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Myasthenia Gravis - A Review on Pharmacotherapy

Naveen Poojar CM
MBBS, MD, Karnataka

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***Corresponding Author Email:** naveenpoojar.cm@gmail.com

Abstract
Myasthenia gravis (MG) is an autoimmune disorder characterized by fluctuating muscular weakness, which is relieved by cessation of activity and aggravated by intense physical activity. In MG, Ach is released normally but its effect on the postsynaptic membrane reduced. The autoantibody against AChRs will result in the destruction of postsynaptic membrane and reduction in the number of available Ach receptors on the muscle end plate membrane. The aim of treatment in a myasthenia gravis patient is maximum and sustained reduction in symptoms, attainment of full functional capacity and minimizing the side effects of drug therapy. The treatment modalities are acetylcholinesterase inhibitors, corticosteroids, immunosuppressants, plasmapheresis, immunogobulins and thymectomy.

Keywords
Myasthenia gravis, AChRs

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INTRODUCTION
Myasthenia gravis (MG) is the most common autoimmune disorder that affects the neuromuscular junction. MG is largely a treatable disease but can result in significant morbidity and even mortality. This can usually be prevented with a timely diagnosis and appropriate treatment of the disease. MG is a heterogeneous disease from a phenotypic and pathogenesis standpoint. The spectrum of symptoms ranges from a purely ocular form to severe weakness of the limb, bulbar and respiratory muscles.[1] Myasthenia gravis (MG) is characterized by fluctuating muscular weakness, which is relieved by cessation of activity and aggravated by intense physical activity. Majority of the patients are adults; however, an increased incidence in children below 15 years of age has been reported in certain Asian regions.[2]

EPIDEMIOLOGY
The incidence rate of myasthenia gravis varies with age, gender, and ethnic groups [3]. Estimates of incidence range from 0.3 to 2.8 per 100,000 worldwide, and the median global estimated prevalence is 10 per 100,000 [4]. In European countries the annual incidence ranges from 0.4 (Norway) to 2.1 (Italy) per 100,000. The incidence is expected to be 1.9 per 100,000 in Australia [5]. In Asia, the incidence rate of MG in Japan is 0.69–0.87/100,000 [6], similar to that in Korea where the incidence rate of is 0.69 per 100,000 [7].
The prevalence rate has increased since the 1950s due to improved diagnostic precision and decreased mortality rate. It occurs in both genders, in all ages from different ethnic groups with variable prevalence and annual incidence rate from one country to another. Female-to-male ratio for incidence is 3:2 in people below the age of 30 and 1:1.5 in people more than 50 years of age. Life-threatening MG crises occur approximately in 15–20% of patients, typically within the first 2 years of diagnosis [8]. Previously, MG crises were associated with 50–80% mortality rate. Older age and respiratory failure were the predictors for death in MG crises [9].

PATHOPHYSIOLOGY

Acetyl choline is normally released in a discrete package from the motor nerve terminal at the neuromuscular junction. These Ach quanta diffuse across the synaptic cleft and bind to receptors on the folded muscle end plate membrane (**Figure 1**).

Motor nerve stimulation will release many Ach quanta causing depolarization of muscle end plate membrane resulting in muscle contraction. In MG, Ach is released normally but its effect on the postsynaptic membrane reduced. The autoantibody against AChRs will result in the destruction of postsynaptic membrane and reduction in the number of available Ach receptors on the muscle end plate membrane (binding site for Ach), which in turn will lead to an inconsistent generation of muscular action potentials manifesting as muscle weakness (Figures 2 and 3). The process of destruction of the postsynaptic membrane is dependent on complement activation. In patients without antibodies against AChRs, a muscle-specific tyrosine kinase (MuSK), an agrin-dependent protein on muscle membrane, has been found to be the antigenic target. These autoantibodies are T-cell dependent and there is interesting differential involvement of muscle groups, especially the extraocular muscles [10].

