TREATMENT OF NEUROMUSCULAR DISORDERS

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TREATMENT OF PAINFUL POLYNEUROPATHY

Painful polyneuropathies are one of the most common neuromuscular referrals for subspecialists and general neurologists. It is important to tell patients up front that despite extensive work-up, perhaps the etiology of the polyneuropathy is found in only half of patients [1]. Guidelines have been published as to the appropriate work-up [2,3]. In general, I obtain a CBC, comprehensive metabolic profile, fasting glucose along with HgbA1C, SPEP with immunofixation, ANA, SSA/SSB, and ESR along with a nerve conduction study. I do not recommend sural nerve biopsies for unexplained polyneuropathy. Nor do I typically order skin biopsies to diagnosis small fiber polyneuropathy as it typically does not tell me more than I already know by doing a good history, exam, and nerve conduction studies or change management. A patient with burning, stabbing, tingling pain in the feet with normal NCS most likely has a small fiber polyneuropathy.

Unfortunately, there is no treatment for slowing the progression or reversing the "numbness" or lack of sensation. Therapies are aimed at symptomatic management of neuropathic pain and reducing the risk of falling through the use of durable medical equipment [4-11]. Most of the randomized controlled trials addressed patients with postherpetic neuralgia or painful neuropathy caused by diabetes. Recent meta-analyses of published clinical trials for painful diabetic neuropathy found that serotonin-norepinephrine reuptake inhibitors duloxetine and venlafaxine (moderate strength of evidence), tricyclic antidepressants (low strength of evidence), the anticonvulsants pregabalin and oxcarbazepine (low strength of evidence), atypical opioids (low strength of evidence), and botulinum toxin (low strength of evidence) were all more effective than placebo. Notably, gabapentin was not more effective than placebo [10, 11]. Unfortunately, due to lack of studies no conclusions could be made for directly comparisons between different drugs.

My approach to treating the painful paresthesias and burning sensation associated with chronic idiopathic sensory neuropathy is uniform regardless of etiology (e.g., painful sensory neuropathies related to diabetes mellitus, HIV infection, and herpes zoster infection). Though there is a lack of strong evidence, if there is pain only in the feet, I start off with Lidoderm 5% patches to the feet, as this treatment is associated with less systemic side effects. If this does not suffice (and it usually does not) or the neuropathic pain is more generalized, my next step is to add an SSRI (e.g., duloxetine, venlafaxine). I usually start at a low dose and gradually increase as necessary and as tolerated. I add an antiepileptic (e.g. , prebabalin, oxcarbazepine) if monotherapy with an SSRI is not effective or there are too many side effects. Tramadol is used to treat breakthrough pain.

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TREATMENT OF MOTOR NEURON DISEASE

Unfortunately, there have been no new, approved medical treatments for ALS. However, the FDA recently approved Nusinersen for the treatment of spinal muscular atrophy (SMA). Nusinersen is an antisense oligonucleotide (ASO) that is designed to alter the splicing of *SMN2*, a gene that is nearly identical to *SMN1*, in order to increase production of fully functional SMN protein. Nusinersen administered into the CSF. The results of the clinical trial that led to FDA approval are not as yet published so information below is based on what has been provided to the community by Biogen:

The efficacy of the agent in patients with infant-onset SMA was established at an interim analysis of the phase 3 ENDEAR trial for patients diagnosed before 6 months of age who were less than 7 months old at the time of their first dose. Efficacy in later-onset disease was established in open-label trials. At the interim analysis of the ENDEAR study, which included 82 evaluable patients, 40% of those treated with nusinersen had an improvement in motor function versus none in a control arm of untreated patients. Findings from the open-label studies supported the clinical efficacy for nusinersen, although there was not a control arm. The efficacy seen in these studies was similar to the infantile-onset patients, according to the FDA.

Overall, 170 patients were treated across studies that led to the approval for nusinersen. This included the interim analysis of the phase 3 ENDEAR trial, which enrolled 122 total patients with infantile-onset SMA. The open-label trials were for patients with pre-symptomatic and symptomatic disease or those with, or likely to develop, Types 1, 2, and 3 SMA. In the analysis of ENDEAR, a statistically significant improvement in motor milestone response was seen with nusinersen versus those who did not receive treatment (40% vs 0%; P <.0001), according to Hammersmith Infant Neurological Examination (HINE). Fewer patients treated with nusinersen had died at the time of the analysis (23%) compared with the untreated patients (43%). The most common adverse events with nusinersen were upper respiratory infection, lower respiratory infection, and constipation. The FDA approved the drug with warnings and precautions for low blood platelet count and renal toxicity.

