Sains Medika: Jurnal Kedokteran dan Kesehatan

journal homepage: http://jurnal.unissula.ac.id/index.php/sainsmedika/

LITERATURE REVIEW

Immunotherapy as an alternative therapy for myasthenia gravis

Meyvita Silviana[1*], Endang Kustiowati[2]

[1]Department of Neurology, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, Indonesia
[2]Department of Neurology, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia

ARTICLE INFO

Keywords:
Myasthenia gravis
Acetylcholinesterase
Acetylcholine receptor
Immunotherapy

ABSTRACT

Myasthenia gravis is an autoimmune disorder characterised by fluctuating, progressive weakness of skeletal muscles and activity-related fatigability. It most commonly affects young women and older men. The disease results from dysfunction at the neuromuscular junction involving acetylcholine signalling and calcium ions. Autoantibodies directed against the nicotinic acetylcholine receptor (AChR) are the principal cause of muscle weakness in many patients with myasthenia gravis. Frequently affected muscles include those controlling eye movements and eyelid elevation, chewing, swallowing, coughing, and facial expression; proximal limb and neck muscles, as well as respiratory muscles, may also be involved. Clinically, patients experience variable skeletal muscle weakness that worsens with exertion and improves with rest. Typical initial symptoms include diplopia, ptosis, dysphagia with recurrent aspiration, and difficulty chewing. Diagnostic investigations commonly used to establish the diagnosis include assays for anti-acetylcholine receptor antibodies and imaging such as chest radiography and MRI. Standard treatments comprise acetylcholinesterase inhibitors, corticosteroids, other immunosuppressive agents, and thymectomy. This review focuses on the pathophysiology of myasthenia gravis and current management strategies, with particular emphasis on immunotherapies that target components of the immune system.

1. Introduction

Myasthenia gravis (MG) is a chronic autoimmune disorder of neuromuscular transmission characterised by muscle weakness. Any skeletal muscle may be affected, but those controlling eye movements, eyelid elevation, chewing, swallowing, coughing, and facial expression are most involved. Proximal limb muscles (shoulders and hips), neck muscles, axial muscles, and respiratory muscles may also be affected. MG is characterized by fatigability, rapid loss of strength with activity that improves after rest (Mantegazza & Cavalcante, 2019; Guidon & Juel, 2025).

The relationships among antibody concentration, specificity, and function and the clinical manifestations of MG have been extensively studied, and the mechanisms by which anti-AChR antibodies impair neuromuscular transmission have been further elucidated (Guidon & Juel, 2025). Treatment of MG aims to control symptoms and disease activity while minimising adverse effects. Mainstays of therapy include pyridostigmine, corticosteroids, and other immunosuppressive agents. Rapid reduction of pathogenic antibodies by plasma exchange or intravenous immunoglobulin (IVIg) is employed in myasthenic crises and during severe exacerbations (Rodolico *et al.,* 2021).

Although many therapies for MG have demonstrated benefit, immunomodulatory and immunosuppressive approaches remain central to achieving favourable outcomes. Notably, several

https://doi.org/10.30659/sainsmed.v16i2.28256
Received: 26 July 2025 | **Revised:** 18 November 2025 | **Accepted:** 25 November 2025 | **Available Online:** 16 December 2025

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effective treatments were introduced before the underlying immunopathogenesis was fully understood (Guidon & Juel, 2025).

More recently, MG treatment has increasingly targeted specific immune-pathogenic mechanisms, with new therapeutics directed at B cells, proinflammatory cytokines and their receptors, the complement cascade, and the neonatal Fc receptor (FcRn) (Rodolico *et al.,* 2021). This article reviews MG and its management, with particular focus on immunotherapies targeting components of the immune system.

2. Definition

Myasthenia gravis is an autoimmune disorder characterised by progressive weakness of skeletal muscles used in continuous activity, accompanied by activity-induced fatigability (Murray *et al.,* 2010). The disease results from impaired synaptic transmission at the neuromuscular junction (Sukockienė *et al.,* 2024; Murray *et al.,* 2010).

