TREATMENT OF NEUROMUSCULAR JUNCTION DISORDERS

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Myasthenia Gravis
Myasthenia Gravis (MG) is the prototypical autoimmune disease and treatment of MG has improved dramatically over the last few decades, with the increasing number of immunomodulatory agents as well as improved intensive care management [1,2].

Medication
The two main groups of medications used for the treatment of MG include choline esterase inhibitors, for symptomatic therapy, and immunomodulatory agents. While exacerbation of symptoms during immunotherapy may require the use of higher doses of the same medication, or the addition or switch to other agents, it is important to exclude and treat provoking factors such as alteration in electrolyte levels, systemic infection, coincidental illness and iatrogenic causes (**Table-1**).

Cholinesterase inhibitors These medications are used for symptomatic therapy of MG [1,2]. They may be the only medication given for ocular MG or used alongside immunomodulatory agents while waiting for their full therapeutic effects. Pyridostigmine is the most common cholinesterase inhibitor prescribed and usually given at the dose of 30-60 mg every 4-6 hours (maximum is usually < 300 mg/day), best taken 30 minutes before meals to improve swallowing. Side effects include nausea, vomiting, abdominal cramps, diarrhea, increased oral and bronchial secretions, bradycardia and rarely confusion or psychosis.[6]

Immunomodulatory agents While the choice of these agents may vary between practitioners, the majority tend to start therapy with corticosteroids and use other agents based on response to steroids and the ability to taper them to a low dose.

Corticosteroids (CS) (**Table-2)** Despite the absence of high-quality randomized controlled trials, CS are considered to be the most effective oral immunotherapy [1-3]. In mild or moderate MG, prednisone is usually started at a low-dose (10-20 mg/day) in the outpatient setting and slowly increased by 5 mg every 5-7 days until the symptoms up to a maximum of 50 mg daily. After a patient has been on a stable dose for 4 wks, the dose is slowly tapered to the lowest amount tolerable. In patients with moderate to severe MG, I usually start high-dose prednisone (0.75-1mg/kg/day). This can be associated with worsening of MG is some patients and some authorities reserved for the inpatient setting where patients can be closely monitored for this reason. Again, once patients are asymptomatic, the prednisone should be tapered. I taper by 5-10 mg per month until the prednisone dosage is 20 mg daily and then by 5 mg per month until they are on 10 mg daily and then by 1 to 2.5 mg a month.

Other immunosuppressive agents (**Table-2)** Secondary agents are usually added to prednisone in steroid resistant patients or for their "steroid sparing" effects [1,2]. Most share common side-effects of bone marrow suppression, opportunistic infections, teratogenicity and oncogenicity that require monitoring and discussion with patients. *Azathioprine* is the most frequently used secondary agent with its efficacy shown in one clinical trial [4]. One of its limitations is delayed onset of action of many months and it is recommended for thiomethyl purine transferase (TPMT) deficiency to be excluded before starting therapy. *Cyclosporin* has also been shown to be effective in MG in clinical trials with an earlier onset of response compared with azathioprine (usually 2–3 months), but less well tolerated with common side effects of hypertension and nephrotoxicity [5]. The favorable response of MG patients to *tacrolimus* as both monotherapy and steroid sparing agent have been demonstrated in case series, retrospective studies as well as an unblinded randomized controlled study [6]. *Mycophenolate mofetil* was felt to be efficacious in retrospective studies [7,8]; however, two randomized, controlled trials failed to demonstrate additional benefit over prednisone in generalized MG, or steroid-sparing effects over a 9 month period [9,10]. Some authorities still feel strongly that mycophenolate is beneficial in some patients and have

suggested the reason for the negative trials include short duration of the studies, insensitive or stringent endpoints and greater than predicted response to prednisone. *Cyclophosphamide* has been used in MG patients refractory to other forms of immunomodulatory agents but the risks and benefits should be carefully weighed given its toxicity [11].

Rituximab appears to be effective in treating refractory MG, particularly in MuSK+MG, through case series and retrospective studies [12]. A large NIH sponsored clinical trial is now underway in patients with non-thymomatous AChR+MG.

