MYASTHENIA GRAVIS

CHI Formulary Indication Review

مجلس الضمان الصحي
Council of Health Insurance

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Abbreviations

AChR: Acetylcholine receptor
ChEI: Cholinesterase inhibitor
CS: Corticosteroids
CTCAE: Common Terminology Criteria for Adverse Events
EFT: Early fast-acting treatment
FT: Fast acting treatment
FDA: Food and Drug Administration
ICIs: Immune checkpoint inhibitors
IS: Immunosuppressive
IVIg: IV immunoglobulin
JMG: Juvenile myasthenia gravis
LOMG: Late onset myasthenia gravis
RCT: Randomized Control Trial
MG: Myasthenia gravis
MGFA: Myasthenia Gravis Foundation of America
MMS: Minimal manifestation status
MuSK: Muscle-specific tyrosine kinase
PIS: Post-Intervention Status
PLEX: Plasma exchange
RAM: RAND/ UCLA Appropriateness Method
RCT: Randomized Control Trial

Executive Summary

Acquired myasthenia gravis (MG) is a common neurological autoimmune disease, resulting from binding of autoantibodies to components of the neuromuscular junction, most commonly the acetylcholine receptor (AChR). The incidence ranges from 0.3 to 2.8 per 100,000,1 and it is estimated to affect more than 700,000 people worldwide. The treatment of MG is undergoing major changes. Despite the absence of guidelines describing the treatment approaches and facilitating the clinical decision making, many consensusbased recommendations are available and multiple trials are under investigation. (Narayanaswami et al., 2021)

The increased use of immunomodulating therapies has been a major factor in improving the prognosis for patients with MG in recent years.

Myasthenia Gravis management is challenging due to the related complications and the frequent relapses.

The main target of treating MG is improving patient's mental health and quality of life while decreasing the disease's symptoms and complications. Steroids are the main stay of MG treatment, however their adverse events remarkably affect patient's lifestyle causing healthcare providers to limit their use and adapt alternative options. As such, consensus recommendations and guidelines support the use of different treatment options and approaches to MG. (Murai et al., 2023). **CHI issued MG guidelines in May 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations**. This report provides **an update on the Myasthenia Gravis Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies. Main triggers for the update** were summarized being **the issuance of new clinical guidelines** namely the **International Consensus Guidance for Management of Myasthenia Gravis- 2020** Update and the **Japanese clinical guidelines 2022 for myasthenia gravis and Lambert-Eaton myasthenic syndrome.** Table 1 below

summarizes the new MG guidelines released and their corresponding major updates.

New MG guidelines released	Major Updates
International Consensus Guidance for Management of Myasthenia Gravis- 2020 Update	The 2020 consensus guidance recommendations represent an update of the 2016 consensus recommendations for the management of myasthenia gravis. The most important update includes **thymectomy use and place in therapy** and mainly addresses **new recommendations regarding the use of rituximab, eculizumab, and methotrexate in addition to early immunosuppression in ocular MG, and MG associated with immune checkpoint inhibitor treatment.**
The Japanese clinical guidelines 2022 for	This is an update of the 2015 Japanese guidelines for MG. The main recommendations related to MG
myasthenia gravis and Lambert-Eaton myasthenic syndrome	treatment approach tackled the following subjects: **high dose oral steroid regimen, early fast-acting treatment strategy and molecular targeted drug (eculizumab).**
Overview of the treatment of myasthenia gravis	Uptodate May 2023

The major changes were the recommendations of **thymectomy, methotrexate use, withdrawal of recommendation for high dose steroid therapy with escalation and deescalation, and finally the inclusion of targeted therapy. Eculizumab, a newly introduced molecule for the MG treatment, represents**

the major change within pharmacotherapy management. This molecule is not SFDA registered.

Table 1: Major changes in Myasthenia Gravis treatment guidelines

MAJOR CHANGES		
Addition of New Molecules	**Drug Class**	**Population**
Eculizumab (Not SFDA registered)	Monoclonal antibody	For refractory AChR+ patients
Efgartigimod (Not SFDA registered)	IgG antibody Fc-fragment molecule	AChR antibody-positive patients with generalized MG
Ravulizumab	A humanized monoclonal antibody that specifically binds with the terminal complement protein C5	AChR antibody-positive patients with generalized MG

Updates were reflected throughout the document as per the below

- **All Additions** are emphasized using a green symbol, situated to the right of the gridlines.
- **All Updates** are emphasized using a red symbol, situated to the right of the gridlines.
- **All modifications or information** subject to re-phrasing are highlighted in yellow.

At the end of the report, key recommendation synthesis section is added highlighting the treatment strategy and the use of each drug class in specific group of patients.

SECTION 1.0 : MYASTHENIA GRAVIS CLINICAL GUIDELINES

1.1. Saudi Guidelines:

There are no guidelines published by Saudi medical bodies on the management of Myasthenia Gravis.

1.2. International Consensus Guidance for Management of Myasthenia Gravis (ICG-MG) [2020]

Due to limited local and international guidelines and view the limited published evidence on myasthenia gravis (MG) worldwide, The Myasthenia Gravis Foundation of America appointed a Task Force to develop treatment guidance for MG. This consensus aims to provide key evidencebased expert recommendations to health care professionals (HCPs) on the management of patients with MG, including referral pathway, definition of remission, and a treat-to-target approach.
The consensus development process was guided by an expert panel of 15 international physicians experienced in the management of MG. The 2020 update consensus is updated version of the 2016 formal consensus-based guidance for the management of MG.
(Narayanaswami et al., 2021)
The main changes and recommendations published in this update are listed below:

- Recommendations related to thymectomy use were updated
- Updated and new recommendations were developed for the use of rituximab, eculizumab, and methotrexate
- New treatment approaches were recommended regarding the use of early immunosuppressants in ocular MG and MG associated with immune checkpoint inhibitor treatment

Drug Therapy Recommendations:

- **Pyridostigmine** should be part of the initial treatment in most patients with MG
- Dose should be adjusted as needed based on symptoms
- Pyridostigmine discontinuation provides a positive indicator that the patient has met the required treatment goals

- **Corticosteroids** (CS) or Immunosuppressive (IS) therapy are indicated for patients who failed initial pyridostigmine therapy.
- **A nonsteroidal IS agent:**
- Used alone as an alternative to corticosteroids if the latter is contraindicated or intolerable.
- Used initially **in conjunction** with corticosteroids when the patient has an increased risk of steroid side effects.
- A nonsteroidal IS agent should be added to corticosteroids when:
- Patient developed or at risk to develop significant steroid side effects
- Response to an adequate trial of corticosteroids is inadequate; or
- The corticosteroid dose cannot be reduced due to symptom relapse.
- Nonsteroidal IS agents that can be used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus, Efgartigimode and Ravulizumab
- Expert consensus and some randomized controlled trial (RCT) evidence support the use of **azathioprine as a first-line** IS agent in MG.
- Oral methotrexate can be used in patients who have not tolerated, or for whom steroid-sparing agents therapy failed **IS agent dosage and duration of treatment:**
- Once patients achieve treatment goals, the corticosteroid dose should be gradually tapered. In many patients, continuing a low dose of corticosteroids long-term can help to maintain the treatment goal.
- For nonsteroidal IS agents, once treatment goals have been achieved and maintained for 6 months to 2 years, the IS dose should be tapered slowly to the minimal effective amount.
- Dosage adjustments should be made no more frequently than every 3–6 monthsc.
- Tapering of IS drugs is associated with risk of relapse, which may necessitate upward adjustments in dose. The risk of relapse is higher in patients who are symptomatic, or after rapid taper.

- It is usually necessary to maintain some immunosuppression for many years, sometimes for life.
- Patients must be monitored for potential adverse effects and complications from IS drugs.
- Changing to an alternative IS agent should be considered if adverse effects and complications are medically significant or create undue hardship for the patient.

1.2.1-Patients with refractory AChR-Ab+ MG:

Approximately 10 percent of patients with severe MG are refractory to, or are limited by the specific toxicities of, the first-line glucocorticoid-sparing therapies (azathioprine, mycophenolate, efgartigimod, ravulizumab, cyclosporine, and tacrolimus). Some require unacceptably high doses of glucocorticoids despite concurrent use of these agents. (Mantegazza & Antozzi, 2018)Refractory disease is generally considered to include patients with any of the following:

●Disease that is unchanged or worse after glucocorticoids and at least one other immunotherapeutic agent, used in adequate dose and duration, with persistent symptoms or side effects that limit function

●Need for ongoing rescue therapy with intravenous immune globulin (IVIG) or plasma exchange, or frequent myasthenic crises, while on immunotherapy

●Intolerable adverse reactions or the presence of comorbid illnesses that preclude use of conventional immunotherapies

Patients with **refractory MG** should be referred to a physician or a center with expertise in management of MG. In addition to the previously mentioned IS agents, the following therapies may also be used in refractory MG: (Narayanaswami et al., 2021)

- Chronic **IVIg** and chronic Plasma exchange (PLEX);
- Cyclophosphamide;

- Rituximab, for which evidence of efficacy is building, but for which formal consensus could not be reached.
- Alternative agent for patients who failed or did not tolerate other IS agents. Efficacy in this population is still uncertain.
- Eculizumab, a monoclonal antibody, recently approved for refractory MG treatment as an alternative agent for patients who failed or did not tolerate other IS agents. However, the efficacy of eculizumab in this population needs to be addressed by further clinical studies.
- Immunization against meningococcal meningitis is required at least 2 weeks before starting eculizumab.
- Future investigations should be done to determine the treatment duration and cost-effectiveness of eculizumab.

1.2.2-IVIg and PLEX

- PLEX and IVIg are appropriately used as short term treatments in patients with MG with **life-threatening signs** such as respiratory insufficiency or dysphagia; in preparation for surgery in patients with significant bulbar dysfunction; when a rapid response to treatment is needed; when other treatments are insufficiently effective; and prior to beginning corticosteroids if deemed necessary to prevent or minimize exacerbations.
- he choice between PLEX and IVIg depends on individual patient factors (e.g., PLEX cannot be used in patients with sepsis and IVIg cannot be used in renal failure) and on the availability of each.
- IVIg and PLEX are probably equally effective in the treatment of severe generalized MG.
- The efficacy of IVIg is less certain in milder MG or in ocular MG.
- PLEX may be more effective than IVIg in MuSKMG.
- The use of IVIg as maintenance therapy can be considered for patients with refractory MG or for those in whom IS agents are relatively contraindicated.

PLEX and IVIg are the mainstay of management in myasthenic crisis:

- Impending crisis requires hospital admission and close observation of respiratory and bulbar function, with the ability to transfer to an intensive care unit if it progresses to manifest crisis. Myasthenic crisis requires admission to an intensive care or step-down unit to monitor for or manage respiratory failure and bulbar dysfunction.
- PLEX and IVIg are used as short-term treatment for impending and manifest myasthenic crisis and in patients with significant respiratory or bulbar dysfunction.
- **In Myasthenic crisis, Corticosteroids** or other IS agents are often started at the same time to achieve a sustained clinical response. (Because corticosteroids may cause transient worsening of myasthenic weakness, it may be appropriate to wait several days for PLEX or IVIg to have a beneficial effect before starting corticosteroids).
- Although clinical trials suggest that IVIg and PLEX are equally effective in the treatment of impending or manifest myasthenic crisis, expert consensus suggests that PLEX is more effective and works more quickly.
- The choice between the 2 therapies depends on patient comorbidity (e.g., PLEX cannot be used in sepsis and IVIg is contraindicated in hypercoagulable states, renal failure, or hypersensitivity to immunoglobulin) and other factors, including availability. A greater risk of hemodynamic and venous access complications with PLEX should also be considered in the decision (many complications of PLEX are related to route of access and may be minimized by using peripheral rather than central venous access).

1.2.3-Impending and manifest myasthenic crisis

- Impending and manifest myasthenic crisis are emergent situations requiring aggressive management and supportive care.
- Although cholinergic crises are now rare, excessive ChEI cannot be completely excluded as a cause of clinical worsening. Also, ChEIs increase airway secretions, which may exacerbate breathing difficulties.

1.2.4- Thymectomy in MG

In non-thymomatous generalized MG, thymectomy is considered the treatment of choice for patients with AChR-Ab and aged 18-50 years. To improve clinical outcomes and minimize immunotherapy and hospitalization due to disease complications, thymectomy should be considered as early as possible (Narayanaswami et al., 2021)

- In patients with AChR-Ab+ generalized MG, who fail to respond to immunotherapy or experienced intolerable side effects, thymectomy should be strongly considered.
- Thymectomy should be performed when the patient is stable and the procedure deemed safe to be undergone since postoperative pain and mechanical factors can limit respiratory function.
- The value of thymectomy in the treatment of prepubertal patients with MG is unclear, but thymectomy should be considered in children with generalized AChR antibody–positive MG:
- If the response to pyridostigmine and IS therapy is unsatisfactory; or
- In order to avoid potential complications of IS therapy.
- For children diagnosed with seronegative generalized MG, the possibility of a congenital myasthenic syndrome or other neuromuscular condition should be entertained, and evaluation at a center specializing in neuromuscular diseases is of value prior to thymectomy.
- With rare exceptions, all patients with MG with thymoma should undergo surgery to remove the tumor. Removal of the thymoma is performed to rid the patient of the tumor and may not produce improvement in MG. All thymus tissue should be removed along with the tumor.
- Further treatment of thymoma will be dictated by histologic classification and degree of surgical excision. Incompletely resected thymomas should be managed after surgery with an interdisciplinary treatment approach (radiotherapy, chemotherapy).
- In elderly or multimorbid patients with thymoma, palliative radiation therapy can be considered in the appropriate clinical setting. Small

thymomas may be followed without treatment unless they are enlarging or become symptomatic.

- An increase in the use of endoscopic and robotic Interventions is noticed. In the absence of data from primary literature, safety data from experienced centers supported the safety of such procedures.

When comparing less invasive to aggressive thymectomy approaches, headto-head trials showed no difference between both approaches.

- Thymectomy may be considered as an alternative option for patients without AChR antibodies who fail to respond to IS therapy, or to avoid intolerable IS's side effects. These recommendations don't include patients with MuSK, LRP4, or agrin antibodies. Juvenile MG (see also Thymectomy in MG, no. 2).

1.2.5-Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) control the immune response and prevent host tissue damage; they are mainly expressed on the surface of T-cells. (Narayanaswami et
al., 2021)

- Candidates for ICIs should be aware of the risk of MG and other immune-mediated neurologic illnesses associated with these agents
- Severe MG accompanied with respiratory crisis is frequently seen in MG associated ICIs
- For patients with well-controlled MG, ICIs are not absolutely contraindicated, however;
- Combined therapy (anti–CTLA-4 plus anti-PD-1/PD-L1 monoclonal antibodies) should be avoided
- Close monitoring is mandatory, especially the respiratory and bulbar function
- Before ICIs treatment, MG patients in a remission state should be receiving an MG treatment

- In patients who develop overt MG; combination treatment with high-dose steroids and plasma exchange or IVIg may be required
- ICIs withdrawal is determined by the oncologist

1.2.6-Ocular MG

In ocular MG (ophthalmoparesis or ptosis), that is resistant to anticholinesterase agents, immunosuppressant agents are used when symptoms are functionally limiting or troublesome to the patient. (Narayanaswami et al., 2021)

- Corticosteroids (CS):
- Treatment of choice
- Results from a single small RCT showed that low-dose CS would be effective for ocular MG avoiding side effects associated with high-dose CS
- Steroid-sparing IS agents:
- Add-on therapy: CS alone are ineffective
- Alternative option: CS are contraindicated, or not tolerated
- Thymectomy can be used as an alternative option to patients who are AChRAb+ with ocular MG for whom acetylcholinesterase's therapy failed to show benefit for whom IS agents is not an option for any reason
- Surgery for ptosis and diplopia — Surgical correction can be performed on patients with stable ptosis. For patients who do not demonstrate stability prior to surgery, recurrence of ptosis is common due to the nature of myasthenia. The optimal duration of stability prior to surgery is unknown, although there are some indications that three to four years of stability prior to ptosis repair is appropriate

1.2.7-MG in Children

1. Children with acquired autoimmune ocular MG are more likely than adults to go into spontaneous remission. Thus, young children with only ocular symptoms of MG can be treated initially with **pyridostigmine**. Immunotherapy can be initiated if goals of therapy are not met.
2. Children are at particular risk of steroid side effects, including growth failure, poor bone mineralization, and susceptibility to

infection, due in part to a delay in live vaccinations. Long- term treatment with corticosteroids should use the lowest effective dose to minimize side effects.

3. Maintenance PLEX or IVIg are alternatives to IS drugs in JMG.

1.2.8-MG with MuSK antibodies

1. Many patients with MuSK-MG respond poorly to ChEIs, and conventional pyridostigmine doses frequently induce side effects

2. . Rituximab should be considered as an early therapeutic option in patients with MuSK-MG who have an unsatisfactory response to initial immunotherapy.

3. Patients with MuSK-MG appear to respond well to corticosteroids and to many steroid- sparing IS agents. They tend to remain dependent on prednisone despite concomitant treatment with steroid sparing agents.

4. MuSK-MG responds well to PLEX, while IVIg seems to be less effective.

1.2.9-MG in pregnancy

1. Planning for pregnancy should be instituted well in advance to allow time for optimization of myasthenic clinical status and to minimize risks to the fetus.

2. Multidisciplinary communication among relevant specialists should occur throughout pregnancy, during delivery, and in the postpartum period.

3. Provided that their myasthenia is under good control before pregnancy, the majority of women can be reassured that they will remain stable throughout pregnancy. If worsening occurs, it may be more likely during the first few months after delivery.

4. **Oral pyridostigmine** is the first-line treatment during pregnancy.

IV ChEIs may produce uterine contractions and should not be used during pregnancy.

5.Thymectomy should be postponed until after pregnancy as benefit is unlikely to occur during pregnancy.

6. Chest CT without contrast can be performed safely during pregnancy, although the risks of radiation to the fetus need to be carefully considered. Unless there is a compelling indication, postponement of diagnostic CT until after delivery is preferable.

7. Prednisone is the IS agent of choice during pregnancy.

8. Current information indicates that azathioprine and cyclosporine are relatively safe in expectant mothers who are not satisfactorily controlled with or cannot tolerate corticosteroids. Current evidence indicates that mycophenolate mofetil and methotrexate increase the risk of teratogenicity and are contraindicated during pregnancy. (These agents previously carried Food and Drug Administration [FDA] Category C (cyclosporine), D (azathioprine and mycophenolate mofetil), and X (methotrexate) ratings.

The FDA has recently discontinued this rating system, and replaced it with a summary of the risks of using a drug during pregnancy and breastfeeding, along with supporting data and "relevant information to help health care providers make prescribing and counseling decisions"[12]).

Although this statement achieved consensus, there was a strong minority opinion against the use of azathioprine in pregnancy. Azathioprine is the nonsteroidal IS of choice for MG in pregnancy in Europe but is considered high risk in the United States. This difference is based on a small number of animal studies and case reports.

