Myasthenia Gravis – Optimal Treatment in Severe Disease

Nils Erik Gilhus
Department of Clinical Medicine, University of Bergen and Department of Neurology, Haukeland University Hospital, Bergen, Norway

Myasthenia gravis (MG) is an autoimmune disorder, where antibodies bind to the postsynaptic membrane at the neuromuscular junction. These antibodies induce acetylcholine receptor (AChR) dysfunction and destruction, leading to muscle weakness. Fluctuations are typical for the MG weakness, being more prominent after repeated muscle use. Patients with MG are separated into subgroups according to localisation of muscle weakness, age, antibody specificity and thymus pathology. All groups have a minority of patients with severe and therapy-resistant MG. Biomarkers may indicate a more severe prognosis. First-line MG therapy includes pyridostigmine, an acetylcholine esterase inhibitor that gives symptomatic relief, as well as immunosuppressive drugs. European guidelines recommend the combination of prednisolone and azathioprine. Thymectomy is recommended in patients with AChR antibodies, generalised disease and age of onset <65 years, as well as in nearly all patients with a thymoma. Second-line therapies, necessary in many severe cases, include mycophenolate, rituximab, methotrexate, cyclosporine and tacrolimus. Complement inhibitors and FcRn inhibitors represent new therapies that seem to be effective. Their clinical use should depend also on cost–benefit considerations. Intravenous immunoglobulin and plasma exchange are fast-acting therapies used for acute exacerbations and in situations where extra muscle strength is necessary, for example before surgery. Some patients receive this therapy repeatedly. Supportive therapy is important for all patients, and this includes an adapted training programme. In patients with severe MG and an unsatisfactory response to several treatments, the clinician should consider comorbidity. Especially in elderly patients, optimal treatment for several combined conditions may represent a challenge. The MG diagnosis should always be revisited in therapy-resistant cases.

Keywords
Myasthenia gravis, treatment, severe disease, autoimmunity, acetylcholine receptor antibodies, MuSK antibodies, thymus, immunosuppressive therapy

Disclosure: Nils Erik Gilhus has received speaker’s honoraria from Octapharma, Alexion and UCB, and consulting honoraria from Argenx and Ra Pharma.

Compliance with Ethics: This article involves a review of the literature and did not involve any studies with human or animal subjects performed by the author.

Authorship: The named author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, takes responsibility for the integrity of the work as a whole, and has given final approval for the version to be published.

Access: This article is freely accessible at touchNEUROLOGY.com. © Touch Medical Media 2020.

Received: 10 December 2019
Accepted: 24 January 2020
Published Online: 7 February 2020
Citation: European Neurological Review. 2019;14(2):81–5
Corresponding Author: Nils Erik Gilhus, Department of Clinical Medicine, University of Bergen, 5020 Bergen, Norway. E: nils.gilhus@uib.no

Support: No funding was received in the publication of this article.
more severe disease are MuSK antibodies, an increase in antibody concentration during treatment, additional antibodies against the muscle antigens titin and ryanodine receptor, thymoma, and a generalised weakness with involvement of respiratory and bulbar muscles.3 Patients with such biomarkers should be treated more vigorously and long-term.

First-line symptomatic treatment

Acetylcholine esterase inhibition increases muscle strength in MG due to increased availability of the transmitter acetylcholine at the neuromuscular synapse. Pyridostigmine is the favoured drug.13 Ambenonium is an alternative, but is usually less effective, has more variable bioavailability, and is not available in all countries. Most patients manage themselves to find their optimal drug dose, balancing effect on muscle strength and side effects. Dose-limiting side effects include gastrointestinal pain, diarrhoea, increased salivation and other manifestations from the autonomic nervous system. More than 90% of patients with MG with AChR antibodies and with severe disease use a daily acetylcholine esterase inhibitor for the symptomatic effect.9,14 The effect does not diminish over time. Acetylcholine esterases usually have little or no effect in MG with MuSK antibodies, and patients with MuSK MG may even be intolerant to such drugs.7 Pyridostigmine is regarded as safe during pregnancy.15,16