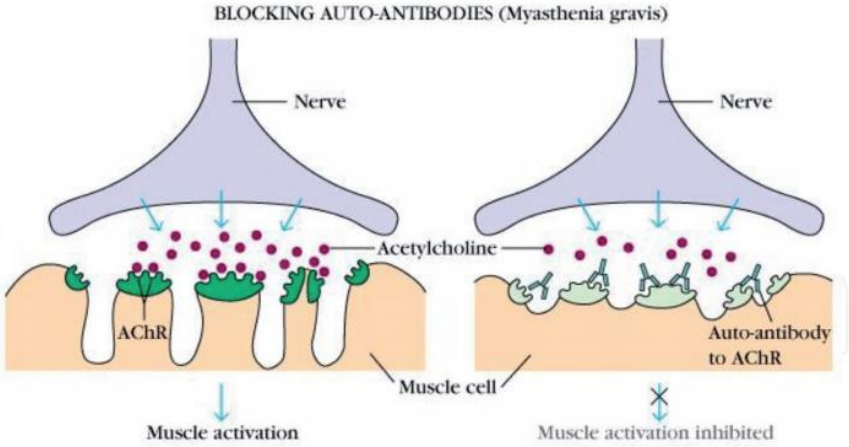


Figure 1. Mechanism of muscle activation.

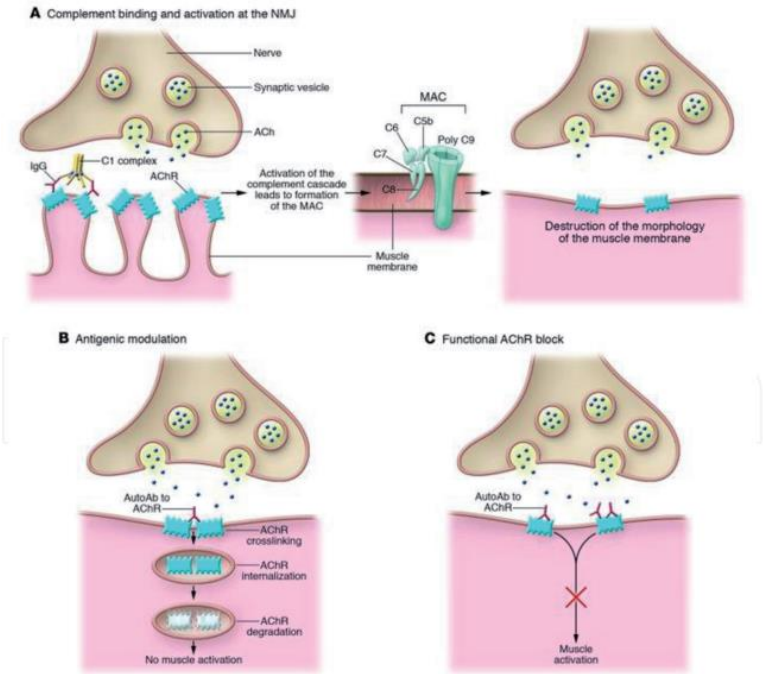


Figure 2. Mechanisms of inhibition of neurotransmission by anti-AChR antibodies.