9. PLEX or IVIg are useful when a prompt, although temporary, response is required during pregnancy.

Careful consideration of both maternal and fetal issues, weighing the risks of these treatments against the requirement for use during pregnancy and their potential benefits, is required.

10. Spontaneous vaginal delivery should be the objective and is actively encouraged

11. Magnesium sulfate is not recommended for management of eclampsia in MG because of its neuromuscular blocking effects; barbiturates or phenytoin usually provide adequate treatment.

12. All babies born to myasthenic mothers should be examined for evidence of transient myasthenic weakness, even if the mother's myasthenia is wellcontrolled, and should have rapid access to neonatal critical care support.

1.3. The Japanese clinical guidelines 2022 for myasthenia gravis and Lambert-Eaton myasthenic syndrome (LEMS)

The Japanese clinical guideline addressed the diagnosis and treatment of myasthenia gravis. .(Murai et al., 2023)

The guideline divides the treatment into 6 main categories:

- Early fast-acting treatment (EFT) for MG
- Steroids vs non-steroidal immunosuppressants for MG
- Intravenous immunoglobulin (IVIG) uses in MG
- Plasmapheresis uses in MG
- Newly recommended medication for MG treatment
- Thymectomy use in non-thymomatous MG patients

1.3.1- Early Fast-Acting Treatment for MG

The Japanese guidelines, strongly recommend the early initiation of fast acting treatment (FT), to achieve a rapid improvement of the symptoms and reduce the steroids dose thus minimizing their side effects. .(Murai et al., 2023)
Early fast acting treatment (EFT) is strongly recommended by the Japanese guidelines and resulted with an increase in the percentage of patients achieving their treatment target when fast-acting treatment was started as early as the patient has been diagnosed with Myasthenia Gravis.

- FT includes plasmapheresis, IVIg, intravenous methylprednisolone or a combination.
- EFT showed to have a higher efficacy rate in achieving the treatment goal defined by the Japanese guidelines as compared to conventional therapy.
- MG treatment goal: minimal manifestations (MM) with oral prednisolone equal to or less than 5mg/day (MM-5mg).
- Failure to achieve this goal or multiple FT requirements is defined as a refractory MG.

1.3.2- Oral immunosuppressive therapy

High-dose oral steroids utilizing dose escalation and de-escalation are effective against MG, but long-term use of oral steroids above a certain dosage level is known to have deleterious effects.(Murai et al., 2023)

- High-dose oral steroids require careful consideration given the other treatment options available (grade C1).
- Long-term oral steroids cause a high incidence of adverse reactions, as well as worsened quality of life and mental health; therefore, high doses should be avoided (grade C1).
- Initiation of low dose steroids at early stages, accelerates the achievement of the treatment goal.
- Calcineurin inhibitors (cyclosporine and tacrolimus) are more effective in patients with a shorter disease duration (grade C1).
- They can be used in combination with oral steroids to improve muscle strength and lower steroids dose.
- Monitoring of drug concentration and side effects is required.

1.3.3- High-dose intravenous methylprednisolone treatment

- High-dose intravenous (IV) methylprednisolone is effective against generalized MG (grade B) but entails transient initial exacerbation. Therefore, such treatment requires caution and measures to protect the patient (grade C1).
- Intermittent treatment with high-dose IV methylprednisolone improves MG symptoms while reducing the use of oral steroids and their associated side effects (grade C1).
- Initial exacerbation of symptoms caused by high dose IV methylprednisolone might be partially mitigated by carrying out the treatment directly after IVIG or plasmapheresis use (grade C1).
- Intravenous methylprednisolone is generally avoided in patients with myasthenic crisis, who are receiving IVIG or plasmapheresis to achieve short-term stabilization, because of a potential to increase the risk of critical illness myopathy.(Lacomis, 2005)

1.3.4- IVIg treatment

IVIg showed to be effective in moderate to severe cases. However, in mild cases or ocular MG its efficacy is uncertain (grade B). (Murai et al., 2023)

- In terms of improvement of exacerbated MG symptoms, IVIg and plasmapheresis showed to be equally efficacious.

  There are no available recommendations regarding long-term treatment efficacy (grade B).

- IVIg standard therapy regimen:

- The total dose of IVIG is 2 g/kg, usually over two to five days. Spreading the dose over more days is preferable in those who have renal disease, have congestive heart failure, or are older adults. In patients with concomitant cardiovascular and cerebrovascular conditions, IVIg dosing and frequency should be adjusted based on the patient's clinical condition, since IVIg is known to increases blood viscosity (grade B).

- For elderly patients or patients with unstable circulatory dynamics, IVIg is more beneficial as compared to plasmapheresis (grade C1).

- Can be administered in outpatient clinics.

1.3.5- Plasmapheresis for MG

Plasmapheresis treatment for MG showed to be effective. However, when used as a long-term treatment, it should be used in combination with immunotherapy such as IVMP. (Murai et al., 2023)

- All plasmapheresis methods showed to have similar effects when used to treat MG.
- When treating anti-MuSK antibody-positive MG patient, plasma exchange is recommended.
- A typical course of treatment consists of five exchanges (3 to 5 L of plasma each) over 7 to 14 days. The replacement fluid is albumin when used in the treatment of MG. Although done daily in some circumstances, exchanges done every other day are probably more effective in reducing the antibody levels due to the time it takes for the extravascular immunoglobulin to re-equilibrate after each plasma exchange. (Overview of the Treatment of Myasthenia Gravis - UpToDate, n.d.)

1.3.6- Eculizumab use for MG treatment

Eculizumab is a newly recommended molecular targeted drug for treatment of MG in patients who are AChR antibody-positive and in refractory MG patients who failed IVIg or plasmapheresis treatment.
(Murai et al., 2023)

1.3.6- Thymectomy for non-thymomatous MG

Might be recommended for non-thymomatous patients with an early onset MG, defined as less than 50 years, and who are positive AChR antibodies with thymic hyperplasia in the early disease stages. (Murai et al., 2023)

1.3.7- Treatment strategies for ocular MG

1- If MG symptoms are limited to the eye muscles in the early stages of the disease, there is little chance it might generalize within 2 years of onset. Therefore, if symptoms are limited to ocular muscles for this long, it is appropriate to diagnose it as ocular MG (grade C1).

2- Immunotherapy is considered effective for ocular MG, but there is no sufficient evidence available (grade C1).

3- For patients with external ophthalmoplegia sufficient to inhibit activities of daily living, steroid pulse therapy results in remission faster than standard oral steroid therapy (grade C1).

4- Anticholinesterase agents are often used for symptomatic treatment, but efficacy against ocular MG is limited, with sufficient efficacy in just 20–50% of cases (grade C1).

5- Naphazoline eye drops are effective for symptomatic treatment when eyelid ptosis is the only MG symptom, or when it is the only symptom persisting post-treatment (grade C1).

6- One treatment option for eyelid ptosis refractory to treatment is eyelid elevation (grade C1).

1.3.8- Treatment strategies for Late onset Myasthenia gravis and elderly MG patients

Ocular MG is more common in late onset myasthenia gravis (LOMG) than in early onset MG (EOMG) or thymoma-associated MG (TAMG) (grade C1). (Murai et al., 2023)

- Generalized LOMG responds well to immunotherapy, and the target of prednisolone MM-5mg or lower is easily achieved (grade C1).
- Full remission is difficult to achieve regardless of whether thymectomy is carried out or not (grade C1).
- For non-thymomatous LOMG, thymectomy is not recommended as a first-line treatment (grade C1).
- IVIg is recommended for elderly patients and is more effective when compared to plasmapheresis (grade C1).

1.4. Myasthenia gravis: Association of British Neurologists' Management Guidelines

TREATMENT OF OCULAR MYASTHENIA GRAVIS

- Starting treatment for ocular myasthenia gravis
- Start pyridostigmine following protocol.
- If the serum ACh-R antibody is positive and the patient is aged under 45: years: consider thymectomy at presentation

- If symptomatic despite pyridostigmine, start prednisolone (generally given on alternate days)xiv
- If symptoms relapse on prednisolone withdrawal at a dose 7.5–10 mg/day (or 15–20 mgalternate days) or greater, consider immunosuppression See sections ‘Patients who do not achieve remission with prednisolone’ and ‘Immunosuppression’.

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Pyridostigmine dose escalation protocol

- Titrate up to find the lowest effective dose:
- ▸ Initially 30 mg (½ tablet) four times daily for 2–4 days.
- ▸ Then 60 mg (1 tablet) four times daily for : days and experiment with timing.
- ▸ Then increase to 90 mg four times daily over 1 week if required. The duration of action varies, and some patients require five divided daily doses.
- If pyridostigmine does not control symptoms satisfactorily within a few weeks, start prednisolone.
- Management of side effects: Propantheline or mebeverine can help cholinergic side effects.

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Withdrawal:

- ▸ If using pyridostigmine monotherapy, prescribe the lowest effective dose. · ▸ If asymptomatic following introduction of prednisolone only, withdraw slowly at 30–60 mg per week, until either withdrawn, or use the lowest effective dose.

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Protocol for starting prednisolone for outpatients with ocular myasthenia gravis

- Start : 5mg on alternate days for three doses and increase by : 5mg every three doses until symptoms improve.
- The maximum dose is :50 mg on alternate days or 0.75mg/kg/alternate day for ocular myasthenia gravis.
- Clinical remission of myasthenia on corticosteroid treatment is defined as the absence of symptoms and signs after pyridostigmine withdrawal.

- Some patients are resistant to corticosteroids or respond very slowly. After 3 months of treatment, non-responders should be referred to a myasthenia specialist.
- Prednisolone may either induce or exacerbate diabetes mellitus. This should be monitored.xix

- Daily rather than alternate day prednisolone may improve glycaemic control in patients taking treatment for elevated plasma glucose.

Bone protection protocol for patients treated with corticosteroids

- Use local agreed guidelines.

Prednisolone withdrawal for ocular myasthenia gravis

- Prednisolone should be titrated down, seeking the lowest effective dose, only after achieving remission (absence of symptoms and signs having withdrawn from pyridostigmine) for at least 2–3 months:
- ▸ Reduce by : 5mg alternate day/calendar month down to 20 mg alternate days.
- ▸ Then reduce by 2.5: mg alternate day/calendar month down to 10 mg alternate days.
- ▸ Below 10 mg alternate days reduce by 1 mg/month.
- ▸ Should symptoms recur, follow guidance for myasthenic relapse (see section 'Assessment and management of the relapsing patient with myasthenia).

Corticosteroid maintenance dose and criteria for introducing immunosuppression

- ▸ A prednisolone dose above 15–20 mg on alternate days is probably too high for long-term use, and is an indication to introduce immunosuppression with azathioprine.xx
- ▸ Intolerable corticosteroid side effects are an indication to introduce immunosuppression to reduce the corticosteroid maintenance dose.

TREATMENT OF GENERALISED MYASTHENIA GRAVIS

- Starting treatment for generalised myasthenia gravis
- 1. Start pyridostigmine following protocol. See section 'Pyridostigmine dose escalation protocol'.
- 2. ACh-R antibody seropositive and aged under 45: years: consider thymectomy.
- 3. If symptomatic despite pyridostigmine, start prednisolone (generally given on alternate days)xxiii See section 'Protocol for starting prednisolone for outpatients with generalised myasthenia gravis'.
- 4. If relapse occurs on prednisolone withdrawal at a dose of 7.5–10 mg/day (or 15–20 mg alternate days) or greater, introduce immunosuppression.xxiv Immunosuppression may also be used for patients with corticosteroidrelated side effects on low-dose

prednisolone.xxv See sections ‘Patients who do not achieve remission with prednisolone’ and ‘Immunosuppression’.

Pyridostigmine dose escalation protocol

- Titrate up to find the lowest effective dose:
- ▸ Initially 30 mg (½ tablet) four times daily for 2–4 days.
- ▸ Then 60 mg (1 tablet) four times daily for : days and experiment with timing. · ▸ Then increase to 90 mg four times daily over 1 week if required.

The duration of action varies, and some patients require five divided daily doses. If pyridostigmine fails to control symptoms satisfactorily within a few weeks, start prednisolone.

- Management of side effects: propanthelinexxvi or mebeverine can help cholinergic side effects. Withdrawal:
- ▸ If using pyridostigmine monotherapy, prescribe the lowest effective dose.
- ▸ If asymptomatic after introduction of prednisolone only, withdraw slowly at 30–60 mg per week, until withdrawn, or use the lowest effective dose.

Protocol for starting prednisolone for outpatients with generalised myasthenia gravis

- Start 10 mg on alternate daysxxviii for three doses and increase by 10 mg every three doses until symptomsimprove. Maximum dose is 100 mg alternate days or 1.5 mg/kg for generalised myasthenia gravis. It may take many months to achieve full remission.
- Remission of myasthenia on corticosteroid therapy is defined as the absence of symptoms and signs after pyridostigmine withdrawal.
- For failure to respond, or side effects on increasing corticosteroids, seek expert opinion for guidance on the use of plasma exchange, intravenous immunoglobulin or immunosuppression. If not in remission after 3 months of corticosteroid treatment, refer for expert opinion.
- Prednisolone may induce or exacerbate diabetes mellitus. This should be monitored.
- Using daily rather than alternate day prednisolone may improve glycaemic control in patients taking treatment for elevated plasma glucose.

Protocol for withdrawal of prednisolone for generalized myasthenia gravis

- ▸ Prednisolone should be titrated down seeking the lowest effective dose only after achieving remission (absence of symptoms and signs having withdrawn pyridostigmine) for at least 2–3 months.
- ▸ Reduce by 10 mg/calendar month down to 40 mg on alternate days.
- ▸ Then reduce by 5 mg/calendar month down to 20 mg on alternate days.
- ▸ Then reduce by 2.5 mg per calendar month down to 10 mg alternate days.
- ▸ Below 10 mg alternate days, reduce by 1 mg/month, aiming for a maintenance dose of 7 or 8 mg.
- ▸ Should symptoms recur, follow guidance for myasthenic relapse (see section 'Assessment and management of the relapsing patient with myasthenia').

Corticosteroid maintenance dose and criteria for starting immunosuppression · ▸ A corticosteroid dose above 15–20 mg on alternate days is probably an indication to introduce alternative immunosuppression with azathioprine.

- Intolerable corticosteroid side effects are an indication to introduce immunosuppression to reduce the corticosteroid maintenance dose.

PATIENTS WHO DO NOT ACHIEVE REMISSION WITH PREDNISOLONE

- Patients who do not achieve symptom remission on the prednisolone escalation protocol

- ▸ Some patients appear to fail to respond to the recommended doses of prednisolone. This may result from a slow response to corticosteroids, which may take up to 3 months and sometimes much longer.
- ▸ The commonest reason for a patient to fail to respond to corticosteroids is using an insufficient dose.
- ▸ If a patient does not respond adequately to the target dose after 3 months, seek a specialist opinion.

IMMUNOSUPPRESSION

- Corticosteroid maintenance dose and criteria for introducing immunosuppression
- ▸ We recommend that an immunosuppressive agent is introduced only if a patient does not achieve remission on corticosteroid monotherapy.
- ▸ A corticosteroid dose above 15–20 mg on alternate days is probably unacceptable for long- term use.
- ▸ Intolerable corticosteroid side effects are an indication to introduce immunosuppression to reduce the corticosteroid maintenance dose. · ▸ Immunosuppression should be considered early on in patients with diabetes mellitus, osteoporosis, or ischaemic heart disease or significant bulbar or respiratory weakness that does not respond rapidly to corticosteroids.
- ▸ Immunosuppression and vaccination: Vaccines are less effective in immunosuppressed patients. Live vaccines are absolutely contraindicated and there is an increased risk from live- attenuated vaccines.
- Patients requiring immunosuppression should have their vaccinations updated. This might include pneumococcus, influenza, Haemophilus influenzae and Varicella zoster. Where feasible, clinicians should plan vaccinations (with blood tests to assess response) before starting immunosuppression.
- Corticosteroids in high doses can reduce the immune response to vaccines and live virus vaccinations should be delayed for at least 1 month after stopping high-dose corticosteroids.

Immunosuppression with azathioprine

- ▸ Azathioprine is the first-line agent. Thiopurine methyltransferase (TMPT) should be measured in view of the association between TMPT

deficiency and myelosuppression with azathioprine. TMPT deficiency is not a contraindication to using azathioprine but may reduce the dose required. Patients with very low TMPT activity should not take azathioprine.

- ▸ Azathioprine should be increased over 1 month to a maintenance dose of 2.5 mg/kg.
- Blood tests should be monitored weekly (full blood count, urea and electrolytes, liver function tests) as the dose is titrated upwards. The dose may need to be modified in light of side effects or changes in blood tests. We recommend using local shared-care protocols.

- ▸ Azathioprine is slow to achieve maximum effect.
- The target is to achieve a maintenance dose of prednisolone of below 20 mg on alternate days after 2 years. Failure to achieve efficacy may be a consequence of inadequate dosing. Not all patients respond to azathioprine.

- Corticosteroids should be withdrawn using the protocol described. There is a debate as to whether taking azathioprine is a contraindication to using intrauterine contraceptive devices. This is based on a few case reports.
- There is probably no good reason to avoid intrauterine contraceptive devices, but specialist advice should be sought. It is possible to take azathioprine during pregnancy, and it is considered safe for breastfeeding mothers.

- ▸ Myasthenia gravis may relapse on corticosteroid withdrawal.
- This may be a consequence of a slow response to azathioprine or using too low a dose. The lowest effective corticosteroid dose before relapse is the maintenance dose. If this is above 20 mg on alternate days, this is considered a relapse and requires action. See section
- **Assessment and management of the relapsing patient with myasthenia'.**

Other immunosuppressive agents

- **Mycophenolate mofetil, methotrexate, cyclosporin, rituximab**
- These agents have a role in managing poorly responsive myasthenia when azathioprine has failed or the patient cannot tolerate it. Poor study design and small numbers means that the literature is unhelpful. Most patients should respond to pyridostigmine, prednisolone and azathioprine if used correctly.
- Non-responders or those with treatment complications should be referred to a myasthenia specialist.

- Selecting a second-line agent must take into account factors such as concurrent renal disease and reproductive intentions; ciclosporin appears no more harmful than azathioprine in pregnancy.
- Methotrexate is teratogenic in men and women, and effective contraception is mandatory until at least 3 months after stopping the drug. Mycophenolate mofetil may cause congenital malformations and so women should use effective contraception during its use and for at least 6 weeks after stopping it.