First-line immunosuppressive treatment

Patients with severe MG need to start immunosuppressive therapy when they have been diagnosed; symptomatic therapy alone is not enough (Table 2). The combination of prednisolone and azathioprine is recommended as the first-line treatment in most guidelines and consensus reports.1,13,17 Prednisolone usually induces an improvement after a few weeks, whereas azathioprine often takes several months to improve the condition. Prednisolone has dose-dependent side effects that are well known and the drug is often given on alternate mornings, as this regime may reduce these side effects while keeping the therapeutic effect. Long-term therapy over years is needed in severe MG, often life-long, but the dose of prednisolone can often be reduced to ≤10 mg per day. Both prednisolone and azathioprine are regarded as safe during pregnancy.15,16 Ten percent of patients with MG are intolerant to azathioprine, in part due to variations in the enzyme thiopurine S-methyltransferase.1 Enzyme activity can be measured before initiating the drug. Blood cell counts and liver function should be monitored regularly during the first 2 months of azathioprine therapy.

Table 1: Classification of myasthenia gravis subgroups

| Subgroup     | Autoantibody | Age at onset | Thymus         |
|--------------|--------------|--------------|----------------|
| Early onset  | AChR         | <50 years    | Hyperplasia common |
| Late onset   | AChR         | >50 years    | Atrophy common |
| Thymoma      | AChR         | Any          | Thymoma         |
| MuSK         | MuSK         | Any          | Normal          |
| LRP4         | LRP4         | Any          | Normal          |
| Seronegative | None detected| Any          | Variable        |
| Ocular       | Variable     | Any          | Variable        |

AChR = acetylcholine receptor; LRP4 = lipoprotein-related protein 4; MuSK = muscle-specific peptide.
Myasthenia Gravis – Optimal Treatment in Severe Disease

Intravenous immunoglobulin, or alternatively plasma exchange, can be given to patients with severe MG at the time of diagnosis. More than 70% will improve markedly during the first week of such treatment. Thus, a remission can be induced, a remission that should be maintained through continuous and long-term immunosuppressive drug therapy. Intravenous immunoglobulin and plasma exchange need hospitalisation and represent relatively expensive therapy, but are safe and generally regarded as cost-effective in exacerbations of severe MG.

Table 2: The most commonly used immunosuppressive drugs in myasthenia gravis

| Drug             | Mode of action                     | Dose* | Side-effects                  |
|------------------|------------------------------------|-------|------------------------------|
| Prednisolone     | Extensive immunomodulation         | Induction: 40–80 mg Stable: 2.5–20.0 mg | Cushingoid GI bleeding Other |
| Azathioprine     | Suppression B, T lymphocytes       | 50–250 mg | Nausea Leukopaenia Liver toxicity |
| Mycophenolate    | Suppression B, T lymphocytes       | 1.5–2.0 g | Nausea Leukopaenia Teratogenic |
| Rituximab        | Suppression B lymphocytes (CD20)   | 500–1,000 mg every 6 months | Infections |
| Methotrexate     | Folate inhibition                   | 20 mg/week | Nausea Leukopaenia Teratogenic |
| Cyclosporine     | Suppression T, NK lymphocytes      | 2.5–5.0 mg/kg BW | Kidney toxicity Nausea Hypertension |
| Tacrolimus       | Suppression T, NK lymphocytes      | 3 mg | Liver and kidney toxicity |
| Intraavenous immunoglobulin | Suppression B, T lymphocytes Widespread | 2 g/kg BW | Allergic reactions Limited source |

*Daily, unless stated otherwise. BW = body weight; GI = gastrointestinal; NK = natural killer.

