

# Advances in the Treatment of Myasthenia Gravis

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## Abstract and Introduction

### Abstract

Myasthenia gravis (MG) should be classified according to antibody status (acetylcholine, MuSK, LRP4, titin), thymus (hyperplasia, neoplasia, atrophy), age at debut (< or >50 years), symptom localization (generalized, ocular) and severity. With optimal treatment, the prognosis is good in terms of daily functions, quality of life and survival. Symptomatic treatment with acetylcholine esterase is usually combined with immunosuppression. A combination of prednisolone and azathioprine remains the first choice alternative, whereas rituximab is a promising second choice drug for severe generalized MG. Thymectomy is recommended for early-onset, generalized MG and for thymoma MG. In acute exacerbations including MG crisis, intravenous immunoglobulin and plasma exchange have good and similar effects. MG in young females needs therapeutic considerations regarding potential pregnancy.

### Introduction

Myasthenia gravis (MG) is an autoimmune and antibody-mediated neuromuscular disease that leads to muscle weakness and fatigue. The weakness can be focal or generalized. Symptoms and signs are restricted to striated skeletal muscles, and all such muscles can be affected. MG has a total prevalence of 140 per million in Caucasian populations, with an annual incidence of 15 per million.<sup>[1,2]</sup> Whereas prevalence and incidence have remained stable and with a constant female preponderance in those experiencing symptom onset before 50 years of age, there has been an increase of MG in the elderly population, and especially in males.<sup>[3]</sup>

MG without any treatment has a 10-year mortality, which is thought to be around 50%,<sup>[4]</sup> and is thus a truly severe disease (gravis). However, with today's optimal treatment including a combination of immunosuppression, symptomatic and supportive therapy, there should be no increased mortality for MG patients.<sup>[5]</sup> Quality of life with MG is generally very good, although most patients experience moderate restrictions regarding selected tasks involving muscular strength and repetitive movements.<sup>[4]</sup>

MG diagnosis is in most cases straightforward for specialists, with typical symptoms and signs and detection of autoantibodies with very high MG specificity, i.e., against acetylcholine receptors (AChR) or MuSK.<sup>[6]</sup> The diagnosis can be supported by neurophysiology, imaging of the mediastinum and response to acetylcholine esterase inhibitors. In antibody-negative cases, the diagnostic process needs more consideration. Extensive neurophysiological testing is crucial. In elderly patients, cerebrovascular disease or amyotrophic lateral sclerosis can be suspected initially, and even more so as the temporal variation with weakness and fatigue is not always prominent.

## Pathogenesis

MG patients should always be diagnosed according to disease subgroup. The MG subgroups reflect pathogenesis as well as therapeutic considerations:

- Early-onset generalized MG
- Late-onset generalized MG
- MG with thymoma
- Ocular MG
- Anti-MuSK MG
- Anti-LRP4 MG
- Autoantibody-negative MG

The distinction between early- and late-onset MG is usually set at a debut age of 50 years.<sup>[7]</sup> Regarding pathogenesis and therapeutic response, this age limit is far from sharp. Thymic hyperplasia, female gender, other autoimmune disorders and HLA-B8, -DR3 support the pathogenetic early-onset subgroup. Approximately 10–15% of all MG patients have a thymoma; 30% of all patients who have a thymoma develop MG at some stage.<sup>[8]</sup> In thymoma patients, MG represents a paraneoplastic disorder. Ocular signs and symptoms are typical for MG, and also in the initial phases of the disease. In a minority of patients, the disease remains purely ocular. Ocular MG is defined as MG with still only ocular symptoms after more than 2 years.<sup>[7]</sup>

Autoantibodies against molecules in the postsynaptic muscle membrane relevant for neuromuscular transmission are the hallmark for MG. 80% of patients with generalized MG symptoms have antibodies against AChR, 1–10% against MuSK and very few against LRP4.<sup>[9,10]</sup> Among the remaining patients, some have low-affinity and/or low-concentration antibodies against AChR or more rarely against MuSK; such antibodies are not detected by the standard diagnostic techniques.<sup>[11]</sup> Some have autoantibodies against yet undefined membrane molecules or epitopes, and a few probably have nonautoantibody-mediated disease.

