in QMG and MG-QoL15 scores, changes in prednisolone and pyridostigmine doses, and the proportion of patients achieving a PASS or MSE yielded comparable results.

SUMMARY/CONCLUSION: In summary, both therapy mechanisms demonstrated comparable benefits in gMG, leading to a significant reduction in disease burden without emergence of new safety concerns. Nevertheless, the proportion of patients with an inadequate treatment response highlights the need for additional treatment options and the identification of factors predicting the individual outcomes.

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B CELL-RELATED GENE VARIANTS AS PERSONALIZED MEDICINE BIOMARKERS TO PREDICT UNRESPONSIVENESS TO IMMUNOSUPPRESSIVE DRUGS IN MYASTHENIA GRAVIS

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INTRODUCTION: Most myasthenia gravis (MG) patients require chronic immunosuppressive (IS) therapy to control disease symptoms, but a proportion (approximately 10-15%) of them is refractory to IS drugs with a considerable disease burden. Genetic variants may underlie inter-individual variability in response to these drugs, whose identification may allow to develop predictive models for selection of patients to be early directed to more effective targeted therapies.

OBJECTIVE: This study aimed at identifying variants in B cell-related genes as possible biomarkers of responsiveness/unresponsiveness to IS drugs in MG patients.

METHODS: To assess the association between variants in genes modulating B cell function (i.e. activation, differentiation, survival) and response to IS therapies, we designed a targeted NGS panel to sequence 70 candidate genes (i.e. all exons, ± 50 bp flanking sequences from intron-exon boundary, 5', 3′ UTRs, and promoter regions) in 88 MG patients stratified as responder (R, n=44) and non-responder (NR, n=44) to these therapies. Selected variants were validated in additional 83 patients (48 R, 35 NR) by allelic discrimination.

RESULTS: Genetic association analyses revealed a set of variants significantly associated with unresponsiveness to IS drugs in MG patients, including: i) rs17259045 (c.4619A>G, p.Asn1990Ser; OR: 4.71, p=0.018), a missense variant in *CR1*, encoding a complement system regulator; ii) rs1128646 (c.965G>A, p.Arg322His; OR: 1.71, p=0.043), a missense variant in *LILRB2*, encoding an Ig-like immunoinhibitory receptor; and iii) rs2464976 (c.-336G>T; OR: 2.20, p=0.017), a promoter variant in *CREB1*, encoding a key inflammatory mediator.

SUMMARY/CONCLUSION: Our results set the basis for the adoption of genetic biomarkers to predict unresponsiveness to conventional IS drugs in MG patients and guide clinicians into the choice of targeted therapies early in the disease course, prospectively leading to reduction of IS treatment failure and improved patients' quality of life.

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ASSOCIATION OF BRITISH NEUROLOGISTS (ABN) AUTOIMMUNE MYASTHENIA GRAVIS MANAGEMENT GUIDELINES (2025 UPDATE)

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INTRODUCTION: The previous Association of British Neurologists guidelines, published in 2015, were developed to support general neurologists in the management of people with Myasthenia Gravis (MG). They were based on evidence where available, and experience of experts where well-established treatments lacked evidence. There have been important developments in the management of MG in the past few years and this has been reflected in the recent publication of updated guidelines by other national MG societies. It is therefore appropriate that the ABN MG guidelines are revised to reflect current practice and review future opportunities

OBJECTIVE: To update ABN treatment guidelines for Myasthenia.

METHODS: The coordinating committee of the ABN Myasthenia special interest group met weekly for 12 months and various topics from the 2015 guidelines and newer therapies were discussed. This was then put through a consensus voting and agreement was reached based on the evidence available. Each coordinating member would participate in a series of discussion-based meetings. Where there was disagreement, discussion continued until a statement could be generated that met a consensus position. Extensive document was first generated which was then

reviewed by each coordinating member for accuracy and relevance. The first draft of the guideline has been circulated to all other members of the Myasthenia SIG, patient organizations (Myaware and MDUK), general neurologists, specialist nurses as well as trainee neurologists for their feedback and the comments, which were reviewed and incorporated into the final guidelines document by the coordinating group.

RESULTS: This 2025 update emphasizes several points that are distinct from the 2015 guidelines:

- The recommendation to prescribe daily steroids rather than the alternate day regimen is now standard practice.
- There is clear emphasis of the beneficial effects of early thymectomy (reflecting the findings from the MGTx study).
- We have also reconsidered the place of rituximab in treatment as randomised controlled trial (RCT) evidence now supports early use (within 1 year of generalised disease onset), although the evidence is less robust in established treatment-refractory MG.
- Finally, several clinical trials have been published for newer targeted therapies in MG, predominantly inhibiting the complement and neonatal Fc gamma receptor (FcRn) pathways, the roles of which are being slowly established around the world.

SUMMARY/CONCLUSION: The management of MG has evolved over the last few years with slightly different approaches to AChR-MG and MuSK-MG. The emphasis is now on lower dose of long-term corticosteroids and ideally these are given once daily. In AChR-MG early thymectomy is recommended in patients less than 50 years of age, and can be considered between the age of 50 and 65. There is reasonable evidence of using a single dose rituximab early on at diagnosis in generalised AChR-MG patients but the evidence for long term maintenance therapy is limited, unlike in MuSK-MG which traditionally responds less to conventional treatments and is usually rituximab-responsive. Newer therapies are still not licensed to use in the UK, but their potential role in the treatment algorithm is discussed.

DISCLOSURES: AP has received consulting and speaker's fees from Argenx, Terumo BCT and UCB Pharma CH has worked as chief investigator/PI in clinical trials – in MG, FSHD, DM1, CIDP, SMA, MMN with sponsors: Avidity, VERTEX, Dyne, Biogen, ARGENX, Immunovant, UCB, Alexion, JnJ, Remgen, Lupin and Advisory boards, speaker honoraria: UCB, ARGENX, Roche, Biogen, Avidity, JnJ and Roche. Advisory role in NICE on novel MG/CIDP/SMA therapies. FN has been in the advisory boards and has received honoraria from argenx, UCB and Roche. JM has received honoraria and/or support for educational meetings from Argenx and Biogen. JSp has been in the advisory boards and has received honoraria from argenx, Johnson&Johnson and UCB. MEF has received honoraria for advisory work for UCB and speaking/chairing at meetings organised by UCB and Argenx. MH has been on advisory boards for UCB and argenx, and accepted support to attend clinical meetings from UCB, argenx, Merck and Janssen-Cilag. MIL is funded by the NHS (Myasthenia and Related Disorders Service and National Specialised Commissioning Group for Neuromyelitis Optica, UK) and by the University of Oxford, UK. She has been awarded research grants from the UK association for patients with myasthenia (Myaware), Muscular Dystrophy Campaign (MDUK) and the University of Oxford. She has received speaker honoraria or travel grants from UCB Pharma, argenx and Amgen and the Neurology Academy (via third party honoraria), and consultancy fees from UCB Pharma. She serves as consultant and is member of scientific or educational advisory

boards for UCB Pharma, Argenx and Amgen. SJ has served as an international advisory board member for Alexion, Alnylam, ArgenX, Immunovant, Janssen, Merck, Novartis, Regeneron and UCB pharmaceuticals, is currently an expert panel member of the Myasthenia Gravis Consortium for Argenx pharmaceuticals and has received speaker's fees from Terumo BCT and Eisai pharmaceuticals. SV has received honorarium and travel expenses from UCB for attending conferences.

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EXTENSIVE PHENOTYPING OF A RAT MUSK MYASTHENIA GRAVIS MODEL – FROM NEUROMUSCULAR *IN VIVO* FUNCTION TO MOLECULAR PROPERTIES

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INTRODUCTION & OBJECTIVE: Myasthenia gravis (MG) is one of the most common diseases that compromise neuromuscular junction (NMJ) integrity and function, resulting in muscle weakness and excessive fatigue. A specific MG subtype, exhibiting antibodies targeting the muscle-specific tyrosine kinase (MuSK), was first described as a distinct MG subtype in the early 2000s. A fundamental tool for developing novel drug treatments for this MG subtype involves the application of pre-clinical disease models. Accordingly, increased pre-clinical model understanding of neuromuscular properties ranging from *in vivo* function to molecular biology may aid the development of treatment modalities for this MG subtype. To this end, we here report on an extensive phenotyping data package in a rat model of MuSK-MG induced by active immunization procedures.

METHODS & RESULTS: *In vivo* measures of body weight, electromyography, and respiratory function highlighted the loss of body weight in conjunction with hindlimb neuromuscular transmission deficits and reduced respiratory function in rats with circulating MuSK antibodies. This was supported by *in situ* and *ex vivo* measures showing noticeable deficits in nerve-evoked muscle contractile force and endurance. Moreover, both muscle organ weighing and immunohistochemistry (IHC) revealed markedly muscle wasting in a muscle-type- and potentially fiber-type-dependent manner. IHC analyses of neuromuscular junction morphology similarly showed fragmented endplates, as well as the presence of MuSK antibodies. Finally, whole-muscle proteomics in hindlimb, respiratory, and neck muscles revealed a muscle-dependent and myopathy-like impact in the MuSK-MG phenotype with evident implications for skeletal muscle health. Several proteins were regulated in the MuSK-MG phenotype both independent and dependent of the muscle wasting.

SUMMARY/CONCLUSION: Taken together, our broad range of phenotyping data highlights the presence of both neuromuscular transmission failure and muscle wasting in a rat model of the MuSK-MG disease, which confirms its relevance as a valuable pre-clinical model for e.g., development of novel pharmacological treatment modalities.

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PATIENT-SPECIFIC THERAPEUTIC BENEFIT OF MUSCLE-SPECIFIC KINASE (MuSK) AGONIST ANTIBODY ARGX-119 IN MuSK MYASTHENIA GRAVIS PASSIVE TRANSFER MODELS

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INTRODUCTION: Muscle-specific kinase (MuSK) orchestrates establishment and maintenance of neuromuscular synapses, facilitating muscle contraction. Autoantibodies targeting MuSK cause myasthenia gravis (MG), a disease characterized by fatigable skeletal muscle weakness. MuSK autoantibodies are predominantly of the immunoglobulin G (IgG) 4 subclass and are bispecific, functionally monovalent antibodies due to Fab-arm exchange. MuSK IgG4 autoantibodies inhibit the MuSK signaling pathway through monovalent binding, impairing neuromuscular synaptic function, whilst bivalent MuSK antibodies activate the MuSK signaling pathway. We therefore hypothesized that a bivalent MuSK agonist could rescue MuSK MG, bypassing the need for immunosuppressive therapies.

OBJECTIVE: To investigate whether an agonist antibody targeting the Frizzled-like domain of MuSK, ARGX-119, could ameliorate disease in MuSK MG models induced by passive transfer of polyclonal IgG4 from unrelated patients.

METHODS: MuSK MG was induced by daily intraperitoneal administration of purified polyclonal IgG4 from four unrelated patients. Every third day the mice were injected with either ARGX-119 or an isotype control. Throughout the experiments, general wellbeing, body weight, grip strength test and inverted hanging mesh test was assessed. Therapeutic efficacy was assessed *in vitro* by measuring acetylcholine receptor clustering in C2C12 myotube culturing co-treated with polyclonal patient IgG4.

RESULTS: ARGX-119 significantly improved survival and muscle weakness in a mouse model induced by one patient material, but not by three others. When efficacious in MuSK MG mice, ARGX-119 followed a bell-shaped dose-effect curve. Mechanistically, the patient-specific efficacy could not be explained by autoantibody epitope specificity, titer, or competition for ARGX-119 binding, but rather seemed related to a fraction of (IgG4) bivalent MuSK-activating antibodies in some patient materials, which warrants further investigation. Furthermore, results from our *in vitro* acetylcholine receptor clustering assay correlated with the therapeutic effects observed *in vivo*, and therefore may predict which patients could potentially benefit from ARGX-119.

SUMMARY/CONCLUSION: Overall, we provide evidence of a first proof of concept of an alternative therapeutic strategy directly activating MuSK in a clinically relevant model for MuSK MG. We anticipate this to be a starting point for investigating the (add-on) therapeutic benefit of

ARGX-119 in MuSK MG patients whose symptoms are not well controlled with existing medication, as well as other neuromuscular diseases hallmarked by neuromuscular synaptic dysfunction.

DISCLOSURES: J.J.Verschuuren, S.M. van der Maarel, M.G. Huijbers and J.J. Plomp are co-inventors on MuSK-related pending patents and receive royalties. LUMC receives royalties on a MuSK ELISA. J.J. Verschuuren and M.G. Huijbers are consultants for argenx, and J.J. Verschuuren is also a consultant for Alexion and NMD Pharma. M.R. Tannemaat reports consultancies for argenx, UCB Pharma, Johnson and Johnson, Peervoice and Medtalks, and research funding from NWO, argenx and NMD Pharma. All reimbursements were received by the Leiden University Medical Center. J.L. Lim, B. Vankerckhoven, C. Kneip, R. Coppejans, C. Steyaert, K. Moens, L. De Clercq, P. Ulrichts, K. Silence and R. Vanhauwaert are employees/consultants of argenx. B.V. and are holders of employee equity in argenx.

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PATTERNS AND PREDICTORS OF THERAPEUTIC RESPONSE TO EFGARTIGIMOD IN ACETYLCHOLINE RECEPTOR-ANTIBODY GENERALIZED MYASTHENIA GRAVIS SUBTYPES

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BACKGROUND: Efgartigimod is an approved biologic for generalized myasthenia gravis (gMG), which can potentially be life-threatening. However, the therapeutic response to efgartigimod among the acetylcholine receptor MG (AChR-MG) subtypes remains inconclusive.

OBJECTIVE: To explore the therapeutic response to efgartigimod in AChR-MG subtypes. Design: This is a prospective, observational study included AChR-MG patients treated at 15 centers in China (September 2023–August 2024).

METHODS: The primary outcome was the proportion of minimal symptom expression (MSE) responders, denoted by a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of 0 or

1 within 4 weeks and maintained for =4 weeks. AChR-MG subtypes were classified into early-onset MG (EOMG), late-onset MG (LOMG), and thymoma-associated MG (TAMG). The predictive factors for MSE responders were identified by univariate and multivariate logistic regression analysis.

RESULTS: In all, 116 patients were included with a median follow-up duration of 238 days (172.5–306.3). There were 50 (43.1%) patients with EOMG, 28 (24.1%) with LOMG, and 38 (32.8%) with TAMG. After efgartigimod initiation, 35 (30.2%) patients were MSE responders, and the proportion of MSE responders was highest in the LOMG group (42.9%). The MG-ADL score reduction in the LOMG group was more significant than in the EOMG group by weeks 16 and 20 (both P=0.022). Response patterns to efgartigimod among the AChR-MG subtypes differed as measured by the proportion of improved patients and MSE. LOMG presented sustained symptom control, while EOMG and TAMG showed more fluctuations. Eight TAMG patients (21.1%) switched to another biologic (P=0.005). Baseline MG-ADL was an independent predictor for therapeutic response to efgartigimod (P<0.001).

SUMMARY/CONCLUSION: Our findings revealed patterns of treatment responses among AChR-MG subtypes, with LOMG patients potentially presenting a more sustained response. These findings likely provide preliminary data for precision therapy in MG in the era of biologics. Registration: NCT04535843.

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ASSOCIATED AUTOIMMUNITY IN MYASTHENIA GRAVIS IN DENMARK: A NATIONWIDE CASE-CONTROL STUDY

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INTRODUCTION: Myasthenia gravis (MG) is an autoantibody-mediated disease of unknown etiology often co-occurring with other autoimmune diseases (AIDs).

OBJECTIVE: In this study, we aimed to determine the association between incident AID occurrence before and after an MG diagnosis.

METHODS: In this nationwide population-based case-control study, each patient was matched in a 1:10 ratio to the general population based on age, sex, and diagnostic index date. Data was obtained from Danish health registers through individual-level data linkage across health registers from 1985 to 2020. Conditional logistic regression was applied to calculate odds ratios (ORs) with 95% confidence intervals. Analyses were stratified by sex and age group (£ 50 and >50). Moreover, analyses were adjusted for baseline comorbidities identified using the Charlson Comorbidity Index (CCI).

RESULTS: Our study population included 2,110 MG patients (1,061 females) and 21,100 matched individuals from the general population, with 27.4% £ 50 years. Before MG diagnosis, 4.7 % of MG patients and 2.7 % of the general population were diagnosed with another AID, resulting in an OR of 1.8 (95% CI 1.5-2.3). After MG diagnosis, 10.1% of MG patients and 5.8% of the matched controls were diagnosed with an AID, resulting in an OR of 1.9 (95% CI 1.6-2.2). Notably, the highest OR was observed for patients £ 50 years before MG diagnosis, with an OR of 3.3 (95% CI 2.1-5.4). Adjusting for comorbidity did not significantly alter the associations before or after MG diagnosis.

SUMMARY/CONCLUSION: MG patients have a 1.8-fold higher risk of having another AID at time of diagnosis, with a similar risk of receiving another AID diagnosis after MG diagnostic index date. These findings suggest a common pathophysiological mechanism that may predispose to poly-autoimmunity. Understanding the predisposing immunological pathways is indispensable for prevention and treatment strategies.

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ASSOCIATION OF RECENT INFECTION AND SUBSEQUENT MYASTHENIA GRAVIS: A NATIONWIDE CASE-CONTROL STUDY FROM 1985 TO 2020

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INTRODUCTION & OBJECTIVE: Myasthenia gravis (MG) is an autoimmune disease of unknown etiology. Infections have been suggested to contribute and trigger MG onset. In this study, we aimed to determine the association and time interval between recent infection and subsequent MG development.

METHODS: We conducted a nationwide, population-based case-control study using data from Danish health registers from 1985 to 2020. By linking individual-level data across these registers, we identified MG patients and matched each patient to ten controls from the general population based on age, sex, and diagnostic index date. Using conditional logistic regression, we computed odds ratios (ORs) with 95% confidence intervals to assess the relative risk of developing MG following recent infection in different time intervals.

RESULTS: We identified 2,110 MG patients and 21,100 age, sex, and index date matched controls from the general population, with 27.4% of the study cohort aged ? 50 years. Within 1 year before MG diagnosis, 6.9% of MG patients had a hospital-diagnosed infection, compared to 3.1% in the general population, corresponding to an OR of 2.4 (95% CI: 2.0–2.9). The strongest associations were observed for lower respiratory tract and ear, nose, and throat infections. In MG patients aged ? 50 years, the association was particularly high, with an OR of 3.3 (95% CI 2.2-5.0). Expectedly, the highest OR was observed within 30 days before MG diagnosis, with an OR of 6.3 (95% CI 4.5-9.0).

SUMMARY/CONCLUSION: MG patients have a 2.4-fold higher risk of having an infection 1 year before diagnosis compared to the general population. These findings suggest that infections may contribute to MG onset before diagnosis is determined, likely due to exacerbation triggering or arising due to respiratory and bulbar dysfunction. Recognizing this potential link between infections and MG onset could offer valuable insights for early intervention and prevention strategies.

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TOWARDS A DIGITAL TWIN FOR MYASTHENIA GRAVIS

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INTRODUCTION: There are no predictors of treatment outcome for patients with myasthenia gravis; however, the advent of large data sets and novel computational methods coupled with machine learning offer the potential to build digital twins, which are in silico models that can be applied to individual patients to aid in treatment selection.

OBJECTIVE: To begin to build a predictive model of myasthenia gravis outcome on an individual patient level.

METHODS: We utilized the MGTX trial data set to develop the core mathematical concept, which involves patient trajectories that describe changes in the patient's state, such as prednisone dose and addition of azathioprine, over time. We first constructed patient trajectories applying denoising and interpolation where necessary. Next, we employed a robust classifier to identify clusters of trajectories that were clearly distinct and represented a significant number of patients. In a second step, we grouped patients into clusters for specific time windows or "phases" of the trial, based on a density function, and assessed the continuity of patient tracking between phases. This allowed estimation of the optimal number of clusters per phase and the predictability of whether a patient would remain in the same cluster over time.

RESULTS: Using prednisone dose as a treatment failure metric across study arms, we identified four distinct patient clusters. Predictability rates ranged from 80% to 90%, depending on the density cluster radius constraints. Consistent with trial results, thymectomy was associated with superior outcomes in certain clusters. Smoking status at study onset was the strongest predictor of poor outcomes. Approximately 20% of patients fell into the poorest response cluster, of whom 80% had not undergone thymectomy and were unresponsive to both prednisone and azathioprine.

SUMMARY/CONCLUSION: Our methodology revealed clear patterns in patient trajectories based on prednisone dose, with promising predictability rates. The development of a digital twin that integrates in the state variable additional features of clinical outcome measures and multi-omic analysis of biological samples from MGTX is ongoing.

DISCLOSURES: Dr. Kaminski is Dr. Kaminski is a consultant for Roche, Candid Therapeutics, Takeda, Cabaletta Bio, UCB Pharmaceuticals, Canopy Immunotherapeutics, Curie.bio, Samsung, EcoR1 and EMD Serono. Argenix provides an unrestricted educational grant to George Washington University. He s an unpaid consultant for Care Constitution. Dr. Kaminski has equity interest in Mimivax, LLC. Dr. Kaminski is principal investigator for the Rare Disease Network, MGNet supported by NIH grant U54NS115054. Marc Garbey is CEO of Care Constitution.

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IDENTIFICATION OF CONGENITAL MYASTHENIC SYNDROMES IN A SERONEGATIVE MYASTHENIA GRAVIS COHORT

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INTRODUCTION: Myasthenia gravis (MG) is an autoimmune disorder, caused by pathogenic autoantibodies (Abs) against antigens on the neuromuscular junction. While Abs can be detected in most cases, around 10% suffer from seronegative MG (SNMG). Various genetic conditions causing similar symptoms, especially congenital myasthenic syndromes (CMS), are often misdiagnosed as SNMG, which may delay appropriate treatment significantly.

METHODS: This prospective study included 50 adult patients diagnosed with SNMG. Cell based assays for Abs against the acetylcholine receptor, the muscle-specific kinase, lipoprotein receptor-related protein 4 and the voltage-gated calcium channels were performed. Whole-exome sequencing was performed in all patients.

RESULTS: In seven patients (14%) a diagnosis of CMS could be established, out of which four had a variant in the CHRNE gene and three had a variant in the RAPSN gene. Additionally, variants of uncertain significance in CACNA1S, DOK7 and RAPSN were found in three cases. Only one patient with CMS reported positive family history, and clinical and demographic factors did not correlate with obtaining a genetic diagnosis. Six patients (86%) with CMS received immunomodulatory treatment or underwent thymectomy prior to this study.

CONCLUSIONS: Our study provides evidence, that a significant number of patients diagnosed with SNMG may indeed suffer from CMS. We propose that comprehensive genetic testing should be offered to all SNMG patients as part of the routine diagnostic workup, given the high diagnostic yield in our study and its potential impact on clinical decision-making.

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DISTRIBUTION AND TEMPORAL CHANGES OF AUTOANTIBODY-MEDIATED PATHOGENIC MECHANISMS AMONG ACHR-POSITIVE MYASTHENIA GRAVIS PATIENTS

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INTRODUCTION: AChR-specific autoantibodies (AChR-Ab) mediate MG pathology through three molecular mechanisms: complement activation, receptor internalization, and acetylcholine binding site blocking. Complement inhibitors and FcRn blockers are therapeutic approaches targeting MG pathology. Given that AChR-Ab isotypes (IgG, IgM and IgA) and the four IgG subclasses mediate pathology with different efficiencies, the emergence of the new therapeutics underscores the importance of investigating the distribution of AChR-Ab isotype/subclass and the pathogenic mechanisms they mediate.

OBJECTIVE: This study aimed to assess the distribution of AChR-specific autoantibody isotypes, IgG subclasses, and the pathogenic mechanisms they mediate in AChR-positive MG patients.

METHODS: Serum samples from 50 AChR+ generalized MG patients collected longitudinally over two years as part of the B-Cell Targeted Treatment in MG (BeatMG) study (clinicaltrials.gov: NCT02110706) were evaluated using a set of cell-based assays.

RESULTS: In cross-sectional samples, IgA and IgM AChR-specific autoantibodies were observed in the co-occurrence of IgG in 10% and 12% of patients, respectively. Among them, 4% had all three isotypes. AChR-IgG1 was found in 67.4%, followed by IgG3 (21.7%) and IgG2 (17.4%). Complement was active in 84.8%, followed by AChR internalization (63%) and blocking (30.4%). Complement and AChR internalization were simultaneously active in 45.6%, complement and blocking were active in 10.8%, and all three pathomechanisms were active in 17.4%. Blocking alone was active in only 2.1%; AChR internalization alone was not found. Temporal fluctuations of autoantibody isotypes/IgG subclasses and the associated pathogenic mechanisms were observed. Rituximab treatment reduced the binding capacity of AChR-specific autoantibodies as well as their ability to mediate AChR internalization and blocking.

SUMMARY/CONCLUSION: These results demonstrate that a subset of patients have autoantibodies that can mediate pathogenic mechanisms and include isotypes/IgG subclasses that current therapeutics may not effectively target. Accordingly, defining individual patient AChR-specific autoantibody profiles may help develop more precise therapeutic approaches targeting specific autoantibody-mediated mechanisms.

DISCLOSURES: KCO has received research support from Ra Pharma, now (UCB Pharma), Alexion Rare Disease (Astra Zeneca), Viela Bio (Horizon Therapeutics/Amgen), argenx, and Seismic Therapeutic. KCO is an equity shareholder of Cabaletta Bio. KCO has served on advisory boards for Roche, Merck (EMD Serono), and IgM Biosciences, and received speaking fees from Amgen and argenx. BR has been a consultant/advisor for Alexion (now part of AstraZeneca), Takeda, and argenx. Additionally, BR has received research support from the Martin Shubik Fund for IBM at Yale University, NIH, Abcuro Pharmaceuticals, Immunovant, Takeda. BR is a shareholder of Cabaletta Bio. RJN has received research support from the NIH, Genentech, Alexion (Astra Zeneca), argenx, Annexon Biosciences, Ra Pharmaceuticals (now UCB), Myasthenia Gravis Foundation of America, Momenta (now Janssen), Immunovant, Grifols, and Viela Bio (Horizon Therapeutics, now Amgen). RJN has also served as a consultant/advisor for Alexion (Astra Zeneca), argenx, Cabaletta Bio, CSL Behring, Grifols, Ra Pharmaceuticals (now UCB Pharma), Immunovant, Momenta (now Janssen), Viela Bio (Horizon Therapeutics, now Amgen).

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CLINICAL CHARACTERISTICS AND TREATMENT STATUS OF THE PATIENTS WITH MYASTHENIA GRAVIS: A SINGLE-CENTER EXPERIENCE

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INTRODUCTION: The symptoms of myasthenia gravis (MG) are variable, with improvement and worsening occurring even during long-term treatment. Therefore, it is challenging to assess the treatment status of patients with MG at a glance.

OBJECTIVE: This study aimed to analyze the treatment status of patients with MG at a specific time point.

METHODS: We retrospectively investigated the medical records of patients with MG who visited Severance Hospital between Oct 2023 and Sep 2024. Patients were excluded if their treatment status for MG could not be accurately assessed. MGFA PIS, MG ADL score and treatment state of the patients at index date were analyzed.

RESULTS: Of the 727 patients with MG who visited neurology clinic during the study period, 59 patients whose treatments state were inaccurate were excluded. Of the 668 patients finally included, 64.2% were female, mean disease duration was 11.4 years, 77.7% were generalized MG, 43.1% underwent thymectomy, and 26.7% had thymoma. 86.2% of the patients had ever been treated with prednisolone. At index date, 67.2% and 46.4% of the patients were under treatment with prednisolone and oral immunosuppressants, respectively. 2.7% were in chronic IVIg therapy and 3.5% were being treated with rituximab. MGFA PIS was CSR in 4%, PR in 16%, MM in 45%, improved in 22%, worse in 4% and exacerbation in 1%. Median MG ADL score was 2.0 (Q1-Q3, 0.0-4.0). 48% of the patients met the definition of MM-5, a state with MM or better with no more than 5 mg of oral prednisolone per day.

SUMMARY/CONCLUSION: Despite the treatment, 5% of the patients experienced worsening, 13.5% had MG ADL score =6, and 52% did not satisfy the definition of MM-5. Active treatment, including the newly developed biologics, should be considered to improve symptoms in patients with insufficient therapeutic effect.

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POST-HOC RESPONDER ANALYSES FROM THE PROOF-OF-MECHANISM STUDY OF NMD670 IN PATIENTS WITH MYASTHENIA GRAVIS

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ABSTRACT: NMD670 is an inhibitor of skeletal muscle-specific chloride channel protein 1 (ClC-1) that enhances neuromuscular transmission and is being developed for the treatment of myasthenia gravis (MG), in which neuromuscular junction (NMJ) transmission is impaired. Despite available treatments, MG patients continue to experience muscle weakness and fatigue. In a recent proof-of-mechanism study in 12 MG patients with mild symptoms (baseline QMG of 9 +/- 3.6), two single doses of NMD670 and a single dose of placebo were administered in a three-way cross over fashion. Recently published data showed significant improvements in the QMG total score with NMD670 versus placebo. A post-hoc responder analysis was subsequently made to better characterize the responders and understand the clinically meaningfulness of the data. This analysis revealed that 42-50% achieved clinically meaningful improvement of 2 points or more with NMD670 versus placebo regardless of dose. A similar trend was observed for the QMG item of grip strength where responder rates between 25-67% were noted dependent on dose and post-dose timepoint. A sensitivity responder analysis revealed that 9 out of 12 patients achieved at least one point improvement with NMD670 versus placebo. The baseline QMG total score predicted the change from baseline in the QMG total score with NMD670 versus placebo ($r= -0.47$, $p=0.02$). When only including patients with baseline QMG scores of 6 or more, average improvements of -3.5 and -1.7 points for 400mg and 1200mg doses were observed. Similar trends were noted between baseline QMG total score and the change from baseline versus placebo on hand grip strength and leg outstretch items. In conclusion, high responder rates were noted with NMD670 despite a relatively mild phenotype of patients enrolled. Worse disease severity was associated with a larger response, indicating that more pronounced treatment benefits with NMD670 may be expected in a more severe population.

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PHASE 2B STUDY DESIGN FOR NMD670, A FIRST-IN-CLASS CLC-1 INHIBITOR IN GENERALIZED MYASTHENIA GRAVIS: THE SYNAPSE-MG DOSE-FINDING STUDY

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ABSTRACT: NMD670 is an inhibitor of skeletal muscle-specific chloride channel protein 1 (ClC-1) that amplifies the skeletal muscle's responsiveness to weak signals is being developed for the treatment of neuromuscular diseases, including myasthenia gravis (MG), in which neuromuscular junction transmission is impaired. Despite available treatments, MG patients continue to experience muscle weakness and fatigue. In a recent phase1/2a study in 12 MG patients with mild symptoms, a single administration of NMD670 led to significant and clinically meaningful improvements in muscle strength as assessed with the Quantitative MG (QMG) score. Furthermore, NMD670 was shown to be safe and well tolerated thus supporting further clinical development for this indication. Therefore, a dose finding study in AchR and MuSK positive adult patients with MG was initiated in June 2024. The aim of this study is to evaluate the efficacy and safety of 3 dose levels of NMD670, administered twice a day for 21 days versus placebo. Adult male and female patients aged 18 to 75, diagnosed with MG and with a MG Foundation of America (MGFA) class II-IV, a QMG score of 11 or more and an MG-Activities of Daily-Living score of 6 or more at screening are being currently enrolled at 38 sites across Europe and North America. Endpoints of this study include changes in the QMG, MG Activities of Daily Living (MG-ADL), MG Composite (MGC), MG Quality of Life 15 revised (QOL15r), and Neuro Qol Fatigue Short Form total scores. Key updates on study status, more detailed study design, and other updates will be provided by NMD Pharma A/S at MGFA 15th International Conference in May 2025 in the Netherlands.

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MY GUESS IS AS GOOD AS YOURS: FACTORS CONTRIBUTING TO DIAGNOSIS AND OVERDIAGNOSIS OF MYASTHENIA GRAVIS

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INTRODUCTION: Seronegative generalized myasthenia gravis (SN gMG) relies on clinical and electrophysiological diagnosis and can be over diagnosed. This can result in inappropriate use of immunosuppression.

OBJECTIVE: To compare the diagnostic and therapeutic patterns, and role of clinical scales in SN gMG against over diagnosed cases and identify potential red flag features in cases of overdiagnosis.

METHODS: Retrospective chart review at a single tertiary care center of patients with presumed SN gMG from 2010-2021

RESULTS: 104 patients referred for SN gMG, 51 confirmed SN gMG and 53 received an alternative diagnosis. 17/31 (54.8%) of the SN gMG patients had abnormal repetitive nerve stimulation studies in contrast to 1/43 (2.3%) of the overdiagnosis group. 31/32 (96.9%) SN gMG had abnormal single fiber EMGs versus 6/36 (16.7%) of the overdiagnosis group. 38 (74.5%) SN gMG patients had a positive response to pyridostigmine versus 3 (5.7%) patients in the overdiagnosis group. Of those patients who tried immunotherapy, 28/47 (59.6%) showed positive response in SN gMG versus 2/19 (10.5%) in overdiagnosis group. MG-ADL was measured over time in 24 SN gMG patients. 10 improved, 6 had no change (<2 point change), and 8 worsened. 4 had MG-ADL trends over time in the overdiagnosis group and had no change.

SUMMARY/CONCLUSION: SN gMG patients consistently have abnormal electrophysiology findings, and often improve with pyridostigmine in contrast to those who are over diagnosed. Many patients in both groups are offered immunotherapy, but SN gMG are more likely to show treatment response than those in the overdiagnosis group. MG-ADL shows change over time in SN gMG patients, but did not show change over time in the overdiagnosis group. We propose incorporating treatment responsiveness into clinical care of SN gMG.

DISCLOSURES: KG consulting for Alexion, argenx, UCB and Amgen pharmaceuticals; Speaking honoraria for Alexion and argenx. QFConsultant for Johnson & Johnson, consultant for UCB Speaker bureau for Alnylam

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WHOLE BLOOD TRANSCRIPTIONAL PROFILES FROM THE MGTX TRIAL REVEAL POTENTIAL MECHANISMS OF THYMECTOMY BENEFIT

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INTRODUCTION: The MGTX trial demonstrated therapeutic benefit of thymectomy for MG, the biological mechanisms contributing to this benefit remain unclear.

OBJECTIVE: To evaluate whole blood transcriptional profile to assess mechanisms underlying the effect of extended transsternal thymectomy (ETTX) in myasthenia gravis (MG).

METHODS: We utilized whole blood RNA samples collected during the MGTX trial and applied generalized linear mixed models and differential gene expression. Our goal was to identify gene expression patterns and biochemical pathways associated with ETTX. We correlated transcriptional profile to QMG (Quantitative MG) and area under the QMG over time analysis (AUQMG).

RESULTS: Filtering the genes based on the prevalence and variation, 3175 genes were included in the analysis. At the false discovery rate (FDR) of 0.05, 222 genes were identified as differentially expressed in ETTX subjects compared to those receiving prednisone only. Sorted by gene ratio, top pathways were focal adhesion, cell-substrate junction, ribosome structure, secretory granule membrane, regulation of cell-cell adhesion and specifically immune response-regulating cell surface receptor signaling pathways. We detected 151 genes upregulated in association with higher QMG scores. The greatest increases involved DEFA3, CYP4F3, LTF, HLA.C_3, AHSP, and KRT. These genes enrich for immune response-activating signaling, mononuclear cell differentiation, GTPase regulator activity, immune response-regulating cell surface receptor signaling, lymphocyte differentiation, and leukocyte cell-cell adhesion. For AUQMG, 307 genes were differentially expressed with 109 genes upregulated in association with higher AUQMG. Among these, CD69, SNORD17, RPS7, NIBAN3, and RPS27 showed the highest expression levels. These genes enrich for regulation of protein catabolic process, immune response-activating signaling, viral process, ubiquitin-like protein ligase binding, and macroautophagy pathways.

SUMMARY/CONCLUSION: Our findings suggest that ETTX modulates distinct transcriptional profiles and biochemical pathways associated with immune signaling, ribosomal function, and cellular metabolism. These insights provide an understanding of the molecular mechanisms underlying the therapeutic effects of ETTX.

DISCLOSURES: Author Linda Kusner has been a consultant for GRO Biotechnology, CSL Behring, Amplo Biotechnology, Alexion and Sanofi. Equity interest in MimiVax, LLC. Author Henry Kaminski has been a consultant for Roche, Takeda, Cabaletta Bio, UCB Pharmaceuticals, Canopy Immunotherapeutics, EMD Serono, Ono Pharmaceuticals, ECoR1, Gilde Healthcare, and Admirix, Inc. Argenx provides an unrestricted educational grant to George Washington University. He is an unpaid consultant for Care Constitution. Equity interest in Mimivax, LLC.

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EVALUATION OF MEASURES FOR OCULAR MANIFESTATIONS IN MYASTHENIA GRAVIS

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INTRODUCTION: Myasthenia Gravis (MG) commonly presents with diplopia and ptosis. There are limited studies assessing the validity and performance of multimodal ocular MG assessments.

OBJECTIVE: Compare different assessments for ocular MG to assess their ability to detect change and discriminate patients with different degrees of severity.

METHODS: Included patients with confirmed MG from 4 clinics in US/Canada. Patients completed questionnaires for demographic data, the ocular component of the Myasthenia Gravis Impairment Index (OMGII) a validated measure of MG impairments, and the diplopia questionnaire, quantifying diplopia for any cause. Raters assessed extra-ocular movements, ptosis, and diplopia in different positions; in centers with neuro-ophthalmologists, prism assessments were completed. Patients with a second visit were reassessed with all measures for change scores and relationship with patient impression. We compared the prevalence of diplopia and ptosis (questionnaires and examinations), correlations between the different assessments, and scores on different measures compared with self-reported symptom satisfaction vs. those dissatisfied.

RESULTS: We enrolled 52 participants (37% female; mean age 67± 13 years), 15 (29%) had generalized disease, with mean disease duration= 8 years± 9.6. For 7 total assessments (visit 1+2), 56 (71.8%) of patients reported diplopia and 41 (52.6%) reported ptosis in OMGII; 32.1% had abnormal EOM exam, 55.1% reported diplopia and 70.5% had ptosis during exam. The OMGII total score correlated moderately (r 0.51-0.69, $p < 0.05$) with most assessments. The OMGII ptosis and diplopia questions correlated highly with ptosis (r 0.73, 0.83, $p < 0.05$) and diplopia (r 0.75, 0.86, $p < 0.05$) assessments, respectively. EOM exam poorly correlated (r 0.36, $p <0.05$) with OMGII and diplopia assessments (r 0.29, $p < 0.05$).

CONCLUSION: Varying strength in relationship between OMGII and different ocular evaluations. This study found self-reported measures more accurately reflected patient impression of disease burden compared to one time-point physical examinations.

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IMPROVEMENT OF OCULAR SUBDOMAIN SCORES WITH ZILUCOPLAN IN PATIENTS WITH GENERALISED MYASTHENIA GRAVIS IN RAISE AND RAISE-XT STUDIES

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INTRODUCTION: Ocular symptoms in gMG impact the daily activities of patients. RAISE (NCT04115293), a Phase 3, double-blind, placebo-controlled study of zilucoplan, a complement component 5 inhibitor, demonstrated clinically meaningful improvements in MG-ADL and QMG total scores in patients with AChR Ab+ gMG.

OBJECTIVE: To evaluate the effect of zilucoplan on MG-ADL and QMG ocular symptoms in patients with gMG in RAISE and RAISE-XT (NCT04225871), an ongoing, Phase 3, open-label extension study.

METHODS: In RAISE, adults with AChR Ab+ gMG were randomised 1:1 to once-daily subcutaneous zilucoplan 0.3 mg/kg or placebo self-injections for 12 weeks. Adults who completed RAISE or a Phase 2 study (NCT03315130) entered RAISE-XT to receive zilucoplan 0.3 mg/kg. The primary outcome of RAISE-XT was incidence of treatment-emergent adverse events (TEAEs). We assessed (*post hoc*) change from baseline (CFB) in MG-ADL and QMG ocular subdomain scores at Week 12 of RAISE and Week 120 of RAISE-XT in patients with baseline scores ≥1 in that subdomain. Ocular subdomains in MG-ADL and QMG both assess ptosis and diplopia, with QMG additionally assessing facial muscles. A decrease in score indicates an improvement in these symptoms.

RESULTS: At Week 12 of RAISE, mean (standard error [SE]) CFB in MG-ADL ocular subdomain scores was −1.53 (0.19) for zilucoplan (n=79) and −0.86 (0.17) for placebo (n=83). For QMG, mean (SE) CFB was −2.05 (0.24) for zilucoplan (n=80) and −1.27 (0.24) for placebo (n=82). At Week 120 of RAISE-XT, mean (SE) CFB was −1.37 (0.27; n=41) and −2.52 (0.30; n=52) for MG-ADL and QMG ocular subdomain scores, respectively. TEAEs occurred in 97.0% (n=194/200) of patients (interim data cut-off: 11 November 2023).

SUMMARY/CONCLUSION: Treatment with zilucoplan led to improvements in MG-ADL and QMG ocular subdomain scores that were sustained through to Week 120, supporting the use of zilucoplan in patients with ocular symptoms.

DISCLOSURES: M. Isabel Leite is funded by the NHS (Myasthenia and Related Disorders Service and National Specialised Commissioning Group for Neuromyelitis Optica, UK) and by the University of Oxford, UK. She has been awarded research grants from UK associations for patients with myasthenia and with muscular disorders (Myaware and Muscular Dystrophy UK, respectively) and the University of Oxford. She has received speaker honoraria or travel grants from Biogen, the Guthy-Jackson Charitable Foundation, Novartis and UCB. She serves on scientific or educational advisory boards for argenx, Horizon Therapeutics (now Amgen) and UCB. Saskia Bresch has served as a paid Consultant for Alexion Pharmaceuticals, argenx, Biogen, Bristol Myers Squibb, Merck, Roche, Sandoz, Sanofi Genzyme (now Sanofi) and UCB. Miriam Freimer has served as a paid Consultant for Alexion Pharmaceuticals, argenx and UCB. She receives research support from Alnylam Pharmaceuticals, Avidity Biosciences, Fulcrum Therapeutics, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), the NIH and UCB. Channa Hewamadduma has received funding for consultancy on scientific or educational advisory boards for argenx, Biogen, Lupin, Roche and UCB, and has received an investigator-led research grant from UCB. His study activities were supported by a Sheffield NIHR BRC UK centre grant. He is a trustee of the myasthenia gravis patient organisation Myaware. Angelina Maniaol has received payment for travel, meeting attendance, consulting honoraria or advisory board participation from Alexion Pharmaceuticals, argenx, Biogen, CSL Behring, Novartis and UCB. Kimiaki Utsugisawa has served as a paid Consultant for argenx, Chugai Pharmaceutical, HanAll Biopharma, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), Merck, Mitsubishi Tanabe Pharma, UCB and Viela Bio (now Amgen); he has received speaker honoraria from Alexion Pharmaceuticals, argenx, the Japan Blood Products Organization and UCB. Babak Boroojerdi, Fiona Grimson and Natasa Savic are employees and shareholders of UCB. James F. Howard Jr. has received research support (paid to his institution) from Ad Scientiam, Alexion/AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, 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), NMD Pharma, PCORI and UCB; has received honoraria/consulting fees from AcademicCME, Alexion/AstraZeneca Rare Disease, Amgen, argenx, Biohaven Ltd, Biologix Pharma, CheckRare CME, Curie.Bio, F. Hoffmann-La Roche, Medscape CME, Merck EMD Serono, NMD Pharma, Novartis, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics, UCB and Zai Labs; and has received non-financial support from Alexion/AstraZeneca Rare Disease, argenx, Biohaven Ltd, Toleranzia AB and UCB.

