Current and Future Standards in Treatment of Myasthenia Gravis

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Summary: Myasthenia gravis (MG) is a prototypic antibody-mediated neurological autoimmune disorder. Herein we characterize modern treatment algorithms that are adapted to disease severity, and introduce the current principles of escalating strategies for MG treatment. In non-thymoma patients younger than about 50 years of age and with generalized weakness, a complete early (but not urgent) thymectomy is considered as state-of-the-art on the basis of circumstantial evidence and expert opinion. In up to 10% of patients, MG is associated with a thymoma (i.e., is of paraneoplastic origin). The best surgical type of procedure is still under debate.

Myasthenic crisis is best treated by plasmapheresis, mostly combined with immunoabsorption techniques. Intravenous immunoglobulins are a reasonable alternative, but a shortage in supplies and high prices limit their use. In generalized MG, a wide array of immunosuppressive treatments has been estab-

lished, although not formally tested in double-blind, prospective trials. With regard to immunosuppression, azathioprine is still the standard baseline treatment, often combined with initial corticosteroids. In rare patients with an inborn hepatic enzyme deficiency of thiomethylation, azathioprine may be substituted by mycophenolate mofetil. Severe cases may benefit from combined immunosuppression with corticosteroids, cyclosporine A, and even with moderate doses of methotrexate or cyclophosphamide. Tacrolimus is under investigation.

In refractory cases, immunoablation via high-dose cyclophosphamide followed by trophic factors such as granulocyte colony-stimulating factor has also been suggested. In the future we may face an increased use of novel, B-cell, or T-cell-directed monoclonal antibodies. **Key Words:** Immunosuppression, immunoglobulins, plasmapheresis, immunoabsorption, acetylcholine receptor, muscle specific kinase, thymoma.

INTRODUCTION*

Myasthenia gravis (MG) is a disease that affects the neuromuscular junction. The annual incidence of MG is 1 to 2 per 100,000 while the prevalence can be as high as 20 to more than 50 per 100,000 in the population, with higher figures in countries where all modern treatments are available. The distribution is age and sex related, with the first peak in the second and third decades of life affecting mostly women, and the second peak in the sixth and seventh decades of life affecting more men. In autoimmune MG, autoantibodies in combination with local deposition of complement reduce the number of available postsynaptic nicotinic acetylcholine receptors (AChR), and thereby impair neuromuscular transmission.^{1,2} When muscle-specific serine kinase (MuSK) is

the target,³ the result is a disruption of the cytoskeleton at the endplate region. The resulting clinical features of MG are fluctuating weakness and fatigability of skeletal muscles, usually in a characteristic distribution. The weakness increases with activity and improves with rest.⁴ The diagnosis is based on these typical clinical findings in conjunction with repetitive nerve stimulation, autoantibodies against AChR or MuSK, and, if necessary, pharmacological testing.

The thymus, containing all the elements required to initiate and sustain an autoimmune response against AChR, is profoundly involved in the pathogenesis of MG, which explains the therapeutic benefit from thymectomy.^{2,5,6}

For the subtype of MG with antibodies to MuSK, it has been proposed that the clinical type and severity differ from the predominant type of MG with antibodies to AChR in that MuSK-positive cases more often have a bulbar distribution with atrophy of the respective muscles⁷; in such cases, standard treatment modalities may be less effective (see below), and the typical thymic abnormalities are absent or less pronounced.⁸

*NOTE : This review does not formally address the different regulations for drug licensing by national health authorities. Every treating physician needs to check the status of a specific drug (on-label or off-label) before prescribing treatments described in this article.