Hopefully a peer-reviewed publication of the study will be available soon.

TREATMENT OF NEUROMUSCULAR JUNCTION DISORDERS

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**).

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

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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) 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 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 [17]. Small studies have shown a very good response to rituximab with long-lasting effects [12, 18].

Juvenile MG While both cholinesterase inhibitors and immunomodulatory agents are used to treat juvenile MG, some differences exist with adult MG [19]. 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 [20]. 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 [1,21,22]. 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 [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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TREATMENT OF INFLAMMATORY MYOPATHIES

There are four major categories of idiopathic inflammatory myopathy: dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), and inclusion body myositis (IBM), which are clinically, histologically, and pathogenically distinct.[1–3] There are many published retrospective studies and small case reports regarding the use of various immunosuppressive and immunomodulating therapies in different types of inflammatory myopathy. Unfortunately, most of these older studies are difficult to interpret because they group adult and childhood DM together with PM, IBM, and IMNM. Many of these reports were retrospective and unblinded and lacked placebo controls. Further, in several reports, patients with subjective improvement or lower serum CK levels were defined as positive responses rather than the more important objective improvement in muscle strength and function. There have been only a few published prospective, double-blinded, placebo-controlled trials in the treatment of PM and DM and none in IMNM.[4-8] Despite the paucity of prospective, double-blinded, placebo-controlled trials, it is clear to experienced clinicians that various modes of immunotherapy are helpful in DM, PM, and IMNM. In contrast, IBM is generally refractory to immunosuppressive therapy.

CORTICOSTEROIDS

Corticosteroids are the treatment of choice for DM, PM, and IMNM.[1-3,8-10] In patients with severe weakness or co-morbiditis (e.g., bad ILD, myocarditis), I often initiate treatment with a short course of intravenous Solumedrol (1 g daily for 3 days) prior to starting oral agents. Noticeable clinical improvement typically begins within 3–6 months of starting prednisone in most patients with DM or PM. IMNM is more refractory, often requires more than just

prednisone alone, and usually takes longer to see a beneficial effect. When no response is noted after an adequate trial of high-dose prednisone, other alternative diagnoses (e.g., IBM or an inflammatory muscular dystrophy) and repeat muscle biopsy should be considered.

In patients with DM, PM, autoimmune necrotizing myopathy, and other idiopathic inflammatory myositides other than IBM (i.e., sarcoidosis), I generally initiate treatment with single-dose prednisone (0.75 to 1.5 mg/kg up to 100 mg) every morning (the most common dose used in adults is 60 mg daily). Some studies suggest that alternate day or intermittent pulses of intravenous corticosteroids may be equally efficacious and associated with fewer side effects than daily steroids.[8,10] I typically follow patients initially at every 2–4 weeks at the onset. I maintain them on high-dose prednisone until strength normalizes or until improvement in strength has reached a plateau (usually 4–6 months). Subsequently, I taper prednisone by 5 mg every 2–4 weeks. Once the dose is reduced to 20 mg every day or every other day, I decrease prednisone by 2.5 mg every 2-4 weeks. I try to get patients to prednisone10 mg daily or less.

Although most patients improve the response may not be complete and many will require at least a small dose of prednisone or a second-line agent to have a sustained remission. I monitor the serum CK levels; however, adjustments of prednisone and other immunotherapies are primarily based on the objective clinical examination and not the CK levels or the patients' subjective response.

Relapse of the myositis needs to be distinguished from steroid myopathy. This quandary may occur in patients who initially improved but then start developing progressive muscle weakness following long-term corticosteroid treatment because it can cause type 2 muscle fiber atrophy. Features that would suggest a "steroid myopathy" as opposed to relapse of myositis would be a normal serum CK, other clinical features of steroid excess such as ecchymoses and "moon facies", and absence of muscle membrane irritability on EMG. In contrast, patients who become weaker during prednisone taper, have increasing serum CK levels, and abnormal spontaneous activity on EMG are more likely experiencing a flare of the myositis.

CONCURRENT MANAGEMENT

I obtain a chest X-ray and, in at risk individuals, I test for TB prior to initiating immunosuppressive medications. Patients with prior history of tuberculosis or a positive PPD may need to be treated prophylactically with isoniazid. If patients have ILD and are to be placed on prednisone plus another immunosuppressive agent, I also start Bactrim or atovaquonefor pneumocystis prophylaxis.