ASSESSMENT AND MANAGEMENT OF THE RELAPSING PATIENT WITH MYASTHENIA

- Determine whether the patient's deterioration is a myasthenic relapse, a side effect of treatment or another condition?
- Is the deterioration due to intercurrent infection (the most common cause of relapse, after drug reduction)?
- Has the patient received medication that causes myasthenic weakness? (eg, antibiotics, betablockers)?
- Is the deterioration a consequence of changes in treatment, particularly steroid withdrawal?
- ▸ If a cause for myasthenia deterioration can be found, it should be managed. · ▸ Patients with myasthenia deterioration should return to the steroid increase protocol, increasing prednisolone until symptoms are controlled up to the target dose of 1.5 mg/kg or 100 mg alternate day for generalised myasthenia and 0.75 mg/kg or 50 mg alternate days for ocular myasthenia. · ▸ If the relapse occurred on a dose of prednisolone above 15–20 mg alternate days in a patient treated without receiving azathioprine, then azathioprine should be introduced following the protocol described above.

- ▸ If the myasthenia deterioration was a result of steroid withdrawal in a patient receiving azathioprine, the relapse may have been a result of too short a duration ofazathioprine for maximum efficacy, or too low a dose.
- The prednisolone should then be titrated up following the protocol until symptomatic control is regained.
- Following the protocol, the prednisolone should then be titrated down to the lowest effective dose. If this is greater than 20 mg alternate days, a specialist opinion should be sought.

INPATIENT MANAGEMENT OF MYASTHENIA GRAVIS

- General principles
- ▸ A patient should be managed in hospital for significant bulbar symptoms, low vital capacity, respiratory symptoms or progressive deterioration.
- ▸ Assessment by speech and language therapist to advise on swallowing is mandatory.
- ▸ Regular assessment of vital capacity is mandatory.
- Intravenous immunoglobulin use for severe bulbar or respiratory symptoms
- ▸ 1–2 g/kg is the total dose.
- ▸ This may be given as 0.5 g/day for 2 days, or 0.4 g/day for 5 days. Follow local practice
- ▸ If symptoms persist despite the use of intravenous immunoglobulin, request specialist opinion on whether to use a second dose of intravenous immunoglobulin or to use plasma exchange.xlviii
- Plasma exchange
- ▸ May be preferred in the presence of specific risk factors for intravenous immunoglobulin.
- Prednisolone
- ▸ Start by following the standard protocol for generalized myasthenia gravis. See section ‘Protocol for starting prednisolone for outpatients with generalised myasthenia gravis’.

MANAGEMENT OF MYASTHENIA GRAVIS IN INTENSIVE CARE UNITSFor ventilated **patients:**

- ▸ Start prednisolone at 100 mg alternate days.
- ▸ Start intravenous immunoglobulin immediately.

▸ Avoid inappropriate use of intravenous magnesium.

- ▸ Consider avoiding pyridostigmine/neostigmine as these may increase secretions.

For non-ventilated patients:

- ▸ Start prednisolone following the standard protocol for generalised myasthenia gravis.
- ▸ Start intravenous immunoglobulin immediately.
- ▸ Avoid using pyridostigmine/neostigmine.

MYASTHENIA GRAVIS IN PREGNANCY

- ▸ It is important to plan well in advance of pregnancy to allow time to optimise myasthenic status, thyroid function and the drug regimen.
- ▸ Use multidisciplinary liaison throughout the pregnancy, delivery and neonatal period.
- ▸ Provided that the myasthenia gravis is under good control before a pregnancy, most women can be reassured that it will remain stable throughout pregnancy and the postpartum months.
- ▸ The aim should be for spontaneous vaginal delivery (and actively encouraged).
- ▸ Those with severe myasthenic weakness need careful multidisciplinary management with prompt access to specialist advice and facilities.
- ▸ Newborn babies of myasthenic mothers risk transient myasthenic weakness (with onset up to a few days postpartum) even if the mother is well controlled. These babies should have access to neonatal highdependency support.
- ▸ Fetal arthrogryposis is a rare but recognised complication of maternal myasthenia gravis.
- ▸ Pyridostigmine is not expected to cross the placenta, and there have been no reports of fetal malformations. It is compatible with breast feeding.
- ▸ Prednisolone has not been shown to increase fetal malformations. ·
  ▸ Azathioprine appears safe in pregnancy, as is ciclosporin.

▸ Mycophenolate mofetil and methotrexate are not safe in pregnancy and methotrexate is not safe in breast feeding.

Criteria for using intravenous immunoglobulin

- Intravenous immunoglobulin should be used only for significant myasthenia symptoms in the inpatient setting. It should not generally be used as a maintenance therapy. Patients whose myasthenia symptoms cannot be controlled without more than one course of intravenous immunoglobulin should have an expert opinion.
- Use pyridostigmine carefully in patients with obstructive respiratory disease, brady- dysrhythmias, impaired renal function and recent coronary occlusion.
- The drug information sheet specifies that propantheline is contraindicated in myasthenia gravis: this is not correct as it is a standard treatment for the side effects of pyridostigmine.
- The evidence suggests that the biggest error in managing myasthenia is the failure to induce remission in a timely manner using corticosteroids. There is a tendency to try to avoid using large doses of corticosteroids. If it is tolerated, the top dose is prednisolone 0.75 mg/kg for ocular disease. Corticosteroid-induced deterioration in myasthenia sometimes occurs. It is particularly associated with starting high-dose corticosteroids. It can occur in patients adhering to the dose regimen recommended in these guidelines, though it may also be confused with the deterioration in symptoms that continues until the benefit from corticosteroids becomes apparent, often within a week or two. If in doubt, seek expert advice.
- The side effects are probably minimised by using alternate day dosing.
- Patients with known diabetes mellitus should be monitored following the introduction of corticosteroids. Experts are aware of non-diabetic patients who developed diabetes mellitus, sometimes months after starting prednisolone. It is beyond the scope of these guidelines to offer specific guidance in this area. Local guidelines should be used.
- There is little hard evidence on the absolute safest long-term dose of corticosteroids. Since a component of the complications can be managed by bone protection, and blood pressure and

lipid management, there may be individual cases with other health problems, in whom higher doses of maintenance corticosteroids would be better than immunosuppression. In principle, however, failure to control myasthenia symptoms with a ‘safe’ dose of corticosteroids is the main indication for starting immunosuppression.

- There is little evidence for the pyridostigmine and prednisolone dose schedules recommended here and there have been no studies comparing treatment regimens. These guidelines are based on the practice of experts in the field. The emphasis is on identifying the optimum dose for each patient. Undertreatment, particularly with corticosteroids, is the commonest cause of persisting symptoms.

- Many experts consider thymectomy, particularly the less traumatic and scarminimising video- assisted thoracoscopic thymectomy in a young person with seropositive generalized myasthenia gravis. Thymectomy appears most effective if carried out early on, say 2 years after symptom onset.
- An alternate day regimen is thought to reduce side effects. Daily corticosteroids may be suitable in some patients, such as those with diabetes mellitus.
- In principle, other than in exceptional circumstances, immunosuppression is not started other than following relapse induced by corticosteroid withdrawal. Some patients with complex medical problems, higher doses of corticosteroids may be preferable to immunosuppression, or vice versa. Exceptional cases should be discussed with a myasthenia expert.
- It is impossible to provide absolute guidance on minimum corticosteroid requirements. There will be some patients in whom even low-dose steroids cause side effects, and who might be treated with immunosuppression. There may be good reasons why other patients are treated with a slightly higher than recommended prednisolone dose in preference to immunosuppression. Exceptions should be discussed with a myasthenia expert.
- Pyridostigmine should be used carefully in patients with obstructive respiratory disease, brady- dysrhythmias, impaired renal function and recent coronary occlusion. The drug information sheet specifies that propantheline is contraindicated in myasthenia gravis: this is incorrect as it is a standard treatment for the side effects of pyridostigmine.
- The evidence suggests that the biggest error in managing myasthenia is not inducing remission in a timely manner using corticosteroids.
- Clinicians tend to try to avoid using large doses of corticosteroids. If the patient tolerates these, the top dose is prednisolone 0.75 mg/kg for ocular disease and 1.5 mg/kg for generalised myasthenia gravis.
- Corticosteroid-induced deterioration in myasthenia may sometimes occur. This can be confused with the ongoing deterioration in symptoms that continues until the corticosteroids start to help, often within a week or two. If in doubt, seek expert advice.
- Alternate day dosing probably minimises side effects.
- We recommend monitoring patients with known diabetes mellitus after starting corticosteroids. Occasionally, non-diabetic patients develop diabetes mellitus, sometimes months after starting prednisolone. It is beyond the scope of these guidelines to offer specific guidance for blood glucose monitoring; local guidelines should be used.

- This is the typical rate of corticosteroid reduction. If there are other factors, such as serious side effects, the corticosteroids might be withdrawn more rapidly. Discuss with a myasthenia expert.
- There is little hard evidence on the absolute safest long-term dose of steroids. Since a component of the complications can be managed by bone protection, and blood pressure and lipid management, there may be individual cases with other health problems, in whom higher doses of maintenance steroids would be preferable to immunosuppression. In principle, however, failure to control myasthenia symptoms with a 'safe' dose of corticosteroids is the primary indication for the initiation of immunosuppression.

- There is little hard evidence on the absolute safest long-term dose of corticosteroids. Since a component of the complications can be managed by bone protection, and blood pressure and lipid management, there may be individual cases with other health problems, in whom higher doses of maintenance steroids would be preferable to immunosuppression. In principle. however, failure to control myasthenia symptoms with a 'safe' dose of corticosteroids is the primary indication for the initiation of immunosuppression.
- There is a range of immunosuppressive agents that can be successfully used in myasthenia despite the lack of robust evidence for their use. All studies are underpowered or suffer from design faults. The criteria for selecting agents might include safety in pregnancy, time to onset of efficacy and risk of complications, although there is often a lack of evidence in these areas. In practice, we recommend that non-experts manage patients with corticosteroids to induce remission, and use azathioprine as a corticosteroidsparing agent. If this fails, then the patient should be referred to a myasthenia expert to advise on alternative immunosuppressive agents.
- Note that TMPT levels will be modified in patients who have received blood products. Patients with low serum TMPT concentrations can be treated with lower doses of azathioprine. Some experts recommend using a dose of 2: mg once daily. In view of the evidence from other conditions that correlates efficacy with a rise in mean corpuscular volume and/or a drop in peripheral lymphocyte count, others titrate the dose up until there is a haematological response. 6-thioguanine nucleotides (6-TGN), which are incorporated into DNA, are the active metabolites of azathioprine. 6-TGN has started to be used to monitor compliance and toxicity. It is not widely available but can be used to guide dosing.
- In rheumatological and gastroenterology patients, azathioprine efficacy correlates with a drop in lymphocyte count and/or an elevation in mean corpuscular volume. In inflammatory bowel disease,

macrocytosis appears to be the better marker. There is no evidence in myasthenia, but anecdotal observations suggest that a failure to respond to azathioprine is more common in patients without a change in these indices. We recommend treating using the initial mg/kg dosing, and following local shared-care protocols. A specialist opinion should be sought if difficulties arise.

- The pivotal azathioprine study4 showed efficacy at 2 years but not at 1 year. It is likely that this varies between patients.
- A patient taking 100 mg alternate day prednisolone would take 14 months to reduce to a safe maintenance dose.
- Azathioprine is widely considered to be low risk in pregnancy and is the drug of choice in the UK. In the USA, it is considered high risk. This differing advice is based on a small number of animal studies and case reports. Other immunosuppressive agents pose more definite risks to the fetus. Studies, largely from patients with inflammatory bowel disease taking azathioprine, suggest a modestly increased risk of low birth weight or atrial or ventricular septal defects, though other studies suggest that these relate to disease activity rather than to azathioprine. A detailed discussion of these issues is beyond the scope of these guidelines. The risks and benefits should be discussed with individual patients.
- Azathioprine is either undetectable in breast milk or is found in very low concentrations. The only concern would be that higher concentrations may occur in the breast milk of mothers with a low serum TMPTconcentration. Asymptomatic low levels of neutrophils may develop in babies, leading some experts to recommend monitoring exclusively breastfed babies, though most feel that this is unnecessary. The concentration of azathioprine in breast milk drops significantly 4–6 h after taking the drug. A detailed discussion of these issues is beyond the scope of these guidelines.
- A comprehensive list of the causes of weakness is beyond the scope of these guidelines. Patients may describe tiredness, which may be hard to distinguish from fatigable muscular weakness. Steroid-induced muscle weakness is recognised. Neurological deterioration is common in patients with intercurrent infection. Other autoimmune conditions are more common in myasthenia, such as thyroid disorders and B12 deficiency, and may cause neurological symptoms. Degenerative spine disease resulting in myelopathy or lumbar canal

stenosis may give rise to weakness. In most cases, the symptoms and signs are inconsistent with myasthenia and careful history and examination with targeted investigations should reveal the diagnosis. If in doubt, a neurological opinion should be sought or an expert in myasthenia should be asked to review.

- A range of medications may cause myasthenia or result in increased weakness in patients known to have myasthenia. Certain antibiotics are particularly implicated, such as aminoglycosides. Some medications are well recognised as having this effect while other agents are described in case reports. Clinical decisions must depend on circumstances. A list of medications can be found on the UK-based Myasthenia Gravis Association website (http://www.myaware.org/information-for-medicalprofessionals/39-
- Contraindications-of-drugs-that-can-make-myasthenia-worse). A more detailed review can be found on the Myasthenia Gravis Foundation of America website. (http://www.myasthenia.org/LinkClick.aspx?fileticket=JuFvZPPq2vg%3D).
- Sometimes, especially when a patient is slowly withdrawing prednisolone at the rate of 1 mg per month, the reversal of one or two of the previous reductions will bring the myasthenia under control. If not, revert to the initial steroid upward titration protocol.
- In the presence of limb symptoms only, treatment should be with corticosteroids in the first instance. These can be slow to take effect, during which time the patient may continue to deteriorate. This should not be confused with corticosteroid-induced deterioration. Intravenous immunoglobulin has rare but life-threatening side effects and should not be used as first-line agent for all myasthenia patients. Corticosteroids are the primary treatment for moderate or severe myasthenia. Note: the duration of efficacy of intravenous immunoglobulin is 3–4 weeks, after which a stable patient may deteriorate if the patient is not established on an effective corticosteroid dose.
- Intravenous immunoglobulin increases blood viscosity. Patients with known vascular occlusive disease might be given this over more rather than fewer days. Careful hydration might be a sensible precaution.
- We prefer intravenous immunoglobulin as the treatment of choice as it is frequently easier and faster to give. Plasma exchange may be better if there are specific immunoglobulin risk factors (thrombotic tendency, unstable angina, recent stroke, IgA deficiency, etc).
- Note that antacids, laxatives and supplements may contain magnesium.

Efgartigimod

Efgartigimod alfa is an IgG antibody Fc-fragment molecule designed to promote degradation of IgG autoantibodies.
fgartigimod was approved by the FDA and in Japan for use in AChR antibody-positive patients with generalized MG.

●Dosing:
Efgartigimod is given as a weekly infusion at 10 mg/kg IV for four weeks with observation of the treatment response afterward to determine the next course of treatment. Some patients may have a robust and prolonged response and may only need one or two treatment cycles a year.

●Adverse effects:
Common adverse included headache, nasopharyngitis, and upper respiratory infection.
Other adverse effects include leukopenia and development of pathogenic serum antibodies.

Ravulizumab
Ravulizumab is a humanized monoclonal antibody that specifically binds with the terminal complement protein C5, preventing disruption of neuromuscular transmission, presumably by inhibiting membrane attack complex-mediated destruction of the postsynaptic membrane. This medication is structurally similar to eculizumab but has been altered to maintain a concentration in the serum that requires less frequent dosing at eight-week intervals.

Ravulizumab was approved by the FDA for use in AChR antibody-positive patients with generalized MG.

●Dosing:
Ravulizumab is given as a variable weight-based dose. After a loading dose, the maintenance dose is given two weeks later and then continued every eight weeks thereafter.

●Adverse effects:
Headache was the most frequently reported adverse effect.
Patients should be immunized with meningococcal vaccines at least two weeks prior to administering the first dose of ravulizumab.

SECTION 2.0: DRUG THERAPY IN MG

2.1 Cholinesterase Inhibitors

Saudi FDA Indications:

Drug	
Pyridostigmine (SFDA approved) Neostigmine (EMA approved for the indication) Rivastigmine (unapproved for the indication and not mentioned by the guidelines)	Myasthenia gravis

Clinical guidelines recommendations and Efficacy *[1][2][3]*

- 1. Pyridostigmine should be part of the initial treatment in most patients with MG.
- **Pyridostigmine** dose should be adjusted as needed based on symptoms.
- The ability to discontinue pyridostigmine can be an indicator that the patient has met treatment goals and may guide the tapering of other therapies.
- 1. Children with acquired autoimmune ocular MG are more likely than adults to go into spontaneous remission. Thus, young children with only ocular symptoms of MG can be treated initially with **pyridostigmine**.
- **Oral pyridostigmine** is the first-line treatment during pregnancy. TREATMENT OF OCULAR MYASTHENIA GRAVIS · Starting treatment for ocular myasthenia gravis
- 1. Start pyridostigmine following protocol.
- Anticholinesterase agents are often used for symptomatic treatment, but efficacy against ocular MG is limited, with sufficient efficacy in just 20–:0% of cases (grade C1).[3]

TREATMENT OF GENERALISED MYASTHENIA GRAVIS ·

Starting treatment for generalised myasthenia gravis

- 1. Start pyridostigmine following protocol.
- 2. ACh-R antibody seropositive and aged under 4: years: consider thymectomy.

- 3. If symptomatic despite pyridostigmine, start prednisolone (generally given on alternate days)
- 4. If relapse occurs on prednisolone withdrawal at a dose of 7.:–10 mg/day (or 1:–20 mg alternate days) or greater, introduce immunosuppression. Immunosuppression may also be used for patients with corticosteroidrelated side effects on low-dose prednisolone.

Conclusion: According to guidelines, cholinesterase inhibitors (especially Pyridostigmine) are effective first line agents for management of myasthenia gravis. They are effective and safe first line options in pregnancy.

2.1.2 Safety profile:

Common

- **Dermatologic:** Diaphoresis
- **Gastrointestinal:** Diarrhea, Excessive salivation, Increased peristalsis, Stomach cramps
- **Musculoskeletal:** Cramp, Muscle fasciculation
- **Neurologic:** Asthenia
- **Ophthalmic:** Miosis
- **Respiratory:** Excessive bronchial secretions conclusion:
- The Most important side effects are the Cholinergic effects: eg, salivation, sweating, urinary incontinence. Overdosage may result in cholinergic crisis (eg, muscle weakness).
- Propantheline is given in Myasthenia Gravis patients ONLY IF the patient is receiving cholinesterase-inhibitors to antagonize the muscarinic side effects, otherwise it's use alone is contraindicated. Propantheline is not available on the Saudi list.

.2.1.4 Drug-Drug interactions profile:[:]

Immunosuppressant drugs

The requirement for pyridostigmine bromide could be decreased when additional therapy (steroids, immunosuppressant drugs) is given although peak plasma concentration and AUC of pyridostigmine may decrease by high doses of corticosteroids. *Methylcellulose*

Methylcellulose and medicine containing methylcellulose as excipients can completely inhibit absorption of pyridostigmine bromide.