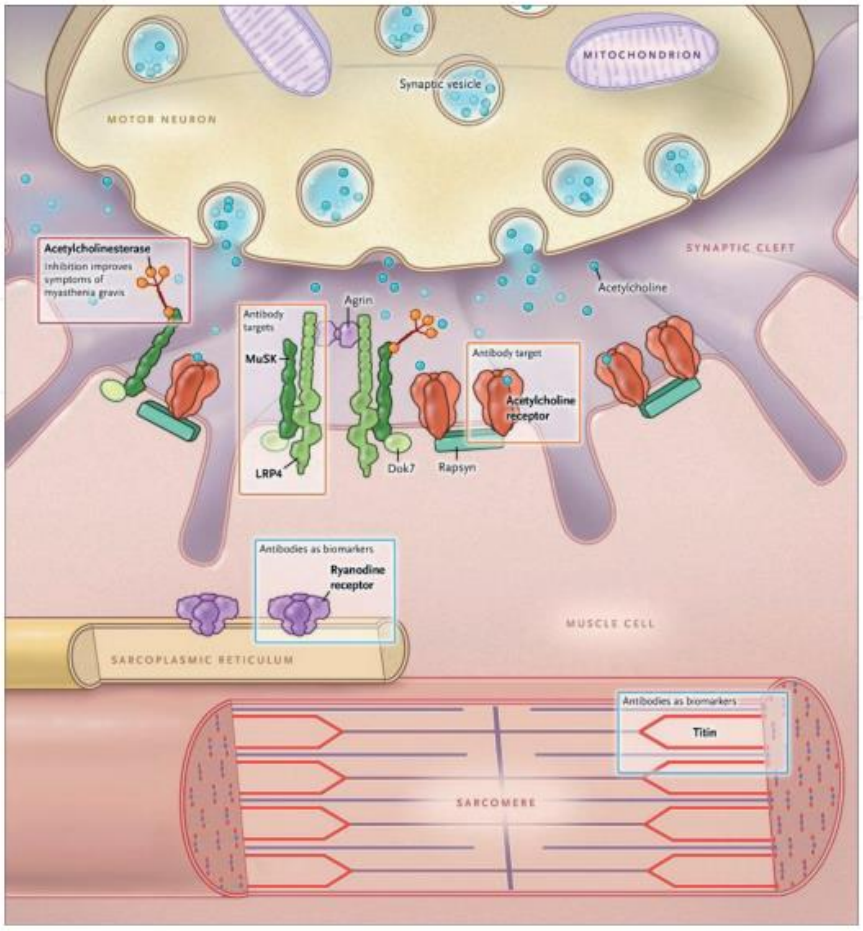


Figure 3. Pathogenesis of MG.

Classification of MG Clinically

Myasthenia gravis is classified clinically into five classes and several sub classes according to MG foundation of American clinical classification, see **Table 1** [11].

Class	Clinical description
Class 1	Any eye muscle weakness, possible ptosis, all other muscles' strength is normal
Class 2	Mild weakness of other muscles; may have eye muscle weakness of any severity
2a	Predominantly limb or axial muscles weakness or both
2b	Predominantly oropharyngeal or respiratory muscle weakness or both
Class 3	Moderate weakness of other muscles; may have eye muscle weakness of any severity
3a	Predominantly limb or axial muscle weakness or both
3b	Predominantly oropharyngeal or respiratory muscle weakness or both
Class 4	Severe weakness of other muscles; may have eye muscle weakness of any severity
4a	Predominantly limb or axial muscle weakness or both
4b	Predominantly oropharyngeal or respiratory muscle weakness or both; use of feeding tube without intubation
Class 5	Intubation needed to maintain airway

ROLE OF THYMUS

The thymus is essential for T-cell differentiation and for the establishment of central tolerance. Interactions between thymic stromal cells expressing self-antigens and developing thymocytes lead to the elimination of autoreactive T cells. The self-tolerant T cells continue their differentiation before being exported to the periphery. Thymic stromal cells include epithelial cells [12], mesenchymal cells [13], and a few myoid cells [14].

Under physiological conditions, most thymic cells are thymocytes and stromal cells. The number of B cells is very small. In the majority of MG patients (i.e., in AChR-MG patients), the thymus exhibits structural and functional changes that are characterized by the presence of a tumor (i.e., thymoma) or by the development of germinal centers (GCs) containing a

large number of B cells (i.e., follicular hyperplasia) [15]. In early onset MG, follicular hyperplasia is very common, while in the late onset MG, thymomas are frequently observed. These morphological changes of the thymus are primarily associated with the Acetylcholine receptor -MG.

Avoidance of drugs that may exacerbate myasthenia

Certain drugs, such as aminoglycosides and neuromuscular blocking agents, have established pharmacologic adverse effects on neuromuscular transmission. Use of these drugs can further reduce the effectiveness of neuromuscular transmission in a patient with MG and cause increased clinical weakness.[16]