The thymus plays an important pathogenetic role in AChR antibody-associated MG. Most patients, and especially those with early-onset MG, have an enlarged and hyperplastic thymus. All thymoma patients have AChR antibodies, and even some thymoma patients without overt MG symptoms have such antibodies.<sup>[12]</sup> Negative T-cell selection, crucial for discrimination between self and nonself, takes place in the thymus. Defunct intrathymic negative selection can lead to autoimmune disease. It is interesting that thymus pathology is specific for MG and is only rarely linked to other autoimmune disorders.<sup>[6–8]</sup> The autoimmune regulator has gained interest as a potentially important intrathymic molecule for MG pathogenesis.<sup>[13,14]</sup> Autoantibodies against cytoplasmic muscle proteins such as titin and ryanodine receptor are characteristic for thymoma MG and also for a subgroup of late-onset MG.<sup>[15]</sup>

The primary cause of MG is unknown, except for those with a thymoma. A virus infection either generally or within the thymus has been suspected but is not yet proven.<sup>[16–18]</sup> Genetic predisposition takes place, the influence of HLA genes being most pronounced,<sup>[19]</sup> but genes do not represent a major cause. Epigenetic causative factors have not been defined so far.

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## Symptomatic Treatment

Acetylcholine esterase inhibition increases the availability of acetylcholine in the neuromuscular synapse and increases the chance of activating AChRs as a response to acetylcholine presynaptic release in MG patients. Thus, acetylcholine esterase inhibitors have a distinct symptomatic effect in most MG patients. The effect tends to be better in AChR antibody-positive patients than in those with MuSK antibodies.<sup>[7,20]</sup> Pyridostigmine is the favored drug by most patients.<sup>[7]</sup> Ambenonium chloride is an alternative, but is not available everywhere. The optimal treatment should balance effect and dose-related side effects, these mainly being caused by cholinergic stimulation in the autonomic nervous system. No long-term negative effect of this cholinergic treatment has been demonstrated.

Drugs increasing acetylcholine release from the presynaptic nerve terminal, such as 3,4-diaminopyridine, are usually much less effective, and they are normally not used for autoimmune MG. They are, however, preferred as symptomatic treatment for Lambert Eaton myasthenic syndrome.<sup>[21]</sup> Most MG patients use an acetylcholine esterase inhibitor daily, in an individually tailored dose, and with possibilities for dose adjustment and variation according to their physical needs. For the majority, symptomatic treatment alone is not sufficient and should be combined with immunosuppressive therapy.

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## Immunosuppressive Treatment

### Drug Treatment

A combination of corticosteroids (prednisone or prednisolone) and azathioprine remains the first-choice immunosuppressive drug alternative for most MG patients.<sup>[4,6,7,22,23]</sup> These drugs have a well-known and documented effect. Corticosteroids act after a few weeks, whereas the azathioprine effect is delayed for several months and up to a year. Corticosteroids in high doses usually have relevant long-term side effects. Thus, combining azathioprine with a relatively low, alternate day dose of prednisolone (10–60 mg) is recommended. The corticosteroid dose is usually reduced gradually. In some patients, the drug can be withdrawn. Azathioprine should be regarded as a long-term drug. When effective and without side effects, it is usually continued for years and is sometimes life-long. Azathioprine also has a dose-response curve, so that the dose can be increased and decreased according to effect and side effects. Weekly hematological monitoring is necessary during the first months of therapy as leucopenia is a feared side effect. A moderate