Antimuscarinics

Atropine and hyoscine antagonise the muscarinic effects of pyridostigmine bromide. It should be noted that the slower gastro-intestinal motility caused by these drugs may affect the absorption of pyridostigmine bromide.

Muscle Relaxants

Pyridostigmine antagonises the effect of non-depolarising muscle relaxants (e.g. pancuronium and vecuronium). Pyridostigmine may prolong the effect of depolarising muscle relaxants (e.g. suxamethonium).

Others

Aminoglycoside antibiotics, local and some general anesthetics, antiarrhythmic agents, and other drugs that interfere with neuromuscular transmission may interact with pyridostigmine bromide.

conclusion: Potential interactions should be carefully reviewed before use.

2.1. : Contraindications Profile:[4]

- Hypersensitivity to anticholinesterase agents (Documentation of allergenic cross-reactivity for anticholinergic muscle stimulants)
- Mechanical intestinal obstruction
- Urinary obstruction conclusion: contraindications should be carefully reviewed before use.

2.1.6 Dosage and administration [4] [2][:]

Table 1: Dosage and Administration

Drug	Strength	Dosage Form	Dose	Maximum daily dose

Pyridostigmine	60 mg tablet.	--	(Syrup, tablets) Initial: 30 to 60 mg 3 times daily; may increase in increments of 30 mg/dose every 2 to 3 days based on response and tolerability to 60 to 120 mg every 3 to 4 hours while awake. orally daily, spaced throughout the day to provide maximum relief when maximum strength is needed; dosage and frequency must be individualized; mild cases may respond to 60 to 360 mg daily, while severe cases may require up to 1:00 mg daily Extended-release tablets) 180 to :40 mg orally once or twice daily, spaced at least every 6 hours; supplemental doses of the pyridostigmine 60-mg conventional tablets or the 60 mg/: mL syrup may be used for optimal control of symptoms • **Pyridostigmine dose escalation protocol** • Titrate up to find the lowest effective dose: · ▸ Initially 30 mg (½ tablet) four times daily for 2–4 days. • ▸ Then 60 mg (1 tablet) four times daily for : days and	

			experiment with timing.	

			· ▸ Then increase to 90 mg four times daily over 1 week if required. The duration of action varies, and some patients require five divided daily doses.	
Neostigmine	2.:mg 0.: mg	IV I M	1 – 2.:mg by IM or SC injection at intervals throughout the day, when maximum strength is needed. The usual duration of action of a dose is two to four hours. The total daily dose is usually : – 20mg by injection but	

			higher doses may be needed by some patients. Neonatal Myasthenia Gravis may be treated with 0.1mg Neostigmine intramuscularly initially. Thereafter, the dose must be titrated individually. But is usually 0.0: – 0.2:mg IM or 0.03mg/kg IM, every two – four hours. Because of the selflimiting nature of the disease in neonates, the daily dosage should be reduced until the drug can be withdrawn. Older Children: (Under 12 years of age) May be given 0.2 – 0.:mg by injection as required. Dosage requirements should be adjusted according to the response of the patient.	

2.1.7 Therapeutic designation and suggested prescribing edits

Table 1: Therapeutic Designation

Drug	Strength	Dosage Form	Therapeutic designation	Prescribing edits
Pyridostigmine	60 mg Tablet		Essential	--
Neostigmine	2.:mg 0.: mg	IV I M	Essential	PA
Rivastigmine	--	--	Non essential	--

conclusion:

- Cholinesterase inhibitors are essential first line options for management of Myasthenia gravis.
- Pyridostigmine is the agent most frequently studied and recommended by guidelines. However, it is not available in KSA. It is available in oral formulation, **adding this agent to the formulary is recommended.**
- Neostigmine is approved for the indication and essential in the formulary.
- Rivastigmine is neither approved for the indication nor mentioned by the guidelines. Prescribing edit

Prior authorization (PA)

- Cholinesterase inhibitors are essential first line options for management of Myasthenia gravis. Their use should be approved and monitored by a specialist.

2.2 Corticosteroids

2.2.1 Saudi FDA Indications:

Drug	
Prednisone Methylprednisolone	Indicated in the management of all conditions deemed likely to benefit from short or long term glucocorticoid therapy. Use in myasthenia gravis is off-labelled, yet it is recommended by the guidelines with moderate evidence.

Clinical guidelines recommendations and Efficacy *[1][2][3]*

- **Corticosteroids** or Immunosuppressive (IS) therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine.
- **In Myasthenic crisis, Corticosteroids** or other IS agents are often started at the same time to achieve a sustained clinical response. (Because corticosteroids may cause transient worsening of myasthenic weakness, it may be appropriate to wait several days for PLEX or IVIg to have a beneficial effect before starting corticosteroids).

- Patients with MuSK-MG appear to respond well to corticosteroids and to many steroid-sparing IS agents. They tend to remain dependent on prednisone despite concomitant treatment with steroid sparing agents.
- Prednisone is the IS agent of choice during pregnancy. TREATMENT OF OCULAR MYASTHENIA GRAVIS
- Starting treatment for ocular myasthenia gravis.
- 1. Start pyridostigmine following protocol.
- 2. If the serum ACh-R antibody is positive and the patient is aged under 4: years: consider thymectomy at presentation.
- 3. If symptomatic despite pyridostigmine, start prednisolone (generally given on alternate days).
- For patients with external ophthalmoplegia sufficient to inhibit activities of daily living, steroid pulse therapy results in remission faster than standard oral steroid therapy (grade C1).

TREATMENT OF GENERALISED MYASTHENIA GRAVIS

- Starting treatment for generalised myasthenia gravis
- 1. Start pyridostigmine following protocol. See section 'Pyridostigmine dose escalation protocol'.
- 2. ACh-R antibody seropositive and aged under 4: years: consider thymectomy.
- 3. If symptomatic despite pyridostigmine, start prednisolone (generally given on alternate days). See section 'Protocol for starting prednisolone for outpatients with generalised myasthenia gravis'.
- 4. If relapse occurs on prednisolone withdrawal at a dose of 7.:–10 mg/day (or 1:–20 mg alternate days) or greater, introduce immunosuppression. Immunosuppression may also be used for patients with corticosteroidrelated side effects on low-dose prednisolone. See sections 'Patients who do not achieve remission with prednisolone' and 'Immunosuppression'.

High-dose intravenous methylprednisolone treatment

- Recommendations
- · High-dose intravenous (IV) methylprednisolone is effective against generalized MG (grade B), but entails transient initial exacerbation. Therefore, such treatment requires caution and measures to protect the patient (grade C1).

- · Intermittent treatment with high-dose IV methylprednisolone improves MG symptoms while reducing quantities of oral steroids and steroidrelated adverse reactions (grade C1).
- · Initial exacerbation of symptoms caused by high dose IV methylprednisolone might be partially mitigated by carrying out the treatment directly after PE/PP (grade C1).

Conclusion: According to guidelines, corticosteroids are effective for the management of myasthenia gravis. Prednisone is used after failure of pyridostigmine to manage the symptoms. prednisone is the recommended immunosuppressive for pregnant women. High dose IV Methylprednisolone is effective against generalized Myasthenia gravis.

2.2.2 Safety profile: [4][2]

Common

- **Cardiovascular:** Hypertension
- **Endocrine metabolic:** Body fluid retention, Increased appetite, And weight gain
- **Musculoskeletal:** Osteoporosis
- **Psychiatric:** Disturbance in mood **Serious**
- **Cardiovascular:** Cardiac arrest, Cardiac rupture due to and following acute myocardial infarction, Congestive heart failure, Fat embolism, Shock, Syncope
- **Dermatologic:** Impaired wound healing
- **Endocrine metabolic:** Cushing's syndrome, Decreased body growth, In pediatric patients with long-term corticosteroid use, Hyperglycemia, Hypocalcemia, Hypocortisolism secondary to another disorder, Hypokalemia
- **Gastrointestinal:** Gastrointestinal perforation, Pancreatitis
- **Hematologic:** Thromboembolic disorder
- **Immunologic:** Anaphylaxis, Angioedema
- **Musculoskeletal:** Aseptic necrosis of bone, Disorder of muscle, Fracture of bone, Rupture of tendon
- **Neurologic:** Paralytic syndrome, Pseudotumor cerebri, Seizure
- **Ophthalmic:** Central serous chorioretinopathy, Glaucoma, Posterior subcapsular cataract
- **Psychiatric:** Psychotic disorder
- **Respiratory:** Pulmonary edema, Pulmonary tuberculosis
- **Other:** At risk for infection, Kaposi's sarcoma · **Monitoring parameters for long term use:**
- Monitor Blood Pressure.

- Obtain hemoglobin, occult blood loss, electrolytes, and blood glucose.
- Monitor growth with long-term use in pediatric patients.
- Assess for signs and symptoms of HPA axis suppression/adrenal insufficiency or infection.
- Assess for ocular changes and obtain IOP with therapy >6 weeks.
- Obtain chest x-ray at regular intervals in patients on prolonged therapy.

conclusion:

- Children are at particular risk of steroid side effects, including growth failure, poor bone mineralization, and susceptibility to infection, due in part to a delay in live vaccinations. Long- term treatment with corticosteroids should use the lowest effective dose to minimize side effects.
- Patients requiring immunosuppression should have their vaccinations updated. This might include pneumococcus, influenza, Haemophilus influenzae and Varicella zoster. Where feasible, clinicians should plan vaccinations (with blood tests to assess response) before starting immunosuppression.
- Prednisolone may either induce or exacerbate diabetes mellitus. This should be monitored.
- Daily rather than alternate day prednisolone may improve glycaemic control in patients taking treatment for elevated plasma glucose.
- Discontinuation of therapy: Withdraw therapy with gradual tapering of dose to avoid Addisonian crisis.

2.2.3 Drug-Drug interactions profile:[:][2]

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Hepatic microsomal enzyme inducers: Drugs that induce hepatic enzyme cytochrome P-4:0 (CYP) isoenzyme 3A4 such as phenobarbital, phenytoin, rifampicin, rifabutin, carbamazepine, primidone and aminoglutethimide may reduce the therapeutic efficacy of corticosteroids by increasing the rate of metabolism. Lack of expected response may be observed and dosage of Prednisolone Tablets may need to be increased.

Hepatic microsomal enzyme inhibitors: Drugs that inhibit hepatic enzyme cytochrome P-4:0 (CYP) isoenzyme 3A4 (e.g. ketoconazole, troleandomycin) may decrease glucocorticoid clearance. Dosages of

glucocorticoids given in combination with such drugs may need to be decreased to avoid potential adverse effects.

Antidiabetic agents: Glucocorticoids may increase blood glucose levels. Patients with diabetes mellitus receiving concurrent insulin and/or oral hypoglycemic agents may require dosage adjustments of such therapy.

Non-steroidal anti-inflammatory drugs: Concomitant administration of ulcerogenic drugs such as indomethacin during corticosteroid therapy may increase the risk of GI ulceration. Aspirin should be used cautiously in conjunction with glucocorticoids in patients with hypoprothrombinaemia. Although concomitant therapy with salicylate and corticosteroids does not appear to increase the incidence or severity of GI ulceration, the possibility of this effect should be considered. Serum salicylate concentrations may decrease when corticosteroids are administered concomitantly. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Salicylates and corticosteroids should be used concurrently with caution. Patients receiving both drugs should be observed closely for adverse effects of either drug.

Antibacterials: Rifamycins accelerate metabolism of corticosteroids and thus may reduce their effect. Erythromycin inhibits metabolism of methylprednisolone and possibly other corticosteroids.

Anticoagulants: Response to anticoagulants may be reduced or less often, enhanced by corticosteroids. Close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

Antiepileptics: Carbamazepine, phenobarbital, phenytoin and primidone accelerate metabolism of corticosteroids and may reduce their effect.

Antifungals: Risk of hypokalaemia may be increased with amphotericin, therefore concomitant use with corticosteroids should be avoided unless corticosteroids are required to control reactions; ketoconazole inhibits metabolism of methylprednisolone and possibly other corticosteroids.

Antivirals: Ritonavir possibly increases plasma concentrations of prednisolone and other corticosteroids.

Cardiac Glycosides: Increased toxicity if hypokalaemia occurs with corticosteroids.

Ciclosporin: Concomitant administration of prednisolone and ciclosporin may result in decreased plasma clearance of prednisolone (i.e. increased plasma concentration of prednisolone). The need for appropriate dosage adjustment should be considered when these drugs are administered concomitantly.

Cytotoxics: Increased risk of haematological toxicity with methotrexate.

Mifepristone: Effect of corticosteroids may be reduced for 3-4 days after mifepristone.

Vaccines: Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished.

Oestrogens: Oestrogens may potentiate the effects of glucocorticoids and dosage adjustments may be required if oestrogens are added to or withdrawn from a stable dosage regimen.

Somatropin: Growth promoting effect may be inhibited.

Sympathomimetics: Increased risk of hypokalaemia if high doses of corticosteroids given with high doses of bambuterol, fenoteral, formoteral, ritodrine, salbutamol, salmeterol and terbutaline.

Antacids can reduce the absorbtion of prednisolone if given in high doses.Indigestion remedies should not be taken at the same time of day as Prednisolone.

Corticosteroids should not be used concurrently with retinoids and tetracyclines due to increased intracranial pressure.

Other: The desired effects of hypoglycaemic agents (including insulin), antihypertensives and diuretics are antagonised by corticosteroids; and the hypokalaemic effect of acetazolamide, loop diuretics, thiazide diuretics, carbenoxolone and theophylline are enhanced.

conclusion: Problematic interactions profile.

- Vaccines are less effective in immunosuppressed patients. Live vaccines are absolutely contraindicated and there is an increased risk from live-attenuated vaccines.
- Corticosteroids in high doses can reduce the immune response to vaccines and live virus vaccinations should be delayed for at least 1 month after stopping high-dose corticosteroids.

2.2. : Contraindications Profile:[4]

- fungal infection, systemic , unless needed to control a drug reaction; risk of exacerbation
- hypersensitivity to predniSONE or any component of the product

- Herpes simplex of the eye, measles, or chickenpox (except when being used for short-term or emergency therapy); peptic ulcer; nonspecific ulcerative colitis; diverticulitis; viral or bacterial infection not controlled by antiinfectives [Canadian labelling]

conclusion: Contraindications should be carefully reviewed before use.

2.2.6 Dosage and administration [2][6][7]

Table 1: Dosage and Administration

Drug	Strength	Dosage Form	Dose	Maximum daily dose

Prednisone	:,10&20,2: m g 3mg/ ml	Tabl et Syru p	An alternate day regimen is thought to reduce side effects. Daily corticosteroids may be suitable in some patients, such as those with diabetes mellitus. **Protocol for starting prednisolone for outpatients with ocular myasthenia gravisxvii** Start : mg on alternate daysxviii for three doses and increase by : mg every three doses until symptoms improve. The maximum dose is :0 mg on alternate days or 0.7: mg/kg/alternate day for ocular myasthenia gravis. **Prednisolone withdrawal for ocular myasthenia gravisxi** Prednisolone should be titrated down, seeking the lowest effective dose, only after achieving remission (absence of symptoms and signs having withdrawn from pyridostigmine) for at least 2–3 months: ▸ Reduce by : mg alternate day/calendar month down to 20 mg alternate days. ▸ Then reduce by 2.: mg alternate day/calendar month down to 10 mg alternate days. ▸ Below 10 mg alternate days reduce by 1 mg/month. **Corticosteroid maintenance dose and criteria for introducing immunosuppression** ▸ A prednisolone dose above 1:–20 mg on alternate days is probably too high for	A corticosteroid dose above 1:–20 mg on **alternate days** is probably unacceptable for long-term use.xxxiv Clinicians tend to try to avoid using large doses of corticosteroids . If the patient tolerates these, the top dose is prednisolone 0.7: mg/kg for ocular disease and 1.: mg/kg for generalised myasthenia gravis.

			long-term use, and is an indication to	

			introduce immunosuppression with azathioprine.xx **Protocol for starting prednisolone for outpatients with generalised myasthenia gravisxxvii** Start 10 mg on alternate daysxxviii for three doses and increase by 10 mg every three doses until symptomsimprove. Maximum dose is 100 mg alternate days or 1.: mg/kg for generalised myasthenia gravis. It may take many months to achieve full remission. **Protocol for withdrawal of prednisolone for generalized myasthenia gravisxxx** ▸ Prednisolone should be titrated down seeking the lowest effective dose only after achieving remission (absence of symptoms and signs having withdrawn pyridostigmine) for at least 2–3 months. ▸ Reduce by 10 mg/calendar month down to 40 mg on alternate days. ▸ Then reduce by : mg/calendar month down to 20 mg on alternate days. ▸ Then reduce by 2.: mg per calendar month down to 10 mg alternate days. ▸ Below 10 mg alternate days, reduce by 1 mg/month, aiming for a maintenance dose of 7 or 8 mg. **MANAGEMENT OF MYASTHENIA**	

			GRAVIS IN INTENSIVE CARE UNITS For ventilated patients: ▸ Start prednisolone at 100 mg alternate days.	

Methyl prednisolone	**40,12:,:00 mg&1g**	IV	2 g of methylprednisolone intravenously every five days or 1 g/day one to three times every 6 months.[:][7]	

2.2.7 Therapeutic designation and suggested prescribing edits

Table 2: Therapeutic Designation

Drug	Strength	Dosage Form	Therapeutic designation	Prescribing edits
Prednisone	:,10&20,2:mg 3mg/ml	Tablet Syrup	Essential	PA
Methyl prednisolone	1g	IV		PA

- Corticosteroids are essential for the management of moderate- severe myasthenia gravis.
- Steroids are recommended in case of the presence of limb symptoms only.[2]
- Corticosteroids are also used as a first line in anti-MUSK patients as they don't respond to cholinesterase inhibitors.
- Prednisone is used after failure of pyridostigmine to manage the symptoms.

prednisone is the recommended immunosuppressive for pregnant women.

- High dose IV Methylprednisolone is effective against generalized Myasthenia gravis.
- The only agents mentioned in the guidelines are prednisone and methylprednisolone. Prescribing edits:

Prior authorization (PA)

- Corticosteroids are essential for the management of moderate- severe myasthenia gravis. Prednisone is used after failure of pyridostigmine to manage the symptoms. prednisone is the recommended

immunosuppressive for pregnant women. Corticosteroids are also recommended in case of the presence of limb symptoms only.

Corticosteroids are also used as a first line in anti-MUSK patients who don't respond to cholinesterase inhibitors. A specialist should approve its use and monitor the possible side effects. The specialist should also decide the duration and the withdrawal protocol.

- High-dose intravenous (IV) methylprednisolone is effective against generalized MG, but entails transient initial exacerbation. Therefore, such treatment requires caution and measures to protect the patient. A specialist should approve and monitor its use.