3. Epidemiology

Myasthenia gravis is a rare, nonhereditary disease and is not contagious. The incidence is approximately 5–10 cases per million population per year. Onset before age 40 is more common in women (about 70%); onset after age 40 predominates in men (about 60%). This pattern is often summarised as myasthenia gravis being a disease of young women and older men. When MG is associated with thymoma, no clear age or sex predilection is observed. Neonatal myasthenia can occur when a fetus acquires maternal antibodies from a mother with MG; these cases are usually transient, with symptoms resolving within weeks after birth. Rarely, MG can occur in more than one family member (Guidon & Juel, 2025).

4. Pathophysiology

Immune mechanisms are central to MG pathophysiology. Clinical associations with other autoimmune diseases (for example, autoimmune thyroiditis, systemic lupus erythematosus, and rheumatoid arthritis) support an autoimmune basis (Skeie *et al.,* 2010).

Since the 1960s, autoantibodies in the sera of patients with MG have been shown to target muscle membrane components, thereby contributing to muscle weakness. Antibodies directed against the nicotinic acetylcholine receptor (anti-AChR) are a major pathogenic factor; anti-AChR antibodies are detected in approximately 90% of patients with acquired generalised MG (Skeie *et al.,* 2010).

The mechanisms underlying loss of tolerance to AChR are not fully understood. MG is largely a B–cell–mediated disease: pathogenic antibodies produced by B cells target AChRs. T cells also contribute; thymic abnormalities (hyperplasia or thymoma) are common in patients with myasthenic symptoms, reflecting the thymus's role in T-cell–mediated immunity (Guidon & Juel, 2025; Skeie *et al.,* 2010).

AChR autoantibodies are mainly IgG subclasses (IgG AChR autoantibodies are mainly IgG subclasses (IgG1 and IgG3). Some antibodies bind to the main immunogenic region on the alpha subunit—the acetylcholine-binding site—thereby interfering directly with receptor function. Antibody binding impairs neuromuscular transmission by multiple mechanisms: cross-linking AChRs and promoting their internalisation and degradation, reducing receptor density at the postsynaptic membrane; activating the classical complement cascade with formation of membrane attack complexes (MACs), which damage the postsynaptic membrane; and thereby reducing endplate potential (EPP) and miniature EPP (mEPP). Complement-mediated injury also reduces voltage-gated sodium channel density, thereby raising the threshold EPP that must be reached to trigger a muscle action potential (Skeie *et al.,* 2010; Phillips and Vincent, 2016).

Variability in muscle weakness among patients and among different muscles within the same patient reflects several factors: the rate of antibody diffusion from serum into individual synaptic clefts, the number of AChRs that must be targeted before transmission fails, local compensatory mechanisms at the neuromuscular junction, and levels of tissue complement regulators that modulate the extent of complement-mediated injury. These variations help explain the characteristic fluctuation and fatigability of MG (Phillips and Vincent, 2016).

5. Clinical Manifestations

Myasthenia gravis is characterised by fluctuating skeletal muscle weakness that worsens with activity and improves with rest (Murray *et al.,* 2010). Common clinical features include:

- Extraocular muscle weakness and ptosis. Ptosis is a frequent presenting complaint. Although the levator palpebrae may be clearly weakened, ocular motility can be variably affected (Murray *et al.,* 2010; Snell, 2011).
- Progression and distribution of weakness. Weakness often spreads from ocular and facial muscles to the neck and limb muscles over time (Murray *et al.,* 2010).
- Bulbar involvement. Weakness of the masseter, pharyngeal, tongue, soft palate, and laryngeal

muscles can cause difficulty closing the mouth, dysphagia, dysarthria, nasal speech, and risk of aspiration (Murray *et al.,* 2010).

