

CME

Treatment of autoimmune myasthenia gravis

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Abstract—Autoimmune myasthenia gravis (MG) is associated with antibodies directed against the nicotinic acetylcholine receptor (AChR) in 85% of patients. Other postsynaptic neuromuscular junction antigens are implicated, e.g., muscle-specific receptor tyrosine kinase (MuSK), in a number of the remaining 15% of patients, so-called seronegative MG. The autoimmune attack generally leads to decreased concentrations of the AChR and damage to the structure of the endplate itself. This information has guided the empiric treatment of patients with MG and has suggested new treatment strategies. Whereas the outcome of patients with MG has improved because of more effective symptomatic treatment, including advances in critical care medicine and the use of cholinesterase inhibitors, the greatest advances have come from therapies that directly reduce the autoimmune attack or modify its effects on the AChR and the surrounding endplate. Immune-directed treatment of patients with MG, which is guided by this information and by data from the management of other autoimmune disease, is aimed at inducing an immunologic remission and then maintaining that remission. Remission induction is usually accomplished through the use of high-dose corticosteroids, frequently in conjunction with IV immunoglobulin or plasmapheresis. Maintenance of the remission is usually accomplished by slow tapering of the corticosteroids along with the use of “steroid-sparing” agents, which include azathioprine, thymectomy, and possibly mycophenolate. Therapy usually begins with cholinesterase inhibitors. If necessary, immune-directed treatment is added, beginning with either thymectomy or high-dose corticosteroids. The short-term therapies, i.e., IV immunoglobulin or plasmapheresis, may be effective in the early stages of treatment or later during an exacerbation. Steroid-sparing medications are usually added to facilitate the tapering phase.

NEUROLOGY 2003;61:1652–1661

Myasthenia gravis (MG) is an acquired autoimmune disease of the neuromuscular junction. In most cases, the target of the autoimmune attack is the nicotinic acetylcholine receptor (AChR) located in the postsynaptic muscle endplate membrane (figure 1).¹ AChR is an intrinsic (transmembrane) protein that functions as a ligand-gated ion channel. It comprises four homologous polypeptide subunits in the stoichiometry of $\alpha_2\beta\gamma\delta$. Each subunit has an extracellular portion, a transmembrane portion, which contributes to the ion channel, and a cytoplasmic tail. The extracellular portion of each of the two alpha subunits contains an acetylcholine (ACh)-binding site, $\alpha 187$ –199. T helper cells and B cells are involved in the autoimmune response, but the specific effector arm of the immune response is comprised solely of AChR antibodies.^{2,3} That is, although T cells play a crucial role in this disease, the attack on the neuromuscular junction is carried out exclusively by antibodies. The target of these antibodies is primarily, but not exclusively, a portion of the extracellular domain of the alpha subunits $\alpha 67$ – $\alpha 76$, the so-called main immunogenic region (MIR).¹ The AChR antibodies, once they

bind to their target, produce disordered neuromuscular transmission—and the resultant clinical symptoms—by three identified effector mechanisms. The first is the blockade of AChR function. Although this represents a potent mechanism,⁴ antibodies with this property are present in small amounts and probably play a minor role in most cases.⁵ The other two mechanisms result in a decrease in the number of AChRs in the postsynaptic membrane. The first of these is antigenic modulation induced by cross-linking of adjacent AChR molecules by a single bivalent antibody molecule. Such cross-linking results in an acceleration of the normal mechanism for removal of intrinsic membrane proteins. This leads to increased AChR turnover and a lowered steady-state concentration of membrane AChR. This mechanism also appears to play a relatively minor role as well.⁶ The data available to date suggest that it is the third effector mechanism of these autoantibodies that is most effective in reducing neuromuscular transmission. The AChR antibodies induce destructive and inflammatory changes in the postsynaptic membrane, reducing the concentration of AChRs and pro-

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Received February 25, 2003. Accepted in final form August 5, 2003.