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LONG-TERM PROPHYLACTIC ANTIBIOTIC USE IN ADDITION TO MENINGOCOCCAL VACCINES DURING ZILUCOPLAN TREATMENT: SINGLE SITE EXPERIENCE FROM PHASE 3 STUDIES

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INTRODUCTION: As is standard practice for complement component 5 inhibitors, including zilucoplan, patients were required to receive vaccination with a quadrivalent meningococcal vaccine and, where available, meningococcal serotype B vaccine ≥14 days before the first dose of zilucoplan in the Phase 3 RAISE (NCT04115293) and RAISE-XT (NCT04225871; 200 patients enrolled) studies. In line with local hospital guidance, patients at one site received long-term prophylactic antibiotics against *Neisseria meningitidis* in addition to their meningococcal vaccines. To date, no meningococcal infections have occurred in zilucoplan-treated patients.

OBJECTIVE: Describe safety outcomes in a subgroup of patients with AChR Ab+ gMG who received long-term prophylactic antibiotics against Neisseria meningitidis in addition to meningococcal vaccines in RAISE and RAISE-XT.

METHODS: We assessed patients enrolled in RAISE and RAISE-XT from a single study site who received low-dose phenoxymethylpenicillin or erythromycin as prophylaxis concomitantly with zilucoplan 0.3mg/kg, in line with local guidance. Adverse events typically associated with antibiotics, including gastrointestinal toxicities, yeast infections and allergic reactions, were described in this subgroup.

RESULTS: Fourteen patients were included. Median (range) follow-up time in studies was 2.4 (0.9–3.6) years (data cut-off: 11 November 2023). Median (range) percentage of time spent on antibiotics was 99.5% (72.9–100). There were 18 adverse events of interest, all non-serious unless otherwise stated: abdominal pain/discomfort (n=5), urticaria (n=4), vulvovaginal candidiasis (n=3), vomiting (n=2; 1 serious), angioedema (n=1; serious; switched from phenoxymethylpenicillin to erythromycin), diarrhoea (n=1), dyspepsia (n=1) and rash pruritic (n=1). One event of abdominal pain was severe; all others were mild/moderate. Relatedness of the adverse events to antibiotics was not captured. None of these adverse events led to study discontinuation or discontinuation of long-term antibiotic use.

SUMMARY/CONCLUSION: Prophylactic long-term antibiotic use was tolerated in this subgroup. It is important for clinicians to remain cautious of potential side effects and emergence of antibiotic resistance.

DISCLOSURES: M. Isabel Leite is funded by the NHS (Myasthenia and Related Disorders Service and National Specialised Commissioning Group for Neuromyelitis Optica, UK) and by the University of Oxford, UK. She has been awarded research grants from UK associations for patients with myasthenia and with muscular disorders (Myaware and Muscular Dystrophy UK,

respectively) and the University of Oxford. She has received speaker honoraria or travel grants from Biogen, the Guthy-Jackson Charitable Foundation, Novartis and UCB. She serves on scientific or educational advisory boards for argenx, Horizon Therapeutics (now Amgen) and UCB. Fiona Grimson, Shital Patel and Babak Boroojerdi are employees and shareholders of UCB.

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IDENTIFICATION OF NOVEL BIOMARKERS FOR MYASTHENIA GRAVIS DISEASE AND PROGRESSION

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INTRODUCTION: Currently, there are no established prognostic biomarkers predicting outcomes in myasthenia gravis (MG) and the understanding of the underlying immunopathogenesis is limited.

OBJECTIVE: To identify plasma protein expression patterns that differentiate MG cases from healthy controls (HC) and to explore potential biomarkers predictive of achieving remission.

METHODS: Plasma from 60 newly diagnosed MG cases and 51 age- and sex-matched HCs was assayed on the Olink EXPLORE 1536 panel, measuring 1460 pre-selected soluble proteins. Protein expression was reported as relative NPX values, and corrected for age, sex, and sample handling. Groupwise expression differences were calculated using post-hoc ANOVA test. Survival analyses were performed to investigate time to remission (defined as quantitative MG score, QMG, = 2 and no rescue treatment within 3 months).

RESULTS: Amongst cases, mean age was 59.5 years (SD 18.6), 36.7% were females, 88.3% AChR+, baseline QMG was 5.9 (SD 4.4) and 86.7% were untreated. Significant expression differences between MG and HC were found in nine proteins, with the strongest association observed in oligodendrocyte myelin glycoprotein (OMG; adj. $p < 0.0001$), which is expressed in both the nervous system also and in leukocytes. Four of the nine proteins were associated to the STAT1/3 pathway. Further, altered expression of proteins linked to T-cell activation, including high expression of IL4R (adj. $p = 0.035$) and Granzyme H (adj. $p = 0.031$), was significantly associated with earlier remission (average 5 months for high expression vs 10 months for low expressors; HR = 0.25, 95% CI 0.12-0.55, $p = 0.00049$).

CONCLUSION: We observed plasma proteins differentially expressed between new-onset MG and matched HC. Additionally, we identified proteins linked to T-cell activation and migration as potential biomarkers of medium-term disease remission.

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MEDICATION USE BEFORE, DURING AND AFTER PREGNANCY IN A POPULATION-BASED COHORT OF NORWEGIAN AND SWEDISH WOMEN WITH MYASTHENIA GRAVIS

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INTRODUCTION: MG-medication is often necessary during pregnancy, and pregnancy can itself trigger a deterioration of MG. Generally, pyridostigmine and prednisolone are considered safe to use in pregnancy. Methotrexate, mycophenolate mofetil and cyclophosphamide are known teratogens and ideally avoided by women planning to conceive. However, discontinuing treatment can jeopardize the health of both mother and child.

OBJECTIVE: To assess medication use in a population-based MG pregnancy-cohort.

METHODS: This drug utilization study is based on linked nationwide health- and population registers from Norway and Sweden, harmonized and pooled to create one cohort. We included all pregnancies lasting at least 22 weeks, from 2010–2020 in Norway and 2008–2019 in Sweden, in mothers with MG. Maternal MG was identified by either an MG-diagnosis (ICD-10: G70.0) or >1 pyridostigmine prescription fills before or during pregnancy. We identified medication use over 3-month periods, from 1 year before pregnancy to 6 months postpartum.

RESULTS: Preliminary analyses show 225 women with MG contributing with 321 pregnancies, from a background population of 1,962,396 pregnancies. Pyridostigmine was used before, during, and after pregnancy by 37%, 34%, and 29%, respectively; prednisolone by 12%, 10% and 11%; and azathioprine by 8%, 7%, and 8%. Known teratogens were rarely used before pregnancy ($N < 5$), and never during pregnancy.

SUMMARY/CONCLUSION: A large proportion did not use any MG-medications around pregnancy. Known teratogens were adequately discontinued before pregnancy. Immunosuppressant use decreased during pregnancy but increased again postpartum, which may indicate MG deterioration. In the next step we will include combinations of medications and drug-use patterns, by employing group-based trajectory modeling, a data-driven technique that will identify groups with similar drug-use patterns (e.g., discontinuers, initiators, etc.). These groups will be described in detail by clinical characteristics. Drug-use trajectories can inform about real-world medication use patterns and act as proxies for disease severity.

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DEVELOPMENT OF A REFINED EXPERIMENTAL AChR-MG MOUSE MODEL

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INTRODUCTION: MG is an autoimmune disorder primarily caused by autoantibodies that target the AChR at the neuromuscular junction (NMJ). The classical experimental autoimmune MG mouse model (C-EAMG) has long been used by immunizing mice with AChR from Torpedo fish (T-AChR), combined with complete Freund's adjuvant (CFA). This mixture is administered via subcutaneous injections in the hind footpads and back, but CFA often causes strong inflammatory reactions.

OBJECTIVE: Our objective was to develop a new EAMG model (N-EAMG) more compliant with animal welfare.

METHODS: C57Bl/6 mice were immunized twice weekly by intraperitoneal (i.p.) injection of T-AChR with a poly(I:C) and lipopolysaccharide (LPS) adjuvant mix. Control mice were injected with either physiological saline or the adjuvant mix alone. Various doses and injection schedules were tested, and the new model was compared with C-EAMG. Clinical symptoms were scored, Anti-AChR subtypes were measured, and NMJ morphology and functionality were evaluated.

RESULTS: We demonstrated that the N-EAMG model was as effective as the C-EAMG model with the production of AChR antibodies. This model also exhibited alterations in transmission at the NMJ due to antibody attack, resulting in a decrease in AChR surface area and increased AChR fragmentation. Symptoms were similar in both models but appeared more rapidly in the N-EAMG model. In addition, by investigating the sensitization mechanism, we demonstrated that this immunization process led to the recruitment of monocytes and changes in the two peritoneal macrophage subpopulations that were able to phagocyte T-AChR. These macrophages may contribute to the specific anti-AChR response.

CONCLUSION: Our results demonstrate that this novel EAMG model is as effective as the C-EAMG model and offers several advantages. In particular, it is more suitable for animal welfare and can serve as a replacement for the classical model in preclinical and fundamental research.

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MULTICENTER, MULTINATIONAL, NATURAL HISTORY STUDY IN PARTICIPANTS WITH DOK7 CONGENITAL MYASTHENIC SYNDROMES

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INTRODUCTION: Congenital Myasthenic Syndromes (CMS) are a heterogenous group of rare, inherited, congenital disorders of the neuromuscular junction (NMJ) characterized by early age of onset and fatigable skeletal muscle weakness. Genetic mutations of the NMJ underlie CMS, and mutations in Docking Protein 7 (DOK7) are one of the more frequent causes of CMS (DOK7-CMS). Due to the rarity of the disease, there is a lack of published natural history data.

OBJECTIVE: To retrospectively and prospectively collect clinical data measuring disease activity and progression over time in patients with DOK7-CMS, to gain a better understanding of disease to inform future study design.

METHODS: This multicenter, multinational, natural history study aims to enrol adult participants with DOK7-CMS. Participants attend up to 3 study visits (Day 1 screening/baseline visit; Month 3 visit; and Month 12/end-of-study visit); Month 3 and 12 visits could be conducted via telephone if an onsite visit was unfeasible.

RESULTS: This study collects participants' demographics, CMS disease history, and HRQoL measures, including age at symptom onset, and diagnosis, biallelic pathogenic mutations in DOK7, healthcare utilization, medications, and change in health status. Secondary endpoints include clinical outcome measures that can potentially be used in future clinical trials studying experimental therapies in CMS. At each applicable timepoint, absolute values and change from baseline for Quantitative Myasthenia Gravis total score, Myasthenia Gravis Activities of Daily Living (MG-ADL) total score, EuroQol 5-Dimension 5-Level, and the Patient-Reported Outcomes Measurement Information System Global Health Scale, Dyspnea Functional Limitations, and Timed Up and Go test are evaluated. MG-ADL is also completed by participants monthly at home as a patient-reported outcome.

SUMMARY/CONCLUSION: By evaluating signs, symptoms and health-related quality of life (HRQoL) in participants with DOK7-CMS, this study aims to improve understanding of both the disease and the clinical outcome measures to evaluate new therapies.

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Limited, Sanofi-Genzyme, Santhera, Sarepta, Satellos, Spark Therapeutics, and Ultragenyx. Author Jaqueline Palace reports disclosures with Alexion, Amplo, argenx, Chugai, Clene, Janssen, Medimmune, Merck Serono, Mitsubishi, Novartis, Roche, Sandoz, Sanofi, Medimmune, Amgen, UCB and Vitaccess. She has a Patent ref P37347WO and license agreement with Numares multimarker MS diagnostics and shares in AstraZeneca. Her group has been awarded an ECTRIMS fellowship and a Sumaira Foundation grant to start later this year. She was a Charcot fellow working in Oxford 2019-2021. She acknowledges partial funding to the trust by Highly Specialized Services, NHS England. She is on the medical advisory boards of the Sumaira Foundation and MOG Project charities, is a member of the Guthy Jackon Foundation Charity, is on the board of the European Charcot Foundation and the steering committee of MAGNIMS and the UK NHSE IVIG Committee, is chairman of the NHSE Neuroimmunology Patient Pathway, and is an ECTRIMS Council member on the educational committee since June 2023. She is on the ABN advisory groups for MS and neuroinflammation and neuromuscular diseases. The remaining authors are all employees at argenx.

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IMMUNE CHECKPOINT INHIBITORS-RELATED MYASTHENIA, MYOSITIS AND MYOCARDITIS: A SINGLE CENTER EXPERIENCE

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INTRODUCTION: Neurological immune-related adverse events (NirAEs), although rare, can be very serious or even fatal. Myositis is the most frequent and usually it presents along with MG and myocarditis, defining the so-called condition ‘triple M syndrome’.

OBJECTIVE: To report the clinical characteristics and the outcome of patients with immune checkpoint inhibitors (ICI)-related triple M syndrome seen in our tertiary referral hospital between 2021 to 2024.

METHODS: Five patients with triple M syndrome were diagnosed, including 1/5 females. Median age at onset was 78 years (range:67-85) and median time from ICI therapy start to the NirAE onset was 48 days (range:17-66). All patients were treated with anti-PD1 or PD-L1.

RESULTS: Myositis symptoms where prevalent over MG in3/5 patients. A mild/moderate proximal weakness and diplopia were the most prevalent signs in all patients, followed by bulbar symptoms, which were present in 4/5 patients. CPK and Troponin T levels were elevated in all cases with respectively median peak of 1578 U/L and 1338,5 pg/mL. Interestingly, in 3/5 patients anti-AChR antibodies were detected, but just 1/5 cases showed a positive nervous repetitive stimulation, while 2/5 patients had signs of myositis on electromyography. No one showed specific myositis antibodies. In spite of a prompt diagnosis and early start of immunotherapy (within a median of 1,5 days (0-15) from diagnosis), 3/5 patients rapidly died because of the severity of the NirAE, preventing the escalation to second line immunotherapies. with a. 2/5 patients survived and went into neurological remission, but ICI treatment was not re-challenged, and one of them died for the tumor progression.

SUMMARY/CONCLUSION: Despite Triple M syndrome is a well-known ICI adverse event and promptly treated in referral centers, the clinical outcome is still poor, especially when myocardial involvement is relevant. Beyond first line, acute immunotherapy, more targeted second lines treatment are warranted.

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TARGETING THE HUMAN NICOTINIC ACETYLCHOLINE RECEPTOR BY NOVEL RECOMBINANT HUMAN MONOCLONAL AUTOANTIBODY

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INTRODUCTION: Myasthenia gravis (MG) is a rare chronic autoimmune neuromuscular degeneration affecting breathing, swallowing, movement and vision. The IgG autoantibodies targeting the alpha subunit of nicotinic acid acetyl choline receptor (nAchR), disrupt post-synaptic communication between nerves and muscles causing debilitating and potentially life-threatening muscle weakness in 85% of MG.

OBJECTIVE: A first-in-kind fully human anti-nAcHR monoclonal autoantibody (nAchR autoHuMAb) was developed to calibrate patient autoantibody levels in the non-radioactive ELISA and cell-based assay to the standard activity measured by radio-receptor immune precipitation assay (RIPA).

METHODS: The nAchR autoHuMAb was produced in the culture supernatants of HEK293D cells by transient expression from two separate plasmids carrying heavy (H) and light (L) chain immunoglobulin genes. Six concentrations of protein A-purified IgG1, range 2-500 ng/mL, were prepared in human serum and measured by RIPA nmole/L activity, immune fluorescence titer Euroimmun Biochip (IIFT-CBA) and ELISA RSR Ltd.

RESULTS: Logistic linear regression analysis of RIPA activity (nmole/L) versus ng/mL anti-nAchR HuMAb, ng/mL, y= 8.017x 1.0947, r=1, $p<0.001$. Binding activity was confirmed by ELISA. nAchR autoHuMAb gave positive adult and fetal nAcHR and null IIFT of muscarinic receptor (MuSKR) 1:10 dilution, 15 ng/mL anti-nAcHR HuMAb.

SUMMARY/CONCLUSION: Anti-nAchR AutoHuMAb ng/mL calibration is robust and stable in immunoassays after repeated freeze-thaw cylces, offering a reference standard for quantitative reporting of autoantibody levels. Cost savings and greater accessibility of non-radioactive myasthenia gravis blood diagnostics are anticipated by use of nAchR autoHuMAb. Therapeutic strategies involving the identification and localization of nAchR in myasthenic thymus and the engineering of nAchR autoHuMAb to block the post-synaptic binding of pathogenic anti-nAcHR autoantibodies are under investigation.

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DAILY EVALUATION OF EARLY EFFECT OF INNOVATIVE THERAPIES IN GENERALIZED MYASTHENIA GRAVIS IN THE FIRST WEEK OF TREATMENT

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INTRODUCTION: Innovative therapies have clearly changed the therapeutic landscape of Myasthenia Gravis (MG) due to their efficacy and safety. In addition, their effect appears to be faster than traditional immunosuppressive drugs, although innovative treatments are not approved as rescue therapy.

OBJECTIVE: To evaluate daily MG-ADL changes over the first week of treatment in generalized MG (gMG) patients treated with innovative therapies in 2 Italian centres.

METHODS: We collected data from 47 gMG patients (32/68% females and 15/32% males, treated with innovative therapies including: zilucoplan in 15 (32%) patients, ravulizumab in 11 (22%), eculizumab in 9 (19%), rozanolixizumab in 8 (17%), efgartigimod in 4 (8%). Antibodies to AChR were present in 39 (83%) patients and to MuSK in 8 (17%), all of which treated with rozanolixizumab. MG-ADL was administered every day for the first 7 days since the start of each innovative treatment to underline early responses. Patients were considered as responders when MG-ADL score was reduced by 2 points.

RESULTS: Mean age at the beginning of treatment was 54.2±13.5 years (range 35-81). Mean MG-ADL score at baseline was 6.3±2.1 (range 4-19). Mean MG-ADL change in the follow-up period was 2.6 ± 2.4. Twenty-nine (61.7%) patients were responders within the first week of treatment: 10/15 (67%) were administered with zilucoplan, 7/11 (64%) with ravulizumab, 5/8 (62.5%) with rozanolixizumab, 4/9 (44%) with eculizumab, and 3/4 (75%) with efgartigimod. Most (26/29) of the patients considered as responders reached a 2-point reduction of MG-ADL within day 4 of the first week of treatment.

SUMMARY/CONCLUSION: Our data showed a response rate according to MG-ADL changes within the first week of treatment in around 60% of the cases, with a similar behavior among the considered drugs, except for eculizumab showing a lower rate of responders, probably related to its indication limited in Italy to refractory MG.

DISCLOSURES: Vincenzo Di Stefano reports support for travel from Alexion, Alnylam, Argenx, and UCB; compensation for speaking from Alexion, UCB, Argenx, and Alnylam; and sub-investigator roles in clinical trials for Alexion, Alnylam, Argenx, Dianthus, and Sanofi.

Fiammetta Vanoli received funding for consulting, speaking, and advisory boards from Alexion Pharmaceuticals, UCB Pharma, and Argenx. Silvia Bonanno received funding for travel, meeting attendance, and advisory board participation from Sanofi Genzyme, Biogen, Alexion, and Roche. Rita Frangiamore received funding for consulting and speaking from Alexion Pharmaceuticals, UCB, and Argenx. Carlo Giuseppe Antozzi received funding for travel, meeting attendance, and advisory board participation from Alexion, Momenta, Sanofi, Argenx, UCB, and Johnson & Johnson. Lorenzo Maggi received funding for travel, meeting attendance, and advisory board participation from Sanofi Genzyme, Roche, Biogen, Amicus Therapeutics, Alexion Pharmaceuticals, Janssen, UCB, Lupin, and Argenx. Pietro Luppino, Sofia Campo, Alessia Bonaventura, Christian Messina, Rachele Colombo, Eleonora Giacopuzzi Grigoli, and Giulia D'Alvano report no conflict of interest related to this work.

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HOCK IMMUNIZATION, A REFINED ALTERNATIVE TO DEVELOPING EXPERIMENTAL AUTOIMMUNE MYASTHENIA GRAVIS IN MICE. A GUIDELINES' UPDATE.

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INTRODUCTION: Experimental autoimmune myasthenia gravis (EAMG) is an active-immunization model that mimics the chronic phase of MG, characterized by muscle weakness and fatigue. In mice, the model requires a bilateral subcutaneous injection of tAChR in the hind footpads and over the scapulas, followed by a booster immunization (or two) in the thighs and over the scapulas. Unfortunately, footpad injections cause severe discomfort and can lead to progressive debilitation. Instead, hock immunization is comparable to footpad immunization in other disease models, with the advantage that it does not affect mobility and cause less discomfort. Thus, we hypothesized that hock immunization is a suitable alternative to injection in the footpads.

METHODS: 7-week-old female C57BL6/6J (B6) mice were injected bilaterally over the scapula and in the hocks or in the footpads for the primary immunization with torpedo Acetylcholine receptor (tAChR) or saline. All animals received a booster immunization 4 weeks later following the standard guidelines. Several parameters were used to assess muscle weakness and discomfort in these animals.

RESULTS: Inverted mesh measurements showed that tAChR hock-immunized animals presented with similar muscle weakness as tAChR footpad-immunized animals, which were both significantly weaker compared to saline-immunized animals. Hock-immunized animals presented a substantial weight loss compared to saline-injected animals before euthanasia. tAChR antibodies were detectable 8 weeks after primary immunization in both, hock and footpad, tAChR immunized animals with no differences between these before euthanasia. Additionally, sensitivity to curare was similar between hock and footpad tAChR immunized animals, both significantly requiring less curare to reach decrement by electromyography compared to saline-immunized animals. Regarding discomfort, hock immunized animals showed reduced sensitivity to mechanical stimuli during the experiment.

CONCLUSION: In conclusion, hock-immunization is a suitable and refined immunization alternative to develop the EAMG mouse model, with a similar disease incidence and severity and reduced immunization-caused discomfort compared to the standardized model.

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COMPLEMENT INHIBITOR THERAPY IN THYMOMA-ASSOCIATED MYASTHENIA GRAVIS: A REAL-WORLD EXPERIENCE

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INTRODUCTION: Thymoma-associated myasthenia gravis (TAMG) accounts for 15–20% of all myasthenia gravis (MG) cases and is typically associated with acetylcholine receptor antibodies. TAMG is characterized by more severe clinical manifestations and a suboptimal response to conventional immunosuppressive therapies. Despite this, TAMG patients are often underrepresented in clinical trials, leaving gaps in evidence for optimal treatment strategies.

OBJECTIVE: To assess the efficacy of complement inhibitors (CI) therapy in TAMG population.

METHODS: We retrospectively reviewed 23 TAMG patients who received CI therapy, with a minimum follow-up of six months. Additionally, we randomly included 22 MG patients without thymoma, treated with CI, in the control group. Clinical outcomes were measured using the Myasthenia Gravis-Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) scores at baseline, three, and six months after initiation of therapy.

RESULTS: Among the 23 TAMG patients, 21 initiated CI after thymectomy, with a median interval of eight years (IQR: 2.5-15) post-surgery. Notably, two patients achieved sufficient stabilization on CI to undergo thymectomy thereafter. The most frequent thymoma histological subtype was WHO type B2, detected in 43.5% of cases. Median MG-ADL score decreased from 11 (IQR: 8-15) to 3 (IQR: 2-5) and 4 (IQR: 1-5) at three and six months, respectively (both $p < 0.001$). Median QMG score decreased from 16 (IQR: 14-22) to 10 (IQR: 5-11) at three and six months (both $p < 0.001$). Prednisone dosage was tapered in 20 patients. No significant differences were observed between TAMG and MG patients without thymoma in MG-ADL, QMG and steroid reduction.

SUMMARY/CONCLUSION: CI therapy demonstrated significant clinical improvements in both MG-ADL and QMG scores, along with a steroid-sparing effect, suggesting its potential as an effective treatment for this challenging patient subgroup.

DISCLOSURES: Author Raffaele Iorio has received consultancy fees and speaker honoraria from Alexion, Argenx, UCB and Dianthus Therapeutics. Author Laura Fionda served as a consultant/advisor for Alexion, Argenx, UCB and Dianthus.

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INVESTIGATING THE EFFECT OF MENINGOCOCCAL VACCINATION IN PATIENTS WITH MYASTHENIA GRAVIS UNDERGOING COMPLEMENT INHIBITOR THERAPY

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INTRODUCTION: Patients receiving complement inhibitor therapy are at increased risk of life-threatening invasive meningococcal disease. Current guidelines recommend vaccination against meningococcal serogroups ACWY and B before initiating therapy. The standard vaccination course includes a single dose for ACWY and two doses for serogroup B, administered one month apart.

OBJECTIVE: To evaluate the rates of protection achieved following meningococcal vaccination in patients with generalized myasthenia gravis (gMG) undergoing complement inhibitor therapy.

METHODS: Serum samples were obtained from 26 patients with gMG and acetylcholine receptor antibodies, collected at least two weeks post-vaccination. Immunogenicity was assessed using a serum bactericidal antibody assay against serogroups ACWY, with baby rabbit complement as an exogenous source. A protective titer was defined as ≥1:8. We analyzed: 1) Protection rates among all patients after the first dose and 2) Protection rates before and after the second dose in a subgroup of patients who received both doses. For five patients, only post-second-dose titers were available.

RESULTS: After the first dose, protection rates were as follows: MenA, 12/21 (57%); MenC, 11/21 (52%); MenW, 9/21 (43%); and MenY, 14/21 (67%). In the subgroup of 17 patients who received both doses, protection rates improved after the second dose: MenA increased from 10/17 (59%) to 14/17 (82%); MenC from 9/17 (53%) to 14/17 (82%); MenW from 6/17 (35%) to 10/17 (59%); and MenY from 11/17 (65%) to 16/17 (94%). No specific type of immunotherapy was associated with reduced vaccine efficacy.

SUMMARY/CONCLUSION: Most patients developed only a partial antibody response against various meningococcal serogroups after the initial vaccination. ACWY booster doses are recommended to enhance protection in patients undergoing complement inhibitor therapy.

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DOSE-DEPENDENT PHENOTYPIC CORRECTION OF COLQ-DEFICIENT MICE BY ADENO-ASSOCIATED VIRUS TYPE RH74-MEDIATED GENE THERAPY

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INTRODUCTION: Mutations in human COLQ, which encodes the collagen-like tail subunit (ColQ) of acetylcholinesterase (AChE), cause congenital myasthenic syndrome (CMS) with deficiency of endplate AChE. There is currently no cure for COLQ-CMS and the response of this syndrome to AChE inhibitors is poor.

OBJECTIVE: Gene therapy of ColQ-knockout mice.

METHODS: ColQ-knockout mice were injected intravenously (IV) at P26-29 with three doses of an adeno-associated virus type rh74 (AAVrh74) carrying full-length human COLQ (AAVrh74-COLQ): 5e13, 1e14, and 2e14 vg/kg. Motor performance was evaluated using rotarod, grip strength and wire hang tests weekly for 12 weeks. Voluntary ambulation and repetitive nerve stimulation (RNS) were assessed once prior to euthanasia. Protein expression was measured via immunohistochemistry (IHC) and RNA expression was assessed using RT-qPCR.

RESULTS: Mice treated with AAVrh74-COLQ at 1e14 and 2e14 vg/kg doses showed 100% survival and no adverse side effects. Mice injected with 2e14 vg/kg showed full recovery and similar scores to wild type that were significantly higher than untreated mutants for grip strength (p-value < 0.0001), voluntary ambulation (p-value < 0.05) and RNS (p-value < 0.0001). Similar improvements were observed in mice injected with 1e14 vg/kg, although the recovery of grip-strength was incomplete. Mice injected with 5e13 vg/kg showed variable, incomplete recovery in most tests. IHC demonstrated full recovery of protein expression in 1e14 and 2e14 vg/kg mice and RT-qPCR unambiguously demonstrated that the source of the ColQ was human COLQ. Expression of human ColQ in heart tissue was dose dependent. Within liver and kidney tissue, organs involved in detoxification, there was no difference in expression between 1e14 and 2e14 vg/kg, but there was a decrease at 5e13 vg/kg.

SUMMARY/CONCLUSION: A single IV injection of AAVrh74-COLQ (1e14 to 2e14 vg/kg) was highly effective, safe and potentially curative for ColQ-knockout mice. These results encourage similar therapy for humans affected with COLQ-CMS causing deficiency of AChE.

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ADAPTATION OF THE MYASTHENIA GRAVIS SYMPTOM PATIENT-REPORTED OUTCOME SCALES FOR USE IN CLINICAL PRACTICE, CLINICAL STUDIES AND OBSERVATIONAL STUDIES

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INTRODUCTION: The five MG Symptoms Patient-Reported Outcome (PRO) scales provide a granular assessment of muscle weakness (ocular, bulbar and respiratory), muscle weakness fatigability and physical fatigue from the patient perspective. The independent scales were developed to capture the variability in MG symptoms over time and were used to demonstrate treatment efficacy in the Phase 3 MycarinG study (NCT03971422).

OBJECTIVE: Adapt the MG Symptoms PRO scales to optimise their future use in clinical practice, clinical studies and observational studies, with patient and clinician input.

METHODS: Qualitative 60-minute telephone interviews were conducted with adults diagnosed with generalised MG for ≥1 year and clinicians with ≥5 years' experience in managing patients with MG. Perspectives on using the scales to monitor symptoms in clinical practice and comprehensiveness of the scales in assessing patient-relevant symptoms were explored. Scale adaptations were guided by a steering committee of expert patients (n=4) and clinicians (n=4).

RESULTS: In total, 23 participants (16 patients; 7 clinicians) from Germany, Italy, Japan, the United States and the United Kingdom were interviewed. Patients indicated that the scales provided comprehensive MG symptom coverage (n=10/16); weak hands/wrists, a symptom not currently captured, was noted by patients (n=12/16). The PRO was considered a good

communication tool for clinical practice (patients: n=4/16; clinicians: n=2/7). The biggest barriers for its usage were its length (n=11/23) and the time required for completion and review (patients: n=13/13; clinicians: n=4/6). Recommendations to facilitate its use included reduction of its length (clinicians: n=3/5), though patients liked the granularity of the symptoms evaluated.

SUMMARY/CONCLUSION: The five MG Symptoms PRO scales monitor symptoms most relevant to patients to aid management of MG. Adaptation is required to improve suitability of the scales for use in clinical settings. Item reduction, informed by the interviews and psychometric analysis of data from clinical trials, is ongoing.

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CLINICAL OUTCOMES AND EVENTS IN A UNITED STATES GENERALIZED MYASTHENIA GRAVIS POPULATION: ANALYSIS OF REAL-WORLD DATA

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INTRODUCTION: Generalized myasthenia gravis (gMG) is a chronic autoimmune condition caused by pathologic autoantibodies that disrupt neuromuscular transmission, causing muscle weakness and fatigue. Treatments aim to improve clinical outcomes and reduce the frequency of exacerbations and life-threatening myasthenic crises.

OBJECTIVE: This analysis describes real-world clinical status and treatment patterns for a gMG population in the United States (US).

METHODS: Data were drawn from the Adelphi Myasthenia Gravis (MG) II Disease Specific Programme, with US data collected from February through August 2024.

RESULTS: Overall, 49 physicians reported on 312 patients with gMG (mean [SD] age, 55.5 [14.2] years; 53.2% male; 79.8% Caucasian/White). Patients had a mean (SD) time since diagnosis of 4.0 (5.3) years, 71.8% were anti-acetylcholine receptor antibody-positive, and 75.3% had comorbidities, most frequently hypertension (39.1%). Most patients were MG Foundation of America Class II or above (78.5%), and the mean (SD) MG-Activities of Daily Living (MG-ADL) score was 4.1 (3.1); mean MG-ADL scores in patients aged <50 and ≥50 years were 3.8 (2.9) and 4.3 (3.3), respectively. Patients had tried a mean (SD) of 1.6 (1.0) treatment regimens, and 81.7% were receiving maintenance treatment, with 46.3% receiving novel therapies (complement inhibitors, 16.5%; neonatal Fc receptor inhibitors, 15.7%; immunoglobulins, 12.5%). Exacerbation and myasthenic crisis since diagnosis were reported for 28.9% and 13.4% of patients, respectively; 45.6% of those with an exacerbation and 31.4% of those with a crisis experienced an event in the prior 12 months. Overall, 14.9% of patients had ≥1 MG-related hospitalization in the prior 12 months, and 17.3% had undergone thymectomy.

SUMMARY/CONCLUSION: Despite the use of novel therapies, patients with gMG continue to experience clinical exacerbations and myasthenic crises, highlighting suboptimal disease control. Further longitudinal analyses are required to understand the real-world impact of new and emerging therapies on clinical outcomes, as well as the associated costs.

DISCLOSURES: Authors Lesley-Ann Miller-Wilson, Lincy Lal, and Yuriy Edwards are employees of Immunovant, Inc. and may hold stock or stock options in Immunovant, Inc. Authors Joe Conyers, Shiva Lauretta Birija, Ciara Ringland, Hannah Connolly, Gregor Gibson, and Niall Hatchell are employees of Adelphi Real World.

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TREATMENT PATTERNS OF A UNITED STATES GENERALIZED MYASTHENIA GRAVIS POPULATION: ANALYSIS OF REAL-WORLD DATA

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INTRODUCTION: Pharmacological management of generalized myasthenia gravis (gMG) historically involved acetylcholinesterase inhibitors (AChEI), corticosteroids (CS) and non-steroidal immunosuppressive therapies (NSIST). Newer options include neonatal fragment crystallizable receptor (FcRn) inhibitors and complement inhibitors (CI).

OBJECTIVE: To describe treatment patterns in patients with gMG.

METHODS: Data were drawn from the Adelphi gMG II Disease Specific Programme™, a cross-sectional survey of US neurologists and their gMG patients from February through August 2024. Oversample data were collected on two recently approved treatments, efgartigimod and ravulizumab. All patients prescribed any gMG treatment were included.

RESULTS: Fifty-two neurologists provided data on 359 patients with gMG (52.4% male; 82.7% White; mean [SD] age, 55.4 [13.7] years). Patients had a mean (SD) time since diagnosis of 3.9 (5.1) years and a mean (SD) Myasthenia Gravis-Activities of Daily Living score of 4.5 (3.4). From diagnosis until the time of the survey, 43.7% of patients were prescribed only first-line treatment for their gMG (most common first-line regimens: AChEI monotherapy [21.7%], AChEI and CS [16.6%], NSIST monotherapy [8.7%]); 33.7% were prescribed second-line therapy (most common second-line regimens: AChEI and NSIST [11.9%], AChEI and CS [10.9%], AChEI and FcRn inhibitors [9.9%]); and 22.6% were prescribed third-line or later-line treatments (most common third-line or later regimens: CI monotherapy [11.1%], FcRn inhibitor monotherapy [9.9%], AChEI and FcRn inhibitors [9.9%]). FcRn inhibitors and CI accounted for 16.1%, 36.6%, and 72.8% of prescriptions for first-, second-, and third-line or later-line therapy, respectively. Mean (SD) duration of first-line, second-line, and third-line or later regimens was 2.0 (3.5), 1.8 (2.3) and 1.3 (1.5) years, respectively.

SUMMARY/CONCLUSION: Targeted therapies for gMG, including FcRn inhibitors and CI, were prescribed more frequently in progressively later lines of therapy. The time spent on each line of therapy suggests an unmet need for treatments that provide more sustained disease control.

DISCLOSURES: Authors Lesley-Ann Miller-Wilson, Lincy Lal, and Yuriy Edwards are employees of Immunovant, Inc. and may hold stock or stock options in Immunovant, Inc. Authors Joe Conyers, Shiva Lauretta Birija, Ciara Ringland, Hannah Connolly, and Gregor Gibson are employees of Adelphi Real World.

THIS IS AN ENCORE PRESENTATION OF: Miller-Wilson, L-A. et.al. (2025, March 16-19). *Treatment Patterns of a United States Generalized Myasthenia Gravis Population: Analysis of Real-World Data* [Conference presentation abstract]. 2025 Muscular Dystrophy Association

(MDA) Clinical & Scientific Conference in Dallas, TX, United States. https://www.mdaconference.org/abstract-library/treatment-patterns-of-a-united-states-generalized-myasthenia-gravis-population-analysis-of-real-world-data/

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PATIENT-REPORTED OUTCOMES FROM A SURVEY OF REAL-WORLD GENERALIZED MYASTHENIA GRAVIS PATIENTS IN THE UNITED STATES

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INTRODUCTION: Generalized myasthenia gravis (gMG) is a chronic neuromuscular condition characterized by skeletal muscle weakness and fatigue. Symptoms impair patients' ability to perform activities of daily living (ADL) and negatively impact employment and quality of life (QoL). This analysis describes patient-reported outcome measures (PROM) in patients with gMG.

METHODS: Data were drawn from a cross-sectional survey of patients with gMG in the US in October 2024. Patients reported demographic characteristics, current symptoms, prescribed treatments, and PROM including the Myasthenia Gravis (MG)-ADL, MG-QoL-15r, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, EuroQol 5-dimension 5-level (EQ-5D-5L) (US tariff), EuroQol Visual Analogue Scale (EQ-VAS), and Work Productivity and Activity Impairment (WPAI) questionnaires.

RESULTS: Patients (N=244) were primarily female (88.1%), with a mean (SD) age of 49.0 (14.5) years at time of survey and 36.0 (16.7) years at first onset of symptoms. The most frequent current symptoms were physical fatigue (88.9%), weakness in the legs (69.3%) or arms (68.4%), blurred or double vision (66.0%) and mental fatigue (65.6%). At the time of survey completion, acetylcholinesterase inhibitors were the most commonly prescribed medications (74.6%), followed by non-steroidal immunosuppressants (43.0%), corticosteroids (40.6%), immunoglobulins/plasmapheresis (29.9%), neonatal fragment crystallizable receptor inhibitors (16.0%) and complement inhibitors (13.9%). Mean (SD) scores on the MG-ADL, MG-QOL-15r, FACIT-Fatigue, EQ-VAS and EQ-5D-5L were 8.3 (3.7), 16.3 (7.4), 20.6 (11.3), 58.6 (18.5), and 0.67 (0.21), respectively. Overall QoL was subjectively reported as "poor" or "very poor" by 18.4% of patients, and 30.3% reported having worse QoL than 12 months ago. Mean (SD) WPAI scores for overall productivity loss and activity impairment were 42.0% (25.0%) and 55.2% (25.2%), respectively.

SUMMARY/CONCLUSION: This gMG patient population reported ongoing symptoms and worsening QoL >10 years after initial onset, despite prescribed treatments. PROM scores highlight specific areas of unmet need, including impaired ADL, fatigue, and reduced ability to work.

DISCLOSURES: Authors Lesley-Ann Miller-Wilson, Lincy Lal, and Yuriy Edwards are employees of Immunovant, Inc. and may hold stock or stock options in Immunovant, Inc. Authors Joe Conyers, Shiva Lauretta Birija, Ciara Ringland, Hannah Connolly, and Gregor Gibson are employees of Adelphi Real World.

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Patients in the United States [Conference presentation abstract]. 2025 Muscular Dystrophy Association (MDA) Clinical & Scientific Conference in Dallas, TX, United States. https://www.mdaconference.org/abstract-library/patient-reported-outcomes-from-a-survey-of-real-world-generalized-myasthenia-gravis-patients-in-the-united-states/

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ESTABLISHING STABLE ACETYLCHOLINE RECEPTOR EXPRESSION IN RD CELLS USING THE PIGGYBAC SYSTEM: IMPROVING PLATFORMS FOR FUNCTIONAL ASSAYS

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ABSTRACT: Cell-based assays (CBAs) and radioimmunoprecipitation assay (RIPA) are the most sensitive methods for detecting anti-acetylcholine receptor (AChR) antibodies in myasthenia gravis (MG). However, CBAs are limited in clinical practice due to the transient nature of transfection and to the variability of the amount of protein expressed. The need for a cell line stably expressing clustered AChR is therefore compelling. To address this, we aimed to establish stable 293T and rhabdomyosarcoma (RD) cell lines expressing human adult clustered AChR (293T-AChR and RD-AChR) using the PiggyBac (PB) transposon system. Cells were transfected with the PB system to enable stable integration of the AChR subunit genes into the genome. This was accomplished using two plasmids: one encoding the CHRNA1, CHRNB1, and RAPSN genes, and a second encoding CHRND and CHRNE. The transfection protocol included hyPBase mRNA encoding the PiggyBac transposase, which facilitated genomic integration and ensured stable AChR expression. In the 293T cell line, RT-PCR confirmed the molecular expression of AChR subunits CHRNA1, CHRNB1, CHRND, and CHRNE; however, assembled AChR was not detectable on the plasma membrane. Conversely, the RD-AChR cell line showed both successful RT-PCR expression of all AChR subunits and surface expression of AChR on the plasma membrane, as confirmed by alpha-bungarotoxin and anti-AChR serum IgG specific binding, observed by flow cytometry. We believe that the RD-AChR cell line represents a reliable platform for diagnostic applications and functional assays, including complement activation, AChR blocking, and antibody-mediated AChR internalization.

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AZATHIOPRINE TOXICITY IN PATIENTS WITH MYASTHENIA GRAVIS: A SINGLE CENTER EXPERIENCE

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INTRODUCTION: Azathioprine (AZA) is widely used as a first-line immunosuppressive agent for myasthenia gravis (MG) based on expert consensus and clinical trials. However, data on its toxicity in MG patients remain limited, as most research focuses on gastrointestinal disorders. A 1986 study examined AZA toxicity in neuromuscular disorders (including 27 MG patients) and another study focused on hepatotoxicity and myelosuppression in AZA in 2016.

OBJECTIVE: To characterize the side-effect profile of AZA in MG patients.

METHODS: Patients were identified using EPIC's SlicerDicer tool. Inclusion criteria: MG diagnosis confirmed by antibody/electrodiagnostic testing, evaluation by a neuromuscular-trained physician at Duke, and AZA use between 1/1/2014-7/1/2023.

RESULTS: Of 155 patients, 19 were excluded due to incomplete data. Among 136 patients, 91 (67%) experienced a lab-defined side effect or flu-like reaction, with 43/91 (32% of total) discontinuing AZA. Patients with side effects were older on average than those who did not have a side effect. The most common reaction was leukopenia (29%), although only 20% of these cases involved infection. Most leukopenia cases improved with dose reduction. Other lab-defined reactions included macrocytosis (26%) (which is expected), elevated liver function tests (21%), thrombocytopenia (5%), and anemia (4%). Flu-like reactions occurred in 11% of patients, with an average onset of 15 days after initiation, dose of 125 mg (1.4 mg/kg), and age of 63 years. The most common flu-like reaction symptoms included fevers (subjective), chills, night sweats, nausea/vomiting, and general malaise. Cancer occurred in 4% of patients post-AZA initiation. Most patients were started on AZA before the routine testing of TPMT and establishment of an EPIC alert.

SUMMARY/CONCLUSION: AZA toxicity is common in MG patients, but most cases are asymptomatic and improve with dose adjustments. The cancer rate was lower than the general population's expected incidence for the cohort's age. Flu-like reactions (11%) rarely exacerbated MG symptoms and resolved after AZA cessation.

