What Is Next in Myasthenia Gravis? Insights on Ocular and MuSK Forms from AAN 2025

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Citation:	Neurol AMJ. 2025;2[1]:30-33 https://doi.org/10.33590/neurolamj/SDSW2308

THE 2025 American Academy of Neurology (AAN) Annual Meeting saw experts in the field travel to San Diego, California, for the field's latest insights. Attendees were presented with these updates in the form of fascinating abstracts, captivating presentation sessions, and exciting discussions around the future of neurology. One of these talks, entitled "Neuromuscular junction disorders: myasthenia gravis, ocular, and MuSK myasthenia", and expertly chaired by Neelam Goyal, Stanford University, California, detailed many aspects of myasthenia gravis (MG), ranging from the current standard-of-care to treatments of the future.

RETHINKING THE FOUNDATIONS OF MYASTHENIA GRAVIS: WHEN TO TREAT, HOW TO TREAT, AND WHY IT MATTERS

Stephen Reddel, University of Sydney, Australia, opened the session by reframing the treatment landscape of MG, emphasizing that: "It's a bad disease, but also a treatable disease," and often dramatically so. He argued strongly for early intervention to avoid unnecessary disability. "Why make people live with disability rather than treat it as early as possible?" he asked, reflecting a key message from his talk: timely therapy can transform lives.

Reddel alluded to the privilege of travelling from Australia to present his talk; a reflection on the privilege afforded by the Australian healthcare system. In Australia, where there is broad access to immunotherapies under a single-payer system, Reddel described a flexible treatment paradigm, where there is no mandated drug sequence, allowing clinicians to tailor treatment to disease severity and patient preference across different stages. This pragmatic flexibility allows for the use of both traditional therapies, such as corticosteroids and azathioprine, as well as newer immunomodulators and biologics.

PATHOPHYSIOLOGY OF MYASTHENIA GRAVIS

One of the central themes of Reddel's talk was the pathophysiological underpinnings of MG, particularly acetylcholine receptor (AChR)-positive disease. He began his discussion with a figure of normal mouse neuromuscular junctions (NMJ) in the background, remarking that: "They're really pretty things," which is testament to his passion for the field. He continued with a brief explanation of the classic synapse and the tests that are currently available for MG. Importantly, Reddel challenged the conventional dogma that AChR antibody levels do not correlate with disease severity. Citing a 23-year longitudinal case study, he showed that antibody titres, when carefully tracked over time, can correlate with clinical