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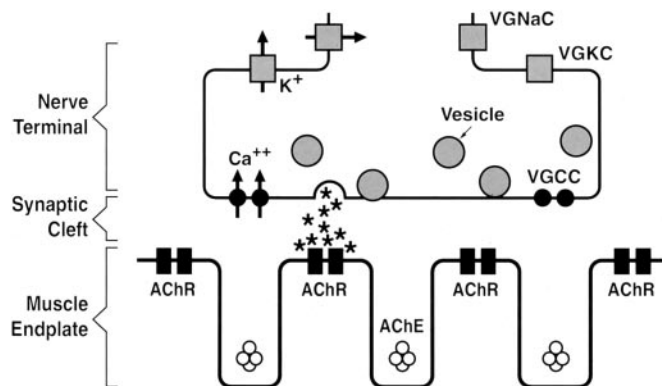


Figure 1. Diagram of the presynaptic and postsynaptic components of the neuromuscular junction. VGNaC = voltage-gated sodium channel; VGKC = voltage-gated potassium channel; VGCC = voltage-gated calcium channel; AChR = acetylcholine receptor; AChE = acetylcholine esterase.

ducing morphologic changes in the entire postsynaptic (endplate) membrane. These destructive changes are mediated primarily through activation of the complement cascade. The end products of complement activation in MG are the membrane attack complex, which lyses the membrane to which the antibody is bound, and chemotactic products, which attract inflammatory macrophages.⁶⁻⁸

The factors involved in the initiation or induction of autoimmune MG are unknown. However, MG is associated with other immune system abnormalities. Particularly prominent are abnormalities in the thymus. Approximately 15% of patients have a thymoma, and another 60% have thymic hyperplasia, i.e., germinal centers in the thymic medulla. There is also a marked increase in other autoantibodies and autoimmune diseases.⁹ Moreover, there is an increased incidence of autoimmune diseases in relatives of patients with MG.⁹

Other antigens in MG. Other neuromuscular junction antigens, distinct from AChR, also play a role in autoimmune attack of patients with MG. In approximately 10% of patients with generalized acquired MG, AChR antibodies are not detected in serum. The characteristics of this disorder, seronegative MG (more accurately AChR antibody-negative MG), appear to be nearly identical to those of patients in whom AChR antibodies are detected.¹⁰ In patients in whom only the extraocular muscles are involved, so-called ocular myasthenia, this proportion is approximately 50%. Recent studies have identified serum antibodies directed against a distinct endplate membrane intrinsic protein, muscle-specific receptor tyrosine kinase (MuSK), in approximately half of the seronegative patients with generalized disease.^{11,12} Hence, it appears likely that targeting by the immune system of proteins in the vicinity of the AChR within the endplate membrane can result in similar abnormalities of neuromuscular transmission. A small per-

centage of patients with seronegative MG may have late-onset forms of congenital myasthenia, a group of nonimmune illnesses that result from mutations in individual proteins involved in normal neuromuscular transmission.¹³

It has been known since 1960 that patients with thymoma have antibodies that react with thymoma cells and muscle striations.¹⁴ The majority of these antibodies have been determined to be directed against the striational cytoskeleton protein titin.^{15,16} Fifty percent of patients with striational antibodies also possess antibodies to the intrinsic membrane protein of the sarcoplasmic reticulum, the ryanodine receptor.¹⁷ Patients with this group of antibodies, including many patients without thymoma but whose disease begins after they are aged 50 years, tend to have more severe symptoms and poorer responses to the usual MG treatments.¹⁸ All of these patients, in contrast with those with MuSK antibodies, have circulating AChR antibodies. Although titin and the ryanodine receptor are intracellular proteins, and hence relatively protected from the serum autoantibodies directed against them, these antibodies appear to play a pathogenic role.

A fifth autoantigen in the muscle endplate has also been identified in patients with acquired MG. Antibodies directed against a small intracellular AChR-associated protein, rapsyn, have been detected in 15% of patients with MG.¹⁹ This protein is located on the inner surface of the AChR and has been shown to play a role in the dense clustering of AChR molecules in the endplate membrane. The identification of antibodies directed at rapsyn¹⁹ and MuSK¹¹ suggests that, in addition to targeting the AChR molecules themselves, immune targeting of proteins involved in AChR clustering at the endplate can also induce MG.