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THE INCIDENCE OF MYASTHENIA GRAVIS IN THE PROVINCE OF BRITISH COLUMBIA, CANADA FROM JANUARY 2004 TO DECEMBER 2023

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INTRODUCTION: Acetylcholine receptor antibodies (AChR Abs) are present in 50% of ocular and over 80% of generalized acquired MG cases. Radio Immunoprecipitation Assay (RIPA) is the traditional method for detection of AChR Abs. Recently, live, and fixed Cell-Based assays have been developed for detection of AChR Abs in MG patients. BC Neuroimmunology laboratory is the sole provider of these tests in British Columbia (BC), Canada.

OBJECTIVE: Although MG is a rare disease, we have shown that its prevalence has increased in BC. We will update these studies and extend them for another 20-year period.

METHODS: In a population-based study for a period of January 1, 2004, to December 31, 2023, we have collected every AChR Ab positive incident case. We retrospectively identified all first-time seropositive tests. Incidence rates (IRs) were calculated per 1 million inhabitants based on annual July population estimates (www.bcstats.gov.bc.ca). Cases were stratified into 4 age groups: ≤19, 20-44, 45-64, and ≥ 65 years. Ninety-five percent confidence intervals were calculated using Poisson distribution.

RESULTS: The overall average IR of first-time AChR Ab seropositive cases over this 20 years period was 18.34 per year per million population. During the period of 2004-2023, seropositivity was higher in elderly males: 19.7 per year per million for males and 17.3 for females. The mean annual IRs of AChR Ab seropositivity increased with age, with a higher rate of increase in males compared to females: Among ≥ 65 years old IRs reached 61.7 per year per million, with 78.9 for males and 49.2 per year per million females.

SUMMARY/CONCLUSION: The overall average anti-AChR seropositivity IR in BC is among the highest reported. Our data indicate that the likelihood of becoming AChR Ab seropositive significantly increases with age and more so among men.

DISCLOSURES: Author Ali Mousavi is an employee at BC Neuroimmunology Lab. Author Joel Oger is a consultant at BC Neuroimmunology Lab. Author Pankaj Kumar is the CEO and lab director at BC Neuroimmunology Lab. Author Tariq Aziz is an employee at BC Neuroimmunology Lab. Author Hans Frykman is the owner of BC Neuroimmunology Lab. and the CSO at Neurocode Lab.

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DEVELOPING A SURFACE PLASMA RESONANCE IMAGE -BASED IMMUNOBIOSENSOR FOR ASSESSING THE AFFINITY MATURATION OF ACETYLCHOLINE RECEPTOR ANTIBODIES IN MYASTHENIA GRAVIS

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INTRODUCTION: Acquired MG is a prototype of B cell-mediated autoimmune disease where IgG class autoantibodies play a pivotal role in pathogenesis, however, 5-10% of MG patients are seronegative. It is believed that the immunopathology of seronegative MG patients is the same as seropositive patients and low-affinity AChR and MuSK Abs have been detected in up to 50% and 13 % of AChR and MuSK seronegative cases. In addition, autoantibodies with pathogenic capacity including the accumulation of somatic mutations have been isolated from patients with AChR Ab associated MG. Moreover, anti-MuSK Abs have been isolated from MG patients with expression of hallmarks of affinity maturation, including somatic mutations. Using an SPR device, the purified MuSK protein has been immobilized while minimizing non-specific binding to the sensor chip, employing a Biacore-patented method involving surface activation, blocking, and immobilization steps and the affinity of MuSK antibodies were measured.

OBJECTIVE: To purify anti-AChR antibodies and measure their autoantibody affinity Using an SPR device.

METHODS: An SPR immunoassay was developed for AChR Abs. Sera were pretreated with Protein A to obtain purified IgG which flowed over a sensorchip composed of AChR captured by immobilized alpha-bungarotoxin. We analyzed the binding responses and further characterized the IgG subtypes. In a separate assay using a low-density surface of AChR, we determined the antibody dissociation rates, an indicator of antibody affinity. A total of 16 sera from AChR Ab seropositive MG patients and 10 healthy sera were analyzed.

RESULTS: This is an ongoing study and in its preliminary results, the developed SPR immunoassay successfully detected all 16 AChR Ab positive samples confirmed by RIPA as positive, while correctly identifying the 10 healthy control sera as negative.

SUMMARY/CONCLUSION: The SPR immunoassay can provide detailed information on the concentration, IgG isotype, and affinity of AChR Abs, enhancing the diagnosis of MG.

DISCLOSURES: Author Ebrima Gibbs is the CSO at BC Neuroimmunology Lab. Author Pankaj Kumar is the CEO and lab director at BC Neuroimmunology lab. Author Ali Mousavi is an employee at BC Neuroimmunology lab. Author Tariq Aziz is an employee at BC Neuroimmunology lab. Hans Frykman is the owner of BC Neuroimmunology Lab and CSO at Neurocode Lab.

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RITUXIMAB IN JUVENILE MYASTHENIA GRAVIS: A SINGLE CENTRE CASE SERIES

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INTRODUCTION: Juvenile myasthenia gravis (JMG) is a rare autoimmune disorder marked by weakness due to autoantibodies targeting the neuromuscular junction, most commonly acetylcholine receptor (AChR) and muscle-specific kinase (MuSK) antibodies. Refractory cases present therapeutic challenges despite standard treatments. Rituximab, a B-cell-depleting monoclonal antibody, has emerged as a potential therapy in adult myasthenia gravis, yet its paediatric applications remain underexplored.

OBJECTIVE: To describe the efficacy and tolerability of Rituximab in eight girls with antibody-positive JMG

METHODS: This case series includes 7 girls (ages 8–18 years) with refractory JMG treated at a single centre with Rituximab after failing conventional therapies, including corticosteroids and immunosuppressants. Baseline and follow-up assessments included Myasthenia Gravis Activities of Daily Living (MG-ADL) scores, corticosteroid doses, number of hospital admissions and adverse events.

RESULTS: Five girls with AChR antibodies and two with MuSK antibodies were included. 5/7(71%) girls demonstrated significant clinical improvement. MG-ADL scores decreased significantly, with the greatest reduction observed in MuSK-positive patients. Steroid-sparing effects were achieved in 5 cases, with two Musk patients benefitting the most. Pharmacological remission was achieved in 5 patients (3 AChR-positive, 2 MuSK-positive). Number if hospital admissions dropped to). One was refractory with no response and one had an allergic response and infusion was abandoned. Rituximab was well-tolerated in the remaining. Redosing was needed in all that responded.The mean duration of follow up was 1.5 years(6m -3 years)

CONCLUSIONS: Rituximab was effective and well-tolerated in this series with refractory JMG, including both AChR- and MuSK-positive cases. These findings highlight its potential as a targeted therapy for antibody-mediated JMG.

DISCLOSURES: P. Munot discloses she has received a travel grant for this meeting from UCB. She has received clinical trial support from ARGNX and UCB.

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DESIGN OF A DIGITAL SOLUTION TO IMPROVE MYASTHENIA GRAVIS PATIENT SYMPTOM TRACKING IN ROUTINE CLINICAL CARE

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INTRODUCTION: The fluctuating nature of myasthenia gravis (MG) symptoms creates challenges for disease management. Validated patient-reported outcomes (PROs) are utilized in clinical research to assess symptom changes over time, but tracking in routine clinical practice could be improved.

OBJECTIVE: Determine design requirements for a digital tool utilizing validated PROs to improve symptom tracking and communication between patients with MG and healthcare practitioners (HCPs) in routine practice.

METHODS: A literature review and preliminary interviews with patients with MG (n=3) and HCPs (n=4) were conducted to assess the current state of MG symptom tracking and identify opportunities for improvement. Structured workshops with HCPs (n=5) and validation interviews with patients (n=10) and HCPs (n=9) were held to design a novel digital tool and understand factors influencing adoption. Participating patients and HCPs were US-based. Transcripts were analyzed for themes regarding challenges, preferred solutions, and benefits and applications of the proposed digital tool.

RESULTS: Key design requirements included a two-sided digital solution where patients input validated PROs between clinic visits, and HCPs visualize longitudinal data on demand via integration with electronic health records. The MG-Activities of Daily Living score was the preferred primary visual, with ability to overlay subscores and other contextual data (ie, Patient Acceptability of Symptom State, Neuro-QoL Fatigue, hospitalizations, and medications). Free text patient diary entries with artificial intelligence-generated summaries for HCPs were desired for additional contextualization and personalization. Factors influencing patient adoption included HCP use and potential for one central MG management tool. HCPs noted streamlined

visualizations enabling quick data synthesis to support treatment decisions and features to simplify insurance prior authorization/reauthorization would facilitate adoption.

SUMMARY/CONCLUSIONS: Patients and HCPs agreed the proposed solution would enhance clinical care by improving MG symptom tracking and ultimately treatment decisions. These results support continued development of the digital tool and studies investigating clinical utility.

DISCLOSURES: SM has served on advisory board meetings for Alexion, AstraZeneca Rare Disease, argenx, Horizon Therapeutics/Amgen, and Ra Pharmaceuticals (now UCB). JA has served as a paid consultant for Alexion Pharmaceuticals, argenx, and UCB; he has served on speakers' bureaus for Alexion Pharmaceuticals, argenx, and UCB. AELA has served on the speaker's bureau for Alexion Pharmaceuticals and has served and on advisory boards and as a paid consultant for Johnson & Johnson. N Silvestri has served as a paid consultant for Alexion Pharmaceuticals, Amgen, Annexon, argenx, UCB, and Immunovant; he has served on speakers' bureaus for Alexion Pharmaceuticals, argenx, and UCB. N Streicher has served as a speaker for Alexion and AstraZeneca Rare Disease. AVP, HJ, and AG are employees of ZS Associates, a company paid by Janssen Pharmaceuticals to undertake the analyses for this study. NC and ZC are employees of Janssen Pharmaceuticals and may hold stock in Johnson & Johnson.

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EFFECT OF APPLYING INCLUSION AND EXCLUSION CRITERIA OF PHASE III MG CLINICAL TRIALS TO TERTIARY MG CENTER CLINICAL CARE

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INTRODUCTION: Recent Complement and FCRN inhibitor therapies for AChR+ve gMG have had similar, restrictive inclusion and exclusion criteria, including moderate symptom burden and restrictions on concomitant therapies.

OBJECTIONS: To analyze the eligibility of acetylcholine receptor antibody-positive generalized myasthenia gravis (AChR+ve gMG) patients for phase III clinical trials

METHODS: This retrospective cohort study included AChR+ve gMG patients with documented myasthenia gravis activities of daily living (MG-ADL) scores seen in the clinic for the first time between January 2021 and December 2021. Longitudinal clinical information including MG history, concomitant treatment(s), and MG-ADL score was analyzed at each clinic visit to determine the clinical trial eligibility of patients until June 2023.

RESULTS: A total of 90 patients had a total of 454 visits between January 2021 and June 2023. Eighty-one out of 90 (90%) patients never met the eligibility criteria. Nine out of 90 (10%) patients at 17 out of 52 (32.7%) visits met the eligibility criteria for the clinical trials. In total, at 437 out of 454 (96.2%) visits, the patients did not meet the eligibility criteria for the clinical trials. MG-ADL >5 was the single most frequent criterion not fulfilled, followed by IVIG use within the last 4 weeks of clinic visit. At 104 out of 454 (22.90%) clinic visits where the MG-ADL score was >5, prior use of complement inhibitor medication and IVIG use within the last 4 weeks of clinic visit were the reasons for not meeting the eligibility criteria.

SUMMARY/CONCLUSION: The majority of AChR+ gMG patients seen for routine clinical care would not have met clinical trial criteria for recently completed phase III complement inhibitor and FCRN inhibitor trials. Broader inclusion criteria would increase patient eligibility and contribute to better generalizability of the results in clinical trials.

DISCLOSURES: Neelam Goyal has been an advisor and consultants for Alexion, Argenx, UCB/Ra Pharma, Janssen, Amgen, EMD Sereno, Novartis and has grant funding from Argenx. Author Srikanth Muppidi has attended advisory board meetings for Alexion, argenx, UCB/Ra, and Amgen Pharma.

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OBSERVED EFFICACY OF EFGARTIGIMOD IN GENERALIZED MYASTHENIA GRAVIS ACROSS PATIENT SUBGROUPS IN THE ADAPT-SC+ STUDY

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INTRODUCTION: Efgartigimod is a human immunoglobulin G1 (IgG1) antibody Fc-fragment that reduces total IgG levels (including pathogenic autoantibodies) through neonatal Fc receptor blockade. In the ADAPT-SC study, subcutaneous (SC) efgartigimod PH20 (coformulated with recombinant human hyaluronidase PH20) showed non-inferior total IgG reduction to intravenous (IV) efgartigimod in participants with gMG. Participants completing ADAPT-SC or enrolled in ADAPT+ (efgartigimod IV open-label extension) were eligible for the ADAPT-SC+ open label extension.

OBJECTIVE: To assess efficacy through post hoc analyses of efgartigimod PH20 SC in AChR-Ab+ participants in ADAPT-SC+ stratified by disease duration, thymectomy status, and concomitant MG therapies.

METHODS: Efgartigimod PH20 SC 1000 mg was administered in cycles of 4 once-weekly injections. Subsequent cycles were initiated based on clinical evaluation. MG-ADL scores assessed clinical efficacy.

RESULTS: In AChR-Ab+ participants (n=141), improvements in MG-ADL total score from cycle baseline (mean change [SE]) were observed at week 4 of Cycle 1 across multiple subgroups. This is demonstrated in participants with disease duration of <3 years (-3.4 [0.62]), 3-<6 years (-4.6 [0.48]), and ≥6 years (-4.1 [0.39]). Thymectomized (-4.5 [0.40]) and nonthymectomized (-3.8 [0.37]) participants showed similar improvements. Participants receiving only concomitant acetylcholinesterase inhibitors (AChEis) (-5.5 [0.77]), any nonsteroidal immunosuppressive treatments (-3.8 [0.38]), or any steroids (-3.8 [0.31]) also demonstrated similar improvements in MG-ADL total score.

SUMMARY/CONCLUSION: Efgartigimod PH20 SC resulted in consistent improvements in AChR-Ab+ participants across subgroups, including those only receiving AChEis. Clinical improvements across subgroups were similar to those seen during ADAPT, reinforcing the efficacy of efgartigimod across a broad gMG population.

DISCLOSURES: Author Srikanth Muppidi discloses he has served on advisory board meetings for Alexion, argenx, UCB/Ra, and Horizon Pharma. Author Tuan Vu discloses he has served as a

speaker for Alexion, argenx, and CSL Behring; performed consulting work for argenx, Alexion/Astra Zeneca, Dianthus, ImmunAbs, and UCB; and participated in trials in MG sponsored by Alexion/Astra Zeneca, argenx, UCB, Amgen, Immunovant, Regeneron, Johnson & Johnson, Dianthus, and Cartesians Therapeutics. Authors Edward Brauer and René Kerstens are employees of Argenx. Author Kimiaki Utsugisawa discloses he has served as a paid Consultant for UCB Pharma, Janssen Pharma, Horizon Therpeutics (Viela Bio), Chugai Pharma, Hanall BioPharma, Merck, and Mitsubishi Tanabe Pharma, and has received speaker honoraria from argenx, Alexion Pharmaceuticals, UCB Pharma, and the Japan Blood Products Organization. Author Andreas Meisel discloses he has received speaker honoraria from Alexion Pharmaceuticals, Inc, argenx, Grifols, SA, Hormosan Pharma GmbH, Novartis, and UCB; honoraria from Alexion Pharmaceuticals, Inc, argenx, Janssen, Merck, and UCB for consulting services; and financial research support (paid to his institution) from Octapharma, argenx, and Alexion Pharmaceuticals, Inc. He is a member of the medical advisory board of the German Myasthenia Gravis Society.

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PROMISE-MG: LESSONS LEARNED

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INTRODUCTION: Promise-MG is the first observational comparative effectiveness study of azathioprine (AZA) and mycophenolate (MMF) for MG.

OBJECTIVES: To compare the effectiveness of (1). AZA vs. MMF and (2). adequate doses/durations (AZA: ≥ 2 mg/kg/day for ≥ 12 months; MMF: ≥ 2g/day for ≥ 8 months) vs. lower doses/shorter durations of AZA/MMF. (3). Discuss lessons learned regarding trial design.

METHODS: Prospective cohort study of adults with MG, naïve to immune treatments/thymectomy. Treating clinicians selected drugs, dose, follow-up intervals and laboratory monitoring. Co-primary outcomes were: MG-QOL15r; composite outcome including MGFA-PIS MM or better with ≤ grade 1 Common Terminology Criteria for Adverse Events (CTCAE). Secondary outcomes were MG-ADL, MG-Composite and MG-MMT. Propensity score weighted regression was used.

RESULTS: Among 167 patients enrolled, 31 were treated with AZA and 47 with MMF. Greatest change in MG-QOL15r: MMF: –10.4; AZA: –6.8, difference (95% confidence interval, CI) –3.3

(–7.7 to 1.2, p=0.15). The composite outcome was achieved in 20% more MMF treated patients (-4.9 to 44.2, p=0.12). Clinically meaningful reduction (CMR) in the 3 secondary outcomes was achieved by 57-84% of AZA and 81-89% of MMF-treated patients, p NS. Time to CMR for 75% of patients: AZA 14-23 months, MMF 13-18 months. Outcomes were not different between adequate and lower dose/duration. Median MMF dose was 2 g/day; AZA 1.2 mg/kg/day. Eleven (32%) AZA-treated vs. 9 (19%) MMF-treated had adverse events (AEs) (RD 13%, -5 to 32, p NS); AEs to AZA: pancytopenia, transaminitis; MMF: gastrointestinal.

SUMMARY/CONCLUSION. AZA and MMF were effective; AEs to AZA were more frequent and serious. This study was designed to replicate clinical care. Statistical imprecision precluded the ability to detect differences between AZA/MMF. Recruitment of drug-naïve patients in tertiary centers proved challenging; including ocular MG reduced the AZA/MMF analysis population. Trial design lessons learned will be discussed.

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EFFECTIVENESS AND SAFETY OF RAVULIZUMAB IN GENERALIZED MYASTHENIA GRAVIS: UPDATED REGISTRY ANALYSES

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INTRODUCTION: In prior analyses from the ongoing, global MG SPOTLIGHT Registry (NCT04202341), ravulizumab was well tolerated and effective in clinical practice.

OBJECTIVE: To assess updated effectiveness and safety data for the complement protein C5 inhibitor therapy (C5IT) ravulizumab among patients with gMG in routine clinical practice.

METHODS: MG-ADL total scores and MGFA classification were assessed in patients enrolled in the MG SPOTLIGHT Registry who received ravulizumab only (ravu-only subgroup) or transitioned from eculizumab to ravulizumab (ecu-to-ravu subgroup) with data available prior to C5IT initiation ("pre-C5IT") and ≥1 assessment post-ravulizumab initiation ("post-ravu"). This descriptive study had no adjustment for covariates. Safety was assessed in all patients.

RESULTS: 114/249 patients enrolled as of 1/1/2024 met inclusion criteria (male: 62%; mean±SD age at MG diagnosis: 57.9±18.6 yrs). Among patients with 1 pre-C5IT and 2 post-ravu assessments (n=52), average ravulizumab treatment duration was 4.1 mo at first post-ravu assessment (FA) and 10.4 mo at last post-ravu assessment (LA). Mean±SD MG-ADL scores improved (pre-C5IT: 7.6±3.6; FA: 3.9±3.6; LA: 3.4±3.3), as did the proportions of patients with minimal symptom expression (MSE, MG-ADL≤1) (pre-C5IT: 1/52 [2%]; FA: 18/52 [35%]; LA: 17/52 [33%]). In the ecu-to-ravu subgroup, improvements were largest post-eculizumab initiation (pre-C5IT vs last eculizumab assessment: mean±SD MG-ADL, 8.0±4.0 vs 4.4±4.2; MSE, 1/24 [4%] vs 7/24 [29%]) with sustained/gradual improvements through LA (3.0±2.8; 9/24 [38%]). In the ravu-only subgroup, outcomes improved post-ravu (pre-C5IT vs LA: mean±SD

MG-ADL, 6.3±3.0 vs 4.0±3.4). Ravulizumab was well tolerated; no meningococcal infections were reported. Updated data will be presented.

SUMMARY/CONCLUSION: Consistent with prior findings, these results demonstrate the long-term effectiveness and safety of ravulizumab in patients with gMG in routine clinical practice.

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SAFETY OUTCOMES IN PREGNANT PATIENTS TREATED WITH THE COMPLEMENT 5 INHIBITOR THERAPY ECULIZUMAB

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INTRODUCTION: Pregnancy can induce protective immunological changes including complement amplification, which may unmask or worsen complement-mediated conditions such as generalized myasthenia gravis (gMG), neuromyelitis optica spectrum disorder (NMOSD), paroxysmal nocturnal hemoglobinuria (PNH), and atypical hemolytic uremic syndrome (aHUS). To date, eculizumab exposures during pregnancy have not suggested safety concerns, but with limited reported exposures since FDA approval (PNH, 2007; aHUS, 2011; gMG, 2017; NMOSD, 2019), further investigation is needed. Available pregnancy-related safety data for complement 5 inhibitor therapies (C5ITs) will provide further information for clinical decision-making.

OBJECTIVE: To report pregnancy-related safety outcomes for eculizumab-treated patients.

METHODS: A cumulative analysis of pregnancy outcomes in patients treated with eculizumab (March 16, 2007–April 1, 2024) from the Alexion pharmacovigilance safety database was conducted across approved indications, unknown indications, and off-label use from all sources (clinical trials, postmarketing data, literature, and registries).

RESULTS: Overall, 2043 eculizumab maternal exposures during pregnancy included patients with PNH (n=1095, 54%), aHUS (n=387, 19%), gMG (n=92, 5%), NMOSD (n=32, 2%), and unknown indications/off-label use (n=437, 21%). Among all exposures, 628/2043 (31%) had known outcomes; of these, 382/628 (61%) resulted in live birth and 140/628 (22%) ended in spontaneous abortion.

SUMMARY/CONCLUSION: Regardless of indication, live birth was the most common outcome with eculizumab exposure; spontaneous abortion rates were aligned with the general US population (15%–20%). Limitations include small proportion of exposures with known outcomes, limited disease-specific data, and selective reporting bias. To address the limitations of pharmacovigilance data, further investigations include exploring pregnancy outcomes with ravulizumab, a long-acting C5IT, in an observational study (currently recruiting; NCT06312644).

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CHARACTERIZING AND QUANTIFYING IMPACTS OF GENERALIZED MYASTHENIA GRAVIS ON PATIENTS AND CAREGIVERS

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INTRODUCTION: The impact of rare diseases is typically defined by the burden of symptoms on patients and of medical costs borne by patients and payers; however, patient and caregiver burdens also encompass other areas of daily life but are often not captured.

OBJECTIVE: To quantitatively assess the indirect impacts of gMG on the daily lives of US patients and caregivers in life domains identified through patient/caregiver interviews.

METHODS: Qualitative semistructured interviews of patients with gMG and caregivers identified 25 patient-centered “impact elements” across 8 life domains (occupation, financial, emotional, physical, sleep, social, planning and autonomy, and safety). Independently recruited patients and caregivers who completed a subsequent electronic, quantitative survey (August-December 2023) rated the 25 impact elements on relevance, frequency, and severity, which were evaluated on a scale of 1 (lowest) to 5 (highest).

RESULTS: Respondents included 239 patients with gMG (aged 18-49y, 63%; female, 69%) and 81 caregivers (aged 18-49y, 58%; female, 42%). The 5 domains most impacted by gMG for patients were occupational (average Domain Score [SD]: 4.0 [1.2]), planning and autonomy (4.0 [1.1]), financial (3.9 [1.2]), physical (3.9 [1.1]), and sleep (3.9 [1.2]). For caregivers, the 5 domains most impacted were financial (3.7 [1.2]), sleep (3.7 [1.1]), occupational (3.6 [1.2]), planning and autonomy (3.6 [1.1]), and safety (3.6 [1.1]). This study was limited by convenience sampling.

SUMMARY/CONCLUSION: This study quantified the indirect impacts experienced by US patients with gMG and caregivers, which extend beyond symptoms and medical costs. These findings provide additional insight into the comprehensive burden of gMG.

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CONCOMITANT IMMUNOSUPPRESSIVE THERAPY USE IN PATIENTS WITH GMG RECEIVING ECULIZUMAB OR RAVULIZUMAB

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INTRODUCTION: Complement component 5 (C5) inhibitor therapies (C5ITs) eculizumab (ecu) and ravulizumab (ravu) are approved for anti-acetylcholine receptor antibody-positive (AChR-Ab+) generalized myasthenia gravis (gMG). Although concomitant immunosuppressive therapies (con-ISTs) can be effective in gMG, high doses may be associated with adverse events (AEs). The global MG SPOTLIGHT Registry (NCT04202341) assesses C5IT safety/effectiveness and con-IST use in adults with gMG in clinical practice.

OBJECTIVE: Describe changes in con-IST use after ecu and/or ravu initiation.

METHODS: This analysis included registry patients who transitioned from ecu to ravu, had available con-IST (azathioprine, mycophenolate mofetil, intravenous immunoglobulin/plasma exchange, oral corticosteroid [OCS]) data, and received ecu and ravu for ≥1yr. Frequency/type of serious AEs were assessed.

RESULTS: 61/226 gMG patients in the Registry (02Oct2023) transitioned from ecu to ravu (male: 60.7%; mean±SD ages: 56.2±20.4yrs [MG diagnosis]; 61.9±16.8yrs [ecu initiation]; 64.8±17.1yrs [ecu-to-ravu transition]), with treatment durations of 2.8±1.8yrs (ecu) and 0.8±0.4yrs (ravu). At ecu initiation, 61.9%, 35.7%, and 2.4% were receiving 1, 2, and 3 con-ISTs, respectively; after C5IT, the number of con-ISTs used decreased in 16/42 patients (38.1%), increased in 4/42 (9.5%), and was unchanged in 22/42 (52.4%). OCS dose (mg/day) decreased from ecu initiation (14.5±15.0; n=32) to last ravu dose assessed (6.2±7.0). The proportion of patients receiving ≤5 and ≤10 mg/day OCS increased from 37.5% and 62.5%, respectively, to 68.8% and 81.3% after C5IT. C5ITs were well tolerated, consistent with previous analyses and clinical trial data.

SUMMARY/CONCLUSION: These descriptive registry results representing clinical practice demonstrate reduced OCS burden in patients with AChR-Ab+ gMG receiving ecu and ravu. No adjustment for confounders was performed. Data for patients receiving ravu only are forthcoming.

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UNDERSTANDING THE LIVED EXPERIENCES OF PEOPLE WITH GENERALISED MYASTHENIA GRAVIS AND THE IMPACT ON DAILY LIFE: A MIXED METHODS STUDY

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INTRODUCTION: Generalised MG (gMG) is a rare autoimmune neuromuscular disorder that can profoundly impact daily life, including physical, mental, and social wellbeing.

OBJECTIVE: To understand the lived experience of people with gMG (PWgMG) and identify diagnostic challenges and needs that persist despite current treatments.

METHODS: Qualitative interviews with PWgMG and specialist healthcare professionals (HCPs) informed development of a quantitative survey of PWgMG (themes: pre-diagnosis, diagnosis, treatment, living with gMG) in Germany, Italy, UK, and US. Interview data underwent thematic analysis. Statistics are descriptive.

RESULTS: Fourteen PWgMG (71% female) and 10 neuromuscular specialists/neurologists were interviewed. PWgMG were surveyed in pilot (n=5) and quantitative phases (n=90; 64% female). The most common pre-diagnosis symptoms among surveyed PWgMG (n=90) were fatigue (66%), generalised muscle weakness (58%), and ptosis (54%). Most PWgMG (89%) reported symptoms affecting daily life. Time to seeking medical advice and time to diagnosis varied by country, symptoms experienced and age. PWgMG typically visited 2–3 HCPs pre-diagnosis and 25–65% were initially misdiagnosed with conditions including mental health (40%) and neurological disorders (30%). PWgMG approached patient organisations (POs) for information at diagnosis more commonly in UK (68%) than Italy (26%), Germany (11%), or US (10%). PWgMG expressed needs for resources to facilitate shared decision-making with HCPs and increase gMG awareness among primary care physicians (PCPs). The most common concerns of PWgMG (54%) at treatment initiation were side effects and long-term safety. Despite treatment, PWgMG reported ongoing fatigue (72%) and continued burdens on social interactions (52%), hobbies (48%), and work/study (48%). Interviewed HCPs identified needs for improved HCP/PCP awareness of gMG and reported challenges related to insurance, comorbidities, speed-of-action, side effects, and family planning.

SUMMARY/CONCLUSION: PWgMG have concerns around treatment side-effects/safety and experience limitations in daily activities. Resources to support shared decision-making and HCP communication are needed.

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IDENTIFICATION OF DISEASE PHENOTYPES IN ACETYLCHOLINE RECEPTOR-ANTIBODY MYASTHENIA GRAVIS USING PROTEOMICS-BASED CONSENSUS CLUSTERING

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INTRODUCTION and OBJECTIVE: The clinical heterogeneity of myasthenia gravis constitutes a challenge for patient stratification and treatment decision making. Novel strategies are needed to classify patients based on their biological phenotypes aiming to improve patient selection and treatment outcomes.

METHODS: To target this knowledge gap, we assessed the serum proteome of a cohort of 140 patients with anti-acetylcholine receptor-antibody-positive MG and employed consensus clustering as an unsupervised tool to assign patients to biological profiles. Further, we performed immunogenomic sequencing on a subset of patients to analyze the B cell repertoire and conducted in vitro assays on primary human muscle cells to study serum-induced complement formation.

RESULTS: This strategy identified four distinct patient phenotypes based on their proteomic patterns in their serum. Notably, one patient phenotype, here named PS3, was characterised by high disease severity and complement activation as defining features. Assessing a subgroup of patients, hyperexpanded antibody clones were present in the B cell repertoire of the PS3 group and effectively activated complement as compared to other patients. In line with their disease phenotype, PS3 patients were more likely to benefit from complement-inhibiting therapies. These findings were validated in a prospective cohort of 18 patients using a cell-based assay.

SUMMARY/CONCLUSION: Our study highlights proteomics-based clustering as a practical approach to stratify MG patients by biological signatures. This clustering approach enables the identification of patients likely likely to benefit from complement inhibition and provides a stratification strategy for clinical practice.

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MYASTHENIA GRAVIS INEBILIZUMAB TRIAL (MINT): UNDERSTANDING THE IMPACT ON QUALITY-OF-LIFE

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INTRODUCTION: Recent topline MINT results support efficacy and safety in generalized Myasthenia Gravis (gMG) as assessed by patient- (MG-ADL) and physician-reported (QMG) measures. However, the extent of disease burden is not fully assessed as they do not take into account the social/work context of disability. A deeper understanding of the impact on quality-of-life (QOL) and patient-reported change is necessary.

OBJECTIVE: To determine if inebilizumab (anti-CD19 B-cell depletion therapy) improves patient-reported QOL in gMG.

METHODS: MINT (NCT04524273) was a phase 3 study aimed to evaluate the efficacy and safety of inebilizumab in adult participants with gMG. The randomized controlled period (RCP) was 52-weeks for AChR+ and 26-weeks for MuSK+ populations. Participants were given 300mg of inebilizumab or placebo on RCP Day-1, Day-15, and Day-183 (AChR+ only). Participants on prednisone underwent a protocol-required steroid taper to ≤5mg/day. Secondary endpoints included a change from baseline in MG Quality-of-Life-15 revised (MGQOL-15r) score and Patient Global Impression of Change (PGIC) score at Week-26 and Week-52 (primary analysis).

RESULTS: 119 participants were randomized to inebilizumab (95 AChR+/24 MuSK+); 119 to placebo (95 AChR+/24 MuSK+). At Week-26, greater numerical improvement in MGQOL-15r scores were observed in the inebilizumab group compared to placebo (inebilizumab vs. placebo (95% CI), combined:-5.7 vs.-4.5 (-2.9, 0.4); AChR+:-4.9 vs.-3.6 (-3.0, 0.6); MuSK+:-6.5 vs.-5.1 (-5.8, 3.1)). At Week-52 in AChR+ subpopulation, numerically greater improvement in MGQOL-15r was observed in the treated group [inebilizumab vs. placebo:-5.7 vs.-1.8 (-5.9, -1.9)]. Using PGIC as a participant's rating of their overall health, participants who received inebilizumab reported a significant improvement in their condition at Week-26 ('Much Improved', inebilizumab vs. placebo, combined:41.2% vs. 23.5%, p=0.001; AChR+:38.9% vs.

21.0%; MuSK+:50.0% vs. 33.3%) and at Week-52 in AChR+ ('Very Much Improved', 21.1% vs. 8.6%).

SUMMARY/CONCLUSION: Findings suggest that inebilizumab treatment has a positive impact on patient-reported quality-of-life and health change in gMG.

DISCLOSURES: R.J. Nowak receives research support from the National Institutes of Health, Genentech, Inc., Alexion Pharmaceuticals, Inc., argenx, Annexon Biosciences, Inc., Ra Pharmaceuticals, Inc. (now UCB S.A.), the Myasthenia Gravis Foundation of America, Inc., Momenta Pharmaceuticals, Inc. (now Janssen), Immunovant, Inc., Grifols, S.A., and Viela Bio, Inc. (Horizon Therapeutics, now Amgen Inc.). Served as a consultant and advisor for Alexion Pharmaceuticals, Inc., argenx, Cabaletta Bio, Inc., Cour Pharmaceuticals, Ra Pharmaceuticals, Inc. (now UCB S.A.), Immunovant, Inc., Momenta Pharmaceuticals, Inc. (now Janssen), and Viela Bio, Inc. (Horizon Therapeutics, now Amgen Inc.). K. Utsugisawa served as a paid consultant for UCB Pharma, argenx, Janssen Pharma, Viela Bio (Horizon Therapeutics, now Amgen Inc.), Chugai Pharma, Hanall BioPharma, Merck and Mitsubishi Tanabe Pharma, and has received speaker honoraria from Argenx, Alexion Pharmaceuticals, UCB Pharma and the Japan Blood Products Organization. M. Benatar receives research support from Immunovant & Alexion. Served as a consultant to Alexion, Cartesian, Canopy, CorEvitas, Horizon Therapeutics (now Amgen Inc.), Immunovant, Sanoi, Takeda, and UCB. E. Ciafaloni received compensation for serving on advisory boards and/or as a consultant for Alexion, argenx, Biogen, Amicus, Pfizer, Italfarmaco, Sarepta, Janssen, NS Pharma, and Roche. M.I. Leite funded by the NHS (Myasthenia and Related Disorders Service and National Specialised Commissioning Group for Neuromyelitis Optica, UK) and by the University of Oxford, UK. She has been awarded research grants from the UK association for patients with myasthenia (Myaware), Muscular Dystrophy UK and the University of Oxford. She has received speaker honoraria or travel grants from Biogen, Novartis, UCB Pharma, and the Guthy-Jackson Charitable Foundation. She serves on scientific or educational advisory boards for UCB Pharma, argenx, and Horizon Therapeutics (now Amgen Inc.). J. Vissing advisor on advisory boards for Regeneron, UCB Pharma, argenx, Alexion Pharmaceuticals, Horizon Therapeutics (now Amgen Inc.), Dianthus Therapeutics, Janssen, and Roche. F. Tang, Y. Wu, C. Najem, S. Cheng are employees of and stockholders in Amgen Inc. M. Rojavin was an employee at the time of the study. J.F. Howard Jr. receives research funding from Ad Scientiam, Alexion AstraZeneca Rare Disease, argenx, Cartesian, Centers for Disease Control and Prevention, MGFA, Muscular Dystrophy Association, NMD Pharma, NIH, PCORI, and UCB Pharma; honoraria/consulting fees from AcademicCME, Alexion AstraZeneca Rare Disease, Amgen, argenx, Biohaven Ltd, Biologix Pharma, CheckRare CME, CorEvitas, Curie.bio, F. Hoffmann-LaRoche Ltd,-Medscape CME, Merck EMB Serono, Novartis Pharma, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics UCB Pharma, and Zai Labs; non-financial support from Alexion, argenx, Biohaven Ltd, Cartesian Therapeutics, Toleranzia AB, UCB Pharma and Zai Labs.

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MYASTHENIA GRAVIS INEBILIZUMAB TRIAL (MINT): REDUCED RISK OF MG EXACERBATIONS, RESCUE THERAPY USE, AND CORTICOSTEROID BURDEN

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INTRODUCTION: Generalized Myasthenia Gravis (gMG) is characterized by fluctuating weakness and by autoreactive B-cells playing an essential role in upstream immunopathogenesis through the production of autoantibodies. The MINT primary endpoint (change in MG-ADL score) was achieved supporting the efficacy of inebilizumab in gMG. MG exacerbations, which may lead to life-threatening respiratory failure, and rescue therapy use are a significant burden on health care resources and patients.

OBJECTIVE: To determine if inebilizumab (anti-CD19 B-cell depletion therapy) reduces the risk of disease exacerbations and rescue therapy (RT) use in patients with gMG.

METHODS: MINT (NCT04524273) was conducted to evaluate efficacy and safety of inebilizumab in adult gMG patients. The randomized controlled period (RCP) was 52-weeks for AChR+ and 26-weeks for MuSK+ populations. Participants received 300mg of inebilizumab or placebo on RCP Day-1, Day-15, and Day-183 (AChR+ only). Participants on prednisone underwent a protocol-required steroid taper to ≤5mg/day. Secondary endpoints included risk of exacerbations and use of RT at Week-26 and Week-52 (primary analysis).

RESULTS: 119 participants were randomized to inebilizumab (95 AChR+/24 MuSK+); 119 to placebo (95 AChR+/24 MuSK+). At baseline, the mean steroid dose (mg/day) was comparable between treatment groups (inebilizumab vs. placebo, combined:16.6±11.5 vs. 18.5±12.5; AChR+:17.7±11.7 vs. 17.8±12.1; MuSK+:12.1±9.6 vs. 21.1±13.6). At Week-26, mean steroid dose was reduced in both treatment groups (inebilizumab vs. placebo, combined:5.4±4.3 vs. 5.5±4.2; AChR+:5.7±4.6 vs. 4.8±2.6; MuSK+:4.1±2.1 vs. 7.9±7.2). Inebilizumab-treated participants experienced lower risk of exacerbation than placebo through Week-26 ([Hazard Ratio, 95% CI, nominal p-value]; combined:0.41(0.24-0.70), p=0.001; AChR+:0.49(0.27-0.90), p=0.021; MuSK+:0.21(0.06, 0.79), p=0.020) and Week-52 in AChR+ (0.40[0.23-0.70], p=0.001). Fewer participants in the inebilizumab group used RT compared to placebo through

Week-26 (inebilizumab vs. placebo, nominal p-value, combined:8.4% vs. 23.9%, p=0.005; AChR+:9.5% vs. 23.7%, p=0.016; MuSK+:4.2% vs. 25.0%, p=0.191) and Week-52 in AChR+ (11.6% vs. 34.4%, p=0.005).

SUMMARY/CONCLUSION: Inebilizumab treatment reduced risk of MG exacerbation and RT use while successfully tapering steroid.

DISCLOSURES: R.J. Nowak receives research support from the National Institutes of Health, Genentech, Inc., Alexion Pharmaceuticals, Inc., argenx, Annexon Biosciences, Inc., Ra Pharmaceuticals, Inc. (now UCB S.A.), the Myasthenia Gravis Foundation of America, Inc., Momenta Pharmaceuticals, Inc. (now Janssen), Immunovant, Inc., Grifols, S.A., and Viela Bio, Inc. (Horizon Therapeutics, now Amgen Inc.). Served as a consultant and advisor for Alexion Pharmaceuticals, Inc., argenx, Cabaletta Bio, Inc., Cour Pharmaceuticals, Ra Pharmaceuticals, Inc. (now UCB S.A.), Immunovant, Inc., Momenta Pharmaceuticals, Inc. (now Janssen), and Viela Bio, Inc. (Horizon Therapeutics, now Amgen Inc.). K. Utsugisawa served as a paid consultant for UCB Pharma, argenx, Janssen Pharma, Viela Bio (Horizon Therapeutics, now Amgen Inc.), Chugai Pharma, Hanall BioPharma, Merck and Mitsubishi Tanabe Pharma, and has received speaker honoraria from Argenx, Alexion Pharmaceuticals, UCB Pharma and the Japan Blood Products Organization. M. Benatar receives research support from Immunovant & Alexion. Served as a consultant to Alexion, Cartesian, Canopy, CorEvitas, Horizon Therapeutics (now Amgen Inc.), Immunovant, Sanoi, Takeda, and UCB. E. Ciafaloni received compensation for serving on advisory boards and/or as a consultant for Alexion, argenx, Biogen, Amicus, Pfizer, Italfarmaco, Sarepta, Janssen, NS Pharma, and Roche. M.I. Leite funded by the NHS (Myasthenia and Related Disorders Service and National Specialised Commissioning Group for Neuromyelitis Optica, UK) and by the University of Oxford, UK. She has been awarded research grants from the UK association for patients with myasthenia (Myaware), Muscular Dystrophy UK and the University of Oxford. She has received speaker honoraria or travel grants from Biogen, Novartis, UCB Pharma, and the Guthy-Jackson Charitable Foundation. She serves on scientific or educational advisory boards for UCB Pharma, argenx, and Horizon Therapeutics (now Amgen Inc.). J. Vissing advisor on advisory boards for Regeneron, UCB Pharma, argenx, Alexion Pharmaceuticals, Horizon Therapeutics (now Amgen Inc.), Dianthus Therapeutics, Janssen, and Roche. F. Tang, Y. Wu, C. Najem, S. Cheng are employees of and stockholders in Amgen Inc. M. Rojavin was an employee at the time of the study. J.F. Howard Jr. receives research funding from Ad Scientiam, Alexion AstraZeneca Rare Disease, argenx, Cartesian, Centers for Disease Control and Prevention, MGFA, Muscular Dystrophy Association, NMD Pharma, NIH, PCORI, and UCB Pharma; honoraria/consulting fees from AcademicCME, Alexion AstraZeneca Rare Disease, Amgen, argenx, Biohaven Ltd, Biologix Pharma, CheckRare CME, CorEvitas, Curie.bio, F. Hoffmann-LaRoche Ltd,-Medscape CME, Merck EMB Serono, Novartis Pharma, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics UCB Pharma, and Zai Labs; non-financial support from Alexion, argenx, Biohaven Ltd, Cartesian Therapeutics, Toleranzia AB, UCB Pharma and Zai Labs.

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MODIFICATIONS EXTENDING THE SERUM HALF-LIFE OF INTRAVENOUSLY ADMINISTERED ACETYLCHOLINE RECEPTOR A1 SUBUNIT EXTRACELLULAR DOMAIN RESULT IN IMPROVED THERAPEUTIC EFFICIENCY IN EXPERIMENTAL AUTOIMMUNE MYASTHENIA GRAVIS

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INTRODUCTION: Currently, treatment options for myasthenia gravis patients remain non-specific and mainly focus on the administration of immunomodulatory agents, which can lead to side effects. Consequently, novel approaches focusing on reprogramming of the autoimmune response to restore immune tolerance, comprise a compelling alternative to mainstay treatments.

