gMG AWARENESS ADVANCES ACTION

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CLINICAL PRACTICE AID:

MYASTHENIA GRAVIS THERAPY DATA DIGEST

This clinical digest offers a curated overview of emerging therapies for generalized myasthenia gravis (gMG), designed to aid your clinical decisions. As the treatment landscape of myasthenia gravis (MG) evolves, it can be challenging to keep up with data spread across multiple trials and journals. This resource consolidates key efficacy and safety results from pivotal studies − along with links to primary publications − to support practical, real-time application in the clinic.

In this digest, you will find:

- Clear summaries of clinical trial data on **neonatal Fc receptor (FcRn) antagonists, complement inhibitors,** and **emerging B- and T-cell-targeted therapies**
- Comparative insights on **efficacy, time to response, and durability of benefit**
- Safety and tolerability profiles, with specific considerations for diverse patient populations
- A section on ongoing and upcoming trials that may influence future clinical pathways

This resource is designed to give you high-yield, accessible information to support timely and personalized care decisions − whether you are optimizing care for a newly diagnosed patient or reassessing options for a patient with refractory disease.

For guidance on patient-centered consultations in gMG care, please refer to the Myasthenia Gravis Care Companion.

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Serotype characteristics of MG

gMG results from autoantibodies that disrupt neuromuscular transmission by targeting key components of the postsynaptic membrane. Characterized by symptoms of fatigable muscle weakness presenting as ptosis, diplopia, dysphagia, dysarthria, limb weakness, and respiratory failure, it is a chronic condition notable for fluctuation in symptoms, which can range from mild and manageable overall to severe and life-threatening, such as in myasthenic crisis.[1] The majority of patients − approximately 80% − have antibodies directed against the acetylcholine receptor (AChR).[2-3] A smaller subset produces antibodies against muscle-specific kinase (MuSK) or low-density lipoprotein receptor-related protein 4 (LRP4).[1-5] While anti-LRP4 antibodies are less specific for MG than those against AChR or MuSK, their clinical relevance continues to be defined. In 10–15% of cases, particularly in patients with gMG, autoantibodies are not detectable (seronegative) − often due to limitations in assay sensitivity − and in these cases, the diagnosis is based on the typical clinical presentation and evidence of a neuromuscular transmission defect on electrodiagnostic testing.[6-7] MG is typically subclassified based on clinical features, age of onset, serologic findings, and thymic pathology.[1]

Key considerations in individualizing treatment for gMG

A primary treatment goal in gMG is to achieve the status of disease remission, meaning that the patient is free of symptoms, or to achieve a status of minimal manifestation, characterized by no functionally limiting signs or symptoms of disease and minimal treatment-related side effects.[8] Many different factors must be taken into consideration in the management of gMG for an individual patient. One of these factors includes the patient's antibody status, as some therapies may be approved only for patients who are positive for AChR antibodies. The table below provides an overview of additional factors to consider when developing a personalized treatment plan in collaboration with your patients.[9]

Treatment planning	Factors to consider
Disease impact	Disease burden ▶ Antibody status ▶ Severity of disease ▶ Rate of progression ▶ Comorbidities ▶ Duration of time since thymectomy ▶ Functional limitations
Treatment burden	▶ Duration of illness ▶ Medications tried previously ▶ Administration route and frequency ▶ Concurrent medications ▶ Plans for childbearing ▶ Potential side effects
Economic burden	▶ Cost ▶ Accessibility ▶ Patient preference

Current standards in established treatment

Well-established treatment options for gMG include pyridostigmine (an acetylcholinesterase inhibitor) and corticosteroids. To help avoid complications of long-term steroid use, many patients are started on a steroid-sparing agent for gMG, such as azathioprine, mycophenolate mofetil, tacrolimus, cyclosporine, or methotrexate. These traditional therapies form the backbone of current guidelines, which are outlined in the publication *International Consensus Guidance for the Management of Myasthenia Gravis*, published in 2016 and updated in 2020.[8,10]

Aside from pharmacologic therapy, thymectomy may also be helpful both early in the disease course to improve outcomes and later in patients who have not responded optimally to pharmacologic treatments. Thymectomy is indicated in patients with non-thymomatous, AChR-antibody-positive gMG and may be considered in patients with gMG without detectable AChR antibodies if they do not respond to immunosuppressive therapy; however, there is no strong evidence to support its use in patients with MuSK or LRP4 antibodies.