I measure bone density with dual-energy X-ray absorptiometry at baseline and yearly while patients are receiving corticosteroids. A bone density score of less than 2.5 standard deviations below normal is considered positive for osteoporosis. Calcium supplementation (1 g/d) and vitamin D (400–800 IU/d) are started for prophylaxis against steroid-induced osteoporosis. Postmenopausal women are also started on a bisphosphonate for prevention and treatment of osteoporosis. I prescribe alendronate 35 mg/week (or another bisphosphonate) as prophylaxis against steroid-induced osteoporosis or 70 mg/week in those with osteoporosis. Because the long-term side effects of bisphosphonates are not known, particularly in men and young premenopausal women, we prophylactically treat (alendronate 35 mg/week) these individuals only if the dual-energy X-ray absorptiometry scan demonstrates a density between 1 and 2.5 standard deviations below normal at baseline or if significant bone loss occurs on follow-up scans. If bone densities are in the osteoporosis range, these are treated with alendronate 70 mg/week. Alendronate can cause severe esophagitis, and absorption is impaired if taken with meals. Therefore, patients must be instructed to remain upright and not to eat for at least 30 minutes following the dose of alendronate in the morning.

Antihistamine-H_2 blockers are not routinely started unless the patient develops gastrointestinal discomfort or has a history of peptic ulcer disease. I instruct patients to start a low-sodium, low-carbohydrate, high-protein diet to prevent excessive weight gain. Physical therapy and an aerobic exercise program are helpful in fending off side effects of prednisone (e.g., weight gain) and preventing contractures and calcinosis that may result from immobility. Blood pressure is measured at each visit as accelerated hypertension and renal failure may occur, particularly in patients with scleroderma or MCTD. In addition, periodic eye examinations for cataracts and glaucoma should be performed. I periodically check fasting blood glucose and serum potassium levels while they are on high doses of prednisone.

SECOND-LINE THERAPIES

These agents are used primarily in patients poorly responsive to prednisone or who relapse during prednisone taper as well as for their potential steroid-sparing effect (**Table 2**).[1-3] There is equipoise regarding when to start second-line agents (e.g., methotrexate, azathioprine, mycophenolate, immunoglobulin, rituximab). The clinician must review with the patient the increased risks of immunosuppression versus possible benefits (e.g., faster improvement, steroid-sparing effect and/or avoidance of the morbidities associated with long-term steroid use). I usually start a second line agent along with corticosteroids in patients with severe weakness or other organ system involvement (e.g., myocarditis, interstitial lung disease), those with increased risk of steroid complications (e.g., diabetics, patients with osteoporosis, or post-menopausal women), and patients who we know from experience have difficult to treat myositis (e.g., IMNM).

A second-line agent should also be strongly considered in patients who fail to significantly improve after 2-4 months of treatment or if there is an exacerbation during treatment with prednisone. In patients who relapse during the taper, I double the dose of prednisone (no more than 100 mg/d). Once a patient has regained their strength, I resume the prednisone taper at a slower rate.

INTRAVENOUS IMMUNOGLOBULIN

Small, uncontrolled studies have reported beneficial response of IVIG in DM and PM.[9,11,12] A prospective, double-blind, placebo-controlled study of IVIG in 15 patients with DM demonstrated significant clinical improvement with IVIG.[7] I usually use IVIG in patients with DM, PM, and IMNM who are refractory to prednisone and at least one second-line immunosuppressive agent, though I have started up along these in patients with very severe myositis.

I initiate IVIG (2 g/kg) slowly over 2–5 days and repeat infusions at monthly intervals for at least 3 months. Subsequently, I try to decrease or spread out or decrease the dosage: 2 g/kg every 2 months or 1 g/kg per month. Treatment schedule needs to be individualized. I generally give IVIG in combination with prednisone. There is no strong medical evidence in the literature regarding its efficacy as an initial monotherapy. Patients should also have renal function checked beforehand, especially those with diabetes mellitus, because of a risk of IVIG-induced renal failure. Flu-like symptoms—headaches, myalgias, fever, chills, nausea, and vomiting—are common and occur in as many as half the patients. Rash, aseptic meningitis, and stroke can also occur.