OBJECTIVE: It has previously been shown that intravenous administration of the human acetylcholine receptor α1 subunit extracellular domain (α1-ECD), resulted in a dose-dependent reduction of clinical symptoms in ongoing disease in our rat experimental autoimmune MG (EAMG) model. We have now explored strategies to improve its pharmacokinetic characteristics.

RESULTS: To this end, protein conjugation to polyethylene glycol (PEG) units improved the protein's half-life in serum following intravenous administration, without affecting its tissue distribution. Furthermore, the use of the PEGylated protein allowed us to significantly lower the therapeutic dose of α1-ECD administered.

SUMMARY/CONCLUSION: These results support the use of modifications extending the serum life of protein therapeutics to improve their potency for intravenous tolerance induction.

DISCLOSURES: Konstantinos Lazaridis discloses he has received research support from Toleranzia AB.

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CLINICAL COURSE OF MYASTHENIA GRAVIS IN PREGNANCY

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INTRODUCTION: Myasthenia gravis (MG) is an autoimmune disorder in which antibodies bind to proteins at the neuromuscular junction and cause muscle weakness. In women, disease onset peaks during the childbearing years. Few large-scale studies examine whether pregnancy is a risk factor for MG exacerbations in the mother.

OBJECTIVE: To examine how pregnancy affects the clinical course of MG in the mother.

METHODS: This a register-based cohort study where the exposure is pregnancy and the outcome is MG exacerbation from after conception up to 1 year after the birth. Exacerbations are defined as inpatient admissions with the main diagnosis MG and/or need for additional immunosuppression.

We identified 112 women with MG in study in Sweden's National Myasthenia Gravis Register who subsequently appear in Sweden's Medical Birth Register i.e. who have had a pregnancy which reached reached week 22. The MG register was established in 1995 and contains detailed data on MG date of diagnosis, MGFA class, subgroups, medications, neurophysiology, HLA group, and thymectomy data recorded by neurologists throughout Sweden.

We analysed data on all inpatient admissions *around pregnancy* using Sweden's National Patient Register. Around pregnancy was defined as 1 year before, during and 1 year after pregnancy. We have all diagnosis codes in ICD format, length of hospital stay and medical and surgical intervention codes for each visit including IVIG/plasmapharesis.

For comparision we have data on inpatient admissions *not around* pregnancy on all 112 women during the years 1987-2019 including number of admissions with MG and length of hospital stay. We also have data on all outpatient visits around pregnancy in these women including diagnosis codes in ICD format and medical and surgical intervention codes for each outpatient visit. From Sweden's Prescribed Drug Register we have data on MG-related medications prescribed around pregnancy.

RESULTS: We are currently comparing the number and duration of all inpatient admissions with the main diagnosis MG during pregnancy and one year after pregnancy compared with one year before pregnancy using Poisson regression to calculate an incidence rate ratio for risk of MG exacerbation requiring inpatient admission during or 1 year after pregnancy. To assess if bias exists in the form of regression to the mean, i.e. that women who have unusually few MG symptoms the year before conception might be more likely to become pregnant, we are performing a Cox proportional hazards regression model. We will use register data on medications to report increased or reduced need for MG-related medications during and 1 year after pregnancy vs. before pregnancy, including IVIG and plasmapheresis

CONCLUSION: We hope that our findings can shape future guidelines for management of MG during pregnancy, a key question for women with MG considering pregnancy and their physicians.

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MULTIPARAMETRIC ANALYSIS REVEALS TWO BIOLOGICALLY, EPIDEMIOLOGICALLY, CLINICALLY, AND SEX-SPECIFIC ENDOTYPES OF MYASTHENIA GRAVIS

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INTRODUCTION: Myasthenia gravis (MG) is a chronic antibody-mediated autoimmune neuromuscular disorder causing fluctuating muscle weakness due to autoantibodies that target the acetylcholine receptor (AChR) in the neuromuscular junction. Despite extensive research, MG remains unpredictable and heterogeneous, underscoring the need for better insight into disease pathogenesis and clinical course.

OBJECTIVE: To determine which clinical and immunological disease-related parameters correlate with disease severity.

METHODS: A multicenter, multinational, large-scale profiling of subunit specific anti-AChR IgG titers in MG patient serum samples to investigate disease patterns and their relation to age, sex, disease onset, disease severity, anti-AChR titer, thymic involvement, and anti-AChR subunit immunodominance.

RESULTS: 513 MG patients with a median age of 64 years (range: 14-98.5) and a female to male ratio of ~1:1 were included. Complete clinical data were available for 232 patients. Age at disease onset distributed bimodally, with females favoring early onset MG (EOMG). Anti-AChR titers increased monotonically with disease severity and were higher in females, in whom titers also decreased monotonically with age. Thymic hyperplasia involved females with EOMG almost exclusively and correlated with higher titers, while thymoma occurred evenly between sexes and disease onsets. Autoantibody immunodominance to the alpha or gamma AChR subunits was observed among males and females, respectively. Gamma immunodominance correlated with higher anti-AChR titer and severe (MGFA IV-V) disease and were further distinctive in females. Unsupervised principal component analysis disclosed two distinct disease endotypes: females with EOMG, gamma subunit immunodominance, high anti-AChR titers, frequent thymic hyperplasia, and moderate to severe disease (Endotype A) and the remaining patients, mostly males with late onset MG (LOMG), alpha subunit immunodominance, low anti-AChR titers, and mild to moderate severity (Endotype B).

SUMMARY/CONCLUSION: Two distinct MG endotypes emerge based on sex, age, thymic involvement, autoantibody titer, severity, and immunodominance, suggesting different underlying etiologies with potential implications for sex-dependent precision medicine, women's health and the development of new therapeutic modalities for MG.

DISCLOSURES: This study was funded by Canopy Immuno-Therapeutics. Kfir Oved, Galit Denkberg, Lena Pinzur, Inbar Arman, Roei D. Mazor, Sharon Reef and Ofer Harel are or were employees of Canopy Immuno-Therapeutics.

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CHARACTERIZING THE (AUTOIMMUNE) B CELL EXPRESSION PROFILE OF MUSK MG PATIENTS

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INTRODUCTION: Recently, a group of autoimmune diseases hallmarked by predominant pathogenic IgG4 autoantibodies (IgG4-AID) was recognized, of which MuSK MG is an archetypical member. Why IgG4 predominates in these autoimmune responses is unknown. IgG4 autoantibody titers correlate with disease severity in MuSK MG, thus targeted removal of pathogenic $IgG4^+$ B cells could have therapeutic value. However, the phenotypical characteristics of (autoreactive) $IgG4^+$ B cells are poorly understood.

OBJECTIVE: To characterize autoreactive ($IgG4^+$) memory B cell responses to find potential therapeutic targets for IgG4-AID.

METHODS: we isolated peripheral blood mononuclear cells (PBMCs) from MuSK MG patients and compared their B cell landscape to PBMCs from AChR MG patients and age-matched healthy donors using flow cytometry. Next, memory B cells (Bmems) were sorted from four MuSK MG patients and three healthy controls for single cell 5' gene expression analysis, DNA-barcoded MuSK reactivity and B cell receptor (BCR) V(D)J mapping.

RESULTS: Flow cytometry data revealed $CD20^-CD138^+$ mature plasma cells are increased sevenfold in MuSK MG patients regardless of isotype and $CD22^+FcRL5^+$ atypical Bmems are increased in MuSK MG patients in the transcriptomics dataset. Single cell transcriptomics identified MuSK-reactive B cells in patients and controls. Only one patient-derived clone confirmed to be MuSK-reactive in ELISA by expressing the BCR sequence as a recombinant antibody thus far, limiting further analysis. Differential gene expression and gene ontology analysis on patient and control $IgG4^+$ Bmems combined revealed upregulated pathways for MHC class I antigen presentation, activation of type II hypersensitivity responses and $CD8^+$ T cell stimulation in IgG4+ Bmems. These observations are currently being validated on protein level.

SUMMARY/CONCLUSION: Autoreactive B cells are extremely rare in MuSK MG patients. MuSK MG B cell landscapes and transcriptomes are mostly comparable to healthy donors, suggesting MuSK MG is resulting from a single antigen-specific response and not by generalized $IgG4^+$ B cell abnormalities.

DISCLOSURES: Jan Verschuuren, Silvère van der Maarel, Maartje Huijbers are coinventors on MuSK-related patents and receive royalties from these patents. LUMC receives royalties on a MuSK ELISA and from aforementioned patents.

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EMPOWERING UNDIAGNOSED MYASTHENIA GRAVIS (MG) PATIENTS: DESIGN OF A NOVEL ONLINE SELF-ASSESSMENT SCREENING TOOL

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INTRODUCTION: Myasthenia Gravis (MG) is a rare condition posing diagnostic challenges because of diverse symptomatology and lack of diagnostic criteria. As a result, patients may have difficulty advocating for themselves.

OBJECTIVE: Develop and pilot a novel self-moderated online assessment tool for participants to determine the likelihood-of-MG and expedite neurologist evaluation.

METHODS: Structured workshops with neurologists (n=4) and patients (n=7) were held to design the self-assessment tool. A survey of MG symptoms affecting daily living and a set of 10 self-moderated physical activities were designed based on current literature and existing MG measures (MG-ADL, QMG, and MG-CE). Participants were recruited through social media. Those completing the symptom survey qualified to proceed with the physical tests based on a scoring system accounting for presence of ocular, bulbar, or axial/limb symptoms. A logic-based approach combining symptom survey and physical test results was used to stratify each participant's likelihood-of-MG, which a remote neurologist then reviewed. Participants received a detailed report, including a letter to their doctor outlining the study results. A list of local neurologists was also provided when indicated. Participants completed a follow-up survey within 1-year to self-report their MG diagnosis status; verification occurred through interviews and medical record review.

RESULTS: 237 eligible participants consented to participate. 215 qualified based on the symptom survey. 141 completed the physical tests and received a report; likelihood-of-MG was stratified as: high 64% (N=90), medium 35% (N=49), and low 1% (N=2). So far, 77 participants followed up; 37 indicated pending workup. Of the remaining 40, 13 self-reported a new MG diagnosis. Positive MG diagnosis was verified on 2 patients.

SUMMARY/CONCLUSION: Our self-assessment tool empowers patients to advocate for their symptoms and expedite workup for MG diagnosis. While this pilot had limitations, we are expanding the study to validate and refine the tool with a larger cohort.

DISCLOSURES: Ananda Vishnu Pandurangadu, Archit Gupta, Michelle Townshend, Vidya Viswanathan, Hari Jayaraman, Anand Trivedi, Vijesh Unnikrishnan are employees of ZS Associates. Author Kevin Neal is a contractor for ZS Associates. Author Pritikanta Paul is an employee of University of California San Francisco and a contractor for ZS Associates. ZS Associates and UCB co-funded this study.

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INCIDENCE AND OUTCOME OF MENINGOCOCCAL INFECTION WITH ECULIZUMAB OR RAVULIZUMAB IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS OR NEUROMYELITIS OPTICA SPECTRUM DISORDER: AN ANALYSIS OF US CLINICAL PRACTICE

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INTRODUCTION: Eculizumab and ravulizumab are effective treatments for generalized myasthenia gravis (gMG) and neuromyelitis optica spectrum disorder (NMOSD). Safety mitigations, including vaccinations, are used to reduce the risk of Neisseria meningitidis (Nm) infection associated with these treatments.

OBJECTIVE: To evaluate US exposure-adjusted Nm infection and mortality in eculizumab- or ravulizumab-treated patients with gMG and NMOSD using postmarketing pharmacovigilance data (Nm case counts) and commercial data (exposure).

METHODS: The US Alexion safety database was searched for eculizumab and ravulizumab (data cutoff: December 2022) across approved indications (gMG, NMOSD, paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome) using the MedDRA High Level Term Neisseria infection. Only Nm-associated cases were included. Reporting rates were calculated cumulatively per 100 patient-years (PY).

RESULTS: US Nm infection and mortality annual reporting rates in eculizumab-treated patients remained stable over 15 years across approved indications (2022: 0.13 and 0.01, respectively; exposure: 29,758.4 PY). In 2022, US postmarketing Nm infection reporting rates in eculizumab-treated patients with gMG and NMOSD were 0.02 (exposure: 8,042.0 PY) and 0.07 (exposure: 1,470.1 PY), respectively. At data cutoff, there were no Nm infections among ravulizumab-treated patients with gMG. No Nm fatalities were noted for eculizumab- or ravulizumab-treated patients with gMG and NMOSD.

SUMMARY/CONCLUSION: Nm infection and mortality reporting rates for patients with gMG and NMOSD remained stable despite increasing eculizumab and ravulizumab exposure over time. These results suggest US Nm-related risk mitigation strategies are effective in patients receiving eculizumab or ravulizumab.

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EFFECT OF ROZANOLIXIZUMAB ON OCULAR SYMPTOMS: A *POST HOC* ITEM-LEVEL ANALYSIS OF MYASTHENIA GRAVIS-SPECIFIC OUTCOMES IN MYCARING

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INTRODUCTION: Patients with gMG may experience disabling ocular symptoms such as diplopia/double vision and ptosis/eyelid drooping due to ocular muscle weakness. In MycarinG, rozanolixizumab demonstrated clinically meaningful improvements across myasthenia gravis (MG)-specific outcomes and was generally well tolerated in patients with gMG.

OBJECTIVE: To investigate the effect of rozanolixizumab on ocular symptoms in patients with gMG in the Phase 3 MycarinG study (NCT03971422).

METHODS: Adults with MGFA Disease Class II–IVa, AChR or MuSK Ab+ gMG were randomly assigned 1:1:1 to once-weekly subcutaneous rozanolixizumab 7mg/kg, 10mg/kg or placebo for 6 weeks (to Day 43). This descriptive *post hoc* analysis evaluated mean change from baseline (CFB) in ocular item scores within the MG Activities of Daily Living (MG-ADL), Quantitative MG (QMG) and MG Symptoms Patient-Reported Outcome (MG Symptoms PRO) Ocular Muscle Weakness scales for patients with baseline score ≥1 in that item.

RESULTS: Overall, 200 patients received rozanolixizumab 7mg/kg (n=66), 10mg/kg (n=67) or placebo (n=67). Mean baseline scores for ocular items were 1.6–1.9 for MG-ADL, 1.8–2.1 for QMG, and 1.5–1.8 for MG Symptoms PRO. For rozanolixizumab 7mg/kg, 10mg/kg and placebo, mean CFB at Day 43 in MG-ADL ocular item scores was −0.6, −0.6 and −0.2, respectively, for double vision, and −0.5, −0.7 and 0.0, respectively, for ptosis. Mean CFB in clinician-assessed QMG scores was −0.6, −0.8 and 0.1, respectively, for double vision, and −0.5,

−1.0 and −0.5, respectively, for ptosis. Mean CFB in MG Symptoms PRO scores was −0.5, −0.6 and −0.2, respectively, for double vision and −0.5, −0.7 and −0.1, respectively, for ptosis. Most treatment-emergent adverse events with rozanolixizumab were mild/moderate.

SUMMARY/CONCLUSION: Overall, greater improvements in ocular item scores across MG-specific outcomes were observed with rozanolixizumab compared with placebo in the MycarinG study, suggesting a benefit for gMG patients with ocular signs and symptoms.

DISCLOSURES: Robert M. Pascuzzi is Professor Emeritus of Neurology at Indiana University and receives compensation for his professional work from Indiana University Health. He has no financial relationship with any pharmaceutical company and receives no compensation from any pharmaceutical company (present or past). Ali A. Habib has received research support from Alexion Pharmaceuticals, argenx, Cabaletta Bio, Genentech/Roche, Immunovant, Regeneron Pharmaceuticals, UCB and Viela Bio (now Amgen). He has received honoraria from Alexion Pharmaceuticals, Alpine Immune Sciences, argenx, Genentech/Roche, Immunovant, Inhibrx, NMD Pharma, Regeneron Pharmaceuticals, and UCB. Zabeen K. Mahuwala has received funding for advisory board participation from Alexion Pharmaceuticals. John Vissing has been a consultant on advisory boards for Amicus Therapeutics, Arvinas, Biogen, Fulcrum Therapeutics, Genethon, Horizon Therapeutics (now Amgen), Lupin, ML Biopharma, Novartis, Regeneron Pharmaceuticals, Roche, Sanofi Genzyme (now Sanofi), Sarepta Therapeutics and UCB. He has received research and travel support and/or speaker honoraria from Alexion Pharmaceuticals, argenx, Biogen, Edgewise Therapeutics, Fulcrum Therapeutics, Lupin, Sanofi Genzyme (now Sanofi) and UCB. He is a Principal Investigator in clinical trials for Alexion Pharmaceuticals, argenx, Genethon, Horizon Therapeutics (now Amgen), Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), ML Biopharma, Novartis, Regeneron Pharmaceuticals, Roche, Sanofi Genzyme (now Sanofi) and UCB. Tuan Vu is the USF Site Principal Investigator for MG clinical trials sponsored by Alexion/AstraZeneca Rare Disease, Amgen, argenx, Cartesian Therapeutics, COUR Pharmaceuticals, Dianthus Therapeutics, Immunovant, Johnson & Johnson, NMD Pharma, Regeneron Pharmaceuticals and UCB, and has served as a speaker for Alexion/AstraZeneca Rare Disease, argenx and CSL Behring. He performed consulting work for Alexion/AstraZeneca Rare Disease, argenx, Dianthus Therapeutics, ImmunAbs and UCB. Jos Bloemers, Fiona Grimson and Thaïs Tarancón are an employees and shareholders of UCB. Vera Bril is a Consultant for Akcea, Alexion Pharmaceuticals, Alnylam, argenx, CSL, Grifols, Ionis, Immunovant, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), Momenta (now Johnson & Johnson), Novo Nordisk, Octapharma, Pfizer, Powell Mansfield, Roche, Sanofi, Takeda Pharmaceuticals and UCB. She has received research support from Akcea, Alexion Pharmaceuticals, argenx, CSL, Grifols, Immunovant, Ionis, Momenta (now Johnson & Johnson), Octapharma, Takeda Pharmaceuticals, UCB and Viela Bio (now Amgen).

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EFFECT OF ROZANOLIXIZUMAB ON MYASTHENIA GRAVIS-SPECIFIC OUTCOME SUBDOMAIN SCORES: POST HOC ANALYSES FROM THE PHASE 3 MYCARING STUDY

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INTRODUCTION: The Phase 3 MycarinG study (NCT03971422) demonstrated that rozanolixizumab significantly improved MG-ADL and QMG total scores in patients with gMG versus placebo.

OBJECTIVE: Treatment may have differential effects across the different muscle groups; the objective of this analysis was to evaluate the effect of rozanolixizumab treatment on MG-ADL and QMG subdomain scores assessing ocular, bulbar, respiratory and limb weakness/gross motor muscle groups.

METHODS: Adults with AChR or MuSK Ab+ gMG were randomised to weekly rozanolixizumab 7 mg/kg, rozanolixizumab 10 mg/kg or placebo for 6 weeks (one cycle). This post hoc analysis assessed change from baseline (CFB) to Day 43 in MG-ADL and QMG subdomain scores.

RESULTS: Overall, 200 patients received rozanolixizumab 7 mg/kg (n=66), 10 mg/kg (n=67) or placebo (n=67). Mean (standard deviation [SD]) CFB in MG-ADL subdomain scores in the rozanolixizumab 7 mg/kg, rozanolixizumab 10 mg/kg and placebo groups: ocular, −0.8 (1.3), −1.0 (1.2) and −0.1 (0.9), respectively; bulbar, −1.3 (1.7), −1.3 (1.5) and −0.2 (1.4), respectively; respiratory, −0.3 (0.6), −0.3 (0.7) and 0.0 (0.5), respectively; limb weakness, −1.0 (1.3), −0.7 (1.1) and −0.3 (1.0), respectively. Similar trends were observed for mean (SD) CFB in the QMG subdomain scores (ocular, bulbar, respiratory and gross motor muscle groups). Rozanolixizumab was generally well tolerated, and most adverse events were mild/moderate.

SUMMARY/CONCLUSION: Rozanolixizumab treatment led to improvements across all MG-ADL and QMG subdomain scores, representing the ocular, bulbar, respiratory and limb weakness/gross motor muscle groups, in patients with gMG.

DISCLOSURES: Robert M. Pascuzzi is Professor Emeritus of Neurology at Indiana University and receives compensation for his professional work from Indiana University Health. He has no financial relationship with any pharmaceutical company and receives no compensation from any pharmaceutical company (present or past). Ali A. Habib has received research support from Alexion Pharmaceuticals, argenx, Cabaletta Bio, Genentech/Roche, Immunovant, Regeneron Pharmaceuticals, UCB and Viela Bio (now Amgen). He has received honoraria from Alexion Pharmaceuticals, Alpine Immune Sciences, argenx, Genentech/Roche, Immunovant, Inhibrx, NMD Pharma, Regeneron Pharmaceuticals and UCB. John Vissing has been a Consultant on advisory boards for Amicus Therapeutics, Biogen, Edgewise Therapeutics, Fulcrum Therapeutics, Genethon, Horizon Therapeutics (now Amgen), Lupin, ML Biopharma, Novartis, Regeneron Pharmaceuticals, Roche, Sanofi Genzyme (now Sanofi), Sarepta Therapeutics and UCB. He has received research and travel support and/or speaker honoraria from Alexion Pharmaceuticals, argenx, Biogen, Edgewise Therapeutics, Fulcrum Therapeutics, Lupin, Sanofi Genzyme (now Sanofi) and UCB. He is a Principal Investigator in clinical trials for Alexion Pharmaceuticals, argenx, Atamyo Therapeutics, Genethon, Horizon Therapeutics (now Amgen), Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), ML Biopharma, Novartis, Regeneron Pharmaceuticals, Roche, Sanofi Genzyme (now Sanofi) and UCB. Tuan Vu is the USF Site Principal Investigator for MG clinical trials sponsored by Alexion/AstraZeneca Rare Disease, Amgen, argenx, Cartesian Therapeutics, COUR Pharmaceuticals, Dianthus Therapeutics, Immunovant, Johnson & Johnson, NMD Pharma, Regeneron Pharmaceuticals and UCB, and has served as a speaker for Alexion/AstraZeneca Rare Disease, argenx and CSL Behring. He has performed consulting work for Alexion/AstraZeneca Rare Disease, argenx, Dianthus Therapeutics, ImmunAbs and UCB. Asha Hareendran is a former employee and shareholder of UCB. Francesca Pannullo is a former contractor for UCB. Thaïs Tarancón is an employee and shareholder of UCB. Vera Bril is a Consultant for Akcea, Alexion Pharmaceuticals, Alnylam, argenx, CSL, Grifols, Immunovant, Ionis, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), Momenta (now Johnson & Johnson), Novo Nordisk, Octapharma, Pfizer, Powell Mansfield, Roche, Sanofi, Takeda Pharmaceuticals and UCB. She has received research support from Akcea, Alexion Pharmaceuticals, argenx, CSL, Grifols, Immunovant, Ionis, Momenta (now Johnson & Johnson), Octapharma, Takeda Pharmaceuticals, UCB and Viela Bio (now Amgen).

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THE RELEVANCE OF COMPLEMENT ACTIVATION IN MYASTHENIA GRAVIS – A QUANTIFICATION STUDY USING THE EXPERIMENTAL PASSIVE TRANSFER MYASTHENIA GRAVIS MODEL

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INTRODUCTION: In myasthenia gravis (MG), the anti-acetylcholine receptor (anti-AChR) antibody dependent activation of the classical complement pathway triggers the membrane attack complex (MAC) formation at the neuromuscular junction (NMJ). The muscle cell damage results in neuromuscular transmission deficiency, subsequent muscle weakness and fatigability. Passive transfer MG (PTMG) is a commonly used rodent model for MG research. Administration of a monoclonal antibody targeting the rat AChR (mAb35) manifests in characteristic acute muscle weakness.

OBJECTIVE: To characterize the complement deposition at the NMJ in PTMG rats and correlate it to the animals' disease status to investigate and compare the efficiency of (new) treatments such as complement inhibitors in the future.

METHODS: 10-weeks-old female Lewis rats were subcutaneously (s.c.) injected with 40pmol/100g mAb35; control non-MG animals received saline injections. 48 hours after disease induction the animals were euthanized, the muscle tibialis anterior (T.A.) was dissected and frozen. T.A. were used for immunofluorescence staining using anti-MAC and anti-AChR markers, and anti-synaptic vesicle protein 2 (anti-SV2) as reference. The intensity of immunofluorescence was quantified; SV2 was used for normalization.

RESULTS: In PTMG animals an increase in MAC deposition was observed while AChR levels were reduced compared to non-MG animals.

SUMMARY/CONCLUSION: The increase of complement proteins at the NMJ in PTMG-animals and the reduction in AChR indicates the activation of the classical complement pathway. The quantification of immunofluorescence raised insights about the relation of AChR reduction and complement deposition and the translation to disease severity in the animals. This methodology may become a useful tool to monitor treatment studies in MG models.

DISCLOSURES: None

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BODY MASS INDEX AND PHYSICAL ACTIVITY AND RISK OF MYASTHENIA GRAVIS: RESULTS FROM THE SWEDISH GEMG-STUDY.

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INTRODUCTION: Myasthenia Gravis (MG) is a complex disease where lifestyle and environment are believed to contribute to disease risk, although specific factors largely remain to be defined.

OBJECTIVE: We here examine the association between body mass index (BMI) and physical activity, and MG risk.

METHODS: The Genes and Environment in Myasthenia Gravis study (GEMG) is a cross-sectional questionnaire study, conducted nationwide in Sweden 2018 to 2019, with cases matched to controls based on birth year, disease onset age, and sex. BMI at disease onset was retrieved from the Swedish MG registry and compared to controls BMI at inclusion. Associations were evaluated by logistic regression.

RESULTS: In total, 912 non-thymomatous MG cases with disease onset ≥20 years of age were matched to 1,778 controls. Mean onset age was 52 (SD 19) years and 57% were Late-onset MG (LOMG). Being overweight at 20 years of age was associated to increased MG risk compared to being normal weight (overweight, OR 1.70, 95% CI 1.26-2.30, P=0.001; obese, OR 2.12 95% CI 1.06-4.25, P=0.035). The effect was stronger in men, both in Early-onset (EOMG) and LOMG

(male EOMG overweight; OR 2.74, 95% CI 1.19-6.31, P=0.018, male LOMG overweight; OR 2.14, 95% CI 1.35-3.41, P<=0.001). Increased MG risk was confirmed when investigating BMI close to onset (average 0.5 (2.1) years before onset) for a subset of patients (n=169) (overweight; OR 4.88, 95% CI 2.07-11.5, P<0.001; obese, OR 6.08, 95% CI 2.36-15.7, P<0.001). We further investigated anamnestic physical activity level prior to onset and compared any activity to being sedentary, and observed a decreased MG risk, OR 0.68 CI 95% 0.48-0.96, P<0.030).

CONCLUSION: Being overweight or obese at 20 years of age is associated with an increased MG risk, especially in male patients. Conversely, higher levels of physical activity prior to onset are associated with decreased risk.

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DIGITAL PHENOTYPING OF PHYSICAL ACTIVITY AND SLEEP IN THE DIG-MG STUDY

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INTRODUCTION: Myasthenia Gravis (MG) is a chronic autoimmune disease characterized by fatigable muscle weakness and generalized fatigue. Although short-term, supervised studies indicate that physical exercise is safe and advantageous for individuals with MG, further research on long-term, unsupervised exercise is necessary to establish evidence-based guidelines for physical activity in this population. Moreover, the role of sleep and sleep hygiene in modulating MG-associated fatigue has yet to be thoroughly investigated.

OBJECTIVE: Determine whether digital physical activity or sleep interventions can reduce MG fatigue and explore digital biomarkers using the OURA smart ring.

METHODS: The DIG-MG trial, a randomized controlled trial, aimed to assess the impact of a digital lifestyle intervention on fatigue in MG patients through remote digital monitoring using smart rings (ClinicalTrials.gov ID NCT05992025). Patients used the OURA ring for more than 6 months, including a 6-week acclimatization, a 3-month intervention, and a 6-week observation phase. Participants were randomized into one of three intervention groups: physical activity counseling, sleep hygiene counseling, or an observation-only group. The MG-Activities of Daily Living (MG-ADL) scale measured the primary outcome, while secondary outcomes included the Fatigue Severity Scale and Chalder Fatigue Scale. Exploratory outcomes focused on metrics derived from OURA ring data, including heart rate variability, temperature changes, and sleep and activity parameters.

RESULTS: After screening, 83 MG patients from Sweden were enrolled, and 74 patients (16 men; 18-86 years) completed the trial. The study proved that digital group counseling and remote monitoring via the OURA ring were possible and could provide digital phenotyping data regarding the effects of physical activity and sleep on MG and general fatigue.

SUMMARY/CONCLUSION: The DIG-MG trial highlights the potential of digital lifestyle interventions in managing fatigue in MG patients and could pave the way for refined guidelines regarding physical activity and sleep in mitigating MG-associated fatigue.

DISCLOSURES: A.R.P. has received consultancy/speaker honoraria from Argenx, UCB, Dianthus, Alexion, and Toleranzia, all of which are unrelated to this study.

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SENSITIVITY AND SPECIFICITY OF INFLAMMATORY PROTEIN BIOMARKERS IN ACETYLCHOLINE RECEPTOR ANTIBODY SEROPOSITIVE (ACHR+) MYASTHENIA GRAVIS

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INTRODUCTION: Myasthenia Gravis (MG) is a very heterogeneous disorder in which the majority, approximately 85%, are seropositive for antibodies against the acetylcholine receptors (AChR+). This heterogeneity and daily and day-to-day fluctuations in skeletal muscle weakness cause difficulties in predicting the clinical course. Despite antibody detection being essential for MG diagnosis, antibody titers do not necessarily correlate with disease severity or response to treatment. There is a critical need for objective MG-specific biomarkers to track disease progression and forecast treatment response. A recent study found a profile of 23 out of 92 inflammatory proteins in the OLINK Inflammation panel with differential expression in MG patients versus healthy controls.

OBJECTIVE: To validate the proposed signature of inflammatory proteins in sera of AChR+ MG patients.

METHODS: The Proximity Extension Assay by Olink Proteomics will assess serum expression levels of previously identified inflammatory serum proteins in a large cohort of more than 550 sera from Swedish and German patients with AChR+ MG, matched healthy controls and patients with neuroimmune disorders (multiple sclerosis and chronic inflammatory demyelinating polyneuropathy). The data analysis methods include Logistic Regression, Principal Component Analysis (PCA), Random Forest, and Boruta Algorithm analysis. The sensitivity and specificity of the validated inflammatory proteins will be defined for AChR+ MG. Further, the serum protein biomarker profile will be correlated to the cytokine and chemokine secreted by the CD4+ T cells from MG patients and HCs

RESULTS: A signature of the least necessary number of inflammatory proteins per MG subgroup that best correlates with disease activity and treatment response will be validated. Biomarkers for MG patient subgroups will also be validated, including late-onset versus early-onset MG and no immunosuppression versus immunosuppressive treatment.

SUMMARY/CONCLUSION: In summary, we will present a validated protein profile that separates AChR+ MG from healthy and neuroimmune disease controls.

DISCLOSURES: A.R.P. has received consultancy/speaker honoraria from Argenx, UCB, Dianthus, Alexion, and Toleranzia. F.S. has received travel support, speaker and advisory board honoraria, and institutional research funding from Alexion, Argenx, and UCB, and serves on the medical advisory board of the German Myasthenia Gravis Society. A.M. has received speaker/consultancy honoraria and institutional research support from multiple companies,

including Alexion, Amgen, Argenx, and UCB, and serves on the medical advisory board of the German MG Society. S.H. has received speaker/consultancy honoraria and institutional research support from Alexion, Argenx, UCB, Grifols, Roche, Novartis, and Johnson & Johnson, and serves on the advisory board of the German MG Society.

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INPATIENT TREATMENT OF MYASTHENIA GRAVIS EXACERBATION WITH EFGARTIGIMOD: A SINGLE ARM, OPEN LABEL PROSPECTIVE COHORT STUDY. PROTOCOL, RATIONALE AND EARLY RESULTS.

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INTRODUCTION: Despite advancements in targeted therapies for myasthenia gravis (MG), intravenous immune globulin (IVIG) and plasmapheresis remain standard treatments for exacerbations in hospitalized patients. Efgartigimod-alfa, a human IgG1 antibody Fc-fragment, selectively reduces IgG concentration by blocking the neonatal Fc receptor (FcRn) and is approved for chronic use in AChR+ gMG. Its IgG-reducing mechanism, like plasmapheresis, supports evaluating its efficacy and safety in hospitalized MG patients. This study presents the protocol design, rationale, and preliminary results from initial patient enrollment.

OBJECTIVE: The study aims to collect preliminary data on the safety, tolerability, and efficacy of efgartigimod in hospitalized AChR+ gMG patients and compare results with our institution's historical controls.

METHODS: 20 adults with AChR+ gMG and worsening symptoms requiring hospitalization will be enrolled within 24 hours of admission. Patients receive 10 mg/kg efgartigimod on days 1 and 4 of admission, with additional dosing on days 11 and 18 as outpatients. Eligibility requires a Quantitative Myasthenia Gravis (QMG) score of ≥ 11 and an MG-ADL score of ≥ 6. Exclusion criteria include active infection, recent IVIG or plasmapheresis, certain monoclonal antibody treatments, and other conditions confounding outcomes. The primary outcome is the change in QMG from baseline to day 11, with secondary outcomes assessing clinical status and cost-effectiveness against historical controls. Data from up to 100 historical patients will be used for comparison.

RESULTS: Initial patient results, enrolled from November 2024 to April 2025, will be compared to historical controls.

SUMMARY/CONCLUSION: This protocol administers efgartigimod on days 1 and 4 during hospitalization, differing from standard dosing, to address acute AChR+ gMG exacerbations. It aims to rapidly assess efgartigimod's safety and efficacy in a hospital setting. Initial results will be presented. This study intends to provide foundational data suggesting the utility of efgartigimod in acute care, with further studies needed to confirm its role in managing MG exacerbations.

DISCLOSURES: Thomas Ragole discloses that he has served on scientific advisory boards for Alexion/AstraZeneca Rare Disease and Annexon Biosciences. He has served as a consultant to UCB Pharma and has received investigator-initiated grant funding from Argenx SE (for this study) and from Alexion/AstraZeneca Rare Disease.

Author Kavita Nair discloses that she has served as a consultant for Bristol Myers Squibb, Genetech, Novartis, TG Therapeutics and PhRMA Foundation. She has served on the speakers bureau for Sanofi-Genzyme, Alexion and MJH Life Sciences. She has received research grants from Genentech, PhRMA Foundation, Bristol Myers Squibb and Novartis.

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LIMITED RESPONSE TO PLASMAPHERESIS OR FCRN ANTAGONISM MAY PREDICT RESPONSE TO COMPLIMENT INHIBITION IN ACHR+ GENERALIZED MYASTHENIA GRAVIS: EXPERIENCE FROM A SINGLE CENTER

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INTRODUCTION: Selection of targeted therapeutics for moderate-severe or refractory generalized AChR+ myasthenia gravis (gMG) remains challenging. Limited efficacy of IgG reduction strategies (plasmapheresis and FcRn antagonists) is seen in a proportion of patients for unclear reasons. This study explores whether limited response to plasmapheresis or FcRn antagonism may predict a favorable response to C5-complement inhibition in patients with recent diagnosis of AChR+ gMG.

OBJECTIVE: To explore the efficacy of complement inhibition in patients with generalized AChR+ myasthenia gravis who exhibited limited response to plasmapheresis or FcRn antagonism.

METHODS: This single-center case series involved seven patients with generalized AChR+ myasthenia gravis (n=7, 5 males) with a mean age of 59.3 (SD 16.8) who required one or multiple hospitalizations in the 6 months prior to C5-inhibitor use and received plasmapheresis or FcRn-antagonists. Assessments included MG-ADL, MGC, MG-MMT scores as well as prednisone doses. Patients were then treated with a C5-inhibitor, and changes in clinical scales and prednisone doses were assessed at 4-6 weeks and ~6 months post-initiation.

RESULTS: At baseline, mean MG-ADL score was 8.3 (SD 1.9), and mean prednisone dose was 39.2 mg (SD 22.1). Following 4-6 weeks of C5 inhibitor treatment, the mean change from baseline in MG-ADL was -6.0 (SD 2.8). At 6 months, the mean change from baseline in MG-ADL was -7.3 (SD 2.3). The mean prednisone dose at 6 months was reduced to 4.2mg (range 0-7.5 mg), representing a mean change from baseline of 39.1 mg (SD 21.4).

SUMMARY/CONCLUSION: Patients with AChR+ gMG who demonstrate limited response to plasmapheresis or FcRn-antagonism may benefit from early switch to C5-inhibition, as shown in our series with significant improvements in MG-ADL scores and reductions in prednisone. Further exploration of mechanisms underlying this disparate response to IgG reduction compared to C5-inhibition are warranted to identify factors that may allow earlier identification of this population.

DISCLOSURES: Thomas Ragole discloses that he has served on scientific advisory boards for Alexion/AstraZeneca Rare Disease and Annexon Biosciences. He has served as a consultant to UCB Pharma and has received investigator-initiated grant funding from Argenx SE (for this study) and from Alexion/AstraZeneca Rare Disease.

Author Varun Sreenivasan reports serving as a consultant to ITF Pharmaceuticals

Author Kavita Nair discloses that she has served as a consultant for Bristol Myers Squibb, Genetech, Novartis, TG Therapeutics and PhRMA Foundation. She has served on the speakers bureau for Sanofi-Genzyme, Alexion and MJH Life Sciences. She has received research grants from Genentech, PhRMA Foundation, Bristol Myers Squibb and Novartis.

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CLINICAL FEATURES, MANAGEMENT AND LONG TERM OUTCOME IN PAEDIATRIC ONSET MUSK-ASSOCIATED MYASTHENIA GRAVIS- A EUROPEAN COHORT STUDY

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INTRODUCTION: MuSK-MG is a rare but severe subtype of MG. There is published limited data on management and long term outcomes in paediatric MuSK-MG.

OBJECTIVE: To characterise the clinical features and long-term outcomes of patients with paediatric onset muscle-specific tyrosine kinase associated myasthenia gravis (MuSK-MG).

METHODS: Eighteen patients with paediatric onset MuSK MG were identified from six neuroscience centres across Europe.

RESULTS: The cohort had a follow up of 1 – 42 years. All apart from one were female, and median age of diagnosis was 14 years. For 5 patients (28%), there was a delay of over 2 years between symptom onset and MG diagnosis. At onset, 67% had isolated ocular symptoms, but all patients apart from one thereafter progressed to generalised MG. 89% were treated with pyridostigmine as first line, of which 31% had some clinical improvement. All patients were treated with prednisolone as first line immunomodulatory agent, of which 88% had some clinical improvement. 61% required a second immunomodulatory agent, 39% required third line immunomodulatory agent and 11% required a fourth- or fifth-line agent. The immunomodulatory agents used included azathioprine, cyclosporin, cyclophosphamide, intravenous immunoglobulin, plasmapheresis and rituximab.10 patients (58%) required hospitalisation at least once for MG management, including 4 (24%) who had myasthenic crises

SUMMARY/CONCLUSION: We present the largest reported cohort of paediatric onset MuSK-MG with long term outcome. Key findings include that most patients have isolated ocular symptoms at onset, but progression to generalised MG is highly likely. About a third of the

patients had a significant delay in diagnosis from symptom onset. All patients required immunomodulatory therapy for disease control and whilst most patients improved with immunomodulation, some may require multiple therapies to achieve this.

DISCLOSURES: Lorenzo Maggi: Has received honoraria for speaking, advisory boards, and compensation for congress participations from Sanofi Genzyme, Roche, Biogen, Amicus Therapeutics, Alexion, Argenx, UCB, Janssen, Lupin, outside the submitted work. Elena Cortés Vicente: Advisory boards/speaking honoraria from UCB Pharma, Alexion, Argenx, and J&J. Imelda Hughes: Advisory board, speaker honoraria, and conference attendance funded by Novartis, Biogen, and Roche, PTC Therapeutics. Teresa Painho: Advisory boards/speaking honoraria from Biogen, Roche, and Novartis. Maria Ds Silva Leite (M. Isabel Leite): Funded by the NHS (Myasthenia and Related Disorders Service and National Specialised Commissioning Group for Neuromyelitis Optica, UK) and by the University of Oxford, UK. Received research grants from Myaware, Muscular Dystrophy UK, and the University of Oxford. Received speaker honoraria or travel grants from the Guthy-Jackson Charitable Foundation, Argenx, and UCB. Serves on scientific or educational advisory boards for Argenx, Horizon Therapeutics (Amgen), and UCB. Jacqueline Palace: Received support for scientific meetings and honorariums for advisory work from Merck Serono, Novartis, Chugai, Alexion, Roche, Medimmune, Amgen, Vitaccess, UCB, Mitsubishi, Amplo, Janssen. Grants from Alexion, Argenx, Clene, Roche, Medimmune, and Amplo biotechnology. Patent ref P37347WO and licence agreement with Numares multimarker MS diagnostics. Shares in AstraZeneca. Acknowledges partial funding by Highly Specialised Services NHS England. On the medical advisory boards of the Sumaira Foundation, MOG project charities, Guthy-Jackson Foundation Charity, and on the Board of the European Charcot Foundation. Member of MAGNIMS, the UK NHSE IVIG Committee, Chairman of the NHSE neuroimmunology patient pathway, ECTRIMS Council member (educational committee), and advisory groups for MS and neuroinflammation. Sithara Ramdas: Received honorarium for advisory board participation from Argenx.

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CROSS SECTIONAL STUDY OF 187 PATIENTS WITH CONGENITAL MYASTHENIA SYNDROME, DESCRIBING THE CLINICAL PHENOTYPES, GENETIC MUTATIONS, AND SINGLE POINT STANDARDISED ASSESSMENT SCORES

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INTRODUCTION: Congenital Myasthenic Syndromes (CMS) are inherited disorders of defective neuromuscular transmission. The clinical phenotype and treatment response vary between the over 30 genetic subtypes. Currently, there is limited published large cohort data in this population.

OBJECTIVE: A multicentre international study was undertaken to identify the genetic spectrum, clinical data, treatments, and outcome measures in genetically confirmed CMS patients.

METHODS: Cross sectional data was collected at the time of routine clinic appointment within the last 12-months. Clinical, genetic information and three outcome measures (Myasthenia Gravis Quantitative Score - QMG, Myasthenia Gravis Activities of Daily Living - MG-ADL and Sit to stand in 1 minute - STS1M) were collected. Cohort data analysis was performed on complete data sets, with sub analysis of common subtypes.

RESULTS: 187 patients were included, with AChR deficiency 29%, DOK7 20%, RAPSN 17%, COLQ 7%, and Slow Channel 6%. Median age at clinic was 25 years (range 1-83 years). Mean age at symptom onset (n=172) was 2.8 years. Median age at genetic diagnosis (n=174) was 8.4 years. Median age at treatment initiation (n=169) was 5 years. QMG score (n=132) was median 12/39 (range 0-34), in AChR deficiency-13 (range 3-34), DOK7-10 (range 0-29), RAPSN-8 (range 2-17). MG-ADL (n=174), median 5/24 (range 0-20), in AChR deficiency-5 (range 0-18), DOK7-7 (range 0-14), RAPSN-3.5 (range 0-10) and STS1M (n=146), median-22 (range 0-50), AChR deficiency-21.5(range 0-38), DOK7-17.5 (range 4-45) and RAPSN-25 (range 9-50).