Epitope spreading in MG. Considerable evidence has been gathered demonstrating that during an immune attack on either a foreign target or an autoimmune target, the immune response begins to be directed against other antigenic regions (epitopes) on the original antigen or even against neighboring antigens on the target.²⁰ These phenomena are referred to, respectively, as intramolecular epitope spreading and intermolecular epitope spreading. The result of such spreading is to widen the autoimmune attack and increase damage to the target. The majority of studies of this phenomenon have been in animal models of immune diseases. In experimental allergic encephalomyelitis, investigators have demonstrated that the initial autoimmune attack is directed against the most immunogenically "dominant" epitopes, i.e., the counterparts of the MIR in MG; however, through the course of the immune response, a significant attack is also mounted against less immunogenic "subdominant" epitopes. The subdominant epitopes may initially be less accessible to the immune attack because of their location (so-called "cryptic epitopes") or may be less immunogenic

in the sense of more adequate immune tolerance. During the autoimmune attack, tissue destruction exposes previously cryptic epitopes and provides the milieu for loss of tolerance.

Intramolecular epitope spreading has been demonstrated in experimental autoimmune MG (EAMG).²¹ Animals immunized with a peptide from a portion of the alpha subunit of the AChR not present on other subunits were used for the development of alpha subunit-specific monoclonal antibodies (mAbs). In addition to a number of alpha subunit-specific mAbs that were obtained from these animals, some mAbs were isolated that bound specifically to either the beta or gamma AChR subunits but not to the alpha subunit. There is also information from human MG suggesting the presence of intermolecular epitope spreading. Screening of sera from patients with MG with AChR antibodies has demonstrated the presence of rapsyn antibodies in 15% of patients.¹⁹

Lessons from other autoimmune diseases.

Many autoimmune diseases follow a relapsing and remitting course.^{22,23} The natural history of these disorders is one of periods of exacerbation followed by periods of relative quiescence. In terms of the major function of the normal immune system, response to infection, the response builds rapidly beginning with the activation of the innate immune system and followed quickly by the recruitment of the components of the adaptive immune system, antigen-specific T cells, and antibody-producing B cells. The effector T cells and antibodies lead to efficient destruction of most invading organisms. Once the target is eliminated, the reduction in the active response is also rapid, permitting the affected host tissue to recover.²⁴ Eventually only memory cells remain (to provide the basis for a secondary antigen-specific response in the future if such a response were to become necessary). This termination of the immune response is mediated to some extent by cytokine loops under the influence of immunoregulatory cells. The mechanisms involve apoptosis of the activated immune cells as a result of 1) loss of stimulatory cytokines and signals; 2) increased production of proapoptotic molecules; or 3) reduction in the production of antiapoptotic molecules.²⁵ In autoimmune disorders, the tissue damage may not completely subside, and complete removal of the autoantigen may not be possible; however, periods of reduced damage are common. (The inability to completely remove the target antigen may be a major distinction between the autoimmune response and the normal immune response.) In a general sense, the goal of treatment for patients with these diseases is to induce and support the quiescent stage and to prevent the exacerbation stage.

There is evidence that the natural history of MG is characterized by exacerbations and remissions similar to those seen in other autoimmune diseases. However, it is difficult to obtain information on the

natural history of this disease.²⁶⁻²⁹ One review of descriptions of patients made before the availability of modern therapeutic agents has suggested various stages of severity superimposed on exacerbations and remissions.³⁰ It is clear in the present era of symptomatic and immune-directed treatments (see below) that patients do experience exacerbations. The most striking initiating factors in the relatively recent past have been infection and surgery.²⁹⁻³¹ However, with the more effective current treatment regimens, patients tolerate these two types of insult, so that exacerbations are most often seen as a consequence of reduction in the doses of immunosuppressive agents. With these agents, the majority of patients are essentially symptom free while given high doses. The symptoms return, generally in an accelerating fashion, when the doses are reduced below a certain level.

The roles of epitope spreading and the exacerbating and remitting nature of autoimmune diseases have been addressed in patients with a more common disease, rheumatoid arthritis. The effectiveness of combinations of immune-directed treatments³² and new agents that block tumor necrosis factor- α (TNF α)³³ for patients with rheumatoid arthritis has led to a number of studies of the optimization of treatment regimens. Remarkably, early vigorous therapy with combinations of immune-directed treatment or with the anti-TNF α agents has proven to be much more effective, in the long run, than withholding these agents until later in the disease or the use of single agents.³⁴⁻³⁶ The data suggest that if a complete remission of symptoms can be induced early in the course of rheumatoid arthritis, less joint damage will occur long term. Stated another way, the earlier a remission can be induced and maintained, the better the long-term prognosis.