2.3 Non-steroidal Oral Immunosuppressive therapies

2.3.1 Saudi FDA Indications:

Drug	
Azathioprine Cyclosporine Mycophenolate mofetil Methotrexate Tacrolimus	Indicated in immunosuppressive regimens as an adjunct to immunosuppressive agents that form the mainstay of treatment (basic immunosuppression). Use in Myasthenia gravis is off-labelled, yet recommended by the guidelines with moderate level of evidence for azathioprine and weak evidence for calcineurin inhibitors.

Clinical guidelines recommendations and Efficacy *[1][2][3]*

- 2. **A nonsteroidal IS agent** should be used alone when corticosteroids are contraindicated or refused.

- A nonsteroidal IS agent should be used initially in conjunction with corticosteroids when the risk of steroid side effects is high based on medical comorbidities.
- A nonsteroidal IS agent should be added to corticosteroids when:
  a. Steroid side effects, deemed significant by the patient or the treating physician, develop;
  b. Response to an adequate trial (table e-1) of corticosteroids is inadequate; or

c. The corticosteroid dose cannot be reduced due to symptom relapse.

- Nonsteroidal IS agents that can be used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. The following factors should be considered in selecting among these agents:
- a. There is widespread variation in practice with respect to choice of IS agent since there is little literature comparing them.
- b. Expert consensus and some RCT evidence support the use of azathioprine as a first-line IS agent in MG.
- c. Evidence from RCTs supports the use of cyclosporine in MG, but potential serious adverse effects and drug interactions limit its use.
- d. Although available RCT evidence does not support the use of mycophenolate and tacrolimus in MG, both are widely used, and one or both are recommended in several national MG treatment guidelines.4–7
- 4. Patients with refractory MG should be referred to a physician or a center with expertise in management of MG. In addition to the previously mentioned IS agents, the following therapies may also be used in refractory MG:
- For nonsteroidal IS agents, once treatment goals have been achieved and maintained for 6 months to 2 years, the IS dose should be tapered slowly to the minimal effective amount.
- It is usually necessary to maintain some immunosuppression for many years, sometimes for life.
- Changing to an alternative IS agent should be considered if adverse effects and complications are medically significant or create undue hardship for the patient.
- **In Myasthenic crisis, Corticosteroids** or other IS agents are often started at the same time to achieve a sustained clinical response. (Because corticosteroids may cause transient worsening of myasthenic weakness, it may be appropriate to wait several days for PLEX or IVIg to have a beneficial effect before starting corticosteroids).
- Patients with MuSK-MG appear to respond well to corticosteroids and to many steroid-sparing IS agents. They tend to remain dependent on

prednisone despite concomitant treatment with steroid sparing agents.

- Current information indicates that azathioprine and cyclosporine are relatively safe in expectant mothers who are not satisfactorily controlled with or cannot tolerate corticosteroids.

- Current evidence indicates that mycophenolate mofetil and methotrexate increase the risk of teratogenicity and are contraindicated during pregnancy. (These agents previously carried Food and Drug Administration [FDA] Category C (cyclosporine), D (azathioprine and mycophenolate mofetil), and X (methotrexate) ratings.
- The FDA has recently discontinued this rating system, and replaced it with a summary of the risks of using a drug during pregnancy and breastfeeding, along with supporting data and "relevant information to help health care providers make prescribing and counseling decisions"12).
- Although this statement achieved consensus, there was a strong minority opinion against the use of azathioprine in pregnancy.
- Azathioprine is the nonsteroidal IS of choice for MG in pregnancy in Europe but is considered high risk in the United States. This difference is based on a small number of animal studies and case reports.

TREATMENT OF OCULAR MYASTHENIA GRAVIS

- Starting treatment for ocular myasthenia gravisxi
- 1. Start pyridostigmine following protocol.
- 2. If the serum ACh-R antibody is positive and the patient is aged under 4: years: consider thymectomy at presentation.xii xiii
- 3. If symptomatic despite pyridostigmine, start prednisolone (generally given on alternate days)xiv
- 4. If symptoms relapse on prednisolone withdrawal at a dose of 7.:–10 mg/day (or 1:–20 mg alternate days) or greater, consider immunosuppression.xv See sections 'Patients who do not achieve remission with prednisolone' and 'Immunosuppression'. TREATMENT OF GENERALISED MYASTHENIA GRAVIS
- Starting treatment for generalised myasthenia gravis

- 1. Start pyridostigmine following protocol. See section ‘Pyridostigmine dose escalation protocol’.
- 2. ACh-R antibody seropositive and aged under 4: years: consider thymectomy.
- 3. If symptomatic despite pyridostigmine, start prednisolone (generally given on alternate days). See section ‘Protocol for starting prednisolone for outpatients with generalised myasthenia gravis’.
- 4. If relapse occurs on prednisolone withdrawal at a dose of 7.:–10 mg/day (or 1:–20 mg alternate days) or greater, introduce immunosuppression.xxiv Immunosuppression may also be used for patients with corticosteroidrelated side effects on low-dose prednisolone.xxv See sections ‘Patients who do not achieve remission with prednisolone’ and ‘Immunosuppression’.
- Immunosuppression should be considered early on in patients with diabetes mellitus, osteoporosis, or ischaemic heart disease or significant bulbar or respiratory weakness that does not respond rapidly to corticosteroids.

Immunosuppression with azathioprine

- ▸ Azathioprine is the first-line agent. Thiopurine methyltransferase (TMPT) should be measured in view of the association between TMPT deficiency and myelosuppression with azathioprine. TMPT deficiency is not a contraindication to using azathioprine but may reduce the dose required. Patients with very low TMPT activity should not take azathioprine.

- failure to control myasthenia symptoms with a ‘safe’ dose of corticosteroids is the primary indication for the initiation of immunosuppression.
- Patients with low serum TMPT concentrations can be treated with lower doses of azathioprine. Some experts recommend using a dose of 2: mg once daily. In view of the evidence from other conditions that correlates efficacy with a rise in mean corpuscular volume and/or a drop in peripheral lymphocyte count, others titrate the dose up until there is a haematological response. 6-thioguanine nucleotides (6-TGN), which are incorporated into DNA, are the active metabolites of azathioprine. 6-TGN has started to be used to monitor compliance and toxicity. It is not widely available but can be used to guide dosing.
- Calcineurin inhibitors (cyclosporine and tacrolimus) are more effective in patients with a shorter disease duration (grade C1).

Conclusion: According to guidelines, oral immunosuppressants are effective agents for management of myasthenia gravis. Azathioprine is the first line agent. Immunosuppressants are added after corticosteroids

(except in patients with diabetes mellitus, osteoporosis, or ischaemic heart disease or significant bulbar or respiratory weakness that does not respond rapidly to corticosteroids.)

2.3.2 Safety profile: [4][2]

Tacrolimus

Common

- **Cardiovascular:** Peripheral edema (6% to 36%)
- **Dermatologic:** Alopecia (systemic formulations: up to 28.9% topical: 1%), Persistent erythema of skin (topical: 7% to 28%), Persistent erythema of skin (20% to :8%), Pruritus (systemic formulations: 1:% to 36% ; topical: 19% to 46%), Rash (10% to 24%)
- **Gastrointestinal:** Constipation (systemic formulations: 14%% to 40% ; topical: between 0.2% and 1%), Diarrhea (Systemic formulations: 13.9% to 72% ; topical: 2% to :%), Nausea (Systemic formulations: 13% to 46% ; topical: 1% to 3%), Vomiting (Systemic formulations: 13% to 29% ; topical: 1% to 6%)
- **Hematologic:** Anemia (systemic formulations: :% to :0% ; topical: between 0.2% and less than 1%
  ), Leukocytosis (8% to 32%), Thrombocytopenia (14% to 24%)
- **Neurologic:** Headache (Systemic formulations, 9% to 64% ; topical, :% to 20%), Insomnia (systemic formulations: 9% to 64% ; topical: 1% to 4%), Paresthesia (Systemic formulations, 17%
  to 40% ; topical, 3%), Tremor (1:% to :4%)
- **Renal:** Serum creatinine raised (Adult, 9% to 23% ; pediatric, 46%)
- **Respiratory:** Increasing frequency of cough (Systemic formulations: 11.4% to 31% ; topical 1% to 18% .) **Serious**
- **Cardiovascular:** Atrial fibrillation (Less than 1:%), Cardiac arrest (Less than 1:%), Cardiomegaly, Congestive heart failure, Hypertension (Systemic formulations: 4% to 89% ; topical: 1% to 2%), Myocardial infarction (Less than 1:%), Prolonged QT interval
- **Endocrine metabolic:** Diabetes mellitus, Post-transplant (10% to 37%), Hyperkalemia (12% to 4:%), Hypomagnesemia (3% to 48%)
- **Gastrointestinal:** Gastrointestinal perforation (3% to 1:%)
- **Hematologic:** Pure red cell aplasia
- **Hepatic:** Hepatitis, Hepatotoxicity

- **Immunologic:** Anaphylaxis, Infectious disease, Lymphoproliferative disorder, Malignant lymphoma, Opportunistic infection
- **Neurologic:** Posterior reversible encephalopathy syndrome, Seizure
- **Renal:** Acute renal failure, Hemolytic uremic syndrome, Nephrotoxicity (36% to :9%)

- **Respiratory:** Acute respiratory distress syndrome (Less than 1:%)
- **Monitoring parameters for tacrolimus:**
- Renal function, hepatic function, serum electrolytes (magnesium, phosphorus, potassium), glucose and blood pressure, measure 3 times/week for first few weeks, then gradually decrease frequency as patient stabilizes.
- Signs/symptoms of anaphylactic reactions during IV infusion should also be monitored. Patients should be monitored for hypersensitivity during the first 30 minutes of the infusion, and frequently thereafter.
- Monitor for QT prolongation; consider echocardiographic evaluation in patients who develop renal failure, electrolyte abnormalities, or clinical manifestations of ventricular dysfunction.
- Whole blood concentrations should be used for monitoring (trough for oral therapy drawn typically within 30 minutes prior to the next dose).

Methotrexate
Common
- **Dermatologic:** Alopecia (0.:% to 3%), Photosensitivity, Rash
- **Gastrointestinal:** Diarrhea (1% to 3%), Nausea and vomiting (greater than 10%)
- **Hematologic:** Leukopenia (1% to 3%), Thrombocytopenia (3% to 10%)
- **Neurologic:** Dizziness (1% to 3%) **Serious**
- **Cardiovascular:** Pericardial effusion, Thromboembolic disorder
- **Dermatologic:** Toxic epidermal necrolysis
- **Gastrointestinal:** Gastrointestinal hemorrhage, Stomatitis (2% to 10%)
- **Hematologic:** Aplastic anemia, Malignant lymphoma, Myelosuppression, Pancytopenia (1% to 3%
)
- **Hepatic:** Cirrhosis of liver (0.1%), Hepatic fibrosis (7%), Hepatitis, Hepatotoxicity, Liver failure
- **Neurologic:** Encephalopathy, Neurotoxicity, Seizure
- **Renal:** Nephrotoxicity
- **Respiratory:** Interstitial pneumonia (Infrequent (0.1%-1.2%) .)
- **Other:** Infectious disease, Tumor lysis syndrome
- **Warnings**
- Appropriate use:
- Because of the possibility of serious toxic reactions (which can be fatal), methotrexate should be used only in life-threatening conditions. Serious adverse reactions, including deaths, have been reported with methotrexate in the treatment of malignancy, psoriasis, and rheumatoid arthritis. Closely monitor for adverse reactions of the bone marrow, GI tract,

liver, lungs, skin, and kidneys. Patients should be informed by their physician of the risks involved and be under a physician's care throughout therapy.

- Pregnancy:
- Bone marrow suppression:

- Renal impairment:
- Hepatotoxicity:
- Hypersensitivity:
- Pneumonitis:
- Gastrointestinal toxicity:
- Secondary malignancy:
- Tumor lysis syndrome:
- Dermatologic toxicity:
- Opportunistic infections:
- Radiotherapy:
- Experienced physician (injection):
- **Monitoring for Methotrexate:**
- CBC with differential and platelets (baseline, 7 to 14 days after initiating therapy or dosage increase, every 2 to 4 weeks for first few months, then every 1 to 3 months depending on leukocyte count and stability of patient)
- BUN and serum creatinine (baseline and every 2 to 3 months) calculate glomerular filtration rate if at risk for renal dysfunction
- consider PPD for latent TB screening (baseline)
- LFTs (baseline, monthly for first 6 months, then every 1 to 2 months; more frequently if at risk for hepatotoxicity or if clinically indicated; liver function tests should be performed at least : days after the last dose)
- chest x-ray (baseline if underlying lung disease); pulmonary function test (if methotrexate- induced lung disease suspected)

<u>Mycophenolate mofetil</u>
Common

- **Cardiovascular:** Edema (Kidney transplant, 21%; heart transplant, 67.:%; liver transplant,
  48.4%),
  Hypertension (Kidney transplant, 27.:%; heart or liver transplant, 62.1% to 78.9%)
- **Endocrine metabolic:** Hyperglycemia (Heart or liver transplant, 43.7% to 48.4%)
- **Gastrointestinal:** Abdominal pain (Kidney transplant, 22.4%; heart transplant,

41.9%; liver transplant, 62.:%), Constipation (Heart or liver transplant, 37.9% to 43.6%), Diarrhea (Kidney transplant, 30.4%; heart or liver transplant, :1.3% to :2.6%), Nausea (Heart or liver transplant, :4.:% to :6.1%), Vomiting (Heart or liver transplant, 32.9% to 39.1%)

- **Musculoskeletal:** Musculoskeletal pain (Kidney transplant, 24.8%; heart or liver transplant 74% to 79.2%)
- **Neurologic:** Headache (Heart or liver transplant, :3.8% to :8.:%), Insomnia (Heart or liver transplant, 43.3% to :2.3%)
- **Renal:** Serum blood urea nitrogen raised (Heart transplant, 36.7%), Serum creatinine raised (Heart transplant, 42.2%)
- **Respiratory:** Dyspnea (Heart transplant, 44.3%; liver transplant, 31%)
- **Other:** Fever (Heart or liver transplant, :2.3% to :6.4%) **Serious**
- **Gastrointestinal:** Gastric ulcer, Gastrointestinal hemorrhage (3% to less than 20%), Gastrointestinal perforation

- **Hematologic:** Anemia (Kidney transplant, 20%; heart or liver transplant, 43% to 4:%), Leukopenia (28.6% to 4:.8%), Neutropenia (Severe) (Up to 3.6%), Pancytopenia (3% to less than 20%), Pure red cell aplasia, Thrombocytopenia (Heart or liver transplant, 24.2% to 38.3%)
- **Hepatic:** Reactivation of hepatitis B viral hepatitis, Reactivation of hepatitis C viral hepatitis
- **Immunologic:** Infectious disease, Lymphoproliferative disorder following transplantation (0.4% to 1.3:%), Opportunistic infection, Sepsis (Approximately 2% to :%)
- **Neurologic:** Progressive multifocal leukoencephalopathy
- **Renal:** Renal impairment caused by Polyomavirus · **Respiratory:** Pleural effusion (Liver transplant, 34.3%) · **Warning:**
- [US Boxed Warning]: Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Avoid if safer treatment options are available. Females of reproductive potential must be counseled regarding pregnancy prevention and planning.
- [US Boxed Warning]: Should be administered under the supervision of a physician experienced in immunosuppressive therapy.
- **Monitoring for Mycophenolate:**
- Complete blood count (weekly for first month, twice monthly during months 2 and 3, then monthly thereafter through the first year);
- renal and liver function
- and symptoms of bacterial, fungal, protozoal, new or reactivated viral, or opportunistic infections.

- neurological symptoms (e.g. hemiparesis, confusion, cognitive deficiencies, ataxia) suggestive of PML.
- pregnancy test (sensitivity of ≥2: milliunits/mL; immediately prior to initiation and 8 to 10 days later in females of childbearing potential, followed by repeat tests during therapy)
- monitor skin (for lesions suspicious of skin cancer); monitor for signs of lymphoma; monitor for signs of pure red cell aplasia or autoimmune hemolytic anemia.

Azathioprine
Common

- **Gastrointestinal:** Nausea and vomiting (12%) **Serious**
- **Cardiovascular:** Pericarditis
- **Dermatologic:** Skin cancer
- **Gastrointestinal:** Pancreatitis, Hypersensitivity
- **Hematologic:** Acute myeloid leukemia, Hematologic toxicity, Leukopenia (Renal transplant, more than :0%; rheumatoid arthritis, 28%), Leukopenia (Severe), Less than 2:00 cells/mm[3] (renal transplant, 16%; rheumatoid arthritis, :.3%), Macrocytic anemia, Myelodysplastic syndrome, Myelosuppression (:%), Pancytopenia, Thrombocytopenia
- **Hepatic:** Hepatotoxicity (less than 1%), Lymphoma involves liver, Venoocclusive disease of the liver
- **Immunologic:** Hypersensitivity reaction, Malignant lymphoma (0.:%), Tcell lymphoma, Hepatosplenic
- **Neurologic:** Progressive multifocal leukoencephalopathy

- **Respiratory:** Adenocarcinoma of lung
- **Other:** Infectious disease (renal transplant, 20%; rheumatoid arthritis, less than 1%), Neoplastic disease (0.:% to 11.9%)
- **Warnings:**
- US Boxed Warning]: Chronic immunosuppression with azathioprine (a purine antimetabolite), increases the risk of malignancy. Malignancies reported have included post-transplant lymphoma and hepatosplenic Tcell lymphoma (HSTCL) in patients with inflammatory bowel disease. Health care providers using this medication should be very familiar with this risk, as well as with the mutagenic potential to both men and women, and with possible hematologic toxicities. Patients should be informed of the risk for malignancy development
- Discontinuation of therapy: Myasthenia gravis: Abrupt cessation of this or any immunosuppressant, especially in clinically unstable individuals, may result in rapid deterioration of myasthenic symptoms and possibly myasthenic crisis

- **Monitoring for Azathioprine:**
- CBC with differential and platelets (weekly during first month, twice monthly for months 2 and 3, then monthly thereafter; monitor more frequently with dosage modifications),
- total bilirubin, liver function tests (every 3 months), CrCl, monitor for signs/symptoms of infection and malignancy (e.g. splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss).
- Patients taking azathioprine for a prolonged time period should avoid sun exposure and be monitored for skin cancer regularly.