SUMMARY/CONCLUSION: This is the largest reported CMS cohort including genetics, clinical data, and standardised outcome measures. Significant variability in the outcome measures was noted within individual CMS subtypes. This highlights the wide spectrum but also provides pivotal information for clinical trial designs. STS1M was identified as a robust easy deliverable outcome measure of fatigable weakness across all ages.

DISCLOSURES: Hayley Ramjattan: Received a research grant from Amplo Biotechnology. Leighann Hennehan: Received a grant from Argenx. Lorenzo Maggi: Received honoraria for speaking, advisory boards, and compensation for congress participations from Sanofi Genzyme, Roche, Biogen, Amicus Therapeutics, Alexion, Argenx, UCB, Janssen, and Lupin, outside the submitted work. Jacqueline Palace: Received support for scientific meetings and honorariums for advisory work from Merck Serono, Novartis, Chugai, Alexion, Roche, Medimmune, Amgen, Vitaccess, UCB, Mitsubishi, Amplo, and Janssen. Received grants from Alexion, Argenx, Clene, Roche, Medimmune, and Amplo Biotechnology. Patent holder (ref P37347WO) and licence agreement with Numares multimarker MS diagnostics. Holds shares in AstraZeneca. Sithara Ramdas: Received honorarium for advisory board participation from Argenx.

THIS IS AN ENCORE PRESENTATION OF: Ramjattan, H., et.al. (2024, Oct 8-12). *Cross Sectional Study of 187 Patients with Congenical Myasthenia Syndrome, Describing the Clinical Phenotypes, Genetic Mutations, and Single Point Standardised Assessment Scores.* [Conference presentation abstract]. The 29th Annual Congress of the World Muscle Society, Prague, CZ https://www.wms2024.com/news/view/highlights-of-wms-2024

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RELIEVE: A PHASE 3 STUDY EVALUATING THE EFFICACY AND SAFETY OF REMIBRUTINIB IN GENERALIZED MYASTHENIA GRAVIS

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INTRODUCTION: Generalized myasthenia gravis (gMG) is a rare, chronic autoimmune disorder caused by autoantibodies against neuromuscular junction (NMJ) components, leading to debilitating muscle weakness and other clinical manifestations. Inhibition of Bruton's tyrosine kinase (BTK), resulting in reduced activation of B cells and innate immune cells, offers a potential mechanism to modulate the immune response and reduce the autoimmune attack on the NMJ. Remibrutinib is a novel, highly selective and potent, covalent, oral BTK inhibitor with a promising pharmacological and safety profile.

OBJECTIVE: To present the design of the Phase 3 RELIEVE study, aimed to evaluate the efficacy and safety of remibrutinib in people living with gMG who are on stable, standard-of-care (SOC) treatment.

METHODS: RELIEVE is a randomized, double-blind, placebo-controlled, multicenter Phase 3 study. The study will enroll patients aged 18 to 75 years diagnosed with gMG (Myasthenia Gravis Foundation of America disease class II–IV) who are either acetylcholine receptor positive (AChR+), muscle-specific tyrosine kinase positive (MuSK+), or double-seronegative (AChR- and MuSK-), with a Myasthenia Gravis Activities of Daily Living (MG-ADL) score ≥6 (>50% non-ocular), and who are on stable SOC treatment. Eligible participants will be randomized 1:1 to receive either remibrutinib or placebo during the 6-month double-blind core treatment period,

followed by an open-label extension with remibrutinib treatment for up to 60 months. The primary endpoint is change from baseline to Month 6 in the MG-ADL total score. Key secondary endpoints include assessments of Quantitative MG (QMG), Minimal Symptom Expression (MSE), and MG Composite (MGC), among others.

RESULTS: The study will enroll approximately 180 eligible participants. Further details of the study design will be presented at the congress.

SUMMARY/CONCLUSION: The pivotal Phase 3 RELIEVE study will investigate the efficacy and safety of remibrutinib versus placebo in adult patients with gMG across serotypes.

DISCLOSURES: Vera Bril has received personal compensation for serving as a Consultant for UCB, CSL, Alnylam, Janssen, Grifols, Takeda, Octapharma, Pfizer, Powell Mansfield, Akcea, Ionis, Immunovant, Sanofi, Roche, Momenta (now J&J), Alexion and NovoNordisk. She has also received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Takeda, Immunovant, Alexion, Akcea, Sanofi, Alnylam, CSL, and argenx. James F. Howard Jr. has received honoraria/consulting fees from AcademicCME, Alexion AstraZeneca Rare Disease, Amgen, Biohaven Ltd, CheckRare CME, CoreEvitas, Curie.bio, Medscape CME, Merck EMB Serono, Novartis Pharma, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics, Toleranzia AB, UCB Pharma, and Zai Labs. He has also received personal compensation for participating on advisory boards with Alexion AstraZeneca Rare Disease, argenx, Novartis, UCB (Ra Pharma), Merck EMB Serono, Amgen, Sanofi, Toleranzia AB. Srikanth Muppidi has received personal compensation for serving as a Consultant for Alexion, argenx, UCB/Ra Pharma and Horizont Pharma. Kimiaki Utsugisawa has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for argenx, UCB pharma, Janssen pharma, Viela Bio, Chugai, Mitsubisi Tanabe pharma and Merck. He has also received personal compensation for serving on a Speakers Bureau for argenx, Alexion phama, Japan Blood Products Organization and UCB. John Vissing has received personal compensation for serving as a Consultant for Sanofi, Dyne Therapeutics, Solid Biosciences, Amicus therapeutics, AskBio, Avidity Therapeutics, Italfarmaco, Alexion, Biogen and Merck. He has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Sanofi, Roche, Pfizer, and UCB Biopharma. He has received personal compensation for serving on a Speakers Bureau for argenx, Alexion Pharmaceuticals, Johnson & Johnson (Janssen) and Edgewise Therapeutics. Heinz Wiendl has received personal compensation for serving as a Consultant for Bristol Myers Squibb, Novartis, Roche, Sanofi, Immunovant, Johnson&Johnson / Janssen, UCB, Idorsia, argenx, Immunic, Merck, Lundbeck, LTS, Samsung, Sangamo, Dianthus, EMD Serono, INmune Bio_Syneos Health, Muna Therapeutics, Myrobalan Therapeutics, PSL Group, Red Nucleus, Swiss Multiple Sclerosis Society, Teladoc Health, Toleranzia and Viatris. He has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Merck Serono, Novartis, Janssen, Alexion, argenx, Bristol Myers Squibb, Sandoz, Sandoz-Hexal, Cellerys, Uniqure, Biocryst, Galapagos. Weihua Cao, Svetlana Jevtic, Wendy Su and Roman Willi are all Novartis employees.

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MGBASE: A GLOBAL, OBSERVATIONAL REGISTRY FOR REAL-WORLD OUTCOMES RESEARCH IN MYASTHENIA GRAVIS

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INTRODUCTION: MGBase is a global observational registry for myasthenia gravis (MG) designed to promote collaborative outcomes research. The registry has been built alongside the successful MSBase registry with shared architecture. MGBase registry is owned and operated by the MSBase Foundation, an independent, not-for-profit entity with a global Board of Directors.

OBJECTIVE: A global MG registry enables big-data transnational MG outcome research.

METHODS: The data fields and minimum dataset for MGBase were selected by a panel of international MG experts. The Myasthenia Gravis Composite (MGC) and Myasthenia Gravis-Activities of Daily Living (MG-ADL) were chosen as the disease-specific outcome measures in the minimum dataset. All standard MG outcome measures are also available. Data is collected on patient demographics, disease characteristics, investigations, treatments, thymectomy, comorbidities, pregnancy and safety. An international MGBase scientific leadership group oversees the scientific direction of the registry. The MGBase registry is built for use during routine outpatient clinic consultations with a customisable graphical display of the patient's course. Data can be entered in real-time including in clinic. Patient identifiable information is only stored at the local level. Deidentified and encrypted data is automatically uploaded to the MGBase registry. Participating centre investigators can request access to the deidentified global dataset for investigator-lead studies. Other entities including pharmaceutical companies can commission the MGBase team to address research questions but cannot access the primary data.

RESULTS: MGBase was officially launched in October 2021. As of 13th November 2024, MGBase had 881 patients from 21 clinics across 11 countries. Interim analysis will be presented

including patient demographics, disease characteristics, treatment patterns and preliminary outcomes. Data examples include: 401 patients currently receiving prednis(ol)one for a median of 566 days, 283 patients ever received IVIG and 207 received rituximab. Four investigator research projects are underway.

SUMMARY/CONCLUSION: MGBase welcomes interested new centres and investigators globally.

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THE EFFICACY AND COST-UTILITY OF PYRIDOSTIGMINE IN PATIENTS WITH MYASTHENIA GRAVIS: A RANDOMIZED, DOUBLE-BLINDED, PLACEBO CONTROLLED CROSSOVER STUDY

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INTRODUCTION: Treatment for myasthenia gravis (MG) consists of symptomatic drugs, which improve muscle strength, and immunomodulating drugs. Pyridostigmine, an acetylcholinesterase inhibitor, is the only symptomatic drug approved for clinical use, but no randomized controlled trials substantiate its widespread use in treating MG.

OBJECTIVE: To assess the efficacy and cost-utility of pyridostigmine in patients with AChR MG currently using pyridostigmine, compared with care without pyridostigmine.

METHODS: Participants were randomly assigned (1:1) to a sequence of two treatment periods for 5 days separated by a 2-day washout, in which patients either first received placebo and then pyridostigmine, or vice versa. Patients received their pre-study dose of pyridostigmine as determined during routine clinical care, based on patient response and tolerance. The primary efficacy end point was change in Myasthenia Gravis Impairment Index (MGII) total score compared to placebo. Secondary efficacy outcome measures included the Myasthenia Gravis–Activities of Daily Living (MG-ADL) scale, the Quantitative Myasthenia (QMG) score and the revised 15-item Myasthenia Gravis Quality of Life (MG-QOL15r) questionnaire. For the cost-utility analysis, a mathematical model was developed to translate the observed study results into long-term annual impact on healthcare and societal costs and on quality-adjusted life-years (QALYs).

RESULTS: Nineteen patients were recruited between March 2023 and April 2024. The least-square mean difference between pyridostigmine and placebo was 5.3 for MGII score (95% confidence interval [CI] 1.9-8.7, p = 0.004), QMG-score: 1.4 (95% CI 0.5-2.3, p = 0.005), MG-ADL-score: 1.2 (95% CI 0.5-1.8, p = 0.001), MG-QoL15r-score: 2.0 (95% CI 0.03-3.91, p =0.047). The cost-utility analysis showed both lower annual healthcare costs (€3816, 95% CI€336-€10489) and societal costs (€5817, 95% CI €16-€13729), and improved QALYs (0.106, 95% CI 0.019-0.210) with pyridostigmine.

SUMMARY/CONCLUSION: Pyridostigmine showed a highly significant benefit across all efficacy outcome measures and substantially reduced healthcare and societal costs.

DISCLOSURES: Teun van Gelder: In the last 3 years, has received consulting fees and lecture fees from Roche Diagnostics, Thermo Fisher, Vitaeris, CSL Behring, Astellas, and Aurinia

Pharma. In all cases, money has been transferred to hospital accounts, and none has been paid to his personal bank accounts. Umesh A. Badrising: Leiden University Medical Center has received funding from the Prinses Beatrix Spierfonds and Association Française contre les Myopathies, and compensation for clinical trial activities from Fulcrum Therapeutics on behalf of UAB. Jan J.G.M. Verschuuren: Involved in MG research sponsored by the Prinses Beatrix Fonds and Health Holland. Member of the Target-to-B! consortium. Coinventor on patent applications based on MuSK-related research. The LUMC receives royalties for MuSK antibody assays. Involved in consultancies for Argenx, Alexion, and NMD Pharma. Reimbursements were received by the LUMC. Member of the European Reference Network for Rare Neuromuscular Diseases [ERN EURO-NMD]. Martijn R. Tannemaat: Reports consultancies for Argenx, UCB Pharma, Johnson and Johnson, Peervoice, and Medtalks, and research funding from ZonMW, NWO, Argenx, and NMD Pharma. All reimbursements were received by the Leiden University Medical Center. Member of the European Reference Network for Rare Neuromuscular Diseases [ERN EURO-NMD].

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THE EFFICACY, TOLERABILITY AND SAFETY OF AMIFAMPRIDINE IN PATIENTS WITH MYASTHENIA GRAVIS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CROSSOVER STUDY

Linda Remijn-Nelissen[1], Wisse R. Bakker[2], Teun van Gelder[2], Annabel M. Ruiter[1], Yvonne J.M. Campman[1], Umesh A. Badrising[1], Chiara S.M. Straathof[1], Jan J.G.M. Verschuuren[1], Martijn R. Tannemaat[1]

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INTRODUCTION: Amifampridine, a short-acting potassium channel blocker, is used for the symptomatic treatment in Lambert-Eaton myasthenic syndrome. Its advantage as an add-on therapy to pyridostigmine in myasthenia gravis (MG) has been hypothesized, although no randomized controlled trials have been conducted.

OBJECTIVE: To evaluate the efficacy, tolerability and safety of amifampridine as an add-on therapy in AChR MG patients whose symptoms are insufficiently controlled with pyridostigmine.

METHODS: Participants were randomized in a 1:1:1 ratio to one of three treatment sequences. Each treatment phase lasted 5 days, with a 2-day washout between treatments, during which participants received either 30 mg or 60 mg of amifampridine base modified release, or a placebo. The primary efficacy outcome was change in Myasthenia Gravis Impairment Index (MGII) total score compared to placebo. Patients opting to continue then received amifampridine in a six-month open-label extension phase. Safety and tolerability were assessed throughout the trial.

RESULTS: Between March 2023 and April 2024, twenty patients were enrolled. There was no significant difference in the primary efficacy outcome. The estimated mean MGII total scores were 26.6 (95% CI 19.2-33.9) for placebo, 25.5 (95% CI 18.2-32.8) for amifampridine 30 mg, and 24.9 (95% CI 17.6-32.2) for amifampridine 60 mg. Sixteen patients continued amifampridine in the open-label extension phase, with thirteen patients remaining on it after 6 months. Compared to placebo (6 patients [30%]), adverse events were more common with amifampridine 30 mg (12 patients [60%]), and 60 mg (15 patients [75%]). Three patients discontinued early due to adverse events, mainly dizziness, nausea and vomiting.

SUMMARY/CONCLUSION: Amifampridine showed no significant benefit on the prespecified outcome measures. Nonetheless, thirteen out of twenty patients wished to continue amifampridine after six months. A post-hoc analysis will follow to assess whether efficacy is related to amifampridine plasma concentrations, with findings to be presented at the conference.

DISCLOSURES: Wisse R. Bakker: Employed by the Department of Clinical Pharmacy and Toxicology which produces and supplies the 3,4-diaminopyridine base modified release tablets to 40–50 users in the Netherlands. Teun van Gelder: In the last 3 years, has received consulting fees and lecture fees from Roche Diagnostics, Thermo Fisher, Vitaeris, CSL Behring, Astellas, and Aurinia Pharma. In all cases, money has been transferred to hospital accounts, and none has

been paid to his personal bank accounts. Umesh A. Badrising: Leiden University Medical Center has received funding from the Prinses Beatrix Spierfonds and Association Française contre les Myopathies, and compensation for clinical trial activities from Fulcrum Therapeutics on behalf of UAB. Jan J.G.M. Verschuuren: Involved in MG research sponsored by the Prinses Beatrix Fonds and Health Holland. Member of the Target-to-B! consortium. Coinventor on patent applications based on MuSK-related research. The LUMC receives royalties for MuSK antibody assays. Involved in consultancies for Argenx, Alexion, and NMD Pharma. Reimbursements were received by the LUMC. Member of the European Reference Network for Rare Neuromuscular Diseases [ERN EURO-NMD]. Martijn R. Tannemaat: Reports consultancies for Argenx, UCB Pharma, Johnson and Johnson, Peervoice, and Medtalks, and research funding from ZonMW, NWO, Argenx, and NMD Pharma. All reimbursements were received by the Leiden University Medical Center. Member of the European Reference Network for Rare Neuromuscular Diseases [ERN EURO-NMD].

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MYASTHENIA GRAVIS CONTROL: EVOLUTION OVER EIGHT YEARS OF FOLLOW-UP IN A REFERRAL UNIT AND PATIENT CHARACTERISTICS

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INTRODUCTION: Generalized myasthenia gravis (gMG) is characterized by chronic fluctuating weakness. Some patients may remain symptomatic regardless of treatment. We aimed to define and describe gMG adequately control status over time.

METHODS: A new definition of adequately-controlled gMG was developed by Spanish expert neurologists using a Delphi process, and was applied to a cohort of newly-diagnosed gMG patients in our referral Neuromuscular disease unit in Spain (1998-2020). Data was analyzed biennially to describe the evolution of control over 8 years. We assessed patient characteristics by gMG control status using descriptive statistics.

RESULTS: Adequately-controlled gMG was defined as achieved MGFA-PIS clinical stable remission, pharmacologic remission or minimal manifestations stable for a year, MG-ADL score ≤ 2, no clinical exacerbations during the last year and no or mild adverse events to therapies. 220 newly-diagnosed gMG patients were included in our study (54.5% women, 58 years of mean age at onset, 84% anti-AChR, 6% anti-MusK 10% seronegative). The proportion who achieved controlled status increased from 62.1% at 2 years to 81.9% at 8 years post-diagnosis. 17.7% remained not adequately controlled during all their follow-up (mean follow-up 3.3 years SD 2.2) and 47.3% kept adequately controlled from the first two years until their last follow up (mean follow-up 5.2 years SD 2.5). 17.2% patients that achieved adequately controlled status changed during their follow-up. Similar patient distribution by gMG control status was found in patients by sex, thymectomy or thymoma except for a higher proportion of inadequately-controlled patients was also found among seronegative patients two years post diagnosis ; and a higher proportion of inadequately-controlled patients in early onset gMG 4 years post-diagnosis was found.

CONCLUSION: A high proportion of gMG patients had inadequately-controlled disease: around 20% even 8 years after diagnosis. Those patients lacked specific clinical features, underscoring the unpredictability of the gMG course.

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LIVE AChR AND MUSK CBA IDENTIFY POSITIVE AChR MG PATIENTS AMONG FIXED CBA NEGATIVE MG PATIENTS

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INTRODUCTION: Fixed Cell Based Assays (CBA) for anti AChR- and MuSK-ab detection are widespread in many laboratories as second step for the identification of autoantibodies after the radioimmunoprecipitation (RIA), the gold standard for the laboratory MG diagnosis, or even suggested as first line option. Live CBA is an alternative to Fixed CBA, and both methods present advantages and limitations and, if possible, should be both used in MG diagnosis.

OBJECTIVE: This study aims to assess the sensitivity of Fixed and Live CBAs in AChR and MuSK antibody detection in a cohort of RIA seronegative MG.

METHODS: Sera from 65 AChR and MuSK RIA-seronegative MG patients, whose disease was clinically and neurophysiologically confirmed, were evaluated by the commercial fixed CBA for fetal and adult AChR isoforms and MuSK CBA. Sera were then tested by means of a live home-made CBA, with HEK-293 cells transfected with cDNA coding for all the AChR subunits and RAPSN-GFP or MuSK-EGFP.

RESULTS: Among the 65 RIA-seronegative sera analysed with the fixed CBA test, only one sample (1.5%) was found positive for the presence of autoantibodies against the fetal AChR isoform; all remaining samples were negative for AChR- and MuSK-ab. When the 65 samples were tested with the live AChR and MuSK CBA, 5 out of 65 (7.7%) sera were positive for anti-adult AChR antibodies.

SUMMARY/CONCLUSION: Even if the fixed CBA for anti AChR- and MuSK-ab represents a relevant step to improve laboratory diagnosis for MG, in our experience its sensitivity is not clearly higher than RIA. On the other side, negative samples from RIA or fixed CBA should be retested with the live CBA, in order to provide a more precise diagnosis of Myasthenia Gravis.

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COMPLEMENT INHIBITORS FOR MYASTHENIC CRISIS: A PROMISING AND FAST-ACTING THERAPY

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ABSTRACT: We report the case of a 32-year-old woman with an 11-year history of thymomatous AChR antibody-positive generalized myasthenia gravis (gMG, MGFA IIIb) who experienced a myasthenic crisis (MC) during the postpartum period, requiring mechanical ventilation (MV).

Initial treatment with plasma exchange (TPE) and high-dose prednisone was ineffective, and pyridostigmine worsened airway secretions. Due to contraindications for IvIg, she was treated with the complement inhibitor Eculizumab, following prophylactic meningococcal vaccination and antibiotic therapy. Six days after starting Eculizumab, the patient showed marked improvement in muscle strength, respiratory function, and was successfully extubated. She was discharged from the ICU and continued bi-weekly Eculizumab infusions without adverse events.

A systematic literature review identified 10 additional cases of MC treated with Eculizumab, examining response timing, treatment efficacy, adverse events, and follow-up data. This case, along with the literature review, suggests the safety and efficacy of Eculizumab for MC in patients unresponsive to conventional therapies.

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RAVULIZUMAB TREATMENT FOR GENERALIZED MYASTHENIA GRAVIS: A MULTICENTER REAL-LIFE EXPERIENCE

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INTRODUCTION: Ravulizumab, a monoclonal antibody targeting C5, was recently approved for the treatment of anti-AChR positive generalized myasthenia gravis (gMG) patients.

OBJECTIVE: The objective of this study is to present the Italian multicenter real-world experience evaluating the safety and efficacy of ravulizumab in gMG within the context of the Expanded Early Access Program (EAP).

METHODS: We conducted a retrospective study in 7 gMG referral centres in Italy. Demographic and clinical characteristics were recorded at baseline and during follow-up through clinical scale changes including Myasthenia Gravis-Activities of Daily Living (MG-ADL), Quantitative Myasthenia Gravis (QMG) and Myasthenia Gravis Composite (MGC). Frequency of minimal symptom expression (MSE) and changes in concomitant medications were also evaluated.

RESULTS: Twenty-four gMG patients (10/24 females) aged between 24 and 82 years (Median 60.5, IQR 52.5-67.5), were included. Fifteen patients had undergone thymectomy, 14 had a

thymoma. Median follow-up duration was 26 weeks (range 10-74, IQR 26-42). MG-ADL and QMG scores showed significant decrease with respect to baseline ($p<0.001$). MSE was achieved by 37.5% patients at the last available follow-up. Tapering of prednisone daily dosage was possible in 76% of patients. Thymoma was significantly associated with QMG score reduction and the frequency of QMG responders at week 2 ($p=0.03$). Three patients discontinued treatment. One patient experienced a myasthenic exacerbation and needed rescue therapy. Infectious adverse events were reported in 5/24 patients, and a Stevens-Johnson syndrome in one patient.

CONCLUSIONS: Real-world data confirm the effectiveness, safety, and prednisone-sparing effect of ravulizumab in patients with gMG, especially in those with thymoma.

DISCLOSURES: VDS received compensation for speaking from Alexion, UCB, Argenx and Alnylam; he is Sub-Investigator in clinical trials for Alexion, Alnylam, Argenx, Dianthus, and Sanofi. RI received speaker honoraria and consultancy fees from Alexion, Aera Therapeutics, Amgen, Argenx, Dianthus Therapeutics, Johnson&Johnson, Merck, UCB. FH received speaker honoraria and consultancy fees from Argx, UCB, Alexion, Johnson Johnson.

MM received speaker honoraria and consultancy fees from Alexion, Argenx, UCB. CV has received honoraria for speakers, manuscript writing , educational events and support for attending meetings and travels from Alexion , ArgenX, UCB, and Sanofi. EMP received speaker honoraria and consultancy fees from Alexion, Argenx, UCB, Sanofi. DR has received honoraria for speakers, educational events and support for attending meeting and travels from Alexiox, UCB, Argenx and CSL Behring. SM received public speaking honoraria and travel grants from Alexion; MG received speaker honoraria and consultancy fees from Sanofi, Dianthus, Kedrion. LL received speaker honoraria and consultancy fees from Argx. GA received conference honoraria, advisory board and travel grants from Kedrion, Alnylam, Alexion, Argenx, Takeda; LF received public speaking honoraria and/or Advisory boards and travel grants from Alexion, Argenx, UCB, Dianthus.

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DIFFERENTIAL EFFECT OF ECULIZUMAB AND EFGARTIGIMOD ON SUBSCORES OF THE MG-ADL AND QMG IN GENERALIZED MYASTHENIA GRAVIS PATIENTS

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INTRODUCTION: Eculizumab (ECU) and Efgartigimod (EFGA) are both approved for the treatment of generalized Myasthenia Gravis (gMG).

OBJECTIVE: To describe the differential response of both treatments on subscores of the MG activities of daily living (MG-ADL), and quantitative MG scale (QMG) in a real-life setting.

METHODS: We included 38 patients (22 ECU and 16 EFGA), and retrospectively collected data on the MG-ADL and QMG. We limited the observation of the MG-ADL to weekly scores for the first 8 weeks of treatment, and of the QMG at baseline and after 5, 12, 24, 36, and 48 weeks. We analyzed the difference between treatments with a General Linear Model for repeated measures.

RESULTS: We found a higher response to ECU at the MG-ADL at week 7 (-6.3 vs 3.8; p=0.038), and at the QMG at week 24 (-6.0 vs -0.9; p=0.032), 36 (-7.7 vs -1.7; p=0.020), and 48 (-8.5 vs -2.6;p=0.018). We found no difference for the ocular (p=0.204) and limb subscores of the MG-ADL (p=0.408), and at ocular (p=0.888) and limb subscores (p=0.229) of the QMG. Response for the bulbar subscores both at the MG-ADL (p=0.037) and QMG (p=0.037), was higher with ECU treated patients. For the MG-ADL this occurred at week 6 (-3-4 vs -1.2, p=0.009), and 7 (-3.1 vs -1.2, p=0.020), and for the QMG at week 12 (-2.1 vs -.8, p=0.025) and 36 (-3.0 vs -1.1, p=0.018). Mean QMG score for the forced vital capacity (FVC) decreased more with ECU throughout the entire observation period (p=0.036).

SUMMARY/CONCLUSION: Our study shows a differential effect of Eculizumab and Efgartigimod on the MG-ADL and QMG with a deeper effect of Eculizumab on bulbar scores. This differential effect should be considered when treating patients with high bulbar scores and ventilatory insufficiency as they may benefit more from Eculizumab

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EFFECT OF ROZANOLIXIZUMAB ON BULBAR AND RESPIRATORY SYMPTOMS IN PATIENTS WITH GENERALISED MYASTHENIA GRAVIS: *POST HOC* ITEM-LEVEL ANALYSIS OF MYCARING

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INTRODUCTION: The predominant manifestation of generalised myasthenia gravis (gMG) is fluctuating muscle weakness, which can be life-threatening if bulbar or respiratory muscles are affected. In the Phase 3 MycarinG study (NCT03971422), rozanolixizumab demonstrated clinically meaningful improvements in Myasthenia Gravis-Activities of Daily Living (MG ADL) and Quantitative Myasthenia Gravis (QMG) total scores versus a placebo comparator in patients with gMG.

OBJECTIVE: Assess the effect of rozanolixizumab on bulbar and respiratory symptoms in gMG.

METHODS: In the double-blind, placebo-controlled MycarinG study, adults with Myasthenia Gravis Foundation of America Disease Class II–IVa, anti-acetylcholine receptor or anti-muscle-specific tyrosine kinase antibody-positive gMG were randomised 1:1:1 to once-weekly rozanolixizumab 7mg/kg, 10mg/kg or placebo for 6 weeks. Mean change from baseline (CFB) at Day 43 in MG-ADL and QMG bulbar and respiratory item scores was assessed *post hoc* for patients with baseline score ≥1 in that item.

RESULTS: Overall, 200 patients received rozanolixizumab 7mg/kg (n=66), 10mg/kg (n=67) or placebo (n=67). Mean baseline scores for bulbar items were 0.8–0.9 (MG-ADL) and 0.4–1.1 (QMG); for respiratory items, these were 0.9–1.0 and 0.5–0.7. At Day 43, mean CFB in MG-ADL bulbar item scores for patients with baseline scores ≥1 in the rozanolixizumab 7mg/kg, 10mg/kg and placebo groups, respectively, were: −0.7, −0.7 and −0.2 for speech/voice; −0.6, −0.6 and −0.3 for swallowing; −0.7, −0.6 and −0.2 for chewing. Mean CFB in QMG bulbar item scores was −1.0, −0.9 and −0.6 for speech/voice and −0.8, −0.7 and −0.5 for swallowing. For respiratory item scores, mean CFB was −0.3, −0.4 and −0.1 for breathing (MG-ADL) and −0.5, −0.6 and −0.2 for forced vital capacity (QMG). Most treatment-emergent adverse events were mild/moderate.

SUMMARY/CONCLUSION: Rozanolixizumab led to bulbar and respiratory item score improvements across myasthenia gravis-specific outcomes versus placebo, suggesting a benefit for patients with gMG exhibiting bulbar and/or respiratory symptoms.

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TOWARD EUROPEAN HARMONIZATION OF NATIONAL MYASTHENIA GRAVIS REGISTRIES: MODIFIED DELPHI PROCEDURE-BASED EXPERT CONSENSUS ON COLLECTABLE DATA

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INTRODUCTION: Myasthenia gravis (MG) is a rare autoimmune disorder. In recent years, several new treatment concepts have emerged. However, access to these treatments varies due to differing national reimbursement regulations, which leads to disparities across Europe. This situation highlights the need for high-quality data collection by stakeholders to establish MG registries.

OBJECTIVE: The objective of this study is to explore the potential of a European MG registry that could help bridge the treatment access gap across different countries. This registry would offer critical data to support regulatory decisions, foster international collaborations, and enhance clinical and epidemiological research.

METHODS: Several national MG registries already exist or are in development. To avoid duplication and ensure harmonization in data collection, a modified Delphi procedure was implemented. This process aimed to identify essential data elements for inclusion in national registries. Following a literature review, consultations with patient associations, pharmaceutical companies, and input from multiple European MG experts, 100 data elements were identified.

RESULTS: Of the 100 data elements identified, 62 reached consensus for inclusion and classification. Notably, only 1 item was agreed for exclusion. Additionally, 30 items failed to reach the ≥ 80% agreement threshold and were consequently excluded. Among the 62 accepted items, the classification revealed that 21 were deemed as mandatory data elements, 32 were optional, and 9 items pertained to the informed consent form.

SUMMARY/CONCLUSION: A consensus was achieved through a modified Delphi procedure involving a multidisciplinary panel of European experts on MG. This expert-driven approach marks a significant step toward data harmonization among European national MG registries. The resulting dataset will serve as a foundation for establishing a European collaboration on MG, addressing key clinical, research, and regulatory questions, and supporting decisions on treatment availability across European countries.

DISCLOSURES: Adela Della Marina participated in the advisory board of the Deutsche Myasthenie Gesellschaft. Andreas Meisel is an advisor, consultant, speaker, and/or investigator and has received research grants (paid to his institution) and honoraria from Alexion AstraZeneca Rare Disease, argenx, Axunio, Grifols, Hormosan, Immunovant, Janssen, Merck, Novartis, Octapharma, Regeneron, Sanofi and UCB. He served as chairman of the medical advisory board of the German Myasthenia Gravis Society. Carlo Antozzi received funding for travel, meeting attendance and advisory board participation from Alexion, Momenta, Sanofi, Janssen, argenx and UCB. Caroline Perriard received sponsorship from Novartis and Jazz

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MYASTHENIA GRAVIS IN LATIN AMERICA AND THE CARIBBEAN. EPIDEMIOLOGY, RESOURCES, AND ACCESSIBILITY TO DIAGNOSIS AND TREATMENT.

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BACKGROUND: Latin-American and Caribbean (LAC) countries strive to provide Universal Health Assistance. One of the main barriers is the out-of-pocket expenses of Health Care. There is little knowledge regarding access to Myasthenia Gravis (MG) diagnostic tests and treatments.

OBJECTIVE: Define the available resources for MG diagnosis and treatment, as well as the costs and access barriers.

MATERIALS AND METHODS: A network of Latin American and Caribbean (LAC) neurologists with expertise in managing myasthenia gravis (MG) was established, comprising representatives from 12 countries. These neurologists were identified during the Latin American

Neuromuscular Society (SOLANE) meeting held in Bogotá, Colombia, in 2023. Each participant completed a data collection form regarding the availability of diagnostic tests and therapeutic options for MG in their respective countries. Additionally, a follow-up questionnaire was administered to clarify or expand upon specific items. The 36 variables assessed were organized into three thematic modules: Epidemiology and Health Economics, MG Diagnosis, and MG Treatment. Availability of healthcare resources was classified by sector—public vs. private—and treatment costs were estimated based on standard dosing regimens. Costs were converted from local currencies to US dollars using the 2023 exchange rates. Descriptive statistics are presented as mean ± standard deviation (SD) or as absolute numbers and percentages, as appropriate.

RESULTS: (Key Findings): Data were collected from 12 countries. The number of neurologists per 100,000 population ranged from 0.29 to 4.7. The average monthly minimum wage was $399 ± $312.36 (range: $15–$1,320 USD). The mean percentage of GDP allocated to healthcare was 5.08% ± 2.58 (range: 1.2–10%). Repetitive nerve stimulation was available in 11 out of 12 countries, single-fiber electromyography (SFEMG) in 10, and chest tomography in all 12 countries. Acetylcholine receptor antibody (AChR-Ab) testing was available in 8 out of 10 reporting countries, while muscle-specific tyrosine kinase antibody (MuSK-Ab) testing was available in 7 out of 10. Regarding treatments, pyridostigmine was available in 11 countries, and corticosteroids, azathioprine, mycophenolate mofetil, intravenous immunoglobulin (IVIG), and plasmapheresis were accessible in all 12. In the public sector, pyridostigmine was accessible in 58% of countries, corticosteroids in 83%, and azathioprine in 75%. Rituximab and eculizumab showed notably lower availability. The ratio of monthly treatment costs (out-of-pocket) to minimum wage was highest in Venezuela, Bolivia, Ecuador, and Argentina.

SUMMARY/CONCLUSION: Although a majority of countries reported access to essential diagnostic and therapeutic technologies for MG, substantial disparities were evident—particularly within public healthcare systems. SFEMG was only available in the public sector in 33% of countries and could cost up to twice the monthly minimum wage. AchR- Ab testing was publicly funded in only 42% of countries, while MuSK-Ab testing was covered in just 17%, with costs reaching up to three times the minimum wage. Critical barriers—including a shortage of neurologists, the need to ship blood samples abroad, and lack of pricing regulations—contribute to high out-of-pocket expenses. A concerted effort by the global neurology community is essential to reduce inequities and improve access to MG care across the region.

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DOMINANT T CELL EPITOPES AND CYTOKINE PROFILE IN IMMUNOTHERAPY NAÏVE ACHR MYASTHENIA GRAVIS

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INTRODUCTION: T and B cell antigenic target in autoimmune MG is nicotinic AChR complex at the neuromuscular junction. In AChR MG, Major Immunogenic Region for B cell epitopes is located on α-chain of AChR. As γ-chain in foetal AChR is replaced by ε-chain in adults, the latter is assumed to have been less exposed to T cells during the thymic selection processes. Thus, to screen for major T cell epitopes in AChR MG patients with no prior exposure to any form of immunotherapy, our study focused on α- and ε- chains.

OBJECTIVE: To identify major T cell epitopes in immunotherapy naïve AChR MG patients

METHODS: Pan HLADR (Human Leucocyte Antigen) binding T cell epitopes were predicted with NetMHCII and ProPred algorithms. Using Tritium labelled Thymidine incorporation assay and flow cytometry based multi-analyte cytokine analysis (LEGENDPlexTM) of culture supernatants, T cell proliferative responses to 46 peptides from α- and ε- chains were determined using peripheral blood mononuclear cells from 40 immunotherapy naïve AChR MG patients and compared with those from 42 healthy participants.

RESULTS: The proliferative responses were significantly more intense and widespread in MG patients than in healthy individuals. 97.5% of MG patients responded to at least 1 α-chain peptide but in contrast ε- chain peptide responses were seen only in 27.5% and all accompanied by mostly extensive α-chain peptides responses. The number of peptides responded also increased with the disease duration. α4 and α10 gave the strongest responses in MG patients whereas it was α7 in healthy participants. IL-17A, IL-17F and IL-22 levels correlated with the T cell proliferative response.

SUMMARY/CONCLUSION: T cell epitope profile in immunotherapy naïve AChR MG patients was dominated by α-chain peptides rather than those from ε-chain and was also different to healthy participants. In addition, an epitope spreading phenomenon was observed in patients.

DISCLOSURES: Pyae Phyo San has been undertaking a PhD with funding from Myaware. David C Wraith declares stock ownership in Apitope International NV. He serves as a consultant to Apitope International NV and has sat on scientific advisory boards for Actelion Pharma and Zealand Pharma; is a senior editor for Immunotherapy; holds patents for peptides, tolerisation-inducing composition, FVIII peptides and their use in tolerising haemophiliacs, composition, disease markers, tolerogenic peptides from myelin basic protein, peptide selection method, and improvements relating to influenza vaccine; has consulted for Peptide Therapeutics Ltd., Teva, GSK Bio, Hoffmann-La Roche, Novartis, DTI, and the Food Standards Agency; received research support within the past 3 years from UCB Celltech and was an expert witness for Geron.

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Jennifer Spillane has received speaker fees from ArgenX, support for attending conferences from UCB and ArgenX, taken part in advisory boards for UCB and ArgenX and has taken part in a Single Technology Appraisal for the National Institute for Clinical Excellence as a clinical expert.

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THYMOMATOUS MYASTHENIA GRAVIS IN A TEENAGER WHO DEVELOPED BREAST CANCER AFTER HIGH-DOSE RADIATION EXPOSURE: A CASE REPORT.

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INTRODUCTION: Approximately 15% of patients with MG patients present with thymoma, which may be treated with chemotherapy, surgery, and radiotherapy. However, exposure to ionizing radiation from radiotherapy and follow-up computed tomography (CT) scans may increase the risk of secondary malignant neoplasms.

OBJECTIVE: To report a case of potential radiation-induced breast cancer in a young woman with thymomatous MG.

METHODS: Case review of clinical history, treatments, follow-up imaging, genetic testing, and disease progression, supplemented with a literature review on radiation-induced malignancies in thymoma patients.

RESULTS: A 33-year-old woman with thymomatous MG diagnosed at 15 years of age, with positive AChR antibodies. The B1 thymoma was treated with surgery, chemotherapy, and six weeks of radiotherapy. During oncological follow-up, chest CT scans were performed biannually for two years and annually thereafter. Ten years post-radiotherapy, she was diagnosed with invasive ductal carcinoma of the left breast, with negative genetic findings. Treated with surgery, tamoxifen, and paclitaxel, the cancer progressed to stage IV.

Her MG remained stable for the year following thymectomy but relapsed, requiring ICU admissions and immunosuppressants such as rituximab and azathioprine. The most recent exacerbation occurred after SARS-CoV-2 infection in March 2022, managed successfully with Zilucoplan.

The absence of genetic mutation or familiar background and the timing of breast cancer onset, suggest a radiation-induced malignancy, due to radiotherapy and long-term CT surveillance. Treatment strategies for thymoma should consider demographic factors such as age at the time of radiation exposure and sex-specific cancer risks. Identifying biomarkers for radiation sensitivity could refine treatment surveillance protocols.

SUMMARY/CONCLUSION: This case reports a possible post-radiation induced cancer. This highlights the importance of considering factors such as age and sex in the treatment and follow-up of thymoma, as well as the need to identify biomarkers to guide surveillance and therapeutic decisions.

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ASSESSING EFGARTIGIMOD DOSING PATTERNS AND MYASTHENIA GRAVIS ACTIVITIES OF DAILY LIVING OUTCOMES IN CLINICAL PRACTICE: RESULTS FROM A LARGE PATIENT SUPPORT PROGRAM DATABASE IN THE UNITED STATES

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INTRODUCTION: Efgartigimod is an engineered human Fc-fragment that is approved globally for treatment of anti-acetylcholinesterase receptor antibody positive (and regardless of antibody status in Japan) generalized myasthenia gravis (gMG). Each efgartigimod cycle consists of 1 infusion each week for 4 weeks; intervals between cycles vary based on individual response, enabling adaptability for heterogeneous phenotypes.

OBJECTIVE: To evaluate dosing patterns and Myasthenia Gravis Activities of Daily Living (MG-ADL) responses following efgartigimod initiation among patients with gMG in the United States (US).

METHODS: US adults (aged ≥18 years) with gMG who initiated efgartigimod by September 26, 2023, and enrolled in the My VYVGART Path patient support program were included. Efgartigimod infusion dates and MG-ADL scores were captured through phone contact. Patients who had both baseline (pre-efgartigimod) and ≥4 MG-ADL scores captured post-efgartigimod initiation were included. To assess dosing patterns, weeks between treatment cycles were analyzed. To analyze outcomes, lowest and patient-averaged MG-ADL scores post-efgartigimod initiation were compared with baseline scores for each patient, then averaged at the population level. MG-ADL change by month and by cycle was also assessed.

RESULTS: 1347 individuals were included. Mean baseline MG-ADL score was 8.8 (range: 2-20), with an average of 4.4 (range: 1-20) treatment cycles initiated. Among 4558 intervals between cycles identified, 4 weeks was the most common (26%). At the population level, the mean largest MG-ADL improvement versus baseline was 5.9 points, with 92% of patients experiencing clinically meaningful improvement (CMI; 2-point improvement in MG-ADL). The

mean patient-averaged improvement in MG-ADL was 3.8 points, with 73% of patients experiencing CMI.

SUMMARY/CONCLUSION: Among patients who initiated efgartigimod in clinical practice, intervals between cycles were most commonly 4 weeks, with a substantial proportion achieving CMI in MG-ADL, consistent with clinical trial results.

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OUTCOMES WITH RAVULIZUMAB OR EFGARTIGIMOD IN GMG: A RETROSPECTIVE MEDICAL RECORD ANALYSIS

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INTRODUCTION: Targeted therapies such as ravulizumab (terminal complement inhibitor) and efgartigimod (neonatal Fc receptor blocker) are approved to treat anti-acetylcholine receptor antibody-positive (AChR-Ab+) gMG. However, there is a lack of real-world data assessing clinical outcomes among patients treated with these therapies.

OBJECTIVE: Evaluate outcomes among patients with generalized myasthenia gravis (gMG) treated with ravulizumab or efgartigimod as first targeted immunotherapy.

METHODS: Physician-abstracted electronic medical records were included for adults with AChR-Ab+ gMG in Cardinal Health's Neurology Provider Extended Network who initiated their first targeted immunotherapy on or after December 1, 2021. Outcomes included clinical characteristics, concomitant medication use, and Myasthenia Gravis Activities of Daily Living (MG-ADL) total scores up to 2 years preinitiation and after treatment initiation with additional efficacy measures (up to 17.7 months of follow-up).

RESULTS: Data were available for 152 patients (ravulizumab, n=45; efgartigimod, n=107). Mean±SD age at initiation was 61.5±13.6 years for the ravulizumab group and ?57.0±16.6 for the efgartigimod group. Preinitiation, mean±SD MG-ADL total scores were 9.3±2.9 in the ravulizumab group and 8.7±3.8 in the efgartigimod group. Mean±SD MG-ADL total scores at 3 months post initiation were 4.7±3.1 and 5.6±3.4 with ravulizumab and efgartigimod, respectively, and at 6 months post initiation, total scores were 2.0±1.8 and 4.3±3.2, respectively. Among patients taking oral corticosteroids (OCS) at treatment initiation, 17/19 (89.5%) ravulizumab patients and 33/46 (71.7%) efgartigimod patients reduced their dose during treatment. No patients increased their OCS dose while on ravulizumab, and 3/46 (6.5%) efgartigimod patients increased OCS dose to >20 mg/day. Additional outcomes will be presented.

