Neuromuscular Therapeutics

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Drs. Juel and Robinson have indicated that their material references an “off-label” use of a commercial product.

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Neuromuscular Therapeutics

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No one involved in the planning of this CME activity had any relevant financial relationships to disclose.

Chair: Bashar Katirji, MD

The ideas and opinions expressed in this publication are solely those of the specific authors and do not necessarily represent those of the AANEM.
Objectives

Objectives - Participants will acquire skills to (1) Recognize the indicated therapies for MG, (2) identify the various types of inflammatory myopathies and their treatment, (3) explain the various immunosuppressive agents indicated in the treatment of NM diseases including potential adverse effects and recommended monitoring, and (4) list the various immunoglobulin products used in the treatment of NM diseases including potential adverse effects.

Target Audience:
- Neurologists, physical medicine and rehabilitation and other physicians interested in neuromuscular and electrodiagnostic medicine
- Health care professionals involved in the diagnosis and management of patients with neuromuscular diseases
- Researchers who are actively involved in the neuromuscular and/or electrodiagnostic research

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Update on Therapies for Myasthenia Gravis

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Treatment of autoimmune, acquired myasthenia gravis (MG) has evolved substantially since the mid-twentieth century when acetylcholinesterase inhibitors represented the mainstay of treatment. The adoption of chronic immune suppression (IS) treatment has significantly improved the prognosis for many MG patients. Along with the observation that mortality in MG has declined significantly in parallel with adoption of long-term IS therapies, a recent review of over 1000 patients treated with IS for at least 1 year showed that all forms of MG benefited from IS, with remission rates ranging from 85% in ocular MG to 47% in thymomatous MG. However, as a rare and rather heterogeneous disorder with spontaneous relapses and remissions, prospective, randomized, controlled clinical trials are difficult to perform in MG, and few therapies have undergone such rigorous trials.

With an expanding armamentarium of treatment options and newly-recognized immunological subtypes, the adage that therapy in MG must be individualized has never been more relevant. The overall treatment objective is to restore normal function with an absolute minimum of treatment-related side effects. Formulation of an appropriate management strategy requires consideration of clinical and immunological characteristics of MG and the risks for treatment complications. Relevant clinical characteristics include the distribution (ocular, bulbar, generalized) and severity (mild, moderate, severe, crisis) of myasthenic weakness and the impact on function. Immunological issues that influence treatment include the presence of acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSK) antibodies and the presence of thymoma. Risks for treatment complications relate to age, gender, medical comorbidities, the ability of the patient to obtain the medication and to comply with drug dosing schedules, and toxicity monitoring. Individual treatments will be discussed below.

ACETYLCHOLINESTERASE INHIBITORS

Acetylcholinesterase inhibitors (AChEis) impair hydrolysis of acetylcholine at the neuromuscular junction and increase the probability for successful neuromuscular transmission. As symptomatic treatment for MG, AChEis may elicit temporary improvement in strength, but do not retard the autoimmune attack on the neuromuscular endplate. Clinical responses to AChEis are often incomplete and variable over time and in different muscle groups. No controlled trials using long-acting AChEis have been performed in MG despite the frequent clinical use of these agents in MG for nearly seven decades.

AChEis are useful as initial therapy for ocular or mild, generalized MG, and as an adjunct treatment for patients receiving immunotherapy who have residual symptoms. The main advantage of AChEis is a lack of long-term side effects. Disadvantages include the transient and often incomplete improvement in myasthenic symptoms, frequent dosing schedule, and muscarinic side effects.

Pyridostigmine bromide (Mestinon) is more widely used than neostigmine bromide (Prostigmin) due to fewer gastrointestinal side effects. A long-acting form of pyridostigmine bromide (Mestinon Timespan 180 mg) is absorbed irregularly and therefore tends to be overdosed. It may be useful in rare patients for bedtime dosing to reduce early morning weakness, though severe weakness on awakening is very rare in MG.

AChEis are started at a low dosage and gradually titrated upward to avoid dose-dependent, though transient, muscarinic side effects including nausea, vomiting, abdominal cramping, diarrhea, sweating, increased bronchial secretions, lacrimation,
Corticosteroids (CSs) have wide effects on the immune system and may ameliorate autoimmune disease by reducing inflammatory cytokine transcription. Prednisone elicits rapid and significant improvement or remission in most MG patients. In a large retrospective trial, most patients experienced significantly improved strength after 2-3 weeks of treatment and 80% experienced marked improvement or remission. The mean time to reach marked improvement or remission was 3.1 months, and the median time to maximum benefit was between 5-6 months.3 Prednisone is an appropriate initial treatment for patients with ocular or generalized myasthenia gravis who fail to achieve a satisfactory response to AChEis.

Although CSs are well known to be rapidly effective in most patients, the primary disadvantages of CSs are the numerous, predominantly dose- and duration-related side effects. Risks for such side effects include baseline hypertension, glucose intolerance, diabetes, obesity, glaucoma, osteoporosis, and affective or thought disorders. An alternative IS therapy may be considered in such patients.

With the high-dose treatment strategy, prednisone is dosed at 0.75-1.0 mg/kg/day or 60-80 mg/day. If sustained improvement is documented at a clinical reassessment after 2-4 weeks, the dose is modified to 100-120 mg on alternate days. The dosage should be tapered gradually at approximately 4-8 week intervals by 10 mg (on dosing days) to 30 mg on alternate days, then by 5 mg (on dosing days) to 20 mg on alternate days. Subsequent tapering should be done very judiciously by 2.5 mg (on dosing days). All dosage reductions should be preceded by clinical assessment of MG. Some patients do not tolerate alternate day dosing due to variations in myasthenia, mood swings, or difficult glycemic control. If symptoms or signs recur at any point, the taper should be stopped. Myasthenic relapses may be delayed for 2-3 weeks after prednisone dose reductions. Although rare patients are successfully tapered off of prednisone, most patients will require indefinite treatment with 10-20 mg on alternate days unless another IS agent is used.

CSs can also be started at a low dosage and slowly increased to reduce risk for corticosteroid-related exacerbation.4 However, the onset of improvement is unpredictable and can be significantly delayed, and the risk for corticosteroid-related exacerbation is not eliminated.

CS side effects are numerous and include glucose intolerance, hypertension, obesity, osteoporosis, cushingoid features, acne, skin friability, cataracts, glaucoma, gastric ulceration, juvenile growth suppression, sodium retention, fluid retention, potassium loss, mood swings, and personality change. Purified protein derivative (PPD) skin testing should be considered to screen for tuberculosis prior to beginning treatment with CSs or any long-term IS therapy. During CS treatment, blood pressure, weight, serum electrolytes, and serum glucose are monitored. Patients are encouraged to maintain a high-protein, low-carbohydrate, low-fat, low-sodium diet. Calcium supplementation at 1500 mg/day and vitamin D at 600 IU/day is recommended in order to minimize bone mineral loss. In postmenopausal women, a baseline bone density study is performed and repeated every 6 months. If bone density decreases, treatment with a bisphosphonate is considered in consultation with the patient’s primary care physician.

Corticosteroid-related myasthenic exacerbations may be precipitated by initial treatment with CSs and result in transient, but potentially serious increases in weakness in up to 15% of MG patients. The increased weakness begins within 7-10 days after beginning CSs and may last for up to 1 week before strength improves.3 Once improvement begins, further worsening related to CSs is rare. Patients at highest risk for serious exacerbations have moderate or severe bulbar and/or generalized MG. As such patients may lapse into myasthenic crisis, they should be observed in an inpatient setting for the first 10 days of CS treatment. Therapeutic plasma exchange (TPE) may be performed in patients at risk prior to beginning CSs in order to circumvent an exacerbation and to achieve more rapid clinical improvement.

AZATHIOPRINE

Azathioprine (AZA) is metabolized by the liver to 6-mercaptopurine, an antimetabolite that interferes with nucleotide synthesis and blocks T lymphocyte proliferation. AZA is most commonly used as a steroid-sparing agent in MG, but it is also used as initial therapy in patients who are at risk for CS side effects. In retrospective studies, AZA was effective in 70-90% MG patients.5-7 A prospective, randomized, double-blind study comparing prednisolone monotherapy to prednisolone combined with AZA demonstrated a more durable benefit, along with reduced treatment failures, side effects, and CS maintenance doses in the combined AZA treatment group.8 AZA may be more effective and better tolerated when used in combination with CSs, and many MG patients taking azathioprine require a low...
dose of adjunctive CSs to maintain control of MG. Although it has a favorable side-effect profile when compared to high-dose CS therapy, a 4-8 month delay to improved strength limits the usefulness of AZA as an initial treatment in patients with symptomatic MG. In addition, there is a very small, but increased risk for lymphoma and other cancers with long-term use.9,10

AZA is initially dosed at 50 mg/day, and the dose is increased by 50 mg/day each week to a target dose of 2-3 mg/kg/day. Relative contraindications include history of AZA idiosyncratic reactions, malignancy, anemia, leucopenia, thrombocytopenia, and thiopurine methyltransferase (TPMT) deficiency.

Dose-dependent side effects include myelosuppression with leucopenia and macrocytic anemia, toxic hepatitis, and alopecia. A rare, idiosyncratic hypersensitivity pancreatitis may occur. Serum lipase and amylase assays should be considered for patients with persistent abdominal pain. A more common idiosyncratic reaction involving fever, nausea, vomiting, abdominal pain, and sometimes rash may occur in 10-15% of patients during the first 3 weeks of treatment.11,12 The reaction resolves within 1 day of stopping AZA and recurs with drug rechallenge. AZA is a potential teratogen and women of childbearing potential should use effective contraception.

Surveillance for AZA toxicity should include blood count and liver transaminases weekly for the first month, then monthly for the first year of treatment, then every 3-4 months thereafter if the dosage remains stable. Erythrocyte macrocytosis is expected and acceptable within the therapeutic dosage range. If the white blood cell (WBC) count falls below 3500/mm3, the dosage should be reduced, and if the WBC count falls below 3000/mm3, AZA should be discontinued. Screening for TPMT deficiency is suggested prior to beginning treatment with AZA and should be considered in patients developing leucopenia on AZA. Concurrent use of allopurinol increases 6-mercaptopurine levels by inhibition of xanthine oxidase with increased immunosuppressive and myelosuppressive effects.

MYCOPHENolate MOFETIL

Mycophenolate mofetil (MMF) selectively suppresses T and B lymphocyte proliferation by blocking lymphocyte purine synthesis. Although several retrospective case series of MMF suggested efficacy in MG,13,14,15,16 two recent randomized, controlled trials failed to demonstrate additional benefit of MMF beyond prednisone (20 mg daily as initial IS therapy) in MG.17,18 Since many experts remain convinced of the effectiveness of MMF, the conflict between the negative-controlled trial findings and the positive retrospective data may owe to study design issues including an unexpectedly positive response to prednisone, a relatively short period of study, and a study population with relatively mild MG.19

In light of a favorable side-effect profile, MMF is used as an initial therapy in patients who are at risk for CS side effects. The onset of benefit occurs around 2-5 months, which is somewhat earlier than observed with AZA treatment (approximately 4-8 months). The standard dosage for MMF is 1000-1500 mg twice daily. Higher doses are associated with myelosuppression and blood counts should be checked periodically as surveillance for myelosuppression. Diarrhea, abdominal pain, and nausea are occasionally observed but rarely require discontinuing the medication. Probenecid, acyclovir, and gancyclovir may increase the effective level of mycophenolate due to reduced renal tubular excretion. Concurrent use with AZA, another purine antagonist, may result in untoward IS and myelosuppression. MMF is teratogenic and contraindicated in pregnancy. Women of childbearing potential on MMF must use two effective forms of contraception.

CYCLOSPORINE

Cyclosporine (CyA) disrupts calcineurin signaling with inhibition of interleukin-2 production and T-cell proliferation. A randomized, placebo-controlled, double-blind trial of CyA in steroid-dependent MG demonstrated significant improvement in the CyA treatment group.20 In a long-term retrospective study of patients taking CyA, 96% of patients demonstrated clinical improvement with CyA treatment and 95% were able to taper or discontinue CSs.21

Although effective, CyA use in MG has been limited by nephrotoxicity and numerous drug interactions. CyA is therefore most often used in refractory, generalized myasthenia gravis and as a steroid-sparing agent in patients who fail treatment with AZA and MMF. With serum levels in a therapeutic range, improved strength is generally observed within the first 2 months of treatment and maximum improvement occurs after about 6 months.

CyA is administered at 5 mg/kg/day in 2 daily dosages given 12 hours apart. The desired serum trough level is 100-150 μg/L. Higher serum trough levels are associated with nephrotoxicity. Serum trough CyA levels, creatinine, and blood pressure should be monitored every other week until a stable dosage is achieved, then every 4-8 weeks thereafter. After stable improvement is achieved, many patients can experience sustained benefit at lower CyA maintenance doses of 3 mg/kg/day or less.

