Autoimmune Myasthenia Gravis: Recommendations for Treatment and Immunologic Modulation

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Opinion statement

Treatment for myasthenia gravis should be individualized to each patient based on the clinical characteristics of myasthenia including the distribution, duration, and severity of weakness and resulting functional impairment; the risks for treatment complications related to age, gender, and medical comorbidities; and the presence of thymoma. Acetylcholinesterase inhibitors provide temporary, symptomatic treatment for all forms of myasthenia gravis. Immune modulators address the underlying autoimmune process in myasthenia gravis, but are associated with potential complications and side effects. Most patients with generalized myasthenia who have significant weakness beyond the ocular muscles and who remain symptomatic, despite treatment with cholinesterase inhibitors, are candidates for immune modulation. Although corticosteroids are effective for long-term immune modulation in myasthenia gravis, several more contemporary immunomodulators including azathioprine, cyclosporine, and mycophenolate mofetil have shown efficacy in myasthenia gravis and are used increasingly as first-line treatments and as steroid-sparing agents. Plasma exchange is used to achieve rapid improvement in patients with myasthenic crisis or exacerbation, to improve strength before a surgical procedure or thymectomy, and to minimize steroid-induced exacerbation in patients with oropharyngeal or respiratory muscle weakness. Intravenous immunoglobulin represents an alternative to plasma exchange in patients requiring relatively rapid short-term improvement in the setting of poor venous access. Because of a lack of controlled trials, the role of thymectomy in nonthymomatous myasthenia gravis is unclear, although evidence suggests that thymectomy increases the probability for myasthenic remission or improvement.

Introduction

Autoimmune myasthenia gravis is a disease involving antibody-mediated, T-cell–dependent immunologic attack on the postsynaptic membrane of the neuromuscular junction. Abnormal neuromuscular transmission and clinical weakness in myasthenia gravis result from the effects of antibodies that bind to various components of the endplate region of skeletal muscle. In most cases, antibodies bind to the main immunogenic region of the α-subunit of the acetylcholine receptor.

Patients with myasthenia gravis experience fluctuating and fatigable weakness of specific muscle groups rather than generalized fatigue or pain. Most patients develop initial symptoms of ocular muscle weakness with asymmetric ptosis and binocular diplopia. Nearly 90% of patients with initial ocular symptoms progress to develop weakness of bulbar and limb muscles within the first 3 years [1]. Initial symptoms of oropharyngeal weakness or limb weakness are less common. Maxi-

mum disease severity is reached within the first year of disease in 75% of patients [1]. Myasthenic crisis involving ventilatory failure attributable to myasthenic weakness occurs in approximately 20% of patients, usually within the first year of illness [2]. Myasthenia may worsen in the setting of systemic illness, particularly viral upper respiratory infections. It also may worsen in thyroid disease, pregnancy, increased body temperature, and during treatment with drugs that impair neuromuscular transmission [3•].

In myasthenia gravis and other autoimmune disorders, loss of tolerance to self-antigens occurs. The thymus is critical for establishing T-cell tolerance to self-antigens, and thymic abnormalities have long been recognized in myasthenia gravis. Approximately 65% of patients with myasthenia gravis have thymic hyperplasia, and thymoma occurs in approximately 10% of patients [4]. Thymoma is associated with more fulminant disease, higher acetylcholine receptor antibody titers, and more severe electrophysiologic abnormalities. Most thymic tumors are benign, well-differentiated, and encapsulated. All patients with myasthenia gravis should have chest imaging with computed tomography to exclude the presence of thymoma. Although resection of a thymoma is necessary to prevent compromise of mediastinal structures, the benefit of thymectomy for remission in nonthymomatous myasthenia gravis is uncertain.

