REVIEW ARTICLE

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Update on myasthenia gravis

ABSTRACT

Myasthenia gravis (MG) is an autoimmune disease mediated by autoantibodies against various transmembrane proteins located on the post synaptic membrane. Our understanding of pathophysiology has vastly improved over the past decade, resulting in the development of individualized therapeutic options. Classification into myasthenia subgroups, depending on the antibody profile, helps to better characterize, treat, and prognosticate patients. It is quite evident that muscle-specific tyrosine kinase myasthenia needs early rituximab intervention for a stable remission. Role of thymectomy was recently proven in a randomized controlled trial. With the advent of monoclonal antibodies and other newer modalities, therapy should evolve beyond the conventional immunosuppressives given their toxicities. Better potential options are now available to treat the refractory subgroup. Future of myasthenia treatment clearly has rosy predictions. Present review is an update on MG.

Key words: Myasthenia gravis, Thymus, Autoantibodies, Treatment guidelines

INTRODUCTION

Myasthenia Gravis (MG) is an autoimmune disease that affects the postsynaptic membrane at the neuromuscular junction (NMJ) presenting clinically as fatigable and fluctuating muscle weakness affecting the ocular, bulbar, axial, and limb muscles.[1] The weakness differs in individual muscles and muscle groups with extraocular muscles most frequently affected. The most common symptoms are intermittent drooping of eyelids and double vision. Up to 15% patients have disease restricted to ocular muscles, but the majority will progress to involve bulbar, axial and limb muscles. Severe disease exacerbations leading to respiratory failure occur in up to 15% patients. Antibodies against the acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSk) are present in majority.[2] Diagnosis confirmation requires detection of autoantibody, evidence of impaired neuromuscular transmission (NMT) on electrodiagnostic study or an objective response to the pharmacological challenge. With optimal treatment, most patients remain stable with only mild weakness. Hence, prompt diagnosis and treatment are essential. Several new drugs have recently been approved and many are in the pipeline. A major challenge however, is to find individualized therapies that can prevent or cure the disease.[2]

EPIDEMIOLOGY

MG affects patients of all ages and has a prevalence of 1 in 5000. AChR MG has a bimodal pattern, with a lower peak around 30 years with female predominance and a second peak after the age of 50 years, affecting males slightly more than females.[3,4] MuSK MG occurs through adolescence to early adulthood with a female predominance.[5] Thymoma associated MG usually occurs around 50 years of age.[6]

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PATHOPHYSIOLOGY

The essential pathology in MG is an antibody mediated damage of the postsynaptic membrane causing decreased folds and simplification resulting in reduced concentration of AChR and voltage gated sodium channels in the postsynaptic membrane, thereby decreasing the efficiency of NMT. This manifests clinically as fatigable and fluctuating weakness in specific muscle groups[7] [Figure 1].

IMMUNOPATHOLOGY

Normal thymus is a site for development of tolerance to "self antigens." This is done by Thymic epithelial cells (and Myoid cells), which express the AChR subunits, and generate "self reactive" T cells, which are primed for destruction in thymus(central tolerance) or in blood stream (peripheral tolerance). In MG, the dysregulation of self tolerance mechanisms eventually leads to a self perpetuating response of generation of autoreactive CD4+ cells (autosensitization), which causes activation of B cells and subsequent autoantibodies, against various extracellular and intracellular

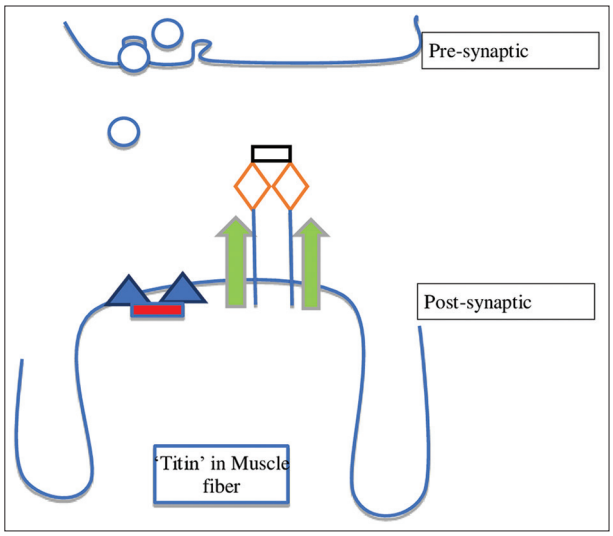

Figure 1: Trans membrane proteins of post-synaptic neuromuscular junction. Acetylcholine in vesicles (blue circles) are released from the presynaptic membrane into the synaptic cleft, to bind to the ACh receptor (blue trianlges) bound by scaffold, the Rapsyn (red bar). The Musk protein (green arrows) are important for the clustering of AChR. Low density lipoprotein receptor protein 4 or LRP4 (brown diamonds) are another transmembrane protein, which are bound by Agrin (black rectanlge), released by the nerve terminal. The 'LRP4-Agrin' complex, phosphorylates MuSK, thus activating it to promote AChR clustering. Titins and Ryanodine are intracellular proteins.

antigens of NMJ.[8] Thymus eventually gets "inflammed" with multiple germinal centers (B cells "production house") causing thymic hyperplasia, seen in >70% of early onset MG (EOMG).[9] Thymoma seen in 10–15% of MG, induces a similar dysregulation of central tolerance, causing severe MG. The role of thymus in late-onset MG (LOMG), seronegative and MuSK MG remains unclear.

