REVIEW ARTICLE

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Myasthenia Gravis

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Myasthenia gravis is an autoimmune disease in which antibodies bind to acetylcholine receptors or to functionally related molecules in the postsynaptic membrane at the neuromuscular junction. The antibodies induce weakness of skeletal muscles, which is the sole disease manifestation.[1-3] The weakness can be generalized or localized, is more proximal than distal, and nearly always includes eye muscles, with diplopia and ptosis.[2] The pattern of involvement is usually symmetric, apart from the eye involvement, which is often markedly asymmetric and involves several eye muscles. The weakness typically increases with exercise and repetitive muscle use (fatigue) and varies over the course of a day and from day to day, often with nearly normal muscle strength in the morning.

With an annual incidence of 8 to 10 cases per 1 million persons and a prevalence of 150 to 250 cases per 1 million,[4] myasthenia gravis and its various subgroups are the major diseases that affect the neuromuscular junction. The Lambert–Eaton myasthenic syndrome and neuromyotonia are additional, rare, presynaptic autoantibody disorders characterized by skeletal-muscle dysfunction.[5] Congenital myasthenic syndromes and toxin-induced conditions (e.g., botulism) can also affect the neuromuscular junction and lead to muscle weakness. This review focuses on new diagnostic tests for myasthenia gravis, updated treatment algorithms, and individualization of therapy according to biomarkers.

The diagnosis of myasthenia gravis is confirmed by the combination of relevant symptoms and signs and a positive test for specific autoantibodies.[6] Antibodies against acetylcholine receptors, muscle-specific kinase, and lipoprotein receptor–related protein 4 (LRP4) are specific and sensitive for the detection of myasthenia gravis, define disease subgroups, and point to pathogenic variations among these subgroups. The localization of the antigens at the neuromuscular junction and in skeletal muscle is shown in Figure 1. The disease-inducing potential of the antibodies depends on the epitope, binding pattern, IgG subclass, antibody cross-linking capacity, antibody concentration, and access of antibody to the muscle end plate.[7]

In antibody-negative cases, neurophysiological tests and a characteristic response to therapy secure the diagnosis.[8] An ice-pack test that reverses ptosis supports the diagnosis. Thymic status should be determined by means of mediastinal imaging.[9] The main value of such imaging is to detect a thymoma; this imaging is neither sensitive nor specific for the identification of thymic hyperplasia. Supplementary antibody tests can provide further help in characterizing the thymus.[10]

Symptomatic, immunoactive, and supportive approaches to therapy have a very good effect, and the prognosis regarding muscle strength, functional abilities, quality of life, and survival is generally good.[11,12] Therapy should be aimed at full or nearly full pharmacologic remission (i.e., the absence of myasthenic symptoms and signs while the patient is receiving therapy).