Two life-threatening presentations that may cause acute respiratory failure are myasthenic crisis and cholinergic crisis. Both present with severe generalised weakness and may require ventilatory support, but their mechanisms and management differ fundamentally:

- **Myasthenic crisis** results from insufficient effective neuromuscular transmission due to worsening autoimmune activity, with too few functional acetylcholine receptors activated at the neuromuscular junction. This produces marked respiratory and bulbar weakness with dyspnea, weak cough, dysphagia, and aspiration risk. Common triggers include infection, surgery, physiological stress, pregnancy, or medications that impair neuromuscular transmission (e.g., aminoglycosides, magnesium). Muscarinic autonomic signs are typically absent, and pupils are usually normal.
- **Cholinergic crisis** caused by excessive acetylcholine, usually from overdosage of acetylcholinesterase inhibitors (for example, pyridostigmine). Excess ACh initially overstimulates receptors and can produce a depolarisation block, resulting in weakness that mimics myasthenic deterioration. Prominent muscarinic features—excess salivation, lacrimation, sweating, diarrhoea, abdominal cramping, bronchial secretions, bronchospasm, bradycardia, and miosis—are typical.

Clinical differentiation and management:

Bedside differentiation relies on the presence of muscarinic signs: worsening weakness without increased secretions (especially after infection) favours myasthenic crisis; weakness with drooling, sweating, diarrhoea, and constricted pupils suggests cholinergic crisis. Edrophonium testing was historically used but is now rarely performed; diagnosis generally depends on clinical context and medication history.

Management differs critically. Myasthenic crisis often requires intubation and ventilatory support and is treated with immunomodulation (IVIG or plasma exchange) while optimising long-term immunotherapy; acetylcholinesterase inhibitors are typically withheld during intubation. In a cholinergic crisis, acetylcholinesterase inhibitors should be discontinued immediately, and atropine should be administered for muscarinic blockade; ventilatory support may be required, but immunotherapy is not an appropriate acute treatment.

In summary, both crises can cause respiratory failure, but myasthenic crisis reflects insufficient effective neuromuscular transmission, whereas cholinergic crisis reflects excessive cholinergic activity with prominent autonomic features; accurate distinction is essential because treatments are antagonistic.

6. Diagnosis

Clinical pharmacologic testing

- Edrophonium (Tensilon) test: Edrophonium chloride is administered intravenously, typically starting with 1 mg (0.1 mL). If no improvement in muscle strength is observed within ~45 seconds, incremental doses of 3–6 mg IV may be administered; if necessary, additional 3–5 mg doses may be given. Total doses up to 10 mg are rarely required, as most patients improve after 3–5 mg. Muscarinic side effects (nausea, vomiting, increased gastrointestinal activity, sweating, salivation) may occur and can be antagonised by subcutaneous atropine (0.8 mg).
- Neostigmine testing: Because neostigmine has a longer duration of action than edrophonium, it is often used as an alternative. Neostigmine methylsulfate 1.5 mg IM produces objective and subjective improvement within 10–15 minutes, peaks at ~20 minutes, and typically wears off by ~1 hour.

Workup (Murray *et al.,* 2010; Snell, 2011)

(1) Laboratory tests

- Anti-acetylcholine receptor (anti-AChR) antibodies: Positive in ~74% of all patients; positive in ~80% of patients with generalised MG and ~50% of patients with purely ocular MG. False positives may occur in patients with thymoma who do not have clinical MG.
- Antistriated muscle (anti-SM) antibodies: Important in the context of thymoma; positive in ~84% of thymoma patients <40 years. Anti-SM antibodies may also be seen in older non-thymoma patients.
- Anti–muscle-specific kinase (MuSK) antibodies: Detected in nearly 50% of patients who are seronegative for anti-AChR antibodies.
- Antistriational antibodies (titin/RyR): Some MG sera contain antibodies that bind cross-striational patterns in skeletal and cardiac muscle, directed against titin and ryanodine receptor (RyR) epitopes. These

antibodies are strongly associated with thymoma in younger MG patients and their presence raises suspicion for thymoma.