Drugs that may unmask or worsen myasthenia gravis
Aesthetic agents
Neuromuscular blocking agents
Antibiotics
Aminoglycosides (eg, gentamicin, neomycin, tobramycin)
Fluoroquinolones (eg, ciprofloxacin, levofloxacin, norfloxacin)
Ketolides (eg, telithromycin)
Macrolides (eg, azithromycin, clarithromycin, erythromycin)
Cardiovascular drugs
Beta blockers (eg, atenolol, labetalol, metoprolol, propranolol)
Procainamide
Quinidine
Other drugs
Anti-PD-1 monoclonal antibodies (eg, nivolumab and pembrolizumab)
Botulinum toxin
Chloroquine
Hydroxychloroquine
Magnesium
Penicillamine
Quinine

Drugs usually well tolerated in myasthenia gravis but occasionally associated with an exacerbation
Anesthetic agents
Inhalation anesthetics (eg, isoflurane, halothane)
Local anesthetics (eg, lidocaine, procaine)
Antibiotics and antiviral agents
Antiretroviral agents (eg, ritonavir)
Clindamycin
Metronidazole
Nitrofurantoin
Tetracyclines (eg, doxycycline, tetracycline)
Vancomycin
Anticonvulsants
Carbamazepine
Ethosuximide
Gabapentin
Phenobarbital
Phenytoin
Antipsychotics and other psychiatric drugs
Butyrophenones (eg, haloperidol)
Lithium
Phenothiazines (eg, chlorpromazine, prochlorperazine)
Glucocorticoids
Dexamethasone
Methylprednisolone

Prednisone
Ophthalmic drugs
Betaxolol
Echothiophate
Proparacaine
Timolol
Tropicamide
Other drugs
Cisplatinum
Emetine (Ipecac syrup)
Fludarabine
Glatiramer acetate
HMG CoA reductase inhibitors (statins)
Interferon alpha
Interleukin-2
Iodinated contrast agents
Riluzole

TREATMENT OF MYASTHENIA GRAVIS

The aim of treatment in a myasthenia gravis patient is maximum and sustained reduction in symptoms, attainment of full functional capacity and minimizing the side effects of drug therapy. The neurological functions and the deficits at the baseline should always be recorded. By this way, the effectiveness of the therapy can be monitored over time as therapies are added or tapered by comparing the parameters before and after the start of therapy. [17] Mortality of the disease has been reduced practically to zero with current therapy available.

The treatment modalities are

- Acetylcholinesterase inhibitors.
- Corticosteroids.
- Immunosuppressants.
- Plasmapheresis.
- Intravenous immunogobulins.
- Thymectomy.

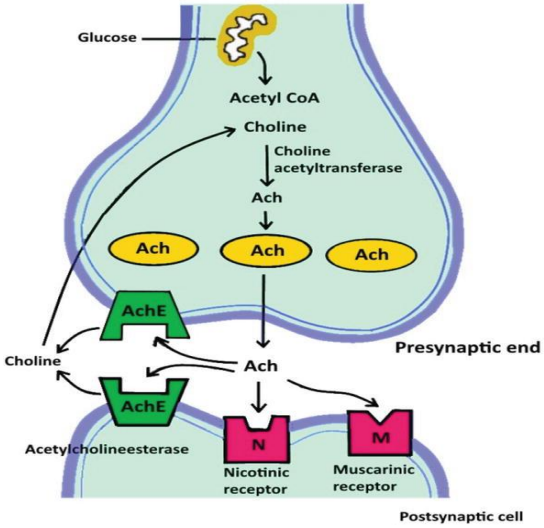
Acetylcholinesterase Inhibitors.

Acetylcholinesterase inhibitors are the first-line treatment in patients with MG. Response to treatment varies from marked improvement in some patients to little or no improvement in others. These drugs enhance neuromuscular transmission by inhibiting the activity of cholinesterases (ChE) which hydrolyse intrasynaptic acetylcholine (Ach). Suppression of hydrolysis of Ach increases the amount of this transmitter in the synaptic cleft of the neuromuscular junction (NMJ), leading to prolongation of the action of Ach on the muscle endplate with partial and temporary correction of the defect in the "safety factor". Because of good efficacy and negligible long-term toxicity, these drugs remain the cornerstone of symptom control in MG.