Antibodies against transmembrane proteins are pathogenic for MG and affect the post-synaptic muscle membrane and NMT either directly (AChR-Ab) or indirectly (MuSk-Ab and LRP4-Ab). Nicotinic AChR is the most common autoantigen in MG. The anti-AChR antibodies, (IgG1) seen in almost 80% of MG, is polyclonal, which binds to multiple domains of the pentameric AChR, the most immunogenic being the central core comprising alpha-1 subunit called "Main Immunogenic region" (MIR).[10] The most common mechanism for the pathogenicity of AChR-Ab (IgG1) include complement mediated damage to the postsynaptic membrane. Antibodies to MuSK are clearly pathogenic and result in impaired AChR clustering, but the mechanism is not clearly understood. It is an IgG4 class antibody and hence doesn't engage complement. Antibodies against LRP-4 are found in 8% with AChR-Ab, 15% with MuSK-Ab, 20% of double seronegative MG (dSNMG) patients, 4% with other neuroimmune diseases and 10–23% of ALS patients.[11] Antibodies against Agrin, ColQ, Kv1.4 and cortactin are also found in some MG patients, but their exact role is not yet clear. Antibodies against intracellular antigens (striated muscle antigens) such as Titin and Ryanodine receptor are not pathogenic, and are usually associated with AChR-Ab. They predict thymoma in EOMG(sensitivity and specificity 90%) and severe disease in LOMG.[12]

CLINICAL FEATURES

The core clinical feature in MG is fatigable and fluctuating muscle weakness in selective muscle groups. Weakness characteristically fluctuates during the day, usually being least in the morning and worse as the day progresses, especially after prolonged use of affected muscles, and typically improves after rest.

OCULAR SYMPTOMS

Ocular manifestations are the most frequent, ultimately developing in the majority (>90%). Most of the patients (>2/3rd of AChR myasthenia) have ocular presentation with asymmetric painless, ptosis (drooping of eyelids) or binocular diplopia, causing blurry vision. Associated eye closure weakness produces discomfort by allowing soap or water in the eyes during bathing. In the early stages, ocular symptoms are present intermittently, typically worse in the evening or while activities such as reading, watching television, or driving in bright sunlight.[13] Careful questioning may reveal frequent purchases of new eyeglasses due to blurred vision. In 10–15% patients (up to 58% in Asians, especially children), the disease remains restricted to the ocular muscles (Ocular MG), but majority will progress to involve the bulbar, truncal and limb muscles in the following 2–3 years (Generalized MG).[14] Compared to AChR myasthenia, in MuSK myasthenia, only 36% have ocular presentation, which quickly generalizes within 2–3 weeks (5% of MuSK patients may never develop any ocular symptom).[15]

BULBAR/FACIAL SYMPTOMS

Bulbar weakness can be the presenting symptom in up to 15% of AChR myasthenia, but eventually develops in over 60% cases. On the contrary, initial bulbar weakness occurs in almost 43% of MuSK myasthenia.[16] Jaw closure weakness causes difficulty chewing tough, fibrous food. Oropharyngeal weakness causes speech difficulty, with nasal twang after prolonged talking. Also, difficulty in swallowing, especially liquids with frequent nasal regurgitation, throat clearing, coughing after eating or a choking sensation in the throat. Laryngeal muscle involvement causes hoarse voice. The symptoms typically are fatigable, becoming progressively worse with continued chewing, eating, or talking. Facial muscle weakness causes an inability to smile, often misinterpreted as a flat or depressed mood, inability to drink through a straw or to whistle. In combination with ptosis, the face appears sleepy and sad.

LIMB AND TRUNCAL WEAKNESS

Limb weakness is usually proximal and symmetric. The upper limbs are more affected than the lower limbs, with extensors more affected in upper limbs and flexors in the lower limbs. Neck flexors are more affected than extensors.[13] The complaints of the patient are fatigability, unexplained sensation of heaviness in limbs, inability to sustain overhead activity and difficulty in going up and down the stairs. Rarely, isolated weakness in selective muscle groups such as neck extensor (dropped head syndrome), finger, wrist and elbow extensors, hip flexors, or ankle dorsiflexors may also occur as presenting features.[17]

RESPIRATORY WEAKNESS

Respiratory insufficiency (Myasthenic crisis [MC]) due to diaphragmatic and accessory breathing muscle weakness develops in a small proportion of myasthenic patients, and rarely can be the presenting manifestation, especially in MuSK MG. Diaphragmatic weakness leads to orthopnea, causing difficulty breathing when patient is supine.[18]

Cognition, co-ordination, tendon reflexes, sensory and autonomic functions remain normal. Local muscle atrophy is rarely seen, except in burnt out disease and MuSK Myasthenia.