Symptomatic (nonimmune) treatments of autoimmune MG.

The pathogenesis of autoimmune MG, as noted previously, consists of autoantibody attack on the AChR in the muscle endplate membrane. This information suggests that primary management of MG would involve reducing this autoimmune attack. However, considerable progress has been made in decreasing morbidity and mortality of patients with MG through the use of a number of symptomatic treatments aimed at managing the aftermath of the antibody attack without directly affecting the attack itself.³⁷ The management of the anti-MuSK form of MG may differ somewhat from the anti-AChR form of the disease discussed here.^{38,39}

Significant reduction in the mortality of patients with autoimmune MG has resulted from improved methods in critical care. Because of the frequent involvement of oropharyngeal and respiratory muscles, respiratory compromise is the most common cause of death of patients with MG. Advancing technology in artificial ventilation and airway protection has significantly contributed to the decreased mortality of MG from 40 to 5%.³⁷ Similarly, improved antibiotics

and management of sepsis during this same period have also reduced mortality from respiratory and other infections in patients with severe exacerbations of MG (myasthenic crisis).

Symptomatic management of autoimmune MG includes the cholinesterase inhibitors, especially pyridostigmine. This group of medications provided the first effective management of MG. The initial use of these drugs in 1934 represents the first therapy derived from an understanding of the pathogenesis of the disease.⁴⁰ A medical registrar in the United Kingdom had learned of the similarity of the symptoms of MG to those of curare poisoning. She reasoned that because it was known that curare was a competitive antagonist of ACh for binding to the AChR, a similar situation might be true for MG. The newly developed cholinesterase inhibitor physostigmine was effective for curare poisoning, presumably by blocking the acetylcholinesterase present in the extracellular matrix of the folded endplate membrane (figure 1), thereby increasing the concentration of ACh at the AChRs and overcoming the competitive blockade. Although we understand now that there is little antagonist effect of the AChR antibodies in MG (see above), physostigmine was effective in the patient in whom it was tried, as it is in many patients with MG. As described previously, there is a decrease in the concentration of AChRs in the postsynaptic membrane in patients with MG. However, the improvement seen in patients with MG appears to result from the increased concentration of ACh (caused by blocking the acetylcholinesterase) inducing the remaining AChRs to be maximally activated.

Cholinesterase inhibitor therapy, primarily with pyridostigmine, is usually effective early in the disease course or for patients with mild cases, presumably because there are still adequate numbers of AChRs present. A common scenario is that at the beginning of treatment there is a marked improvement in MG, but over months increasing doses are required for the same result. Then eventually the effect lessens even at maximal doses. Patients tend to “bond” to the drug as a result of the marked improvement at the beginning of therapy, but they should be encouraged to discontinue it if no effect is seen initially (with maximal doses) or if remission is induced by the immune-directed treatments. Because these agents have no effect on the autoimmune attack at the neuromuscular junction, it is important to remember that their use involves the risk of masking underlying progression of the disease or even permitting the phenomenon of epitope spreading (see above).

The side effects of the cholinesterase inhibitors are relatively mild and related to the high concentrations of ACh at nicotinic and muscarinic synapses. (What gives pharmacologic specificity to these two types of synapses are the receptors, whereas the cholinesterases are similar.) So although the muscarinic synapses are not affected in patients with MG, the

cholinesterase inhibitors affect them. Common muscarinic side effects are gut hypermotility (abdominal cramps, diarrhea), excessive perspiration, excessive respiratory and gastrointestinal secretions, and bradycardia. The nicotinic effects can be muscle fasciculations and increased blockade of neuromuscular transmission (so-called cholinergic crisis). The muscarinic side effects can be reduced by the addition of muscarinic antagonists, such as propantheline. There are two important limitations to the use of these antagonists. First, they result in markedly increased viscosity of the respiratory secretions, which in a patient with MG can lead to airway mucous plugging and atelectasis. Second, in a number of patients, their use masks the symptoms of cholinergic “overdose” at the muscarinic synapses, which may mirror impending overdose at the nicotinic synapses (increased neuromuscular blockade).