Acetylcholinesterase inhibitors are used as a symptomatic therapy and act by increasing the amount of available acetylcholine at the NMJ [18]. They do not alter disease progression or outcome. Pyridostigmine is the most commonly used drug. It has a rapid onset of action within 15 to 30 minutes reaching peak activity in about two hours. The effect lasts for about three to four hours. The initial oral dose is 15–30 mg every 4–6 hours and is titrated upwards depending on the patient's response. Adverse side effects of Pyridostigmine are mostly due to the cholinergic properties of the drug such as abdominal cramping, diarrhea, increased salivation and bronchial secretions, nausea, sweating, and bradycardia. Nicotinic side effects are also frequent and include muscle fasciculation and cramping. High doses of pyridostigmine exceeding 450 mg daily, administered to patients with renal failure, have been reported to cause worsening of muscle weakness [19]

Despite their good diagnostic utility and dramatic initial therapeutic success, these drugs have four common limitations:

1) Muscarinic effect. Abdominal cramping and secretory diarrhea result from excess cholinergic stimulation in smooth muscle and exocrine glands.
2) Incomplete restoration of decrement in power.
3) Poor efficacy in restricted forms of MG.
4) Loss of efficacy after a few years of use. [20]



Corticosteroids.

Corticosteroids were the first and most commonly used immunosuppressant medications in MG. Steroids suppress IgG secretion rather weakly. They also produce lysis of cortical thymocytes and sequestration of circulating T lymphocytes in the bone marrow, resulting in lymphocytopenia. They inhibit lymphocyte activation by reducing the production of lymphokines (like IL-2) and expression of IL2 receptors. Steroids also inhibit recruitment of cells into the inflammatory site.

Prednisone is generally used when symptoms of MG are not adequately controlled by cholinesterase inhibitors alone. Good response can be achieved with initial high doses and then tapering it to the lowest dose to maintain the response. Temporary exacerbation can occur after starting high doses of prednisone within the first 7–10 days which can last for several days [21,22]. In mild cases, cholinesterase inhibitors are usually used to manage this worsening.

Immunosuppressants.

Patients who do not respond to corticosteroid or who cannot tolerate it are candidates for immunosuppressive agents using azathioprine (they are first-line agents and can be used with Corticosteroid), Cyclosporine, Methotrexate, Mycophenolate mofetil, or Tacrolimus [23]. Recently, promising results are shown by two monoclonal antibodies, Rituximab and Eculizumab. The use of Rituximab in refractory MG may show clinical improvement and reduction for the need of corticosteroid and therapeutic plasma exchange [24].

Azathioprine

Azathioprine suppresses the immune system, is a treatment for myasthenia gravis and other conditions. Azathioprine disrupts the formation of DNA, decreasing the production of new cells. Azathioprine especially hampers the growth of white blood cells. By stopping the growth of white blood cells, whose role is to make antibodies, azathioprine reduces the production of harmful autoantibodies which attack and damage acetylcholine receptors.[25] Common side effects include fatigue, nausea, vomiting and mild fever. The overall activity of the immune system, liver and pancreas may also be affected, so regular blood tests are necessary to check for these serious side effects.

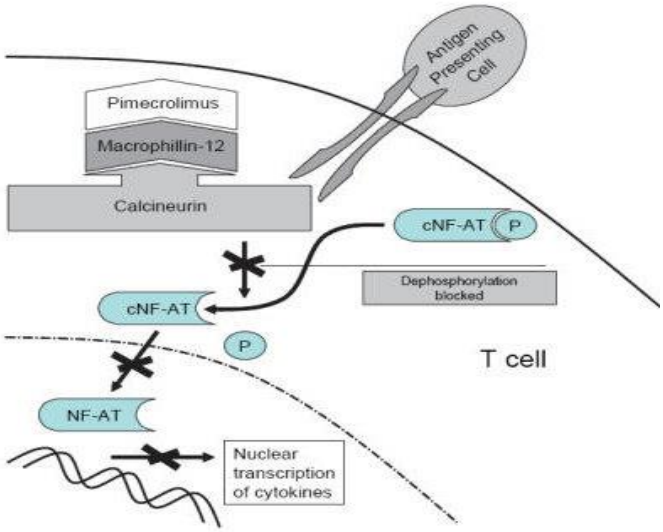
Azathioprine has to be taken for long periods, and it usually takes months for improvements in myasthenia gravis symptoms to become noticeable.