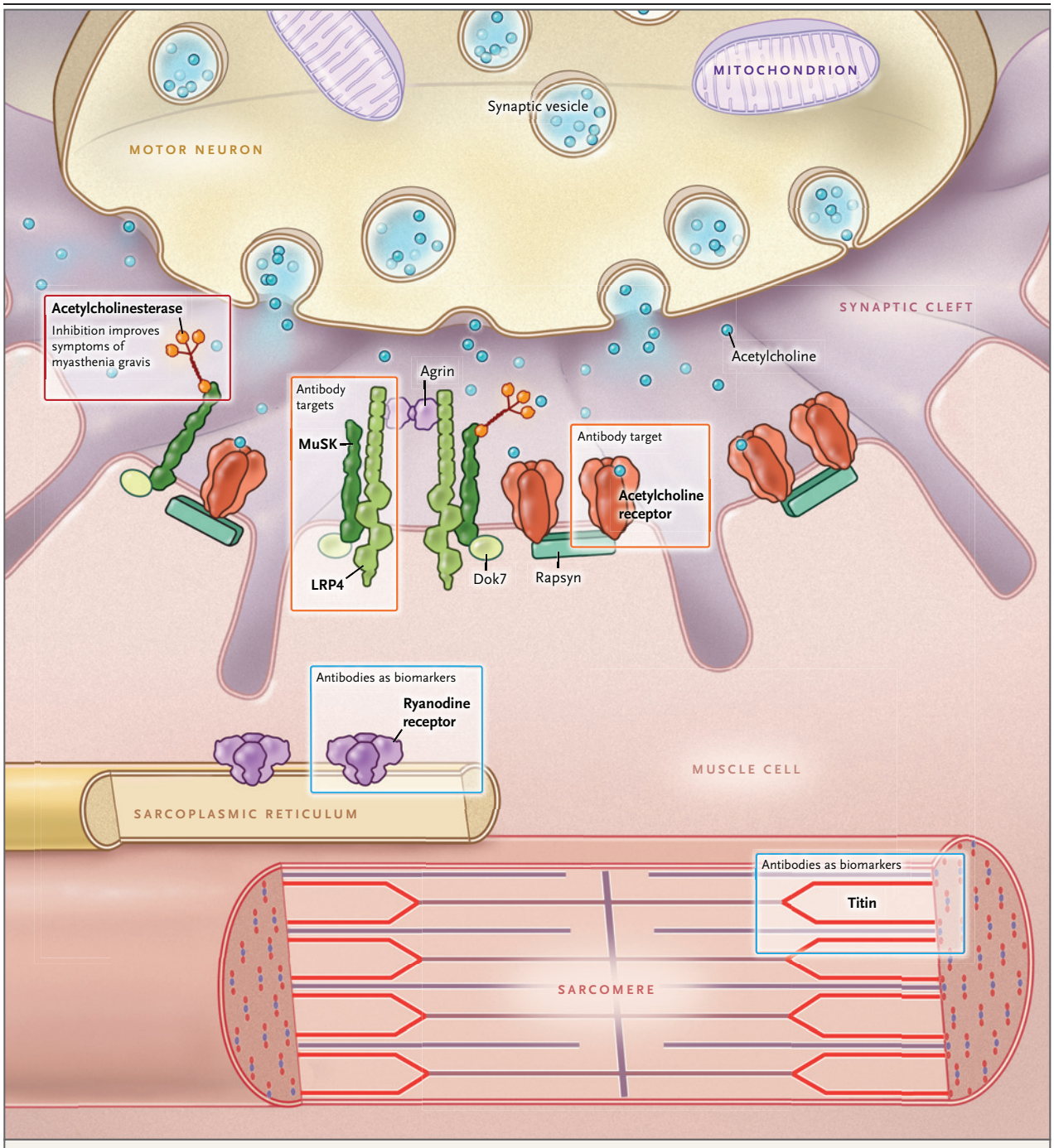

Figure 1. Neuromuscular Junction and Key Elements for the Pathogenesis of Myasthenia Gravis.

Neuromuscular transmission involves release of presynaptic acetylcholine, which binds to acetylcholine receptors in the postsynaptic membrane. The receptors interact with several other proteins in the membrane, including Dok7 and rapsyn. Mutant Dok7 and rapsyn are important in the development of congenital myasthenia. Antibodies against acetylcholine receptors, as well as antibodies against muscle-specific kinase (MuSK) and lipoprotein receptor–related peptide 4 (LRP4), induce myasthenic weakness. Antibodies against the intramuscular proteins titin and ryanodine receptor are relevant biomarkers in some subgroups of myasthenia gravis. Acetylcholine is degraded by local acetylcholinesterase, and acetylcholinesterase inhibition leads to symptomatic improvement in patients with myasthenia gravis.

CLINICAL AND PATHOGENIC VARIANTS

Variants of myasthenia gravis are defined on the basis of autoimmune and antibody disease mechanisms, target molecules of skeletal muscle, thymic status, genetic characteristics, response to therapy, and disease phenotype. Patients with myasthenia gravis should always be subgrouped on the basis of all these variables (Fig. 2A) and should be assigned to only one subgroup. To combine disparate clinical and nonclinical features in the classification of individual patients is a challenge (Table 1). Subgroups influence therapeutic decisions and prognosis.

In 15% of all patients with myasthenia gravis, symptoms and signs are confined to ocular muscles. Only half of patients with ocular myasthenia gravis have detectable muscle antibodies.[13] Ptosis and diplopia are common initial symptoms, but the disease remains restricted to ocular muscles in only a minority of patients. In 90% of patients who continue to have purely ocular myasthenia gravis 2 years after the start of symptoms, the disease will persist as a focal eye-muscle weakness and never become generalized. Myasthenia gravis with muscle-specific kinase antibodies is not manifested as ocular myasthenia, whereas both acetylcholine receptor and LRP4 antibodies can be found in the ocular subgroup.[2] The presence of muscle antibodies increases the risk of subsequent generalized disease.

Ten percent of patients with myasthenia gravis have a thymoma, and the prevalence increases with increasing age. Two thirds of patients with myasthenia gravis have generalized early-onset or late-onset disease and no thymoma. Among patients who have myasthenia gravis with acetylcholine receptor antibodies, the age at onset has a bimodal pattern, supporting the use of a cutoff age of 50 years to distinguish between early-onset and late-onset disease.[14] Juvenile myasthenia gravis, which is included in the early-onset group and is defined as an onset before the age of 15 years, is much more common in East Asian populations than in whites.[15,16] Early-onset myasthenia gravis tends to be characterized by thymic hyperplasia, whereas thymic atrophy is characteristic of late-onset disease. Early-onset myasthenia gravis is associated with *HLA-DR3*, *HLA-B8*, and non-HLA genes that are known to influence the immune system and probably the risks of autoimmune disease; late-onset disease is associated with *HLA-DR2*, *HLA-B7*, and *HLA-DRB1 15.01*.[17,18] Thymic status and HLA pattern represent strong subgroup markers, probably pointing directly to variation in pathogenic pathways. Early-onset myasthenia gravis is three times as likely to be diagnosed in females as it is in males, whereas males slightly outnumber females in the late-onset group. Coexisting auto-