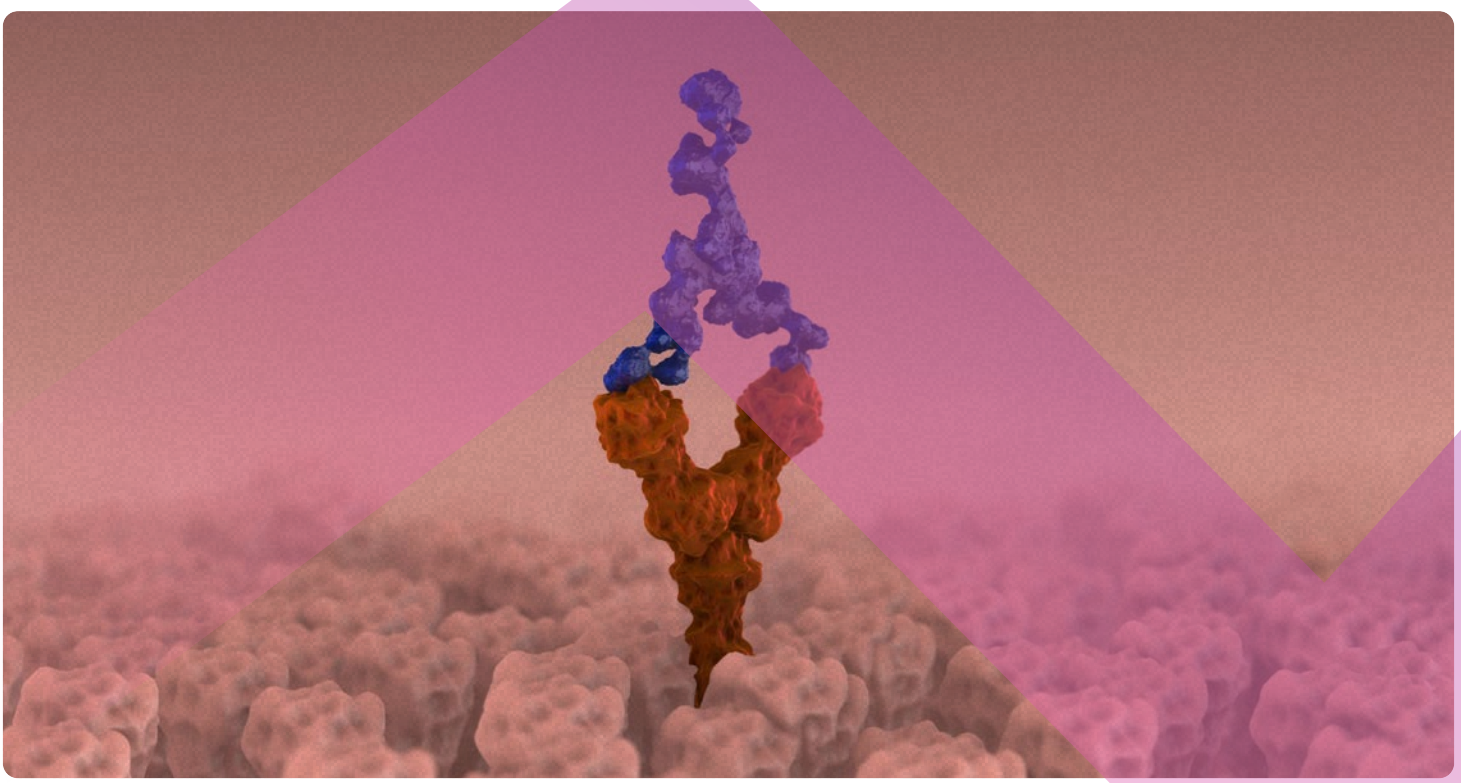
fluctuation; a valuable point for those managing complex cases in the long term.

After detailing the strategy for the clinical management of MG, he continued by explaining the four pathogenic antibody mechanisms in MG: receptor blockade, complement activation, receptor internalization, and antibody-dependent cellular cytotoxicity. He noted that treatments, must be matched to mechanism accordingly. Reddel presented a structured approach to MG therapy, ranging from the perhaps underutilised thymectomy, to targeted B cell depletion (e.g., rituximab in muscle-specific kinase [MuSK] MG) and upstream agents targeting BAFF/APRIL and CD19. He stressed that: "The critical issue that people get wrong is the time-to-treatment onset of the therapies," while explaining the time-to-treatment onset of the available therapeutic options.

He stressed that while some treatments like corticosteroids are widely available and effective, they come with well-established long-term toxicities. "The toxicity is horrendous," he expained, which he underscored with sobering epidemiological data. For upstream therapies like azathioprine or mycophenolate, he emphasized realistic timelines: no clinical benefit before 12–15 months. Hence, bridging agents or more rapid-acting therapies (e.g., intravenous immunoglobulin [IVIG], plasma exchange [PLEX], and calcineurin inhibitors) may be needed in patients with significant disease burden.

OCULAR AND MuSK MYASTHENIA GRAVIS DIAGNOSIS AND TREATMENT

On ocular MG, he advocated for careful diagnostic scrutiny, especially in seronegative cases. Treating early with corticosteroids may reduce generalization, but overtreatment carries its own risks. As for MuSK MG, he emphasized its distinct phenotype; bulbar features, poor steroid response, and excellent response to PLEX or rituximab; and highlighted emerging challenges in combining therapies like anti-neonatal Fc receptors (FcRn) with B cell depleting agents.



> **The critical issue that people get wrong is the time-to-treatment onset of the therapies**

He closed with a poignant case of a patient who recovered from a ventilator-dependent state that began in their 20s, including being on a ventilator at home for an extended period. He mentioned that this must have been traumatic, and described the patient's slow journey into remission, leaving the audience to ponder his take home message: MG is a plastic but manageable disease.