There are two additional symptomatic medical treatments available. Both appear to increase the amount of ACh released from the presynaptic nerve terminal. From the perspective of the endplate membrane, this is an identical effect to that of cholinesterase inhibitors. Based on limited data, it appears that neither is as effective or safe as pyridostigmine. One of these is ephedrine,⁴¹ which is available but frequently difficult to obtain. The second, 3,4-diaminopyridine,⁴² is experimental and has not been approved for any medical indication.

Other symptomatic treatments include avoidance of situations in which neuromuscular transmission may be compromised. A number of drugs or conditions may have a direct pharmacologic effect on the neuromuscular junction.⁴³ The important ones include penicillamine (an agent capable of initiating or worsening the autoimmune response to AChR), aminoglycosides, and thyroid dysfunction.

Immune-directed treatment of autoimmune MG. The more effective treatments for patients with MG are those that directly target the autoimmune response. They may either modify AChR antibody production or modify the damage to the neuromuscular junction induced by the binding of these antibodies. In general, there are two sets of treatments: those that have a rapid but relatively short-lived effect on the disease and those that have a long-term effect. The use of these two groups of treatments should be considered in the context of the overall treatment strategy for patients with MG.

As discussed previously, the natural history of MG, like that of other autoimmune diseases, tends to be characterized by exacerbations and remissions. The strategy of treatment is to first induce a remission and then to maintain the remission, the latter with the least possible cost-to-benefit ratio. (In this context, remission can be defined as complete or nearly complete absence of symptoms.) The current management of autoimmune diseases in general involves immunosuppressive medications. Therefore, the strategy usually translates into inducing a re-

mission with high doses of the immunosuppressive agent. Once remission is achieved, the dose is reduced to the smallest that will maintain the remission. For most autoimmune diseases—and this is especially true for MG—the reduction in dose must be made slowly. It is also important to take the long-term view of the illness when trying to calculate the cost-to-benefit ratio. How many years of remission can be achieved? How many years of exposure to the risks of the treatment will accrue? A final point is that remission is generally the goal for patients with MG. It can be attained in many patients with this disease. However, because in the past this was not the case, there is a certain school of thought that managing in the face of continuing symptoms represents a means of “living with MG.” Many patients markedly modify their daily activities to manage without giving serious consideration to the cost-to-benefit analysis that follows.

Long-term immune-directed treatments. Thymectomy is the classic long-term treatment. Its effect is usually not apparent until after 1 year, and the full effect is not felt for 5 years.^{31,44} There are two histologic abnormalities of the thymus that occur in patients with MG. With frankly neoplastic thymoma, removal of the tumor is usually indicated because of the risk of extension of the tumor into adjacent structures in the mediastinum. For these patients, the concurrent removal of other thymic tissue may be less effective in managing MG than is the case for patients without thymoma. In the second group of patients, there is frequently the presence of germinal centers within the medulla of the gland, so-called thymic hyperplasia. However, there are no data demonstrating reduced effectiveness of thymectomy when no hyperplasia is identified.

Thymectomy is the treatment for patients with MG in which the cost-to-benefit ratio appears to decrease with time. Essentially all of the risk of the treatment occurs in the operative and postoperative periods. Other than these perioperative issues, there is no evidence of other side effects, either short term or long term, of thymectomy. In the overall strategy of MG therapy, thymectomy appears to increase the likelihood of remission and possibly reduces the long-term exposure to immunosuppressive drugs. The crucial factor in the cost-to-benefit ratio at present is the risk of the surgical procedure at any particular institution. There is considerable controversy concerning the effectiveness in patients with onset of disease after age 50 years. A meta-analysis of a number of studies has demonstrated a 25% lower remission rate in the older-onset group compared with the younger patients.⁴⁵ Aarli et al.⁴⁶ have noted that the reduced effectiveness appears to occur in those patients in this group who have thymoma or antiskelletal muscle antibodies but no thymoma. A number of studies have suggested that the earlier thymectomy is performed during the course of the disease, the more effective it is for all patients. The limited data

suggest it is most effective when performed during the first 2 years of the disease.⁴⁷

The effectiveness of thymectomy for patients with MG is based on data from nonrandomized studies. Most of these were not controlled. A review of these studies showed that the majority demonstrated efficacy but that the inability to control for confounding variables prevented definitive conclusions.⁴⁵ A multinational, randomized, single-blinded (the examining physician but not the patient), multicenter study of thymectomy is presently being organized.