SUMMARY/CONCLUSION: Despite varying patient characteristics, results suggest both treatments improved patient outcomes and decreased OCS dosing. Patients who received ravulizumab trended toward greater improvements in MG-ADL total score than those who received efgartigimod.

DISCLOSURES: Christopher A. Scheiner: Has consulted for Alexion and CSL Behring. Samir P. Macwan: Has served as a consultant for AbbVie, Alexion, argenx, Catalyst, Grifols,

KabaFusion, Supernus, and UCB. Nicholas Streicher: Is a paid speaker for Alexion and Catalyst. Karen S. Yee: Is an employee of Alexion, AstraZeneca Rare Disease, and holds stock or stock options in AstraZeneca and Takeda. Chloe Sader: Is an employee of Alexion, AstraZeneca Rare Disease, and holds stock or stock options in AstraZeneca. Michael Blackowicz: Is an employee of Alexion, AstraZeneca Rare Disease, and holds stock or stock options in AstraZeneca. Nana Numapau: Is an employee of Alexion, AstraZeneca Rare Disease, and holds stock or stock options in AstraZeneca. Danielle Gentile: Is an employee of Cardinal Health, which received funding to conduct this research. Jason Sharpe: Is an employee of Cardinal Health, which received funding to conduct this research. Prathamesh Pathak: Is an employee of Cardinal Health, which received funding to conduct this research. Michael T. Pulley: Has received compensation for medical advisory board membership or regional advisory board participation from Alexion, AstraZeneca Rare Disease, argenx, Catalyst, CSL Behring, Immunovant, and UCB.

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ACETYLCHOLINE RECEPTOR ANTIBODIES ISOFORM SPECIFICITY: A POTENTIAL PROGNOSTIC BIOMARKER IN MYASTHENIA GRAVIS

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INTRODUCTION: Myasthenia gravis (MG) is an autoimmune disorder mediated in most cases by autoantibodies against the nicotinic acetylcholine receptor (AChR). It is known that antibodies can target specifically either the adult or the fetal AChR isoform, but their clinical significance remains uncertain.

OBJECTIVE: No reliable biomarker of MG clinical outcome has been proven to date, therefore we investigated whether preferential antibody reactivity for the adult-AChR or the fetal-AChR isoform and the AChR-IgG subclass prevalence during disease course correlates with MG clinical outcome.

METHODS: Patients with a confirmed MG diagnosis and positive radioimmunoassay for AChR-antibodies were included in the study (n=174). Antibody reactivity against the adult-AChR vs the fetal-AChR isoforms and AChR-IgG subclasses were assessed by live cell based assay on flow cytometry. Clinical outcome was assessed through the “patient acceptable symptom state” (PASS-question) and the post-intervention status (PIS).

RESULTS: We found a lower adult/fetal AChR immunoreactivity ratio (A/F) in less severely affected patients (those who answered “yes” to the PASS-question vs “no”; p=0.039, Mann-Whitney test) indicating that when clinical outcome is acceptable (PASS=yes) most serum antibodies bind to fetal-AChR. This finding was confirmed not only when comparing A/F between patients with a PIS of minimal manifestations or better (“MM or better”) vs those who were still symptomatic (p=0.001, Mann-Whitney test), but also between patients in complete stable remission vs those with MM (p=0.04, Mann-Whitney test). No differences in A/F were found between patients with ocular or generalized MG. The AChR-IgG subclass profile was similar for A-AChR and F-AChR-Abs and no significant correlation were found with the clinical outcome both by using PASS and PIS outcome values.

SUMMARY/CONCLUSION: The adult/fetal AChR immunoreactivity ratio is a promising predictive biomarker of AChR-MG outcome and should be investigated in larger prospective studies.

DISCLOSURES: Author Alessandro Barilaro has received public speaking honoraria from Alnilam. He declares no competing interest regarding this work. Author Luca Massacesi has received research support from Merck- Serono and personal compensation in the range of $500-

$4,999 for serving on a Speakers Bureau for Biogen, Novartis, Roche, Merck-Serono, Johnson and Johnson, Alexion and Horizon. The institution of author Luca Massacesi has received personal compensation in the range of $10,000-$49,999 for serving as a Consultant for Biogen and research support from Tuscan Region Government, Sanofi, and Roche. Author Amelia Evoli has received personal compensation in the range of $500-$4,999 for serving as a Consultant for Dianthusand, as a jury member for research grant with Grifols and as a speaker with UCB. Author Valentina Damato has received public speaking honoraria and compensation for advisory boards and/or consultations fees from UCB, Alexion, Dianthus, Roche. She declares no competing interest regarding this manuscript.

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CLINICAL CHARATERISTICS AND MANAGEMENT OF IMMUNOTHERAPY IN SERONEGATIVE MYASTHENIA GRAVIS: A SYSTEMATIC REVIEW OF THE LITERATURE

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INTRODUCTION: Seronegative myasthenia gravis (SNMG) encompasses all MG cases negative for AChR and MuSK antibodies by standard assays. The clinical presentation is usually heterogeneous, and both diagnostic and treatment guidelines are currently lacking.

OBJECTIVE: To define clinical features, diagnostic clues and treatment outcome of SNMG patients.

METHODS: We searched MEDLINE, Embase and Cochrane Library databases for all the articles published between 2001 and 2024 using the search query (seronegative myasthenia gravis OR double-negative myasthenia gravis OR triple-negative myasthenia gravis OR negative antibody myasthenia gravis OR SNMG) AND (outcome OR immunotherapy). We screened for original English-language articles whose full text was available for revision. Studies including patients with negative anti-AChR, anti-MuSK and, if tested, anti-LRP4 antibodies and at least one criteria between a positive electroneuromyography or positive response to anticholinesterase drugs were included. MG foundation of America post intervention scale (MGFA-PIS) was used to assess the therapeutic outcome. Favourable outcome was defined as achievement of an MGFA-PIS of Improved or better.

RESULTS: Of the 572 SNMG patients included, 60% had ocular MG, while, among those with generalised MG, up to 65% had a mild disease course, with MGFA = II. Interestingly, thymectomy was performed in 32% of patients; thymoma was diagnosed in 12 cases. Corticosteroid therapy was used in 69% of patients, and it was associated with at least one additional immunosuppressant in half of the cases. Clinical outcome was unfavourable in 24% of patients, despite long-term immunotherapy.

SUMMARY/CONCLUSION: SNMG is confirmed to be mostly ocular and generally mild in severity. However, immunosuppressive treatment was administered to the majority of patients. Moreover, despite prolonged immunotherapy, a significant proportion of patients did not improve, suggesting that the management of SNMG can be challenging and may benefit from a more targeted therapeutic approach.

DISCLOSURES: Alessandro Barillaro: Has received public speaking honoraria from Alnilam. Declares no competing interest regarding this manuscript. Luca Massacesi: The institution of Luca Massacesi has received personal compensation in the range of $10,000–$49,999 for serving as a consultant for Biogen. He has received personal compensation in the range of $500–$4,999 for serving on speaker bureaus for Biogen, Novartis, Roche, Merck-Serono, Johnson and

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ITIH3: A SERUM BIOMARKER FOR DISEASE ACTIVITY IN MYASTHENIA GRAVIS

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INTRODUCTION: Myasthenia gravis is a chronic antibody-mediated autoimmune disease disrupting neuromuscular synaptic transmission.

OBJECTIVE: Informative biomarkers remain an unmet need to stratify patients with active disease requiring intensified monitoring and therapy; their identification is the primary objective of this study.

METHODS: We applied mass spectrometry-based proteomic serum profiling for biomarker discovery. We studied an exploration and a prospective validation cohort consisting of 114 and 140 anti-acetylcholine receptor antibody (AChR-Ab)-positive myasthenia gravis patients, respectively. For downstream analysis, we applied a machine learning approach. Protein expression levels were confirmed by ELISA and compared to other myasthenic cohorts. Anti-AChR-Ab levels were determined by a radio receptor assay. Immunohistochemistry and immunofluorescence of intercostal muscle biopsies were employed for validation in addition to interactome studies of inter-alpha-trypsin inhibitor heavy chain H3 (ITIH3).

RESULTS: Machine learning identified ITIH3 as potential serum biomarker reflective of disease activity. Serum levels correlated with disease activity scores in the exploration and validation cohort and were confirmed by ELISA. Lack of correlation between anti-AChR-Ab levels and clinical scores underlined the need for biomarkers. In a subgroup analysis, ITIH3 was indicative of treatment responses. Immunostaining of muscle specimens from these patients demonstrated ITIH3 localization at the neuromuscular endplates in myasthenia gravis but not in controls, thus providing a structural equivalent for our serological findings. Immunoprecipitation of ITH3 lead to identification of its interaction partners playing crucial roles in neuromuscular transmission.

SUMMARY/CONCLUSION: This study provides data on ITIH3 as a potential pathophysiological-relevant biomarker of disease activity in myasthenia gravis. Future studies are required to facilitate translation into clinical practice.

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STUDY DESIGN OF SUBCUTANEOUS EFGARTIGIMOD PH20 IN JUVENILE GENERALIZED MYASTHENIA GRAVIS

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INTRODUCTION: Efgartigimod is a human immunoglobulin G1 (IgG1) antibody Fc-fragment that blocks neonatal Fc receptor (FcRn). Previous phase 3 trials have demonstrated that both efgartigimod IV (ADAPT/ADAPT+) and efgartigimod PH20 SC (ADAPT-SC/ADAPT-SC+) is efficacious and well tolerated in adults with gMG. The incidence of juvenile gMG (1-5:1,000,000) is considerably lower than adult gMG and there remains an unmet need for effective and safe treatments in this population. A clinical trial assessing efgartigimod IV in juvenile gMG (NCT04833894) is currently underway. Here, we present the study design evaluating efgartigimod PH20 SC in patients with juvenile gMG (NCT06392386).

OBJECTIVE: This study aims to confirm the age-appropriate dose of subcutaneous efgartigimod coformulated with recombinant hyaluronidase (efgartigimod PH20 SC).

METHODS: This study will recruit ≥12 patients, aged 2-17 years, and has a staggered design starting with the older age group (12-17 years). Participants must have a confirmed diagnosis of MGFA class II, III, or IVa, seropositivity for anti-AChR autoantibodies, and be on a stable dose of MG therapy. The study will consist of a 2-week screening period, 4-week treatment period, and 8-week follow-up period. During the treatment period, patients will receive 4 once-weekly injections of efgartigimod PH20 SC.

RESULTS: Pharmacokinetics (PK), pharmacodynamics (PD), safety, tolerability, immunogenicity, and clinical effect of efgartigimod PH20 SC will be assessed, along with evaluation of antibody responses to vaccines during efgartigimod treatment. Assessments include MG-ADL, QMG, EQ-5D-Y, Quality of Life in Neurological Disorders Pediatric Fatigue Score, and Clinical Global Impression of Improvement. Age-appropriate adaptations to assessments will be made during the study.

SUMMARY/CONCLUSION: This study will use PK/PD modeling to confirm the appropriate efgartigimod PH20 SC dose and evaluate efficacy and safety for pediatric patients with gMG. Efgartigimod PH20 SC may address an unmet need and provide additional flexibility for the treatment of pediatric patients with gMG.

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EXPLORATORY QUALITATIVE STUDY OF THE EXPERIENCES OF WOMEN LIVING WITH MYASTHENIA GRAVIS

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INTRODUCTION: Inequality in women's health across chronic conditions is well documented; however, there is limited insight into the specific experiences of women living with MG. A cross-functional programme will assess the challenges faced by women living with MG, starting with exploratory research into the impact of MG on societal roles expected of women.

OBJECTIVE: To explore the lived experiences of women with MG and understand how living with this disease impacts their daily lives and societal roles.

METHODS: This exploratory, qualitative study included women from the USA, Spain and France with an MG diagnosis. Participants were interviewed online via semi-structured 90-minute virtual interviews. Qualitative ethnographic data pertaining to personal narratives of diagnosis, everyday life, professional life and social life relating to MG were collected. Data were coded and analysed using NVivo software and grounded theory. Results were triangulated through independent coding by three researchers, followed by a collaborative review and consensus-building process to resolve discrepancies.

RESULTS: Twelve women living with MG were interviewed between 14 August and 19 September 2024. From these interviews, 172 unique observations were recorded, guided by a framework of anthropology and social psychology, leading to the identification of six core roles that women living with MG navigate: woman; mother; partner; friend; professional; patient. These roles resulted in 10 preliminary themes relating to forms of role-based dissonance including, for example, 'cultural expectations versus self-advocacy' and 'motherhood versus "sick" mother' roles.

SUMMARY/CONCLUSION: This unique research looking through the lens of women's roles (rather than traditional symptom-focussed approaches) highlights dissonance between societal and self-imposed expectations placed on women, on top of the realities of living with a chronic condition like MG. The programme will continue to explore and validate these insights through ongoing co-creation sessions with patient advocates.

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STEROID SPARING EFFECT OF TACROLIMUS IN ANTI-MUSK ANTIBODY POSITIVE MYASTHENIA GRAVIS

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INTRODUCTION: In the treatment of patients with anti-muscle-specific kinase antibody-positive myasthenia gravis (MuSK-MG), B-cell depletion therapy has proven highly effective, and promising therapies like FcRn inhibitors and chimeric autoantibody receptor T cells are emerging. However, access to these treatments is limited in many parts of the world.

OBJECTIVE: This study aimed to evaluate the steroid-sparing effect of tacrolimus, a relatively affordable drug, in patients with MuSK-MG.

METHODS: This retrospective, single-center study included patients diagnosed with MuSK-MG who had been followed for over 6 months and had a history of tacrolimus use for more than 3 months. Baseline characteristics related to diagnosis and tacrolimus prescription were analyzed, and steroid dosages and MG-ADL scores were assessed before and after 2 years of initiating tacrolimus.

RESULTS: A total of 27 MuSK-MG patients who had been prescribed tacrolimus were analyzed. These patients were diagnosed with MG at a mean age of 41.0 ± 14.7 years, with four of them being male. At the initial visit, 46% were classified as MGFA class IIB, and 37% had experienced a myasthenic crisis. The median duration from MG diagnosis to the first administration of tacrolimus was 6.3 years (IQR, 2.9–10.3 years), with an initial dose of 2.8 ± 0.7 mg. The prednisolone dose was higher at the time of tacrolimus initiation (25 [15-30] mg/d) compared to 12 months prior (20 [15-20] mg/d) (P=0.029). Six months after starting tacrolimus, the dose (20 [10-25] mg/d) was lower than at initiation (P=0.010) and continued to decrease, with the dose 2 years later (8.75 [5-14.4] mg/d) being lower than at 6 months (P<0.001). The MG-ADL score decreased 6 months after tacrolimus initiation (5 [4-8] vs. 3 [1-5]; P=0.005).

SUMMARY/CONCLUSION: Tacrolimus may help reduce corticosteroid burden and improve functional status in patients with MuSK-MG.

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COMBINED USE OF ZILUCOPLAN AND RITUXIMAB FOR ACETYLCHOLINE RECEPTOR ANTIBODY POSITIVE (ACHR+) GENERALIZED MYASTHENIA GRAVIS

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INTRODUCTION: Zilucoplan, a macrocyclic peptide C5 inhibitor, was approved for AChR+ myasthenia gravis in October 2023. Rituximab is a chimeric anti-CD20 monoclonal antibody. There is no data on combined use of zilucoplan and rituximab for myasthenia gravis. We report a case of refractory generalized myasthenia gravis, previously partially responsive to monoclonal antibody complement inhibitors, in which zilucoplan and rituximab were used in combination to better manage myasthenia symptoms.

CASE REPORT: A 23-year-old woman with AChR+ myasthenia gravis since age 17 status post thymectomy was on eculizumab every 2 weeks with breakthrough symptoms within 5 days of her infusions. Her initial AChR antibody titer was 475nmol/L. She was trialed on efgartigimod for 2 cycles, but developed upper respiratory symptoms with myasthenia exacerbations that were responsive to plasma exchange. She received one cycle of rituximab 1g IV x 2. AChR titers dropped to 263.8 nmol/L. She remained symptomatic with MG-ADL > 6, restarted eculizumab, and started prednisone and mycophenolate mofetil. After 3 months, she transitioned to ravulizumab; approximately 6 weeks later, she had a myasthenia exacerbation that responded to plasma exchange. She resumed eculizumab, continued to have breakthrough symptoms, and 2 months later was started on zilucoplan. With zilucoplan, she had intermittent breakthrough weakness and still required prednisone and mycophenolate. Rituximab 1g IV x 2 every 6 months was added to her regimen, mycophenolate was stopped, and she had more stability in her myasthenia symptoms, less fluctuation, and improvement of MG-ADL to 3.

SUMMARY/CONCLUSION: Zilucoplan was developed as therapy for treatment refractory cases of AChR+ generalized myasthenia gravis. As prior use of rituximab was an exclusionary criterion in the RAISE trial, this case demonstrates combination therapy of a C5 peptide inhibitor and a CD20 monoclonal antibody as a possible treatment strategy to better manage the clinical symptoms of refractory myasthenia gravis.

REFERENCES: Howard JF Jr, et al; RAISE Study Team. Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Neurol. 2023 May;22(5):395-406. doi: 10.1016/S1474-4422(23)00080-7. PMID: 37059508.

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RESIDUAL SERUM FIBRINOGEN AS A UNIVERSAL BIOMARKER FOR ALL SEROTYPES OF MYASTHENIA GRAVIS

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INTRODUCTION: Myasthenia Gravis (MG) is an autoimmune disease associated with severe neuromuscular weakness. Diagnostic confirmation of MG is typically delayed and secured in about 85% and 50% of patients with generalized and ocular MG, respectively with serum antibodies.

OBJECTIVE: To identify a sensitive and specific diagnostic biomarker for various MG serotypes with quantitative proteomics.

METHODS: Serum proteomes of 18 individuals (MG patients, healthy controls (HC), Rheumatoid Arthritis (RA) were quantified in a pilot study and occurrence of high residual fibrinogen was validated by immunoblotting and further investigated by targeted mass spectrometry on the sera of 79 individuals (31 MG of various serotypes, 30 HC, 18 RA).

RESULTS: Initial proteomic analysis identified high residual fibrinogen in MG patient sera which was then validated by antibody-based testing. Subsequently, a blinded study of independent samples showed 100% differentiation of MG patients from controls. A final serological quantification of 14 surrogate peptides derived from a-, ß-, and ?-subunits of fibrinogen in 79 individuals revealed fibrinogen to be highly specific and 100% sensitive for MG (p?<?0.00001), with a remarkable average higher abundance of?>?1000-fold over control groups.

SUMMARY/CONCLUSION: Our discovery of high levels of residual serum fibrinogen in all MG patients has the potential to secure rapid bedside diagnosis of MG. Further large scale studies are ongoing to develop an ELISA kit for use in clinics and to further characterize the prognostic value of the biomarker.

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SERUM PROFILING REVEALS PROTEOMIC CHANGES ASSOCIATED WITH THE IMMUNE SYSTEM AND SIGNAL TRANSDUCTION IN MYASTHENIA GRAVIS

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INTRODUCTION: Identifying proteomic signatures associated with MG is essential for understanding immunological pathways underlying pathogenesis. Utilizing unsupervised omics approaches presents an opportunity to reveal biological distinctions between MG and non-autoimmune subjects to inform on disease mechanisms.

OBJECTIVE: This study aims to identify immunological alterations associated with myasthenia gravis (MG) using serum proteomics.

METHODS: Using liquid chromatography-mass spectrometry, we analyzed serum samples from 86 patients enrolled at the outset of the MGTX trial and 37 non-autoimmune controls (HC) to identify proteomic profiles that could inform on potential immunological mechanisms of disease. After preprocessing, which included data cleaning, log transformation, and Perseus imputation, we determined the differentially expressed proteins with the *limma* package. We then performed functional enrichment analysis on the differentially expressed proteins between MG and HC. This approach allowed us to discern biologically relevant signatures associated with MG

RESULTS: Four hundred and four differentially expressed proteins were identified between MG and HC subjects, of which 382 were upregulated and 22 downregulated. Gene set enrichment analysis identified upregulated proteins in MG were associated with cytoskeleton and actin remolding, the immune system, and signal transduction. In the top 10 differentially expressed proteins TAGLN2, ZYX, CNN2, and PDLIM1 are involved in cytoskeletal and actin remodeling and implicated in cell adhesion and migration. Upregulated immune system proteins in MG are associated with innate immunity (LY6GF, PSTPIP2), B cell receptor signaling (PTPN6, SYK, and SRC), and regulation of cytokine production (PCBP2). The most differentially expressed proteins involved in signal transduction included RAB7A, RAB8A, and MYLK which are associated with GTPase signaling important in regulating immune cell migration, activation, and apoptosis.

SUMMARY/CONCLUSION: Our findings confirm that several upregulated immunological pathways and altered signal transduction pathways underlie immune dysregulation driving MG pathogenesis. Further studies are needed to understand the pathophysiological significance of these pathways in MG.

DISCLOSURES: Author L.L. Kusner serves as a consultant for GRO Biotechnology, CSL Berhing, Amplo Biotechnology, Alexion and Sanofi. Dr. Kusner has equity interest in MimiVax, LLC. Author Dr. Henry Kaminski is a consultant for Roche, Takeda, Cabaletta Bio, UCB Pharmaceuticals, Canopy Immunotherapeutics, EMD Serono, Ono Pharmaceuticals, ECoR1,

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EVALUATING THE COMPARATIVE EFFECTIVENESS OF EMERGING IMMUNOMODULATORY THERAPIES FOR PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS

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INTRODUCTION: Several novel therapies have recently been approved in the United States for generalized myasthenia gravis (gMG), while inebilizumab and nipocalimab are either currently under FDA review or expected to undergo evaluation. Comparative evaluations of these treatments are necessary for guiding informed clinical decision-making.

OBJECTIVE: To assess the relative effectiveness of immunomodulatory treatments for gMG.

METHODS: A Bayesian NMA was conducted to compare the efficacy of neonatal Fc receptor inhibitors (efgartigimod intravenous [IV], rozanolixizumab) and complement inhibitors (ravulizumab, zilucoplan) versus placebo. Efficacy outcomes included changes from baseline, and ≥3- and ≥5-point reductions in MG-ADL and QMG scores. Number needed to treat (NNT) versus placebo were derived from NMA outputs. The analysis will be updated to include inebilizumab, and nipocalimab as new data becomes available.

RESULTS: The NMA results suggest efgartigimod IV was associated with the greatest improvement in changes from baseline in MG-ADL (not significantly better than other treatments) and QMG (significantly better than ravulizumab and zilucoplan). Efgartigimod IV also had the lowest NNT vs. placebo for achieving ≥5-point reduction in MG-ADL and ≥3-point reductions in QMG (significantly lower vs. ravulizumab and zilucoplan), and ≥5-point reduction in QMG (significantly lower than zilucoplan). Rozanolixizumab had the lowest NNT for ≥3-point reduction in MG-ADL (not statistically lower than other treatments). The poster will present updated results incorporating nipocalimab, and inebilizumab.

SUMMARY/CONCLUSION: Fc receptor inhibitors, particularly efgartigimod IV, show a more favorable benefit-risk profile compared to ravulizumab and zilucoplan. Further results, including data on nipocalimab, and inebilizumab, will be presented in the upcoming updates.

DISCLOSURES: Author A. Gordon Smith discloses he has received consulting fees from Abalone, Alexion, argenx, Disarm Therapeutics, Eidos, Lexicon, and Sangamo. Author Gil Wolfe discloses he has served as member of advisory boards or provided paid consultations to Alexion, argenx, Cartesian, Janssen, and UCB, is on speaker bureaus for Alexion and UCB, and has received research support from Alexion, argenx, Immunovant, Roche, UCB, and the MG Foundation of America. Author Ali A. Habib discloses he has received research support from

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HIGHER RISK OF FRACTURES IN MYASTHENIA GRAVIS PATIENTS IN COMPARISON WITH GENERAL POPULATION- HEALTHCARE DATABASE STUDY

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INTRODUCTION: NFZ is a mandatory health insurance in Poland. MG is the only indication for reimbursement of pyridostygmine bromide and ambenonium chloride.

OBJECTIVE: To determine incidence of fractures in myasthenia gravis as compared with the general population (GenP).

METHODS: MG patients were identified retrieving all reimbursed prescriptions for pyridostigmine and ambenonium dispensed between 1.01.2013-31.12.2023. A control group of the same size matched for age and gender distribution, was randomly assigned. All fractures diagnosed in 2023 by ICD-10 codes were analyzed by localization.

RESULTS: There were 10,300 MG patients in 2023; F (61%), mean age 62 years, median age 66 years. Patients with MG had 158,8% higher chance for osteoporotic fracture than GenP ($p<0.001$, $R2=0.104$). Independent risk factors for osteoporotic fractures were: age, female sex, MG, adrenal insufficiency, diabetes, cataract and using steroids > 180 days. MG patients had 32% higher chance for other than osteoporotic fracture ($p<0.01$, $R2 = 0.025$) with independent risk factors as follows: age, female sex, MG, adrenal insufficiency and cataract. MG patients had 127.9% higher chance for spine fractures than GenP ($p<0.001$, $R2=0.043$). MG patients did not have higher risk of pelvis, long bones, small bones and wrist fractures or other fractures including skull bones and chest bones (p=ns). MG patients treated with glucocorticosteroids (GCS) >180 days had 149.9% higher risk of having spine fractures than MG patients not treated with GCS ($p<0.001$, $R2=0.05$). MG, age and female gender were independent risk factors for these fractures. MG patients treated with GCS >180 days had in general 58.6% higher risk of having any nonosteoporotic fracture than MG patients not treated with GCS ($p<0.01$, $R2=0.017$). MG, age and female gender were found to be independent risk factors for these fractures.

SUMMARY/CONCLUSION: MG patients have higher risk of fractures in comparison with general population.

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MYASTHENIC CRISIS- 15-YEARS' SINGLE NEUROMUSCULAR CENTER EXPERIENCE

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INTRODUCTION: Myasthenic crisis (MC) is a life-threatening episode developing in 15-20% MG patients.

OBJECTIVE: To assess MC causes, treatment, complications and outcomes.

METHODS: Retrospective analysis of all MC patients between 2009-2024.

RESULTS: There were 89 MCs in 77 MG patients (F 48.3%); 14% had $\geq$2 MCs. Mean age at MC was 63.6$\pm$18.3 years, 73% had late onset MG. 70.1% had AChR-MG, 5.2% MuSK-MG, 6.5% had history of thymoma. Mean MG duration before MC was 50.7$\pm$72.3 months. In four (4.8%) MC was the initial MG presentation.

18 (20%) of cases had previous MC; they were younger at MG onset; had longer ICU stay ($p<0.05$) and MG duration ($p<0.01$).

Before MC, 60.7% of patients were treated with glucocorticosteroids, 25.8% with nonsteroidal immunosuppressants.

48.3% patients received IVIg, 34.8% PLEX, 11.2% both. Mean length of mechanical ventilation (MV) was 12.9$\pm$8.6 days. Mean length of ICU stay was 28.9+/-30.3 days, longer in threated with IVIG+PLEX (55.7+/-44.0) than with PLEX (18.6/-$\pm$6.9), $p<0.05$. Patients requiring multiple therapies were significantly younger at MC ($p<0.01$) and MG onset ($p<0.05$).

In 38.2% MC was preceded by infection, 13.5% therapy change. CRP and WBC were increased at admission in 50.6 and 41.6% respectively; 22.5% had anaemia, 22.5% bacteriuria. Bacteriuria at admission was independent risk factor for longer MV and ICU stay.

MC was complicated by pneumonia 33.7%, urinary infections 19.1%, myocardiac infarct (9%), pulmonary embolism (7.9%), critical care neuropathy (5.6%). In 3.4% PEG, 4.5% tracheostomy, 4.5% nasogastric tube were maintained after extubation.

Mortality was 4.5% (N=4), age at death 77.5$\pm$4.8 years. In all fatal cases inflammation parameters were significantly increased at admission (CRP>80 mg%, N 0-5) and MC was complicated with other diseases, most commonly myocardial infarct.

SUMMARY/CONCLUSION: MC in gMG patients is most often triggered by infection or therapy change, with 4.5% mortality in our cohort.

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OPTIMIZATION OF MESENCHYMAL STROMAL CELLS CONDITIONING IN PERSPECTIVE OF A TREATMENT FOR MYASTHENIA GRAVIS

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INTRODUCTION: Conventional treatments of MG by immunosuppressants cause severe side effects, therefore cell-based approaches represent innovative therapeutic tools. Adipose-derived Mesenchymal Stem Cells (MSC) are multipotent progenitors capable of modulating the activity of the immune system through soluble mediators, extracellular vesicles (EV), and direct cell-to-cell contact. Their effectiveness is increased by conditioning by co-culture with circulating mononuclear cells (PBMC) or by treatment with cytokines. Previously, molecular, phenotypic and functional characterizations of conditioned MSC (cMSC) provided activation signatures, and secretome analysis suggested a list of 30 candidate molecules responsible for conditioning.

OBJECTIVE: We identify a combination of molecules that could substitute to the co-culture with PBMC for conditioning. In parallel, we evaluate an acellular therapy using EVs secreted by cMSC. Then, we compare the efficacies of resting MSC, of MSC activated by the combination of active molecules, and of the EV they produce. Our final goal will be to translate these observations into our humanized animal model of MG.

METHODS: The most active molecules and combinations are identified through phenotypic changes (flow cytometry). EV produced by MSC are collected by ultracentrifugation and analysed by NTA. The efficacies of cells and EV are assessed in vitro, testing the inhibition of proliferation of PBMC from healthy and MG patients (CFSE assay), and the phenotypic modulation of mononuclear immune cells (flow cytometry).

RESULTS: Among the candidates, the pro-inflamatory cytokines TNFα, IFNγ, and IL-1β modified the expression of readout markers (CD26, CD54) in MSC cultures when used alone, or differentially when used in combinations. We optimize and downsize the culture conditions to set a medium-throughput screening based on readout markers modulations.

SUMMARY/CONCLUSION: Our work unveils treatment-dependent markers of MSC conditioning. Upon transfer to clinically usable procedures, cellular or acellular products may have therapeutic applications in the context of MG and other autoimmune diseases.

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A GENOME WIDE ASSOCIATION STUDY OF MYASTHENIA GRAVIS UNCOVERS NEW LOCI AND GIVES FIRST INSIGHTS INTO THE PERFORMANCE OF POLYGENIC PREDICTION

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INTRODUCTION: Myasthenia gravis (MG) is a rare autoantibody-mediated disease affecting the neuromuscular junction that is characterized by muscle weakness and fatigue. Understanding the underlying genetic basis can provide crucial insights into pathogenesis which may aid in identifying individuals at risk and facilitate drug development efforts.

OBJECTIVE: To identify common genetic variants associated with MG and to assess the utility of polygenic risk scores.

METHODS: We conducted discovery and replication case-control genome-wide association meta-analyses, association analyses of imputed human leukocyte antigen and complement component 4 alleles, a transcriptome-wide association study, polygenic risk scoring, and genetic correlation analyses.

RESULTS: The discovery meta-analysis included 5,708 MG patients with clinically diagnosed MG and 432,028 control subjects. The results were replicated and meta-analyzed with a sample of 3,989 self-reported MG cases and 226,643 controls provided by 23andMe, Inc.

We identified 12 genome-wide significant ($p<5e^{-8}$) index SNPs associated with MG. Subgroup analyses revealed two of these were associated with early-onset (at age <50) and four of the 12 with late-onset MG (at age ≥50). Imputation of human leukocyte antigen alleles identified inverse effect sizes for late- and early-onset, suggesting a potential modulatory influence on the time of disease manifestation. Complement component 4 copy number was associated with increased MG risk. Polygenic risk scores significantly predicted MG in an independent cohort, explaining 4.2% of the phenotypic variation. We identified five significant genetic correlations with MG, with the strongest observed for type 1 diabetes (r_g=0.523, p=1.42e^{-6}, SE=0.109) and rheumatoid arthritis (r_g=0.508, p=1.11e^{-6}, SE=0.104).

SUMMARY/CONCLUSION: The discovery and replication meta-analyses identified six novel associations and validated six known loci, advancing our understanding of the genetics of MG. Furthermore, polygenic risk scores for MG may offer a promising addition to diagnostic and prognostic procedures.

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EFFECT OF INTRAVENOUS AND SUBCUTANEOUS EFGARTIGIMOD ON MG-ADL AND QMG SUBDOMAINS IN THE ADAPT-SC STUDY IN PARTICIPANTS WITH GENERALIZED MYASTHENIA GRAVIS

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INTRODUCTION: Efgartigimod is a human immunoglobulin G1 (IgG1) antibody Fc-fragment that blocks the neonatal Fc receptor (FcRn). In the ADAPT-SC study, subcutaneous (SC) efgartigimod PH20 (coformulated with recombinant human hyaluronidase PH20) was shown to have noninferior total IgG reduction to intravenous (IV) efgartigimod in participants with gMG.

OBJECTIVE: To determine the impact of efgartigimod IV and efgartigimod PH20 SC on specified subdomains of MG-ADL and QMG in AChR-Ab+ participants of ADAPT-SC.

METHODS: In ADAPT-SC, clinical and functional outcomes were measured by MG-ADL and QMG, respectively. Post hoc analyses were conducted to examine these efficacy measures in four different subdomains: ocular, bulbar, limb/gross motor, and respiratory. Changes from baseline in each subdomain were calculated for each group over a 10-week period.

RESULTS: 91 AChR-Ab+ participants were treated with either efgartigimod IV or efgartigimod PH20 SC in the ADAPT-SC trial and both treatment arms showed improvements from baseline across MG-ADL subdomains. The mean (SE) score change from baseline to Week 4 in MG-ADL subdomains in participants receiving efgartigimod PH20 SC with baseline symptoms in MG-ADL subdomains were: ocular, -1.18 (0.18 [n=40]); bulbar, -2.36 (0.26 [n=39]); limb/gross motor, -1.51 (0.19 [n=41]); and respiratory, -0.69 (0.10 [n=39]). Similarly, improvements in participants receiving efgartigimod IV with baseline symptoms in MG-ADL subdomains were: ocular, -1.23 (0.17 [n=40]); bulbar, -1.86 (0.20 [n=43]); limb/gross motor, -1.19 (0.18 [n=42]); and respiratory, -0.56 (0.10 [n=41]). Similar improvements were seen in QMG subdomain scores in both treatment groups.

SUMMARY/CONCLUSION: Treatment with efgartigimod IV and efgartigimod PH20 SC demonstrated improvement across all MG-ADL and QMG subdomains in AChR-Ab+ participants of the ADAPT-SC study, reinforcing the efficacy of efgartigimod across a broad gMG population.

DISCLOSURES: Authors Sophie Steeland, Kristin Heerlein, Jeffrey Guptill, and Sihui Zhao are employees of argenx. Author Jan L. De Bleecker discloses he has served as a consultant for argenx, Alexion Pharmaceuticals, Inc., CSL, UCB Pharma, Alnylam Pharmaceuticals, Inc., Janssen, and Sanofi Genzyme. Author Yuebing Li discloses he has served as a consultant for argenx, Alexion, and Amgen.

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COMBINED ANALYSES OF PARTICIPANTS WITH ANTI-ACETYLCHOLINE RECEPTOR SERONEGATIVE GENERALIZED MYASTHENIA GRAVIS TREATED WITH EFGARTIGIMOD ACROSS CLINICAL STUDIES

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INTRODUCTION: Antibodies directed against AChR are absent in approximately 15% of patients with gMG. Lack of approved treatment options for the AChR-Ab- gMG population represents an unmet need in the gMG treatment landscape. Efgartigimod is an immunoglobulin G (IgG)1 antibody Fc-fragment that selectively reduces IgG levels by blocking neonatal Fc receptor (FcRn)-mediated IgG recycling. Data from previous clinical trials examining efgartigimod have demonstrated efficacy in participants with both AChR-Ab+ and AChR-Ab- gMG.

OBJECTIVE: To describe the efficacy of efgartigimod in AChR-Ab- participants with gMG receiving either efgartigimod IV or subcutaneous (SC) efgartigimod PH20 (coformulated with recombinant human hyaluronidase PH20) across clinical studies.

METHODS: Post hoc analyses were conducted to examine the efficacy and safety of efgartigimod IV and/or efgartigimod PH20 SC in AChR-Ab- participants in the ADAPT/ADAPT+ and ADAPT-SC/ADAPT-SC+ trials.

RESULTS: Among the pooled AChR-Ab- participants (n=56), the mean (SE) MG-ADL total score improvement from baseline to Week 3 of Cycle 1 was -3.7 (0.44 [n=55]). Consistent improvements in MG-ADL were observed with repeated cycles. Clinically meaningful improvements (CMI; decrease of ≥2 in MG-ADL total score) in MG-ADL at week 3 of Cycle 1 were seen in 76.4% (n=42/55) of AChR-Ab- participants. Achievement of minimal symptom expression (MSE; MG-ADL total score of 0 or 1) at any time during Cycle 1 was seen in 23.2% (n=13/56) of AChR-Ab- participants. Similar CMI and MSE results were observed across all cycles. The overall safety profile was similar between AChR-Ab+ and AChR-Ab- participants.

SUMMARY/CONCLUSION: Both efgartigimod IV and efgartigimod PH20 SC were well tolerated and led to clinically meaningful improvements in symptoms for participants with AChR-Ab- gMG. An additional clinical trial is currently recruiting that will assess efgartigimod in the AChR-Ab- gMG population (ADAPT SERON; NCT06298552).

DISCLOSURES: Authors Sophie Steeland, Ming Jiang, René Kerstens, and Kristin Heerlein are employees of argenx. Author Andreas Meisel discloses he has received speaker honoraria from Alexion Pharmaceuticals, Inc, argenx, Grifols, SA, and Hormosan Pharma GmbH; honoraria from Alexion Pharmaceuticals, Inc., UCB, Janssen, and Merck for consulting services; and financial research support (paid to his institution) from Octapharma, argenx, and Alexion Pharmaceuticals, Inc. He is a member of the medical advisory board of the German Myasthenia Gravis Society. Author Vera Bril discloses she has received research support from AZ-Alexion, Grifols, CSL, UCB, argenx, Takeda, Octapharma, Akcea, Momenta (J&J), Immunovant, Ionis, and Viela. Author James F. Howard Jr discloses he has received research support (paid to his institution) from Ad Scientiam, Alexion AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, Centers for Disease Control and Prevention, MGFA, Muscular Dystrophy Association, NIH, NMD Pharma, PCORI, and UCB Pharma; honoraria/consulting fees from AcademicCME, Alexion AstraZeneca Rare Disease, Amgen, argenx, Biohaven Ltd., Biologix Pharma, CheckRare CME, Curie.bio, F. Hoffmann-LaRoche Ltd, Medscape CME, Merck EMB Serono, Novartis Pharma, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics, UCB Pharma, and Zai Labs; nonfinancial support from Alexion AstraZeneca Rare Disease, argenx, Biohaven Ltd., Cartesian Therapeutics, Toleranzia AB, UCB Pharma, and Zai Labs. Author Tuan Vu discloses he has served as a speaker for Alexion, argenx, CSL Behring, and Allergan/Abbvie; performed consulting work for argenx, Alexion/Astra Zeneca, Dianthus, Remegen, ImmunAbs, and UCB; and participated in MG trials sponsored by Alexion/Astra Zeneca, argenx, UCB, Amgen, Immunovant, Regeneron, Johnson & Johnson, Remegen, Dianthus, and Cartesians Therapeutics. Author Renato Mantegazza discloses he has received consulting fees/honoraria or support for meeting participation from Alexion Pharmaceuticals, Inc., argenx, Ra Pharmaceuticals Inc., BioMarin, Catalyst Pharmaceuticals, Inc,, UCB, Teva, Merck, Roche, and Biogen, Inc. Author Kimiaki Utsugisawa discloses he has served as a paid consultant for argenx, UCB Pharma, Janssen Pharma, Viela Bio, Inc (now Horizon Therapeutics), Chugai Pharma, Merck, and Mitsubishi Tanabe Pharma Corporation, and has received speaker honoraria from argenx, Alexion Pharmaceuticals, Inc., UCB Pharma, and the Japan Blood Products Organization.

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STRUCTURE -FUNCTION ANALYSIS OF ARGX-119, A FIRST-IN-CLASS HUMANIZED AGONIST MONOCLONAL ANTIBODY SPECIFIC FOR MUSCLE-SPECIFIC KINASE

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INTRODUCTION: ARGX-119 is a novel, humanized, agonist monoclonal SIMPLE Antibody™ specific for muscle-specific kinase (MuSK) being developed for treatment of patients with neuromuscular diseases. ARGX-119 is the first monoclonal antibody (mAb) that binds with high affinity to the Frizzled-like (Fz-like) domain of human, non-human primate, rat, and mouse MuSK, without off-target binding, making it suitable for clinical development.

OBJECTIVE: To elucidate the crystal structure of the ARGX-119 Fab fragment in complex with the human MuSK Fz-like domain.

METHODS: N/A

RESULTS: Both the heavy and light chain collectively contribute to the binding of the Fz-like domain. In-depth analysis revealed that the light chain of ARGX-119 engages with the MuSK Fz-like domain via a remarkably dense network of electrostatic interactions. However, aside from the energetic term, the geometry of that network also provides critical support, allowing the light chain to dive into a hydrophobic groove of the MuSK Fz-like domain, and to secure the anchoring at the bottom via a hydrogen bond. The importance of this electrostatic network is arguably best demonstrated by the observation that a single substitution, detected in the CD-1 mouse strain, influences the binding of ARGX-119 to MuSK.

SUMMARY/CONCLUSION: These results not only led to a better understanding of the mode of action of ARGX-119, but also highlighted the relevance of sequencing the target protein in the selected species during pre-clinical toxicology and efficacy evaluation.

DISCLOSURES: Author Maartje G. Huijbers is an employee at Leiden University Medical Center. She is an inventor on MuSK-related patents, and both she and Leiden University Medical Center receive royalties from these patents. Leiden University Medical Center receives royalties over a MuSK ELISA. She is a consultant for argenx. Author Steven J. Burden is an employee at MGH/Harvard University and holds the following patents: US9329182, US20150125442A1, and US11492401. The remaining authors are all employees at argenx.

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SAFETY AND EFFECTIVENESS OF EFGARTIGIMOD IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS IN JAPAN: INTERIM ANALYSIS OF POST-MARKETING SURVEILLANCE DATA

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OBJECTIVE: Efgartigimod for intravenous infusion (IV), a neonatal Fc-receptor inhibitor, is approved in Japan for generalized myasthenia gravis (gMG), regardless of autoantibody profiles. Post-marketing surveillance (PMS) was mandated by regulatory authorities to assess the safety and effectiveness of efgartigimod in real-world settings.
METHODS: Patients with gMG who were administered efgartigimod for IV at least once from May 2022 to September 2023 were registered in PMS. The interim analysis data were cutoff in June 2024 and included patients whose institutes agreed to publish their data.