reduction in blood cells is expected as part of the drug effect. Long-term tolerance of azathioprine is generally good. No increased occurrence of malignant disease has been proven,<sup>[5]</sup> and the drug does not increase the risk of other inflammatory disorders.<sup>[23]</sup> Infections are not reported with increased severity or frequency in MG patients treated with azathioprine and/or prednisolone.<sup>[23]</sup> MG patients with thymoma, with antibodies against titin and/or ryanodine receptor, or with previous MG-related respiratory dysfunction, usually need long-term immunosuppression.<sup>[4,6,7,22]</sup> Patients with focal or less severe symptoms, thymectomized for thymic hyperplasia and younger patients can more often reduce or withdraw the immunosuppressive drug treatment after being in a stable condition for some time. For patients with purely ocular MG, prednisolone in a low dose may be sufficient. Azathioprine and prednisolone are also used in young females. Both drugs are regarded as relatively safe during pregnancy. However, for general safety reasons, it is recommended that women plan pregnancies for periods when immunosuppression is not needed, or to withdraw immunosuppressive drugs temporarily before pregnancy if possible.<sup>[4,7,24]</sup> Prednisolone, and also IVIg, plasma exchange and acetylcholinesterase inhibitors are all recognized as safe in pregnancy.

For severe, generalized MG not responding to prednisolone and azathioprine, rituximab should be regarded as an early alternative. Rituximab is a monoclonal antibody with a direct effect on B cells. The binding of rituximab to CD20 molecules on B lymphocytes has widespread consequences for many aspects of immune function. The binding of rituximab to B cells is specific, but the resulting immune changes are widespread and much less specific. Rituximab is regarded as especially effective in antibody-mediated autoimmune disorders such as MG. In recent years, a lot of case reports and several uncontrolled patient series have been published, clearly demonstrating the disease-modifying effect of rituximab in MG.<sup>[20,25,26]</sup> The effect is also apparent for MuSK MG. Rituximab may even be more effective for this MG subgroup.<sup>[20]</sup> The main limitation for this treatment is risk of severe infection. As there is a lack of controlled MG studies, approved treatment protocols for MG do not exist. It has been suggested that rituximab can be tried in somewhat lower doses than has been customary for rheumatological disorders.<sup>[27]</sup> This may reduce the risk of side effects. Patients at risk may be defined from pretreatment screening for the presence of specific viruses. The effect on B cells can be monitored.<sup>[27]</sup> The effect on AChR or MuSK antibody concentrations does not seem to be of definite value in predicting sufficient dose or future effect. Long-term results are not yet known, including the need for long-term treatment, but a remission lasting for more than a year has been reported in many patients after two to four initial doses.

For milder MG not responding to prednisolone and azathioprine, mycophenolate mofetil should be regarded as an alternative.<sup>[4,7,23]</sup> The drug failed to demonstrate an impact in placebo-controlled studies as an add-on therapy to prednisolone.<sup>[28,29]</sup> Its advantages are few side effects, easy administration and a clinical response being evident after just a few weeks. Methotrexate and cyclosporine are alternative immunosuppressive drugs with a proven effect on generalized MG.<sup>[30,31]</sup> Tacrolimus should also be on the list of possible MG drugs.<sup>[32]</sup> A lot of new immunoactive drugs are marketed or in the pipeline, most of them being monoclonal antibodies, and they therefore bind specifically to one set of epitopes in the immune system. This does not, however, necessarily mean that they have immunospecific actions. These drugs are mostly being tested in severe and relatively common autoimmune disorders. MG is not among them. That represents a challenge; their potential benefit in MG treatment often remains unknown.

### Thymectomy

The thymus plays a key pathogenetic role in MG with AChR antibodies. This is illustrated by the clinical improvement seen after thymectomy in patients with a hyperplastic thymus. No well-controlled, randomized and prospective studies have been undertaken for thymectomy in MG, similar to what is true for most other surgical procedures. However, published evidence has led to clear recommendations of early thymectomy in patients with early-onset MG.<sup>[7,23,33]</sup> Thymus hyperplasia seen on a CT scan or MRI of the mediastinum strengthens the indication for thymectomy. Thymectomy usually has an excellent effect on childhood-onset MG and it can be safely undertaken in children as young as 5 years.<sup>[7]</sup> This indicates that the thymus exerts its major physiological role very early in life. Patients with low-affinity AChR antibodies have the same thymus pathology as those with ordinary AChR antibodies.<sup>[11]</sup> Thymectomy for this group should be undertaken according to the same criteria. The presence of cytoplasmic antimuscle antibodies in addition to anti-AChR antibodies (anti-titin and antiryanodine receptor) probably makes the improvement of MG weakness after thymectomy less likely. For those 10–15% of MG patients with a thymoma, the tumor should be surgically removed. Nearly all thymoma MG patients have anti-titin antibodies, half of them in addition antiryanodine receptor antibodies.