The disease course is variable, but progressive. Maximum weakness occurs during the 1st year in two-thirds of patients.[14] Improvement, even remission may occur early on, but is rarely permanent.[19] The disease course is characterized by exacerbations due to known or unknown factors. Severe exacerbations causing respiratory failure is called myasthenic crisis(MC). With currently available treatments, mortality rate is <5%.

PHYSICAL EXAMINATION

In mild MG, weakness may be apparent only when muscles become fatigued. The aim is to demonstrate fatigable weakness in specific muscle groups by checking strength at rest and after repetitive or sustained activity.

Ptosis, due to weakness of eyelid elevators, increases during sustained upgaze, and is associated with compensatory wrinkling of the forehead. Asymmetric ptosis of alternating sides over time, is considered pathognomonic of MG. Bilateral ptosis often gives the appearance of a sleepy face. Unilateral frontalis contraction is a clue that lid elevators are weak on that side. Functional ptosis can be differentiated by noting that eyebrow of the affected eye is lower than the unaffected side, opposite to that seen in MG. Weakness affects one or more extraocular muscles, the most frequently and most severely affected is the medial rectus. Isolated weakness of medial rectus may give appearance of a pseudo-internuclear ophthalmoplegia. Eyelid closure is weak in MG, including in ocular MG, due to orbicularis oculi involvement, despite all other facial muscles having normal power. It may be the only residual weakness in a patient with otherwise complete remission.[20]

Mild weakness may only be brought out by provocative testing [Table 1]

The facial appearances in myasthenia can be characteristic [Table 2].

CLASSIFICATION OF MG

A clinical classification developed by the MG Foundation of America (MGFA) [Table 3] provides an uniform description of the different subgroups, and has been accepted for clinical research as well as for use in clinical practice.[23]

Table 1: Bedside tests in MG

Muscle group	Bedside tests
Ocular muscles	• Sustained up gaze for 30 s or more produces ptosis • Sustained lateral gaze for 30 s or more produces diplopia • Cogans lid twitch: Sudden elevation of a rested eyelid in downgaze, produces a brief overshoot twitch (50–75% sensitivity, >90% specificity)[21] • Ice pack on affected eye for 2–5 min (sensitivity and specificity>90%). A negative ice pack test in a ptotic eye essentially rules out MG[22] • Curtain sign: Passively lifting the more ptotic lid may cause opposite lid to droop • Covering the more ptotic eye will relieve contraction of the opposite frontalis in asymmetric ptosis • Peek sign: forced eyelid closure will cause fatigue and involuntary opening of the eyelids in severe eye closure weakness • Moderate eye closure weakness causes inability to bury eyelashes during forced eye closure • With limited ocular excursion, saccades are super-fast producing "ocular quiver"
Facial and masticatory muscles	• Inability to whistle or suck through a straw or pout • Jaw muscle weakness may be tested by asking to open and close the jaw against resistance
Oropharyngeal muscles	• Asking the patient to speak aloud without interruption produces nasality and/or hoarseness • Iced drink test for bulbar myasthenia: Improvement in dysphagia is documented after drinking a cold liquid
Limb muscles	• Perform full arm abduction for 4 min or 20 repetitive abductions •Rise from a chair repeatedly without any support, 20 times, which will bring out weakness

Table 2: Facial appearances in MG

Sleepy face	Due to bilateral severe ptosis
Expression-less or depressed face	Due to facial muscle weakness
Myasthenic snarl	attempted smile causes contraction of the medial part of upper lip and horizontal contraction of the corners of mouth, instead of normal upward curling, giving the smile an appearance of a sneer
Worried or surprised face	Due to chronically contracted frontalis muscles to compensate for ptosis
Studious or attentive face	Severe jaw closure weakness causes jaw to hang open and the patient actively holds the mouth closed with the thumb under the chin, middle finger below the lower lip and index finger above the upper lip for support

Table 3: Myasthenia Gravis Foundation of America clinical classification of MG

Class	Description
I	Any ocular muscle weakness May have weakness of eye closure All other muscle strength is normal
II	Mild weakness affecting other than ocular muscles May also have ocular muscle weakness of any variety IIa predominantly affecting limb or axial muscles or both May also have lesser involvement of oropharyngeal muscles IIb predominantly affecting oropharyngeal or respiratory muscles or both May also have lesser or equal involvement of limb or axial muscles or both
III	Moderate weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity IIIa predominantly affecting limb or axial muscles or both May also have lesser involvement of oropharyngeal muscles IIIb predominantly affecting oropharyngeal or respiratory muscles or both May also have lesser or equal involvement of limb or axial muscles or both
IV	Severe weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity IVa predominantly affecting limb or axial muscles or both May also have lesser involvement of oropharyngeal muscles IVb predominantly affecting oropharyngeal or respiratory muscles or both May also have lesser or equal involvement of limb or axial muscles or both
V	defined by intubation, with or without mechanical ventilation, except when employed during routine post-operative management; the use of a feeding tube without intubation places a patient in class IVb