RESULTS: The safety analysis set consisted of 373 patients; 53.35% (n=199) for anti-AChR antibody positive (AChRMG), 14.21% (n=53) for anti-MuSK antibody positive (MuSKMG), and 31.64% (n=118) for double-seronegative (SNMG). Median number of cycle/patient (range) was 3.0 (1-17). Adverse drug reaction (ADR) and serious ADR were reported in 80 (21.45%) and 16 (4.29%) patients, respectively. Although 6 deaths were reported, none of them were related to efgartigimod. Of 373 patients, 246 patients with MG-Activities of Daily Living (MG-ADL) score records were subjected to the efficacy analysis; 54.88% (n=135) for AChRMG, 13.01% (n=32) for MuSKMG, and 30.89% (n=76) for SNMG. In the 1st cycle of efgartigimod treatment, mean (standard deviation) score of MG-ADL was decreased from 7.5 to 4.5 (-3.0 [2.84], $p< 0.001$). Subgroup analysis of autoantibody profiles demonstrated significant decreases of mean (SD) MG-ADL score; 7.0 to 4.2 (-3.0 [2.97], $p< 0.001$) for AChRMG, 7.2 to 2.8 (-4.1 [3.24], $p< 0.001$) for MuSKMG, and 8.4 to 5.6 (-2.8 [2.45], $p< 0.001$) for SNMG. Significant decreases of MG-ADL score were also observed in a broad patient population regarding MGFA classification, disease duration of gMG, past treatment for gMG, and IgG concentration before efgartigimod administration.

CONCLUSION: In the Japanese real-world settings, efgartigimod was well tolerated and effective for broad patient populations, e.g., patients across autoantibody profiles.

DISCLOSURES**:**All authors are employees of argenx Japan K.K.

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AN ANTIGEN-SPECIFIC CHIMERIC AUTOANTIBODY RECEPTOR T CELL STRATEGY FOR THE ELIMINATION OF ANTI-MAIN IMMUNOGENIC REGION ANTIBODY-SECRETING B CELLS

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INTRODUCTION: Myasthenia gravis (MG) results from the immune system's aberrant production of auto-antibodies (autoAbs) directed to the acetylcholine receptors (AChRs) located at neuromuscular junctions. 50–70% of the anti-AChR autoAbs in MG sera and in the sera of its animal model, *experimental autoimmune myasthenia gravis*, are directed to an immunological hot spot on the AChR called the main immunogenic region (MIR). These anti-MIR Abs represent most of the pathogenic components in MG sera. Removing the B cells producing these anti-MIR Abs, offers a targeted antigen-specific approach to treating MG. Our objective is to develop MIR chimeric auto-antibody receptor (CAAR)-expressing T cells (MIR CAAR T cells) to specifically target the B cells that secrete the anti-AChR autoAbs, with little or no effect on the rest of the normal functioning of the immune system.

OBJECTIVE: To develop a CAAR T cell therapy for MG that removes the MIR producing B-cells.

METHODS: Autologous rat T cells are being engineered to express a CAAR consisting of our engineered MIR peptide, which mimics the MIR domain, fused to CD137-CD3ζ T cell receptor signaling domains (MIR CAAR). The MIR CAAR directs the CAAR T cells to bind to and kill anti-MIR Ab-producing B cells by targeting their surface B cell receptors, which resemble the combining sites of the pathogenic anti-MIR Abs they secrete.

RESULTS: As an initial therapeutic for EAMG treatment, we attached the MIR peptide to the N-termini of an Fcγ1. EAMG rats were treated with daily IP injections, 2mg/kg, of the soluble MIR-Fc biologic (n=5), or vehicle only control (n=5). The anti-AChR titers and anti-MIR titers in the control-treated group continued to increase while titers in the treated group leveled off and remained low. To assess the MIR CAAR expression, HEK 293 cells were transiently transfected with the lentiviral plasmid expressing MIR CAAR. Anti-AChR sera stained these HEK 293 cells (37.5%), while normal rat sera did not (1.05%).

SUMMARY/CONCLUSION: The observation that the titer of anti-MIR Abs correlates with disease severity, while the total anti-AChR titer does not, supports the pathogenic role for this subset of Abs. We are developing a CAAR T cell therapeutic capable of killing B cells producing anti-MIR autoAbs which has the potential to durably treat MG.

DISCLOSURES: Author Vu B. Trinh discloses he has equity in Sierra Biopharma, Inc.

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JUVENILE MYASTHENIA GRAVIS IN A FRENCH COHORT: FOCUS ON THYMIC HISTOLOGY

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ABSTRACT: Myasthenia gravis (MG) is an autoimmune disease characterized by muscle fatigability due to autoantibodies against the acetylcholine receptor (AChR). In this form of the disease, the neuromuscular junction is the target of the anti-AChR attack, while the thymus acts as an effector organ. The thymus in MG is characterized by B-cell infiltration and the presence of ectopic germinal centers. To better characterize juvenile MG (JMG), we analyzed 85 pre- and 132 post-pubescent JMG (with a cutoff age of 13) compared to 721 adult MG patients under 40 years old using a French database. Clinical data, anti-AChR antibody titers, thymectomy, and thymic histology were analyzed.

The proportion of females was higher in each subgroup. No significant difference in the anti-AChR titers was observed. Interestingly, the proportion of $AChR^+$ MG patients was notably lower among adult MG patients aged between 30 and 40 years, at 69.7%, compared to over 82.4% in the other subgroups.

Thymic histological data were examined in patients who underwent thymectomy during the year of MG onset. Notably, in pre-JMG, the percentage of thymectomized patients was significantly lower (32.9% compared to more than 42.5% in other subgroups), and the delay to thymectomy was twice as long. We found a positive correlation between anti-AChR antibodies and germinal center grade across patient categories. Additionally, only females, particularly post-JMG patients, exhibited the highest rates of lymphofollicular hyperplasia (95% of cases) and germinal center grade.

This study reveals differences between patients depending on the age of onset of MG. Puberty seems to be the age from which follicular hyperplasia is mainly found in women, highlighting the potential impact of sex hormones in the triggering of autoimmune diseases.

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DIFFERENCES BETWEEN FEMALES AND MALES IN THE DIAGNOSTIC DELAY AND CLINICAL COURSE OF THYMECTOMIZED MYASTHENIA GRAVIS

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INTRODUCTION: Myasthenia gravis (MG) is an autoimmune disease presenting typically at an earlier age in females compared to males. However, whether sex affects diagnostic delay and clinical course of MG has not been extensively explored in systematic cohorts.

OBJECTIVE: We studied the effect of sex on diagnostic delay and clinical course of MG in thymectomized patients.

METHODS: We conducted a retrospective single-center cohort study on 251 thymectomized MG patients, including 124 males and 127 females. Mean follow-up was 10.7 (± 9.1) years post-thymectomy. We analyzed factors associated with longer diagnostic delay and type of first-onset symptoms (ocular vs generalized). For 195 patients with nonthymomatous generalized MG (gMG) pre-thymectomy, we estimated the effect of diagnostic delay, symptoms at onset and sex on reaching complete stable remission (CSR) or minimal need for medication (MNM) during postoperative follow-up. We also assessed their effect on overall need for in-hospital treatments, immunosuppressant use and pyridostigmine dose at the last follow-up visit.

RESULTS: Generalized symptoms at onset were more frequent for females than males (n = 90, 70.9% vs n = 65, 52.4%, respectively; $p<0.001$). Diagnostic delay was significantly longer in females (6.0 months [0-117.5] vs 3.2 months in males [0.1 - 84.0]; $p= 0.012$). First-onset symptoms and diagnostic delay did not affect post-thymectomy prognosis of gMG. However, females achieved CSR (17.1% vs. 4.5%; $p=0.006$) and MNM (30.8% vs. 16.9%; $p=0.029$) more frequently and required fewer in-hospital treatments (40.6% vs. 55.2%; $p=0.010$) and immunosuppressants (29.2% vs. 61.7%; $p<0.001$) than males.

SUMMARY/CONCLUSION: We report sex-related differences in symptoms at MG onset, length of diagnostic delay and prognosis, the origins of which should be further studied.

DISCLOSURES: Author Chris Myllynen discloses he has received a grant from Maire Taponen Foundation. Author Anni Tuulasvaara discloses she has received expenses related to scientific congresses from Merck and UCB Pharma. Author Sari Atula has received a lecture fee from UCB Pharma. Author Sini Laakso has received lecture fees from Alexion, Argenx, Biogen, Lundbeck, Merck, Novartis, UCB Pharma, and Teva. She has received expenses related to scientific congresses from Merck, Novartis, Roche, and UCB Pharma. She has been or is a scientific advisor for Alexion, Argenx, and Janssen.

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EFFICIENCY OF THE FIXED- AND LIVE-CELL-BASED ASSAYS TO DETECT ACHR ANTIBODIES IN MG SERA WITH LOW ANTIBODY CONCENTRATIONS AS DETERMINED BY RADIOIMMUNOPRECIPITATION ASSAY

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INTRODUCTION: Cell-based assay (CBA) and radioimmunoprecipitation assay (RIPA) are reliable and sensitive assays for the detection of AChR antibodies in MG. Yet comparison between AChR-CBA and -RIPA in MG sera with low RIPA AChR-antibody values has not yet been sufficiently studied.

OBJECTIVE: We investigated whether AChR fixed- and live-CBAs (F-CBA and L-CBA), are efficient for the detection of AChR-antibodies in sera from MG patients with low antibody concentrations as determined by RIPA.

METHODS: In this retrospective diagnostic cohort study, MG patients who were evaluated at three Greek University clinics, were initially assessed by RIPA. We included 36 available MG sera with low-to-medium RIPA-positive titers (1.0-2.8 nM) and 150 randomly chosen sera with $\geq$3 nM anti-AChR titers. Sera were subsequently tested by a commercial F-CBA and an in-house L-CBA for the detection of clustered-AChR antibodies.

RESULTS: The sensitivity of L-CBA and F-CBA in detecting 36 sera with low AChR-antibody levels (1.0-2.8 nM) was relatively high for L-CBA (83.3%), and low for F-CBA (45.7%). Both CBAs were 100% sensitive for sera with $\geq$3 nM AChR-RIPA values. Antibodies of RIPA+/CBA- sera could be immunoadsorbed on AChR-transfected cells, proving that CBA negativity was simply due to low antibody concentrations. In addition, dilutions of CBA-positive, high RIPA-titer sera, to ~1nM titers, resulted in mostly negative CBA results. However, both CBAs could detect AChR-antibodies in some RIPA-negative MG sera: 8 RIPA-negative/L-CBA-positive sera were identified, 5 of which were also F-CBA-positive.

SUMMARY/CONCLUSION: Collectively, AChR F-CBA was not efficient for the detection of low RIPA AChR-antibody concentrations. L-CBA was much more sensitive than F-CBA. Given that the cluster-AChR CBAs also detect some antibodies undetectable by RIPA, we suggest that ideally both RIPA and CBA (preferably L-CBA) should be used in MG diagnosis.

DISCLOSURES: S. Tzartos has shares in the research and diagnostic laboratory Tzartos NeuroDiagnostics.

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FREQUENCY AND SEVERITY OF MYASTHENIA GRAVIS EXACERBATIONS ASSOCIATED WITH THE USE OF CIPROFLOXACIN, LEVOFLOXACIN AND AZITHROMYCIN

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INTRODUCTION: Fluoroquinolones and macrolides are the two major classes of antibiotics that have been traditionally linked to MG exacerbation based on retrospective analyses or case series with conflicting observations. The true incidence of fluoroquinolone or macrolide-induced MG exacerbation and its severity currently remain unknown.

OBJECTIVE: We aimed to investigate the association between ciprofloxacin, levofloxacin and azithromycin, and MG exacerbation.

METHODS: A retrospective review was performed on MG patients seen at a single institution between 2002-2022 who received ciprofloxacin, levofloxacin or azithromycin. Amoxicillin was chosen as a reference antibiotic for comparison. The strength of association between antibiotic usage and MG exacerbation was scored using the Adverse Drug Reactions Probability Scale. Mixed-effects logistic regression model was constructed to evaluate the predictors of antibiotic-associated MG exacerbation (AAMGE).

RESULTS: Three hundred sixty-five patients had a total of 918 episodes of antibiotic usage (n=339 for ciprofloxacin, n=187 for levofloxacin, n=392 for azithromycin). Frequencies of MG exacerbation following antibiotic use were as follows: 8 (2.4%) episodes for ciprofloxacin, 3 (1.6%) for levofloxacin, 6 (1.5%) for azithromycin, and 17 (1.9%) for all. Six patients had impending crisis or crisis, and 9 required rescue therapy. MG exacerbation was associated with a history of MG-related hospitalization or emergency department visit in the preceding 6 months (p=0.012), female sex (p=0.023) and diabetes (p=0.032). Infection was the most common confounder in exacerbations (88.2%). A similar rate of MG exacerbation was seen in 8 of 603 (1.3%) episodes of amoxicillin use.

SUMMARY/CONCLUSION: Usage of ciprofloxacin, levofloxacin or azithromycin was associated with MG exacerbation in a minority of patients. Underlying infection may play a significant role in AAMGE.

DISCLOSURES: Yuebing Li, MD, PhD served as a consultant for Advisory Board Meeting by Alexion, Amgen, Argenx, Catalyst, Immunovant, and UCB Pharma. He received grant support from Argenx.

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Levofloxacin and Azithromycin [Conference presentation abstract]. 2024 annual meeting of the American Academy of Neurology in Denver, CO, United States. https://www.aan.com/events/2024-annual-meeting

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FIRST-IN-HUMAN DOSE SELECTION AND PHARMACOKINETICS, SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF ARGX-119, AN AGONIST ANTIBODY FOR HUMAN MUSCLE-SPECIFIC KINASE |CONFERENCE POSTER TONKE

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INTRODUCTION: ARGX-119 is the first agonist antibody for human MuSK. Upon activation of MuSK, ARGX-119 may stabilize the NMJ in patients with neuromuscular diseases such as congenital myasthenic syndrome (CMS) and amyotrophic lateral sclerosis (ALS). Nonclinical, proof-of-concept (PoC) studies of ARGX-119 showed restoration of NMJ signaling in mouse models of Docking Protein 7 (DOK7)-CMS and MuSK-myasthenia gravis. Results from nonclinical, repeated dose toxicity studies supported initiation of this first-in-human (FIH) study with ARGX-119.

OBJECTIVE: To present the approach for selection of FIH doses and the results of a phase 1, FIH, double-blinded, placebo-controlled study (NCT05670704) of single ascending doses (SAD) and multiple ascending doses (MAD) of ARGX-119 in healthy participants.

METHODS: Dose selection was based on the determination of the (minimally) active dose in nonclinical PoC studies and human pharmacokinetic (PK) predictions based on a non-human primate PK model. This FIH study evaluated the safety, tolerability, PK, and immunogenicity of ARGX-119 versus placebo, administered as intravenous SAD (9 cohorts), subcutaneous SAD, and intravenous MAD (4 once-weekly intravenous doses in 4 cohorts) in healthy participants.

RESULTS: Preliminary results from the FIH study suggest that ARGX-119 has a favorable safety profile in healthy participants at the doses investigated. There were no changes in the original design of single and multiple doses as decided by the Data Review Team evaluating accumulating PK and safety data. PK data in humans showed nonlinear elimination, suggesting target-mediated elimination as the relevant elimination pathway at low ARGX-119 concentrations, as observed in nonclinical studies.

SUMMARY/CONCLUSION: ARGX-119 was well tolerated and has a favorable safety profile in healthy participants at the doses investigated in single- and multiple-dose cohorts in this FIH study. ARGX-119 is currently being evaluated in a phase 1b study in adult participants with DOK7-CMS (NCT06436742) and a phase 2a study in adult participants with ALS (NCT06441682).

DISCLOSURES: Author Tonke van Bragt is an employee at Curare Consulting and a consultant at argenx. Rachelle Mutch is an employee and consultant at argenx and PPD Clinical Research Services of Thermo Fisher Scientific. The remaining authors are all employees at argenx.

THIS IS AN ENCORE PRESENTATION OF: van Bragt, T. et.al. (2025, April 5-9). *First-in-Human Dose Selection and Pharmacokinetics, Safety, Tolerability, and Immunogenicity of ARGX-119, an Agonist Antibody for Human Muscle-Specific Kinase* [Conference poster abstract]. 2025 annual meeting of the American Academy of Neurology in San Diego, CA, United States.

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MUSK ANTIBODIES DIFFERENTLY AFFECT THE MUSK SIGNALING CASCADE DEPENDING ON VALENCY AND EPITOPE

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INTRODUCTION: Muscle-specific kinase (MuSK) is a pivotal player in forming and maintaining healthy neuromuscular junctions (NMJ). In myasthenia gravis (MG), autoantibodies targeting MuSK disrupt its function, leading to impaired neuromuscular transmission. Notably, these MuSK autoantibodies predominantly belong to the IgG4 subclass, which bind in a monovalent fashion to MuSK due to Fab-arm exchange. Monovalent and bivalent MuSK antibodies have opposite effects on MuSK activation. However, the interplay between antibody valency and other antibody attributes and their impact on MuSK's interactions with partner molecules and downstream intracellular pathways remains largely unknown.

OBJECTIVE: To further unravel the pathogenic mechanisms underlying MuSK MG, we have investigated how MuSK antibody binding affects MuSK functioning.

METHODS: Binding kinetics of a diverse panel of human (patient-derived) monoclonal MuSK antibodies was assessed using surface plasmon resonance. C2C12 myotubes were treated with these MuSK antibodies. MuSK phosphorylation, Dok7-MuSK interaction, cellular Dok7 levels and surface MuSK were assessed using western blotting on (co-)IP, whole cell lysate or biotinylated IP samples respectively. In addition, gene expression of NMJ genes was measured with qPCR in masseter muscle from mice exposed to monoclonal MuSK antibodies.

RESULTS: Our findings reveal that the valency of antibody-binding influences binding kinetics to MuSK, inhibition of agrin-induced MuSK activation, Dok7 binding to MuSK and NMJ gene expression. Monovalent binding to the frizzled domain of MuSK did not inhibit agrin-induced MuSK activation, while monovalent binding to the Ig-like 1 domain does. Moreover, the kinetics of Dok7 degradation induced by bivalent MuSK antibodies appear to depend on epitope binding between and within structural domains of MuSK. Surprisingly, none of the clones tested (both bivalent and monovalent) increased MuSK internalization.

SUMMARY/CONCLUSION: The cumulative pathogenic effect of polyclonal MuSK antibodies in individual MuSK MG patients thus likely depends on autoantibody titer, affinity and the distinct composition of MuSK autoantibodies varying in epitope-binding and valency. This research enriches our understanding of the intricate interactions between antibodies and MuSK in MuSK MG, and offers potential insights into novel therapeutic strategies using MuSK antibodies.

DISCLOSURES: Maartje Huijbers receives royalties for MuSK related patents and is a consultant for argenx. Jan Verschuuren receives royalties for MuSK related patents and is a consultant for argenx, Alexion and NMD pharma. Silvère van der Maarel receives royalties for MuSK related patents.

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FAMILIAL AUTOIMMUNITY IN MYASTHENIA GRAVIS

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INTRODUCTION: Clinical observations indicate an increased frequency of autoimmune diseases in families of patients with autoimmune disorders. Some studies suggest a preponderance of maternal inheritance of autoimmune disorders in families of patients with autoimmune myasthenia gravis (MG).

OBJECTIVE: To investigate the frequency and nature of autoimmune diseases (AIDs) in parents of patients with acetylcholine receptor (AChR) MG, muscle specific kinase (MuSK) MG, and Lambert-Eaton myasthenic syndrome (LEMS).

METHODS: AIDs were assessed by reviewing the family history in two independent cohorts: one based on physician-reported prevalence of autoimmunity in patients seen at the LUMC (n=298, Cohort 1), and one based on patient-reported frequencies derived from the Dutch-Belgian registry (n=277, Cohort 2). Risk ratios were calculated to determine whether the risk of AIDs among parents in the overall myasthenia group and its subgroups (defined by tumour status and age of onset) was higher than would be expected in the general population (women 6.4% and men 2.7%).

RESULTS: In total, 298 patients in Cohort 1 and 277 patients in Cohort 2 were included. In Cohort 1 23% of the AChR MG patients had at least one parent with a positive history for an AID. In the overall myasthenia gravis group and in its subgroups, the relative risk of having a parent with an AID was higher compared to the general population (All MG patients 2.69 (2.1-3.3), early onset 3.06 (2.3-4), late onset 2.25 (1.5-3.2), thymoma 2.05 (0.9-3.9), no thymoma 2.64 (2.0-3.4)).

SUMMARY/CONCLUSION: In our study population, AIDs were approximately three times more frequently found in parents of MG patients. Contrary to our expectations, the higher relative risk persisted across all subgroups, including those with tumour-associated MG and later age of onset. This might be helpful to identify additional genetic factors that contribute to the susceptibility for autoimmune MG.

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BUILDING AN INDUCED PLURIPOTENT STEM CELL-BASED THREE-DIMENSIONAL NEUROMUSCULAR JUNCTION ON A CHIP: A NOVEL MODEL TO STUDY NEUROMUSCULAR DISEASE

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ABSTRACT: Myasthenia Gravis (MG), like many other neuromuscular disorders, is hallmarked by neuromuscular junction (NMJ) defects. Impairment of neuromuscular transmission may lead to muscle weakness, paralysis, or even death. To better understand these defects and test therapeutic strategies that improve NMJ function, the NMJ has been widely studied in a variety of models. However, many existing models have limitations: 2D *in vitro* models lack structural context and do not allow for the study of muscle contraction and function, while animal models often fail to accurately represent human genetic backgrounds and exhibit different pathophysiological characteristics when modelling neuromuscular diseases. We hypothesize that a human induced pluripotent stem cell (hiPSC)-derived 3D NMJ on a chip model can bridge this gap and can propel *in vitro* NMJ and neuromuscular disease research to the next level. To this end, we have developed an innovative chip design that supports the co-culture of hiPSC-derived motor neurons and hiPSC-derived 3D muscle bundles. We have established the culture conditions and chip design that optimize the functional (i.e., contraction), structural (i.e., morphology), and developmental outcomes (i.e., gene and protein expression) of the 3D NMJ model. The conditions that significantly improved the longevity, strength and maturity of the model were: number of motor neurons, timing, and combination of neurological growth factors and chip design. At the conference we will present the model as is optimized thus far with the ultimate ambition to use it for modelling of MG, other neuromuscular disorders, and drug screening.

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VALIDATION OF THE "PATIENT-ACCEPTABLE SYMPTOM STATE" QUESTION AS OUTCOME MEASURE IN ACHR MG: A MULTICENTER, PROSPECTIVE STUDY

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INTRODUCTION**:** Patient reported outcome (PRO) measures incorporate patient perspective of disease burden and treatment efficacy in myasthenia Gravis. In this study we aimed to validate the "patient acceptable symptom state" (PASS) question and identifying its main determinants.

METHODS: adult acetylcholine receptor antibody-positive MG patients were assessed with MG-ADL, MG-QOL15r and QMG scores. Favorable outcomes were defined by PASS=YES and PIS of minimal manifestation (MM)-or-better. ROC curve analysis was used to determine cut-off values of MG scales in relation to PASS and PIS and were subsequently validated. Univariate and multivariate were used to identify factors associated with PASS.

RESULTS: QMG≤8, ADL≤2 and QOL15r≤6 were found as thresholds to identify patients with PASS=YES. In the multivariable logistic regression MG-ADL and QOL15r were independently associated with PASS. PIS and PASS status showed substantial agreement but were discordant in 15% of cases. Ocular items subgroup of MG ADL, QMG, and question 2 (related to ocular symptoms) of MG-QOL15r were independently associated with favourable PASS.

CONCLUSIONS: in this study we independently validated the PASS question as PRO measure, which enables the incorporation of the patient perspective in the MG outcome evaluation. This assessment should be included in clinical practice and in randomized clinical trials, as it can contribute to improove MG patients care.

DISCLOSURES: Alesandro Barilaro has received public speaking honoraria from Alnilam. He declares no competing interest regarding this manuscript. The institution of Luca Massacesi has received personal compensation in the range of $10,000-$49,999 for serving as a Consultant for Biogen. Luca Massacesi has received personal compensation in the range of $500-$4,999 for serving on a Speakers Bureau for Biogen. Luca Massacesi has received personal compensation in the range of $500-$4,999 for serving on a Speakers Bureau for Novartis. Luca Massacesi has received personal compensation in the range of $500-$4,999 for serving on a Speakers Bureau for Roche. Luca Massacesi has received personal compensation in the range of $500-$4,999 for serving on a Speakers Bureau for Merck-Serono. Luca Massacesi has received personal compensation in the range of $500-$4,999 for serving on a Speakers Bureau for Johnson and Johnson. Luca Massacesi has received personal compensation in the range of $500-$4,999 for serving on a Speakers Bureau for Alexion. Luca Massacesi has received personal compensation in the range of $500-$4,999 for serving on a Speakers Bureau for Horizon. The institution of Luca Massacesi has received research support from Tuscan Region Government. The institution of Luca Massacesi has received research support from Sanofi. The institution of Luca Massacesi

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ANALYSIS OF THE DIAGNOSTIC PROCESS IN A SPECIALIZED MYASTHENIA GRAVIS CLINIC OVER 9 YEARS.

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INTRODUCTION: Myasthenia gravis (MG) is a autoimmune disease mediated by antibodies against proteins of the neuromuscular junction. Diagnosis can be challenging due to the heterogeneous and fluctuating clinical picture.

METHODS: A retrospective, single-center, observational study was designed. Patients referred with a diagnostic suspicion of MG between 2015 and 2023 were included, collecting clinical and analytical variables, as well as alternative diagnoses.

RESULTS: Out of 561 patients referred with suspected MG, 359 were diagnosed with MG (294 seropositive and 65 seronegative). In 167 cases, MG diagnosis was ruled out, with an alternative diagnosis reached in 89 cases (53.9%), showing great variability among the mimics. The diagnostic delay was significantly longer in the mimic group (2.9 ± 5.1 years vs. 0.6 ± 2.1 in seropositive and 1.31 ± 3.6 in seronegative patients). Phenotypic differences were found between the groups, with ocular symptoms and isolated fatigue being more common among the mimics ($p < 0.001$).

During the diagnostic process, clinical evaluation and examination were the fundamental tools, such that in 30% of seronegative patients no further studies were needed to rule out MG. In 22 seropositive MG cases, the previous antibody result was falsely negative. Notably, single-fiber electromyography showed low specificity, with 19% of mimics showing abnormalities in this study. 40% of patients with mimics received immunosuppressive treatment during the diagnostic process.

SUMMARY/CONCLUSION: Up to 26% of patients with an initial diagnosis of MG actually have another condition, with great variability among alternative diagnoses. Diagnostic delay in these patients can reach up to three years.

DISCLOSURES: A. Vesperinas has received public speaking honoraria and compensation for advisory boards and/or consultation fees from Argenx and Alexion. E. Cortés-Vicente has received public speaking honoraria and compensation for advisory boards and/or consultation fees from UCB, Argenx, Alexion, Janssen and Lundbeck. J. Rocaspana-Codana, D. Reyes-Leiva, M. Caballero-Ávila, A. Carbayo, R. Collet-Vidiella, L. Llansó, E. Gallardo, J. Turon-Sans and R. Rojas-García report no disclosures.

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DEVELOPMENT OF A MOBILE APPLICATION FOR MONITORING PATIENTS WITH MYASTHENIA GRAVIS: RESULTS FROM THE FIRST SIX MONTHS

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INTRODUCTION: Myasthenia gravis (MG) is an autoimmune disease mediated by antibodies against the neuromuscular junction, causing muscle weakness that worsens with exercise. Symptoms are fluctuating and may present with exacerbations, making the follow-up and monitoring process a challenge.

METHODS: The development of digital technologies can be a useful tool for monitoring these patients. A smartphone application has been developed to allow patients to self-complete the MG-ADL scale weekly and share the information with their treating neurology. In parallel, monthly home visits were conducted by specialized healthcare personnel, who completed the MG-ADL, QMG, and MGC scales. A correlation and concordance study was performed.

RESULTS: A total of 30 MG patients were included (18 men (56.3%); 59 ± 15 years) after experiencing an exacerbation (n = 11 (36.6%)) or being at risk due to medication reduction (n = 19 (63.3%)). Seven rescue treatments were administered, with improvement noted. During six months of follow-up, 11 patients showed worsening, 5 requiring a therapeutic change. The MG-ADL reported by patients showed excellent correlation with the MG-ADL reported by healthcare professionals ($r = 0.92$; p-value < 0.001) and strong correlation with the QMG and MGC scales ($r = 0.65$ and 0.72, respectively; p-value < 0.001). The inter-observer concordance between the self-reported MG-ADL and that reported by healthcare professionals was excellent (ICC = 0.96, p-value < 0.001).

CONCLUSION: The use of self-completed clinical scales through smartphone applications can be useful for monitoring MG patients. The self-completed MG-ADL scale shows good correlation and concordance with those reported by healthcare professionals.

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RESPONDER AND MINIMAL SYMPTOM EXPRESSION RATES WITH ROZANOLIXIZUMAB IN GENERALISED MYASTHENIA GRAVIS: FINAL POOLED ANALYSIS OF PHASE 3 STUDIES

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INTRODUCTION: Subcutaneous rozanolixizumab treatment administered once weekly over 6 weeks significantly improved MG-specific outcomes versus placebo in the Phase 3 MycarinG study (MG0003/NCT03971422). Following MycarinG, patients could enrol in open-label extension studies (MG0004 then MG0007, or MG0007 directly).

OBJECTIVE: To assess the efficacy and safety of repeated rozanolixizumab treatment cycles in patients with generalised MG.

METHODS: In MG0004 (NCT04124965), patients received once-weekly rozanolixizumab 7mg/kg or 10mg/kg for ≤52 weeks. In MG0007 (NCT04650854), patients received an initial 6-week cycle (rozanolixizumab 7mg/kg or 10mg/kg), with subsequent cycles administered upon symptom worsening at the investigator's discretion. Final data were pooled across MycarinG, MG0004 (first 6 weeks) and MG0007 for patients with ≥2 symptom-driven cycles for efficacy

outcomes (up to 13 cycles) or ≥1 treatment cycle for safety. The proportion of patients achieving MG-ADL and QMG response (≥2.0-point and ≥3.0-point improvement from baseline, respectively) at Day 43 in each cycle and the achievement of minimal symptom expression (MSE; MG-ADL score of 0 or 1) were assessed.

RESULTS: Overall, 129 patients received ≥2 symptom-driven cycles of rozanolixizumab 7mg/kg (n=70) or 10mg/kg (n=59). Across Cycles 1–13, MG-ADL responder rates ranged from a minimum of 63.7% (72/113) in Cycle 3 to a maximum of 88.2% (15/17) in Cycle 13. QMG responder rates ranged from a minimum of 60.6% (20/33) in Cycle 11 to a maximum of 82.4% (14/17) in Cycle 13. Achievement of MSE tended to increase across cycles and ranged from a minimum of 26.5% (30/113) in Cycle 3 to a maximum of 47.1% (8/17) in Cycle 13. Treatment-emergent adverse events occurred in 83.0% (112/135) and 94.7% (126/133) of patients receiving ≥1 treatment cycle of rozanolixizumab 7mg/kg and 10mg/kg, respectively.

SUMMARY/CONCLUSION: Repeated rozanolixizumab treatment showed consistent efficacy across MG-specific outcomes up to 13 cycles and was generally well tolerated.

DISCLOSURES: Tuan Vu is the USF Site Principal Investigator for MG clinical trials sponsored by Alexion/AstraZeneca Rare Disease, Amgen, argenx, Cartesian Therapeutics, COUR Pharmaceuticals, Dianthus Therapeutics, Immunovant, Johnson & Johnson, NMD Pharma, Regeneron Pharmaceuticals and UCB, and has served as a speaker for Alexion/AstraZeneca Rare Disease, argenx and CSL Behring. He has performed consulting work for Alexion/AstraZeneca Rare Disease, argenx, Dianthus Therapeutics, ImmunAbs and UCB. Carlo Antozzi has received funding for congress and Institutional Review Board participation from Alexion Pharmaceuticals, argenx, Biogen, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), Momenta (now Johnson & Johnson) and UCB. Julian Grosskreutz has served as a Consultant for Alexion Pharmaceuticals, Biogen and UCB, and his institution has received research support from the Boris Canessa Foundation. Ali A. Habib has received research support from Alexion Pharmaceuticals, argenx, Cabaletta Bio, Genentech/Roche, Immunovant, Regeneron Pharmaceuticals, UCB and Viela Bio (now Amgen). He has received honoraria from Alexion Pharmaceuticals, Alpine Immune Sciences, argenx, Genentech/Roche, Immunovant, Inhibrx, NMD Pharma, Regeneron Pharmaceuticals and UCB. Kimiaki Utsugisawa has served as a paid Consultant for argenx, Chugai Pharmaceutical, HanAll Biopharma, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), Merck, Mitsubishi Tanabe Pharma, UCB and Viela Bio (now Amgen); he has received speaker honoraria from Alexion Pharmaceuticals, argenx, the Japan Blood Products Organization and UCB. John Vissing has been a Consultant on advisory boards for Amicus Therapeutics, Biogen, Edgewise Therapeutics, Fulcrum Therapeutics, Genethon, Horizon Therapeutics (now Amgen), Lupin, ML Biopharma, Novartis, Regeneron Pharmaceuticals, Roche, Sanofi Genzyme (now Sanofi), Sarepta Therapeutics and UCB. He has received research and travel support and/or speaker honoraria from Alexion Pharmaceuticals, argenx, Biogen, Edgewise Therapeutics, Fulcrum Therapeutics, Lupin, Sanofi Genzyme (now Sanofi) and UCB. He is a Principal Investigator in clinical trials for Alexion Pharmaceuticals, argenx, Atamyo Therapeutics, Genethon, Horizon Therapeutics (now Amgen), Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), ML Biopharma, Novartis, Regeneron Pharmaceuticals, Roche, Sanofi Genzyme (now Sanofi) and UCB. Fiona Grimson, Thaïs Tarancón and Jos Bloemers are employees and shareholders of UCB. Vera Bril is a Consultant for Akcea, Alexion Pharmaceuticals, Alnylam, argenx, CSL, Grifols, Immunovant, Ionis, Janssen Pharmaceuticals (now Johnson & Johnson Innovative

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NON-STEROIDAL IMMUNOSUPPRESSANT THERAPY CHANGES DURING ZILUCOPLAN TREATMENT IN GENERALISED MYASTHENIA GRAVIS: 120-WEEK FOLLOW-UP OF RAISE-XT

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INTRODUCTION: The efficacy and safety of zilucoplan in patients with AChR Ab+ gMG were assessed in two double-blind studies (NCT03315130/NCT04115293). During these studies, and the first 12 weeks of the ongoing open-label extension RAISE-XT (NCT04225871), baseline non-steroidal immunosuppressant therapies (NSISTs) remained unchanged. Thereafter, NSISTs could be changed at the investigator's discretion.

OBJECTIVE: To evaluate NSIST changes in patients with gMG during zilucoplan treatment in RAISE-XT.

METHODS: In RAISE-XT, adults self-administered once-daily subcutaneous zilucoplan 0.3 mg/kg. This post hoc analysis assessed the proportion of patients who changed NSIST relative to double-blind baseline, and change from baseline (CFB) in MG-ADL and QMG scores at Week 120 (interim data cut: 11 November 2023).

RESULTS: In RAISE-XT, 200 patients were enrolled. Of patients on NSISTs at double-blind baseline with Week 120 data, 29.8% (n=14/47) had decreased NSIST dose, including seven patients (14.9%) who discontinued NSIST. Mean (standard deviation [SD]) CFB in MG-ADL

score at Week 120: −7.57 (4.69, decreased dose) and −7.00 (6.08, discontinuation); mean (SD) CFB in QMG score: −12.14 (6.29, decreased dose) and −13.00 (9.02, discontinuation). Among all patients with Week 120 data, only two increased NSIST dose (2.4%), including one patient who initiated a new NSIST; mean (SD) CFB in MG-ADL and QMG score: −6.50 (4.95) and −11.50 (0.71). Over a median of 2.2 years' follow-up, treatment-emergent adverse events occurred in 97.0% (n=194/200) of patients.

SUMMARY/CONCLUSION: Treatment with zilucoplan permitted discontinuation or dose reduction of NSIST for some patients while demonstrating sustained efficacy.

DISCLOSURES: Tuan Vu is the USF Site Principal Investigator for MG clinical trials sponsored by Alexion/AstraZeneca Rare Disease, Amgen, argenx, Cartesian Therapeutics, COUR Pharmaceuticals, Dianthus Therapeutics, Immunovant, Johnson & Johnson, NMD Pharma, Regeneron Pharmaceuticals and UCB, and has served as a speaker for Alexion/AstraZeneca Rare Disease, argenx and CSL Behring. He has performed consulting work for Alexion/AstraZeneca Rare Disease, argenx, Dianthus Therapeutics, ImmunAbs and UCB. Miriam Freimer has served as a paid Consultant for Arcellx, argenx and UCB. She receives research support from Abcuro, Alnylam Pharmaceuticals, argenx, Avidity Biosciences, COUR Pharmaceuticals, Dianthus Therapeutics, Fulcrum Therapeutics, Johnson & Johnson Innovative Medicine, the NIH, RemeGen Biosciences and UCB. Angela Genge has served as a paid Consultant for Alexion Pharmaceuticals, ALS Pharmaceuticals, Amicus Therapeutics, Amylyx Pharmaceuticals, Anelixis Pharmaceuticals, Annexon Biosciences, Apellis Pharmaceuticals, Atlantic Research Group, Biogen, Calico, Cytokinetics, Eli Lilly, Ionis Pharmaceuticals, Medtronic, Mitsubishi Tanabe Pharma, Orion, QurAlis, Ra Pharmaceuticals (now UCB), Roche, Sanofi Genzyme (now Sanofi), UCB and Wave Life Sciences. Channa Hewamadduma has received funding for consultancy on scientific or educational advisory boards for argenx, Biogen, Lupin, Roche, and UCB, and has received an investigator-led research grant from UCB. His study activities were supported by a Sheffield NIHR BRC UK centre grant. He is a trustee of the myasthenia gravis patient organisation Myaware. M. Isabel Leite is funded by the NHS (Myasthenia and Related Disorders Service and National Specialised Commissioning Group for Neuromyelitis Optica, UK) and by the University of Oxford, UK. She has been awarded research grants from UK associations for patients with myasthenia and with muscular disorders (Myaware and Muscular Dystrophy UK, respectively) and the University of Oxford. She has received speaker honoraria or travel grants from Biogen, the Guthy-Jackson Charitable Foundation, Novartis and UCB. She serves on scientific or educational advisory boards for argenx, Horizon Therapeutics (now Amgen) and UCB. Kimiaki Utsugisawa has served as a paid Consultant for argenx, Chugai Pharmaceutical, HanAll Biopharma, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), Merck, Mitsubishi Tanabe Pharma, UCB and Viela Bio (now Amgen); he has received speaker honoraria from Alexion Pharmaceuticals, argenx, the Japan Blood Products Organization and UCB. Babak Boroojerdi, Fiona Grimson and Natasa Savic are employees and shareholders of UCB. James F. Howard Jr. has received research support (paid to his institution) from Ad Scientiam, Alexion/AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, the Centers for Disease Control and Prevention, the Muscular Dystrophy Association, the Myasthenia Gravis Foundation of America, the National Institutes of Health, NMD Pharma and UCB; has received honoraria/consulting fees from AcademicCME, Alexion/AstraZeneca Rare Disease, Amgen, argenx, Biohaven Ltd, Biologix Pharma, CheckRare CME, CorEvitas, Curie.Bio, Hansa Biopharma, Medscape CME, Merck EMD Serono, Novartis, PeerView CME,

Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics, Toleranzia AB and UCB; and has received non-financial support from Alexion/AstraZeneca Rare Disease, argenx, Biohaven Ltd, Cartesian Therapeutics, Toleranzia AB and UCB.

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LONG-TERM SAFETY AND EFFICACY OF SUBCUTANEOUS EFGARTIGIMOD PH20 IN ADULT PARTICIPANTS WITH GENERALIZED MYASTHENIA GRAVIS: INTERIM RESULTS OF THE ADAPT-SC+ STUDY

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INTRODUCTION: Efgartigimod is a human immunoglobulin G1 (IgG1) antibody Fc-fragment that reduces IgG levels (including pathogenic autoantibodies) through neonatal Fc receptor blockade. In the ADAPT-SC study, subcutaneous (SC) efgartigimod PH20 (coformulated with recombinant human hyaluronidase PH20) was shown to have noninferior total IgG reduction to intravenous (IV) efgartigimod in participants with gMG. Participants completing ADAPT-SC or enrolled in ADAPT+ (efgartigimod IV open-label extension (OLE)) were eligible for the ADAPT-SC+ OLE.

OBJECTIVE: To evaluate long-term safety and efficacy of efgartigimod PH20 SC in participants with gMG enrolled in the ADAPT-SC+ OLE.

METHODS: Efgartigimod PH20 SC 1000 mg was administered in cycles of 4 once-weekly injections. Subsequent cycles were initiated based on clinical evaluation. MG-ADL score assessed clinical efficacy.

RESULTS: As of December 2022, 179 participants received ≥1 dose of efgartigimod PH20 SC, with a mean (SD) study duration of 413 (105) days. Participants each received a mean (SD) of 26.2 (11.7) SC administrations. Adverse events were predominantly mild/moderate. Localized injection site reactions were mild/moderate, did not lead to treatment discontinuation, and decreased in incidence with subsequent cycles. Improvement from cycle baseline (mean [SE]) in MG-ADL total scores were observed in Week 4 of cycle 1 (-4.1 [0.27]) in anti-acetylcholine receptor antibody positive participants, with a consistent pattern of improvement seen through

cycle 9. Similar results were seen on quality-of-life measures. The proportion of participants achieving minimal symptom expression (MG-ADL score, 0-1) at any time through 9 cycles was 54.6%. Clinical improvements were similar to those seen with efgartigimod IV during ADAPT/ADAPT+. Updated data analysis will be presented at the congress.

SUMMARY/CONCLUSION: Treatment with multiple cycles of efgartigimod PH20 SC was well tolerated and efficacious.