Cyclosporine and Tacrolimus

Cyclosporine and tacrolimus selectively inhibit calcineurin, thereby impairing the transcription of interleukin (IL)-2 and several other cytokines in T lymphocytes. Calcineurin inhibitors have been mainstays of immunosuppression in solid organ transplantation for over three decades. Cyclosporine and tacrolimus are also used in the treatment of various immune-mediated diseases and autoimmune disorders.

Mechanism of Action- Cyclosporine is a lipophilic cyclic peptide of 11 amino acids, while tacrolimus is a macrolide antibiotic. Both drugs have been isolated from fungi and possess similar suppressive effects on cell-mediated and humoral immune responses. Both drugs bind with high affinity to a family of cytoplasmic proteins present in most cells: cyclophilins for cyclosporine and FK-binding proteins for tacrolimus. The drug-receptor complex specifically and competitively binds to and inhibits calcineurin, a calcium- and calmodulin-dependent phosphatase [26-28]. This process inhibits the translocation of a family of transcription factors (NF-AT), leading to reduced transcriptional activation of cytokine genes for interleukin (IL)-2, tumor necrosis factor (TNF)-alpha, IL-3, IL-4, CD40L, granulocyte-macrophage colony-stimulating factor, and

interferon-gamma [26,27,29,30]. Ultimately, proliferation of T lymphocytes is reduced.



Methotrexate

Methotrexate (MTX) is a cost-effective immunosuppressant. MTX is a structural analog of folic acid and exerts an anti-proliferative effect by metabolic interference with DNA synthesis and prevents the proliferation of lymphocytes. In MG, these are responsible for the production of autoantibodies that inhibit the neurotransmission of acetylcholine, which is a key component of the autonomic nervous system. However, many recent reviews on MG therapies either do not include MTX as an option [31, 32] or only regard this agent as an alternative if other drugs have failed [33].

Mycophenolate mofetil

Mycophenolate mofetil (MMF) inhibits the immune system by preferentially depleting guanosine and deoxygunaosine on both T and B-lymphocyte lines [34]. MMF is thought to selectively inhibit inosine monophosphate dehydrogenase type II, an enzyme that facilitates the production of an intermediate metabolite of guanosine [35]. Ultimately, MMF is able to reduce the proliferation of T and B-lymphocytes and affect antibody formation and cell-mediated responses. MMF also acts on the immune system by: 1) Reducing lymphocytic recruitment to inflammation; 2) Limiting tissue-damaging nitric oxide; 3) Inhibiting the expression of adhesion molecules; 4) Reducing the secretion of tumor necrosis factor alpha; 5) Increasing the expression of interleukin-10; and, 6) Elevating the rate of lymphocytic apoptosis [34,35]. Given the unique immunosuppressive properties of MMF, it has been tried as a therapy for many autoimmune conditions including MG.

Adverse effects-gastrointestinal intolerance (usually diarrhea), nausea, vomiting, headaches, bone marrow suppression, sepsis, hypertension, tremor, neoplasia, depression, teratogenicity and an increased risk of infection.

Rituximab

Rituximab (RTX), a chimaeric monoclonal antibody specific for human CD20 that targets B lymphocytes. CD20 (the target of RTX) is expressed from the early pre-B-cell stage and remains present in mature B cells. It is not present on stem cells and is lost before the differentiation of B cells into plasma cells. RTX is known to deplete B cells by three mechanisms:

- antibody-dependent cellular cytotoxicity (ADCC): natural killer cells, macrophages and monocytes are recruited through their Fcγ receptors bound to surface CD20, inducing B-cell lysis [36].
- complement-dependent cytotoxicity as a result of complement activation by the B cell–RTX complex and the generation of a membrane attack complex, again leading to B-cell lysis [37]
- direct apoptosis of B cells induced by RTX binding.[37]