Second-line immunosuppressive therapy

If there is an insufficient clinical effect of first-line therapies, or in the case of significant side effects, one should initiate alternative immunosuppressive drugs, which should lead to minimal or moderate improvements in MG symptoms only. Our treatment attitude for patients with MG should be proactive and ambitious. Rituximab represents a B-cell directed therapy and should, therefore, be well suited for antibody-mediated diseases such as MG. Many uncontrolled case-based series have reported excellent effect in up to 70% of patients with severe MG. However, the only placebo-controlled, prospective and blinded study confirmed that rituximab was safe in MG, but failed to demonstrate clinical benefit (ClinicalTrials.gov Identifier: NCT02110706). In a series of 38 patients with MG treated in a single centre for severe and often refractory MG, followed for a mean of 55 months, 28 patients improved and 10 of them with a remission. Similar improvements were recently reported in a series of 12 patients with refractory generalised MG from China. Rituximab is recommended as a second-line immunosuppressive drug in severe MG and it is especially effective in MuSK MG. Long-term therapy is necessary in most patients in combination with the first-line drugs. Alternative second-line immunosuppressive drugs are methotrexate, cyclosporine and tacrolimus. For all immunosuppressive drugs, it is necessary to control and assess the amount of general immunosuppression and take into consideration the slightly increased risk for infections. Dosing of the drugs should depend on the clinical situation. MG manifestations may vary over time, leading to adjustment of drug doses.

Intravenous immunoglobulin improves severe MG rapidly and the effect lasts for 3–4 months. Some patients receive such treatment with regular intervals and over time to maintain a stable improvement. Subcutaneous administration of immunoglobulin is possible and is more convenient for most patients. However, the therapeutic effect is, to date, less well documented than for the intravenous treatment.

Third-line immunosuppressive therapy

The C6 complement inhibitor eculizumab represents a new and effective treatment for MG that appears to be well tolerated. In most patients, the effect is moderate, but some patients improve more than with other drugs. Long-term treatment seems to be necessary to maintain the improvement. Exceptionally high drug costs mean that eculizumab, in the great majority of patients with severe MG, does not fulfill cost–benefit criteria. Alternative complement inhibitors are under way. Complement inhibition should be a useful therapy for a disease where complement-binding antibodies mediate cell-membrane destruction and muscle weakness.

Autologous haematopoietic stem-cell therapy is a promising therapeutic option in severe and refractory MG. Reported single cases and small case series have shown remission in several patients. At least seven such patients have been reported, with a durable, complete, stable remission and without any other MG therapy. No controlled studies have been published, and indications for stem-cell therapy in MG have not been defined. Both cost–benefit and risk–benefit considerations should be important.

Acute exacerbations

Intravenous immunoglobulin and plasma exchange are equally effective for MG exacerbations. Both are fast-acting, with a marked effect after just a few days. Thus, these treatments represent cornerstone in MG treatment and can be life-saving during severe exacerbations. Megadoses of corticosteroids can be added in patients with an insufficient response. Although intravenous immunoglobulin and plasma...
exchange have the same response rate of around 70%, individual patients may respond to one of the treatments but not to the other. Intravenous immunoglobulin or plasma exchange can be given before expected exacerbations, for example before major surgery. Plasma exchange probably has a slightly higher risk for severe complications compared to intravenous immunoglobulin.

The threshold for intensive care observation is low during MG exacerbations. Muscle weakness may deteriorate rapidly with the need of assisted ventilation. Aspiration is also a threat. Infection is the most common precipitation factor for acute MG exacerbations. Therefore, infections should be treated vigorously in MG. The antibiotics teicoplanin (in particular), fluoroquinolones, macrolides and aminoglycosides should be used with caution as they can induce an MG deterioration.3

Supportive therapy
A well-adapted training programme can improve muscle strength and general well-being in patients with severe MG,3,4 and all patients should be encouraged to take part in such training. Being overweight will reduce physical capacity and should be avoided. Potosis and double vision can be counteracted with local devices.2 Comorbidities often represent a challenge, especially in older patients, which should be considered when judging the various aspects of the patient’s weakness, mix of symptoms, and reduced health, as well as when trying to combine various treatments for an optimal result. Cardiovascular disease, lung disease and diabetes are all common comorbidities. Patients with MG have a markedly increased prevalence of all autoimmune disorders.3 Repeated antibody concentration measurements (AChR, MuSK) may be helpful in deciding if a deterioration in health is due to worsening of MG or to another medical condition.1 If the expected response to therapies is not achieved, the diagnosis of all patients with MG should be re-evaluated. This is especially important in patients without antibodies and in patients with established or suspected comorbidities.