Cyclosporin

Common

- **Cardiovascular:** Hypertension (13% to :3%)
- **Dermatologic:** Hirsutism (21% to 4:%)
- **Gastrointestinal:** Drug-induced gingival hyperplasia (4% to 16%)
- **Neurologic:** Headache (1% to 1:%), Tremor (12% to ::%)
- **Ophthalmic:** Blepharitis (Ophthalmic route 1% to :%), Burning sensation in eye (Ophthalmic route, 17%), Conjunctival hyperemia (Ophthalmic route, 1% to 6%), Eye irritation (Ophthalmic route, 1% to :%), Pain in eye (Ophthalmic route, emulsion 1% to :% ; solution, 22%) **Serious**
- **Endocrine metabolic:** Hyperkalemia, Hypomagnesemia
- **Hepatic:** Hepatotoxicity (7% or less)
- **Immunologic:** Disease due to Polyomavirus
- **Neurologic:** Encephalopathy, Progressive multifocal leukoencephalopathy, Seizure (1% to :%)
- **Renal:** Hemolytic uremic syndrome, Nephrotoxicity (2:% to 38%)
- **Other:** Infectious disease · **Warnings:**
- [US Boxed Warning]: May cause hypertension; risk is increased with increasing doses/duration.
- [US Boxed Warning]: Renal impairment, including structural kidney damage has occurred (when used at high doses); risk is increased with increasing doses/duration; monitor renal function closely.

- [US Boxed Warning]: Prescribing and dosage adjustment should only be under the direct supervision of an experienced physician. Adequate laboratory/medical resources and follow- up are necessary.
- [US Boxed Warning]: The modified/non-modified formulations are not bioequivalent; cyclosporine (modified) has increased bioavailability as compared to cyclosporine (non- modified) and the products cannot be used interchangeably without close monitoring.

- [US Boxed Warning]: Cyclosporine non-modified absorption is erratic; monitor blood concentrations closely.
- **Monitoring for cyclosporine:**
- Monitor plasma concentrations.
- Obtain serum creatinine and BUN, CBC, hepatic function, urinalysis, serum potassium and uric acid (baseline and periodic thereafter).
- Measuring blood pressure periodically and following the addition, modification, or deletion of other medications
- Monitor for hypersensitivity reactions (IV cyclosporine)
- Monitor for signs/symptoms of hepatotoxicity, secondary malignancy, diabetes mellitus, infection.
- Monitor for progressive cognitive or motor deficits; magnetic resonance imaging may be required for diagnosis of posterior reversible encephalopathy syndrome (PRES)

Conclusion:

- Myelosupression is the adverse effect of concern.
- [US Boxed Warning]: Immunosuppressant agents, including tacrolimus, increase the risk of infection that may lead to hospitalization or death
- [US Boxed Warning]: Immunosuppressant agents, including tacrolimus, may be associated with the development of malignancies that may lead to hospitalization or death
- Patients requiring immunosuppression should have their vaccinations updated. This might include pneumococcus, influenza, Haemophilus influenzae and Varicella zoster.xxxv Where feasible, clinicians should plan vaccinations (with blood tests to assess response) before starting immunosuppression.
- Blood tests should be monitored weekly (full blood count, urea and electrolytes, liver function tests) as the dose is titrated upwards.
- Methotrexate is teratogenic in men and women, and effective contraception is mandatory until at least 3 months after stopping the drug. Mycophenolate mofetil may cause congenital malformations and so women should use effective contraception during its use and for at least 6 weeks after stopping it.

2.3.3 Drug-Drug interactions profile:[4]

Methotrexate

- Concurrent use of METHOTREXATE and NONSTEROIDAL ANTIINFLAMMATORY AGENTS may result in increased methotrexate exposure.

- Concurrent use of METHOTREXATE and WARFARIN may result in increased risk for elevated INR and subsequent bleeding.

- Concurrent use of DICLOFENAC and METHOTREXATE may result in methotrexate toxicity (leukopenia, thrombocytopenia, anemia, nephrotoxicity, mucosal ulcerations).
- Concurrent use of METHOTREXATE and PHENYTOIN may result in decreased phenytoin effectiveness and an increased risk of methotrexate toxicity (myelotoxicity, pancytopenia, megaloblastic anemia).
- Concurrent use of METHOTREXATE and PANTOPRAZOLE may result in increased concentration of methotrexate and its metabolite and an increased risk of methotrexate toxicity.
- Concurrent use of COTRIMOXAZOLE and METHOTREXATE may result in an increased risk of methotrexate toxicity (myelotoxicity, pancytopenia, megaloblastic anemia).

Mycophenolate mofetil

- Concurrent use of MYCOPHENOLATE MOFETIL and BILE ACID SEQUESTRANTS may result in reduced exposure to mycophenolic acid (MPA), the active metabolite of mycophenolate mofetil.
- Concurrent use of MYCOPHENOLATE MOFETIL and RIFAMPIN may result in decreased mycophenolate exposure and possible reduced efficacy.
- Concurrent use of MYCOPHENOLATE MOFETIL and PROTON PUMP INHIBITORS may result in reduced exposure to mycophenolic acid (MPA), the active metabolite of mycophenolate mofetil.
- Concurrent use of AMOXICILLIN/CLAVULANIC ACID and MYCOPHENOLATE MOFETIL may result in decreased mycophenolic acid plasma exposure.
- Concurrent use of METRONIDAZOLE/NORFLOXACIN and MYCOPHENOLATE MOFETIL may result in decreased mycophenolate plasma exposure and possible reduced efficacy.
- Concurrent use of CIPROFLOXACIN and MYCOPHENOLATE MOFETIL may result in decreased mycophenolic acid plasma exposure.

Azathioprine

- Concurrent use of AZATHIOPRINE and FEBUXOSTAT may result in increased azathioprine plasma concentrations.

- Concurrent use of AZATHIOPRINE and LIVE VACCINES may result in an increased risk of infection by the live vaccine .
- Concurrent use of ALLOPURINOL and AZATHIOPRINE may result in azathioprine toxicity (nausea, vomiting, leukopenia, anemia).
- Concurrent use of AZATHIOPRINE and MYCOPHENOLIC ACID may result in greater inhibition of purine metabolism.
- Concurrent use of AZATHIOPRINE and SULFAMETHOXAZOLE/TRIMETHOPRIM may result in increased risk of bone marrow suppression. Cyclosporin

- Concurrent use of METOCLOPRAMIDE and CYCLOSPORINE may result in an increased risk of cycloSPORINE toxicity (renal dysfunction, cholestasis, paresthesias).
- Concurrent use of CYCLOSPORINE and OCTREOTIDE may result in decreased cycloSPORINE effectiveness.
- Concurrent use of CYCLOSPORINE and DILTIAZEM may result in an increased risk of cycloSPORINE toxicity (renal dysfunction, cholestasis, paresthesias).
- Concurrent use of CYCLOSPORINE and ORLISTAT may result in decreased cycloSPORINE plasma levels.
- Concurrent use of CYCLOSPORINE and MORPHINE may result in increased morphine exposure; increased risk of abnormalities or malfunction of the nervous system.
- Concurrent use of CYCLOSPORINE and NONSTEROIDAL ANTIINFLAMMATORY AGENTS
  may result in an increased risk of cycloSPORINE nephrotoxicity.
- Concurrent use of CYCLOSPORINE and VORICONAZOLE may result in increased cycloSPORINE plasma concentration.
- Concurrent use of CYCLOSPORINE and ITRACONAZOLE may result in increased cycloSPORINE plasma concentrations and risk of cycloSPORINE toxicity (renal dysfunction, cholestasis, paresthesias).
- Concurrent use of CYCLOSPORINE and DRONEDARONE may result in increased dronedarone plasma concentrations.
- Concurrent use of COLCHICINE and CYCLOSPORINE may result in increased colchicine and cycloSPORINE plasma concentrations.

- Concurrent use of CYCLOSPORINE and SIMVASTATIN may result in an increased risk of myopathy or rhabdomyolysis.

Tacrolimus

- Concurrent use of FENTANYL and TACROLIMUS may result in decreased tacrolimus clearance.
- Concurrent use of ESOMEPRAZOLE and TACROLIMUS may result in increased tacrolimus exposure.
- Concurrent use of CLOTRIMAZOLE and TACROLIMUS may result in increased tacrolimus concentration.
- Concurrent use of DRONEDARONE and QT INTERVAL PROLONGING DRUGS may result in increased risk of QT-interval prolongation.
- Concurrent use of RITONAVIR and TACROLIMUS may result in increased tacrolimus trough concentrations and increased risk of QT-interval prolongation.
- Concurrent use of MIFEPRISTONE and TACROLIMUS may result in increased tacrolimus exposure and risk of adverse events.
- Concurrent use of FLUCONAZOLE and TACROLIMUS may result in increased tacrolimus exposure and risk of tacrolimus toxicity, including QT-interval prolongation. conclusion: problematic interactions profile; especially for tacrolimus and cyclosporin. Potential interactions should be carefully reviewed before use.

2.3.: Contraindications Profile:[4]

Methotrexate

- Breastfeeding
- Known hypersensitivity to methotrexate
- Male patient, sexually active; avoid impregnating woman during and for a minimum of 3 months after therapy
- Patients with psoriasis or rheumatoid arthritis with alcoholism, alcoholic liver disease, or other chronic liver disease
- Patients with psoriasis or rheumatoid arthritis who have preexisting blood dyscrasias (such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia)
- Patients with psoriasis or rheumatoid arthritis with overt or laboratory evidence of immunodeficiency syndromes

- Pregnant women with psoriasis or rheumatoid arthritis

Tacrolimus

- Hypersensitivity to polyoxyl 60 hydrogenated castor oil with IV formulation
- Hypersensitivity to tacrolimus or any component of the product

Mycophenolate mofetil

- Hypersensitivity to mycophenolate mofetil, mycophenolic acid, or any other component of the drug product

Azathioprine

- Hypersensitivity to the drug
- Treatment of rheumatoid arthritis in pregnant women
- Patients with rheumatoid arthritis previously treated with alkylating agents

Cyclosporin

- Active ocular infections (ophthalmic emulsion)
- Hypersensitivity to cycloSPORINE or any of ingredient in the formulation of the product , including polyoxyethylated castor oil (Cremophor(R) EL) in Sandimmune(R) injection

conclusion: Contraindications should be carefully reviewed before use.

2.3.6 Dosage and administration [2]

Table 1: Dosage and Administration

Dru g	Strength	Dosage Form	Dose	Maximu m daily dose
Azathioprine	:0mg	Tablet	For detailed dosing recommendat ion, see APPENDIX I	
Cyclosporin	:0mg 2:,:0,10 0 100mg	Tablet Capsul e Oral solution		
Methotrexate	2.:mg	Tablet		
Tacrolimus	0.:,1,3 &: mg	Capsule		
Mycophenola te mofetil	2:0,360&:00m g	Tablet and capsule		

2.3.7 *Therapeutic designation and suggested prescribing edits*

Table 3: Therapeutic Designation

Drug	Strength	Dosage Form	Therapeutic designation	Prescribing edits
Azathioprine	:0mg	Tablet	Essential	PA
Cyclosporin	:0mg 2:,:0,100 0 100mg	Tablet Capsule Oral solution		
Methotrexate	2.:mg	Tablet		
Tacrolimus	0.:,1,3 &: mg	Capsule		
Mycophenolate mofetil	2:0,360&:00 mg	Tablet and capsule		
Azathioprine	:0mg	Tablet		

conclusion:

- Oral immunosuppressants are essential agents for management of myasthenia gravis. Azathioprine is the first line agent.
- Cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus are used as an alternative first line but there is little evidence comparing their efficacy
- Cyclosporin and Methotrexate use is limited due to safety concerns.

Prescribing edits:

Prior authorization (PA)

- Oral immunosuppressants are essential agents for management of myasthenia gravis. Azathioprine is the first line agent. Immunosuppressants are added after corticosteroids (except in patients with diabetes mellitus, osteoporosis, or ischaemic heart disease or significant bulbar or respiratory weakness that does not respond rapidly to corticosteroids.) These drugs may cause serious side effects and have several US box warnings. Cyclosporin and Methotrexate use is limited

due to safety concerns. Use should be carefully reviewed and monitored by the specialist.

2.4 I.V Immunoglobulin (IVIg)

2.4.1 Saudi FDA Indications:

Drug	
IV Immunoglobulin	FDA approved for myasthenia gravis

Clinical guidelines recommendations and Efficacy *[1][3]*

- 4. Patients with **refractory MG** should be referred to a physician or a center with expertise in management of MG. In addition to the previously mentioned IS agents, the following therapies may also be used in refractory MG:
- a. Chronic **IVIg** and chronic Plasma exchange (PLEX);
- b. Cyclophosphamide;
- c. Rituximab, for which evidence of efficacy is building, but for which formal consensus could not be reached. IVIg and PLEX.
- 1. PLEX and IVIg are appropriately used as short term treatments in patients with MG with **life- threatening signs** such as respiratory insufficiency or dysphagia; in preparation for surgery in patients with significant bulbar dysfunction; when a rapid response to treatment is needed; when other treatments are insufficiently effective; and prior to beginning corticosteroids if deemed necessary to prevent or minimize exacerbations.
- 2. The choice between PLEX and IVIg depends on individual patient factors (e.g., PLEX cannot be used in patients with sepsis and IVIg cannot be used in renal failure) and on the availability of each.
- 3. IVIg and PLEX are probably equally effective in the treatment of severe generalized MG.
- 4. The efficacy of IVIg is less certain in milder MG or in ocular MG.
- :. PLEX may be more effective than IVIg in MuSKMG.

- 6. The use of IVIg as maintenance therapy can be considered for patients with refractoryMG or for those in whom IS agents are relatively contraindicated. PLEX and IVIg are the mainstay of management in myasthenic crisis.
- PLEX and IVIg are used as short-term treatment for impending and manifest myasthenic crisis and in patients with significant respiratory or bulbar dysfunction. Corticosteroids or other IS agents are often started at the same time to achieve a sustained clinical response. (Because corticosteroids may cause transient worsening of myasthenic weakness, it may be appropriate to wait several days for PLEX or IVIg to have a beneficial effect before starting corticosteroids).
- 3. Although clinical trials suggest that IVIg and PLEX are equally effective in the treatment of impending or manifest myasthenic crisis, expert consensus suggests that PLEX is more effective and works more quickly.
- The choice between the 2 therapies depends on patient comorbidity (e.g., PLEX cannot be used in sepsis and IVIg is contraindicated in hypercoagulable states, renal failure, or hypersensitivity to immunoglobulin) and other factors, including availability. A greater risk of hemodynamic and venous access complications with PLEX should also be considered in the decision (many complications of PLEX are related to route of access and may be minimized by using peripheral rather than central venous access).
- Maintenance PLEX or IVIg are alternatives to IS drugs in JMG.
- MuSK-MG responds well to PLEX, while IVIg seems to be less effective.
- PLEX or IVIg are useful when a prompt, although temporary, response is required during pregnancy.

Conclusion: According to guidelines, Iv Immunoglobulin is effective for management of refractory or severe cases of myasthenia gravis.

2.4.2 Safety profile: [4][2][3]

Adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally in connection with intravenous administration of human immunoglobulin.

Rarely, human normal immunoglobulins, may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Cases of reversible aseptic meningitis and rare cases of transient cutaneous reactions (including cutaneous lupus erythematosus – frequency unknown) have been observed with human normal immunoglobulin.

Reversible haemolytic reactions have been observed in patients, especially those with non-0 blood groups in immunomodulatory treatment. Rarely, haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment (see section 4.4).

Increase in serum creatinine level and/or acute renal failure have been observed Very rarely: Transfusion-related acute lung injury and thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses.

IVIg increases blood viscosity, so dosage quantities and infusion speed should be adjusted appropri- ately based on the patient's overall condition if the patient has concomitant cardiovascular or cerebrovascular conditions (grade B).

Monitoring:

- Renal function (prior to initial infusion and at appropriate intervals)
- Infusion- or injection-related adverse reactions
- blood pressure (prior to, during, and following infusion)
- anaphylaxis, signs and symptoms of thrombosis, signs and symptoms of hemolysis blood viscosity (in patients at risk for hyperviscosity)
- volume status
- neurologic symptoms (if AMS suspected)
- pulmonary adverse reactions **Conclusion:**
- Intravenous immunoglobulin increases blood viscosity hematological side effects and allergic reactions are the adverse effects of concern.. Careful hydration might be a sensible precaution.
- [US Boxed Warning]: Thrombosis may occur with immune globulin products even in the absence of risk factors for thrombosis.
- [US Boxed Warning]: Acute renal dysfunction (increased serum creatinine, oliguria, acute renal failure, osmotic nephrosis) can rarely occur and has been associated with fatalities in predisposed patients. Patients predisposed to renal dysfunction include elderly patients, patients with renal disease, diabetes mellitus, hypovolemia, volume depletion, sepsis, paraproteinemia, and nephrotoxic medications due to risk of renal dysfunction. Drug-Drug interactions profile:[:]

Live attenuated virus vaccines

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps, and varicella. After administration of this medicinal product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore, patients receiving measles vaccine should have their antibody status checked.

conclusion: Potential interactions should be carefully reviewed before use.

2.4.: Contraindications

Profile:[:][3]

- Hypersensitivity to immune globulin or any component of the formulation;
- IgA deficiency (with anti-IgA antibodies and history of hypersensitivity [excluding Gammagard S/D]); hyperprolinemia (Hizentra, Privigen);
- hypersensitivity to corn (Octagam :%);
- hereditary intolerance to fructose (Gammaplex :%);
- infants/neonates for whom sucrose or fructose tolerance has not been established (Gammaplex :%);
- hypersensitivity to hyaluronidase, human albumin, or any component of the hyaluronidase formulation (HyQvia).

Conclusion: IVIg is contraindicated in hypercoagulable states, renal failure, or hypersensitivity to immunoglobulin

2.4.6 Dosage and administration [2]

Table 1: Dosage and Administration

Dru g	Strength	Dosag e Form	Dose	Maximu m daily dose
I.V Immunoglobu lin	:%,10% 16% 100mg/m l	IV	Intravenous immunoglobulin use for severe bulbar or respiratory symptomsxlvi ‣ 1–2 g/kg is the total dose. ‣ This may be given as 0.: g/day for 2 days, or 0.4 g/day for : days.	

2.4.7 Therapeutic designation and suggested prescribing edits

Table 4: Therapeutic Designation

Dru g	Strengt h	Dosag e Form	Therapeut ic designatio n	Prescribin g edits

I.V Immunoglobulin	:%,10% 16% 100mg/ ml	IV	Essential	PA

conclusion:

- I.V immunoglobulin is essential for managing refractory and severe case of myasthenia gravis.
- Intravenous immunoglobulin has rare but life-threatening side effects and should not be used as first-line agent for all myasthenia patients.
- IV IG and PLEX are the mainstay of management in patients with manifest myasthenic crisis and impending myasthenic crisis as a short-term treatment.
- IV IG is also used in preparation for surgery in patients with significant bulbar dysfunction; when a rapid response to treatment is needed; when other treatments are insufficiently effective; and prior to beginning corticosteroids if deemed necessary to prevent or minimize exacerbations.