Myasthenia gravis is termed ocular myasthenia when weakness is exclusive to the eyelids and extraocular muscles, and generalized myasthenia when weakness extends beyond these ocular muscles. Seropositive (SP) myasthenia gravis defines disease with circulating antibodies to the acetylcholine receptor, whereas patients who are seronegative (SN) lack these antibodies. Fifty-nine percent of patients with ocular myasthenia gravis and 78% of patients with generalized myasthenia gravis are seropositive [5]. Recently, antibodies to muscle-specific tyrosine kinase (MuSK) have been shown in more than 40% of patients with generalized, SN myasthenia gravis [6,7••,8–10]. MuSK initiates aggregation of acetylcholine receptors at the muscle endplate during development [7••], but the role of MuSK in mature skeletal muscle and the pathophysiology of myasthenia gravis related to MuSK antibodies currently is unknown.

Several clinical tests are available to support a clinical diagnosis of myasthenia gravis. Edrophonium (Tensilon) testing uses a short-acting acetylcholinesterase inhibitor to elicit objective improvement in a muscle strength parameter. Because of the subjectivity involved in evaluating bulbar or limb muscle strength, edrophonium testing is most useful in the context of severe ptosis or restricted extraocular motility. Electrophysiologic testing with repetitive nerve stimulation studies and single-fiber electromyography (SFEMG) may directly demonstrate abnormal neuromuscular transmission. Although repetitive nerve stimulation is widely available, their diagnostic sensitivity is low in ocular or in mild generalized myasthenia gravis. SFEMG is the most sensitive diagnostic test in myasthenia gravis, though other neuromuscular disorders may cause abnormal findings in SFEMG. SFEMG is technically demanding and available only at specialized centers. In the appropriate clinical context, positive serologic testing with acetylcholine receptor or MuSK antibodies confirms a clinical diagnosis of myasthenia gravis.

Though the early use of acetylcholinesterase inhibitors for myasthenia gravis represented a significant therapeutic breakthrough [11], these agents neither retard the autoimmune attack on the neuromuscular junction nor do they alter the natural history of myasthenia gravis. Before the widespread use of immunomodulators, prognosis for patients with myasthenia gravis was grim with approximately 30% mortality [12]. In addition to improved mechanical ventilators and intensive care, immunotherapy is one of the major factors contributing to improved outcome in myasthenia gravis, and disease-specific mortality currently is less than 5% [1]. Long-term immunotherapies for myasthenia gravis include thymectomy, corticosteroids (namely prednisone and prednisolone), azathioprine, cyclosporine, and mycophenolate mofetil. Short-term immunotherapies include plasma exchange and intravenous immunoglobulin (IVIg) infusions.

Treatment

Diet and lifestyle

- Some patients may experience variably compromised chewing or swallowing relating to myasthenic weakness of oropharyngeal muscles. This may present as difficulty chewing candy or tough meats, nasal regurgitation of liquids, or difficulty swallowing. Aspiration of food, liquid, or saliva may occur in severe cases. There are several measures to manage this issue:
  - To prevent aspiration, patients who cannot swallow medication or saliva or who choke frequently should not have oral administration of drugs and nourishment. The underlying myasthenic weakness should then be treated.

  - Solid food consistency may be modified by chopping, mashing, or pureeing.
  - Thickeners may be added to liquids if thin liquids elicit choking.
  - Eating and drinking should be done in an upright position.
  - Pyridostigmine bromide may be taken approximately 1 hour before meals to optimize oropharyngeal muscle strength.
- Some patients may experience muscarinic side effects of acetylcholinesterase inhibitors including diarrhea, abdominal cramping, and increased salivation. Along with reductions in medication dosage, patients experiencing these symptoms may find it useful to avoid fatty foods, insoluble fiber, and caffeine. Increased oral secretions may additionally compromise patients with difficulty swallowing.
- Patients taking corticosteroids also should take supplementary calcium (1500 mg/day) and vitamin D (600 IU/day) to prevent osteopenia. A low-fat, restricted-calorie, reduced-sodium diet also should be followed during corticosteroid treatment, particularly when higher doses are used.
- Patients with more severe degrees of myasthenia may experience significant fatigue with exertion and with high body temperatures. Energy conservation measures and avoidance of high-temperature environments are reasonable for these patients until their myasthenic control is improved.