METHOTREXATE

There are no prospective, blinded, controlled studies of methotrexate in DM or PM. However, retrospective studies report that as many as 71–88% of patients with DM and PM, including those refractory to prednisone, improve at least partially with the addition of methotrexate.[1,13-15] Methotrexate is administered only 1 day a week. I usually begin methotrexate orally at 5.0 mg/week. The dose is gradually increased by 2.5 mg each week up to 20 mg/week given in three divided doses 12 hours apart. The dose should be reduced and used cautiously in patients with renal insufficiency. If there is no improvement after 1 month of 20 mg/week of oral methotrexate, I switch to weekly parenteral (usually subcutaneous) methotrexate and increase the dose by 5 mg every week -I rarely go higher than 35 mg/week. The major side effects of methotrexate are alopecia, stomatitis, ILD, teratogenicity, oncogenicity, risk of infection, and pulmonary fibrosis, along with bone marrow, renal, and liver toxicity. Doses over 50 mg/week require leukovorin rescue, although I do not use such high doses. However, all patients are concomitantly treated with folate.

Because methotrexate can cause pulmonary fibrosis, I usually try to avoid in those who already have the associated ILD and in patients with Jo-1 antibodies. I obtain baseline and periodic pulmonary function tests including forced vital capacity and diffusion capacity and repeat these periodically on patients treated with methotrexate. I monitor CBC and liver function tests (LFTs)—AST, ALT, bilirubin, and gamma-glutamyl transpeptidase (GGT) every 2 weeks until the patient is on a stable dose of methotrexate, then every 1–3 months. It is important to check the GGT, as it is the most reliable indicator of hepatic dysfunction, because the AST and ALT can be elevated from muscle involvement.

AZATHIOPRINE

Retrospective studies suggest that azathioprine is an effective therapy in DM and PM.[1] A prospective, double-blind study comparing azathioprine (2 mg/kg) in combination with prednisone to placebo plus prednisone found no significant difference in objective improvement at 3 months.[4] However, in the open-label follow-up period, patients on the combination of azathioprine and prednisone did better than those on prednisone alone and required lower doses of prednisone.[16]

Prior to beginning azathioprine, patients can be screened for thiopurine methyltransferase (TPMT) deficiency. Patients who are heterozygous for a mutation in TPMT may be able to tolerate azathioprine at lower dosages but those who are homozygous for TPMT mutations should not receive drug as they cannot metabolize it and may have severe bone marrow toxicity. In those patients without TPMT mutations, we initiate azathioprine at a dose of 50 mg/d in adults and increase the dose by 50 mg every 2 weeks up to 2–3 mg/kg/d. Approximately 12% of patients develop a systemic reaction characterized by fever, abdominal pain, nausea, vomiting, and anorexia that requires discontinuation of the drug.[17] This systemic reaction generally occurs within the first few weeks of therapy and resolves within a few days of discontinuing the medication. Recurrence of the systemic reaction usually follows restarting azathioprine. Other major side effects of azathioprine are bone marrow suppression, hepatic toxicity, pancreatitis, teratogenicity, oncogenicity, and increased risk of infection. Allopurinol should be avoided, because combination with azathioprine increases the risk of bone marrow and liver toxicity. A major drawback of azathioprine is that it may take 6–18 months to be effective.

CBCs and LFTs need to be followed closely. If the white blood count (WBC) falls below 4000/mm^3, we decrease the dose. Azathioprine is held if the WBC declines to 2500/mm^3 or the absolute neutrophil count falls to 1000/mm^3. Leukopenia can develop as early as 1 week or as late as 2 years after initiating azathioprine. The leukopenia usually reverses within 1 month, and it is possible to then rechallenge the patient with azathioprine without recurrence of the severe leukopenia.[17] In addition, we discontinue azathioprine if the LFTs increase more than twice the baseline values. Liver toxicity generally develops within the first several months of treatment and can take several months to resolve. Patients can occasionally be successfully rechallenged with azathioprine after LFTs return to baseline without recurrence of hepatic dysfunction.[17]

MYCOPHENOLATE MOFETIL

Mycophenylate mofetil inhibits the proliferation of T and B lymphocytes by blocking purine synthesis in only lymphocytes. Mycophenylate has been tried in patients with myositis with reported benefit.[1,18-21] The starting dose is 1.0 g twice daily and can be increased to 3 g daily in divided doses if necessary. Mycophenylate is renally excreted; therefore, the dose should be decreased (no more than 1 g/d total dose) in patients with renal insufficiency. A benefit of mycophenylate compared to other immunosuppressive agents is the lack of renal or liver toxicity. Mycophenolate appears to be beneficial in some patients; however, we have seen a number of severe infections as a complication.[18] The most frequent side effect is diarrhea. Less common side effects include abdominal discomfort, nausea, peripheral edema, fever, and leukopenia.