- In some cases (juvenile MG and refractory cases) maintenance IVIG could be used as a chronic treatment Prescribing edits:

Prior authorization (PA)

- I.V immunoglobulin is used for managing refractory and severe case of myasthenia gravis. Intravenous immunoglobulin has rare but lifethreatening side effects and should not be used as first-line agent for all myasthenia patients. IV IG and PLEX are the mainstay of management in patients with manifest myasthenic crisis and impending myasthenic crisis as a short-term treatment. IV IG is also used in preparation for surgery in patients with significant bulbar dysfunction; when a rapid response to treatment is needed; when other treatments are insufficiently effective; and prior to beginning corticosteroids if deemed necessary to prevent or minimize exacerbations. In some cases (juvenile MG and refractory cases) maintenance IVIG could be used as a chronic treatment A specialist should review the case and approve the indication before use.

2.5 Rituximab

2.:.1 Saudi FDA Indications:

Drug	
Rituximab	Use in refractory myasthenia gravis is off labelled

:.2 Clinical guidelines recommendations and Efficacy *[1]*

- 4. Patients with **refractory MG** should be referred to a physician or a center with expertise in management of MG. In addition to the previously mentioned IS agents, the following therapies may also be used in refractory MG:
- a. Chronic **IVIg** and chronic Plasma exchange (PLEX);
- b. Cyclophosphamide;
- c. Rituximab, for which evidence of efficacy is building, but for which formal consensus could not be reached.
- Rituximab should be considered as an early therapeutic option in patients with : muscle- specific tyrosine kinase (MuSK-MG) who have an unsatisfactory response to initial immunotherapy.

Conclusion: According to guidelines, rituximab is an effective agent for management of refractory myasthenia gravis. Rituximab should be considered as an early therapeutic option in patients with : muscle-specific tyrosine kinase (MuSK-MG) who have an unsatisfactory response to initial immunotherapy.

Drug	Adverse effects
Rituximab	Common Cardiovascular: Peripheral edema (Granulomatosis with polyangiitis and microscopic polyangiitis, 16%) Dermatologic: Pruritus (:% to 14%) Gastrointestinal: Diarrhea (Granulomatosis with polyangiitis and microscopic polyangiitis, 17%), Nausea (Non-Hodgkin's lymphoma, 23%; rheumatoid arthritis, 8%; granulomatosis with polyangiitis and microscopic

polyangiitis, 18%) Hematologic: Anemia, All Grades (Non-Hodgkin's lymphoma, 8% to 3:%; Granulomatosis with polyangiitis and microscopic polyangiitis, 16%), Lymphocytopenia, All Grades (Non-Hodgkin's lymphoma, 48%), Neutropenia, All grades (Non-Hodgkin's lymphoma, 8% to 14%; chronic lymphocytic leukemia, equal to or greater than 2:%)

Musculoskeletal: Spasm (Granulomatosis with polyangiitis and microscopic polyangiitis, 17%)

Neurologic: Asthenia (Non-Hodgkin's lymphoma, 26%), Headache (Pemphigus vulgaris, :% ; non-Hodgkin's lymphoma, 19%; Granulomatosis with polyangiitis and
microscopic polyangiitis, 17%)

Renal: Urinary tract infectious disease (Rheumatoid arthritis, greater than 10%)

Respiratory: Nasopharyngitis (Rheumatoid arthritis, greater than 10%), Respiratory tract infection (Rheumatoid arthritis, greater than 10%), Upper respiratory infection
(Rheumatoid arthritis, 7% to greater than 10%
)

Other: Fever (Pemphigus vulgaris, :% ; non-Hodgkin's lymphoma, :3%; diffuse large B-cell lymphoma, :6%; rheumatoid arthritis, :%), Shivering (Non-Hodgkin's lymphoma, 33%; diffuse large B-cell lymphoma, 13%)

Serious

Cardiovascular: Cardiac complication (Diffuse large B-cell lymphoma, 29%; rheumatoid arthritis 1.7%), Cardiogenic shock, Hypotension (Non- Hodgkin's lymphoma, 10%), Myocardial infarction, Supraventricular arrhythmia (Diffuse large B-cell lymphoma, 4.:%), Ventricular fibrillation
Dermatologic: Lichenoid dermatitis, Pemphigus paraneoplastica, Stevens- Johnson syndrome, Toxic epidermal necrolysis

Endocrine metabolic: Hypophosphatemia (Rheumatoid arthritis, 12% to 21%)

Gastrointestinal: Gastrointestinal perforation

Hematologic: Anemia, Grade 3 or 4 (Non-Hodgkin's lymphoma, 3%), Febrile neutropenia, Grade 3 or 4 (Chronic lymphocytic leukemia, 9% to 1:%), Leukopenia, Grade 3 or 4

	(Non-Hodgkin's lymphoma, 4%; chronic lymphocytic leukemia, 23%), Lymphocytopenia, Grade 3 or 4 (Non-Hodgkin's lymphoma, 40%), Neutropenia, Grade 3 or 4 (Non-Hodgkin's lymphoma, 4% to 6%; chronic lymphocytic leukemia, 30% to 49%), Pancytopenia, Grade 3 or 4 (Chronic lymphocytic leukemia, 3%), Thrombocytopenia, Grade 3 or 4 (Non Hodgkin lymphoma, 2%; diffuse large Bcell lymphoma, 9%; chronic lymphocytic leukemia, 11%) Hepatic: ALT/SGPT level raised (Granulomatosis with polyangiitis and microscopic polyangiitis, 13%), Reactivation of hepatitis B viral hepatitis Neurologic: Progressive multifocal leukoencephalopathy Renal: Nephrotoxicity

	Respiratory: Bronchospasm (Non-Hodgkin's lymphoma, 8%), Injury of lung, Pneumocystis pneumonia, Pulmonary toxicity (Non-Hodgkin's lymphoma, 18%) Other: Angioedema (Non-Hodgkin's lymphoma, 11%), Infectious disease (Adults: Pemphigus vulgaris, 37% ; non- Hodgkin's lymphoma, 19% to 37%; rheumatoid arthritis, 39%; granulomatosis with polyangiitis and microscopic polyangiitis, :3% to 62% ; Pediatric: 28%), Infusion reaction (Adult, non-Hodgkin's lymphoma, equal to or greater than 2:%; chronic lymphocytic leukemia, :9%; rheumatoid

arthritis 9% to 27%; granulomatosis with polyangiitis and

Monitoring of rituximab

- CBC with differential and platelets (obtain prior to treatment and prior to each treatment course, and at weekly to monthly)
- Screen all patients for hepatitis B virus (HBV) infection prior to therapy initiation (eg, hepatitis B surface antigen [HBsAG] and antiHBc measurements)
- Reactivation of tuberculosis (TB) has been reported in pediatric patients receiving biologic response modifiers (infliximab and etanercept); prior to therapy, patients with no TB risk factors should be screened for latent TB infection
- Monitor for infusion-related reactions; signs of active hepatitis B infection (during and for up to 12 months after therapy completion);
- cardiac monitoring during and after infusion in patients with preexisting cardiac disease or if arrhythmias develop during or after subsequent infusions);
- monitor for signs/symptoms of bowel obstruction/perforation (abdominal pain, vomiting)
- signs or symptoms of progressive multifocal leukoencephalopathy
- signs/symptoms of TLS and/or mucocutaneous skin reactions.
- fluid/hydration status balance; blood pressure, vital signs.

Conclusion: problematic adverse effects profile. Use should be monitored by the specialist

2. :.4 Drug-Drug interactions profile:

- Currently, there are limited data on possible drug interactions.
- Co-administration with methotrexate had no effect on the pharmacokinetics of rituximab in rheumatoid arthritis patients.

- Patients with human anti-mouse antibody (HAMA) or anti-drug antibody (ADA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.
- Interaction with other immunosuppressive drugs enhance the immunosuppressive effect.
- Interaction with vaccines can diminish the therapeutic effect of Vaccines (Inactivated) and enhance the adverse/toxic effect of Vaccines (Live)

conclusion: Potential interactions should be carefully reviewed before use.

2. :.: Contraindications Profile:[:]

· Known type 1 hypersensitivity or anaphylactic reaction to murine proteins, Chinese Hamster Ovary (CHO) cell proteins, or any component of the formulation; patients who have or have had progressive multifocal leukoencephalopathy (PML); patients with severe, active infections

conclusion: Contraindications should be carefully reviewed before use.

2.:.6 Dosage and administration

Table 1: Dosage and Administration

Drug	Strength	Dosage Form	Dose	Maximum daily dose
Rituximab	10mg/ml	IV	For detailed dosing recommendation, see APPENDIX I	

2. :.7 Therapeutic designation and suggested prescribing edits

Table 5: Therapeutic Designation

Drug	Strength	Dosage Form	Therapeutic designation	Prescribing edits

Rituximab	10mg/ml	IV	Essential	P A

conclusion:

- Rituximab is essential for management of refractory myasthenia gravis. Rituximab should be considered as an early therapeutic option in patients with : muscle-specific tyrosine kinase (MuSK-MG) who have an unsatisfactory response to initial immunotherapy.

Prescribing edits:

Prior authorization (PA)

- Rituximab is essential for management of refractory myasthenia gravis (after failure of pyridostigmine, steroids and other oral immunosuppressants). Rituximab should be considered as an early therapeutic option in patients with : muscle-specific tyrosine kinase (MuSK-MG) who have an unsatisfactory response to initial immunotherapy. A Specialist should approve and monitor the indication before use.

2.6 IV Cyclophosphamide

2.6.1 Saudi FDA Indications:

Drug	

Clinical guidelines recommendations and Efficacy *[1]*	Cyclophosphamide	Use in refractory myasthenia gravis is Off-labelled (recommended by the international guidelines [1] with low level of evidence)

- 4. Patients with **refractory MG** should be referred to a physician or a center with expertise in management of MG. In addition to the previously mentioned IS agents, the following therapies may also be used in refractory MG:
- a. Chronic **IVIg** and chronic Plasma exchange (PLEX);
- b. Cyclophosphamide;
- c. Rituximab, for which evidence of efficacy is building, but for which formal consensus could not be reached.

Conclusion: According to guidelines, cyclophosphamide is effective for management of refractory Myasthenia gravis.

2.6.2 Safety profile: [4]

Common

- **Dermatologic:** Alopecia, Disorder of skin pigmentation, Nail damage, Rash
- **Gastrointestinal:** Abdominal discomfort, Diarrhea, Loss of appetite, Nausea and vomiting
- **Hematologic:** Leukopenia, Neutropenia
- **Reproductive:** Amenorrhea **Serious**
- **Cardiovascular:** Cardiac tamponade, Cardiotoxicity, Congestive heart failure, Pericardial effusion
- **Dermatologic:** Erythema multiforme, Malignant tumor of dermis, StevensJohnson syndrome, Toxic epidermal necrolysis
- **Hematologic:** Acute myeloid leukemia, Chronic myeloid leukemia, Malignant tumor of lymphoid hemopoietic and related tissue, Myelodysplastic syndrome
- **Hepatic:** Angiosarcoma of liver
- **Immunologic:** Anaphylaxis
- **Renal:** Acquired contracture of bladder neck, Bladder cancer, Fibrosis of urinary bladder, Hemorrhagic cystitis, Pyelitis, Renal hematuria, Secondary malignant neoplasm of renal pelvis
- **Reproductive:** Azoospermia, Oligozoospermia
- **Respiratory:** Interstitial pneumonia, Pulmonary fibrosis
- **Other:** Infectious disease
- **Add Assessment and monitoring tips:**
- Adequate hydration is required for all uses, but protocol and method of administration may be indication-specific. Monitor IV site for signs of extravasation.
- Assess results of urinalysis, BUN, and serum creatinine to evaluate for nephrotoxicity.
- Monitor CBC with differential and platelet count to identify myelosuppression. Monitor for hemorrhagic cystitis and renal tubular necrosis, especially in high doses.
- Educate patient of the importance of follow-up to monitor for secondary malignancies.
- Obtain CBC with differential and platelets, serum electrolytes, BUN, serum creatinine, and urinalysis.

- Premedicate with an antiemetic and MESNA.

conclusion: myelosuppression is the adverse effect of concern. Also, Assess for signs and symptoms of hemorrhagic cystitis, renal toxicity, pulmonary toxicity, cardiac toxicity, and liver toxicity.

2.6.3 Drug-Drug interactions profile:

- Concurrent use of CHEMOTHERAPEUTIC AGENTS and CONTRAINDICATED LIVE VACCINES may result in an increased risk of infection by the live vaccine.
- Concurrent use of CYCLOPHOSPHAMIDE and CYCLOSPORINE may result in decreased serum cycloSPORINE concentration.
- Concurrent use of CYCLOPHOSPHAMIDE and PHENYTOIN may result in increased plasma concentrations of the active metabolite of cyclophosphamide and an increased risk of toxicity.
- Concurrent use of TAMOXIFEN and CYCLOPHOSPHAMIDE may result in an increased risk of thromboembolism.
- Concurrent use of CYCLOPHOSPHAMIDE and PROTEASE INHIBITORS may result in increased risk of chemotherapy-induced mucositis, neutropenia, and infection. **conclusion: Potential interactions should be carefully reviewed before use.**

2.6.: Contraindications Profile:[4]

- Hypersensitivity, severe, to cyclophosphamide, any of its metabolites, or any component of the product; anaphylactic reactions, some fatal, have been reported; cross-sensitivity with other alkylating agents may occur
- Urinary outflow obstruction conclusion: Contraindications should be carefully reviewed before use.

2.6.6 Dosage and administration

Table 1: Dosage and Administration

Drug	Strength	Dosage Form	Dose	Maximum daily dose
Cyclophosphamide	200,:00,1000 mg	IV	For detailed dosing recommendation, see APPENDIX I	

2.6.7 Therapeutic designation and suggested prescribing edits

Table 6: Therapeutic Designation

Dru g	Strength	Dosag e Form	Therapeut ic designatio n	Prescribing edits
Cyclophosphamid e	200,:00,1000 mg	IV	Essential	P A

conclusion:

- Cyclophosphamide is essential for management of refractory myasthenia gravis.

Prescribing edits:

Prior authorization (PA)

- Cyclophosphamide is essential for management of refractory myasthenia gravis. Myelosuppression and potential toxicity should be carefully monitored. A specialist should approve and monitor its use.

2.6- Eculizumab:

Eculizumab is a monoclonal antibody approved for refractory MG treatment. Table 3 summarizes the role of eculizumab in Myasthenia Gravis as supported by the guidelines. (*Lexicomp*, n.d.)

Table 2: Role of eculizumab in MG

ROLE OF ECULIZUMAB IN MG		
Guidance for treatment	**Supporting Guideline Recommendations/Evidence**	**Reference Guidelines**
A monoclonal antibody, approved	Eculizumab should be considered in the treatment of severe, refractory, AChR-Ab+ generalized MG	**International Consensus GuidanceMG 2021**

for refractory MG treatment.	More cost-effective and treatment duration research data needs to be available before starting recommended eculizumab as a firstline treatment.	
	Until then, eculizumab should be considered after failure of other immunotherapies	
	Eculizumab is effective against AChR antibody-positive MG	**Japanese clinical guidelines-2022**
	Should be only considered in patients when MG symptoms are uncontrolled with IVIg or plasmapheresis treatment	

Saudi FDA Indications:

N.B: Eculizumab is not available yet in Saudi Arabia

Eculizumab proved to have promising outcomes in AChR+ MG patients. However, more studies should be performed regarding its duration of treatment and cost-effectiveness.

Prescribing Information:

Therapeutic Designation:

A humanized monoclonal antibody works against the terminal C5 complement molecule. **Note:** For use in patients with anti-acetylcholine receptor antibody positive (AChR+) myasthenia gravis.

A detailed drug information discussing eculizumab's pharmacological information, prescribing information, dosage and administration, and safety profile are presented in table
3. (*Lexicomp*, n.d.)

Table 3: Eculizumab detailed drug information

Scientific Name	**Eculizumab**
Trade Name(s) on Saudi Market	Not available (N/A) (Soliris)

Scientific name SFDA code	N/A
SFDA Classification	N/A
SFDA Registration Number (New)	N/A
Scientific Description Code	N/A
SFDA	N/A

US FDA	▫ registered: approved in 18/02/2022 for MG
EMEA	▫ registered: approved in 14/08/2017 for MG
MHRA	▫ registered: Not approved yet for MG
PMDA	▫ registered: approved in 08/12/2020 for MG
Indication (ICD-10)	G70
Drug Class (ASHP)	Monoclonal antibody
Drug Sub-class (ASHP)	Recombinant humanized monoclonal antibody
ATC Code	L04AA25
ATC Description	Myasthenia gravis with/ without (acute) exacerbation
Drug Information	
Dosage Form	Solution for injection
Pharmaceutical Form Code	G70.00 G70.01
Strength	10mg/ml
Route of Administration	IV
Administration Route Code	J1300

Dose (Adult) [DDD]*	Induction: 900mg once weekly for 4 doses Maintenance: 1.2 g at week 5, then 1.2g every 2 weeks thereafter *-Supplemental dosing for patients receiving plasmapheresis or plasma exchange:* • If most recent dose was ≥600 mg: Administer 600 mg within 60 minutes after each plasmapheresis or plasma exchange. • If most recent dose was 300 mg: Administer 300 mg within 60 minutes after each plasmapheresis or plasma exchange. *-Supplemental dosing for patients receiving fresh frozen plasma infusion:* • If most recent dose was ≥300 mg: Administer 300 mg within 60 minutes prior to each infusion of fresh frozen plasma
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Not indicated for pediatrics in MG
Maximum Daily Dose Pediatrics*	NA
Adjustment	Renal: No dose adjustment required Liver: No dose adjustment required
Prescribing edits*	PA, ST

Safety	
Main Adverse Drug Reactions (most common and most serious)	-Cardiovascular: Hypertension (17% to 59%), tachycardia, peripheral edema (20% to 29%), hypotension -Central nervous system: Headache (37% to 50%), insomnia, dizziness -Dermatologic: Skin rash (12% to 22%), pruritus -Endocrine & metabolic: Hypokalemia (10% to 18%) -Gastrointestinal: Diarrhea (16% to 47%), vomiting (10% to 47%), nausea (12% to 40%) -Genitourinary: Urinary tract infection (15% to 35%), proteinuria (5% to 12%) -Hematologic & oncologic: Anemia (17% to 35%), neoplasm (6% to 30%), leukopenia (5% to 24%) -Infection: Infection (24%), influenza (11%) -Local: Catheter infection (17%) -Neuromuscular & skeletal: Asthenia (5% to 20%), back pain (5% to 19%), arthralgia, musculoskeletal pain -Ophthalmic: Eye disease (10% to 29%) -Renal: Renal insufficiency (15% to 29%) -Respiratory: Cough (20% to 60%), nasopharyngitis (17% to 55%), nasal congestion, upper respiratory tract infection (5% to 40%), rhinitis, bronchitis -Miscellaneous: Fever
Drug Interactions*	**Category X:** Baricitinib, Brivudine, Cladribine, Deucravacitinib, Filgotinib, Nadofaragene, Firadenovec, Natalizumab , Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene, Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib **Category D:** Coccidioides immitis Skin Test, Denosumab, Leflunomide, Meningococcal Group B Vaccine, Polymethylmethacrylate, Sipuleucel-T: (immunosuppressants)
Special Population	N/A
Pregnancy	Crosses the placenta: risk vs benefits
Lactation	Crosses breast milk: risk vs benefits

Contraindications	-Unresolved serious *Neisseria meningitidis* infection -Patients not currently vaccinated against *Neisseria meningitidis*

	-Hypersensitivity to eculizumab, murine proteins, or any component of the formulation
Monitoring Requirements	-Infusion site reaction
Precautions	-Infections -Meningococcal infections -Infusion reactions
Black Box Warning	-Meningococcal infection
REMS*	- Prior to dilution, store intact vials at 2°C to 8°C (36°F to 46°F); do not freeze
Others (devices and supplies required)	N/A

Safety Considerations:

The Food and Drug Administration (FDA)- approved prescribing information placed a black box warning of an increased risk of meningococcal infections for patients receiving complement inhibitors such as eculizumab. (*Lexicomp*, n.d.)