Eculizumab is a monoclonal antibody that binds membrane attack complex that was shown to be beneficial in patients with refractory generalized MG, in a small double-blind placebo controlled study [13]. Results of a large phase 3 clinical trial were released in July 2016 (14) and the drug is undergoing FDA review for approval. The study's primary efficacy endpoint of change from baseline in Myasthenia Gravis-Activities of Daily Living Profile (MG-ADL) total score, a patient-reported assessment, at week 26, did not reach statistical significance (p=0.07) as measured by a worst-rank analysis. However, 18 of 22 pre-defined endpoints and pre-specified analyses in the study, based on the primary and five secondary endpoints, achieved p-values <0.05.

Intravenous immunoglobulin (IVIg) and plasma exchange (PLEX) both have shown to be equally efficacious in patients with moderate to severe MG [15, 16]. While they are usually used for those in myasthenic crisis or to bolster patient strength in anticipation of thymectomy, they are sometimes used as maintenance therapy in patients refractory or intolerant of other medications. IVIG is given at the dose of 2 gm/kg IV divided over 2-5 days, with monthly infusions followed by tapering down to the smallest dose and longest interval tolerable(**Table-3)**. PLEX is usually used as 5 exchanges over 10 days (based on body weight) with major side-effects of sepsis, pneumothorax, thrombophlebitis and cardiovascular instability with large volume transfer.

Thymectomy
Thymectomy is clearly indicated when there is a thymoma, regardless of whether or not a patient has ocular or generalized MG or if they are seropositive or negative. A large multicenter, international trial of thymectomy in non-thymomatous AChR+MG (126 participants) recently demonstrated that participants who underwent thymectomy had a lower time-weighted average Quantitative Myasthenia Gravis score over a 3-year period than those who received prednisone alone (6.15 vs. 8.99, P<0.001); those in the thymectomy group also had a lower average requirement for alternate-day prednisone (44 mg vs. 60 mg, P<0.001) [17]. Fewer subjects in the thymectomy group required azathioprine (17% vs. 48%, P<0.001) or were hospitalized for exacerbations (9% vs. 37%, P<0.001). Treatment-associated complications did not differ significantly between groups (P=0.73), but subjects in the thymectomy group had fewer treatment-associated symptoms related to immunosuppressive medications (P<0.001) and lower distress levels related to symptoms (P=0.003).

Special Circumstances
MuSK MG. While more than half of MuSK-MG respond to cholinesterase inhibitors, side effects are common including marked fasciculations, cramps and worsening of symptoms in a small percent. The majority of these patients respond well and rapidly to PLEX and more than half benefit from IVIG [18]. Small studies have shown a very good response to rituximab with long-lasting effects [12, 19].

Juvenile MG While both cholinesterase inhibitors and immunomodulatory agents are used to treat juvenile MG, some differences exist with adult MG [20]. In children, side effects of chronic steroid use are a concern, which are mostly similar to those noted for adults with the addition of reduction in linear growth that is not fully reversible. Other immunosuppressive medications are also not frequently used given their side effects. Thymectomy, including less invasive thoracoscopic surgery, has been shown to be effective through retrospective studies. Given the limitation of these observations, however, it is usually reserved for medically refractory generalized disease. Controversy exists regarding the timing of thymectomy given its role in immune system development of younger children.[44]

Pregnancy Pregnant patients with myasthenia should be considered at high risk and followed closely by a neuromuscular clinician, obstetrician and neonatologist. The effect of pregnancy on MG is variable and its course may vary from pregnancy to pregnancy. Exacerbations mostly commonly occur during the first trimester, last four weeks of gestation, and puerperium [21]. Women with MG should seek counseling before deciding to become pregnant to determine the need for thymectomy, optimize control of their disease and review the plan for therapy. Pyridostigmine and prednisone have been classified as pregnancy category C, but felt to be reasonably safe to

use. IVIg and PLEX can be used to manage severe symptoms or MG crisis. Azathioprine and mycophenolate mofetil (category D) pose risk to the fetus and their use is not recommended. Magnesium sulfate, given for management of eclampsia, should be used with extreme caution as it may lead to worsening of MG symptoms. The mother and fetus should be closely monitored during labor, and if required, regional anesthesia is preferred over general anesthesia.