An additional unsettled question of thymectomy is the type of surgical procedure used.⁴⁵ At one extreme is the radical thymectomy involving a combined trans-sternal thoracotomy, cervical dissection, and hilar dissection. At the other extreme is a transcervical approach to the cervical dissection and anterior mediastinum dissection. Newer surgical approaches relying on less-invasive video-assisted techniques are currently being assessed.

Corticosteroids are currently the mainstay of the immune-directed treatment for patients with MG. Their major effect is anti-inflammatory by reducing expression of inflammatory cytokines and adhesion molecules and reducing trafficking of inflammatory cells. High doses may also induce apoptosis in immune cells.^{48,49} When applied appropriately, these medications appear to be effective in inducing remission in at least 50%, but perhaps in as many as 80%, of patients. Remarkably, the efficacy of these medications in patients with MG has never been studied in an adequate double-blinded, placebo-controlled trial. Initial studies of high-dose steroids demonstrated a worsening of the disease. It eventually became clear that the worsening occurred 7 to 14 days after initiation of the high doses but usually lasted less than 1 week. It appears that gradually increasing the dose of steroids over 1 to 2 months reduces the risk of the early worsening of the disease.⁵⁰

Although the corticosteroids appear to be effective in inducing a remission, they have major side effects, making the cost-to-benefit ratio an important issue for some patients.⁵¹ Common side effects include weight gain, hypertension, diabetes, anxiety/depression/insomnia (“steroid psychosis”), glaucoma, osteoporosis, cataracts, ulcer/gastrointestinal perforations, myopathy, opportunistic infections, and avascular necrosis of large joints. In many ways, this therapy is the equivalent of “trading one disease for another.” The therapeutic decision is made more difficult by the problems in predicting the likelihood of any of the side effects for a given patient. We suggest that physicians experienced in the long-term use of steroids and the management of their complications should mainly carry out treatment of patients with this modality. Some of these complications can now be prevented or managed. Osteoporosis, with associated compression fractures, can now be readily prevented with the addition of bisphosphonates to the therapeutic regimen.⁵² Peptic ulcers can be pre-

vented using any of the acid-reducing medications now available.

In light of the strategy described previously of inducing remission, followed by reduction of the immunosuppressive therapies while maintaining the remission, the goal should be to reach a high dose of corticosteroids as rapidly as possible. To facilitate this, we recommend starting the patient on daily high doses. For prednisone, this would involve 1 mg/kg/d in three divided doses. Any transient worsening that occurs during the first 2 weeks is to be managed with one of the short-term modalities described below. One alternative is to slowly increase the dose to this level over 4 to 6 weeks in an attempt to reduce the risk of the transient worsening. A third alternative is to begin with an every-other-day regimen (120 mg every other day).

The maximum dose is maintained until complete remission is accomplished. Typically improvement is noted by approximately 6 weeks and remission by 3 months. Once remission occurs, the tapering phase can begin. There is reasonable evidence that every-other-day dosing results in fewer side effects of steroids. Hence, there are two goals in this phase. The first is to taper the dose slowly enough that an exacerbation does not occur. The second is to move to an every-other-day schedule. As a rough rule of thumb, we would recommend a monthly reduction in total dose of 5 to 10% of the current dose. It is crucially important to modify the reduction schedule continuously in response to the patient's symptoms. A recent randomized, double-blinded trial has demonstrated that the addition of azathioprine (see below) as a steroid-sparing agent increased success during the tapering phase.⁵³ The overall strategy is to reduce the cost-to-benefit ratio as much as possible. For some patients, this may mean they can be completely weaned from the steroids. For others, the disease begins to exacerbate at some point during the tapering process. This situation requires the reinduction of a remission (see below), followed by a second tapering phase. Because of a reduction in the rate of tapering or simply because more time on treatment has passed (especially if the patient has previously had a thymectomy), many times the patient's dose can be reduced beyond the dose that resulted in the previous flare-up. Adding to the difficulty in tapering decisions, and an additional reason for making reductions slowly, is the apparent observation that there is a lag of up to 3 months between a dose reduction and the exacerbation it induces. To some extent, one may consider thymectomy as a steroid-sparing therapy.