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TREATMENT PRINCIPLES

With the treatment options available today, a great majority of patients with MG can lead essentially normal lives. Also, sudden deterioration with respiratory failure (myasthenic crisis) is now rare (less than 2%) in patients adequately treated with long-term immunosuppression and monitored by trained experts. However, many patients must take immunosuppressive medication for years, or even indefinitely, despite of the risk of associated adverse effects. In thymoma patients, the prognosis is related to the course and histological stage of the tumor.⁹ Anti-cholinesterase agents are the basic symptomatic treatment, which partially compensates for the reduced safety margin at the neuromuscular junction. This may rarely be sufficient in cases of mild MG and purely ocular involvement.¹⁰ In patients with generalized autoimmune MG, immunosuppression, typically with a combination of drugs, is usually required, as described below (Table 1).^{4,11}

Myasthenic patients have an increased incidence of several associated disorders that require treatments in addition to, and potentially different from, the standard regimen in isolated MG. Malignant thymic tumors occur in 10% to 15% of patients.¹² A thyroid disorder occurs in up to 8% of myasthenic patients, and either hyperthyroidism or hypothyroidism may aggravate myasthenic weakness. Tests for thyroid function and thyroid autoantibodies should be obtained routinely. Disorders that may interfere with long-term immunosuppressive therapy include unsuspected infections such as tuberculosis, diabetes, peptic ulcer, occult gastrointestinal bleeding, and occult malignancies.

Glucocorticosteroids

The anti-inflammatory and immunosuppressive effects of glucocorticosteroids (GS) have several different components. A gradual effect of prednisone (or equivalent GS) is expected, which starts after a few days but is usually obvious after two weeks, and the achievement of maximum benefit may take months.⁴ The few published trials of prednisone *versus* placebo, or in combination with other drugs, all support its therapeutic efficacy.¹³

Up to 10% of patients may show a transient GS-induced worsening of myasthenic weakness. This adverse effect may come from a direct action on neuromuscular transmission, carry a considerable risk of steroid-induced worsening, and may even require assisted mechanical ventilation when bulbar symptoms are dominant. This may be avoided by gradually increasing the dose of the steroid medication over the course of weeks, or ameliorating symptoms by preceding courses of plasma exchange or intravenous (i.v.) immunoglobulin (Ig), which may reduce the likelihood of early steroid-induced exacerbation.

Side effects of long-term treatment with GS include all features of Cushing's syndrome, for which patients should be closely monitored and treated, including osteoporosis, hypertension, exacerbation or precipitation of diabetes, obesity, gastrointestinal ulcers, cataracts, opportunistic infections and sepsis, hypertension, and serum electrolyte derangement (in particular potassium loss). Regular slit lamp examinations (every 6 months) help to detect GS-induced cataracts early. Gastrointestinal discomfort is best dealt with by drinking skim or low-fat milk during the day. If a patient has a history of recurrent ulcers, histamine H2 receptor antagonists such as ranitidine, or H⁺, K⁺ adenosine triphosphatase inhibitors, such as omeprazole, may be given, especially in the evening.

Thymectomy

Thymectomy has not yet been investigated in a prospective, randomized, controlled clinical trial in MG. However, this form of treatment has been found useful empirically and is widely applied. Thymectomy is recommended for patients with non-thymomatous autoimmune MG as an *option* to increase the probability of remission or improvement.¹⁴ Most studies report better response when thymectomy is performed early in the disease's progression, and a trans-sternal surgical approach is preferable. On the basis of histopathological data, AChR-negative, MuSK-negative patients have a thymic pathology similar to the classical 'anti-AChR MG' and should be thymectomized.⁸

There is no consensus about the lower and upper age limits for thymectomy, the indication for thymectomy in pure ocular myasthenia, or the benefit of early or late thymectomy compared with the natural course of MG. Thymectomy is usually recommended in patients between 10 and 50 years of age with relatively recent onset of MG (i.e., within three to five years after the first manifestation). Between ages six and 10 years, the indication for thymectomy is controversial. It is usually not recommended to operate on patients with pure ocular myasthenia, although this may be an effective treatment.⁴ Patients aged more than 60 to 65 years are usually not thymectomized, except for those with thymoma. If the severity of MG is marked or severe, pretreatment with immunosuppressive drugs or plasmapheresis is clearly recommended. Minimally invasive, endoscopically-guided thymectomy is now advocated by some surgeons, but its benefits have not been established in any type of controlled clinical study. Thymectomy is not recommended in patients with antibodies to MuSK because retrospective analyses indicate a lack of the typical thymus pathology, which is clearly different from the more common type of MG, but formal clinical trials are lacking.⁸ A malignant thymoma is generally considered an abso-

lute indication for thymectomy at any age. There is no need to discontinue azathioprine (AZA) before or after surgery. During the immediate preoperative and postoperative period, oral pyridostigmine can be replaced by continuous flow i.v. pyridostigmine.