Age remains an important consideration. The 2020 International Consensus Guidance recommends thymectomy in patients aged 18−50; however, age 50 should not be viewed as an absolute cutoff, especially in cases involving refractory disease or thymoma, where selected patients over age 50 may still benefit from surgery.[10,11]

Myasthenia gravis treatments

Medications[8,10]	
Acetylcholinesterase inhibitors	Pyridostigmine
Corticosteroids and other immunosuppressants	Corticosteroids ▶ Prednisone ▶ Prednisolone Steroid-sparing agents ▶ Azathioprine ▶ Mycophenolate mofetil ▶ Tacrolimus ▶ Cyclosporine ▶ Methotrexate
Plasma exchange and immunoglobulin treatment	
Intravenous immunoglobulin and plasma exchange	▶ May be used as treatment for myasthenic crisis or, in rare cases, as maintenance therapy
Surgery	
Thymectomy	▶ Indicated in patients with non-thymomatous, AChR-antibody-positive gMG ▶ May be considered in patients with seronegative gMG if they do not respond to immunosuppressive therapy ▶ No evidence to support its use in patients with MuSK or LRP4 antibodies[10,11]

AChR=acetylcholine receptor; gMG=generalized myasthenia gravis; LRP4=low-density lipoprotein receptor-related protein 4; MuSK muscle-specific tyrosine kinase.

The primary treatment goal in gMG is to achieve remission or minimal manifestation with no functional limitations and low treatment toxicity.

New and emerging therapies

In recent years, numerous new therapies have emerged for the treatment of MG, providing more options for patients and clinicians navigating this condition. New treatment options are greatly needed due to side effects of existing therapies and to manage refractory symptoms in patients with challenging disease profiles.

FcRn antagonists

Efgartigimod alfa is an antibody fragment that inhibits the FcRn, thereby reducing levels of immunoglobulin G (IgG) autoantibodies. Efgartigimod alfa is available in intravenous (IV) and subcutaneous infusion formulations, and it is approved for gMG in patients with AChR-antibody-positive disease. Data from the Phase 3 ADAPT trial demonstrated that efgartigimod alfa was effective and well tolerated compared to placebo and offered an advantage of more individualized dosing, as repeat dosing is flexible and may vary depending on the patient's clinical response.[12] Efgartigimod alfa benefits typically last 4–12 weeks, and it has been reported to be associated with significant reduction in steroid doses.[13]

Rozanolixizumab is a FcRn humanized monoclonal antibody administered as subcutaneous infusion. Clinical trial data suggest that it is generally well tolerated, and treatment yielded meaningful clinical improvement in the MycarinG placebo-controlled trial.[14,15] **Nipocalimab** is another FcRn monoclonal antibody, which has demonstrated efficacy in gMG and is administered as IV infusion.[16,17] Rozanolixizumab and nipocalimab are unique among the new therapies in that they are approved for the treatment of both AChR-antibody-positive and MuSK-antibody-positive gMG.

Complement inhibitors

Eculizumab is a humanized monoclonal antibody that inhibits complement protein C5. In the US, it is approved for the treatment of AChR-antibody-positive gMG in adult and pediatric patients and available as an IV infusion.[18] In the EU, its indication extends to both adults and children aged 6–17 years with AChR-antibody-positive gMG, including those with refractory disease.[19,20] In the Phase 3 REGAIN study, the primary analysis for Myasthenia Gravis Activities of Daily Living Scale (MG-ADL) change did not show a significant difference compared to placebo; however, subgroup analyses and open-label extension demonstrated long-term efficacy.[21-23]

Ravulizumab is a long-acting monoclonal antibody that, like eculizumab, inhibits complement protein C5 and is administered by IV infusion. In the CHAMPION trial, ravulizumab has similarly shown sustained improvement in patient outcomes for patients with AChR-antibody-positive gMG.[24,25] Of note, both eculizumab and ravulizumab, while generally well tolerated, may confer an increased risk of meningococcal meningitis, and all patients considering these treatments must be administered the meningococcal meningitis vaccinations and be educated on the signs and symptoms of meningitis.[26]

Most recently, **zilucoplan** was approved for patients with AChR-antibody-positive gMG, offering a different route of administration with daily, self-administered subcutaneous injection. The RAISE study of zilucoplan showed a good safety profile and sustained responses in patients over the long-term, open-label extension study.[27-29] Of note, patients who entered the open-label extension study were also found to have reduction in fatigue, a multifactorial but common and debilitating symptom in gMG.[30] As another inhibitor of complement protein C5, zilucoplan also poses an increased risk of meningitis, and all patients embarking on treatment are required to be vaccinated.