DIAGNOSIS AND SCREENING TESTS

Serological Testing

Recommended first step in confirming MG is testing for AChR-Ab. which if positive, is confirmatory. Positive assay for AchR-Ab is noted in 80–85% of generalized MG, 50% of ocular MG, and 50% children with MG.[24]

The binding AChR-Ab is routinely detected by Radio-Immuno Precipitation Assay (RIPA) which has higher sensitivity and specificity than ELISA. Low affinity binding antibodies can be detected by Cell based assays (CBA) employing clustered AChRs in native form. AChR-Ab has no role in predicting disease severity, prognosis or assessing response to the treatment. False positives can occur in thymoma patients without MG (35%) and rarely in conditions such as GBS, ALS, autoimmune hepatitis, lupus and in first degree relatives of autoimmune MG patients. The next step is testing for MuSK-Ab. One third patients without AChR-Ab (Seronegative) will be positive for MuSK-Ab. "Double seronegative" MG refers to patients who are negative for both AChR-Ab and MuSK-Ab (10–15% patients). Approximately, 20% of these have LRP4-Ab.[25]

Neurophysiological Testing

In seronegative cases, the next step is electrodiagnostic test, to confirm the abnormal postsynaptic NMT. Low frequency RNS study (2–5 Hz) finding of more than 10% decrement indicates abnormal NMT and is confirmatory of MG in the appropriate clinical setting. It has higher sensitivity for generalized MG (80%) than ocular MG (<50%) and MuSK MG (50%). Sensitivity is higher if tested in the clinically weak muscles.

Single muscle fiber electromyography to determine abnormal excessive jitter, when performed in a weak muscle, is the most sensitive test (97%) to confirm abnormal NMT, but has low specificity. It has the greatest value in patients with ocular MG who frequently have negative serological and RNS studies. If normal in the clinically affected muscles, MG is ruled out.[26]

Edrophonium Test

In seronegative patients with negative electrodiagnostic test, an unequivocal response after a rapid and short acting ChEI (Cholinesterase inhibitors) such as IV edrophonium can be used to confirm the diagnosis of MG. Improvement is observed within 30 s at which time the test is stopped and the effect lasts about 5 min.[27] It is important to select a parameter that can be objectively graded, such as improvement in ptosis. The test is avoided when suspecting MuSK MG as these patients often worsen with ChEIs. Muscarinic side effects like excessive salivation, lacrimation, sweating, nausea, vomiting, diarrhea and serious adverse effects such as bronchospasm and bradyarrhythmia may rarely occur with the edrophonium test. Reported sensitivity of the Edrophonium test is in the range of 60–95% for ocular MG and 72–95% for generalized MG.

Ice Pack Test

This can be used as an alternative, especially in patients with ocular MG and patients in whom cholinesterase inhibitors are contraindicated due to cardiac or respiratory co-morbidities.[22]

A chest CT to rule out thymoma, thyroid function tests, testing for latent tuberculosis (Mantoux test or QuantiFERON TB Gold

test) and testing for chronic viral infections (HIV, HBV, HCV) should be done in all patients, prior to starting immunosuppression.

MG SUBTYPES AND SPECIFIC CLINICAL SITUATIONS

Several MG subtypes are determined based on clinical manifestations, age at onset, autoantibody profile, and the thymic pathology. These subtypes have unique genetic associations, disease mechanisms, prognosis, and the treatment responses [Table 4].[6]

Double Seronegative MG(dSNMG)

Almost 50 % of ocular and 15% of generalized MG can be double seronegative (negative for both AChR and MuSK antibodies). These patients pose diagnostic dilemma and are diagnosed based on positive neurophysiological tests. About 20–50% have low affinity antibodies to AChR and MuSK, which are detected only by cell-based assays. Since these low affinity antibodies are pathogenic *in vivo*, the clinical features and response to immunotherapy is similar to the seropositive myasthenia. 2–27% of dSNMG are positive for LRP4 antibodies, These are usually females with mainly ocular or mild generalized weakness (MGFA 2A). About 24% of ocular dSNMG are positive for the rare cortactin antibodies.[28]

Checkpoint Inhibitor-Induced MG

Immune checkpoint inhibitors (ICI) have revolutionized the cancer treatment. Due to upregulation of the immune system, multisystem side effects including neurological complications such as MG, myositis, and polyradiculoneuropathy are seen. MG incidence ranges from 0.12% to 0.2% and may be isolated or overlapping with myositis. Patients often develop severe generalized MG with respiratory and bulbar weakness. AChR-Ab positivity is less frequent. Corticosteroids results in favorable outcome.[29]