Pharmacologic treatment

- Pharmacologic treatment must be individualized to each patient with myasthenia gravis. The overall goal is to return the patient to normal function while minimizing the adverse side effects of treatment. Few treatments have been subjected to rigorous, prospective, placebo-controlled study in myasthenia gravis. Issues to be considered in choosing pharmacologic treatments include the distribution, duration, and severity of myasthenic weakness and resulting functional impairment, the risk for treatment complications relating to age, gender, and medical comorbidities, and the ability of the patient to obtain the medication and to comply with drug dosing schedules and toxicity monitoring.

Acetylcholinesterase inhibitors

Acetylcholine inhibitors impair the hydrolysis of acetylcholine at the neuromuscular junction and improve the probability for successful neuromuscular transmission. They represent symptomatic treatment and provide temporary strength improvement in myasthenia gravis, but they do not alter the natural history of the autoimmune attack on the neuromuscular junction. Clinical responses to cholinesterase inhibitors often are incomplete and variable between patients, within the same patient with time, and in different muscle groups within the same patient. Although acetylcholinesterase inhibitors represent one of the oldest and most widely used treatments for myasthenia gravis, no controlled trials using long-acting acetylcholinesterase inhibitors have been done in myasthenia gravis. In patients with ocular or mild generalized myasthenia gravis, acetylcholinesterase inhibitors alone may provide satisfactory functional benefit without the potential side effects of long-term immune modulators. These agents also may serve as a useful adjunct in patients receiving immunotherapy with residual myasthenic symptoms.

Pyridostigmine bromide (Mestinon, Valeant Pharmaceuticals, Int, Costa Mesa, CA) is better tolerated and more widely used than neostigmine bromide (Prostigmin, ICN Pharmaceuticals, Costa Mesa, CA) because of fewer gastrointestinal side effects. Although a long-acting form of pyridostigmine (Mestinon Timespan 180 mg, Valeant Pharmaceuticals) is available, it is absorbed irregularly and tends to be overdosed. Some practitioners believe that it may be useful in rare patients

when given at bedtime to reduce weakness on awakening. However, most patients do not experience incapacitating weakness on awakening and can take the regular pyridostigmine formulation in the morning.

Standard dosage Acetylcholinesterase inhibitors must be adjusted for each patient so that myasthenic weakness is minimized without excessive muscarinic side effects. The initial dose of oral pyridostigmine bromide usually is 30 mg three times per day. The dosing schedule should be individualized to treat the most symptomatic weakness, and may be advanced to 90 mg three to four times per day. Although rare patients tolerate higher doses, overdosing may cause increased weakness. If a patient becomes weaker despite increasing pyridostigmine dosages, no additional increase in the dosage should be made, and an immunomodulating agent should be considered. Improved muscle strength usually is apparent 20 to 30 minutes after dosing with a peak effect at approximately 45 minutes. The improved strength may last up to 4 hours. Dose frequency usually is every 4 to 8 hours or three to four times per day.

Contraindications Contraindications include reactive airway disease, mechanical intestinal or urinary obstruction, and hypersensitivity to cholinesterase inhibitors.

Main side effects Side effects are dose-dependent and self-limited. Muscarinic complications include nausea, vomiting, abdominal cramping, diarrhea, increased bronchial secretions, and salivation. These symptoms may be managed with glycopyrrolate, diphenoxylate hydrochloride with atropine, and loperamide hydrochloride.

Special points Excessive dosing of cholinesterase inhibitors can potentially increase weakness attributable to depolarization blockade at diseased neuromuscular junctions. The muscarinic effects of cholinesterase inhibitors also may increase oropharyngeal and bronchopulmonary secretions, which also may obstruct the airway and be aspirated. In addition to weakness indistinguishable from underlying myasthenia, signs of cholinergic crisis include muscle fasciculations, miosis, excessive lacrimation, salivation, bronchial secretions, abdominal cramping, nausea, vomiting, diarrhea, diaphoresis, and bradycardia.