Immunosuppressive drugs

AZA acts as a purine analogue primarily on proliferating lymphocytes and induces both B-cell and T-cell lymphopenia. Immunosuppression occurs in AZA-treated patients rather than in patients treated with cytotoxic drugs, such as cyclophosphamide. AZA also has mild anti-inflammatory properties. AZA is seen most commonly as an adjunct, to reduce the dose of steroids required, but it may be used alone as a long-term maintenance treatment. AZA was introduced into MG therapy by Mertens,¹⁵ and is one of the best-tolerated therapeutic agents in use. In a randomized, placebo-controlled, double-blind study, AZA in combination with prednisone was tested *versus* AZA and placebo.¹⁶ None of these trials or any other long-term trials had a placebo arm because it was considered to be unethical.¹³

Three aspects should be considered in regards to AZA. First, patients may show an acute idiosyncratic reaction, with general malaise, fever, skin reactions, and gastrointestinal symptoms of nausea and vomiting, even after the first dose. Some of these adverse reactions may be based on a genetic defect in the enzyme thiopurine methyltransferase.¹⁷ Since heterozygote individuals often show borderline enzyme values, tolerability can best be tested by slow tapering of AZA to tolerable doses. In situations of severe gastrointestinal symptoms, the drug should be discontinued immediately. In cases of pronounced leucopenia or other intolerable side effects for AZA, the drug should be replaced by another immunosuppressive compound like mycophenolate mofetil (see below). Second, the beneficial effects for MG begin slowly, typically requiring many months for an adequate trial. Third, an important drug interaction occurs with allopurinol. The inhibition of xanthine oxidase by allopurinol impairs the conversion of AZA to 6-thiouric acid, which accumulates and eventually leads to potentially deleterious bone-marrow suppression. If allopurinol must be administered concurrently, the dose of AZA must be reduced empirically to 25%, or uricosuric medication must be used.

The incidence of serious side effects of AZA is surprisingly low, despite the fact that it has to be continued as long-term treatment in many patients.¹⁸ The most serious long-term adverse effect is the development of a lymphoma. Mild intestinal discomfort can usually be alleviated by dividing the dose into three or more doses, taking the drug after meals, starting treatment with an initial 50 mg bedtime dose, and reducing the dose temporarily. Elevation of liver enzymes up to three times

baseline may be tolerated because it is usually reversible after the dose has been reduced. Patients should be monitored carefully for side effects during treatment. Complete blood counts should be obtained at least biweekly during the first two months, and monthly thereafter. If the total white blood count (WBC) is reduced to less than 3000/ μ L, the medication should be discontinued for a few days and treatment continued at a lower dose after the WBC returns to more than 3500/ μ L. The long-term dose can be adjusted to maintain WBC between 4000/ μ L and 5000/ μ L, and lymphocyte counts ranging between 800/ μ L and 1000/ μ L. Since AZA is potentially teratogenic and mutagenic, patients should be advised to use contraceptive measures during treatment and for at least several months after its completion whenever this is possible. Although there is no conclusive report on AZA-associated teratogenicity, we would still not recommend initiating conception under therapy.

Cyclosporine A (Cic A) belongs to the group of immunophilin-binding drugs. The cyclosporine-cyclophilin complexes inhibit the phosphatase calcineurin and its substrate, the transcription factor NFAT, thus preventing the transcription of messenger RNAs for key cytokines, such as interleukin-2. Cic A was the first effective drug in MG to be studied in a prospective, double-blind, and placebo-controlled trial. By indirect comparison with AZA-studies, Cic A seems to be about as effective as AZA, but its onset of action is clearly faster (two to four weeks), and side effects are more frequent.