(2) Imaging

- Chest radiography: AP and lateral views may identify a thymoma as an anterior mediastinal mass.
- Chest CT: A negative chest X-ray does not exclude a small thymoma; chest CT is often required, especially in older patients or when suspicion is high.
- Brain and orbit MRI: Not routine for MG diagnosis; reserved for cases in which the diagnosis is unclear after standard testing or to evaluate alternative causes of ocular or cranial nerve deficits.

(3) Electrodiagnostic studies

- Nerve conduction studies with repetitive nerve stimulation
  Myasthenia is characterised by a rapid decrement in compound muscle action potential amplitude with low-frequency repetitive stimulation (typically 3 Hz). The decremental response typically improves after neostigmine or edrophonium. Decrement may be seen in facial, hand, or proximal limb muscles and must be distinguished from post-tetanic potentiation or post-activation fatigue.
- Single-fibre electromyography (SFEMG)
  Using a single-fibre electrode, SFEMG detects increased jitter (variability in interpotential intervals between muscle fibres of the same motor unit) and may show increased fibre density. SFEMG is the most sensitive electrodiagnostic test for detecting impaired neuromuscular transmission.

7. Management

a. Anticholinesterase

Dosage and dosing frequency vary by patient. According to Drachman, the maximum therapeutic dose of pyridostigmine is 120 mg every 3 hours. If clinical response is inadequate and escalation fails to improve symptoms, consider the risk of cholinergic crisis—worsening weakness with muscarinic adverse effects (nausea, vomiting, abdominal cramping, sweating, hypersalivation, bronchorrhea, diarrhoea, miosis, and bradycardia). If bradycardia produces hypotension, administer slow intravenous atropine sulfate 0.6 mg (Melzer *et al.,* 2016).

b. Steroids

Prednisolone is commonly used for MG and is often given on alternate days to reduce side effects. Start with a low dose (e.g., 10 mg) and increase gradually (5–10 mg/week) to avoid exacerbation; titrate until symptoms are controlled or until an alternate-day dose of up to 120 mg is reached. In severe cases, a high initial alternate-day dose may be used to obtain rapid improvement, while monitoring for adverse effects and providing potassium supplementation as needed. Once improvement occurs, taper slowly (approximately 5 mg/month) to the minimum effective dose. Avoid abrupt changes in prednisolone dosing (Melzer *et al.,* 2016).

c. Thymectomy

Thymectomy is indicated in selected patients. Meticulous perioperative care and airway monitoring are essential. Postoperative deterioration or increased weakness in the days after surgery may reflect respiratory infection or other complications and should prompt immediate treatment, including physiotherapy and antibiotics when indicated (Meyer *et al.,* 2009).

d. Plasmapheresis

Plasmapheresis (plasma exchange) is typically performed in multiple sessions (commonly 3–8 exchanges), using approximately 50 mL/kg per session. It produces rapid clinical improvement by removing pathogenic antibodies and is particularly useful in myasthenic crisis or in severe cases preoperatively. When combined with immunosuppressive therapy, plasmapheresis benefits severe disease; it is less useful as a chronic maintenance therapy (Salahoru *et al.,* 2019).

e. Immunotherapy

- **T-cell signalling targets**
  JAK inhibitors block intracellular signalling downstream of cytokine receptors (including those for IL-2, IL-4, IL-7, IL-9, IL-15, IL-21) by inhibiting JAK1/2/3. JAK1/2 blockade suppresses effector T and B cells while sparing regulatory T-cell function, offering a potential approach for refractory MG by restoring immune balance (Dalakas, 2019).
- **B-cell targets**
  B cells contribute to antibody production, complement activation, antigen presentation, and cytokine secretion (e.g., IL-1, IL-6, IL-10). Targeting B cells can reduce pathogenic antibody production and modulate immune dysregulation. Second- and third-generation anti-B-cell agents targeting CD20 and CD19 may be more effective than earlier agents for MG (Dalakas, 2019).
- **Complement inhibitors**
  Complement activation by IgG1 anti-AChR antibodies contributes to NMJ damage.