Myasthenia gravis in children and during pregnancy
Among children with MG, only a few have a severe disease.3,6,7,8 Children with MG usually respond well to thymectomy, first-line immunosuppressive therapy and symptomatic therapy. The possibility of growth inhibition as a prednisolone side-effect should be considered. Complete stable remission and pharmacological remission are more common in childhood MG than later in life.

MG is usually unaffected by pregnancy.11 An increased weakness in the post-partum phase is common. Mycophenolate and methotrexate are teratogenic and should not be given at time of conception and in pregnancy.12 Pyridostigmine, azathioprine and corticosteroids are regarded as safe. Ten percent of the babies have a transient, and usually mild, neonatal myasthenia.13,14 In rare cases, the ACHR antibodies that cross the placenta bind so severely to the babies’ postsynaptic membrane that they induce malformations, permanent muscle weakness or spontaneous abortion.15 This outcome can be prevented by treatment with intravenous immunoglobulin or plasma exchange during the pregnancy. This should be done in patients with a previous history of such an outcome. Most patients with MG should give birth without any specific precautions. Caesarean section is slightly more common for the MG group.

New treatments
Patients with severe MG need better therapy. Most patients have a reduced quality of life, have symptoms of weakness, and side effects of their current therapy are common. Most patients with severe disease do not reach a complete stable remission or complete pharmacological remission.1 MG cannot be prevented.

Complement inhibitors are already on the market but are still too expensive for ordinary use. FcRn antagonists have shown promising results in phase II studies. Elgartigomod was safe and well tolerated in 35 patients with MG.16 Seventy-five percent of the patients had a rapid and clinically meaningful improvement. Phase III studies are now ongoing, and new B-cell inhibitors, in addition to rituximab, are on trial.3 Beneficial effects have been reported in single patients on the anti-interleukin-6 drug tocilizumab,17 and the JAK1 and JAK2 inhibitor, ruxolitinib, has also improved a patient with MuSK MG.18 Many other new immunomodulatory drugs would be expected to have the potential to improve MG, but studies are lacking for a disease that is relatively rare, and which, in most patients, is well-controlled on standard therapy.13 Specific therapies for ACHR and MuSK antibodies have been developed in experimental models, but are not yet in use for human MG.20 Experimental MG in rats could be prevented by vaccination with ACHR cytoplasmic domains, and established experimental MG was reversed in the rats.21

Conclusions
Most patients with severe MG do well. They are able to take part in ordinary daily life and they do not have a reduction in life expectancy. However, even with optimal therapy, they have reduced muscle strength and physical capacity, side-effects from their symptomatic and immunosuppressive therapy, and a reduced quality of life. There is a need for new therapies with even better treatment effects and fewer side effects, while fulfilling cost-benefit aspects. The aim for all patients with severe MG should be complete stable pharmacological remission or minimal symptoms only.1