Neonatal MG and arthrogryposis multiplex congenita (AMC). Transient neonatal myasthenia may occur in about 10% of babies born to women with MG, even when the mother is asymptomatic, due to transplacental transfer of maternal autoantibodies. Symptoms usually start a few days after birth and include ptosis, hypotonia, generalized weakness, difficulty feeding and even respiratory problems. It typically resolves in an average of 3 weeks but may need treatment with cholinesterase inhibitors and even ventilatory support in severe cases. In rare cases, maternal MG is associated with AMC, characterized by multiple joint contractures as well as dysmorphic features and other anomalies.

Myasthenic crisis Refers to severe MG exacerbation that may endanger life, due to respiratory muscle weakness or bulbar dysfunction, that can occur 15 to 20% of cases and predominantly in the first two years of disease onset [1,2]. Patients need to be closely monitored in an intensive care unit with consideration for earlier elective intubation. Treatment requires use of PLEX or IVIg followed by high-dose corticosteroids. Cholinesterase inhibitors are usually withheld while patients remain intubated.

COMPLICATIONS
The main complications are related to severe disease leading to respiratory compromise and bulbar dysfunction as well as side effects of therapy noted above.

PROGNOSIS
In MG patients presenting with ocular symptoms, weakness may remain restricted to the ocular muscles in 15% to 20% (pure ocular MG); however, the majority will develop weakness in other parts of the body (generalized MG) [1]. In the latter group, 90% will develop generalized disease within the first 12 months. Spontaneous remission occur in 10% to 15% of cases, usually within the first year or two of the disease. This makes it important to slowly taper patients off their immunosuppressive medication, once the disease is brought under control.

In AChR-MG, correlation between disease severity and anti-AChR antibody titers is poor, hence they cannot be used to determine prognosis or response to treatment. MuSK-MG, has long-term outcomes similar to AChR-MG, but has been shown to have an acute onset with rapid progression to maximum severity over a short time. Levels of anti-MuSK antibody may correlate with disease severity and treatment response.

Lambert-Eaton Myasthenic Syndrome (LEMS)

LEMS is the second most common NMJ disorder and the result of involvement of presynaptic voltage gated calcium channels (VGCC) [1]. LEMS in patients over the age of 40 years is usually paraneoplastic in nature. However, in younger adults in is more typically an autoimmune disorder with no underlying cancer, much like myasthenia.

MANAGEMENT
The treatment for paraneoplastic LEMS relies on identification of the tumor and its therapy. Patients with primary autoimmune LEMS without an underlying malignancy and those with cancer who are symptomatic despite treating the underlying cancer treatment (more common than not) typically require the combination symptomatic and immunotherapy.

For symptomatic treatment, we first start pyridostigmine as in myasthenic patients. However, most patients though do not have significant clinical improvement with this alone. In such cases, 3,4-diaminopyridine (3,4-DAP) given at the dose of 10-20 mg 3-4 times per day can be beneficial [1,22,23]. The aminopyridines block voltage-dependent potassium conductance, thereby prolonging nerve terminal depolarization and facilitating AChR release. Two recent clinical trials demonstrated the efficacy of 3,4-DAP). Treatment with the 3,4-DAP compound from Jacobus Pharmaceutical Company (Princeton, NJ) is usually started at 5-10 mg three times daily and is gradually increased every two weeks as tolerated up 15-20 mg four or five times a day, as clinically needed and

tolerated. The upper limit is 20 mg at a time and a total of 100 mg/day. The other compound that has been shown to be effective is Firdapse® (Amifampridine Phosphate, 3,4 Diaminopyridine Phosphate) by Catalyst Pharmaceuticals, Inc. The medication comes as 250 mg tablets, each containing the equivalent of 10 mg 3,4 DAP. The starting dose is one tablet three times daily and increased as needed up to 2 tablets four or five times a day as needed and tolerated. Amifampridine Phosphate should be taken with food. 3,4 DAP appears to be well tolerated, with a few patients experiencing perioral and acral paresthesias. It is recommended that the dosage not exceed 100 mg/d as higher doses may result in seizures.

Common side-effects include perioral and acral paresthesias; however, high doses (>100 mg daily) may result in seizures. In the absence of symptom control, immunotherapy, such as prednisone with or without a second-line immunosuppressive agent (e.g. azathioprine), may become necessary. IVIg has shown to be beneficial in one crossover trial. Plasma exchange and rituximab may be used in severe or refractory cases. In general, we manage patients with LEMS, in regard to immunotherapy, similar to that way we treat myasthenics.