The most common side effects include hypertension, nephrotoxicity, tremor, hirsutism, gingival hypertrophy, headaches, nausea, and increased risk of malignancy. Contraindications include uncontrolled hypertension, renal failure, pregnancy, and malignancy.

CyA is associated with numerous drug interactions that may result in nephrotoxicity, accumulation of drugs in circulation, and increases or reductions in serum CyA levels. Concurrent use of nonsteroidal anti-inflammatory drugs in combination with CyA may elicit azotemia. Hyperkalemia may occur when CyA is used with angiotensin converting enzyme inhibitors, and myopathy may occur when CyA is used with statins.

TACROLIMUS

Like CyA, tacrolimus (FK506) inhibits calcineurin with reduced interleukin-2 production resulting in T-cell suppression. Although thought to be less nephrotoxic than CyA, hyperglycemia due to transcriptional inhibition of insulin has been problematic in transplant populations treated with tacrolimus. There are several
reports of effectiveness in MG\textsuperscript{22,23} including a randomized, unblended trial,\textsuperscript{24} At present, tacrolimus may be a consideration for refractory, generalized MG patients for steroid sparing who fail to respond to AZA, MMF, and CyA. The typical dosing range for MG is 3-5 mg/day.

**CYCLOPHOSPHAMIDE**

Cyclophosphamide is an alkylating agent that has been used in a limited fashion for MG, most often in selected cases of severe, refractory, generalized disease. In a small controlled trial, monthly pulsed dose intravenous cyclophosphamide (500mg/m2) improved strength and reduced the CS requirement in patients with refractory, generalized MG.\textsuperscript{25} In a few cases, cyclophosphamide has also been administered at high doses (50 mg/kg) with marrow ablation and rescue with durable improvement in MG.\textsuperscript{26} Cyclophosphamide side effects include myelosuppression, hemorrhagic cystitis, infection, and increased cancer risk. Owing to its toxicity and risk profile, cyclophosphamide should be reserved for the rare patient with severe, highly refractory, generalized MG.

**PLASMA EXCHANGE**

TPE is an effective short-term treatment for myasthenic exacerbations or crises, to prepare symptomatic patients for thymectomy or other surgical procedures, and to prevent steroid-induced exacerbation in patients with moderate to severe oropharyngeal or generalized MG. TPE may also be used chronically in the rare patient with MG refractory to all other treatments. During TPE, plasma containing AChR antibodies is removed and replaced by albumin or by fresh frozen plasma. Most centers perform a series of five to six exchanges of 2-3 liters every other day.

Significantly improved strength in a majority of patients in myasthenic crises with TPE is well documented in several series,\textsuperscript{27,28,29} and is supported by a National Institutes of Health Consensus Statement.\textsuperscript{30} Onset of improvement is variable, but generally occurs after two or three exchanges. Following a TPE series, improvement in strength is temporary and may last several weeks at best, unless an immune modulator is used.

Many complications of TPE are associated with large-bore, central venous catheters, such as venous thrombosis, infection, and pneumothorax, or are associated with the large volume shifts occurring during the procedure, such as hypotension, bradycardia, and congestive heart failure. Wherever feasible, TPE should be performed via peripheral access using antecubital veins to reduce morbidity.\textsuperscript{31}

**INTRAVENOUS IMMUNOGLOBULIN**

Intravenous immunoglobulin (IVIg) is an effective, short-term immunotherapy for myasthenic exacerbations or crises and for surgical preparation. It may also be used as a chronic therapy for selected patients with refractory disease, or as an alternative to TPE for individuals with poor venous access. The mechanism for improved MG likely relates to down-regulation of AChR antibodies and/or induction of anti-idiotypic antibodies.

Several controlled trials have demonstrated the effectiveness of IVIg in MG.\textsuperscript{32} A recent controlled trial comparing TPE (1 plasma volume exchange times five exchanges) with IVIg (1 gm/kg daily on 2 consecutive days) revealed comparable efficacy in response rates and duration of improvement in patients with moderate to severe MG.\textsuperscript{33} IVIg is administered as a 10% solution, and the standard dosage is 2 gm/kg over 2-5 days. Treatment over a greater number of days reduces the risk for volume overload or for solute-induced renal failure. A standard infusion protocol should be followed allowing for frequent monitoring of vital signs by experienced staff.

Patients with renal insufficiency or diabetic nephropathy are at risk for acute tubular necrosis with renal failure due to the large solute load associated with the infusions. In the setting of cardiomyopathy or valvular heart disease, the large volume associated with the infusions may precipitate congestive heart failure.

Idiosyncratic side effects are similar to those observed in blood transfusions such as headache, chills, fever, and malaise that may be controlled by pretreatment with acetaminophen and diphenhydramine. Patients may develop severe vascular headaches with nausea and vomiting and sterile meningitis. Volume overload with congestive heart failure and renal failure may develop in susceptible patients. High-infusion rates may be associated with thrombosis and stroke.\textsuperscript{34}

**THYMECTOMY**

Since Blalock’s early demonstration of remissions following thymectomy in nonthymomatous myasthenia gravis,\textsuperscript{35,36} thymectomy procedures have been widely performed to induce remissions in MG. To date, there have been no prospective, randomized studies to assess the technique or effectiveness of thymectomy in nonthymomatous MG. In an evidence-based literature review of the role of thymectomy in MG management,\textsuperscript{37} although thymectomy in nonthymomatous MG was associated with disease remission or improvement, it was concluded that this association could be due to either thymectomy or differences in the study populations.\textsuperscript{38} It was therefore recommended that in nonthymomatous MG, thymectomy be considered as an option to increase the probability of remission or improvement.\textsuperscript{39} A large, international multi-center trial is currently being conducted to assess the effect of thymectomy in nonthymomatous MG.\textsuperscript{40} The response to thymectomy is not immediate and may be delayed for several years.\textsuperscript{41} Patients with moderate to severe, generalized or bulbar MG should undergo preoperative TPE or IVIg infusions to improve strength.\textsuperscript{42}

Thymectomy is rarely performed after the age of 60 years due to increased surgical risk. It is thought that thymectomy is more effective when performed early in the course of MG,\textsuperscript{43} though this may owe to the nonlinear remission rate in MG\textsuperscript{44} with remissions more likely early in the disease.\textsuperscript{45} Whether patients with nonthymomatous ocular MG should undergo thymectomy remains controversial.\textsuperscript{46,47,48} Clinical series of patients with MuSK-positive myasthenia gravis raise doubt about the benefits of thymectomy in this patient subgroup,\textsuperscript{49,50} and there have been no reports to date of thymoma in MuSK-positive myasthenia gravis.
Though more invasive, the combined transternal-transcervical technique is considered by many to be optimal, as it permits the widest surgical exposure for complete removal of thymic tissue that may be widely distributed in the mediastinum and neck. The future role for video-assisted, robotic procedures for thymectomy remains undefined, though these less invasive procedures promise reduced perioperative morbidity along with the possibility for complete removal of thymic tissue.

**EMERGING THERAPIES**

Although the current chronic IS therapies for MG are effective, they exert broad and relatively nonspecific effects on the immune system. TPE and IVIg also provide effective, though transient, immune modulation with nonantigen specific effects. Several novel biological agents with highly focused and specific effects on the immune system have shown promise in MG.

Rituximab is a chimeric, monoclonal antibody directed against the CD20 B cell surface marker that depletes circulating B lymphocytes. Rituximab has been utilized for treatment of B-cell lymphomas and was recently approved for use in rheumatoid arthritis. Findings emerging in case reports and small series suggest that rituximab is effective in some cases of refractory, generalized, AChR antibody-positive MG. Rituximab may be particularly effective in refractory MuSK MG and may induce durable remissions lasting for many months. The dosing strategies for rituximab treatment of lymphoma and rheumatoid arthritis differ, and the optimal dosing strategy for MG remains undefined. Infusions may be associated with fever, chills, nausea, and hypotension. Though very rare, progressive multifocal leukoencephalopathy represents the most serious potential complication of rituximab therapy.

Eculizumab is a humanized, monoclonal antibody that blocks formation of terminal complement membrane attack complex by inhibiting cleavage of C5. It is currently approved for use in paroxysmal nocturnal hemoglobinuria. In a recent small, controlled phase 2 trial, 86% of patients exhibited significant improvement and over 50% exhibited a marked improvement in refractory generalized MG.

Belimumab, a human monoclonal antibody against B lymphocyte stimulator was recently approved for use in systemic lupus erythematosus, and is currently undergoing clinical trials in refractory generalized MG.

**SUMMARY**

With the overall goal of restoring normal function while minimizing side effects, an individualized approach to MG management is increasingly relevant. Treatment selection is determined by the clinical and immunological features of the MG, along with the risk factors for treatment complications that exist in each patient. Additional controlled studies are needed to help determine the safety and effectiveness of existing and novel MG therapies.

**REFERENCES**

UPDATE ON THERAPIES FOR MYASTHENIA GRAVIS


INTRODUCTION

The major idiopathic inflammatory myopathies (IIMs) consist of dermatomyositis (DM), inclusion body myositis (IBM), and polymyositis (PM). Autoimmune forms of necrotizing myopathy are also considered part of this spectrum. An expanded classification scheme includes cancer-associated myositis (mainly due to DM), overlap syndromes of myositis and connective tissue diseases (CTDs), and focal myositis. “Nonspecific myositis” refers to outliers. Finally, a different, pathology-based classification scheme has been provided by Pestronk for “immune-mediated myopathies.”

The incidence of IIMs is approximately 6-8 per 100,000 with a prevalence of 14.0-17.4 per 100,000. The first diagnostic criteria for myositis—for PM and DM—were presented by Bohan and Peter in 1975. Subsequently, IBM became recognized, and diagnostic criteria were published by Griggs and colleagues. Other important advances in classification have come with the identification of myositis-specific or -associated autoantibodies (MSAs/MAAs).

DERMATOMYOSITIS

Dermatomyositis (DM) (Table 2) has a bimodal distribution of juvenile and adult onset. Women are twice as likely to be affected. Clinical features include a characteristic rash that usually occurs before or with the onset of weakness and includes Gottron’s papules or raised skin lesions on an erythematous base on the knuckles, Gottron’s sign which is an area of erythema especially over extensor surfaces, and a heliotrope or purplish discoloration...
over the eyelids. Dilated tortuous periungual capillaries usually are present. Some children and rare adults develop subcutaneous calcifications. 2, 9

Weakness involves proximal more than distal muscles. Onset usually is subacute to chronic. Dysphagia occasionally occurs. About 30% have an associated CTD (overlap), and at least 50% have autoantibodies (auto-Ab) such as an antinuclear antibody (ANA). Creatine kinase (CK) levels are elevated in about 80% and up to 50-fold. Some patients have the MSA anti-Mi-2. 8

This antibody (Ab) is directed against a nuclear helicase protein involved in transcription. Patients with this Ab have typical DM along with a sun-sensitive, erythematous rash on the chest in a V-shape and over the shoulders and back (known as a shawl sign). Some Asians and rare non-Asians who have the DM rash and often without weakness have aggressive interstitial lung disease (ILD) with an Ab against anti-melanoma differentiation associated gene 5 (MDA5); this Ab acts against the retinoic acid-inducible gene receptor that recognizes viral proteins. 10

Table 1. Diagnostic criteria for myositis (polymyositis and dermatomyositis) by Bohan and Peter

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Sex/Age</th>
<th>Signs</th>
<th>CK</th>
<th>Serology/Assoc</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>M/F</td>
<td>Rash, Proximal weakness</td>
<td>Inc in 80%, &lt;50x</td>
<td>ANA in up to 50%; CTD overlap; Mi-2 Ab; TIF1γ Ab in cancer; synthetase Ab with ILD</td>
<td>Perimysial, Perivascular Inflamm (Macrophages, dendritic cells, CD4+ T-cells); perifascicular atrophy; capillary microangiopathy (MAC+)</td>
</tr>
<tr>
<td>IBM</td>
<td>M&gt;F/ &gt; 50 years old</td>
<td>Prox weakness (esp quads); dist. weak (esp finger flexors); Dysphagia</td>
<td>NL or Mild Inc, &lt;10x</td>
<td>ANA, RF, SS A/B Ab in 20%; HIV, HTLV-1 rarely</td>
<td>Chronic myopathic changes &amp; rimmed vacs, endomyosial inflam, mitochondrial abnormalities; congophilic inclusions, TDP43++; filamentous inclusion by EM</td>
</tr>
<tr>
<td>PM</td>
<td>F&gt;M/Adult</td>
<td>Prox weakness</td>
<td>Inc in most up to 50x</td>
<td>ANA in 16-40%; overlap with CTDs; synthetase Ab and ILD</td>
<td>Myofiber deg/en/regen</td>
</tr>
<tr>
<td>Nec Myo with SRP Abs</td>
<td>F=M/Adult</td>
<td>Prox &gt; Distal weakness</td>
<td>Inc &gt; 10x usually</td>
<td>SRP Abs; Cardiac &amp; Lung in some</td>
<td>Myofiber necrosis/ regen Chronic myopathic changes MHC-1+ fibers, MAC in capillaries in some</td>
</tr>
<tr>
<td>Nec Myo with HMG CoA Abs</td>
<td>F=M/Adult</td>
<td>Prox &gt; Distal weakness</td>
<td>Inc &gt; 10x usually</td>
<td>Statin in majority</td>
<td>Myofiber necrosis/ regen Myophagocytosis; MHC-1+ fibers, MAC in capillaries in some</td>
</tr>
</tbody>
</table>

Abbreviations:


Most other MSAs are directed against cytoplasmic ribonucleoprotein particles involved in translation. Overall, approximately 25-30% of patients with IIM have identifiable MSAs. About 35-40% of DM and PM patients have IIM. 12 Anti-synthetase Abs are a marker of ILD. Other organs that may be affected in DM include the esophagus and rarely the heart. 12 In juvenile DM, vasculitis sometimes affects the gastrointestinal tract. An underlying malignancy occurs in 20-30% of adults, especially in older patients, necessitating cancer screening. In some, an anti-155/140 kd auto-Ab has been identified as antitranscription intermediary factor-1 gamma (TIF1γ). 13 The TIF1γ proteins are involved in oncogenesis, and some patients who have this Ab and DM have various cancers, but some do not.