Azathioprine has been used extensively for patients with MG. It acts by inhibiting purine synthesis and hence cell proliferation.⁵⁴ The most rapidly dividing cell populations are affected, e.g., lymphocytes. A few studies have suggested that it is useful alone to induce a remission, but most studies have described its use in conjunction with corticosteroids.⁵⁵⁻⁵⁷ As noted previously, a large double-blinded, randomized study has

demonstrated its effectiveness as a steroid-sparing agent. Its use with high-dose steroids may increase the risk of opportunistic infections. The therapeutic dose of azathioprine is 2 to 3 mg/kg. (The initial dose should be 1 mg/kg with gradual increase to the therapeutic dose.) In light of the principle of reducing the cost-to-benefit ratio, this drug should also be tapered if possible.

Azathioprine has considerably fewer side effects than do corticosteroids. It can induce leukopenia or thrombocytopenia, intractable vomiting, or hepatic dysfunction.⁵⁸ Occasionally patients with inborn errors of metabolism, e.g., thiopurine methyltransferase deficiency, may develop bone marrow suppression at lower doses.^{59,60}

Cyclophosphamide is also useful for the treatment of patients with MG. It is a strong alkylating agent that acts on DNA, inhibiting cell proliferation. The effect is greater on B cells than on T cells, making it an excellent agent for antibody-mediated diseases.⁶¹ It appears to be nearly as effective as corticosteroids in inducing remissions, although there are no controlled studies of this drug for induction of remission in patients with MG.^{62,63} The risks of the side effects of this medication are even greater than those of steroids. The side effects are severe bone marrow suppression with risk of opportunistic infections, bladder toxicity, and a dose-related risk of neoplasms. Cyclophosphamide has generally been used for patients with severe MG who have been unable to tolerate corticosteroids. It has also been used in conjunction with high-dose steroids for patients with severe disease who have not responded well to high-dose steroids alone. Severe infections are a risk for patients treated with this combination.

Cyclosporine A has been studied for patients with MG, primarily as a steroid-sparing medication for steroid-dependent patients.⁶⁴ It is an inhibitor of T helper cell function through blockade of calcineurin-mediated cytokine signaling.⁶⁵ It has been marginally effective in this situation but has not been shown to be better than azathioprine for these patients. It has a much higher cost-to-benefit ratio than azathioprine with side effects including hypertension and renal damage. It is reasonable to consider cyclosporine for patients who are intolerant to azathioprine.

Newer long-term agents. A number of newer immunosuppressant agents are presently being studied for patients with MG. The most-studied agent is mycophenolate mofetil. It is an inhibitor of the pathway for de novo purine synthesis by directly blocking the enzyme inosine monophosphate dehydrogenase. It is highly specific for proliferating lymphocytes, which do not make use of the purine salvage pathway.⁶⁶ This agent has been examined in two relatively small, uncontrolled studies involving a variety of types of patients with MG.^{67,68} It has appeared to be effective for patients with poorly controlled disease taking the therapeutic combinations described previously. Addition of the mycophenolate to those medi-

cations has resulted in remission of the disease. It also appears to be useful as a steroid-sparing medication. It is unclear whether it is useful as a sole agent to induce remission. The calcineurin inhibitor tacrolimus and mitoxantrone and rituximab, which are B cell-directed agents that have been effective for other autoimmune diseases, are all reasonable candidates for study in patients with MG.

Short-term immune-directed treatments. Plasmapheresis and infusion of IV immunoglobulin (Ig) are two immune-directed treatments that have rapid onset of effect but relatively short duration of action. The rationale for plasmapheresis was that because MG was mediated by circulating AChR antibody, the bulk removal of antibody (by removing plasma) would reduce the autoimmune attack at the neuromuscular junction. Uncontrolled studies have demonstrated efficacy with the onset of improvement within the first week.⁶⁹⁻⁷¹ The standard protocol is to remove one plasma volume every other day for five treatments. Studies have indicated that the effectiveness of plasmapheresis is improved if the patient is treated concomitantly with an immunosuppressive agent such as corticosteroids, azathioprine, or cyclophosphamide. In general, the effect lasts 1 to 2 months.