Cost/cost effectiveness The annual cost for treatment with pyridostigmine bromide 60 mg three times a day is approximately $650.

Corticosteroids

Corticosteroids have wide effects on the immune system and may ameliorate autoimmune disease by reducing the production of cytokines. Prednisone rapidly elicits a high degree of improvement or remission in most patients with myasthenia gravis. In retrospective studies, prednisone treatment was associated with significant improvement in strength within 2 to 3 weeks [13,14, Class III]. In one large series, prednisone caused marked improvement or remission in 80% of patients. The mean time to reach at least marked improvement was 3.1 months, and the median time to maximum benefit was between 5 and 6 months [13, Class III].

Prednisone is an appropriate initial treatment for patients with ocular or generalized myasthenia gravis who fail to achieve a satisfactory functional response to acetylcholinesterase inhibitors. The drawbacks to using corticosteroids include numerous side effects (listed below), many of which are dose related, and steroid-related myasthenic exacerbations. Patients at particular risk for such side effects include those with baseline hypertension, glucose intolerance, diabetes, obesity, patients with osteoporosis or post-menopausal women, and patients with affective or thought disorders. An alternative immunotherapy may be considered in such patients.

Standard dosage Patients typically begin a high-dose daily prednisone regimen at 1.5 to 2 mg/kg/day or 60 to 80 mg/day. The patient is reassessed in 2 to 4 weeks, and if sustained improvement is documented, the dosing is changed to an alternate-day schedule at 100 to 120 mg every other day to reduce side effects. The dosage should be slowly tapered subsequently at approximately 4 to 8 week intervals by 10 mg ever other day to 30 mg every other day, then by 5 mg every other day to 20 mg every other day. Subsequent tapering should be done judiciously by 2.5 mg every other day. All dosage reductions should be preceded by a clinical assessment. Some patients do not tolerate alternate day dosing because of variations in myasthenia, mood swings, or difficult glycemic control in the setting of diabetes. If at any point, the patient experiences recurrent symptoms, the taper should be halted. Myasthenic

relapses may be delayed for 2 to 3 weeks after reducing the prednisone dosage. Although rare patients are successfully tapered off of prednisone, most patients will require indefinite treatment with 10 to 20 mg every other day unless another immune modulator is used.

Contraindications Untreated tuberculosis.

Main side effects Corticosteroid side effects are numerous and include hypertension, obesity, osteoporosis, Cushingoid facies/habitus, acne, skin friability, cataracts, glaucoma, gastric ulceration, juvenile growth suppression, sodium retention, fluid retention, potassium loss, mood swings, and personality change. Before beginning corticosteroids, PPD testing may be performed as a screen for tuberculosis. Serum electrolytes, serum glucose, blood pressure and weight are monitored. Patients are encouraged to maintain a high protein, low carbohydrate, low fat, low sodium diet. To minimize bone mineral loss, patients take calcium supplementation at 1500 mg/day and vitamin D 600 IU/day. In post-menopausal women, a baseline bone density study is done and is repeated every 6 months. If bone density decreases, treatment with a bisphosphonate is considered in consultation with the patient's primary care physician. We do not prophylactically use histamine-2 blockers or proton pump inhibitors unless symptoms of gastric irritation develop.

Special points Transient exacerbations of myasthenia gravis may follow initial treatment with corticosteroids and result in temporary, but potentially serious, increases in myasthenic weakness in up to 15% of patients [13, Class III]. The increased weakness begins within 7 to 10 days after beginning corticosteroids and may last for up to 1 week before strength improves [13,15, Class III]. At highest risk for this phenomenon are patients with more severe bulbar and generalized myasthenia gravis. Such patients with marginal respiratory or bulbar muscle function may lapse into myasthenic crisis and should be observed in an inpatient setting for the first 2 weeks of corticosteroid treatment. Alternatively, such patients may be treated initially with plasma exchange to circumvent or minimize the severity of such an exacerbation and to achieve a more rapid response. After patients begin to improve, subsequent worsening related to steroids is rare. Corticosteroids also can be started at a lower dosage to reduce risk for exacerbation and slowly increased [16, Class III]. However, this strategy does not eliminate the risk for corticosteroid-related exacerbation, and the onset of improvement is unpredictable and can be significantly delayed.