Electrodiagnostic Testing

In the electrodiagnostic (EDX) approach to patients with possible DM, as well as other myopathies, a motor and sensory nerve conduction study in an arm and a leg should be performed. 14 Sensory responses are normal unless there is an underlying polyneuropathy. Motor responses are normal unless there is distal involvement as may be seen in IBM and rare patients with severe diffuse DM or PM. A needle examination should be performed on the proximal and distal arm and leg as well as paraspinal muscles. When the paraspinal muscles are included, the yield for finding fibrillation potentials and positive waves is 95-99% in patients with IIMs. 15 In addition to positive waves and fibrillation potentials, complex repetitive discharges sometimes are seen in more chronic IIMs. Motor unit potentials (MUPs) tend to be short in duration, polyphasic, and of low amplitude. There is early or increased recruitment. Findings vary with disease severity.
The needle electromyography (EMG) findings can also be utilized to select a biopsy site and to assess disease activity. In very longstanding IIMs, insertional activity can be decreased, and muscles with that finding should be avoided for biopsy. In myositis patients who are treated with corticosteroids and develop new weakness, needle EMG can also help differentiate steroid myopathy from inflammatory myopathy, since fibrillation potentials are not seen with steroid myopathy.

**Imaging**

Imaging will not be addressed in detail, but magnetic resonance imaging of muscle may be used to confirm the presence of edema seen in myositis. T1-weighted images and axial fluid-sensitive sequences such as short tau inversion recovery (STIR) or fat-suppressed T2-weighted sequences are utilized. Fat infiltration and atrophy patterns can be seen also. Imaging findings may be used to select a site for biopsy, but generally imaging is only performed in the lower extremities. Needle EMG sampling can offer a more widespread evaluation of the patient.

**Histopathologic Findings**

A muscle that is substantially affected clinically and electrodiagnostically should be chosen for biopsy, but not one that is “end-stage.” The histopathologic findings predominantly affect the perifascicular region and the perimysium, the connective tissue between muscle fascicles. (Figure 2) A typical perimysial inflammatory infiltrate consists of macrophages, plasmacytoid dendritic cells, CD4+ helper T-cells, and some B-cells and CD8+ cytotoxic T-cells.

Perifascicular atrophy and myofiber degeneration is seen in all juvenile patients and in many adults. There is often a microangiopathy manifested as deposition of membrane attack complex (MAC, or C5b-9) especially in the perifascicular regions. Over time, capillaries are lost. In juvenile DM and in rare adults, the inflammation can simulate lymphoid follicles, consisting of predominately CD4+ T-cells and some B and CD8+ cells.

In all IIMs, there is upregulation of major histocompatibility (MHC) Class I antigens that are not normally expressed in skeletal muscle. In IIMs, they are present at the cell surface and in the cytoplasm, probably in the endoplasmic reticulum. In DM, the upregulation is predominantly in the perifascicular region. The presence of dendritic cells appears to be especially important in DM. These cells are involved in capturing, processing, and presenting antigen to T-cells. Plasmacytoid dendritic cells are a source of interferon α which is upregulated, and the levels correlate with response to treatment. Other small molecules, such as toll-like receptors, that are also involved in induction of type 1 interferons (α and β) may be of importance in DM as well as in PM.

**Treatment**

Most of the treatments used in DM (Table 3) have not been subject to double-blind, placebo controlled trials, but they are based on clinical experience and retrospective series. The first-line treatment is oral corticosteroids with or without a steroid-sparing agent, usually methotrexate or azathioprine. Typically, at least 60 mg of daily prednisone is used initially, but there are no firm guidelines on duration of treatment at that dose, rate of taper, or use of daily or every other day regimens. Typically, patients require 4-8 weeks of higher dose treatment followed by a slow taper and some maintenance dose. More severely affected patients can be initially treated with intravenous (IV) methylprednisolone boluses, usually 1 g/day for up to 3 days.

Patients need to be monitored clinically and via CK levels. They should receive prophylaxis for osteoporosis with vitamin D and calcium. Bisphosphonates should be provided to post-menopausal women. All should be monitored for hyperglycemia, cataracts, and other typical side-effects from corticosteroids. Cancer screening should be performed in adults.

Patients with DM and PM should be screened for ILD with pulmonary function tests (i.e., spirometry, lung volumes, diffusion lung capacity for carbon monoxide [DLCO], and inspiratory and expiratory pressures), and those with abnormal results or the
Second- or first-line add-on therapy includes methotrexate administered at 7.5-25 mg weekly. Such second-line therapies may be initiated at onset in severe cases and earlier in patients with diabetes or significant osteoporosis. Methotrexate usually is avoided in patients with ILD since it does have potential pulmonary toxicity. Patients should be given 1 mg daily folic acid and monitored for side effects. Other options include azathioprine and mycophenolate (Table 3). Mycophenolate also may be used for refractory rash. A double-blind controlled study of intravenous immunoglobulin (IVIg) did show benefit in patients with DM, and IVIg is a first- or second-line option and add-on to other drugs for severe or refractory disease.19 IVIg may be especially useful in patients with very severe autoimmune myopathies and with dysphagia.18

Rituximab, a B-cell depleting monoclonal Ab, has been used in refractory DM with apparent success in open label studies. A blinded, National Institutes of Health-sponsored crossover study of patients with refractory disease did not show benefit regarding the primary endpoints; however, patients in both groups—83% overall—improved.20

Patients with ILD may benefit from tacrolimus or cyclosporine (discussed later). The most refractory patients are sometimes given cyclophosphamide (1-2 mg/kg/day orally in the morning or 0.6-1.0 gm/m2 IV every 4 weeks). The role of tumor necrosis factor-α inhibitors remains uncertain.

### INCLUSION BODY MYOSITIS

IBM (Table 2) is the most common acquired myopathy in patients over the age of 50.21 In contrast to DM and PM, men are more commonly affected. The incidence is approximately 1/100,000 overall, but it is 3.5/100,000 in those over the age of 50. The course is slowly progressive which leads to diagnostic delay. Patients usually have proximal weakness affecting the upper and lower extremities with the quadriceps being predominantly affected. In the upper extremities, the biceps may be more affected than the deltoid muscles. Weakness of wrist extensors and flexors and especially finger flexors can be quite prominent as the disease progresses. The weakness can be asymmetric. Distal leg muscles such as the tibialis anterior are also typically affected. One-third to 60% of patients have dysphagia.21

There is no association with malignancy, ILD, or heart disease. Rare patients have Sjögren’s syndrome, and IBM also has been associated with human immunodeficiency virus (HIV) and human T-cell leukemia virus-1 (HTLV1) infections. About 20% of patients will have ANA or anti-Sjögren’s syndrome A/syndrome B (SSA/SSB) Abs or elevated rheumatoid factor. Until recently, an MSA had not been identified. Salajegheh rand colleagues reported a 43 kDa protein in 13 of 25 (52%) IBM patients.22 Pluk and colleagues reported Abs to a 44 kDa protein in 33% of IBM patients and rare patients with DM and PM.23 Subsequently, it was found that both of these Abs are directed against cytosolic 5’ nucleotidase Ia (cN-1a or NT5c1A), a protein apparently used in cell replication, repair, and nucleic acid degeneration.24 Overall, it appears that this Ab may be up to 70% sensitive for IBM, but further work will be required to be certain.
**Electrodiagnostic Testing**

The CK levels are normal to moderately elevated up to 1000 to 2000 IU/L. EDX findings are similar to those described for DM except that there is often a mixture of short as well as normal to long duration MUPs that are often polyphasic. High as well as low amplitude MUPs also may be present either in the same muscle, or the patient may have some muscles with short duration and others with longer duration MUPs.

**Histopathologic Findings**

The histopathologic findings are distinctive (Table 2), but they are not always seen at the time of the initial biopsy. Site selection is very important. The vastus lateralis often is a good choice earlier in the disease, but it may become “end-stage” later and not provide diagnostic information. In the upper extremity, the biceps brachii has been found to be a good choice in many patients. Distal leg muscles such as the tibialis anterior could also be biopsied. The major findings include those of a chronic inflammatory myopathic process with “rimmed” cytoplasmic vacuoles on frozen sections. (Figure 2) With Gomori trichrome stain, there are often ragged red fibers consistent with a mitochondrial disturbance. Cytochrome oxidase negative fibers also are common. Eosinophilic inclusions, cytoid bodies, appear in about 50%. The inflammatory infiltrate is in the endomysium, and invasion of non-necrotic fibers by invading CD8+ cytotoxic T-cells is common. Other inflammatory cells include plasma cells, macrophages, dendritic cells, and some helper T- and B-cells. It is thought that the rimmed vacuoles are due to degeneration of nuclei. There are inclusion seen in the vacuoles or cytoplasm; some exhibit staining using Congo red especially when viewed under fluorescence filters, consistent with amyloid. Other aggregates occur in the cytoplasm and vacuoles especially those reactive to TAR DNA-binding protein-43 (TDP-43) as well as a number of other proteins.21 Electron microscopy often reveals 15-20 nm diameter tubulofilamentous inclusions in the vacuoles, other regions of cytoplasm, or occasionally in the nuclei. MHC1 is upregulated in myofibers, especially those under invasion by cytotoxic T-cells.

The inflammatory infiltrate (associated with certain human leukocyte antigen haplotypes, Sjögren’s syndrome, and rarely HIV and HTLV1 infection) and the newly recognized Ab suggest an immune component. However, the inclusions suggest a degenerative feature supported by the lack of response to immunotherapy. Some belie that the immune-mediated injury results in increase protein loading on the cell, abnormal cell signaling, and activation of pathways via cytokines that result in stress on the endoplasmic reticulum leading to protein misfolding.23 The true pathogenesis for IBM remains unknown.

**Treatment**

Unfortunately, there is no proven benefit to any immunosuppressive therapies in IBM.24 Some attempt treatments with corticosteroids and methotrexate,4 but such treatments are unproven. IVIg has provided little benefit.27 Experimental trials continue including those using combination therapy. A small trial with alemtuzumab suggested some benefit but a larger study has not been performed.28 Therefore, the mainstay of treating IBM patients includes physical therapy, bracing as needed, and assistive devices.

**Neuromuscular Therapeutics**

PM (Table 2) primarily occurs in adults. It is a rare disease, affecting females more than males. Some patients have an associated CTD overlap.7 There may be an association with malignancy in the minority, but this association is much weaker than is seen with DM. Few with PM have been infected by HIV and HTLV1. Some patients have ILD; cardiac involvement is uncommon.12 CK levels generally are highly elevated. Needle EMG findings are similar to those noted in DM. MSAs occur in some patients with PM, especially those with ILD.11 Histopathologic findings consist of myofiber degeneration and regeneration and an endomysial more than perimysial inflammatory infiltrate consisting of T- more than B-cells. (Figure 2) Invasion of non-necrotic fibers by CD8+ T-cells is seen in some patients. However, it is not always seen, and frequently endomysial T-cells are found but not within myofibers. When myofiber invasion is not seen, one must be wary of PM mimics; and even when it is seen, a diagnosis of IBM should still be considered, and patients need to be re-evaluated and followed closely.