The effect of thymectomy on late-onset MG is doubtful. However, deciding on whether to undertake thymectomy or not from age of onset alone is not recommended. In a patient with generalized MG, for whom symptoms started at age 50–65 years, with an enlarged thymus on imaging, and antibodies against AChR only, thymectomy should be recommended.

For MG with ocular symptoms only, thymectomy is not recommended according to existing evidence.<sup>[7]</sup> For patients with

anti-MuSK MG and anti-LRP4 MG, no pathogenetic significance of the thymus gland has been shown. [10,20] Thymectomy is not recommended for such patients.

As thymectomy has been an established treatment for MG for decades, and with clinical evidence strongly supporting the positive effect for defined MG subgroups, it is unlikely that a prospective, well-controlled study of unselected MG patients will ever occur. The multicenter initiative for such a study has succeeded in recruiting only a few of all available MG patients, resulting in a considerable and undefined selection.

Total thymectomy is necessary to obtain a therapeutic effect. This can be achieved either by trans-sternal access with a sternum split or with a video-assisted thoracoscopic procedure. [34] The patient should not have severe weakness with a threatening respiratory deficit at the time of surgery. Preoperative IvIg treatment or plasmapheresis is necessary in severe or moderately severe MG cases. In conclusion, thymectomy represents a well-established, safe and recommended treatment for major MG subgroups.

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## Supplementary Treatment

MG patients should find the optimal balance between physical activity and rest. It is not possible to cure the weakness by active physical training. However, most MG patients are more passive than they need to be. Physical activity and physical training of low to medium intensity is recommended. [7] On the other hand, patients should be aware that fatigue is the hallmark of the disease and that rest after exercise is usually needed. There are no controlled studies published regarding the effect of physical training in MG.

Weight control is of importance in MG, especially in patients with involvement of their respiratory function. [7] The negative effect of being overweight is thought to be the same as for other disorders involving muscle weakness.

All infections can trigger an exacerbation in MG. Infections of the lower respiratory tract are especially important as they can impair the lung function directly. Infections in MG patients should be treated early and vigorously. Complications and exacerbations of infections should also be avoided by preventive measures.

Some drugs inhibit neuromuscular signal transmission. Such drugs should be avoided in MG. Before prescribing a new drug to a MG patient, one should always check for information about interference with neuromuscular function. Antibiotics, anesthetics and sedatives should be evaluated in particular. [7]

MG is not usually markedly influenced by pregnancy. [35,36] Postpartum worsening of MG weakness has been described. All types of MG autoantibodies are of the IgG class, and they therefore pass across the placenta to the fetus. Between 10 and 15% of the babies of MG mothers have a transient neonatal MG, lasting for days or a few weeks. Neonatal MG is well known for MG with AChR antibodies, and has also been described for anti-MuSK MG. The neonatal weakness usually needs no treatment, but acetylcholine esterase inhibitors, intravenous IvIg and respiratory support should be given if necessary. Respiratory weakness represents the main threat, but also sucking and swallowing difficulties can be of significance. Neonatal myasthenia gives no weakness after the postpartum period. In a small percentage of MG mothers, the antibodies have a more severe effect on the developing fetus. Due to severe movement inhibition *in utero*, these babies develop arthrogryposis with malformations and hampered limb development. [37] Skeletal malformations were reported in three out of 127 MG births, but the total malformation rate was not significantly increased compared with a very large control group. [24] MG does not seem to be among the major causes of arthrogryposis. [38] MG mothers for whom the disease has had a severe influence on the developing child (repeated spontaneous abortions, malformations, severe neonatal MG) should in their next pregnancies be treated with plasmapheresis or IvIg to reduce the concentration of the causative autoantibodies and minimize the risks.