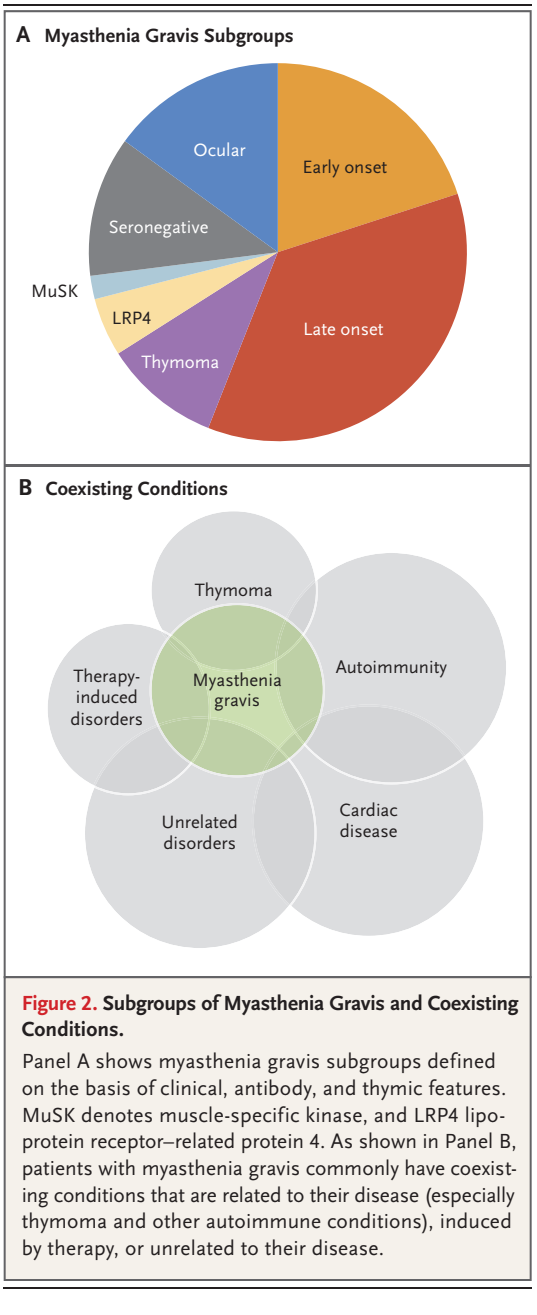

Figure 2. Subgroups of Myasthenia Gravis and Coexisting Conditions.

Panel A shows myasthenia gravis subgroups defined on the basis of clinical, antibody, and thymic features. MuSK denotes muscle-specific kinase, and LRP4 lipoprotein receptor–related protein 4. As shown in Panel B, patients with myasthenia gravis commonly have coexisting conditions that are related to their disease (especially thymoma and other autoimmune conditions), induced by therapy, or unrelated to their disease.

Table 1. Features of Myasthenia Gravis Subgroups.*

Subgroup	Antibody	Age at Onset	Thymus
Early onset	Acetylcholine receptor	<50 yr	Hyperplasia common
Late onset	Acetylcholine receptor	≥50 yr	Atrophy common
Thymoma	Acetylcholine receptor	Any age	Lymphoepithelioma
Muscle-specific kinase	Muscle-specific kinase	Any age	Normal
LRP4	LRP4	Any age	Normal
Seronegative	None detected	Any age	Variable
Ocular	Variable	Any age	Variable

* LRP4 denotes lipoprotein receptor–related protein 4.

immune disorders are more common in early-onset disease than in late-onset disease.[19]

Titin antibodies, which occur primarily in patients with a thymoma and late-onset myasthenia gravis, in addition to acetylcholine receptor antibodies,[10,20] have been shown to be a marker for severe disease. Ryanodine receptor antibodies, which are present in 70% of patients with a thymoma and myasthenia gravis and in 14% of those with late-onset myasthenia gravis,[10] are a marker for more severe disease but have no disease-modifying effects. Kv1.4 antibodies are detected in 10 to 20% of patients with acetylcholine receptor antibodies.[21,22] The disease phenotype does not differ between early-onset and late-onset myasthenia gravis.

Myasthenia gravis with muscle-specific kinase antibodies accounts for 1 to 10% of cases.[23] This disorder is more common in the Mediterranean area of Europe than in northern Europe and is also more common in the northern regions of East Asia than in the southern regions.[24] The reason for this variation is thought to be a genetic predisposition rather than environmental factors. Patients with myasthenia gravis and muscle-specific kinase antibodies, as compared with patients without these antibodies, have more severe weakness, sometimes with muscle atrophy, and have marked symptoms from facial and bulbar muscles. Limb weakness and ocular weakness are less common and fluctuations in muscle strength are less pronounced than in disease characterized by acetylcholine receptor antibodies.