DISCLOSURES: Author Tuan Vu discloses he has served as a speaker for Alexion, argenx, CSL Behring, and Allergan/AbbVie; performed consulting work for argenx, Alexion AstraZeneca, Dianthus, Remegen, ImmunAbs, and UCB; and participated in trials in MG sponsored by Alexion AstraZeneca, argenx, UCB, Amgen, Immunovant, Regeneron, Johnson & Johnson, Remegen, Dianthus, and Cartesian Therapeutics. Author Jan L. De Bleecker discloses he has served as a consultant for argenx, Alexion Pharmaceuticals, Inc., CSL, UCB Pharma, Alnylam Pharmaceuticals, Inc., Janssen, and Sanofi Genzyme. Author Yuebing Li discloses he has served as a consultant for argenx, UCB Pharma, Alexion, Catalyst, and Immunovant. Author James F. Howard Jr discloses he has received research support (paid to his institution) from Ad Scientiam, Alexion AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, Centers for Disease Control and Prevention, MGFA, Muscular Dystrophy Association, NIH, NMD Pharma, PCORI, and UCB Pharma; honoraria/consulting fees from AcademicCME, Alexion AstraZeneca Rare Disease, Amgen, argenx, Biohaven, Ltd, Biologix Pharma, CheckRare CME, Curie.bio, F. Hoffmann-LaRoche Ltd, Medscape CME, Merck EMB Serono, Novartis Pharma, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics, UCB Pharma, and Zai Labs; nonfinancial support from Alexion AstraZeneca Rare Disease, argenx, Biohaven, Ltd, Cartesian Therapeutics, Toleranzia AB, UCB Pharma, and Zai Labs. Author Denis Korobko discloses he has received speaker honoraria from Roche, Novartis Russia, Sanofi, Merck, Janssen (Johnson & Johnson company); received research grants from Novartis, UCB, argenx, Viela Bio, Inc. (now Horizon Therapeutics), and Bristol Myers Squibb; and was compensated for consulting and serving on scientific advisory boards for Novartis Russia, Janssen (Johnson & Johnson company), and BIOCAD. Authors Sophie Steeland, Wan-Yi Huang, Ming Jiang, and Moana Hodari are employees of argenx. Author Kimiaki Utsugisawa discloses he has served as a paid consultant for UCB Pharma, Janssen Pharma, Horizon Therpeutics (Viela Bio), Chugai Pharma, Hanall BioPharma, Merck, and Mitsubishi Tanabe Pharma and has received speaker honoraria from argenx, Alexion Pharmaceuticals, UCB Pharma, and the Japan Blood Products Organization. Author Francesco Sacca discloses he has received speaker honoraria from Alexion Pharmaceuticals, Inc., Biogen, Mylan, Novartis, Roche, Sanofi, and Teva; received honoraria from Alexion Pharmaceuticals, Inc., Almirall, argenx, Avexis, Biogen, Forward Pharma, Lexeo Therapeutics, Merk, Novartis, Pomona, Roche, Sanofi, and Takeda for consulting services; and served as PI in clinical trials supported by Alexion Pharmaceuticals, Inc., argenx, Novartis, Prilenia, and Sanofi. Author Renato Mantegazza discloses he has received consulting fees/honoraria or support for meeting participation from Alexion Pharmaceuticals, Inc., argenx, Ra Pharmaceuticals Inc, BioMarin, Catalyst Pharmaceuticals, Inc., UCB, Teva, Merck, Roche, and Biogen Inc.

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presentation abstract]. 2025 annual meeting of the American Academy of Neurology (AAN) in San Diego, CA, United States. index.mirasmart.com/AAN2025/

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COVID-19 VACCINATION RESPONSE IN PARTICIPANTS ACROSS CLINICAL TRIALS INVESTIGATING EFGARTIGIMOD IV AND EFGARTIGIMOD PH20 SC

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INTRODUCTION: Patients with gMG experience a greater risk of adverse outcomes from respiratory infections, including COVID-19. Some immunosuppressive therapies used in the management of gMG may increase risk of infection and impair vaccine responses.

OBJECTIVE: To investigate the effect of treatment with efgartigimod [administered intravenously (IV) or subcutaneously (SC, coformulated with recombinant human hyaluronidase PH20)], a human immunoglobulin G1 (IgG1) antibody Fc-fragment that reduces total and pathogenic IgG levels through neonatal Fc receptor blockade, on humoral immune responses to COVID-19 vaccination in participants with various antibody-mediated autoimmune diseases, including gMG.

METHODS: In ADAPT-SC+, efgartigimod PH20 SC (1000 mg) was administered in cycles of 4 once-weekly injections. COVID-19 receptor binding domain-specific IgGs were assessed, nominally, at prevaccination, ≥4 weeks after vaccination, and subsequently at 1 week after the fourth efgartigimod PH20 SC injection (when total IgG levels were maximally reduced). One sample was collected if postvaccination time points coincided with each other. Responses to COVID-19 vaccinations were similarly assessed across other clinical trials investigating efgartigimod IV or PH20 SC in different diseases.

RESULTS: Eighteen participants in ADAPT-SC+ received a COVID-19 vaccine during or after a cycle. For 78% (n=14/18) of participants, this was their second or third vaccine dose. A 35.9-fold increase in SARS-CoV-2-IgG-RBD levels occurred from prevaccination to ≥4 weeks

postvaccination. Similarly, from prevaccination to 1 week after the fourth efgartigimod PH20 SC injection, a 33.8-fold increase was seen. Additional data across multiple clinical trials assessing efgartigimod IV or PH20 SC will be presented at the congress.

SUMMARY/CONCLUSION: Participants with antibody-mediated autoimmune diseases, including gMG, receiving efgartigimod IV and efgartigimod PH20 SC, were able to mount antigen-specific IgG responses to COVID-19 immunization, further adding to the available data suggesting that treatment with efgartigimod does not impair response to vaccination against COVID-19.

DISCLOSURES: Author Tuan Vu discloses he has served as a speaker and consultant for argenx and participated in trials sponsored by argenx; served as a speaker for Alexion, CSL Behring, and Allergan/AbbVie; performed consulting work related to MG for Alexion/AstraZeneca and UCB; participated in trials in MG sponsored by Alexion/AstraZeneca, argenx, UCB, Horizon, Johnson & Johnson, Dianthus, Remegen, Regeneron, Immunovant, Cartesian, and Sanofi. Author Francesco Saccà discloses he has received speaker honoraria from Alexion Pharmaceuticals, Inc, Biogen, Mylan, Novartis, Roche, Sanofi, and Teva; received honoraria from Alexion Pharmaceuticals, Inc, Almirall, argenx, Avexis, Biogen, Forward Pharma, Lexeo Therapeutics, Merk, Novartis, Pomona, Roche, Sanofi, and Takeda for consulting services; and served as PI in clinical trials supported by Alexion Pharmaceuticals, Inc, argenx, Novartis, Prilenia, and Sanofi. Author James F. Howard Jr discloses he has received research support (paid to his institution) from Ad Scientiam, Alexion AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, Centers for Disease Control and Prevention, MGFA, Muscular Dystrophy Association, NIH, NMD Pharma, PCORI, and UCB Pharma; honoraria/consulting fees from AcademicCME, Alexion AstraZeneca Rare Disease, Amgen, argenx, Biohaven, Ltd, Biologix Pharma, CheckRare CME, Curie.bio, F. Hoffmann-LaRoche Ltd, Medscape CME, Merck EMB Serono, Novartis Pharma, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics, UCB Pharma, and Zai Labs; non-financial support from Alexion AstraZeneca Rare Disease, argenx, Biohaven, Ltd, Cartesian Therapeutics, Toleranzia AB, UCB Pharma and Zai Labs. Author John W. Sleasman discloses he receives research and salary support from the National Institutes of Health, Cellective, Enzyvant, and the Jeffrey Modell Foundation and is a consultant for argenx. Authors Fien Gistelinck, Paul Duncombe, Benjamin Van Hoorick, and Sophie Steeland are employees of argenx. Author Renato Mantegazza discloses he has received consulting fees/honoraria or support for meeting participation from Alexion Pharmaceuticals, argenx, Ra Pharmaceuticals, Biomarin, Catalyst, UCB, TEVA, Merck, Roche, and Biogen. Author Jan L. De Bleecker discloses he has served as a consultant for argenx, Alexion Pharmaceuticals, Inc, CSL, UCB Pharma, Alnylam Pharmaceuticals Inc, Janssen, and Sanofi Genzyme. Author Antoine Azar discloses he has received research support from X4 and Grifols and is a consultant for Grifols, Takeda, Pfizer, Janssen, and argenx. Author Kevin Winthrop discloses he has received research support from Bristol Myers Squibb and Pfizer and consulting honoraria from Pfizer, AbbVie, UCB, Eli Lilly, Galapagos, GSK, Roche, Gilead, Bristol Myers Squibb, Regeneron, Sanofi, AstraZeneca, and Novartis.

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CLINICAL CHARACTERISTICS IN MYASTHENIA GRAVIS WITH IN-HOSPITAL MORTALITY AND ETIOLOGY ANALYSIS

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INTRODUCTION: The existing literature lacks consistent information regarding the causes of death in patients with myasthenia gravis (MG).

OBJECTIVE: This study aims to investigate the characteristics and underlying causes of mortality in patients diagnosed with myasthenia gravis (MG) who have deceased.

METHODS: This 10-year study conducted a retrospective analysis of data obtained from hospitalized MG patients who were prospectively enrolled in an MG cohort at two large general hospitals in China. The mortality rate was assessed alongside comprehensive demographic information. Experienced physicians identified both the underlying and direct causes of death.

RESULTS: Among a cohort of 3,723 patients, the overall hospitalized mortality rate was recorded at 79 individuals (2.12%). Thymoma was identified in 52 patients, representing 65.82% of the total. A comparative analysis revealed that patients with thymomatous MG (TMG) (n=52) were significantly younger at the time of death than those in the non-thymomatous MG (NTMG) group (n=27), with mean ages of 53.71 ± 14.01 years and 65.37 ± 14.61 years, respectively (p=0.001). Septic shock emerged as the predominant underlying cause of death, affecting 32 patients (40.51%), followed by myasthenic crisis (MC), which impacted 18 patients (22.78%). This pattern was consistent across both the TMG and NTMG groups. Within the TMG cohort, fulminant myocarditis ranked as the third leading cause of death, affecting 9 patients (17.31%), whereas no instances of fulminant myocarditis were documented in the NTMG group. Among the deceased patients, pneumonia was the most frequently observed infection, affecting 55 individuals (69.62%), followed by urinary tract infections in 14 patients (17.72%), bloodstream infections in 13 patients (16.46%), and intracranial infections in 7 patients (8.86%).

SUMMARY/CONCLUSION: The research indicates that thymoma may elevate mortality risk, with septic shock and MC identified as the most prevalent underlying causes in patients with MG.

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MuSK AGONIST ANTIBODY DID NOT SUCCEED TO RESCUE PHENOTYPE OF AChR DEFICIENCY CONGENITAL MYASTHENIC SYNDROME (CMS) MOUSE MODEL

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ABSTRACT: CMS caused by deficiency in post-synaptic acetylcholine receptors (AChR) is treated with cholinesterase inhibitors like pyridostigmine. Long term high dose pyridostigmine treatment causes deterioration of AChR clustering and neuromuscular junction structure, leading to loss of effectiveness. Beta adrenergic agonist (salbutamol) addition can improve AChR clustering, but most patients remain disabled. Agonist antibodies targeted to the frizzled domain of MuSK promote MuSK phosphorylation and AChR clustering. They are effective in treating DOK-7 CMS mice and ARGX-119, a first-in-class humanized MuSK agonist monoclonal antibody has begun clinical trials in DOK-7 CMS. We tested whether MuSK agonist antibodies effectively treated AChR deficiency mice. Male AChR deficiency mice were treated with MuSK-agonist antibody or isotype control via weekly intraperitoneal injections for 11 weeks from 12 weeks of age, with or without established treatment of pyridostigmine and salbutamol. Mice were assessed for muscle strength, fatiguability and bodyweight by weekly hang tests, weighing, and assessed for changes in NMJ morphology and neurotransmission at end of study. Serum samples were taken monthly to titre MuSK-agonist antibodies, revealing ~58% of mice had lower than expected concentrations. In these samples anti-drug antibodies (ADA) were detected. Irrespective of their MuSK antibody titre, comparisons with isotype control antibody treated mice showed no improvement in weight or strength throughout the study. Additionally, no change in NMJ morphology or neuromuscular transmission was observed. As ADA rendered MuSK antibody titres to be sub-optimal in ~ 58 % of treated mice, the statistical power of our study was compromised. This demonstrates the importance of monitoring serum therapeutic antibody concentration and the presence of ADA. For those mice that did achieve higher serum MuSK antibody levels, we can tentatively state that the treatment appears not to phenotypically or functionally improve AChR deficiency CMS model mice. We speculate that the pathogenic mechanism of different congenital myasthenic syndromes subtypes determine the potential for improvement with MuSK agonist therapy.

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EFFICACY AND SAFETY OF IPTACOPAN IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS: STUDY DESIGN

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INTRODUCTION: Generalized myasthenia gravis (gMG) is a rare, chronic autoimmune disorder caused by autoantibodies against neuromuscular junction components, leading to debilitating fatigable muscle weakness and other clinical consequences. Current therapies for the treatment of gMG have limitations, including infections, systemic side effects, and often require parenteral administration. Iptacopan (LNP023) is an oral, potent, and selective inhibitor of factor B in the alternative complement pathway, currently in clinical development for the treatment of gMG.

OBJECTIVE: This Phase III study aims to evaluate the efficacy and safety of iptacopan (LNP023) in patients with anti-acetylcholine receptor antibody-positive (AChR+) gMG on stable standard of care (SOC) treatment.

METHODS: This ongoing randomized, double-blind, placebo-controlled, multicenter Phase III study (NCT06517758) is enrolling patients aged 18-75 years with Class II-IV MG (according to the Myasthenia Gravis Foundation of America) who test positive for AChR+ antibodies and are on SOC treatment. Participants must have a baseline Myasthenia Gravis Activity of Daily Living (MG-ADL) score ≥6, with ≥50% due to non-ocular symptoms, and inadequate disease control on one or more non-steroidal immunosuppressant treatments (NSIST) or frequent plasmapheresis/plasma exchange/IVIG therapy. Eligible participants will be randomized (1:1) to receive either iptacopan or placebo during the 6-month double-blind core period, followed by

iptacopan administration in the open-label extension (up to 60 months). The primary endpoint is the change in MG-ADL score from baseline to Month 6. Key secondary endpoints include assessments of Quantitative MG (QMG), and MG Composite (MGC), among others.

RESULTS: The study will enroll approximately 146 eligible participants.

SUMMARY/CONCLUSION: This study will investigate the efficacy and safety of iptacopan versus placebo in adult patients with AChR+ gMG.

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SAFETY OF REMIBRUTINIB ACROSS IMMUNE-MEDIATED DISEASES

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INTRODUCTION: Remibrutinib is a potent, highly selective, covalent, oral Bruton's tyrosine kinase inhibitor. The high selectivity of remibrutinib has the potential to result in a favorable safety profile by minimizing off-target effects.

OBJECTIVE: To report the integrated safety profile of remibrutinib using pooled data from completed phase 2 clinical trials in chronic spontaneous urticaria (CSU), Sjögren's disease (SjD), and asthma, including long-term treatment (up to 52 weeks).

METHODS: Pooled data from completed phase 2 studies of CSU (including the 52-week open-label extension), SjD, and asthma were analyzed. Safety assessments included adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESIs). Analyses were conducted for patients in the remibrutinib and placebo groups using exposure-adjusted incidence rates (EAIRs) per 100 patient-years.

RESULTS: Patients receiving any remibrutinib dose had an EAIR of 260.8 for AEs. The EAIR for AEs leading to treatment discontinuation was 8.3, and the EAIR for SAEs was 4.2. Infections

and infestations were the most frequently reported grouped AESIs (EAIR: 68.0) and were mild to moderate in severity, with mostly upper respiratory tract infections and nasopharyngitis. Other reported grouped AEs with EAIRs ≥20 were: skin/subcutaneous tissue disorders, gastrointestinal disorders, nervous system disorders, and musculoskeletal disorders. AESIs, other than infections, included bleeding (mostly minor cutaneous) and cytopenia (rare), which were mild to moderate in severity. Overall, EAIRs were generally similar for remibrutinib and placebo.

SUMMARY/CONCLUSION: This integrated safety analysis confirmed the consistently favorable safety profile of remibrutinib across indications and doses, with up to 52 weeks of long-term exposure. A dedicated Phase 3 study has been initiated to establish the benefit/risk profile of remibrutinib in myasthenia gravis.

DISCLOSURES: Heinz Wiendl has received honoraria for acting as a member of Scientific Advisory Boards from Alexion, Argenx, Biocryst, Bristol Myers Squibb (BMS), Cellerys, Galapagos, Janssen, Merck, Novartis, Sandoz-Hexal, uniQure biopharma, speaker honoraria and travel support from Alexion, AOCN, AstraZeneca, Biogen, BGP Products Operations, BMS, CEMCAT, EPG Health/Medthority, Genzyme, Kohlhammer, Merck, MS at the Limits, Neurodiem, NMSS, Novartis, Ology, Roche, Sanofi, Springer, Streamed up, TEVA, Uvet, WebMD Global, acting as consultant for Alexion, Argenx, Argobio, BMS, Dianthus, EMD Serono, Fondazione Cariplo, Idorsia, Immunic, Immunovant, INmune Bio_Syneos Health, Janssen, LTS, Lundbeck, Merck, Muna Therapeutics, Myrobalan Therapeutics, Novartis, PSL Group, Red Nucleus, Roche, Samsung, Sangamo, Sanofi, Swiss MS Society, Teladoc Health, Toleranzia, UCB, Viatris; and research funds from Deutsche Forschungsgemeinschaft, Deutsche Myasthenie Gesellschaft e.V., European Union, Alexion, Amicus Therapeuticus, Argenx, Biogen, CSL Behring, F. Hoffmann - La Roche, Genzyme, Merck KgaA, Novartis, Roche, UCB Biopharma. Laura Airas has received institutional research funding from Genzyme and Merck and compensation for lectures and advising from Novartis, Sanofi Genzyme, Merck, Biogen, Roche and Janssen. Robert Bermel has served as a consultant for AstraZeneca, Biogen, EMD Serono, Genzyme/Sanofi, Genentech/Roche, Novartis, TG Therapeutics and VielaBio. He receives research support from Biogen, Genentech and Novartis, and shares rights to intellectual property underlying the Multiple Sclerosis Performance Test, currently licensed to Qr8 Health and Biogen. Thomas Dörner has received support for clinical studies and honoraria for scientific advice from BMS, GSK, Novartis, Roche/GNE, Janssen. Ana Giménez-Arnau has been a speaker and/or advisor for and/or has received research funding from Almirall, Amgen, AstraZeneca, Avene, Blue-Print, Celldex, Escient Pharmaceutials, Genentech, GSK, Harmonic Bio, Instituto Carlos III- FEDER, Jaspers, Leo Pharma, Menarini, Mitsubishi Tanabe Pharma, Noucor, Novartis, Sanofi–Regeneron, Septerna, Servier, Thermo Fisher Scientific, Uriach Pharma. Michihiro Hide has received honoraria for speaker and/or advisor from Kaken, Kyorin, Kyowa Kirin, Meiji Pharma, Mitsubishi-Tanabe, Novartis, Sanofi/Regeneron, Taiho, and Teikoku. Xavier Montalban has received compensation for lecture honoraria and travel expenses, participation in scientific meetings, clinical trial steering committee membership, or clinical advisory board participation in recent years from Abbvie, Actelion, Alexion, Bial PD, Biogen, Bristol-Myers Squibb/Celgene, EMD Serono, Genzyme, Hoffmann-La Roche, Immunic Therapeutics, Janssen Pharmaceuticals, Medday, Medscape, Merck, Mylan, Nervgen, Neuraxpharm, Novartis, Peervoice, Samsung-Biosys, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, ECTRIMS, MSIF, and NMSS or any of their affiliates. Jin Nakahara has received personal fees (honoraria and/or consultant fees) from

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INCREASED PREVALENCE OF EXTRATHYMIC NEOPLASM IN MYASTHENIA GRAVIS PATIENTS FROM CLALIT MACHINE-LEARNING REGISTRY

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INTRODUCTION: Myasthenia gravis (MG) is known to be associated with thymic neoplasms. However, an increased prevalence of extrathymic neoplasms has also been reported in MG patients.

OBJECTIVE: This study aims to evaluate the rates of malignancy in MG patients, while also accounting for risk factors such as co-morbidities and immunomodulatory treatments.

METHODS: Data were obtained from the Clalit Health Services (CHS) database, including MG patients, along with a sex- and age-matched control group in a 1:3 ratio. We compared the prevalence and hazard ratios of extrathymic neoplasms. To avoid MG misclasification , we utilized a machine-learning (ML) model to identify MG patients within the registry.

RESULTS: Of the 4,436 patients with MG-related codes in the CHS, 1,840 patients with a high probability of MG according to our ML model were compared to 9,690 non-myasthenic individuals. MG patients had a higher prevalence of malignancy, with 48.48% affected compared to 30.94% in the control group (HR 2.1, 95% CI 1.9–2.32, $P < 0.001$). Cancers with significantly higher prevalence included colorectal cancer (HR 1.28, 95% CI 1.05–1.56), breast cancer (HR 1.48, 95% CI 1.1–2.01), prostate cancer (HR 1.78, 95% CI 1.31–2.42), and hematologic malignancies such as myeloproliferative neoplasms (HR 2.9, 95% CI 1.76–4.78), non-Hodgkin lymphoma (HR 1.63, 95% CI 1.23–2.16), and multiple myeloma (HR 1.49, 95% CI 1.1–2.02).

SUMMARY/CONCLUSION: MG patients have higher prevalence of extrathymic neoplasms compared to controls, particularly colorectal, breast, and prostate cancers and hematologic malignancies. Our machine-learning model provided an accurate and reliable assessment of the MG population.

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MULTICENTER VALIDATION OF THE OCULAR MYASTHENIA GRAVIS RATING SCALE QUESTIONNAIRE

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BACKGROUND & OBJECTIVES: We sought to validate a novel patient-reported outcome measure (PROM) for Ocular Myasthenia Gravis (OMG), using the OMG Rating Scale Questionnaire (OMGRate-q).

METHODS: A prospective study of adult OMG patients at three centers (1/2022-10/2023) using the 10-item OMGRate-q. Response data were analyzed using exploratory factor analysis followed by Andrich rating scale model fitting. Poorly fitting items were eliminated & the model was refitted to produce the final items, item locations, & thresholds. Latent scores (theta) were estimated, test-retest reliability was established with repeat measures, & correlation with other myasthenia gravis PROMs was measured.

RESULTS: 134 (33.6% women, 73.9% white) patients were included. Median age (interquartile range [IQR]) 64.6 years (52.6-73.9 years). A ptosis-related item showed significant item-trait deviation ($p<.001$) & was kept as a separate factor from the remaining diplopia-related items. After excluding this item, there were no misfitting items. Theta estimation for the diplopia scale ranged from -3.47 to 5.51 with median (IQR)=-0.53 (-2.33, 0.72). Test-retest reliability was high (intraclass correlation coefficient [95% confidence interval]=0.95 [0.90, 0.98]) for the diplopia subscale & good (weighted kappa=0.56) for the ptosis item. No significant differences were observed in OMGRate-q diplopia subscale scores or the ptosis item between the three sites (diplopia P=0.44; ptosis P=0.32). OMGRate-q scores were moderately-to-highly correlated with

Myasthenia Gravis Quality of Life 15 questionnaire (n=122; diplopia: r=0.68, P<.001; ptosis: r=0.48, P<.001) & Myasthenia Gravis Impairment Index (n=130; diplopia: r=0.76, P<.001; ptosis: r=0.77, P<.001). OMGRate-q length was acceptable to most participants (125/130 [96.2%]), completed in 80.7(±45.2) seconds.

SUMMARY/CONCLUSION: The OMGRate-q is a valid & reliable disease-specific PROM for OMG for patient-centered research & care. However, the OMGRate-q emphasizes the impact of diplopia, therefore future studies are planned to add measures of ptosis to this scale or to create a separate measure.

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ECULIZUMAB AS A NEW OPTION FOR PERIOPERATIVE TREATMENT IN THYMOMA-ASSOCIATED MYASTHENIA GRAVIS: A PROSPECTIVE CASE SERIES

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INTRODUCTION: Thymoma-associated myasthenia gravis (TAMG) is a rare autoimmune disorder characterized by autoantibodies against the acetylcholine receptor (AChR), often complicating thymoma management. Thymectomy remains a cornerstone therapy, yet perioperative exacerbations of myasthenic symptoms pose significant risks, including respiratory failure and prolonged hospitalization. Conventional immunosuppressive therapies, such as corticosteroids may have delayed onset or insufficient efficacy in acute settings .Eculizumab, a monoclonal antibody targeting complement protein C5, has demonstrated efficacy in refractory generalized myasthenia gravis (gMG) and thymoma-associated myasthenia gravis (TAMG) by inhibiting terminal complement-mediated neuromuscular junction destruction. However, its role in the perioperative management of TAMG remains unexplored. This study evaluates the safety and efficacy of eculizumab as an add-on therapy for perioperative symptom control in TAMG patients undergoing thymectomy.

Granzymes (GZMs) are a family of serine proteases implicated in several processes, including proinflammatory cytokine release, cell death, extracellular matrix degradation, cell junction disruption, epithelial barrier dysfunction, and/or autoantigen generation, making them prime targets in drug development for inflammatory diseases. Acute inflammatory demyelinating polyneuropathy (AIDP) is an immune-mediated neuropathy with an incompletely understood pathogenesis and lacks targeted treatment. This study investigated whether GZMs are present in the cerebrospinal fluid (CSF) of individuals with AIDP, which could implicate them in the pathophysiology of this condition.

OBJECTIVE: This study aims to report a case series of TAMG who have eculizumab as an add-on therapy for perioperative treatment.

METHODS: This is a single-centre observational prospective study. Patients were stratified into two cohorts: an eculizumab add-on group (initiated eculizumab before thymectomy) and a control group (standard therapy without eculizumab). The clinical outcomes, Surgical outcomes, MG-activities of daily living (ADL), Myasthenia Gravis Foundation of America (QMG), Manual Muscle Test (MMT) score, were compared between groups. Lymphocytic phenotypes and adverse events were also assessed pre-thymectomy and post-thymectomy.

RESULTS: Both groups exhibited significant postoperative reductions in QMG,MMT and ADL scores compared to preoperative baseline levels ($p<0.05$). Eculizumab add-on group showed earlier improvement for ΔOMG (median 8.5 vs -1.0, $p<0.0001$), ΔMMT (6.0 vs -3.0, $p=0.0001$), and ΔADL (5.0 vs -3.5, $p=0.0006$) at 1 week. This advantage persisted through week 2 for OMG (7.0 vs 2.0, $p=0.0046$), MMT (6.0 vs 1.0, $p=0.0044$), and ADL (4.0 vs 0.5, $p=0.0365$).In Eculizumab add-on group, The percentages of $CD3^+CD4^+$Th lymphocytes in peripheral blood significantly declined from 41.17%±7.98% to 30.39%±8.12%（$p<0.05$）, the $CD3^+$Tcell lymphocytes in peripheral blood significantly declined from 74.21%±8.91% to 67.82%±11.39%（$p<0.05$）,while there were no significant changes in $CD3^+CD8^+$Tc lymphocytes and CD19+B lymphocytes.

SUMMARY/CONCLUSION: This small case series highlights the use of eculizumab in TAMG as a rapid symptom-control treatment during the perioperative period. Future prospective cohort studies with a large sample size are expected to validate these findings, particularly for those TAMG with moderate to severe myasthenia before thymectomy.

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THE SWEDISH MYASTHENIA GRAVIS REGISTRY: A NATIONWIDE, POPULATION-BASED HIGH COVERAGE REGISTRY

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INTRODUCTION: Despite advances in MG research, population-based cohorts are needed to provide a comprehensive, generalizable view of the disease in real-world settings.

OBJECTIVE: Here we present the cohort profile and preliminary findings of the Swedish MG registry (MG-reg).

METHODS: MG-reg was initiated in 2011 as a voluntary, publicly funded, nationwide register open to all neurology clinics in Sweden, comprising data on demographics, diagnostic workup, as well as longitudinal disease activity and therapeutic interventions. Starting from 2020, nationwide validation and update against medical records was initiated. Characteristics of the study population were summarized using means (SD) and counts with frequencies (%). Logistic regression was performed to identify factors associated with minimal manifestation status (MMS, defined as QMG score>2).

RESULTS: As of 2024, 1,841 MG cases were included in the cohort, of which 1455 were alive and 1,277 had been validated and updated against medical charts. The mean age at onset was 52 years, 51% were female and 91% were AChR+ and 2% MuSK+. Non-steroidal immunosuppressants had been prescribed to 52% of patients, of which 58% had ever received rituximab and 54% azathioprine. At data excerpt 30% were treated with non-steroidal immunosuppressants, of which 63% were on rituximab and 30% azathioprine.

In a subset of patients (n=183) with QMG scores recorded within 12 months of disease onset and with minimum two yearly follow-ups, a significant reduction in disease activity was observed at two years (QMG 6.0 vs. 2.0 p, $p<0.001$).

SUMMARY/CONCLUSION: The Swedish MG-reg represents a resource for exploring real-world disease and treatment outcomes in a large and well-characterized MG population covering approximately 55% of the nationwide prevalent population.

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WHO WOULD BENEFIT FROM THYMECTOMY IN NON-THYMOMATOUS MYASTHENIA GRAVIS? A MULTICENTER STUDY FROM NORDIC COUNTRIES

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INTRODUCTION: Thymic hyperplasia is common in early-onset myasthenia gravis (EOMG; disease onset <50 years), but much more rarely in late-onset MG (LOMG; onset ≥50 years). However, neither reliable imaging nor biomarkers for thymic hyperplasia are available. Still, thymectomy is recommended up to an age span of 50-65 years in the Nordic MG guidelines.

OBJECTIVE: To identify clinical factors that could predict hyperplasia in non-thymomatous patients.

METHODS: We identified 327 thymectomized non-thymomatous MG patients in the Swedish MG Register. A Finnish cohort will be used as validation. Co-variates comprised sex, age of disease onset, body mass index (BMI), anti-acetylcholine receptor (AChR) antibody titers, and disease duration in a complete set of 229 patients analyzed with logistic regression to estimate the odds ratio (OR) of hyperplasia with 95% confidence intervals (CI).

RESULTS: A majority was female (n=169; 73.8%) and the mean age at disease onset and thymectomy were 31.4 (SD: 14.8) and 35.5 (SD: 15.0) years, respectively. Patients with hyperplasia predominantly were female, younger, had lower BMI, and were more likely to be anti-AchR positive compared to those lacking thymic hyperplasia. In the multivariate model, a one-year increase in age at onset was associated with an 8% lower probability of hyperplasia (OR: 0.92, 95%CI 0.89, 0.95). A marginal impact on hyperplasia risk was found for BMI (OR per 1-kg/m2: 0.93, 95%CI 0.85, 1.00), female sex (OR: 2.24, 95%CI 0.97, 5.17), and disease duration (OR per year: 0.92, 95%CI 0.83, 1.01), respectively.

SUMMARY/CONCLUSION: Age at onset, BMI, female, and disease duration may be predictive factors for thymic hyperplasia. Patients aged >50 years more rarely undergo thymectomy in Sweden. Thus, these results will be validated in a Finnish cohort where thymectomy frequencies in LOMG are higher. Future work on clinical and environmental factors incorporating disease prognosis after thymectomy is also in preparation.

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INITIAL COMBINATION THERAPY OF TACROLIMUS AND EFGARTIGIMOD INDUCE MINIMAL SYMPTOM EXPRESSION IN NEW-ONSET GENERALIZED MYASTHENIA GRAVIS: A SINGLE-CENTER, REAL-WORLD CASE SERIES

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INTRODUCTION: A large scale of myasthenia gravis (MG) patients show intolerance and concerns of steroids, the first-line treatment in the current MG therapeutic strategy. Efgartigimod is a FcRn-antagonist and is approved in generalized myasthenia gravis (gMG) patients as a fast-acting biological targeted therapy. Here, we aim to investigate whether combined therapy of tacrolimus and efgartigimod would offer a new steroids-free regimen to new-onset gMG patients.

OBJECTIVE: This is a real-world, prospective observational study, and evaluates the efficacy and safety of initial combined therapy of tacrolimus and efgartigimod in acetylcholine receptor antibody-positive (AChR+) new-onset, naïve gMG patients.

METHODS: We prospectively followed 14 acetylcholine receptor (AChR) antibody-positive new-onset gMG patients, with a disease duration shorter than 12 months and sparing of immunosuppressive agents at the first visit. All the patients received one cycle of efgartigimod treatment (10mg/kg qw, consequently for 4 weeks) and oral tacrolimus (dosage adjusted due to blood drug concentration). MG-activities of daily lives (MG-ADL) scores were collected every week. Blood glucose, immunoglobulin, lymphocytes, cholesterol and liver functions were tested every month.

RESULTS: Female and male ratio is 10:4. Average onset age is 52±22 years old. Average disease duration is 3.9±3.6 months. Four out of 14 (28.4%) patients are thymoma-associated cases and all underwent thymectomy. Early-onset MG and late-onset MG both account for 35.7% of total population. Median follow-up time is 19 weeks (10-49 weeks). 21.4% (3/14) of patients received two episodes of efgartigimod treatment. Thirteen out of 14 (92.9%) patients achieved minimal symptom expression (MSE, ADL 0-1), while one patient remained with refractory ptosis and ophthalmoplegia (ADL=5). Average time from initial therapy to MSE is 6.4±6.0 weeks. No remarkable adverse effects were reported.

SUMMARY/CONCLUSION: This study first demonstrates the efficacy and safety of initial add-on of efgartigimod and tacrolimus in new-onset gMG, which may offer a steroid-free regimen for clinical practice.

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RISK AND DETERMINANTS OF FALSE ACETYLCHOLINE RECEPTOR AUTOANTIBODY POSITIVITY BY RADIOIMMUNOPRECIPITATION ASSAY IN A REAL-LIFE SETTING

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INTRODUCTION: Antibodies against the acetylcholine receptor (AchR-IgG) confirm a diagnosis of autoimmune myasthenia gravis (MG). Radioimmunoprecipitation assay (RIPA) is the gold standard for AchR-IgG detection with a reported specificity of ˜99%. However, its accuracy in large, unselected populations has not been fully elucidated.

OBJECTIVE: To determine the positive predictive value (PPV) and risk of false AchR-IgG positivity in a real-life setting.

METHODS: The retrospective analysis included 4795 patients consecutively tested between January 2003-March 2022. Medical records of patients with AchR-IgG positivity (antibody titer of =0.5 nmol/L) were reviewed to determine true vs false antibody positivity. AchR-IgG-positive patients with insufficient clinical information were excluded (n=84). Diagnostic performance was summarized with point specificity, positive predicted values and their 95% confidence intervals (CIs).

RESULTS: Of 362 AchR-IgG-positive patients included in the study, 50 (13.8%) were designated as false positives. Specificity and PPV were 98.9% (95% CI, 98.5-99.2) and 86.2% (95% CI, 82.2-89.6), respectively. Alternative diagnoses included ocular diseases (n=8), rheumatic diseases (n=7), pseudoptosis (n=5), myopathy (n=4), and others. Main reasons for antibody testing included isolated diplopia (n=18), nonspecific asthenia (n=16), isolated eyelid ptosis (6), or others. Compared to patients with true AchR-IgG positivity, false positive patients were younger (median age, 65 [range, 7-91] vs 38 [range, 5-80] years), more frequently female (155/312 [49.8%] vs 37/50 [74%]), and had a lower antibody titer (median, 6 [range, 0.5-28] vs 0.7 [range, 0.5-5.5] nmol/L). After stratification by AchR-IgG titers of =1 nmol/L, specificity and PPV increased to 99.8% (95% CI, 99.6-99.9) and 96.6% (95% CI, 94-98.3), respectively.

SUMMARY/CONCLUSION: Despite the high specificity of AchR-IgG testing by RIPA, the risk of false antibody positivity is not negligible in clinical practice (14% in this study). Caution is needed when low titer AchR-IgG positivity (0.5-0.9 nmo/L) is detected in patients with symptoms that are nonspecific for MG or explainable by more common alternative etiologies.

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GRO CHEMOKINES-INDUCED NEUTROPHIL EXTRACELLULAR TRAP CITH3 AS A NEW BIOMARKER RELATED TO MG SEVERITY

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INTRODUCTION: The role of innate immunity, particularly neutrophils, remains understudied in Myasthenia Gravis (MG) pathogenesis.

OBJECTIVE: To identify novel MG biomarkers through multi-omics screening.

METHODS: We performed eQTL GWAS analysis on 3273 proteins in Caucasian populations (3273 MG patients, 3301 controls), followed by validation in a Chinese Han population using ELISA and Luminex assays. Single-cell and bulk RNA sequencing analyses, flow cytometry, blood smear staining, and immunofluorescence were used to further investigate the ligand-receptor mechanism of candidate biomarkers.

RESULTS: Genetically elevated plasma GRO chemokine levels significantly correlated with increased MG risk in Caucasians ($p = 5.39e-06$). ELISA and Luminex multiplex protein assays confirmed significantly higher plasma GRO chemokines in Chinese Han MG patients than controls (100 patients and 40 healthy controls, $p < 0.0001$). Hemogram analysis and flow cytometry revealed elevated neutrophil counts and CXCR2 (GRO receptor) expression in MG patients (50 patients and 50 controls, $p < 0.0001$). Neutrophil single-cell ($n = 6$) and whole blood bulk RNA-seq ($n = 20$) analyses demonstrated prominent CXCR2-induced neutrophil extracellular traps (NETs) in MG, confirmed by blood smear staining and immunofluorescence. ELISA measurements showed elevated plasma CITH3, a major NETs component, in MG patients (49 patients, 73 controls, $p < 0.0001$), which strongly correlated with MG severity scales and GRO levels ($r > 0.4$, $p < 0.001$).

SUMMARY/CONCLUSION: CITH3 derived from neutrophil-death induced NETs emerges as a novel potential biomarker for MG severity.

DISCLOSURES: None

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EFGARTIGIMOD FOR INDUCTION AND MAINTENANCE THERAPY IN MUSCLE-SPECIFIC KINASE MYASTHENIA GRAVIS: A MULTI-CENTER STUDY

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INTRODUCTION: The efficacy of efgartigimod in treating myasthenia gravis (MG) patients with muscle-specific kinase (MuSK) antibodies has not been demonstrated in the clinical trial, existing case reports, or observational studies.

OBJECTIVE: To evaluate the efficacy and safety of efgartigimod combined with immunotherapies such as tacrolimus or B-cell depleting agents, as maintenance treatment for MuSK-MG patients.

METHODS: This retrospective study included 14 MuSK-MG patients treated with efgartigimod at 3 tertiary hospitals from 2023 to 2024.Data on Activities of Daily Living (ADL) scores, Quantitative Myasthenia Gravis (QMG) scores, and the time reaching minimal symptom expression (MSE) were collected. The combined use of steroids, immunosuppressants, and rescue therapies, as well as the adverse event incidence, were also recorded.

RESULTS: The mean age at first efgartigimod treatment was 55±18 years old with a median follow-up time of 28 weeks. From baseline to week 4, MG-ADL scores decreased significantly from 10.1±4.0 to 2.2±3.1 (n=14, p=0.001). The majority of patients (92.9%) maintain a reduction of at least 2 points for more than 8 weeks. The median time to achieve MSE was 4 weeks, with 71.4% (10/14) of patients reaching MSE by week 12. In patients receiving CD20 B cell depleting therapy or tacrolimus as maintenance, the time-weighted average dosage of prednisone was 16 mg while that in those with prednisone alone was 37 mg. Of all 14 patients, one developed an upper respiratory tract infection 4 weeks after rituximab and one was infected with herpes zoster virus 13 weeks after rituximab.

SUMMARY/CONCLUSION: A single-cycle efgartigimod as an induction therapy, combined with immunotherapies such as tacrolimus or B cell deplete agents, as maintenance treatment, could benefit MuSK-MG patients.

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RESPONSE TO SINGLE LOW-DOSE RITUXIMAB CAN PREDICT A BETTER OUTCOME OF MULTI-CYCLE TREATMENT IN REFRACTORY MYASTHENIA GRAVIS: A SINGLE-CENTER STUDY

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INTRODUCTION: No studies have been performed to compare the efficacy of subsequent multi-cycle low-dose rituximab (RTX) treatment in myasthenia gravis (MG) patients with or without response to a single cycle of RTX treatment.

OBJECTIVE: To assess the long-term clinical outcomes of MG patients treated with multi-cycle low-dose RTX.

METHODS: This retrospective cohort study with prospectively collected data involved 47 refractory patients who received low-dose RTX (500/600 mg every six months) in Huashan Hospital from 2016 to 2023. We divided them into a response group (n=30) and a non-response group(n=17) based on a decrease of >=3 points from baseline in Quantitative Myasthenia Gravis (QMG) score 6 months after the first RTX treatment. We compared the change of QMG and Activities of Daily Living (ADL) scores and the time to minimal symptom expression (MSE, i.e., ADL 0-1 score) between the two groups.

RESULTS: There were no significant differences in demographic and clinical characteristics at baseline. There were significant group×visit interactions for the QMG score and ADL score. Six months after the fourth rituximab treatment, QMG score was lower for the response group (-6.07; p=0.005;95%CI, -10.26 to -1.88) compared with the non-response group; the equivalent mean changes from baseline were -9.95(95%CI, -11.78 to -8.12) and -0.45(95%CI, -3.38 to 2.49), respectively. ADL score was lower for the response group (-2.84; p=0.006;95%CI, -4.83 to -0.852) compared with the non-response group; the equivalent mean changes from baseline were -5.40(95%CI, -6.74 to -4.05) and -1.99(95%CI, -4.18 to 0.21), respectively. The median time to MSE was shorter in the response group (6.5 months versus not available; HR:15.83; 95%CI,3.53-70.91; $p < 0.001$ after adjustment for sex, age, disease duration, baseline therapies, and disease severity).

SUMMARY/CONCLUSION: The improvement of QMG score and ADL score was greater in the response group compared with the non-response group. The response to single low-dose RTX can predict a better outcome of multi-cycle treatment in refractory MG.

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TREATMENT REFRACTORY LRP4-ANTIBODY POSITIVE MYASTHENIA GRAVIS RESPONSIVE TO EFGARTIGIMOD ALFA INFUSION

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INTRODUCTION: In MG, autoantibodies attack postsynaptic NMJ components, leading to muscle weakness. About 80% of MG cases are associated with antibodies against AChR. Antibodies against agrin/LRP4/MuSK pathway as another target in MG, with LRP4 antibody-positive patients showing more severe symptoms. FcRN inhibitors (e.g., Efgartigimod alfa) have been effective in AChR-positive MG by blocking IgG recycling, though their impact on LRP4-positive cases remains uncertain.

METHODS: Chart review.

RESULTS: A 66-year-old-female presents with weakness, dysarthria, dysphagia, diplopia, ptosis and dyspnea since 1989; initial work-up did not lead to definitive diagnosis but suspicious of seronegative myasthenia. The patient had repeated flares of worsened weakness and dyspnea, requiring frequent hospitalizations, and chronic outpatient non-invasive ventilation. She received various pharmacotherapies including IVIG, IV steroids, azathioprine and mycophenolate without significant improvement. In 2023, she re-established in neurology clinic following a flare and underwent repeat work-up. Lab-work was notable for positive LRP4 antibodies, with negative AChr, MuSK and VGCC antibodies. EMG/NCS showed mild sensory neuropathy. She re-started mycophenolate in 2023. In February 2024, her MG-ADL was 15. She was hospitalized, underwent PLEX, and prednisone was started, with improvement in symptoms. In August 2024, she underwent her first Efgartigimod alfa infusion cycle. During her September 2024 office visit, her MG-ADL was 5, and she reported improved strength and speech, and less time on NIV during daytime hours. Since initiating Efgartigimod alfa, she has not required hospitalization, her symptoms have remained well controlled, with plan to taper her prednisone soon.

SUMMARY: LRP4-antibody positive MG makes up an exceptionally small percentage of MG cases. Accordingly, there is a dearth of evidence to demonstrate efficacy of new FcRN inhibitors in the treatment of LRP4 patients. This case points towards Efgartigimod alfa potentially being effective as a steroid-sparing treatment of LRP4 MG, however data on a greater number of patients is needed.