Congenital Myasthenic Syndromes

The congenital myasthenic syndromes (CMS) are a heterogeneous group of disorders that cause failure of neuromuscular transmission as a result of genetic defects in presynaptic, synaptic or postsynaptic proteins that are important for the structure or function of the NMJ (Table 3) [1].

MANAGEMENT

Cholinesterase inhibitors are usually tried in the initial management of all patients, and continued prophylactically even when asymptomatic; however, some patients may not respond to, or even worsen, with chronic use. Some patients may respond favorably to 3,4-diaminopyridine (3,4-DAP) starting at 1 mg/kg/day in divided dosages (see LEMS section). In addition, albuterol starting at 2 mg BID and going up to 6 mg TID may be beneficial in cases of slow channel syndrome, AChE deficiency, and those associated with mutations in Dok-7, agrin, MuSK, DPAGT1, and LAMB2. Quinidine may help in slow-channel syndrome by shortening and even normalizing the duration of mutant channel openings. Administration of quinidine with serum levels of 0.7 to 2.5 µg/mL improved the clinical and electrophysiologic features in patients with slow-channel syndrome. However, the FDA has warned against the off-label of quinidine because of the risk of significant side effects (e.g., hemolytic uremic syndrome, cardiac arrhythmia). Ephedrine may be beneficial in patients with Dok-7 mutations.

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Table-1: Drugs with potential adverse effects on the neuromscular junction.

Drugs reported to unmask or exacerbate MG	
Antimicorbials	Aminoglycosides, polymyxins clindamycin, fluoroquinolones, azithromycin, erythromycin, quinine, tetracyclines, sulfonamides, penicillins, nitrofurantoin
Antiarrhythmic agents	Lidocaine, quinidine, procainamide
Corticosteroids	
Magnesium (parenteral)	
Neuromuscular blocking agents	Depolarizing and nondepolarizing agents
Drugs possibly unmasking or exacerbatingMG	
Sedatives and anesthetics	Diazepam, ketamine
Anticonvulsants	Phenytoin, ethosuximide, barbiturates, carbamazepine, gabapentin
Beta blockers	Propanolol, timolol, atenolol, labetalol, metoprolol, nadolol
Calcium channel blockers	Verapamil
Drugs of abuse	Cocaine
Gastrointestinal	Cimetidine
Ophthalmics	Echothiophate, tropicamide
Psychiatric drugs	Phenothiazenes, lithium, amitriptyline, imipramine, amphetamines, haloperidol
Iodinated contrast agents	
Other	L-carnitine, trihexiphenidyl

Table-2: Common immunomodulatory agents used for treatment of MG.

Medication	Starting Dose	Dose adjustment	Severe Side Effects	Monitoring	Comments
Prednisone	Start low, go slow: 10-20 mg/day Starting high: 0.75-1.5 mg/kg/day	For start low, go slow: Increase by 5 mg every 2-4 days until symptom plateau or 0.75-1.5 mg/kg/day. Switch to alternate-day (if possible) and taper slowly until minimal dose possible	Hypertension, diabetes, glaucoma, osteoporosis, aseptic necrosis of the joints, cataracts, glaucoma, GI ulcers, psychologic disorders, steroid myopathy, infection	K+, glucose, bone density, blood pressure, eye exam	Prednisone can be started at doses of 0.75-1.5 mg/kg but needs close monitoring for 7-10 days as risk for exacerbation
Azathioprine	50 mg twice daily	Increase by 50 mg increments as needed every 2-4 weeks until 2–3 mg/kg/day in three divided dosages	Systemic reaction (fever, nausea, vomiting, abdominal pain), myelosuppression, pancreatitis, hepatotoxicity, infection	CBC, LFTs	Consider thiomethyl purine transferase (TPMT) assay before treatment; do not use with allopurinol
Cyclosporin	3 to 4 mg/kg/day in two divided doses	Increase slowly up to total 6 mg/kg/day as needed	Hypertension, nephrotoxicity, tremor, PRES, seizure, hepatotoxicity, infection	CBC, LFTs, BUN, Cr, electrolytes, drug trough levels, blood pressure	Bioequivalence differs between preparations; avoid other nephrotoxicity drugs
Mycophenolate mofetil	1000 mg twice daily (no more than 500 mg twice a daily in patients with renal insufficiency)	Increase as needed to 1500 mg twice daily	Diarrhea, vomiting, myelosupression, infection	CBC, Cr	Lack of additional benefit over prednisone in two trials
Rituximab	375 mg/m2/week for 4 weeks (alternatively 1000 mg IV 2 weeks apart)	Repeat infusion based on patient response every 6 to 24 months	Infusion reaction, anaphylaxis, myelosupression, infection, cardiac dysrhythmia	CBC, ECG during and following infusion	Premedicate with acetaminophen and antihistamines
Intravenous immunoglobulin (IVIg)	2 g/kg over 2–5 days	Give monthly infusion and taper to lowest dose (0.4–1 g/kg) with longest interval	Infusion reaction, aseptic meningitis, nephrotoxicity, stroke, fluid overload	BUN, Cr	Premedicate with acetaminophen and antihistamines to reduce headaches