LRP4 antibodies are present in 1 to 3% of all patients with myasthenia gravis.[25,26] Such patients tend to have only mild-to-moderate symptoms. Neither cases of myasthenia gravis with LRP4 antibodies nor those with muscle-specific kinase antibodies are associated with any proven thymic disease. A few patients with muscle-specific kinase or LRP4 antibodies in combination with acetylcholine receptor antibodies have been described.[1,6] Such patients should be classified according to the muscle-specific kinase or LRP4 antibodies.

In some patients with myasthenia gravis, no serum antibodies against neuromuscular junction proteins can be detected. After standard testing with commercially available kits, 10 to 15% of patients remain seronegative. Cell-based assays for antibody detection are more sensitive than serum tests because the antigens expressed on cell membranes can be clustered and maintain their natural conformation.[27] Such cell-based assays have been developed for acetylcholine receptor, muscle-specific kinase, and LRP4 antibodies.[1,6] One third of patients with generalized myasthenia gravis who are seronegative on standard testing are seropositive on cell-based testing. The seronegative group probably includes some patients with acetylcholine receptor, muscle-specific kinase, or LRP4 antibodies that are not detected because of insufficient test sensitivity. Some patients may have pathogenic antibodies against other postsynaptic membrane antigens. These antigens interact with acetylcholine receptors. Some patients may have disease that is not mediated by antibodies.

Agrin antibodies, in the absence of other muscle antibodies, have been found in a minority of patients with myasthenia gravis.[28] These antibodies seem to be specific for myasthenia gravis. Agrin has regulatory properties in the postsynaptic membrane and is linked to neuromuscular transmission, but so far, a pathogenic effect of agrin antibodies has not been estab-

lished. Collagen Q and cortactin antibodies have been detected in some patients.[1,29] The specificity of these antibodies for myasthenia gravis has been questioned.

In seronegative patients with myasthenia gravis, the diagnosis should be reevaluated, and antibody tests should be repeated after 6 to 12 months. Before sensitive cell-based assays are included in clinical practice, standard procedures for these assays, as well as their disease specificity, need to be defined.

COEXISTING DISORDERS

Coexisting conditions are common in patients with myasthenia gravis and should always be considered (Fig. 2B). Approximately 15% of patients have a second autoimmune disease,[19,30] which occurs most frequently in patients with early-onset myasthenia gravis and thymic hyperplasia. Thyroiditis is the most common coexisting condition, followed by systemic lupus erythematosus and rheumatoid arthritis. In patients with ocular myasthenia, thyroid disease is especially common.

Myasthenia gravis occurs in one third of all patients with a thymoma. Although the strong association between thymoma and myasthenia gravis is unique, thymoma is also associated with an increased risk of certain other autoimmune disorders. Blood cytopenias, hypogammaglobulinemia, polymyositis, the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M component, and skin changes), neuromyotonia, and autoimmune encephalitis occur with an increased frequency among patients with a thymoma but are rare in patients with myasthenia gravis.

Neuromyelitis optica with aquaporin-4 antibodies has a prevalence of 40 cases per 1 million population,[31] has a specific association with myasthenia gravis, and can occur either before or after the onset of myasthenia gravis.[32] Amyotrophic lateral sclerosis (ALS) occurs in patients with myasthenia gravis more often than would be expected on the basis of the risk in the general population. Autoimmune disease in general represents a risk factor for ALS, but the association with myasthenia gravis is especially strong.[33,34]

Myocarditis is rare but occurs with an increased frequency in patients with myasthenia gravis, as indicated by numerous single case series and reports.[35] However, myasthenia-related clinical heart disease and heart dysfunction are very rare. In population-based studies, myasthenia gravis has not been associated with an increase in mortality related to heart disease.[36] Functional imaging studies have shown minor and subclinical dysfunction.[37] Myocarditis in myasthenia gravis is associated with Kv1.4 muscle antibodies.[22] Antibodies against acetylcholine receptor, muscle-specific kinase, and LRP4 do not cross-react with heart muscle, in contrast to nonjunctional antibodies against Kv1.4, titin, and ryanodine receptor.[38]

For the most part, patients with myasthenia gravis do not seem to have any clinically relevant increase in the risk of cancer.[39,40] The exception is the subgroup of patients with thymoma. The increased cancer risk among patients with thymoma is the same whether or not they have myasthenia gravis.[41] Cancer was not overrepresented as a cause of death in a Norwegian population-based study.[36] Lymphomas have consistently been seen with a slightly increased frequency in patients with myasthenia gravis.[42] Azathioprine used as immunosuppressive treatment for myasthenia did not influence the general cancer risk in a Danish population study,[43] whereas this treatment used for inflammatory bowel disease slightly increased the cancer risk in a similar Dutch study,[44] and the risk of lip cancer also increased with high-dose azathioprine.[45]

Treatment for myasthenia gravis can increase the risk of coexisting disorders. Prednisolone necessitates prophylaxis against osteoporosis, and patients should be monitored for weight gain, elevations in blood glucose levels, and hypertension. Anticholinergic drugs for symptomatic treatment have transient and dose-limiting effects on the autonomic nervous system.