**Anti-Synthetase Syndrome**

Patients with anti-synthetase syndrome have features of DM or PM and Abs directed against an aminoacyl-tRNA synthetase, especially Jo-1.8-11 Other anti-synthetases include anti-PL-7, PL-12, EJ, OJ, and KS. Cutaneous features are common and include cracked fingers called “mechanics hands.” Some also have arthritis or arthropathy, Raynaud’s syndrome, or fever. ILD is often seen. Overall, at least 30% of patients with IIM (PM or DM) have ILD, and anti-Jo-1 Abs are present in 50-75%. Histologically, there tends to be more perimysial pathology with connective tissue fragmentation and inflammation.2 Treatment may need to be more aggressive for management of the ILD given its substantial morbidity.

**Treatment**

Treatment for PM is the same as DM (Table 3); however, there has been some suggestion that a combination of cyclosporine A (3-6 mg/kg/day in split doses) and corticosteroids may be more useful in patients with ILD compared to corticosteroids alone. There is also evidence that tacrolimus (0.1-0.15 mg/kg/day in 3-6 mg/kg/day in split doses) and corticosteroids may be more beneficial in patients with ILD.18 Both of these drugs can cause tremor, hirsutism, gingival hyperplasia, hypertension, and renal, hepatic, and central nervous system toxicity. Mycophenolate may also be useful for treating ILD.

**Autoimmune Necrotizing Myopathy**

Necrotizing myopathy refers to a histopathologic process characterized by myofiber degeneration and regeneration with little or no lymphocytic inflammation. (Figure 2) The inflammatory infiltrate predominantly consists of macrophages. Associated clinical features typically include acute to subacute or even chronic onset of proximal-predominant weakness, and a highly elevated serum CK is usually present.129
There are several examples of necrotizing myopathy of autoimmune origin. One group involves patients with serum Abs directed against signal recognition particle (SRP). SRP is a six protein complex that escorts newly synthesized protein from the cytoplasm to the endoplasmic reticulum. Patients can have a PM-like clinical presentation, but their biopsy findings generally lack lymphocytic inflammation. In addition to having features of a necrotizing myopathy, there may be MAC deposition on capillaries. Chronic pathologic findings include significant fibrosis as may be seen in a dystrophy.

Patients may have acute onset of weakness that can be very severe. They usually do not have another CTD. Younger patients may be affected and develop a more chronic course misdiagnosed as muscular dystrophy. Patients often develop muscle atrophy. CK levels are highly elevated. Cardiac involvement, ILD, and dysphagia occasionally occur. Some patients have a poor response to conventional immunotherapy, while others respond well.

Another autoimmune necrotizing myopathy subtype includes those who develop weakness following exposure to statins, and the weakness does not resolve with drug discontinuation. Such patients were found to have an anti-200/100 kd auto-Ab directed against HMG CoA reductase which is upregulated in regenerating myofibers from these patients. Forty-five of 750 (6%) of patients seen at the John Hopkins Myositis Center were found to have HMG CoA Abs. Overall, about two-thirds had been exposed to statins; and, 92% over the age of 50 who had these Abs were exposed to statins. Of 23 patients at the author’s center diagnosed with statin-induced necrotizing myopathy, 78% were found to have HMG CoA reductase Abs. These Abs also were found in some patients with necrotizing myopathy unrelated to statin use. MHC1 may be upregulated on myofibers, and some muscle specimens exhibit MAC deposition in capillaries. Patients with necrotizing myopathy with HMG-CoA Abs have been treated with various immunosuppressive agents used to treat PM or DM with success. No controlled studies have been performed.

A rarer group consists of patients with or without cancer who have proximal myopathy and histopathologic findings that include myofiber necrosis and “pipestem” capillaries. It does appear that there is a broader category of necrotizing myopathy of paraneoplastic origin, based on a number of other case reports. However, a recent study performed in South Australia on 64 patients with necrotizing myopathy found that there was no increased risk for malignancy in these patients compared to the population at large. It will be of interest to see whether or not other auto-Abs are identified in patients with necrotizing myopathy including those who have an underlying malignancy.

Last, some muscle biopsy specimens from patients with synthetase syndrome exhibit myonecrosis without a substantial lymphocytic inflammatory infiltrate, and those from patients with PM and DM on immunotherapy may have a paucity of lymphocytes.

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37. Emslie-Smith AM, Engel AG. Necrotizing myopathy with pipestem capillaries, microvascular deposition of the complement membrane attack complex (MAC), and minimal cellular inflammation. Neurology 1991;41:936-939.


Immunosuppressive Therapy of Neuromuscular Disease

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Director, Autonomic Laboratory, University Hospitals Case Medical Center
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INTRODUCTION

Immunosuppressive medications in neuromuscular disease are used off-label with the exception of the use of prednisone, which is approved to treat polymyositis and dermatomyositis. The choice of a medication should be based, therefore, on the risk-benefit ratio for the patient. This depends on the following factors:

- Probability of a response for the given diagnosis
- Severity of the disease
- Time course (i.e., how rapid a response is needed)
- Patient factors (e.g., comorbid conditions, age, patient preferences, and history of prior treatments)
- Drug factors (e.g., cost and likelihood of adverse events)

The discussion with the patient as part of informed consent will need to include these factors to be complete.

The recommendations for dosage and monitoring protocols presented below take into account Food and Drug Administration (FDA) recommendations for approved medication indications, available studies, and anecdotal evidence. FDA-approved indications, mechanisms of action, and major adverse events are summarized in Tables 1 and 2.

The comprehensive review of the evidence for the off-label neuromuscular uses of immunosuppressive medication is beyond the scope of this presentation. This discussion is not intended as a blanket endorsement of the use of these medications for off-label indications. Review of the treatment of myasthenia gravis and inflammatory myopathies is covered elsewhere in this course. The focus here is to review pharmacology, adverse events, contraindications, and appropriate drug monitoring for the selected medications.

IMMUNOSUPPRESSIVE MEDICATIONS

Corticosteroids

**Mechanism of Action**

The anti-inflammatory effects of steroids arise from decreased migration of leukocytes and inhibition of cytokine production. Corticosteroids are effective in T-cell mediated and humorally-mediated diseases.

**Uses**

Corticosteroids are used for long-term immunosuppression. Onset of action is over 1-3 months.

A usual treatment strategy is to start prednisone at a high dose and then taper. In myasthenia gravis, however, treatment commonly is started at a lower dose of 10-20 mg and then may be increased to 40-50 mg. Tapering of prednisone usually is initiated after clinical improvement of the symptoms, unless there are intolerable side effects. Typically this may be after 3-6 months of treatment. In some conditions, alternate day dosing may be used to reduce side effects of steroids. The rationale for alternate day dosing presumes that the anti-inflammatory effects of corticosteroids persist longer than their physical presence, and that every other morning dosing allows for more nearly normal hypothalamic–pituitary–adrenal activity.
<table>
<thead>
<tr>
<th>Immunosuppressive drug</th>
<th>FDA-approved indication</th>
<th>Off-label neuromuscular uses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>Multiple indications, however the only approved neuromuscular indications are dermatomyositis and polymyositis</td>
<td>Duchenne muscular dystrophy, myasthenia gravis, LEMS, CIDP, and vasculitis</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Renal transplantation, rheumatoid arthritis</td>
<td>Myasthenia gravis, myositis, and vasculitis</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Renal, hepatic, and cardiac transplantation; rheumatoid arthritis; and psoriasis</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Renal, hepatic, and cardiac transplantation</td>
<td>Myasthenia gravis and CIDP</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Renal, hepatic, and cardiac transplantation</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Leukemia, lymphoma, and carcinoma</td>
<td>Refractory myasthenia gravis and CIDP, and other refractory neuromuscular autoimmune diseases</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Gestational choriocarcinoma, chorioadenoma, destruens and hydatidiform mole; other antineoplastic indications; rheumatoid arthritis; and psoriasis</td>
<td>Myositis and myasthenia gravis</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Non-Hodgkin’s lymphoma, rheumatoid arthritis, Wegener’s granulomatosis, and MPA</td>
<td>Myasthenia gravis, CIDP, multifocal motor neuropathy with conduction block, anti-MAG neuropathy, and other refractory neuromuscular autoimmune diseases</td>
</tr>
</tbody>
</table>

*The level of evidence for a given treatment is not included in this table. This table is not intended to imply equivalent evidence of efficacy for the listed treatments.

CIDP=chronic inflammatory demyelinating polyneuropathy, FDA=Food and Drug Administration, LEMS=Lambert–Eaton myasthenic syndrome, MAG=myelin-associated glycoprotein, MPA=microscopic polyangiitis

For Duchenne muscular dystrophy weekly dosing of prednisone has been shown to be as effective as daily prednisone (Class I evidence). For chronic inflammatory demyelinating polyneuropathy pulsed dexamethasone every 4 weeks has been used for treatment.

**Monitoring and Precautions**

Weight and blood pressure, glucose, and bone density should be monitored with long-term use of corticosteroids. In general, supplement treatment with calcium and vitamin D. Additionally, long-term use requires regular ophthalmic assessments.

Other appropriate precautions are also necessary. Corticosteroids should be taken in the morning to decrease adrenal suppression and with food or milk to reduce gastric irritation. They should not be used in the presence of systemic fungal infections. Latent tuberculosis, amebiasis, and strongyloides all may re activate. Live vaccinations are contraindicated. The dose of rapidly acting corticosteroids must be increased before, during, and after a physiologically stressful situation; “stress steroids” may be needed for up to 12 months following discontinuation of corticosteroids. The clinician must monitor for elevation of blood pressure and congestive heart failure. Salt restriction and potassium supplementation may be needed. Use after myocardial infarction only with great caution. Metabolic clearance is increased in hyperthyroid patients and decreased in hypothyroid patients. Consider use of a proton-pump inhibitor if the patient has gastrointestinal symptoms.

**Contraindications and Pregnancy Risks**

Prednisone is contraindicated in systemic fungal infections and known hypersensitivity to drug components.

Corticosteroids are Pregnancy Category C. There are no well-controlled studies of prednisone in pregnant women. In animal studies, use of corticosteroids is associated with an increased incidence of cleft palate. If used in pregnancy, the infant should be observed for signs of adrenal insufficiency.

Corticosteroids are found in breast milk. For approved indications, the FDA recommends that a decision be made to stop breastfeeding if it is necessary to use corticosteroids in a nursing mother.

**Adverse Reactions**

Adverse reactions for corticosteroids include the following:

- Cardiovascular: Aggravation of hypertension, myocardial rupture following myocardial infarction and congestive heart failure.
- Dermatologic: Acne, angioneurotic edema, angioedema, skin atrophy, bruising, lupus-like skin lesions, thinning scalp hair, and edema.
- Endocrine: Adrenal insufficiency, Cushingoid state, secondary diabetes mellitus, thyroid disturbances, abnormal lipids, and pituitary gland suppression.
**Table 2. Mechanism of action and adverse reactions**

<table>
<thead>
<tr>
<th>Immunosuppressive Drug</th>
<th>Mechanism of Action</th>
<th>Serious Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>Decreased migration of leukocytes and decreased production of pro-inflammatory cytokines</td>
<td>Cushingoid features, Weight gain, Osteoporosis, avascular necrosis, Myopathy, Diabetes, Acne, thinning of the skin, Hypertension, Mood change, Pseudotumor cerebri, Glaucoma, Secondary infections, Pregnancy category C Not compatible with breastfeeding</td>
</tr>
<tr>
<td><strong>Azathioprine</strong></td>
<td>Inhibition of purine nucleotide synthesis (i.e., adenine and guanine)</td>
<td>Leukopenia and bone marrow failure, Pancreatitis, Hepatotoxicity, Malignancy, Pregnancy category D Patients of childbearing potential must be advised not to become pregnant, Not compatible with breastfeeding</td>
</tr>
<tr>
<td><strong>Cyclosporine</strong></td>
<td>Suppression of humoral more than cell-mediated immunity via reversible inhibition of T-helper cells</td>
<td>Hypertension, Nephrotoxicity, Hepatotoxicity, Malignancy, Pregnancy category C Not compatible with breastfeeding</td>
</tr>
<tr>
<td><strong>Mycophenolate mofetil</strong></td>
<td>Inhibition of guanosine nucleotide synthesis</td>
<td>Gastrointestinal symptoms, Lymphopenia, Infections, Pregnancy category D Patients of childbearing potential must use two forms of contraception, Not compatible with breastfeeding</td>
</tr>
<tr>
<td><strong>Tacrolimus</strong></td>
<td>Suppression of T-cell–mediated immunity &gt; humoral immunity</td>
<td>Insulin-dependent diabetes mellitus, Nephrotoxicity, Hypertension, Hyperkalemia, Pregnancy category C Little is known of the risks of the medication in pregnancy, Not compatible with breastfeeding</td>
</tr>
<tr>
<td><strong>Cyclophosphamide</strong></td>
<td>Cross-linkage of DNA (intercalation)</td>
<td>Leukopenia and bone marrow failure, Hemorrhagic cystitis, Bladder malignancy, Myeloproliferative disorders, Malignancy, Infertility, Pregnancy category D Patients of childbearing potential must be advised to avoid becoming pregnant, Not compatible with breastfeeding</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
<td>Inhibits dihydrofolate reductase, a necessary enzyme for purine and thymidylate biosynthesis</td>
<td>Hepatotoxicity, Interstitial fibrosis, Bone marrow suppression, Malignancy, Pregnancy category X Teratogenic, Patients of childbearing potential must use contraception, Not compatible with breastfeeding</td>
</tr>
<tr>
<td><strong>Rituximab</strong></td>
<td>Binds to CD-20 antigen; specifically eliminates B-cells and B-cell precursors by inducing cell lysis</td>
<td>Pregnancy class C Little is known of the risks of the medication in pregnancy and with breastfeeding</td>
</tr>
</tbody>
</table>

- Gastrointestinal: Weight gain and increased appetite, elevation of serum liver enzyme levels, candidiasis, peptic ulcer perforation, and ulcerative esophagitis.
- Hematologic: Anemia and possibly neutropenia.
- Musculoskeletal: Aseptic necrosis of femoral and humeral heads, increased risk of fracture, loss of muscle mass, muscle weakness, and osteoporosis.
- Neurological: Impaired cognition, steroid myopathy, and possibly lower seizure threshold.
- Ophthalmic: Cataract, glaucoma, and secondary bacterial, fungal, and viral infections.
- Immunosuppression: Masking of infection.
- Other: Moon face, abnormal fat deposits, and decreased sperm count.
Drug Interactions
Corticosteroids may induce hepatic enzymes and increase clearance of multiple medications. Amphotericin B and potassium-depleting diuretics enhance potassium loss from prednisone and may lead to arrhythmia. Concurrent use with cyclosporine leads to increased activity of both medications. Aspirin use increases risk of gastrointestinal side effects.  