Table 4: MG subtypes

MG subtype (Frequency)	Age at onset M: F	Thymic pathology	Antibody	Comments and Response to immunotherapy (+++ good+poor)
Ocular MG (15%)	Any age 1:2	Variable	AChR (50%) LRP4 rarely	Restricted to ocular muscle in 20% (up to 58% in Asians, especially children), 2 years after onset. +++
Early Onset MG (EOMG) (20%)	<50 years 1:3	Hyperplasia	AChR	Generalized disease/max within 2–3 years +++
Late Onset MG (LOMG) (45%)	>50 years 5:1	Atrophy	AChR Titin Ryanodine receptor	Generalized disease/max within 2–3 years +++
MuSK MG (6%)	<40 years 1:3	Normal	MuSK	Generalized disease/Selective facial, oropharyngeal, respiratory weakness in many. Minimal ocular and limb weakness. Wasting and fasciculations in tongue and facial muscles. +
LRP-4 MG (2%)	Variable 1: 2	Variable (Atrophic in 2/3 rd)	LRP-4 2–20% of Double Seronegative cases	Mild Generalized disease or ocular
Seronegative MG (double) (4%)	Variable	Hyperplasia in some	Antibodies against clustered AChR Agrin, LRP-4 & Cortactin	Generalized disease +
Juvenile MG	<18 years	Hyperplasia in some, Thymoma rare	AChR (50%)	High frequency of spontaneous remission Mild Ocular weakness to severe generalized MG Distinction from CMS challenging in seronegative cases
Thymoma associated MG (10–15%)	>40 years	Thymoma	AChR (100%) Titin (70%) Ryanodine receptor (70–80%)	Severe generalized MG Worst prognosis Thymectomy always indicated +

DIFFERENTIAL DIAGNOSIS

The diagnosis of MG can be challenging and delayed because of the fluctuating nature of muscle weakness and the overlap of signs and symptoms with other neuromuscular diseases. Congenital Myasthenic Syndrome (CMS) presenting in childhood or early adulthood mimics acquired MG. Symptom worsening with pyridostigmine may indicate some CMS like slow channel, ColQ or DOK7 syndromes. Presynaptic syndromes like, Lambert Eaton Myasthenic Syndrome (LEMS) present with a triad of muscle weakness (often spares ocular), areflexia and autonomic disturbances. 60% have an underlying malignancy, usually SCLC. Low-frequency RNS shows decremental response, but an incremental response is seen with high frequency RNS (typically >100%). Purely ocular MG needs to be differentiated from mitochondrial disorders like chronic progressive ophthalmoplegia (CPEO) as well as Oculopharyngeal Muscular Dystrophy (OPMD). The ocular involvement in these conditions is symmetric, without diplopia or fluctuation. Muscle biopsy or genetic testing confirms the diagnosis. Bulbar-predominant MG with minimal ocular symptoms, especially MuSK MG, with tongue atrophy and fasciculations can mimic bulbar ALS.

TREATMENT OF ACQUIRED MG

The goal of treatment is restoring the muscle strength and improving quality of life. This is often achieved by a combination of Symptomatic treatment (CI) and Immunosuppressive drugs (IS). Due to limited controlled studies, treatment is individualized and based upon expert consensus and experiences. Initial choice of therapy differs with the myasthenia severity (ocular v/s generalized) and the subtype (AChR v/s MuSK).[30]

CHOLINESTERASE INHIBITORS (CI)

Pyridostigmine

It is the most used drug for symptomatic relief of myasthenic symptoms. It acts by increasing the availability of acetylcholine at the synaptic cleft. Typically used in 180–240 mg total daily dose (max 480 mg), in 4–5 divided doses, it provides a good control of myasthenic weakness. Action lasts for 4–5 h, peaking at ½ h. The dosing should be timed to provide relief from chewing or swallowing difficulties, esp. during meals. Long-term use provides mild to moderate relief from weakness, but not enough to avoid the immunosuppressives. Patients with MUSK myasthenia, are often intolerant to cholinesterase inhibitors, and can develop cramps and fasciculations, even with lower doses. Muscarinic side effects are very common, esp. gastrointestinal disturbances, such as bloating, diarrhea, abdominal cramps, and nausea. Furthermore, hypotension, bradycardia, urinary frequency, and increased bronchial secretions are often noted, necessitating dose reduction. Rarely, aggravation of weakness can occur due to "Cholinergic crises." Caution should be exercised in dysphagic patients, as increased salivation can sometimes aggravate the swallowing difficulties.[31]

Neostigmine can be used subcutaneously (avoid iv), as an alternative to pyridostigmine, in patients who cannot tolerate oral medications. Cardiac inhibitory side effects are common and need close vigilance.

IMMUNO SUPPRESSIVES (IS)

Corticosteriods

Steroids are the first line IS therapy, due to its rapid effect, and should be offered to patients, who have not met treatment goals with pyridostigmine, despite adequate trial. Efficacy of steroids was shown in retrospective studies (74% response rate, as monotherapy), although controlled trials are lacking.[32] Following three regimens are used.