IV Ig has a similar effect. Considerable speculation has been made concerning the mechanism of action of this agent with few data to support any of the possibilities.⁷² The process involves daily infusions of polyclonal human Ig, usually 0.4 g/kg/d for 5 consecutive days.⁷³ Improvement usually begins within a few days of the onset of treatment. A multicenter, randomized, controlled study comparing plasmapheresis with IV Ig has demonstrated equal efficacy but significantly fewer and less severe side effects for the IV Ig treatment.^{74,75} Hence, the latter is the modality of choice. As with plasmapheresis, the effect of IV Ig treatment is usually short lived, from 1 to 2 months, and seems to be enhanced if the patient is taking immunosuppressive medications.

Therefore, these treatments tend to be used for patients with acute worsening of MG, such as actual or impending myasthenic crisis. For patients with severe crisis, more than one course of plasmapheresis or IV Ig may be necessary. Other acute situations for which these therapies are useful include surgery or severe medical illness.

Occasionally when plasmapheresis or IV Ig is performed in a patient taking an immunosuppressive medication, the effect is one of remission that may last indefinitely. Presumably, in this instance, the plasmapheresis or IV Ig is able to push the overall immunosuppression over the threshold needed to induce a remission—applying a jump-start to an already primed engine. This effect seems to occur also in patients whose disease is beginning to flare up as a result of reduction in the dose of immunosuppressive medication or as the result of physical stress. Hence, the first response to a flare-up that occurs

during the tapering phase of steroids, or of other immunosuppressive agents, is to hold the dose of the immunosuppressant steady and begin a course of plasmapheresis or IV Ig. If these short-term treatments are not effective, then the dose of the immunosuppressant will need to be increased significantly, with or without a second course of plasmapheresis or IV Ig.

A protocol for the treatment of MG. As noted previously, the goal of the protocol discussed here is to optimize the use of the aforementioned various treatments by taking into account our knowledge of the pathogenesis of MG and the nature of the autoimmune attack. For many patients, the agents and their combinations will have to be appropriately tailored. A number of specific treatment goals can be derived from the information discussed previously concerning the roles of epitope spreading and exacerbations and remissions in patients with MG and other autoimmune diseases. In particular, the bias should be to make use of immune-directed treatments as early as is reasonable to reduce the likelihood of epitope spreading. In addition, the aim should be for complete remission (absence of symptoms). Finally, in general, maintenance of remission for patients with MG requires slow tapering of immunosuppressive treatment.

The following is a treatment protocol for patients with generalized acquired MG based on these principles (figure 2). The patient is treated with a cholinesterase inhibitor until it is clear that an early spontaneous remission has not occurred and that the risks of the ongoing autoimmune attack outweigh the risks of immune-directed treatment. Each step in the treatment of the patient requires that the long-term cost-to-benefit ratio for that patient be lower than the other alternatives. The patient is started on high-dose (1 mg/kg) daily prednisone, initially in divided doses (commonly 20 mg three times per day), with the goal of inducing remission. Any worsening in symptoms in the first 2 weeks is treated with a course of either IV Ig or plasmapheresis. These two short-term therapies appear to be effective in overcoming the worsening that can occur in this period after initiation of high-dose corticosteroids. They may also assist in the induction of the remission. Therefore, it is also reasonable to start the short-term treatment concomitantly with the initiation of the steroids. Once remission is established, the tapering of the prednisone is begun (see above), aimed at an every-other-day dosing schedule. In this phase, the goal is to reach the minimum dose of prednisone that will maintain the remission. Once some reduction in prednisone dose has been accomplished, a steroid-sparing agent, e.g., azathioprine or mycophenolate mofetil, is added. (A major role for thymectomy is as a steroid-sparing treatment. Its timing is discussed previously.) It is important also to begin a bisphosphonate to prevent steroid-induced osteoporosis. Any other side effects of prednisone or the other immunosuppressants are treated as they appear,

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