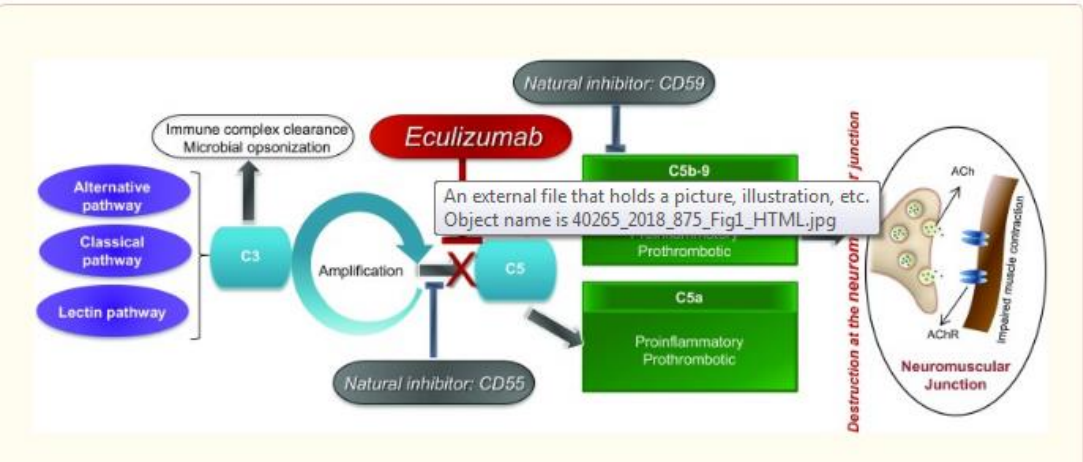
B cells function as antigen-presenting cells and provide important co-stimulatory signals (such as cytokines) required for CD4+ T-cell clonal expansion and effector functions [38]. T cells also play an important role in the physiopathogenesis of MG.

By depleting B cells, RTX may benefit MG through one of several RTX, mechanisms.

Eculizumab

Eculizumab is a recombinant humanized monoclonal IgG2/4$_K$ antibody that binds to human C5 complement protein and inhibits the activation of terminal complement [39, 40]. eculizumab was also approved for the treatment of adults with anti-AChR antibody-positive gMG in the USA [39], anti-AChR antibody-positive refractory gMG in the EU [40] or patients with anti-AChR antibody-positive gMG whose symptoms are difficult to control with high-dose IVIg therapy in Japan.[41]

Side effects includes headache, tiredness, diarrhea, nausea/vomiting, muscle pain, infection, swelling hands / ankles / feet, fast heartbeat, allergic reactions.



Other new medications

Ravulizumab

Ravulizumab (ALXN1210), is a humanized monoclonal antibody functionally similar to Eculizumab, that binds with high affinity to C5 preventing the generation of complement activation products C5a and C5b-9

Zilucoplan

Zilucoplan is a synthetic, macrocyclic peptide that binds C5 with sub-nanomolar affinity inhibiting its cleavage into C5a and C5b intercepting MAC formation.

Plasmapheresis.

It improves strength in most patients with MG by directly removing AChR from the circulation [42]. Plasma Exchange involves apheresis where circulating immunoglobulins, complement, immune complexes, cytokines and other inflammatory mediators are removed. Typically one exchange is done every other day for a total of four to six times. Adverse effects of plasmapheresis include hypotension, paresthesias, infections, thrombotic complications related to venous access, and bleeding tendencies due to decreased coagulation factors [43].