Eculizumab, a monoclonal antibody against C5, prevents MAC formation and can be effective in refractory AChR-positive MG; reported adverse effects include headache and nasopharyngitis. Ravulizumab is a long-acting humanised C5 inhibitor with an extended half-life and utility in patients responsive to complement blockade (Rodolico *et al.,* 2021).

- **FcRn inhibitors**
  The neonatal Fc receptor (FcRn) rescues IgG and albumin from lysosomal degradation, prolonging their half-lives. FcRn inhibitors block IgG recycling, reducing circulating IgG levels and increasing IgG clearance. FcRn blockade is a promising strategy for both AChR- and MuSK-positive MG. Efgartigimod is an engineered Fc fragment that reduces pathogenic IgG (Dalakas, 2019).
- **Cytokines and cytokine receptors:** Cytokines such as IL-6 and IL-17 contribute to MG pathogenesis by impairing Treg function and modulating antibody responses at the NMJ. Targeting cytokines or their receptors may benefit refractory MG. Tocilizumab, an IL-6 receptor antagonist, has shown improvement in some refractory patients unresponsive to rituximab or IVIg (Dalakas, 2019).

8. Prognosis

(a) Life expectancy and mortality

Modern management has markedly improved survival. Historically, MG carried a 10-year mortality of 20–30% without effective treatment, but with current therapies and intensive care support mortality is now very low and most patients have a near-normal life expectancy (Sukockienė *et al.,* 2024). Severe complications such as respiratory failure during crises still carry risk, and mortality remains possible, particularly in older patients or those with recurrent crises (Dresser *et al.,* 2021).

(b) Patterns of disease course

MG has a fluctuating, variable course. Symptoms often worsen during the first few years after onset (peaking around 1–3 years), after which many patients stabilise or improve with treatment. Patients may experience recurrent exacerbations and remissions throughout life, and the overall course is often unpredictable (Mao *et al.,* 2010).

(c) Remission and minimal manifestations

Complete remission is possible but uncommon; many patients instead attain minimal manifestations or pharmacologic remission. In a large multicenter study, the cumulative probability of complete remission was approximately 1% at 1 year, 8% at 3 years, 13% at 5 years, and 21% at 10 years (Arroyo & Torres, 2022). Other follow-up studies indicate that most patients eventually achieve minimal manifestations (MGFA class 0–1) or remission with appropriate treatment (Salins, 2016).

9. Conclusions

Myasthenia gravis is a chronic autoimmune disorder of the neuromuscular junction that produces fatigable skeletal muscle weakness. Commonly affected muscles control eye movements, eyelid elevation, chewing, swallowing, coughing, and facial expression; proximal limb, neck, axial, and respiratory muscles may also be involved. MG is primarily a B-cell–mediated disease in which autoantibodies target acetylcholine receptors, although T-cell–mediated mechanisms, often linked to thymic abnormalities such as thymic hyperplasia or thymoma, play important roles in pathogenesis.

Diagnostic investigations include anti-acetylcholine receptor antibody testing and imaging (chest radiography/CT or MRI when indicated). Standard treatments include acetylcholinesterase inhibitors, corticosteroids (titrated gradually), other immunosuppressants (for example, azathioprine), and thymectomy in selected patients. For refractory or severe disease, targeted biological therapies—such as rituximab, complement inhibitors (eculizumab, ravulizumab), and FcRn-directed agents (eg, efgartigimod)—have demonstrated efficacy and are transforming management strategies. These immunotherapies expand options for treating early, chronic, acute, and refractory MG.

Conflict of interest

No conflict of interest in this article.

Acknowledgment

The authors acknowledge the use of artificial intelligence–based tools, including Grammarly (Grammarly Inc., San Francisco, California, United States) and Elicit (Ought Inc., San Francisco, California, United States), which assisted with language editing, improving clarity, and organizing the literature search during manuscript preparation. AI tools were not used for the screening or selection of studies, critical appraisal of evidence, or formulation of conclusions; these tasks were performed entirely by the authors. All AI-assisted outputs were carefully reviewed, validated, and edited by the authors to ensure accuracy and appropriateness.

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