Azathioprine

Mechanism of Action and Metabolism
Azathioprine is a prodrug of 6-mercaptopurine (6-MP). The active metabolite of azathioprine is an inhibitor of purine synthesis. The effect is to inhibit DNA synthesis. The clinical effect of the drug correlates with thiopurine levels in tissues, and not with drug levels of azathioprine or 6-MP. The metabolic pathway for 6-MP is depicted in the Figure.  

A substantial number of patients are deficient in thiopurine methyltransferase (TPMT) activity (Table 3). If TPMT is deficient, metabolism is driven towards 6-thioguanine nucleotide (6-TGN). 6-TGN is incorporated into DNA, causing toxicity. Clinical testing for TPMT genotyping and serum levels is available. The FDA states that: “It is recommended that consideration be given to either genotype or phenotype patients for TPMT . . . TPMT testing cannot substitute for complete blood count (CBC) monitoring in patients receiving Imuran.”  

A second inactivation pathway for azathioprine is oxidation catalyzed by xanthine oxidase. Xanthine oxidase is blocked by allopurinol, and a patient taking allopurinol requires a dosage reduction in azathioprine to avoid excessive toxicity from 6-TGN metabolites.  

Uses
Azathioprine is used for long-term immunosuppression, usually with the goal of decreasing or discontinuing more toxic medications. A drawback of azathioprine is a slow onset of action over many months.  

<table>
<thead>
<tr>
<th>Table 3. Prevalence of nonfunctioning thiopurine methyltransferase alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasians</td>
</tr>
<tr>
<td>One nonfunctioning TPMT allele: intermediate level of activity</td>
</tr>
<tr>
<td>Two nonfunctioning TPMT alleles: low or absent activity</td>
</tr>
</tbody>
</table>

Monitoring and Precautions
Prior to beginning therapy, patients should have a CBC with differential, liver and renal function tests, and assessment of the TPMT enzyme either by genetic or enzymatic testing. If the patient is of childbearing potential, a pregnancy test also should be performed. For approved indications, the FDA recommends a CBC be performed weekly for the first month of treatment, twice monthly for the second and third months of treatment, and monthly thereafter. Dosage alterations or other therapy changes should prompt more frequent testing. Live vaccinations should not be given during treatment with azathioprine. Azathioprine has multiple drug interactions described below.  

Contraindications and Pregnancy Risks
Azathioprine is contraindicated in patients with prior hypersensitivity to the drug. Patients previously treated with an alkylating agent (e.g., cyclophosphamide and melphalan) have a significantly higher risk of malignancy, and azathioprine should be avoided if possible.  

Azathioprine is Pregnancy Category D, and it has been reported to cause fetal harm. Fetal immunodeficiency, polydactyly, and other birth anomalies have been reported. Azathioprine should not be used in a pregnant woman for a neuromuscular indication. Women of childbearing potential should be advised to avoid becoming pregnant.  

Adverse Reactions
Relative incidences of serious side effects with use of azathioprine appear to be significantly higher in patients with a renal homograft than those with rheumatoid arthritis. The relative incidence of serious side effects is not well-characterized for the routine use of these medications for neuromuscular conditions.
Adverse reactions of azathioprine include the following:

- Hematologic: Leukopenia is dose dependent and may occur late in the course of therapy. Infections occur as a secondary issue.
- Malignancy risk: Higher in a patient previously treated with an alkylating agent (e.g., cyclophosphamide, melphalan, and chlorambucil). It is now understood azathioprine has a direct mutagenic effect. The FDA recommends that: “Patients receiving immunosuppressants, including IMURAN, are at increased risk of developing lymphoma and other malignancies, particularly of the skin. Physicians should inform patients of the risk of malignancy with IMURAN. As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.”
- Gastrointestinal and flu-like symptoms: These occur in approximately 10% of patients treated with azathioprine and may require cessation of treatment.
- Pancreatitis and hepatotoxicity have been reported.

**Selected Drug Interactions**
In the setting of allopurinol treatment the dose of azathioprine should be decreased by half. As a class, angiotensin-converting enzyme inhibitors in combination with azathioprine have been reported to induce anemia and severe leukopenia. Ribavirin is known to cause accumulation of a toxic metabolite of azathioprine and may cause severe myelotoxicity. Azathioprine may inhibit the anticoagulant effects of warfarin. Aminosalicylate derivatives used in the treatment of inflammatory bowel disease inhibit the TPMT enzyme and therefore raise the risk of toxic metabolites. The FDA recommends that azathioprine not be given concomitantly with mycophenolate mofetil.

**Cyclosporine**

**Mechanism of Action**
Cyclosporine inhibits the clonal expansion of activated T-helper cells while allowing activation of T-suppressor lymphocytes. The drug binds to cyclophilin to form a complex that inhibits calcineurin, thereby suppressing interleukin-2.

**Uses**
Cyclosporine A is used for long-term immunosuppression, especially when prednisone cannot be used or is ineffective. Cyclosporine is effective in T-cell mediated disorders. An advantage is its relatively fast onset of clinical effect (about 1-3 months).

**Monitoring and Precautions**
Prior to beginning therapy, a CBC, hepatic and renal function tests, a magnesium test, a uric acid test, and lipid panels should be checked. Evaluation for occult infections should be performed as needed. A skin examination and blood pressure measurement on at least two occasions should be performed. For ongoing monitoring, renal and hepatic function testing should be performed every 2 weeks for the first 3 months of therapy, and thereafter monthly if the patient is stable.

For use with psoriasis, an approved condition for cyclosporine, the FDA recommends that blood pressure should be checked every 2 weeks during the initial 3 months of therapy and then monthly if the patient is stable. If there is no history of previous hypertension, a dose reduction can be made, but if this does not resolve cyclosporine should be discontinued.

Renal function testing guidelines for dosage adjustment were also suggested by the FDA for an elevated creatinine (Cr) level as below:

- If serum Cr ≥25% of baseline, repeat in 2 weeks.
- If serum Cr still ≥25% of baseline, decrease dose by 25-50%.
- If serum Cr at any point ≥50% of baseline, decrease dose by 25-50% and recheck the level in 2 weeks.

Discontinue the medication if the Cr elevation is not reversed.

If any non-steroidal anti-inflammatory drug (NSAID) is started during treatment, it is advisable to check serum Cr frequently.

**Contraindications and Pregnancy Risks**
Cyclosporine is contraindicated if the patient has had a hypersensitivity reaction, abnormal renal function, uncontrolled hypertension or malignancies. Avoid using cyclosporine with tacrolimus or other nephrotoxic drugs (e.g., colchicine, NSAIDs, ranitidine, methotrexate, fenofibrate, and selected antibiotics).

Other drug interactions will be described below. Use cautiously in elderly patients. Advise the patient to not drink grapefruit juice and to check carefully with the prescribing physician before beginning an antibiotic or other new medication in order to avoid drug interactions.

Cyclosporine is Pregnancy Category C. There are reports of premature birth, preeclampsia, low birth rate and fetal loss. The medication should be avoided in pregnancy if possible. Cyclosporine is not compatible with breastfeeding.

**Adverse Reactions**
Adverse reactions for cyclosporine include the following:

- Hypertension: Occurs in 20-33% of patients under treatment.
- Nephrotoxicity: This is a common issue. Serum Cr and blood urea nitrogen levels commonly are elevated with high doses. Cyclosporine-associated nephropathy that does not resolve after the stopping the medication can occur.
- Hepatotoxicity: Usually found in patients with significant comorbidities.
- Neurological: Migraines (common), posterior reversible encephalopathy syndrome (PRES) (infrequent).
Mycophenolate Mofetil

Mechanism of Action and Metabolism
The active metabolite mycophenolic acid (MPA) is a reversible and competitive inhibitor of inosine monophosphate dehydrogenase (IMPDH) decreasing de novo guanosine nucleotide synthesis. Lymphocytes are dependent on de novo synthesis of purines, and the inhibition of this pathway leads to decreased lymphocyte proliferation. Other cell types can use salvage pathways. The drug is believed to induce programmed cell death of activated human T-cells, suppress the expression of vascular adhesion molecules, and reduce lymphocyte trafficking. MPA is metabolized by glucuronyl transferase to make 7-O-mycophenolic acid glucuronide (MPAG). MPAG is not active and is excreted in the urine.

Uses
Mycophenolate mofetil is used for long-term immunotherapy with the goal of replacing corticosteroids or other more toxic drugs. It is effective against both humorally and T-cell mediated diseases. The onset of clinical effect can be relatively fast (i.e., months). Mycophenolate mofetil has been studied in combination with cyclosporine and corticosteroids. It has not been evaluated in combination with other immunosuppressive medications.

Monitoring and Precautions
Prior to beginning therapy, perform a CBC and a pregnancy test if the patient is of childbearing potential. For ongoing monitoring, a CBC with differential performed weekly for the first month, twice monthly for the second and third months of treatment, then monthly throughout the first year of treatment is recommended by the FDA when mycophenolate mofetil is used in transplant patients. Mycophenolate mofetil is cleared through the kidney and renal insufficiency requires a dosage adjustment. Hepatic parenchymal disease does not require a dosage adjustment. Mycophenolate mofetil should be used with caution in the older adult.

Prior to beginning therapy, a pregnancy test within 1 week of the start of therapy must be performed if the patient is of childbearing potential. A CBC with differential and hepatic and renal function testing should be performed. The FDA has mandated that female users of childbearing potential must use effective contraception and specifies that this requires two forms of contraception unless the patient is completely abstinent.

Contraindications and Pregnancy Risks
Mycophenolate mofetil is Pregnancy Category D. Use of the medication during pregnancy is associated with an increased incidence of first trimester miscarriage and fetal anomalies including cleft palate as well as anomalies of the external ear, distal limbs, heart, and esophagus. Due to fetal harm, the FDA has mandated a risk evaluation and mitigation strategy (REMS). The website is: https://www.mycophenolaterems.com.

The FDA recommends that mycophenolate mofetil not be administered concomitantly with azathioprine. Mycophenolate mofetil is contraindicated in patients with a prior hypersensitivity reaction.

Adverse Reactions
Adverse reactions for mycophenolate mofetil include the following:

- Hematologic: Dose-dependent lymphopenia is the most common side effect, and it is seen in 2% of myasthenic patients undergoing treatment. Anemia, severe neutropenia, thrombocytopenia, and pure red cell aplasia may occur.
- Gastrointestinal: Nausea, vomiting, diarrhea, and cramping occur but usually do not require cessation of the medication.
- Immunosuppression: Cases of PML have been reported with mycophenolate mofetil in patients with organ transplants and systemic lupus erythematosus. Other opportunistic infections may occur.
- Malignancy risk: In transplant patients receiving mycophenolate mofetil, 0.4-1.0% of patients developed lymphoproliferative disease or lymphoma if followed for at least 1 year. Three-year safety data were similar. Non-melanoma skin carcinomas occurred in 1.6-4.2% of patients and other types of malignancy occurred in 0.7-2.1% of patients. Cases of primary central nervous system lymphoma in myasthenia gravis have been reported.