Cost/cost effectiveness Prednisone is inexpensive. The annual cost for maintenance therapy with prednisone 20 mg every other day is approximately $25.

Azathioprine

Azathioprine is hepatically metabolized to 6-mercaptopurine, an anti-metabolite which interferes with nucleotide synthesis and blocks T lymphocyte proliferation. In myasthenia gravis, azathioprine is most commonly used as a steroid-sparing agent, but it has occasionally been used as an initial therapy and as a combination therapy in patients with incomplete responses to steroids. Although it is effective and has a favorable side effect profile when compared to high dose corticosteroids, the 4 to 8 month delay to improved strength limits the usefulness of azathioprine as an initial treatment in patients with symptomatic myasthenia.

A prospective, randomized, double-blind study comparing prednisolone treatment to prednisolone combined with azathioprine demonstrated longer remissions, fewer treatment failures, fewer side effects, and reduced maintenance doses of prednisolone in patients in the combined azathioprine treatment group [17•, Class I].

Standard dosage The initial dose is 50 mg per day, increased by 50 mg/day each week to a target dose of 2 to 3 mg/kg per day.

Contraindications Relative contraindications include history of azathioprine idiosyncratic reaction (see below), malignancy, anemia, leucopenia, thrombocytopenia, and hypersensitivity to azathioprine.

Main side effects Dose-dependent side effects include myelosuppression with leucopenia and macrocytic anemia, toxic hepatitis with liver transaminase elevations, and alopecia. Hypersensitivity pancreatitis represents a rare idiosyncratic reaction, and serum lipase and amylase assays should be considered for patients with persistent abdominal pain. Azathioprine is potentially teratogenic, and women of childbearing potential should use effective

contraception. A serious idiosyncratic allergic reaction comprised of rash, fever, nausea, vomiting, and abdominal pain occurs in 10% to 15% of patients within the first 3 weeks of treatment [18,19]. The reaction resolves within 1 day of stopping azathioprine, and will recur on rechallenge with azathioprine.

Blood monitoring for patients taking azathioprine should include blood count and liver transaminases weekly for the first month, then monthly for the first year of treatment, then every 3 months thereafter if the dosage remains stable. Erythrocyte macrocytosis is expected and acceptable within the therapeutic dosage range. If the leukocyte count falls below 3500/mm^3, the dosage should be reduced, and if the leukocyte count falls below 3000/mm^3, azathioprine should be discontinued. There is a small, but increased risk for lymphoma with long-term use [20].

Main drug interactions Concurrent use of allopurinol increases the level of 6-mercaptopurine by inhibition of xanthine oxidase. This increases the immunosuppressive and myelosuppressive effects of azathioprine. Because azathioprine and mycophenolate mofetil are purine antagonists, the combination use of these agents may result in untoward immunosuppression and myelosuppression.

Cost/cost effectiveness Azathioprine is relatively expensive. The annual cost for treatment with azathioprine at a dose of 150 mg/day is $2200.

Cyclosporine

Cyclosporine originally was developed to prevent rejection of transplanted organs. It blocks interleukin-2 production and T cell proliferation with inhibition of T helper cell function and facilitation of T suppressor cell function. A randomized, placebo-controlled, double-blinded trial of cyclosporine in steroid-dependent myasthenia gravis showed significantly improved strength in the cyclosporine treatment group [21, Class I]. In a long-term retrospective study of patients taking cyclosporine, 96% of patients showed clinical improvement, and steroids could be tapered or discontinued in 95% of patients [22•, Class III]. Because of its expense, nephrotoxicity, and numerous drug interactions, cyclosporine is used primarily in refractory generalized myasthenia gravis as a steroid-sparing agent. With serum levels in a therapeutic range, improved strength may be expected within 2 months of beginning treatment.