RITUXIMAB

Rituximab is a monoclonal antibody directed against CD20+ B-cells, which it depletes for 6 months or more. A number of small series have suggested that rituximab may be effective in DM, PM, and necrotizing myopathies.[22-25] A large prospective, double-blind, NIH trial found no benefit but there were significant flaws in the study design.[5] A subset of patients do likely respond,[26] and it has been my experience that Rituximab can be beneficial in patients with refractory DM, PM, and IMNM. I use it in patients who are refractory to prednisone and at least one of the other second-line agents discussed above. The typical dosage is 750 mg/meter-squared (up to 1 gm) IV and then repeat the infusion in two weeks. Alternatively, patents can be treated with a 4 week course (375 mg/m^2 weekly x 4 weeks). A course of rituximab as above is usually repeated every 6 to 18 months depending on how well they are doing. There is a very small risk of progressive multifocal leukoencephalopathy, which is discussed with patients before prescribing.

TABLE 2. IMMUNOTHERAPY FOR INFLAMMATORY MYOPATHIES

THERAPY	ROUTE	DOSE	SIDE EFFECTS	MONITOR
Prednisone	oral	0.75 to 1.5 mg kg/day to start	Hypertension, fluid and weight gain, hyperglycemia, hypokalemia, cataracts, gastric irritation, osteoporosis, infection, aseptic femoral necrosis	Weight, blood pressure, serum glucose/potassium, cataract formation
Methylprednisone	intravenous	1 gm in 100 ml/normal saline over 1-2 hours, daily or every other day for 3-6 doses	Arrhythmia, flushing, dysgeusia, anxiety, insomnia, fluid and weight gain, hyperglycemia, hypokalemia, infection	Heart rate, blood pressure, serum glucose/potassium
Azathioprine	oral	2-3 mg/kg/day; single a.m. dose	Flu-like illness, hepatotoxicity, pancreatitis, leukopenia, macrocytosis, neoplasia, infection, teratogenicity	Blood count, liver enzymes
Methotrexate	oral	7.5-20 mg weekly, single or divided doses; one day a week dosing	Hepatotoxicity, pulmonary fibrosis, infection, neoplasia, infertility, leukopenia, alopecia, gastric irritation, stomatitis, teratogenicity	Liver enzymes, blood count;
	subcutaneously	20-50 mg weekly; one day a week dosing	Same as oral.	Same as p.o.
Cyclophosphamide	Oral	1.5-2 mg/kg/day; single a.m. dose	Bone marrow suppression, infertility, hemorrhagic cystitis, alopecia, infections, neoplasia, teratogenicity	Blood count, urinalysis
	intravenous	0.5 to 1.0 g/m^2 per month x 6-12 months		
Cyclosporine	oral	4-6 mg/kg/day, split into two daily doses	Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsuitism, tremor, gum hyperplasia, teratogenicity,	Blood pressure, creatinine/BUN, liver enzymes, cyclosporine levels,
Tacrolimus	oral	0.1 – 0.2 mg/kg/day in two divided doses	Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsuitism, tremor, gum hyperplasia, teratogenicity,	Blood pressure, creatinine/BUN, liver enzymes, tacrolimus levels,
Mycophenolate mofetil	oral	Adults (1 gm BID to 1.5 gm BID) Children (600 mg/m^2/dose BID (no more than 1 gm per day in patients with renal failure)	Bone marrow suppression, hypertension, tremor, diarrhea, nausea, vomiting, headache, sinusitis, confusion, amblyopia, cough, teratogenicity, infection, neoplasia	Blood count
Intravenous Immunoglobulin	intravenous	2 gm/kg over 2-5 days; then 1-gm/kg every 4-8 weeks as needed	Hypotension, arrhythmia, diaphoresis, flushing, nephrotoxicity, headache, aseptic meningitis, anaphylaxis, stroke	Heart rate, blood pressure, creatinine/BUN
Rituximab	intravenous	A course is typically 750 mg-meter squared (up to 1 gm) and repeated in 2 wks Courses are then repeated usually every 6-18 months	Infusion reactions (as per IVIG), infection, progressive multifocal leukoencephalopathy	Some check B-cell count prior to subsequent courses (but this may not be warranted)

With permission from: Amato AA, Russell J. Neuromuscular Disease, 2nd ed. New York: McGraw-Hill, 2016, p. 859, Table 33-8-1.

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.

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