Concomitant disease represents a major challenge in treating patients with myasthenia gravis. An increasing number of patients are elderly, with reduced mobility, respiratory function, and quality of life due to the combined effects of several health issues.

THERAPY

DRUGS FOR SYMPTOMATIC THERAPY

All subgroups of myasthenia gravis respond to acetylcholinesterase inhibition (Fig. 1). Pyridostigmine is the preferred drug for the treatment of symptoms in all myasthenia gravis subgroups[2,11,12]

(Table 2). Neostigmine and ambenonium chloride are also inhibitors of acetylcholinesterase but are less effective than pyridostigmine in most patients. Increasing the release of acetylcholine presynaptically by administering 3,4-diaminopyridine or ephedrine usually has a mild beneficial effect, but it is rarely sufficient for practical use. Myasthenia gravis with muscle-specific kinase antibodies generally has a less favorable response to drugs administered for symptomatic therapy than do the other disease subgroups.[23] Juvenile myasthenia gravis often has an excellent response to pyridostigmine.[15,16] The dose of pyridostigmine is decided on the basis of the effect on muscle strength and dose-dependent side effects, most frequently involving the gastrointestinal tract. Typical side effects are diarrhea, abdominal pain or cramps, increased flatus, nausea, and increased salivation, as well as urinary urgency and increased sweating. Most patients are capable of adjusting their own dose, with possible variation from day to day. The effect of pyridostigmine remains unchanged over a period of years. For patients who have mild disease and nearly full remission with symptomatic therapy with drugs, no other drug therapy is recommended (Fig. 3A).

IMMUNOSUPPRESSIVE DRUG THERAPY

Most patients with myasthenia gravis need immunosuppressive medication to meet the treatment goals of full or nearly full physical function and high quality of life. Immunosuppressive medication is given to all patients who do not have a fully satisfactory functional result with symptomatic and supportive therapy alone. Expert consensus and data from limited controlled trials support the use of prednisone or prednisolone in combination with azathioprine as first-line treatment.[11,12,46] Prednisone and prednisolone are regarded as equally effective. Alternate-day dosing, which is often used to reduce the side effects of glucocorticoids, does not usually lead to unwanted disease fluctuations, but the evidence for reduced side effects is weak.[2] The dose is usually increased gradually (up to 60 to 80 mg on alternate days) to avoid an initial deterioration. After stable control of symptoms has been achieved and the addition of other treatments has further improved symptom control, the glucocorticoid dose should be slowly reduced to the lowest effective level, which is often 10 to 40 mg on alternate days. A major aim of treatment for ocular myasthenia gravis is to prevent generalization of the disease. Retrospective and observational studies strongly indicate that prednisolone monotherapy reduces this risk. Low-dose glucocorticoid treatment is therefore recommended by many experts for patients with ocular myasthenia gravis who have persistent symptoms and risk factors such as detectable acetylcholine receptor antibodies, an enlarged thymus,[47] or results of neurophysiological tests showing additional disease involvement of nonocular muscles.[13,48,49]

In most patients, azathioprine is added to prednisolone because this combination provides a better functional result with fewer side effects than prednisolone monotherapy.[50] If glucocorticoids are contraindicated or if the patient declines them, azathioprine can be given alone. The recommended dose is 2 to 3 mg per kilogram of body weight. Azathioprine inhibits purine synthesis and thus cell proliferation, with a particularly strong effect on B and T cells. Thiopurine methyltransferase activity should be tested before treatment, if the test is available, because low activity increases the risk that azathioprine will have toxic side effects.[51,52] Enzyme activity is absent in only 0.3% of the general population, whereas low enzyme activity is found in up to 10% of the population, with some variation reflecting genetic variants. Azathioprine is not recommended in patients with no thiopurine methyltransferase activity and should be used with caution and only at a low dose in patients with low activity. The effect of azathioprine on myasthenic weakness often takes months to appear, and patients need to receive other immunosuppressive medication during this period. Long-term treatment is safe in all patients, including those who are young.[43]

Most guidelines recommend mycophenolate mofetil for mild or moderate myasthenia gravis, even though an additional benefit with this medication was not proven in two short-term prospective studies, which had methodologic limitations.[53-55] The drug blocks purine synthesis and interferes with B-cell and T-cell proliferation. Methotrexate, cyclosporine, and tacrolimus are alternative secondary immunosuppressive drugs.[56-58] The effect of these drugs is probably similar to that of azathioprine.

Rituximab represents a potentially potent treatment for myasthenia gravis.[59] This monoclonal

Table 2. Drugs Used Most Frequently for the Treatment of Myasthenia Gravis.