Selected Drug Interactions
Cholestyramine, sevalamer, antacid medications, rifampin, and metronidazole have been reported to decrease the concentration of MPA. Mycophenolate mofetil may reduce the effectiveness of oral contraceptive agents.
Tacrolimus

**Mechanism of Action**
Tacrolimus is an inhibitor of T-cell activation. Tacrolimus is believed to bind to FKBP-12 and subsequently form a complex with calcineurin. Calcineurin activity is inhibited, similar to the mechanism of cyclosporine. The clinical effect largely is due to the parent drug. Tacrolimus is extensively metabolized by the P-450 system and the metabolites primarily are eliminated in the stool.

**Uses**
Tacrolimus is used for longterm immunosuppression. It is effective in T-cell mediated diseases, but it also suppresses humoral immunity.

**Monitoring and Precautions**
Prior to beginning treatment check CBC and renal function, including potassium and fasting glucose. Consider a pregnancy test in women of childbearing potential. For ongoing monitoring check a CBC and renal panel at least monthly. In patients with hepatic impairment, the dosage may need to be lowered. Patients should be informed that tacrolimus can cause diabetes mellitus and neoplasia. Grapefruit juice may raise serum concentrations of tacrolimus.

**Contraindications and Pregnancy Risk**
Tacrolimus is contraindicated in patients with a hypersensitivity to tacrolimus or to HCO-60 (polyoxyl 60 hydrogenated castor oil).

**Adverse Reaction**
Adverse reactions to tacrolimus includes the following:

- Renal: Nephrotoxicity is the major limiting factor for the use of tacrolimus in transplant patients. Limited experience to date in myasthenia suggests this is not a frequent issue. Hyperkalemia and hypomagnesemia are also seen.
- Endocrine: Transplant patients treated with tacrolimus have a clearly increased risk of insulin-dependent diabetes mellitus that may be reversible with a change in therapy. Hyperglycemia and glycosuria have been reported in patients taking tacrolimus for treatment of myasthenia gravis. Hypertriglyceridemia also occurs.
- Cardiovascular: Hypertension is a common adverse effect but usually is mild.
- Malignancy risk: A lymphoproliferative disorder associated with Epstein–Barr virus infection has been reported. Lymphoma and skin malignancies may occur.
- Neurological: Tremor and PRES have been reported.
- Gastrointestinal: Diarrhea and abdominal pain.
- Immunosuppression: Cases of PML have been observed in patients taking tacrolimus.

Selected Drug Interactions
Cyclosporine, sirolimus, and other drugs with nephrotoxic potential increase the risk of nephrotoxicity and should not be used with tacrolimus. Potassium-sparing diuretics are contraindicated due to increased risk of hyperkalemia with tacrolimus.

Cyclophosphamide

Cyclophosphamide generally should be considered as a treatment of last resort due to serious side effects.

**Mechanism of Action and Metabolism**
Cyclophosphamide cross-links DNA of rapidly dividing cells. The drug has an elimination half-life of 3-12 hours. The drug is metabolized by the microsomal oxidase system into active alkylating metabolites.

**Uses**
Cyclophosphamide is used for long-term immunosuppression with failure of other immune treatments, or in vasculitis. The advantages are a rapid response (1-3 months) and many otherwise refractory disorders will respond to treatment.

Specific neuromuscular uses for disorders of peripheral nerve include:

- Demyelinating neuropathies with immunoglobulin M (IgM) antibodies, multifocal motor neuropathy, and neuropathy with anti–myelin-associated glycoprotein (MAG) antibodies
- Vasculitis

**Monitoring and Precautions**
Prior to beginning therapy, a CBC with differential and liver and renal function tests should be checked. A pregnancy test should be performed within 1 week prior to starting cyclophosphamide. For ongoing monitoring CBC and urinalysis should be regularly checked. A total lifetime dose of greater than 75 g is highly associated with increased risk of secondary neoplasm.

**Contraindications and Pregnancy Risk**
The use of cyclophosphamide is contraindicated in patients with severely depressed bone marrow function and in patients with a hypersensitivity to cyclophosphamide.

Cyclophosphamide is Pregnancy Category D. Fetal harm has been reported. Ectrodactylia has been reported. Women should be advised to avoid becoming pregnant. Cyclophosphamide is not compatible with breastfeeding.

**Adverse Reactions**
Adverse reactions to cyclophosphamide include the following:

- Hematologic: Serious and fatal infections may occur during treatment.
- Malignancy risk: Malignancies have developed with the use of cyclophosphamide, most commonly of the urinary bladder, or myeloproliferative or lymphoproliferative malignancies. Incidence of skin cancer is also increased.
• Fertility: Cyclophosphamide may cause sterility in both sexes. The dose of cyclophosphamide and duration of therapy are factors. Sterility may be irreversible. Sexual potency and libido are not impaired.

• Hemorrhagic cystitis: Bladder injury is thought to be due to metabolites excreted in the urine. Forced fluid intake after cyclophosphamide results in frequent voiding and reduces the amount of time the medication spends in the bladder.

• Cardiovascular: Acute cardiac toxicity has been reported, but a clear causal link has not been established. Hemorrhagic myocarditis and hemopericardium have been reported.

• Dermatologic: Secondary malignancies have been reported.

**Selected Drug Interactions**

Cyclophosphamide persistently inhibits cholinesterase, leading to a prolonged effect of succinylcholine. Phenobarbital increases the rate of metabolism.

**Methotrexate**

**Mechanism of Action**

Methotrexate inhibits dihydrofolate reductase. This enzyme reduces dihydrofolate to tetrahydrofolate, an essential cofactor for purine and thymidylate biosynthesis. Therefore, methotrexate interferes with DNA biosynthesis and repair. The serum half-life is 3-10 hours at normal doses. Methotrexate is partially protein bound and is excreted unchanged in the urine. Folic acid blocks reabsorption of the methotrexate from the proximal tubule and therefore enhances excretion. In high-dose methotrexate therapy leucovorin (folinic acid) is used to limit toxic effects. Aspirin, other NSAIDs, and probenecid inhibit secretion in the proximal tubule and may increase toxicity.

**Uses**

Methotrexate is used for chronic immunosuppression. A relatively rapid clinical effect over a few months is an advantage of the drug. Methotrexate is effective in T-cell mediated diseases. A usual starting dose is 7.5 mg/week with gradual increases in dose to up to 25 mg once a week, as needed. These doses are used for rheumatoid arthritis and usually are well tolerated. In general, methotrexate is continued for 1-2 years following remission of symptoms.

**Monitoring and Precautions**

Prior to beginning treatment, a CBC with differential, hepatic and renal function tests, and chest X-ray should be performed. A pregnancy test within 1 week prior to beginning treatment should be performed in a woman of childbearing potential. On an ongoing basis, a CBC should be checked at least monthly, liver function and renal function tested monthly and a chest X-ray at least annually. The patient and family must be educated that the medication is to be taken once a week as accidental overdoses due to daily use have occurred. Extra precautions are appropriate in older patients. Live vaccinations should not be used while the patient is under treatment.

**Contraindications and Pregnancy Risk**

Methotrexate is contraindicated in pregnancy. Methotrexate is Pregnancy Category X, and it is a known teratogen. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be counseled on the serious risk to the fetus should she become pregnant during treatment. Pregnancy should be avoided for a full ovulatory cycle after therapy for female patients. Pregnancy should also be avoided if the male partner is receiving methotrexate and for a minimum of three months after cessation of therapy. Methotrexate is found in breast milk. Methotrexate use is not compatible with breastfeeding.

Methotrexate is contraindicated in the following conditions: alcoholism, chronic liver disease, immunodeficiency syndromes, blood dyscrasias, and hypersensitivity reactions.

**Adverse Reactions**

Serious side effects are rare at doses used for neuromuscular disease.

Adverse reactions to methotrexate include the following:

- Constitutional: Fatigue, malaise, and chills.
- Gastrointestinal: Nausea, stomatitis, diarrhea, and hepatotoxicity (e.g., fibrosis, elevated aspartate aminotransferase [AST]) may occur. Hepatotoxicity is more common in patients with a MTHFR mutation, prolonged use, and administration of folic acid.
- Pulmonary: Interstitial fibrosis may occur and requires a yearly chest X-ray to monitor.
- Hematologic: Bone marrow suppression may occur.
- Neurologic: Headache and lethargy.
- Malignancy risk: Carcinogenic potential has not been fully evaluated. Cases of malignant lymphoma arising during treatment with low-dose methotrexate have been reported.
- Fertility: Pregnancy is contraindicated during use for both the male and female partner, as described above; however, methotrexate is not thought to cause sterility.
- Opportunistic infections.

**Selected Drug Interactions**

Many drug interactions occur with methotrexate. Especially avoid aspirin and NSAIDs as these medications block secretion into the renal tubule.

Drugs that displace methotrexate from plasma proteins and result in elevated methotrexate levels include phenytoin, salicylates, sulfonamides, tetracyclines, chloramphenicol, and sulfonyleureas.

Use cautiously in patients with renal impairment and avoid medications that cause renal impairment.
Rituximab

Mechanism of Action

Rituximab is a monoclonal antibody that binds to the CD20 antigen in mature B-cells and precursor B-cells, causing cell lysis. Peripheral B-lymphocyte counts are reduced by 90% within 3 days of a dose. Plasma cells are not targeted.

Uses

Rituximab may be used for acute management or chronic immunosuppression and has a relatively rapid clinical effect.

Specific neuromuscular uses include disorders of the neuromuscular junction (i.e., myasthenia gravis) and disorders of the peripheral nerve (e.g., chronic inflammatory demyelinating polyneuropathy [CIDP], multifocal motor neuropathy, neuropathy with anti-MAG antibodies, and cryoglobulinemic vasculitis). Specific neuromuscular uses include disorders of the neuromuscular junction (i.e., myasthenia gravis) and disorders of the peripheral nerve (e.g., chronic inflammatory demyelinating polyneuropathy [CIDP], multifocal motor neuropathy, neuropathy with anti-MAG antibodies, and cryoglobulinemic vasculitis).

Dosing may be achieved using different protocols. One protocol is 375 mg/m² intravenous infusion each week for 2 weeks, followed by additional dosing once every 2 months. Rituximab may be dosed at 2- or 4-week intervals. Acetaminophen, antihistamine, and corticosteroids are administered with rituximab due to the frequency of allergic reactions.

Monitoring and Precautions

Prior to beginning treatment, obtain a CBC with differential. During active treatment, a CBC with a platelet count should be performed monthly or every 2 months.

Contraindications and Pregnancy Risks

Hypersensitivity is a contraindication.

Rituximab is an FDA Pregnancy Category C medication. There are no adequate studies of rituximab in pregnant women. B-cell lymphocytopenia lasting less than 6 months is known to occur in infants exposed to rituximab in utero. It is not known whether rituximab is secreted into human milk, however human IgG is excreted into human breast milk.

Adverse Reactions

- Allergic: Infusion reactions have resulted in death; mucocutaneous reactions such as Stevens–Johnson also have been reported from 1-13 weeks following exposure.

- Immunosuppressive: Mature B-lymphocytes are absent, and they remain suppressed for up to 6 months. The risk of infection is higher in patients with chronic lung or cardiac disease and patients who have taken multiple immunosuppressive medications. Hepatitis B reactivation with fulminant hepatic failure has been reported. PML has been reported in patients treated with rituximab for non-malignant conditions. Prolonged neutropenia and late-onset neutropenia have been reported.

- Cardiovascular: Cardiac arrhythmia and angina can occur and be life threatening.

- GI: Bowel perforation has been reported.

- Malignancy risk: Currently unknown.

Selected Drug Interactions

Formal drug interaction studies have not been performed with rituximab. As rituximab is an antibody, plasma exchange should not be performed in close proximity after dosing with rituximab.

REFERENCES

1. Roxane Laboratories I. PrednISONE tablets USP, 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg. Retrieved from http://www.accessdata.fda.gov/Drugs/default.htm; 2012.


IMMUNOSUPPRESSIVE THERAPY OF NEUROMUSCULAR DISEASE

INTRODUCTION

Immunoglobulins (Igs) are proteins produced by mature B lymphocytes. They are the main effector molecules of the humoral immune system and are produced as responses to antigens. Immunoglobulin G (IgG) is the main immunoglobulin in serum. It has an Fc portion, a constant region, which is responsible for binding to macrophages and neutrophils to promote intracellular killing, activating complement or lymphokines, stimulating B-cell proliferation and binding to lymphocytes to induce cell-mediated cytotoxicity. The Fab portion, or variable region, provides antibody specificity. This is also called the idiotypic determinant.

Passive immunotherapy was first used with human serum in the early 1900s to prevent measles. Igs were not successfully extracted from human plasma until the 1940s when the use of ethyl alcohol fractionation to obtain an enriched gammaglobulin fraction was described. This preparation, however, could only be used intramuscularly as it contained aggregates of IgG and, if given intravenously, resulted in anaphylactic reactions. The intramuscular route, however, limited the dose that could be administered along with causing the patient substantial discomfort because of its presence in a highly concentrated solution. Further methods, such as ultrafiltration, ion exchange, and alkylization were developed in the 1970s to purify the IgG fraction, making it suitable for intravenous administration. In 1981, the first intravenous immunoglobulin (IVIg) product was licensed in the United States.