Complement inhibitors are generally well tolerated; however, they carry an elevated risk of meningococcal infection. You must ensure that patients receive appropriate meningococcal vaccinations prior to initiating therapy and are thoroughly counseled on recognizing the early signs and symptoms of meningitis. Those on long-term complement treatment will require regular revaccination booster doses, as per Advisory Committee on Immunization Practices (ACIP) guidelines, for continued protection.[26]

B-cell-targeted therapies

Studies examining the effect of rituximab in patients with gMG with AChR antibodies have shown mixed results. The BeatMG study suggested a low probability of having a clinically meaningful steroid-sparing effect.[31] However, the RINOMAX study suggested some benefit in this population, with greater probability of minimal gMG manifestations and reduced need for rescue medications.[32] In patients with MuSK antibodies, however, rituximab is often considered early in the disease course, due to data from observational studies and meta-analyses that demonstrate a long-lasting benefit in this patient population.[33,34]

New therapeutic options in gMG

New therapies in gMG target the FcRn, complement system, and B-cell depletion, providing treatments with novel mechanisms of action and a wider range of treatment options for patients.

Medication	Mechanism of action	Patient population	Route of administration & dosages	Side effects
Eculizumab (Soliris®)[18]	C5 complement inhibitor	AChR-antibody-positive gMG	IV infusion; induction at 900 mg/week for weeks 1–4, then 1,200 mg every 2 weeks	Headache, URI, myalgias, increased risk of meningitis (vaccination required)
Ravulizumab-cwvz (Ultomiris®)[35]	Long-acting C5 complement inhibitor	AChR-antibody-positive gMG	IV infusion; 2,400–3,000 mg loading dose, then 3,000–3,600 mg (weight based) every 8 weeks	Headaches, URI, myalgias, increased risk of meningitis (vaccination required)

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Medication	Mechanism of action	Patient population	Route of administration & dosages	Side effects
Zilucoplan (Zilbrysq®)[36]	C5 complement inhibitor	AChR-antibody-positive gMG	Subcutaneous injection of a fixed, weight-based dose; self-administered once per day	Injection site reaction, URI, diarrhea, pancreatitis, increased risk of meningitis (vaccination required)
Efgartigimod alfa-fcab (Vyvgart®), Efgartigimod alfa and hyaluronidase-qvfcas (Vyvgart Hytrulo®)[37,38]	FcRn inhibitor	AChR-antibody-positive gMG	IV infusion 10 mg/kg weekly or subcutaneous infusion at a fixed dose of 1,008 mg/11,200 units weekly; given for 4 consecutive weeks; repeat cycles based on clinical response	Headache, urinary or respiratory infection, pancytopenia
Rozanolixizumab-noli (Rystiggo®)[39]	FcRn blocker	AChR-antibody-positive gMG and MuSK-antibody-positive gMG	Subcutaneous infusion of a weight-based dose every week for 6 weeks; repeat cycles based on clinical response	Headache, infection, diarrhea, hypersensitivity reaction
Nipocalimab-aahu (Imaavy™)[40]	FcRn blocker	AChR-antibody-positive gMG and MUSK-antibody-positive gMG	IV infusion of a 30 mg/kg loading dose is given once, followed by a maintenance dose of 15 mg/kg IV given every 2 weeks thereafter	Respiratory tract infection, muscle spasms, peripheral edema
Rituximab (Rituxan®)*[,41]	B-cell depletor	AChR-antibody-positive gMG and MuSK-antibody-positive gMG	IV infusion with variable dosing regimens proposed	Bone marrow suppression, infusion reaction, rarely PML