Drug	Mode of Action	Dose	Side Effects	Risks and Contraindications
Pyridostigmine	Symptomatic; acetylcholinesterase inhibition	Single dose: 10–120 mg; daily dose: 40–600 mg	Cholinergic autonomic effects	Cholinergic crisis
Prednisone or prednisolone	Immunomodulation	Induction dose: 40–80 mg daily; stable dose: 5–20 mg daily; alternate-day treatment is an alternative	Widespread dose-dependent glucocorticoid effects	Gastrointestinal bleeding, cushingoid appearance
Azathioprine	Suppression of B and T cells	50–250 mg daily	Nausea, vomiting, tiredness, infections, night sweats	Leukopenia, liver toxicity
Mycophenolate mofetil	Suppression of B and T cells	1.5–2 g daily	Nausea, vomiting, diarrhea, joint pain, infections, tiredness	Leukopenia, progressive multifocal leukoencephalopathy; contraindicated during pregnancy
Rituximab	Suppression of B cells	0.5–1 g, repeated after 2 wk; can be repeated at 6-mo intervals	Nausea, infections, infusion-related problems	Progressive multifocal leukoencephalopathy
Methotrexate	Inhibition of folate metabolism	Gradual increase to 20 mg/wk	Nausea, infections, lung disease	Leukopenia, liver toxicity; contraindicated during pregnancy
Cyclosporine	Suppression of T cells and natural killer cells	2.5–5 mg/kg of body weight daily	Nausea, hypertension, infections, hypertrichosis	Kidney toxicity
Tacrolimus	Suppression of T cells and natural killer cells	3 mg daily	Nausea, infections, lung disease, hypertension, neuropsychiatric problems	Liver and kidney toxicity
Cyclophosphamide	Suppression of B and T cells	1–5 mg per kg administered by intravenous infusion every 4 wk for a limited period	Nausea, vomiting, alopecia, discoloration of nails and skin, infections	Leukopenia
Intravenous immune globulin	Suppression of B and T cells, neutralization of autoantibodies	2 g per kg administered over a period of 2 to 5 days	Nausea, headache, fever, hypotension or hypertension, local skin reactions	IgA deficiency, allergic reactions

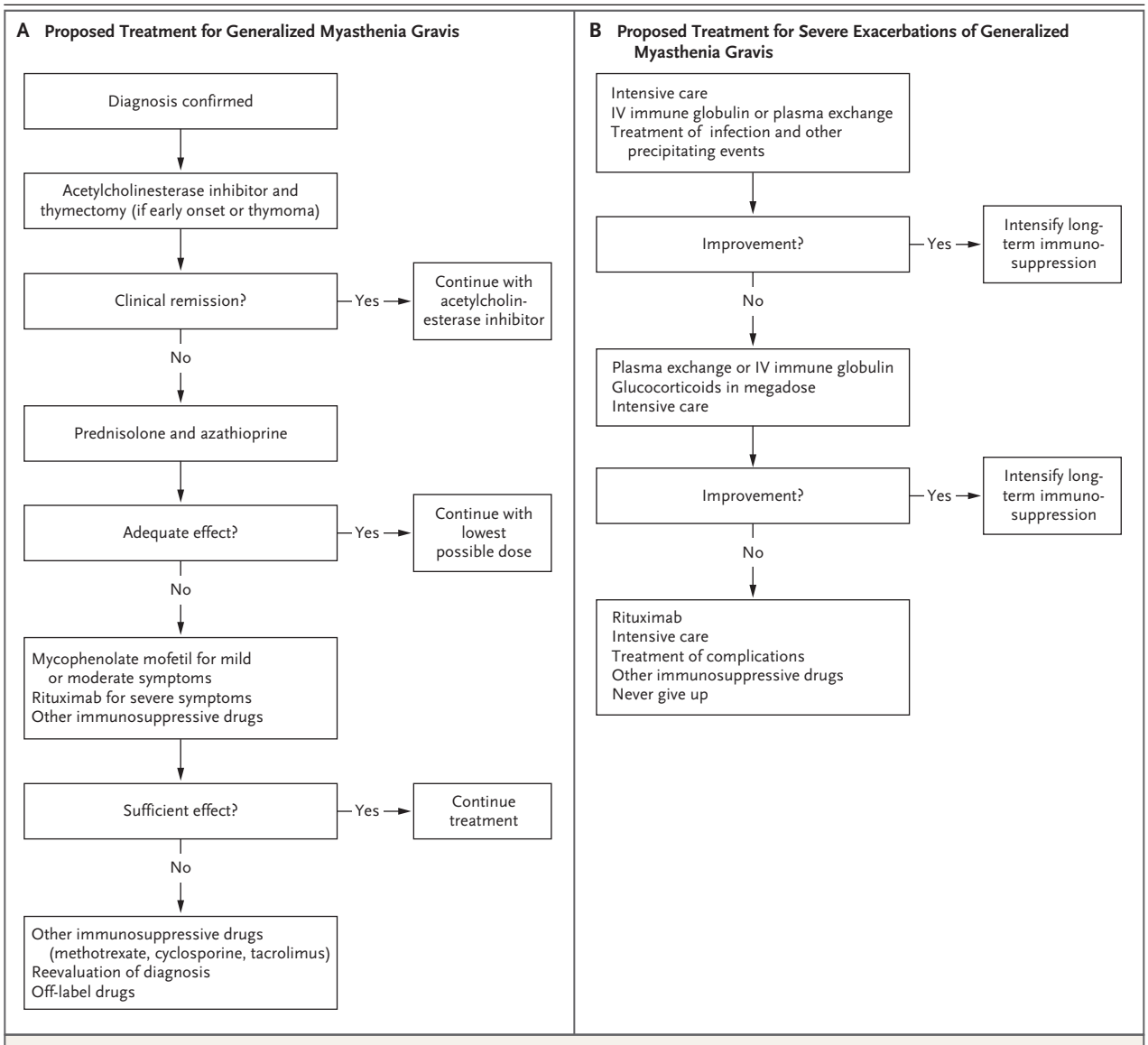

Figure 3. Proposed Treatment Algorithms for Generalized Myasthenia Gravis and for Severe Exacerbations of Generalized Disease.