Acetylcholine esterase inhibitors, prednisolone and IvIg are regarded as safe for the developing fetus, and can therefore be given to women in fertile age and during pregnancy. Other immunosuppressive drugs could have negative effects. However, good evidence is generally lacking, especially so for the new drugs such as rituximab. Azathioprine has been widely used for many years, and the general view is that the drug has very low, if any, teratogenic risks. The general recommendation is to avoid all drugs except acetylcholine esterase inhibitors, prednisolone and IvIg during pregnancy, but at the same time, continuous immunosuppression may be necessary in severe MG. In such cases, azathioprine is probably the safest alternative. Lactation should be supported in MG, as well as in women using immune-active drugs.

MG patients have an increased risk for all other autoimmune disorders. Such disorders should be treated in the ordinary way. Immunosuppressive drugs with an effect on both conditions should be preferred. For MG patients with a thymoma,

the tumor should be treated by surgical removal. Supplementary treatment with radiation and cytostatic drugs is usually only regarded as necessary if there is proven local infiltration.

There are several reports of nonatherosclerotic, noncoronary heart disease in MG. [39,40] Such cases usually have severe generalized MG, antibodies against muscle antigens outside the neuromuscular junction and a thymoma. An autoimmune cardiomyopathy, potentially influencing cardiac conduction as well, has been suspected. It has been difficult to confirm increased risk of cardiac involvement in MG cohort studies. [41] Cardiac monitoring is recommended during severe MG exacerbations, and a general awareness of cardiac function is necessary, especially in generalized MG and with a broad spectrum of muscle antibodies. Cancer (apart from thymoma) does not seem to occur with any markedly increased frequency in MG. [5,42]

### Treatment of MG Crisis

Respiratory failure is a big threat in MG. The respiratory function can deteriorate rapidly from being near normal to a need for artificial ventilation. Awareness of respiration is especially important during infections and postoperatively. There should be a low threshold for acute hospitalization of MG patients with suspected respiratory dysfunction, and similarly a low threshold to observe MG patients in an intensive ward. Cardiac function should be monitored in MG patients with respiratory failure or threatening failure. [40] Due to the widespread use of effective immunosuppressive treatment in MG patients, MG crisis and severe MG exacerbations occur much more rarely than before. [6,23]

Ivlg and plasma exchange are the two effective and alternative treatment procedures for severe MG exacerbations. In a couple of prospective and controlled studies, these two treatments have been shown to be similar. [43–46] The effect is rapid, occurring after just 3–5 days. The treatment is well tolerated in most patients. Standard protocols include treatment for 3–6 days. The response rate is at least 65%. Patient responders are not always the same for Ivlg and plasma exchange, so that the two treatments should be given in sequence to nonresponders. Although this is not clearly supported by the prospective controlled trials, it is thought that plasma exchange has a slightly more rapid effect, but is also associated with more frequent and severe side effects compared with Ivlg. A small minority of MG patients need ventilatory support for an extended period of time. These patients should receive intense immunosuppressive treatment (high doses, long time, several drugs tried), and the situation should always be regarded as reversible, even after weeks and months.

Ivlg and plasma exchange can be given to induce a rapid improvement in severe MG, often combined with the initiation or change of long-term immunosuppressive drug therapy or thymectomy. Similarly, this treatment can be used to prevent exacerbations and the need for ventilatory support, for example, prior to surgery, including thymectomy.

In acute MG exacerbations, it is a key point to identify and treat the cause of the exacerbation, which is most often an infection. All patients with a severe exacerbation should be re-evaluated for their long-term immunosuppressive drug treatment. In most cases, this should be intensified by increasing the dose, adding or changing immunosuppressive drugs, or both.

Registry-based population studies from highly developed countries have shown that the mortality rate for MG patients has become similar to that of the general population. [5] This is also true for deaths due to respiratory dysfunction. This shows that MG crisis can be well treated, and also reflects the rarity of severe exacerbations in a well-treated patient population.