IgG is a sterile, highly purified IgG preparation made from pooled human plasma. Several preparations of IVIg have become available in the United States. All IVIg preparations contain small amounts of immunoglobulin A (IgA). This is important as patients with anti-IgA antibodies (IgA deficient patients) may get an anaphylactic reaction with IVIg infusion.

IVIg was initially used for primary immunodeficiency states such as agammaglobulinemia and chronic lymphocytic leukemia (CLL) but has been increasingly used in a number of immunological disorders. These include idiopathic thrombocytopenic purpura (ITP), Kawasaki disease, Crohn’s disease, myasthenia gravis (MG), chronic inflammatory demyelinating polyneuropathy (CIDP), Guillain-Barré syndrome (GBS), multifocal motor neuropathy, multiple sclerosis, lupus erythematosus, polymyositis, dermatomyositis and rheumatoid arthritis. Currently, the Food and Drug Administration (FDA) has given a labeled indication for the use of IVIg in several conditions including: primary immunodeficiency disease, CLL, ITP, CIDP, and multifocal motor neuropathy.

<table>
<thead>
<tr>
<th>FDA-approved indications for intravenous immunoglobulin</th>
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<tbody>
<tr>
<td>• Primary immunodeficiency disease</td>
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<td>• Chronic lymphocytic leukemia</td>
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<td>• Pediatric HIV infection</td>
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<td>• Kawasaki disease</td>
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<td>• Allogeneic bone marrow transplantation</td>
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<td>• Kidney transplantation involving a recipient with a high</td>
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<td>antibody titer or an ABO-incompatible donor</td>
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<tr>
<td>• Chronic inflammatory demyelinating polyneuropathy</td>
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<td>• Multifocal motor neuropathy</td>
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IMMUNOGLOBULIN THERAPY IN NEUROMUSCULAR DISORDERS

Additional Medicare-approved indications for intravenous immunoglobulin

Neurological disorders
- Guillain–Barré syndrome
- Relapsing-remitting multiple sclerosis
- Myasthenia gravis
- Refractory polymyositis
- Polyradiculoneuropathy
- Lambert–Eaton myasthenic syndrome
- Opsoclonus–myoclonus
- Birdshot retinopathy
- Refractory dermatomyositis

Hematologic disorders
- Autoimmune hemolytic anemia
- Severe anemia associated with parvovirus B19
- Autoimmune neutropenia
- Neonatal alloimmune thrombocytopenia
- HIV-associated thrombocytopenia
- Graft-versus-host disease
- Cytomegalovirus infection or interstitial pneumonia in patients undergoing bone marrow transplantation

Dermatologic disorders
- Pemphigus vulgaris
- Pemphigus foliaceus
- Bullous pemphigoid
- Mucous-membrane (cicatricial) pemphigoid
- Epidermolysis bullosa acquisita
- Toxic epidermal necrolysis or Stevens–Johnson syndrome
- Necrotizing fasciitis

MECHANISM OF ACTION OF IVIg IN AUTOIMMUNE DISORDERS

IVIg has multiple potential actions and mechanisms in treating autoimmune disorders but it is likely that more than one action is operant in the various neuromuscular diseases for which IVIg has shown efficacy. These include:
- Interference with Fc receptors bindings on macrophages or B lymphocytes, rendering them incapable of interacting with cytotoxic CD8+ cells
- Competition or neutralization of autoantibodies
- Inhibition of cytokines or complement deposition
- Interference with antigen recognition by sensitized T cells
- Blocking the Fc receptors on target antigen
- Restoration of idiotypic/anti-idiotypic networks
- Blockade of leukocyte-adhesion-molecule binding
- Targeting of specific immune cell surface receptors
- Modulation of maturation and function of dendritic cells

Administration

The usual dose of IVIg employed in these disorders is 400 mg/kg/day for 5 days (this is the same dose used in treating ITP), (i.e., a total of 2 gm/kg for initial course). Some physicians have used it in shorter courses, for example, 1 gm/kg for 2 days. Each IVIg preparation has a different recommended infusion rate, usually starting at a low infusion rate and titrating upwards every 15 minutes to the maximum infusion rate unless side effects develop. Most preparations require infusion over 2-6 hours.

Adverse Reactions

Adverse reactions to IVIg are reported in 3-12% of patients. These reactions are usually mild and may include headache, fever, chills, nausea, abdominal pain, malaise, dizziness, and joint pain. They are usually rate related and can be alleviated when the infusion rate is decreased.

Severe reactions include anaphylaxis, which is infrequent and occur almost exclusively in patients with IgA deficiency. There have been a few reports in the 1990s of hepatitis transmission after IVIg infusion. These occurred with European preparations, in which a different fractionation method may have been used. There have been no further reports of hepatitis transmission following IVIg infusion. Although antibodies to human immunodeficiency virus (HIV) have been found in IVIg preparations prior to the availability of a test to detect HIV antibodies, transmission of HIV infection has not been documented.

There have been a number of case reports of aseptic meningitis occurring after IVIg. Onset of symptoms occurred 10 hours to 7 days after IVIg infusion. Symptoms improved quickly and resolved in a few days. The mechanism is unknown, but it has been suggested that this may represent an allergic response to IVIg similar to allergic aseptic meningitis seen with drugs like ibuprofen.

Myocardial and cerebral infarctions after IVIg use occur almost exclusively in patients with cardiovascular and cerebrovascular disease. These cases were thought to be related to earlier products with high blood viscosity. Acute renal failure after IVIg has rarely been reported, mostly in patients with mild renal disease who are infused rapidly. The majority recover completely. High solute load from stabilizers used in IVIg is the likely cause of the tubular damage. Other rare reports of adverse reactions include hemolytic anemia, eczema, seizures, and erythema multiforme.

INDICATIONS IN NEUROMUSCULAR DISORDERS

Guillain-Barré Syndrome

Guillain-Barré syndrome is the prototypical disorder of acquired demyelinating polyneuropathy. Several large, randomized, controlled trials showed the benefit of plasmapheresis in GBS. However, plasmapheresis is only available in selected medical centers and requires good vascular access.
IVIg was introduced as an alternative to plasma exchange because of its efficacy in other immune-mediated disorders, its relative safety, and ease of administration. A randomized trial comparing IVIg (400 mg/kg/day for 5 days) to plasma exchange in 150 patients with GBS established that: (1) IVIg is an effective therapy for GBS, (2) the efficacy is comparable to plasma exchange, and (3) there was a low frequency of adverse effects. A larger, international, randomized, multicenter, controlled trial of 379 patients with GBS (the Sandoglobulin trial) subsequently compared IVIg (400 mg/kg/day for 5 days), plasma exchange (50 ml/kg exchanges over 8-13 days), and combined therapy. It established that IVIg and plasma exchange had equivalent efficacy and that plasma exchange followed by IVIg provided no additional benefit. There was no difference in functional disability scores at 4 and 48 weeks between IVIg, plasma exchange, or combined therapy, nor was there any difference in secondary outcome measures (time required to wean from mechanical ventilation, number of days to recover ambulation, and the proportion of patients unable to walk after 48 weeks). These findings were subsequently confirmed by several studies and meta-analysis, despite the lack of placebo studies in IVIg.

Large prospective studies showed that oral and intravenous high-dose corticosteroids made no difference in outcome. In combination with intravenous immunoglobulin, intravenous methylprednisolone may have a short-term effect and hasten recovery but does not significantly affect the long-term outcome.

A recent report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) concurred also that there is strong evidence (Level A) to support the use of IVIg in GBS, which should be initiated during the first 2 weeks of disease onset. Also, the analysis determined that the combination of plasmapheresis and IVIg is probably not better than either treatment alone.

The optimal IVIg dose needed for patients with GBS remains somewhat controversial. The dose of IVIg was set arbitrarily at 400 mg/kg/day for 5 days (total dose 2g/kg) and this was used in most studies on IVIg in patients with GBS. A longer duration or higher dose of IVIg treatment in patients with severe disease may be beneficial. Indeed, in select patients on mechanical ventilation, a 6-day course of IVIg (total dose 2.4g/kg) is more beneficial than a 3-day treatment (total dose 1.2g/kg) with a more rapid rate of recovery. In addition, patients with slight or no increase in serum IgG at 2 weeks after the standard dose of IVIg (total dose 2g/kg) have more severe clinical deficit at nadir, and fewer were able to walk at 6 months. An international study is currently assessing whether additional IVIg in patients who do not show a meaningful rise in IVIg level is beneficial.

Approximately 10% of GBS patients treated with IVIg relapse after initial treatment. This rate is equal with the use of plasma exchange or IVIg. The cause of these relapses is unknown but may be related to persistence of active disease after completing therapy or a rebound in antibody production. Patients with a more protracted course may be at higher risk for a relapse but no other predictive factors have been identified. Occasionally, a relapse may be triggered by an intercurrent infection or an ongoing cytomegalovirus or Epstein-Barr virus infection. A repeated course of IVIg administered to patients who do not respond or relapse following the initial treatment may be of some benefit, but this regimen is currently being evaluated by a controlled study. A GBS relapse raises the concern of a more chronic disorder, namely CIDP. However, GBS patients deteriorate more rapidly (2-4 weeks) while CIDP worsens much more slowly (4-9 weeks). Also, GBS exhibit less than two treatment-related fluctuations while CIDP should be suspected if a patient with presumed GBS exhibits more than two treatment-related fluctuations.

The difficult issue of how to treat patients with severe GBS who have not improved with standard therapies remains not well clarified. The Sandoglobulin trial showed that a course of plasma exchange followed by IVIg is not better than plasma exchange or IVIg alone. A repeated dose of IVIg has only been shown to be effective in a small study. An international study is being conducted assessing the use of additional IVIg in unresponsive severe GBS patients or those who relapse.

** Chronic Inflammatory Demyelinating Polyneuropathy **

A number of retrospective, uncontrolled, or nonrandomized studies have shown the efficacy of IVIg in some patients with CIDP when administered at a dosage of 2 mg/kg divided over 3-5 consecutive days. Improvement usually begins in 3-8 days, but may occur as early as 2 days, while some patients only improve after 6 weeks and a second course of IVIg. Corticosteroids, plasma exchange, and IVIg are effective in CIDP, with approximately 50-70% of the patients responding to each of these treatments. In addition, almost 50% of patients not responding to one of these treatments respond to the second therapy. In general, about 80% of patients improve with these therapies.

The efficacy of these therapies was confirmed in recent Cochrane Reviews, updated Guidelines of the European Federation of Neurologic Societies/Polish Neurological Society, a consensus statement of the American Association of Neuromuscular and Electrodagnostic Medicine, and evidence-based guideline of the AAN. CIDP is the first neurological disorder approved for IVIg by the FDA.

Corticosteroids and IVIg have a comparable short-term efficacy in CIDP. Also, both IVIg and corticosteroids have prolonged efficacy in CIDP. However, IVIg is more frequently effective and tolerated than steroids, although corticosteroids were less frequently associated with deterioration than IVIg after therapy discontinuation during the first 6 months of treatment. It remains unclear whether these advantages are sufficient to balance the much higher cost of IVIg compared to steroids.

IVIg is effective as long-term treatment of CIDP. The long-term efficacy of IVIg was confirmed by the ICE Study Group. This study confirmed that pulse IVIg every 3 weeks is effective for 24, and possibly 48, weeks. During the first 24 months, treatment with IVIg resulted in a significantly greater improvement in disability and impairment, and prevented further axonal degeneration compared to placebo. Continuing treatment for the following 24 weeks was associated with a significantly lower proportion of relapses. IVIg also had a significant beneficial effect on quality of
life related to health. It is not clear whether the 48 week duration of the study translates into the very long-term treatment of CIDP, whose course is measured in several years. Patients with relapsing courses continue to respond to intermittent infusions of IVIg for 4 years or longer. Although controlled studies have not been done, IVIg is also efficacious in childhood CIDP. These results argue for the use of IVIg as a first-line therapy. An alternate-day prednisone regimen combined with IVIg therapy in difficult cases has considerable success and minimal toxicity.

The necessary dose and interval to prevent or treat relapses varies greatly. In the majority of patients, the expected relapse occurs 3-22 weeks after prior IVIg therapy. The ICE study was effective using 1gm/kg every 3 weeks. Maintenance IVIg doses vary significantly, ranging from 0.25 gm/kg every 10 days to 2 gm/kg once every 6-14 weeks.