References
1. Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol. 2015;14:1023–36.
2. Gilhus NE. Myasthenia gravis. N Engl J Med. 2016;375:2571–81.
3. Gilhus NE, Tzartos S, Evoli A, et al. Myasthenia gravis. Nat Rev Dis Primers. 2019;5:30.
4. Andersen JB, Heldal AT, Engeland A, Gilhus NE. Myasthenia gravis epidemiology in a national cohort; combining multiple disease registers. Acta Neurol Scand Suppl. 2014;129:36–91.
5. Heldal AT, Owe J, Gilhus NE, Romø F. Sensory myasthenia gravis: a nationwide epidemiologic study. Neurology. 2017;88:e1–11.
6. Hong Y, Skeie GJ, Zimosopoulos P, et al. Juvenile-onset myasthenia gravis: autoantibodies status, clinical characteristics and genetic polymorphisms. J Neurol. 2017;264:56–62.
7. Evoli A, Alborn PE, Damato V, et al. Myasthenia gravis with antibodies to MuSK: an update. Ann NY Acad Sci. 2018;142:82–9.
8. Hong Y, Li HF, Romø F, et al. HIa and MuSK-positive myasthenia gravis: a systemic review and meta-analysis. Acta Neurol Scand. 2018;138:219–29.
9. Andersen JB, Gilhus NE, Sanders DB. Factors affecting outcome in myasthenia gravis. Muscle Nerve. 2014;49:1041–9.
10. Owe J, Dalvø AK, Gilhus NE. Causes of death among patients with myasthenia gravis in Norway between 1981 and 2001. J Neurol Neurosurg Psychiatry. 2006;77:203–7.
11. Hansen JS, Danielson DH, Sommers FE, et al. Mortality in myasthenia gravis: a nationwide population based follow-up study in Denmark. Muscle Nerve. 2016;53:73–7.
12. Mantegazza R, Antonini C. When myasthenia gravis is deemed refractory: clinical signs and treatment strategies. Ther Adv Neurol Disord. 2018;11:1–11.
13. Skeie GJ, Aarnes S, Evoli A, et al. Guidelines for treatment of autoimmune neuromuscular transmission disorders. Eur J Neurol. 2017;11:899–902.
14. Andersen JB, Engeland A, Owe JF, Gilhus NE. Myasthenia gravis requiring pyridostigmine treatment in a national population cohort. Eur J Neurol. 2010;17:1445–50.
15. Norwood F, Dhanjal M, Hill M, et al. Myasthenia gravis: autoantibody status, clinical characteristics and genetic influence. Eur J Neurol. 2014;21:1400–6.
16. Sanders DB, Wright J, Benatar M, et al. International consensus guidelines for management of myasthenia gravis: executive summary. Neurology. 2016;87:419–25.
17. Sanders DB, Hart K, Martegazza R, et al. An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. Neurology. 2008;71:400–6.
18. Sanders DB, McDermott M, Thornton C, et al. A trial of mycophenolate mofetil with prednisolone as initial immunotherapy in myasthenia gravis. Neurology. 2008;71:394–9.
19. Garcia P, Chevret S, Toyka KV. Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev. 2012;12:CD002277.
20. Wolfe GI, Kaminski A, Aban RE, et al. Randomized trial of thymectomy in myasthenia gravis. N Engl J Med. 2016;375:511–22.
21. Kethe E, Elias A, Avgov Z, et al. ENS/ENS Guidelines for the treatment of ocular myasthenia. Eur J Neurol. 2014;21:687–93.
23. Lette MJ, Jacob S, Viegas S, et al. IgG1 antibodies to acetylcholine receptors in ‘seronegative’ myasthenia gravis. Brain. 2008;131:1490–52.
24. Jing SS, Lu J, Song J, et al. Effect of low-dose rituximab treatment on T- and B-cell lymphocyte imbalance in refractory myasthenia gravis. J Neurol Sci. 2019;392:216–23.
25. Tandan R, Hehir MK, Waheed W, Howard DB. Rituximab treatment of myasthenia gravis: a systematic review. Muscle Nerve. 2017;56:185–96.
26. Chan F, Swayne A, Gillis D, et al. Long-term follow-up of patients with myasthenia gravis treated with low-dose rituximab. J Neurol Neurosurg Psychiatry. 2019;90:372–8.
27. Kovacs E, Danko K, Nagy-Vince M, et al. Long-term treatment of refractory myasthenia gravis with subcutaneous immunoglobulin. Ther Adv Neurol Disord. 2017;10:363–6.
28. Budagaxwe S, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis. Ann Neurol. 2017;81:365–74.
29. Howland AL, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis. JAMA Neurol. 2017;74:37–43.
30. Hacohen Y, Jacobson UA, Byrne S, et al. Fetal acetylcholine receptor inhibition syndrome: a myopathy due to maternal antibodies. Neurol Neuroimmunol Neuroinflamm. 2020;7: e761–73.
31. Fram JF, Sato Y, Benatar M, et al. Remission of myasthenia gravis with MuSK antibodies during ruxolitinib treatment. Neurology. 2017;90:766–73.
32. Dalakas MC. Immunotherapy in myasthenia gravis in the era of biologics. Nat Rev Neurol. 2019;15:113–24.
33. Luo J, Lindstrom J. Antigen-specific immunotherapeutic vaccine for experimental autoimmune myasthenia gravis. J Immunol. 2014;193:5044–55.