Standard dosage The standard cyclosporine dosage is 5 mg/kg per day divided into two daily dosages given 12 hours apart. The desired serum trough level is 100 to 150 μg/L. Higher serum trough levels are associated with nephrotoxicity. Serum trough cyclosporine levels, creatinine, and blood pressure should be monitored every 2 weeks until a stable dosage is achieved, then at least monthly thereafter.

Contraindications Relative contraindications include uncontrolled hypertension, renal failure, malignancy, and hypersensitivity to cyclosporine.

Main side effects The most common side effects include hypertension, nephrotoxicity, tremor, hirsutism, gingival hypertrophy, headaches, nausea, and increased risk of malignancy.

Main drug interactions Cyclosporine is associated with numerous drug interactions, which may result in nephrotoxicity, accumulation of drugs in circulation, and either an increase or reduction in cyclosporine levels. Nonsteroidal anti-inflammatory drugs may compromise renal function when used in combination with cyclosporine. Additionally, hyperkalemia may occur when cyclosporine is used with angiotensin converting enzyme inhibitors, and myopathy may occur when it is used with HMG CoA reductase inhibitors. The Myasthenia Gravis Foundation of America web site contains a complete listing of the currently known interactions [23•]. When a new medication is begun, patients should have repeat trough cyclosporine level, creatinine, and blood pressure testing.

Cost/cost effectiveness Cyclosporine is expensive. The annual cost for maintenance treatment with cyclosporine 150 mg twice a day is approximately $7000.

Mycophenolate mofetil

Mycophenolate mofetil, one of the newest immune modulators used in myasthenia gravis, selectively inhibits T and B lymphocyte proliferation by blocking purine synthesis only in lymphocytes. It has been used successfully in human kidney

transplant trials and has shown minimal toxicity [24]. A retrospective case series of patients with myasthenia gravis [25, Class III], an open-label pilot study in patients with steroid-dependent or refractory myasthenia gravis [26, Class III], and a double-blind, placebo-controlled pilot trial in myasthenia gravis [27, Class I] showed significant improvement in patients treated with mycophenolate mofetil. In these trials, the improvements occurred within 2 months of starting mycophenolate mofetil treatment. Blood count should be checked monthly in light of the potential for myelosuppression. A multi-center, randomized, controlled trial of low-dose prednisone versus low-dose prednisone with mycophenolate mofetil currently is in progress. Although the exact role of mycophenolate mofetil remains to be defined, given its favorable side effect profile, it may replace cyclosporine as an agent for refractory generalized myasthenia gravis.

Standard dosage The standard dosage for mycophenolate mofetil is 1000 to 1500 mg twice a day. Higher doses used in renal transplant patients have been associated with myelosuppression.

Contraindications Relative contraindications include malignancy, anemia, leucopenia, thrombocytopenia, and hypersensitivity to mycophenolate.

Main side effects Leukopenia and anemia may occur with higher dosages. Diarrhea, abdominal pain, and nausea seem to be the most common side effects observed in 27% of patients, though the severity of these side effects only resulted in discontinuing mycophenolate mofetil in 6% of patients [28•, Class III].

Main drug interactions Probenecid, acyclovir, and gancyclovir may increase the effective level of mycophenolate attributable to reduced renal tubular excretion. Concurrent use with azathioprine, another purine antagonist, may result in untoward immunosuppression and myelosuppression.

Cost/cost effectiveness Mycophenolate mofetil is expensive. The annual cost for treatment with mycophenolate mofetil 1250 mg per day is approximately $11,000.

Interventional procedures

Plasma exchange

Plasma exchange (PEX) is an effective short-term treatment for myasthenic exacerbations or crises, to prepare symptomatic myasthenic patients for thymectomy or other surgery, and to prevent steroid-induced exacerbation in patients with oropharyngeal or respiratory muscle weakness. PEX also is used in the rare patient with myasthenia gravis who is refractory to all other treatments. During the procedure, a patient's plasma containing AChR antibodies is removed and replaced by albumin or by fresh frozen plasma.