(1) Most used regimen is the slow escalation of steroids, starting with the initial dose of 10-20 mg prednisolone per day and gradually increasing by 5 mg/day every week, up to 1 mg/kg/day. Almost 70–80% will achieve a stable remission within 4–8 weeks. Alternatively, 25 mg alternate days (AD), with 12.5 mg escalation every 3rd day to 100 mg AD. To avoid disease, flare up or crisis, tapering should be very gradual, at 10–20 mg every 1–2 months, to reach the lowest effective dose.
(2) Much faster response (2–4 weeks) can be attained in severe disease, with initial high oral dose (1–1.5 mg/kg/day) followed by tapering once remission occurs. The drawback being the risk of transient worsening of myasthenic weakness, seen in almost 50% of patients, with 10% needing ventilation or feeding tube, and hence, should be given only in admitted patients. The temporary dip, probably due to direct membrane effect of steroids, starts within 1–2 days and lasts around 4–5 days. Worsening does not predict the subsequent steroid response.
(3) Intravenous pulse methylprednisolone (500–2000 mg/day, daily for 3–5 days), followed by oral taper, is also used, to achieve a very rapid response. This regimen is often used in MC (or impending), combined by iv Ig or PE.

Lowest effective doses are needed to maintain the remission, for long periods (or lifelong) in generalized myasthenia. Patients should be made aware of its side effects, including osteoporosis, weight gain, depression, hypertension, skin atrophy, impaired glucose tolerance, glaucoma, and increased risk of infections. To minimize the risks of long-term exposure to steroids, steroid sparing immunosuppressants are added, often from the beginning.

NON-STEROIDAL IS

Non-steroidal IS are often added to the steroid regimen, in generalized MG, as steroid sparing agents or if steroids are proving ineffective or intolerable.

Among various non-steroidal IS drugs in use, the efficacy of Azathioprine (AZT), the most used, is backed by the expert consensus and one randomized controlled trial (RCT).

Mycophenolate and Tacrolimus are commonly used, despite lack of support from controlled trials. Cyclosporine use, although backed by 2 RCTs, is limited due to toxicity. Oral Methotrexate, cheapest of all, can be considered, as steroid sparing agent, if others fail or are not tolerated. Overall, the efficacy of AZT (and others) is around 70-80%, as per clinical experience. These drugs have delayed onset of action, which is longer for AZT (6 months) and shorter for Cyclosporine (2 months). Often, they are needed for prolonged periods, and sometimes lifelong. The dose can later be reduced once stable remission is attained. Treatment related adverse events need close monitoring.[33]

Choice of drugs varies, as per perceived risk : benefit ratio, countries, availability, and cost concerns. While AZT is commonly used in United states, Mycophenolate is preferred in European countries. In India, cost concerns allow more use of AZT and Methotrexate. Furthermore, AZT is considered safe during pregnancy, while Mycophenolate is not Table 5.

OCULAR MG

While 80% of myasthenia begins with the ocular symptoms and later generalize, 20% remain as pure ocular and almost never progresses beyond 2 years. However, the symptoms of ptosis and esp. diplopia can be very disabling. Most respond to pyridostigmine alone, but a few would need prednisolone, fortunately in lower doses (max 25 mg daily or 50 mg AD).[34] Steroid sparing IS drugs may be needed if steroids fail to alleviate ocular symptoms. Thymectomy can be offered as a last resort.[33] Use of frenzel lens for diplopia and ptosis repair surgery are useful nonpharmacological options.

GENERALIZED MG

Initial approach varies as per the subtype, as shown in the figure 2. While AChR Ab+ve myasthenia would typically need a combination of cholinesterase inhibitors (CI) and steroids (and other IS), MuSK myasthenia are intolerant to CI and would need IS drugs combined with the early use of rituximab (RTX). Rescue therapies (PLEX/IVIg) are used in cases of worsening/crisis. Thymectomy is an option only for AChR Ab+ve myasthenia, as discussed later [Figure 2].[35]

THYMECTOMY

Pathogenetic role of thymus in myasthenia is known since the 1900s, and thymectomy for non thymomatous MG has been done for several decades with documented remissions.[36] However, randomized controlled trials were lacking, till the recently published MGTX trial, which confirmed the benefits of thymectomy. The trial randomized 126 patients of AChR-Ab+ve myasthenia (with MGFA class 2–5) to thymectomy (by Extended transsternal method) with prednisolone or prednisolone alone. Thymectomy arm needed lesser steroids and IS drugs to maintain the remission. The benefits were sustained for 5 years.[37]

Hence, as per recent AAN guidelines,[33]

(1) Thymectomy should be considered an early option in AChR-Ab+ve generalized MG, non thymomatous patients (Level B), aged between 18-50 yrs. It should be strongly considered in patients, who either fail or do not tolerate the initial immunotherapy.
(2) Robotic and other minimally invasive techniques for thymectomy are reasonable options, in place of the conventional extended sternotomy.
(3) Thymectomy can be considered in antibody negative generalised MG cases, if they fail or cannot tolerate immunosuppressive drugs.
(4) Evidence do not support the role of thymectomy in myasthenia with MuSK, LRP4 or Agrin antibodies.

Thymectomy is an elective procedure and should be done in a well controlled myasthenia, with preop IV Ig, given 10–30 days before the surgery.