Panel A shows treatments for generalized myasthenia gravis, and Panel B shows treatments for severe exacerbations. Both algorithms are from Gilhus and Verschuuren.[2] IV denotes intravenous.

antibody binds specifically to the CD20 surface antigen on B lymphocytes and should therefore be effective in antibody-mediated diseases such as myasthenia gravis. T-cell responses are also influenced by rituximab. A group of experts who recently issued guidelines for the management of myasthenia gravis could not reach a consensus on the role of rituximab.[11] Evidence from small case series indicates that two thirds of patients with severe myasthenia gravis and an insufficient response to prednisolone and azathioprine have a substantial improvement with rituximab.[60] A recommended induction dose has not been established. The treatment should be repeated if the symptoms recur after several months. Concerns regarding rituximab are the risk of precipitating additional autoimmune disorders and JC virus–related progressive multifocal leukoencephalopathy. The treatment scheme for generalized myasthenia gravis is summarized in Figure 3A.

A number of monoclonal antibody drugs have

a proven effect in the treatment of other autoimmune disorders. They interfere with B cells, T cells, complement, or other immunoactive elements.[61,62] Formal evidence and cost–benefit information are lacking for the use of these drugs in patients with myasthenia gravis, although preliminary observations and mechanisms of drug action make several of them promising alternatives. Autologous hematopoietic stem-cell transplantation was recently reported to provide stable and treatment-free remission in seven patients.[63]

Patients with myasthenia gravis that develops late or is associated with thymoma or muscle-specific kinase antibodies tend to have the most severe disease and usually need long-term immunosuppressive drug treatment, although some patients with late-onset myasthenia gravis have disease that is milder and more similar to early-onset disease. The presence of antibodies against muscle-specific kinase, titin, ryanodine receptor, or Kv1.4 is an indication for immunosuppression. Myasthenia gravis associated with muscle-specific kinase antibodies has a particularly favorable response to rituximab.

THYMECTOMY

In patients with a thymoma and myasthenia gravis, thymectomy should be performed to remove the tumor. A benefit after total thymectomy has been reported for this subgroup; an even greater benefit of total thymectomy has been reported for patients with early-onset myasthenia gravis without a thymoma. The thymus has a key role in inducing acetylcholine receptor antibody production in patients with myasthenia gravis.[64] Many studies have compared the outcomes for patients who undergo thymectomy with the outcomes for those who do not, and nearly all the studies have shown a better outcome in the thymectomy group.[65,66] A recent international, randomized, controlled trial involving 126 patients with early-onset or late-onset myasthenia gravis confirmed a distinct benefit from early thymectomy, supporting thymectomy in patients with generalized disease, a disease duration of less than 3 to 5 years, an age of less than 60 to 65 years, and symptoms not fully relieved by anticholinesterase drugs.[67] Patients who underwent thymectomy, as compared with those who did not receive surgical treatment, had significant reductions in symptoms, immunosuppressive drug treatment, and exacerbations during 3 years of observation. The differences were regarded as clinically meaningful. All thymic tissue needs to be removed, including the tissue embedded in mediastinal fat. Video- and robot-assisted methods minimize the surgical procedure, are preferred by most patients, and provide the same benefit as traditional open, transsternal thymectomy as long as all tissue is removed.

Guidelines and consensus statements recommend early thymectomy for patients with early-onset myasthenia gravis.[2,11,12] These patients most often have thymic hyperplasia. Thymectomy should also be considered in children.[68] Most patients with late-onset disease have an atrophic thymus.[64] However, thymic hyperplasia can occur in younger patients in the late-onset subgroup. Thymectomy should also be considered in patients with generalized myasthenia gravis who have acetylcholine receptor antibodies and whose symptoms developed at the age of 50 to 65 years,[67] especially when the biomarkers show similarities with early-onset disease. Current evidence does not support thymectomy in patients with myasthenia gravis and muscle-specific kinase or LRP4 antibodies.[11] Thymectomy is also not recommended for patients with ocular myasthenia, since there is insufficient evidence that surgery prevents generalization or results in remission. However, it has been argued that thymectomy should be considered for the treatment of ocular myasthenia gravis when drug treatment has failed, the patient has acetylcholine receptor antibodies, and neurophysiological tests indicate a risk of generalized disease.[13]