Although a controlled clinical trial has never been done, significantly improved strength in most myasthenic crises with PEX is well documented in several series [29–31, Class III], and is supported by a National Institutes of Health Consensus Statement [32]. PEX trials in myasthenia gravis have been summarized in a Cochrane Review [33•]. Onset of improvement is variable, but generally occurs within 2 to 3 days. After a PEX series, improvement in strength is temporary and may last several weeks at best, unless an immune modulator is used.

Standard dosage Many centers perform a series of five to six exchanges of 2 to 3 L every other day.

Contraindications Sepsis, hypotension.

Main side effects Many complications of PEX 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.

Main drug interactions Angiotensin converting enzyme inhibitor use has rarely been associated with anaphylactoid reactions during plasma exchange with on-line membrane filters [34]. Drugs that are highly protein-bound may be removed from circulation during PEX.

Cost/cost effectiveness A course of six plasma exchanges costs $40,000. This figure does not include costs for central venous catheters, inpatient bed, or nursing care.

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) represents an alternative short-term immunomodulating treatment for myasthenic exacerbations or crises or for surgical preparation in patients who are poor candidates for plasma exchange due to vascular access problems or septicemia. The mechanism for improvement may relate to down-regulation of AChR antibodies and/or induction of anti-idiotypic antibodies.

A randomized, controlled trial of intravenous immunoglobulin (IVIg) at 1.2 and 2 g/kg given over 2 to 5 days in myasthenic exacerbations and crises showed comparable efficacy between PEX and IVIg, though a relatively small sample size was evaluated [35, Class I]. In a retrospective multicenter study of myasthenic crisis, PEX was more favorable compared with IVIg on ability to extubate at 2 weeks and on 1-month functional outcome [36, Class III]. However, in both studies patients treated with PEX experienced a higher rate of cardiovascular and infectious complications. Although the magnitude of treatment responses to IVIg and PEX may be fairly comparable in some patients, treatment failures to IVIg subsequently responding to PEX have been reported [37, Class III]. IVIg trials in myasthenia gravis have been summarized in a Cochrane Review [38•]. Recent experience with preoperative IVIg for thymectomy in myasthenia gravis suggests that the time course of maximal response may be considerably delayed in some patients for up to 19 days [39, Class III].

Standard dosage Intravenous immunoglobulin currently is given as a 5% or 10% solution. The dosage is 2 g/kg given over 2 to 5 days. Giving IVIg 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 during the infusions.

Contraindications Patients with IgA deficiency may experience anaphylaxis because of the trace amounts of IVIg in the preparation. Where feasible, serum immunoglobulin quantitation should be done to screen for IgA deficiency. Patients with renal insufficiency or diabetic nephropathy are at risk for acute tubular necrosis with renal failure because of the large solute load associated with the infusions [40]. In the setting of cardiomyopathy or valvular heart disease, the large volume associated with the infusions may precipitate congestive heart failure.

Main side effects 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 [41].

Cost/cost effectiveness The cost for IVIg is approximately $100 per gram. A course of IVIg at the standard dosage of 2 g/kg in an individual of average weight administered during 2 days costs approximately $14,000 in addition to infusion costs and associated outpatient nursing fees, which are variable, but may increase the medication cost by four- to five-fold.

Surgery

Thymectomy

Subsequent to early observations of remissions after thymectomy in nonthymomatous myasthenia gravis [42,43, Class III] thymectomy has been widely performed to achieve medication-free remissions in myasthenia gravis. To date, there have been no prospective, randomized studies to assess the technique or effectiveness of thymectomy in nonthymomatous myasthenia gravis. The Quality Standards Subcommittee of the American Academy of Neurology recently did an evidence-based review to address the role of thymectomy in the management of myasthenia gravis [44••, Class II]. The outcomes of thymectomy in controlled, nonrandomized studies were systematically reviewed. Although patients having thymectomy in nonthymomatous myasthenia gravis were more likely to achieve medication-free remission, become asymptomatic, or to exhibit clinical improvement, the association between thymectomy and improved outcomes could attribute either to

thymectomy or to differences in the study populations. Therefore, in nonthymomatous myasthenia gravis, thymectomy should be considered as an option to increase the probability of remission or improvement [44••, Class II] A large, international multi-center trial is being developed to address the effect of thymectomy in nonthymomatous myasthenia gravis [45]. The response to thymectomy is not immediate and may be delayed for several years [46,47, Class II; 48, Class III]