Table 5: Overview of the conventional non-steroidal IS.

Name	Mech of action	Dose	Side effects	Contraindications
AZT	Purine analogue Interferes with DNA synthesis	2–3 mg/kg/d	Altered hepatic function, nausea, macrocytosis, leukopenia, thrombocytopenia, idiosyncratic reaction	Impaired liver function, leukopenia, hematological malignancies or low TPMT activity
Mycophenolate	Interferes Purine synthesis	1.5–2 g/d	Nausea, diarrhea, leukopenia, elevated liver enzymes	Cancer, leukopenia, before pregnancy
Cyclosporine	Calcineurin inhibitor	3 mg/kg/d	Nephrotoxicity, hypertension, tremor, encephalopathy	Impaired kidney function, severe hypertension, or cancer
Tacrolimus	Calcineurin inhibitor	1–2 mg/d	Hypertension, tremor, diabetes mellitus, nephrotoxicity, encephalopathy	Impaired kidney function, severe hypertension, congenital long QT syndrome or cancer
Methotrexate	Folate analogue Interferes with DNA synthesis	10–20 mg/per week	Stomatitis, nausea, hair loss, leukopenia, macrocytic anemia, lung fibrosis,	Impaired liver function, pregnancy

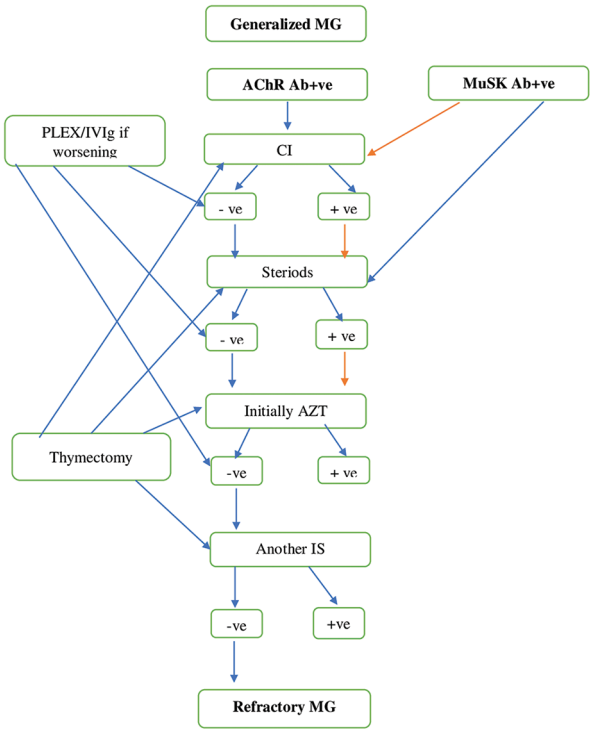

Figure 2: Approach to generalized MG.[24] –ve: poor response, +ve; good response. Blue line: recommended approach. Orange line: potential approach

MYASTHENIC CRISIS (MC)

About 15–20% of patients experience at least one crisis, mostly within first 2 years of the disease. MC is a life threating maximal manifestation of the disease, evolving rapidly within days, with profound bulbar and respiratory weakness, needing mechanical ventilation. Often it is preceded by worsening bulbar or generalized weakness over several days (impending crisis). Common triggers of MC are bronchopulmonary infections (30–40%), certain drugs, and rapid withdrawal of steroids/IS drugs. Half of the patients have no identifiable trigger. Antibiotics (Aminoglycosides, Macrolides, Quinolones), magnesium sulfate, NM blockers (Pancuronium, D-tubocurarine) can worsen MG. D-penicillamine, alpha-interferon and ICI can induce MG.[38]

Cholinergic crisis, although rare, must be ruled out. It is characterized by both nicotinic (muscle weakness, fasciculations) and muscarinic (diaphoresis, increased bronchial secretions, nausea/vomiting, diarrhea, bradycardia) toxicity.

Early identification of impending crisis is the key. Single breath count(SBC) <20 implies expiratory muscle weakness. Anti-cholinesterase medications should be lowered or discontinued in myasthenic crisis to prevent excessive pulmonary secretions. PLEX or IV Ig remains the mainstay short-term therapy for MC. Although both are equally effective, expert consensus says that PLEX acts more rapidly. Improvement is typically seen within 1–2 weeks and lasts 1–2 months. It cannot be done in the presence of sepsis and hypotension. Contraindications to IV Ig use are renal failure and hypercoagulable states. Screening for selective IgA deficiency before using IV Ig, is recommended. Corticosteriods and other IS drugs are started along with PLEX/IVIg treatment, to sustain the clinical response. It is prudent to start high dose steroids (60-100 mg prednisolone) few days after PLEX/IVIg, to mitigate the transient worsening effect of steroids. Options for refractory crisis are rituximab(RTX) and pulse cyclophosphamide.[30]

REFRACTORY MG

Most patients can achieve a stable remission with steroids and available IS drugs. However, a fraction (about 10–20%) remains refractory to the treatment and continues to show myasthenic weakness. Although there is no consensus-based definition of "treatment refractory" myasthenia, following criteria are used to define "refractoriness. "[39]

(1) Failure to respond to steroids and at least two other conventional IS drugs, used in optimum dosages for adequate duration.[30]
(2) Inability to reduce the doses of steroids (and IS drugs), after achieving remission, without causing worsening or frequent need of rescue therapies to maintain the remission.
(3) Unable to tolerate or give the immunotherapy drugs, due to various comorbidities.
(4) Frequent MC while on treatment.