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## Conclusion

Optimal treatment of MG depends on correct subclassification of the disease in all individual patients. This includes classification according to autoantibody (AChR, MuSK, titin, other), thymus status, symptom generalization, age of onset and severity. If acetylcholine esterase inhibitor treatment does not give a remission, early thymectomy should be undertaken in early-onset MG, and in those with a thymoma. Immunosuppressive drug treatment should be given to the other patients, and also when thymectomy does not have sufficient effect on MG symptoms. Prednisolone and azathioprine are recommended as first choice drugs, usually in combination. Several second choice options exist. Rituximab has emerged as effective for severe MG. Intense and general treatment is crucial if threatening respiratory failure occurs or is suspected. MG has a good prognosis with no increased death rate, with most patients maintaining all their daily functions including professional working capacity. Follow-up by specialists is necessary to secure optimal treatment regarding effect on muscle strength, as well as to avoid unnecessary side effects. Antibody-specific treatment of the well-characterized autoimmune dysfunction is not yet possible. The cause of MG is unknown apart from in thymoma cases, where the tumor initiates specific autoantibody production. Prevention of the disease, or a cure, remains a

challenge for the future, when disease cause(s) have been identified.

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## Future Perspective

Although today's MG treatment is effective in most patients, leaving them with relatively mild symptoms and moderate side effects, the treatment is by no means specific or curative. It remains a paradox that the pathogenesis of the disease is known in detail, pin-pointing specific autoantibodies as the cause of the symptoms, but that the immune system is still treated without using this specific knowledge. The aim should be to suppress the anti-AChR, anti-MuSK or anti-LRP4 immune response in MG patients without influencing the rest of the immune system. That means treating MG patients at the specific autoantibody, B-cell or T-cell level.

Until an antigen-specific MG treatment is available, it remains a challenge to evaluate new and promising immunoactive drugs for MG. Many such drugs are licensed for a hematologic disease, multiple sclerosis or in oncology, and many more are in the pipeline. Several of them would most probably be effective in MG as well. However, it is difficult to get experience regarding such a rare disease, and for a disease where the great majority of patients are well controlled with the present standard therapy. Prospective and controlled studies will probably not be undertaken for most of these potential treatments.

The ultimate aim is to identify the cause of MG, and then to prevent or treat this cause. Genetic predisposition is relevant, but external causative factors are probably more important. Intrathymic Epstein-Barr virus infection has been suggested, but any presence of virus in the MG thymus has not been confirmed. <sup>[16–18]</sup>

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## Sidebar

### Executive Summary

#### ***Pathogenesis & epidemiology***

- Myasthenia gravis (MG) should be subgrouped into early-onset, late-onset, thymoma, ocular, anti-MuSK, anti-LRP4 and antibody-negative MG.
- MG has a prevalence of 140 per million, and an annual incidence of 15 per million.
- The cause of MG is unknown.

#### ***Symptomatic treatment***

- Acetylcholine esterase inhibitors are used by most MG patients.
- Dose of acetylcholine esterase inhibitors should be balanced according to effect and side effects.
- Long-term use of acetylcholine esterase inhibitors is safe.

#### ***Immunosuppressive drug treatment***

- A combination of prednisolone and azathioprine represents first-choice treatment.
- Rituximab is a promising second-choice drug for severe generalized MG.
- Immunosuppressive drug treatment should be actively undertaken until all major symptoms are in a stable remission.

#### ***Thymectomy***

- Early thymectomy is recommended for early-onset, generalized MG with thymic hyperplasia and acetylcholine receptor antibodies.
- Early thymectomy is recommended for thymoma MG.
- All thymus tissue needs to be removed surgically.

## Crisis

- Intensive care and ventilatory support is life-saving in severe MG exacerbations.
- Intravenous immunoglobulin and plasma exchange have a similar effect, and can be given in sequence if necessary.
- MG crisis and severe exacerbations are always reversible.

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Papers of special note have been highlighted as:

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