BUN: blood urea nitrogen; CBC: complete blood count; Cr: creatinine; ECG: electrocardiogram; GI: gastrointestinal; IgA: immunoglobulin A; LFT: liver function test; m2: body surface area; mo: month(s); PFT: pulmonary function test; PRES: posterior reversible encephalopathy syndrome.

Table-3: Congenital Myasthenic Syndromes

Congenital Myasthenic Syndromes (CMS)	Mutated Gene	Suggestive Features
Presynaptic defects		
Defect in choline acetyltransferase (ChAT)	*CHAT*	Apneic episodes (spontaneous or triggered by fever, vomiting, or excitement); worsening in cold temperature
Paucity of synaptic vesicles	Unknown	
Congenital Lambert-Eaton like syndrome	Unknown	Facilitation of CMAP amplitude with RNS
Synaptic defect		
Endplate AChE deficiency	*COLQ*	Repetitive CMAPs and negative edrophonium test; refractory to CEI but may respond to ephedrine and albuterol
β2 laminin deficiency	*LAMB2*	May have nephrotic syndrome and ocular abnormalities (Pierson syndrome); refractory to CEI
Postsynaptic defects		
Primary kinetic abnormality	--	
A. Slow channel syndromes	AChR subunits	AD inheritance; Prominnent cervical, wrist and finger extensor weakness but mild in cranial innervated muscles; Repetitive CMAPs and negative edrophonium test; Worsened by CEI but may respond to quinidine, or fluoxetine
B. Fast channel syndromes	AChR subunits	Most respond to combination of 3,4-DAP and CEI
Primary AChR deficiency	AChR subunits (mostly ε)	Prominent ophthalmoparesis; partially respond to CEI with addedd benefit from 3,4-DAP or albuterol
Rapsyn CMS	*RAPSN*	Multiple joint contractures or dysmorphic features in some cases; strabismus, facial and bulbar weakness common; respond to CEI with addedd benefit from 3,4-DAP
Plectin CMS	*PLEC*	May present with epidermolysis bullosa simplex or progressive muscular dystrophy
Na channel myasthenia	*SCN4A*	May have abrupt attacks of respiratory and bulbar paralysis
Defects in endplate development and maintenance		
Dok-7 CMS	*DOK7*	Possible stridor and vocal cord paralysis in neonates and infants; mainly limb-girdle and axial weakness with mild facial weakness and ptosis and normal ocular movement; some with severe bulbar involvement; may worsen with pyridostigmine but may respond to ephedrine and albuterol
MuSK CMS	*MUSK*	Some reports of response to low dose pyridostigmine and 3,4-DAP
Agrin CMS	*AGRN*	May have ptosis with weakness of the facial and hip-girdle muscles
GFPT1 CMS	*GFPT1*	Predominantly limb-girdle and axial weakness; muscle biopsy with tubular aggregates in most

3,4-DAP: 3,4 diaminopyridine; AChR: acetylcholine receptor; AD: autosomal dominant; AR: autosomal recessive; CEI: choline esterase inhibitors; CMS: congenital myasthenic syndrome; Dok-7: downstream of tyrosine kinase 7; GFPT1: Glutamine–fructose-6-phosphate transaminase deficiency; MuSK: muscle specific kinase; RNS: repetitive nerves stimulaton;