Clinical variables associated with "treatment refractoriness" are well recognized. Most important factor appears to be the antibody subtype. MuSK Ab+ve myasthenia are much more likely to be refractory compared to AChR-Ab+ve.[40] But because the latter comprises the bulk of myasthenic subtype in the population, the absolute number of refractory AChR-Ab+ve cases are nearly equal (or even more) than the MuSK subtype. Reason for MuSK subtype being severe is unclear but appears to be due to extensive damage to the NMJ, including the scaffold on the post synaptic membrane that holds the AchR clusters. Thymoma presence is another significant marker of refractoriness and the severe disease.

Following options are available for refractory MG:

RITUXIMAB(RTX)

RTX is an anti-CD 20, chimeric monoclonal antibody, leading to B lymphocyte depletion. Off label use of RTX for refractory MG has prevailed over the past two decades.

RTX response is clearly dependent on the subtype of myasthenia.

The response in MuSK myasthenia is extremely good and hence advocated as an early therapeutic option.[41] In AChR-Ab+ve myasthenia, the far commoner subtype, the response is relatively less striking. In a recent systematic review of 165 patients, use of RTX resulted in significant clinical improvement in 113(68%), with 36% achieving remission. Many retrospective (and a few prospective) studies, clearly show that RTX use in AChR-Ab+ve myasthenia results in significant

and sustained beneficial response with reduction in steroid dosages and need for other IS.[42] However, a phase 2 RCT (Beat MG), which studied 52 patients, with two 6 monthly cycles of RTX, failed to show meaningful reduction in steroid doses, over 52 weeks. The role of RTX in AChR-Ab+ve myasthenia continues to be debated, and is presently considered an option, if other agents fail or are not tolerated.[33] There is evidence that RTX performed better when used early in the disease course. The protocol for RTX infusion and re-infusion varied widely across studies. Lower doses (500 mg every 6 monthly) also proved beneficial. Overall, RTX was well tolerated.

The differing responses to RTX in MuSK and AChR-Ab+ve myasthenia are probably based on the causative antibody subtypes. While the former is due to IgG4 (produced by Plasma cells), the latter occurs due to IgG1 & 3 antibodies. RTX predominantly depletes the short-lived Plasma cells, leaving the long-lived B cells intact.

ECULIZUMAB

Eculizumab is a humanized monoclonal antibody against the terminal C5 complement and prevents the formation of the membrane attack complex by complement fixing AChR antibodies. In a phase 3 multicenter RCT in refractory AChR Ab+ve MG (REGAIN), primary end point of change in MG-ADL score was no different than control arm, but most of the secondary end points improved.[43] It is approved for AChR Ab+ve MG by FDA and European Medicine Agency (EMA). Vaccination against Neisseria meningitidis is needed at least 2 weeks before the eculizumab use. High cost prohibits its common usage.

NEONATAL FC RECEPTOR (FCRN) INHIBITORS

The neonatal FcRn present in the myeloid and endothelial cells, upregulate the levels of IgG in blood by preventing their degradation. Monoclonal therapy targeted at FcRn reduces the level of pathogenic IgG, thus appears promising.[44]

SUBCUTANEOUS IMMUNOGLOBULIN (SCIG)

SCIG is a novel, efficacious and patient friendly replacement for IV Ig for refractory myasthenia. It avoids the venous access, and its slow, prolonged intravascular absorption prevents abrupt vascular load. High cost can be prohibitive.[45]

MYASTHENIA IN PREGNANCY

About 17–40% of myasthenic patients can experience worsening during pregnancy. Steroids, pyridostigmine and AZT are safe during pregnancy, while mycophenolate, methotrexate and tacrolimus are unsafe. Among short-term therapies, IVIg and PLEX are very safe. Toward the end of pregnancy, magnesium sulfate for eclampsia and opiates for pain relief are contraindicated.[46]

CONCLUDING REMARKS

MG remains a relatively common disease. While the mortality has significantly reduced due to improved therapeutics, morbidity continues. Subgrouping the patients help in better prognostication. Our understanding of pathophysiology has improved by leaps and bounds over the past decades, and this has reflected in the émergence of newer therapeutic options, such as the monoclonal antibodies, e.g., RTX. Their position however, in the treatment hierarchy continues to be hotly debated. Given the fact that conventional immunosuppressives, although effective, are needed for prolonged periods, invariably leading to silent morbidity, rôle of early use of RTX needs to be probed, esp in cases anticipated to be refractory. As we gain more experience with the newer drugs, individualistic treatment paradigms for MG are on the horizon.

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