Meningococcal infection: **[US Boxed Warning]:**

- Meningococcal (*Neisseria meningitidis*) infections have occurred in patients receiving eculizumab; may be fatal or life-threatening if not detected and treated promptly.
- Close monitoring for early signs of infection should be done to all patients starting eculizumab treatment
- Immunization against *Neisseria meningitidis* is a mandatory at least two weeks prior treatment initiation

Conclusion Statement: Place in Therapy

Place in Therapy

- Based on guideline recommendations; eculizumab should be considered as a treatment for refractory patients who do not respond to previous immunotherapy.
- It should be only recommended for patients with AChR antibody positive MG after failure of IVIg or plasmapheresis treatment.
- Upcoming research is needed to indicate the duration of treatment.

- Patients started on eculizumab should be vaccinated against Neisseria meningitidis at least 2 weeks prior treatment initiation.

2.7. Ravulizumab

Rivalizumab is a monoclonal antibody used in the treatment of MG. A detailed drug information discussing eculizumab's pharmacological information, prescribing information, dosage and administration, and safety profile are presented in table 4. (Drugs List | Saudi Food and Drug Authority, n.d.; Ravulizumab (Lexi-Drugs Multinational), n.d.)

Table 4: Ravulizumab Detailed Drug Information

Scientific Name	**Ravulizumab**
Trade Name(s) on Saudi Market	Ultomiris
Scientific name SFDA code	
SFDA Classification	Prescription
SFDA Registration Number (New)	1208210929
Scientific Description Code	7000001685
SFDA	▫ registered: March 2023
US FDA	▫ registered: June 2022
EMEA	▫ registered: September 2022
MHRA	▫ registered: September 2022
PMDA	▫ registered: August 2022
Indication (ICD-10)	G70
Drug Class (ASHP)	Immunoglobulin
Drug Sub-class (ASHP	Humanized monoclonal antibody
ATC Code	L04AA
ATC Description	7000001685-10-100000073871
Drug Information	
Dosage Form	Concentrate solution for infusion
Pharmaceutical Form Code	100000073871
Strength	10 mg/mL
Route of Administration	IV
Administration Route Code	100000073871

Dose (Adult) [DDD]*	*Dose should be weight based* *-Weight 40 kg to <60 kg:* Loading dose: 2,400 mg IV as a single dose. Maintenance dose: 3,000 mg IV once every 8 weeks starting 2 weeks after the loading dose. *-Weight 60 kg to <100 kg:* Loading dose: 2,700 mg IV as a single dose. Maintenance dose: 3,300 mg IV once every 8 weeks starting 2 weeks after the loading dose. *-Weight ≥100 kg:* Loading dose: 3,000 mg IV as a single dose. Maintenance dose: 3,600 mg IV once every 8 weeks starting 2 weeks after the loading dose.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	*Note: this dosing is for hemolytic uremic syndrome treatment. No dosing regimen available for MG treatment.* Weight-based dosing regimen: Patients one month or older weighing 5 kg or greater. *5 kg to <10 kg:* • Loading dose: 600 mg IV • Maintenance dose: 300 mg IV every 4 weeks starting 2 weeks after the loading dose *10 kg to < 20 kg:* • Loading dose: 600 mg IV • Maintenance dose: 600 mg IV every 4 weeks starting 2 weeks after the loading dose *20 kg to < 30 kg:* • Loading dose: 900 mg IV • Maintenance dose: 2100 mg IV every 8 weeks starting 2 weeks after the loading dose *30 kg to < 40 kg:* • Loading dose: 1200 mg IV • Maintenance dose: 2700 mg IV every 8 weeks starting 2 weeks after the loading dose Patients over 40 kg have the same dosing that adult patients.

Maximum Daily Dose Pediatrics*	N/A
Adjustment	☐Renal: No dose adjustment required ☐Liver: No dose adjustment required
Prescribing edits*	PA, ST
Safety	
Main Adverse Drug Reactions (most common and most serious)	-Gastrointestinal: Diarrhea -Local: Injection-site reaction -Nervous system: Headache -Respiratory: Upper respiratory tract infection
Drug Interactions*	**Category X:** Baricitinib, Brivudine, Cladribine, Deucravacitinib, Filgotinib, Nadofaragene, Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene, Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib **Category D:** Denosumab, Leflunomide, Meningococcal Group B Vaccine, Polymethylmethacrylate, Sipuleucel-T: (immunosuppressants)
Special Population	N/A
Pregnancy	It's unknown whether it can cause fetal harm.
Lactation	Not recommended.
Contraindications	-Unresolved *Neisseria meningitidis* infection
Monitoring Requirements	-Infusion site reactions
Precautions	-Infections -Meningococcal infections -Infusion reactions
Black Box Warning	Meningococcal infections
REMS*	N/A
Others (devices and supplies required)	N/A

Conclusion Statement: Place in Therapy

Place in Therapy

- Rivaluzimab is a newly approved monoclonal antibody that can be used for AChr antibody positive MG patients.

- Its use can help minimizing the side effects associated with glucocorticoid use.
- Patients started on eculizumab should be vaccinated against Neisseria meningitidis at least 2 weeks prior treatment initiation.

Another Section for Efgartigimod and Ravulizumab needs to be added

SECTION 3.0 KEY RECOMMENDATIONS SYNTHESIS

Treatment Strategy and Timeline for Assessment of Disease Activity:

- In all patients with myasthenia gravis, follow a symptoms-targeted treatment strategy to reach a treatment goal of remission or low disease activity, and improve patient's quality of life and mental health. Full remission is difficult to achieve in cases of adult-onset MG.

Role of Corticosteroids in MG:

- Steroids whether IV or PO are widely recommended and used in MG cases.
- Low dose oral steroids started at early disease state is more beneficial that high dose steroids started later, due to increased risk of adverse events associated with corticosteroids use.
- The first goal in MG treatment is to achieve an MM-5mg of prednisolone.
- IV methylprednisolone might be used for generalized MG to improve the symptoms and decrease oral steroids dose.

Role of non-steroidal immunosuppressants treatment:

- Cyclosporine and tacrolimus can be used in combination with steroids to increase muscle strength and lower steroids dose.

Role of Pyridostigmine in MG treatment:

- Recommended to be used as part of the initial treatment in most patients with MG.
- Pyridostigmine is the first-line agent in MG pregnant females

Role of IVIg and Plasmapheresis in MG:

- Both showed to be effective in moderate-to-severe cases
- Both should be combines with immunotherapy when used for treating MG
- Plasma exchange is the plasmapheresis therapy of choice in treating patients with anti-
  MuSK antibody-positive MG

Role of monoclonal antibodies in MG treatment:

- Patients with MuSK-Ab+ MG who failed to respond to initial immunotherapy treatment, can be treated with rituximab.
- Eculizumab, a newly recommended molecular targeted drug for MG, can be used for patients with AChR antibody-positive MG when symptoms were uncontrolled with IVIg or plasmapheresis treatment.
- Efgartigimod alfa and ravulizumab are newly recommended biologic agents used to treat AChR antibody-positive MG.
  - They are given as a chronic immunotherapy or as a bridge therapy to slower-acting immunotherapies to avoid or minimize glucocorticoid use.

Role of methotrexate in MG treatment:

- Can be used as steroid-sparing agent for patients with generalized MG who did not tolerate or failed other steroid-sparing agents

Role of thymectomy in MG treatment:

- For nonthymomatous patients, thymectomy can be considered to treat patients with early onset MG and who have positive AChR antibodies

Ocular MG treatment: Patients who do not respond to anticholinesterase agents should be treated with immunosuppressants

- Corticosteroids are the immunosuppressant agents of choice in ocular MG treatment

SECTION 4.0 CONCLUSION

The recommendations provided in this report are intended to assist in the management of myasthenia gravis. Health-care providers are highly encouraged to use this guidance in their treatment approach of MG. however, these recommendations should not replace clinical decision-making in individual patient management. When treating their patients, healthcare providers shall use their clinical judgment supported by this guidance and taking into consideration the patient's clinical presentation and preferences.

Eculizumab is showing promising results in the treatment of MG, more data and studies should be performed before adding it to the SFDA, yet to CHI formulary.

Efgartigimod and Ravulizumab are recently approved by the FDA and in Japan for AchR positive MG. Their safety profile and efficacy from the real world evidence and the clinical trials are promising.

SECTION 5.0: UPDATED REFERENCES:

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SECTION 3.0 APPENDIX

APPENDIX I: Dosage recommendation for agents used in Myasthenia gravis- American Academy of Neuroscience nurses (AANN) guidelines for the care of patients with Myasthenia gravis

Table 5. Medications Used in the Management of Myasthenia Gravis			
Classification	**Drug**	**Dose**	**Special Considerations (Recommendations)**
Symptomatic Therapy: **Acetylcholinesterase inhibitors**	Pyridostigmine (Mestinon, Mestinon Time Span)	30, 60, 90, mg every 4-6 hours orally Mestinon SR 180 mg of a time-span (slow-release form) at bedtime	Doses increased and adjusted to efficacy and side effects Take 30-60 minutes before eating with bulbar symptoms Adverse gastrointestional effects include nausea and vomiting, abdominal cramping, and diarrhea. Effectiveness may dissipate if taken with food May require an antidiarrheal agent Other side effects include increased salivation, drooling, and tearing; increased bronchial secretions; and perspiration. Late-evening time span preparations are indicated only with marked myasthenic weakness in the morning. A liquid form is available for children and adults with swallowing difficulties. Do not substitute regular Mestinon or generic pyridostigmine for Mestinon SR. The dose schedule for a particular patient may vary from time to time, even daily, particularly during periods of stress or infection (Mehndiratta, Pandey, & Kuntzer, 2011; MGFA, 2012b). **Nursing recommendation: Nurses should administer and educate patients to take pyridostigmine as prescribed. (Level 2).**
Glucocorticosteroids (GCS): General immunosuppressives for the short or long term	Prednisone Not FDA approved for MG	0.75–1.0 mg/kg daily or 60–100 mg on alternate days orally, option for long-term therapy; a lower dose (10–25mg) every other day may be used when combined with other treatments to decrease side effects	Option to slowly increase doses; after reaching near remission, gradual dose reduction Monitor for side effects. Increased risk for osteoporosis: exercise and supplement diet with increased calcium, vitamin D Increased risk for glaucoma; eye checks are needed Increased susceptibility for infection; take precautions such as immunization against the flu Increased risk for obesity, diabetes, hypertension, electrolyte imbalance (hypokalemia) (Schneider-Gold, Gaidos, Toyka, & Hohlfeld, 2005) **Nursing recommendation: Nurses should monitor for side effects associated with glucocorticosteroids and adjust dosage as prescribed (Level 2).**
Targeted immunosuppressive (long-term use)	Azathioprine (Imuran) Not FDA approved for MG	2–4 doses of 50 mg/day (2–3 mg per kg body weight/day) oral Often Initially combined with GCSs	Use an initial trial dose of 1-50 mg as a test dose for primary hypersensitivity. Divided daily doses are better tolerated than single doses. One dosing schedule is 50 mg/day and increase by 50 mg/day every 7 days until 150–200 mg/day is obtained. Dose decreases may result in worsening of symptoms. May administer with corticosteroids Gradual improvement in 6–12 months May cause flu-like illness in 10% of patients (Gold, Hohlfeld, & Toyka et al., 2008; Saperstein & Barohn, 2004) Discontinue if liver enzymes are elevated or white blood cells decrease below 3,000 cells/mm^3 (Saperstein & Barohn, 2004; Hart, Sathasivam, & Sharshar, 2007; Angelini, 2011). **Nursing recommendation: Nurses should monitor for signs and symptoms of infection, hepatotoxicity, nephrotoxicity, bone marrow suppression, and skin cancer (Level 3).**
Targeted immunosuppressive (long-term use)	Cyclosporine A (Sandimmune, Neoral) Not FDA approved for MG	Starting dose 5mg/kg body weight in 2 divided doses (q12h) Optimal dosing monitored by measuring trough drug levels	Steroid sparing if intolerant of Azathioprine Measure blood trough levels until ideal dosing is obtained and during drug dose change. Blood levels should be checked at 1 month and adjusted as needed. Monitor serum creatinine related to nephrotoxicity. Monitor for side effects Off-label status despite evidence (Tindall, Phillips, Rollins, Wells, & Hall, 1993; Ciafaloni, Nikhar, Massey, & Sanders, 2000) **(Nursing recommendation: Nurses should monitor for nephrotoxicity (Level 3).**
Targeted immunosuppressive (long-term use)	• Mycophenolate mofetil (CellCept) Not FDA approved for MG	1000–2000 mg/day orally Twice-per-day scheduling	Well-documented single case studies available; publication of a randomized clinical trial pending Gastrointestinal symptoms and infection possible side effects. Monitor complete blood count and differential every 2 weeks six times. and then monthly (Saperstein & Barohn, 2004). **Nursing recommendation: Nurses should monitor for myelosuppression (Level 3).**

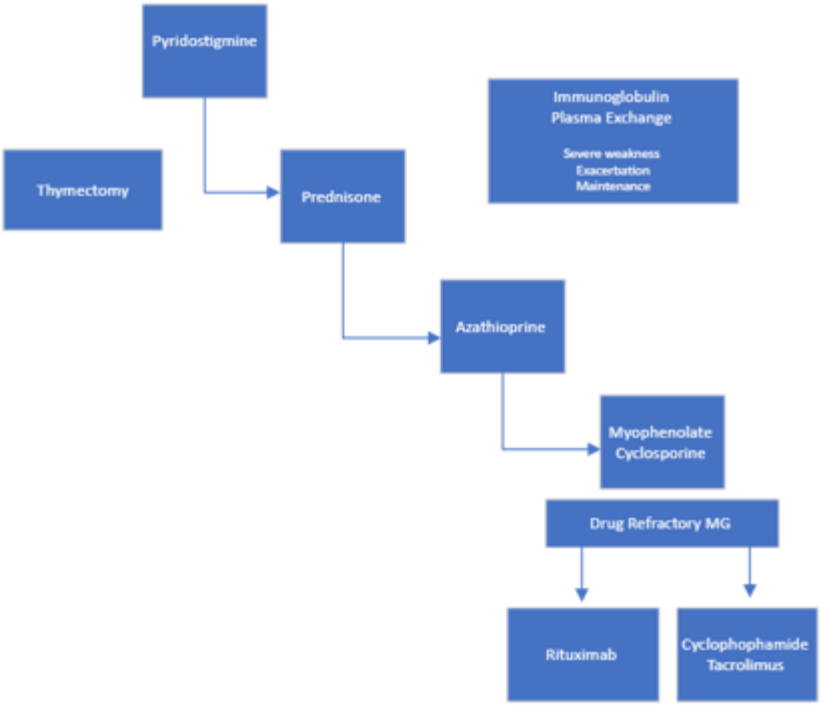
Table 5. Medications Used in the Management of Myasthenia Gravis			
Targeted immunosuppressive (long-term use)	• Methotrexate sodium (Methotrexate) Not FDA approved	7.5 mg to 15 mg/week orally	Well-documented single case studies available; publication of a randomized clinical trial pending Monitor for infection.
Targeted immunosuppressive (long-term use)	• Cyclophosphamide (Cytoxan)	500 mg/m^2 every 4–12 weeks IV or 1–2 mg/kg body weight per day orally	Well-documented single case studies available; publication of a randomized clinical trial pending Adverse effects include myelosupression, hemorrhagic cystitis, and increased risk for malignancy (Silvestri & Wolfe, 2012). **Nursing recommendation: Nurses should monitor for myelosuppression, hemorrhagic cystitis, and increased risk for malignancy (Level 3).**
Targeted immunosuppressive (long-term use)	• Tacrolimus (FK506) (Prograf)	0.1 mg/kg/day orally titrated to blood levels 0.2 (2 x 2-5mg/day) orally	Adverse effects include nephrotoxicity and hyperglycemia (Angelini, 2011) **Nursing recommendation: Nurses should monitor for nephrotoxicity and hyperglycemia. (Level 3).**
Other Immunosuppressive	• Rituximab (Rituxin)	375 mg/m^2 IV weekly	For refractory MG, and MuSK MG Adverse effects include pancytopenia (Ibrahim, Dimachkie, & Shaibani, 2010; Silvestri & Wolfe, 2012). **Nursing recommendation: Nurses should monitor pancytopenia associated with long-term immunosuppression (Level 3).**

• Off-label option; available for nonresponders, in cases of very severe MG, or when intolerable side effects occur. Abbreviations: FDA, U.S. Food and Drug Administration; IV, intravenous; MG, myasthenia gravis. Source: Tindall et al., 1993; Cialaloni et al., 2000; Schneider-Gold et al., 2005; Gold et al., 2008; Hart et al., 2007; Vassar et al., 2008; Meriggioli, 2009; Mehndiratta et al., 2011; Saperstein & Barohn, 2004; Angelini, 2011; Myasthenia Gravis Foundation of America, 2012b; Silvestri & Wolfe, 2012; Myasthenia Gravis Foundation of America, 2012b; Schneider-Gold, Gaidos, Toyka, & Hohlfeld, 2005; Vassar et al., 2008)

Commonly used therapies for myasthenia gravis

	Time to onset of effect*	Time to maximal effect*
Symptomatic therapy		
Pyridostigmine	10 to 15 minutes	2 hours
Chronic immunotherapies		
Prednisone	2 to 3 weeks	5 to 6 months
Azathioprine	~12 months	1 to 2 years
Mycophenolate mofetil	6 to 12 months	1 to 2 years
Cyclosporine	~6 months	~7 months
Tacrolimus	~6 months	~12 months
Efgartigimod alfa	1 to 2 weeks	~4 weeks
Ravulizumab	1 to 2 weeks	~4 to 10 weeks
Rapid immunotherapies		
Plasmapheresis	1 to 7 days	1 to 3 weeks
Intravenous immune globulin	1 to 2 weeks	1 to 3 weeks
Surgery		
Thymectomy	1 to 10 years	1 to 10 years

* Estimated times are rough guidelines based upon clinical experience in myasthenia gravis.



Treatment algorithm for myasthenia gravis