In addition to potential efficacy for improving myasthenia, there are several other unresolved issues regarding thymectomy including timing of surgery with respect to age and the course of myasthenia gravis, surgical technique, distribution of myasthenia, and immunologic status. Thymectomy is done infrequently in patients older than 60 years, because of increased surgical risk and the relatively long latency to benefit in the context of reduced life span. Many think that the best responses to thymectomy occur if it is done early in the course of myasthenia gravis [49, Class III], although this observation may relate to the nonlinear remission rate in myasthenia gravis [44••, Class II] where remission is more likely to occur shortly after diagnosis rather than later [50, Class II]. Another controversy is whether patients with nonthymomatous ocular myasthenia gravis should have thymectomy [51,52, Class III]. In nonthymomatous ocular myasthenia gravis, older patients with longstanding myasthenia may not represent optimal candidates for thymectomy. Lastly, recent clinical series of patients with MuSK-positive myasthenia gravis raise doubt about the benefits of thymectomy in this patient subpopulation [6,7••,9]. There have been no reports to date of thymoma in MuSK-positive myasthenia gravis.

Standard procedure Though it is more invasive, many consider the combined transsternal-transcervical technique to be optimal, as it permits the widest surgical exposure for complete removal of thymic tissue which may be distributed widely in the mediastinum and neck [53]. Surgical techniques for thymectomy have reviewed by Jaretzki *et al*. [54•].

Contraindications Contraindications include those precluding median sternotomy and mediastinal surgery. Patients with moderate to severe generalized or bulbar myasthenia with oropharyngeal and/or respiratory compromise should have preoperative PEX or IgA infusions to improve strength [55].

Complications Mortality in modern thymectomy series is less than 1% [56, Class III]. Complications include acute respiratory failure due to myasthenic crisis (6%), infection (11%), and recurrent laryngeal or phrenic nerve injury (2%) [56, Class III].

Physical/speech therapy and exercise

- Physical exercise in uncontrolled generalized myasthenia gravis may cause fatigue, and energy conservation measures may be reasonable until the myasthenia is more effectively treated. Physical exercise has many overall health benefits, particularly in patients taking corticosteroids. There is no evidence that exercise improves or worsens the natural history of myasthenia gravis.

Emerging therapies

- Patients with myasthenia gravis will benefit from ongoing development of medications to prevent transplant rejection and to treat autoimmune diseases. Examples of such agents showing early promise in case reports include tacrolimus, which blocks interleukin-2 production and T cell proliferation [57,58, Class III] and rituximab, a monoclonal antibody which binds to and depletes B cells [59,60, Class III]. Future development of

immunotherapy specific for myasthenia gravis may induce remission by inducing tolerance, by targeting antigen-specific B and T-helper lymphocytes, or by attenuating cytokine responses.

Pediatric considerations

- The primary issue in pediatric forms of myasthenia gravis relates to making a correct diagnosis. Juvenile myasthenia gravis is autoimmune disorder, whereas congenital myasthenia gravis results from genetic mutations that affect the structure of the neuromuscular junction. Transient neonatal myasthenia gravis is a self-limited disorder related to maternal autoimmune myasthenia gravis. It may be difficult to make the distinction between juvenile myasthenia gravis and congenital myasthenia gravis, particularly in the absence of AChR or MuSK antibodies, or a clear history of ptosis and other manifestations of hypotonia from the time of birth that would suggest genetic disease. These issues are discussed in depth by Andrews [61•].

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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