Subcutaneous immunoglobulin (SCIg) reduces the inconvenience of intravenous infusions, which require suspending daily activities, the need for permanent venous access, and possible repeated hospital admissions for chronic CIDP. Two patients with CIDP were reported to maintain the improvement achieved with IVIg assuming the same dose subcutaneously at home during the week. These observations were recently confirmed in a randomized, placebo controlled study on 15 patients indicating that SCIg is safe and effective in CIDP and may improve the quality of life of the patients who do not need to suspend their daily activities to receive periodic infusions.

IgM Monoclonal Gammopathy

Almost 80% of patients with neuropathy and IgM paraprotein have IgM monoclonal gammopathy of undetermined significance (MGUS), while the remaining patients have Waldenstrom macroglobulinemia. IgM MGUS neuropathy is almost invariably associated with a homogeneous clinical pattern. It is characterized by a distal and symmetric, predominantly large fiber sensory involvement, gait ataxia, and postural tremor in the upper limbs. Motor impairment is usually less prominent and often appears later. This is sometimes referred to as demyelinating acquired demyelinating symmetric neuropathy (DADS) and considered as a variant of CIDP. DADS is also sometimes misdiagnosed as Charcot-Marie-Tooth disease, which indeed shows uniform slowing of conduction velocities. Anti-myelin-associated glycoprotein (MAG) antibodies are found in almost half of the patients with IgM neuropathy. CIDP, MGUS neuropathy, and anti-MAG neuropathy are overlapping entities.

Almost 50% of reported patients improve, at least temporarily, after one of more immune therapies including steroids, plasma exchange, a number of cytotoxic agents, and, more recently, IVIg, fludarabine, cladribine, interferon-α, and the anti-B lymphocyte (CD20) humanized monoclonal antibody rituximab. More recently, a number of open pilot trials have suggested the efficacy of the humanized monoclonal antibody (rituximab) directed against the CD20 antigen in patients with anti-MAG IgM neuropathy. The efficacy of rituximab in anti-MAG neuropathy was recently assessed in two randomized, controlled trials, one on 26 patients and the other on 54 patients. These studies showed a 20-30% absolute improvement in the number of patients improving on the disability scale in patients treated with rituximab compared to placebo.

Multifocal Motor Neuropathy

IVIg is the gold standard for the treatment of this neuropathy and is now an approved treatment by the FDA. Almost 80% of patients with multifocal motor neuropathy (MMN) respond to IVIg. IVIg induces a rapid improvement which often occurs within 1 week of treatment. The improvement is usually more evident in recently affected regions while there is often little effect on old and stabilized deficits. In the majority of patients, the beneficial effect of IVIg lasts for a few weeks and has to be maintained with periodic IVIg infusions, often indefinitely. IVIg therapy in MMN is usually started at the standard dose of 2g/kg on 2-5 consecutive days, followed by maintenance infusions ranging from 0.4g/kg once a week to 1-2g/kg every 2-5 weeks. Over time, some patients become progressively less responsive to IVIg and require increasing dosage (in case of insufficient response) or frequency (in case of reduced duration of the response) of IVIg to maintain improvement.

FDA approval of IVIg for MMN was based on the results of a randomized, double blind, placebo controlled crossover study conducted to evaluate the efficacy, safety, and tolerability of one IVIg product (GAMMAGARD LIQUID) in 44 adult subjects with MMN. The pivotal clinical study results were presented in an abstract in April 2012 (http://www.baxter.com/press_room/press_releases/2012/06_25_12_gammagard_mmn.html). During IVIg treatment, the difference in relative change in mean grip strength in the more affected hand was 22.94% compared to placebo. A greater proportion of patients who received placebo experienced deterioration in their disability, as measured by Guy’s Neurological Disability Scale which measures the patient’s ability to perform daily tasks such as zipperung, buttoning, tying shoe laces, washing, and feeding, compared to those receiving IVIg (35.7% versus 11.9%, respectively).

Maintenance therapy may be also performed at home with SCIg, whose efficacy as a maintenance treatment has been confirmed in two small, randomized, controlled trials.

A minority of patients with MMN do not respond or become resistant to IVIg. Steroids are, however, ineffective in MMN, even when given at high dose intravenously, and almost 20% of treated patients were reported to worsen under this therapy.

Myasthenia Gravis

Myasthenia gravis is a disorder of neuromuscular transmission and is characterized by fluctuating weakness and fatigability. Antibodies to acetylcholine receptors are present in the serum of 80-90% of patients. Plasma exchange has been used to produce short term improvement in patients with myasthenic crisis.

IVIg is used in similar clinical situations as plasma exchange including myasthenic crisis and severe exacerbations. Treatment regimens range from 400 mg/kg/day dose for 5 days to 2 gm/kg/day dose for 2 days. Treatment response may be rapid.
(days) but often 3 weeks is the expected time for a significant therapeutic benefit. IVIg therapy may serve as an alternative to plasma exchange in individuals with poor vascular access or contraindications to plasma exchange. IVIg may overall be a less expensive treatment for hospitalized patients.

IVIg is used as chronic therapy in patients resistant to standard immunosuppressive therapy to reduce the need for corticosteroids, however, such a practice has never undergone formal evaluation.

IVIg has also been shown to be efficacious in MG in a number of uncontrolled trials. In the largest review of IVIg in MG, eight independent studies of 60 patients reported an overall improvement in 73%. Most were receiving azathioprine and/or prednisone. Different immunoglobulin preparations were used along with different dosing regimens. Improvement occurred as soon as 3.6 days and within 3 weeks.

IVIg seems useful as an adjunct to steroid therapy, but not as the sole therapeutic modality. Patients who were receiving steroids along with IVIg had a longer duration of response than those not receiving steroids (64 days versus 34 days). IVIg did allow the reduction in steroid dose in half of patients. IVIg may be advantageous over steroid use because of its quicker onset of action and relative lack of long-term toxicity. However, it only has a temporary effect and the response rate of 73% is lower than that reported with steroids, azathioprine, or thymectomy (90%). Further studies will be required to evaluate whether IVIg is as efficacious as plasmapheresis.

IVIg may be useful as a temporizing measure while waiting for the gradual improvement seen later with steroids and immunosuppressant drugs. It may also be useful in reducing steroid dosage.

**Inflammatory Myopathies**

Polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM) are characterized by muscle weakness and inflammation in muscle biopsy. In refractory cases of PM, IVIg was demonstrated to have a beneficial effect in uncontrolled studies. For DM, a placebo controlled study showed dramatic improvement in muscle strength and skin rash. Repeated muscle biopsies showed improvement in the muscle fiber diameters with resolution of the immunopathology. A double blind, placebo controlled trial gave monthly treatments of IVIg to patients with refractory dermatomyositis and found improvement in 11 of the 12 patients treated with IVIg. The improvement seen occurred after the first infusion but lasted only 6 weeks after the last infusion.

A double blind, placebo controlled crossover study of IVIg in IBM failed to show a statistically significant improvement in overall muscle strength. There was, however, a trend toward improvement in swallowing and lower limb strength, suggesting that a role may yet be found for IVIg in IBM, perhaps as a stabilizing modality.

**REFERENCES**


Neuromuscular Therapeutics

CME Questions:

1. Which myasthenia gravis treatment is teratogenic?
   A. Pyridostigmine bromide.
   B. Therapeutic plasma exchange.
   C. Intravenous immunoglobulin.
   D. Mycophenolate mofetil.
   E. Neostigmine bromide.

2. A patient develops a syndrome of malaise, fever, and abdominal pain 2 weeks after beginning an oral medication for treatment of myasthenia gravis. Which medication is most likely to be responsible for the syndrome?
   A. Mycophenolate mofetil.
   B. Cyclosporine.
   C. Azathioprine.
   D. Prednisone.
   E. Pyridostigmine bromide.

3. In a patient with myasthenia gravis and renal insufficiency, standard dosing of which treatment would be most likely to compromise renal function?
   A. Cyclosporine.
   B. Azathioprine.
   C. Mycophenolate mofetil.
   D. Prednisone.
   E. Pyridostigmine bromide.

4. Which treatment is expected to exhibit the most delayed therapeutic response in myasthenia gravis?
   A. Cyclosporine.
   B. Azathioprine.
   C. Mycophenolate mofetil.
   D. Prednisone.
   E. Pyridostigmine bromide.

5. Weakness of finger flexors is most commonly seen in which of the following disorders?
   A. Inclusion body myositis.
   B. Dermatomyositis.
   C. Polymyositis.
   D. Necrotizing myopathy with signal recognition particle (SRP) antibodies.
   E. Necrotizing myopathy from statins.

6. Which of the following autoantibodies are most often associated with interstitial lung disease?
   A. SRP.
   B. HMG CoA.
   C. Jo-1.
   D. Transcription intermediary factor-1γ.
   E. Mi-2.

7. Which of the following muscles has the highest yield for revealing fibrillation potentials in a patient with inflammatory myopathy?
   A. Deltoid.
   B. Thoracic paraspinal.
   C. Vastus lateralis.
   D. Tibialis anterior.
   E. First dorsal interosseous of the hand.

8. In a muscle biopsy specimen from a patient with myopathy, the presence of perifascicular atrophy is most commonly associated with which of the following disorders?
   A. Dermatomyositis.
   B. Inclusion body myositis.
   C. Polymyositis.
   D. Necrotizing myopathy with HMG CoA antibodies.
   E. Paraneoplastic myopathy.
9. A double-blind, controlled study of intravenous immunoglobulin showed significant benefit in patients with which of the following disorders?
   A. Inclusion body myositis.
   B. Dermatomyositis.
   C. Polymyositis.
   D. Necrotizing myopathy with HMG CoA antibodies.
   E. Necrotizing myopathy with SRP antibodies.

10. You have decided to prescribe azathioprine to a patient with myasthenia gravis. On reviewing the medication list you see he is already prescribed allopurinol for gout. The patient confirms gout is an active clinical problem. What dosage adjustment should be made to the azathioprine?
   A. Azathioprine and allopurinol cannot be prescribed together. A different medication must be chosen.
   B. Azathioprine and allopurinol have no significant interactions.
   C. Azathioprine dosage should be decreased by half.
   D. Azathioprine dosage should be doubled.

11. The FDA recommends that consideration be given to either genotype or phenotype patients for thiopurine S-methyltransferase (TPMT) prior to beginning therapy with which of the following medications?
   A. Azathioprine.
   B. Cyclophosphamide.
   C. Methotrexate.
   D. Tacrolimus.

12. A 30-year-old woman with refractory chronic inflammatory demyelinating polyneuropathy presents for evaluation. You are advising her on treatment options for her condition. Of the following medications, which one may cause premature ovarian failure and sterility?
   A. Azathioprine.
   B. Cyclophosphamide.
   C. Methotrexate.
   D. Tacrolimus.

13. A 55-year old man with a past history of hypertension and diabetes mellitus is under treatment for myasthenia gravis. You are planning to start a new medication. Which of the following medications would be the most likely to further elevate his blood glucose?
   A. Azathioprine.
   B. Cyclophosphamide.
   C. Methotrexate.
   D. Tacrolimus.

14. Which of the following medications interferes with folate metabolism?
   A. Azathioprine.
   B. Cyclophosphamide.
   C. Methotrexate.
   D. Tacrolimus.

15. A patient with severe Guillain-Barré syndrome did not show any signs of improvement after receiving a total of 2g/kg of intravenous immunoglobulin (infused as 0.4g/kg/day x 5 days). The best next therapeutic action is:
   A. Infuse with an additional dose of intravenous immunoglobulin.
   B. Infuse with intravenous corticosteroids.
   C. Initiate plasma exchange.
   D. Start immunosuppressive therapy.
   E. Initiate plasma exchange followed by another dose of intravenous immunoglobulin.

16. In the Ice study, the following maintenance dose of intravenous immunoglobulin was proven safe and effective in chronic inflammatory demyelinating polyneuropathy (CIDP):
   A. 1g/kg/day x2 days every 3 weeks.
   B. 1g/kg/day x1 day every 3 weeks.
   C. 2g/kg/day x2 days every 4 weeks.
   D. 1g/kg/day x1 day every 2 months.
   E. 0.4g/kg/day x5 days every 2 months.

17. Intravenous immunoglobulin is FDA-approved for one of the following disorders:
   A. Lewis-Sumner syndrome.
   B. IgM Neuropathy.
   C. Multifocal motor neuropathy.
   D. Demyelinating acquired demyelinating symmetric (DADS) neuropathy.
   E. Guillain-Barré syndrome.

18. Randomized controlled studies have shown that the most effective therapy for myasthenia gravis is:
   A. Intravenous immunoglobulin.
   B. Plasma exchange.
   C. Corticosteroids.
   D. Mycophenolate mofetil.
   E. None of the above.

19. A double-blind, placebo controlled trial showed that intravenous immunoglobulin is effective in one of the following inflammatory myopathies:
   A. Polymyositis.
   B. Inclusion body myositis.
   C. Sarcoïd myopathy.
   D. Anti-synthetase syndrome.
   E. Dermatomyositis.