Thymectomy is usually not recommended for patients in whom all muscle antibody tests are negative. However, some of these patients have acetylcholine receptor antibodies that are not detected by routine assays. Therefore, in patients with negative muscle antibody tests who have generalized disease with biomarkers similar to those in patients with early-onset disease, thymectomy may be considered if the disease fails to respond to immunosuppressive drugs.[11]

MYASTHENIA GRAVIS CRISIS

Patients with worsening weakness who require intubation or noninvasive ventilation should receive fast-acting immunosuppressive agents and intensive care. An impending myasthenic crisis with rapid worsening and severe weakness war-

rants a similar intervention.[69] The threshold for deciding to admit a patient to an intensive care unit should be low. Increasing generalized weakness, respiratory dysfunction, cardiac dysfunction, severe infection, and coexisting conditions are all relevant factors to consider in making this decision. Measures such as vital capacity and blood gas levels have limited value, since deterioration can be rapid and unexpected as a result of the characteristic myasthenic fatigability.

Intravenous immune globulin and plasma exchange are regarded as equally effective in treating severe myasthenia gravis.[70-72] The choice between them depends on individual patient factors and institutional experience, availability, and tradition. Intravenous immune globulin is often regarded as more convenient with less severe side effects. A patient may have a response to one treatment approach but not the other. The treatment effect is restricted to a period of a few months and should therefore be combined with long-term immunosuppressive treatment. In some patients, the treatment response is delayed. Vigorous immunosuppressive treatment combined with intensive care should be maintained as long as necessary to induce remission. Myasthenic crisis with a need for respiratory support is now rare in patients with myasthenia gravis, and mortality during myasthenic crisis is also low.[69] The treatment scheme for severe exacerbations of myasthenia gravis is shown in Figure 3B.

SUPPORTIVE THERAPY AND MANAGEMENT

Physical activity and systematic training programs at a low or medium level of intensity should be recommended for patients with myasthenia gravis and tailored to the individual patient.[2,11,12] Overweight should be avoided. Assistive devices can be helpful with ocular symptoms.[13]

Muscle relaxants, penicillamine, and some antibiotics (fluoroquinolones, macrolides, and aminoglycosides) should be avoided, if possible, in patients with myasthenia gravis. Statins can aggravate and unmask myasthenia gravis, but the presence of myasthenia gravis is not regarded as a contraindication if statins are needed, and the indications for statin treatment in patients with myasthenia gravis are the same as the indications for such treatment in patients without myasthenia gravis.[73,74] If a drug appears to be indicated, vigilance in looking for worsening of weakness is important when the new drug is introduced, and this approach is preferable to withholding the drug altogether.

Respiratory insufficiency due to diaphragmatic and intercostal muscle weakness is a major threat. Special attention should be paid to respiratory function during any surgical procedure, including thymectomy, in a patient with myasthenia gravis. Optimal treatment of all coexisting conditions is an important component of the management of myasthenia gravis. This can be a particular challenge in elderly patients with multiple coexisting conditions.

Oral administration of pyridostigmine and prednisone or prednisolone is safe during pregnancy.[75,76] Current information indicates that treatment with azathioprine and cyclosporine is safe as well. Mycophenolate mofetil and methotrexate are contraindicated during pregnancy because of teratogenic risks. Women are advised to avoid pregnancy for up to 1 year after finishing rituximab treatment. Intravenous immune globulin and plasma exchange are useful for worsening weakness during pregnancy. Lactation should be encouraged. Transient neonatal myasthenia occurs in 15% of children as a result of transplacental IgG transfer of antibodies against acetylcholine receptor, muscle-specific kinase, or LRP4.[76,77]

FUTURE DIRECTIONS

With specialized treatment, the great majority of patients with myasthenia gravis do well. They are able to perform daily tasks and maintain a near-normal quality of life. However, only a few patients have a full remission, and most do not even have a full pharmacologic remission. Although the disease-inducing antibodies have been characterized in detail, the treatment is far from immunospecific. Data from prospective, blinded, controlled studies comparing treatments are lacking, and there have been few well-controlled studies of individual drugs and nondrug interventions. Apart from paraneoplasia associated with thymoma, the causes of myasthenia gravis are unknown.

Monoclonal antibodies have selective binding and a high specificity regarding immunologic actions but do not necessarily have any specificity for the treatment of myasthenia gravis. Ongoing trials are evaluating more targeted immunoactive therapy. Antigen-specific treatment is

being developed for myasthenia gravis associated with acetylcholine receptor, muscle-specific kinase, and LRP4 antibodies, through interaction with regulatory B or T cells.[7,78,79]

Even with today's knowledge and available treatments, it is a challenge to find the optimal treatment for the individual patient. Specialized diagnostic procedures and expert follow-up over time improve treatment results. Standards and possibilities for the diagnosis and treatment of myasthenia gravis show great variation within and between countries. Implementing best-practice standards universally represents a major challenge. This is especially important because myasthenia gravis is a potentially reversible disorder with treatment options that can make a huge difference for the patient.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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