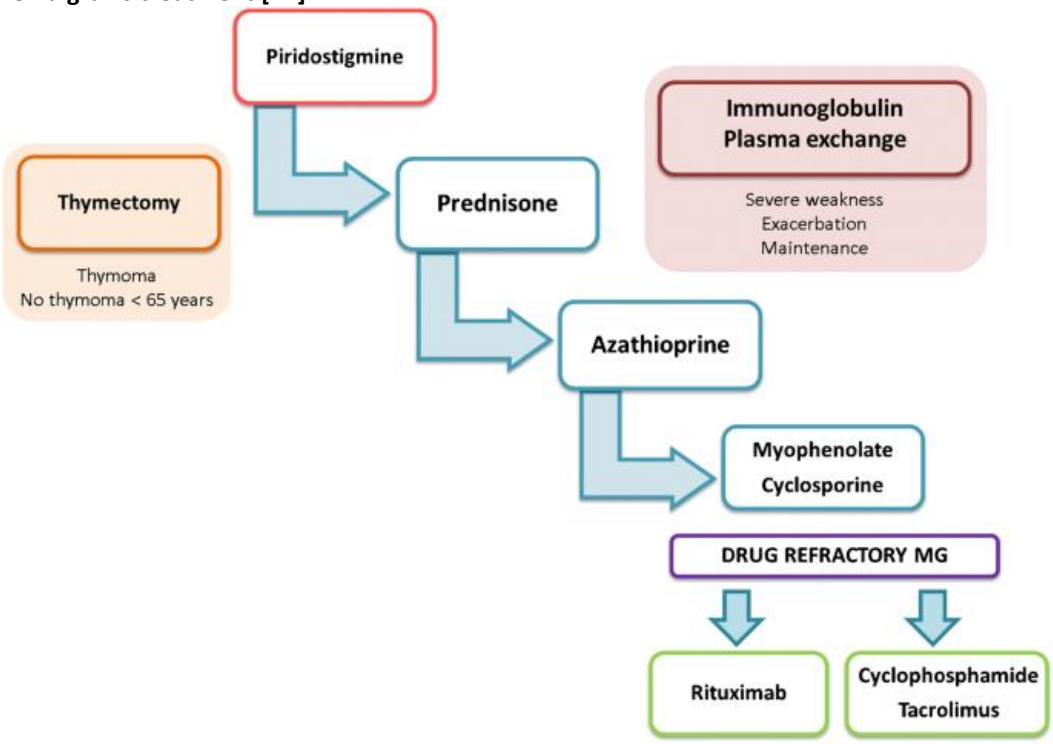
Intravenous immunoglobulin (IVIG)

The mechanism of action of IVIG is complex and may involve inhibition of cytokines and complement deposition, competition with autoantibodies, interference with binding of Fc receptor on macrophages and immunoglobulin receptor on B cells, and interference with antigen recognition by sensitized T cells [44]. It is used as an acute treatment in patients with severe generalized MG and MuSK-MG, as a maintenance therapy in patients with refractory and juvenile MG, and in myasthenia crises [45]. More specific techniques to remove pathogenic anti-AChR antibodies utilizing immune adsorption have been developed recently, which offer a more targeted approach to MG treatment.

Thymectomy

Myasthenic patients commonly have thymic abnormalities. Patients with generalized MG have thymic hyperplasia and thymoma. Those patients are usually anti-AChR antibody positive. Thymectomy is indicated for all patients with thymoma and for patients aged 10–55 years who have generalized MG but without thymoma. In fact, thymectomy is proposed as first – line therapy in most patients with generalized MG. Thymectomy not indicated in patients with antibodies to MuSK, LRP4, or agrin antibodies because the thymic pathology is different from the more common type of MG characterized by seropositivity to AChR, and also it is not indicated in patients with ocular MG during the first 2 years after diagnosis because the possibility of spontaneous remission [46].

Myasthenia gravis treatment [47]



Prognosis

With the recent advances in the management of MG in both supportive intensive care and specific therapeutic options, most patients enjoy normal or near normal life span. The mortality rate is about 3–4% and the risk factors for death include a short history of a progressive disease, age more than 40 years, and thymoma. Morbidity in MG results from intermittent muscle weakness, which may result in aspiration pneumonia, difficult breathing, and even respiratory failure requiring ventilator assistance and in possible side effects of medications used in the treatment [48].

CONCLUSION

Myasthenia gravis is an autoimmune disorder characterised by the weakness and fatigability of the voluntary muscles that is caused by autoantibodies against the nicotinic AChR on the postsynaptic membrane at the neuromuscular junction. Understanding of the pathogenesis, immunology, and molecular biology of myasthenia gravis is important for the treatment. It is almost always possible to establish the diagnosis of myasthenia gravis with the current tests. Modern treatment is highly successful, and mortality of treated disease is practically zero. The availability of more focused immune therapies provides greater treatment options for both patients and treating physicians in the management of MG.

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