TARGETING THE IMMUNE CASCADE: COMPLEMENT BLOCKADE AND NEONATAL Fc RECEPTOR INHIBITION

Francesco Saccà, Federico II University of Naples, Italy, followed with an in-depth look at the immunological mechanisms that are now shaping the next generation of MG therapies. He reflected on how far the field has come since his medical training, when AChR blockade was the only described mechanism. Today, complement activation and FcRn pathways are known to be central drivers of pathology, and thus prime therapeutic targets.

Saccà structured his talk around two major downstream strategies: complement inhibition and IgG reduction via FcRn inhibition. He began with a clear primer on the complement cascade, outlining how antibody–antigen complexes (such as those in AChR-positive MG) activate the classical pathway, ultimately damaging the NMJ. Blocking C5 with agents like eculizumab and ravulizumab halts this cascade. Ravulizumab, a long-acting C5 inhibitor requiring only bimonthly infusion, has demonstrated durable benefits in clinical trials such as CHAMPION-MG,[1] including rapid Quantitative Myasthenia Gravis (QMG) score improvement and long-term reduction in corticosteroid use.

Further innovations, including zilucoplan, a subcutaneous macrocyclic peptide, offer promising dual-action complement inhibition with the potential for home-based administration and compatibility with other therapies like IVIG and anti-FcRn.

ANTI-NEONATAL Fc RECEPTORS

Following his discussion of complement inhibition, Saccà shifted focus to another promising strategy: FcRn inhibition, describing it as: "An entire new chapter in therapy." FcRn normally rescues IgG from lysosomal degradation, giving them a long half-life. Drugs like efgartigimod, rozanolixizumab, nipocalimab, and batoclimab disrupt this process, lowering circulating IgG (including pathogenic autoantibodies) by up to around 80%. Unlike complement inhibitors, some anti-FcRn (efgartigimod and rozanolixizumab) are given cyclically, and show a pattern of clinical improvement followed by deterioration between treatment cycles, a feature absent in continuously administered agents.

Real-world data comparing complement inhibitors to anti-FcRn was another highlight of Saccà's presentation. A retrospective Italian study showed both were effective in improving MG-Activities of Daily Living, but complement inhibitors achieved deeper QMG improvements and greater steroid reduction.[2] Similarly, U.S. data from electronic medical records showed faster and more substantial corticosteroid tapering with C5 inhibitors compared to efgartigimod.[3] However, Saccà also presented a German cohort where outcomes between the two strategies were more closely matched, emphasizing that clinical context and patient-specific factors remain key.[4]

In summarizing, Saccà evaluated the differences between the two approaches. The effect of complement inhibitors results in complete complement blockade, whereas anti-FcRn can only reduce IgG by 60–70%. The administration of C5 inhibitors is continuous, whereas anti-FcRn are administered both cyclically (in the

case of efgartigimod and rozanolixizumab) or continuously (with nipocatimab and satoclimab). He briefly mentioned how intercycle fluctuations are not seen for complement inhibitors but are seen with cyclically administered anti-FcRNs. When describing the steroid-sparing effect, he noted that the effects are reported in open-label extension trials for complement inhibitors, and observed to be greater for complement inhibitors in many real-world evidence studies. For anti-FcRns, effect is not reported in open-label extension trials, yet is seen to be lower in many real-world evidence studies, but not all of them.[4] He concluded with the safety considerations for complement inhibitors, including meningococcal infections and the need for vaccinations, and anti-FcRNs, including bacterial infections of the respiratory or urinary tract.

Looking to the future, Saccà hinted at even more upstream immunomodulation, including agents targeting C1 and early components of the immune cascade. These therapies may balance efficacy with safety by preserving alternative immune pathways.

CONCLUDING THOUGHTS

This two-part session offered both a grounded clinical approach and a visionary outlook on MG management. Reddel's practical treatment strategies and pathophysiological insights were the ideal prelude to Saccà's discussion of precision immunotherapies. Together, they made one point abundantly clear: MG is no longer a disease of therapeutic despair. With smart strategy and evolving tools, clinicians can now aim not just for symptom control, but for remission, and perhaps one day, a cure.

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