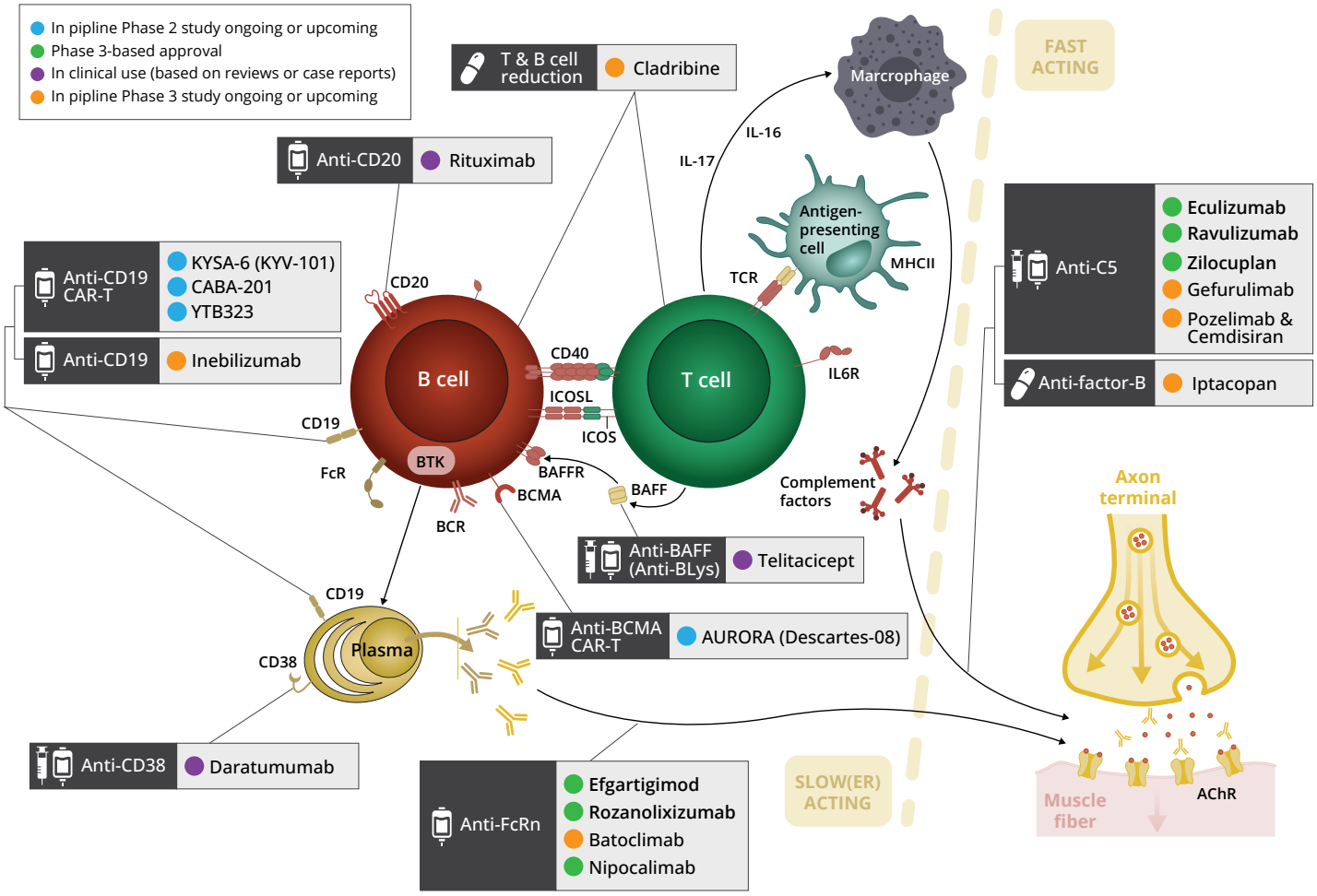
*Off-label use.

AChR=acetylcholine receptor; FcRn=neonatal Fc receptor; gMG=generalized myasthenia gravis; IV=intravenous; MuSK=muscle-specific tyrosine kinase; PML=progressive multifocal leukoencephalopathy; URI=upper respiratory infection.

Future directions

With these new, expanded treatment options comes the prospect of more individualized care for patients across the gMG symptom spectrum.[42] Newer therapies offer more options for patients with refractory symptoms and comorbidities that limit their use of more established therapies. Furthermore, these newer treatments may offer more targeted therapeutic mechanisms, more rapid onset of action, and more favorable side effect profiles. However, questions remain regarding how these therapies will ultimately fit into the overall framework for the management of gMG and whether these medications will replace older, established therapies or perhaps demonstrate even more efficacy as part of combination regimens that capitalize on different mechanisms of action. Further questions remain regarding the long-term efficacy and safety over time, whether new studies or additional data may someday support extension of use of these therapies in patients with ocular MG and seronegative disease, and whether any of these treatments may be beneficial in the setting of a myasthenic crisis. Still more potential treatments for gMG are in the pipeline, with a particular focus on research trials of FcRn inhibitors, complement inhibitors, and B-cell depletors.[43] There is also a research focus on development of chimeric antigen receptor T-cell (CAR-T) therapy and hematopoietic stem cell transplant for MG.[44]

New and Emerging Therapies[42-48]



Adapted from Gerischer L, et al. *BioDrugs*. 2025;39:185-213 (CC BY-NC 4.0).

Abbreviations

AChR: acetylcholine receptor
ACIP: Advisory Committee on Immunization Practices
CAR-T: chimeric antigen receptor T-cell
FcRn: neonatal Fc receptor
gMG: generalized myasthenia gravis
IgG: immunoglobulin G
IV: intravenous
LRP4: low-density lipoprotein receptor-related protein 4
MG: myasthenia gravis
MG-ADL: Myasthenia Gravis Activities of Daily Living
MuSK: muscle-specific receptor tyrosine kinase

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