The more serious potential side effects of cyclosporine include dose-dependent nephrotoxicity, and hepatic disorders. Further adverse reactions include arterial hypertension, tremor, weight gain, and hirsutism. Most of the adverse effects correlate with the dose and duration of treatment. Optimal dosage is monitored by measuring "trough" drug levels 12 hours after the last dose (the best time to take measurements is in the morning). The starting dose is 5 mg/kg body weight divided into two daily doses. If the creatinine level increases by 50% over baseline levels or to more than 1.5 mg per 100 mL during treatment, the dose should be reduced or the drug discontinued. A more sensitive indicator of nephrotoxicity is the measurement of the creatinine clearance. Cyclosporine must be discontinued if idiosyncratic or allergic reactions develop. The risk of late malignancies is not established, but may be similar to that of AZA. With overt malignancy including thymic carcinoma, Cic A is not recommended. Because of its multiple and potentially serious side effects and its higher cost, it is considered to be a second-line drug. Tacrolimus is a more recent development that aims at the same pathways as does cyclosporine, yet with a higher efficacy, lower side effects, and at higher cost.¹⁹

Other immunosuppressive drugs

The most recent drug evaluated for refractory MG in open trials is the much less toxic compound mycophenolate mofetil.¹⁹ Like AZA, mycophenolate mofetil is an immunosuppressive agent acting on DNA metabolism. In transplantation medicine, mycophenolate mofetil has proved useful and seems more effective than AZA. In patients with neuroimmunological disease (e.g., MG), mycophenolate mofetil has been used as an alternative to AZA. Mycophenolate mofetil inhibits inosine monophosphate dehydrogenase and thereby depletes guanine nucleotides, leading to inhibition of DNA synthesis in lymphocytes but not in other cells (which have an alternative "salvage pathway" of purine synthesis). Its adverse effects include gastrointestinal symptoms, gastrointestinal hemorrhage, leucopenia, and infection; recently, a case of progressive multifocal leukoencephalopathy (PML) has been described in patients treated with mycophenolate mofetil after organ transplantation or who had systemic lupus. Compared to AZA, mycophenolate mofetil's hepatotoxicity is low, but the risk of secondary lymphoma may be slightly higher with mycophenolate mofetil. Also, in contrast to AZA, the combination of mycophenolate mofetil and allopurinol is not problematic. Although two recent controlled studies have not confirmed the efficacy of mycophenolate in MG, this may be due to a problematic study design.²⁰

Thus far, a number of case reports²¹ and trials indicate that mycophenolate mofetil is beneficial in MG,

suggesting that at least 50% of the patients improved to some degree. Despite several case reports in which AZA-nonresponders improved with mycophenolate, a recent multicenter study failed to show superiority for steroid-sparing effects.²² In general, clinical benefit from mycophenolate mofetil occurs as late as three to six months, and thus the study duration of nine months may have been too short. Overall, mycophenolate mofetil seems to be an effective alternative immunosuppressant in severe refractory myasthenia gravis.

Cyclophosphamide and methotrexate are potentially useful in patients with very severe MG that does not respond to the basic treatments, but these drugs have serious side effects in the long term. They may have a place in treatment-resistant patients after all other options have been tried (treatment escalation).

IMMUNOMODULATING AND ANTIBODY-DEPLETION TREATMENTS

i.v. Igs

The potential mechanisms of action of i.v. Igs include, among others, interactions with inhibitory Fc receptors on phagocytic and antigen-presenting cells. Moreover, they can directly neutralize the blocking effects of AChR-antibodies.²³ There is now convincing evidence that i.v. IgG treatment is effective in MG. IgG has a potential role as an acute intervention in rapidly progres-

FIG. 1. Clinical course and AChR antibody levels in severe MG. Arrows indicate treatment with anti-CD20. IA = immunoadsorption; PE = plasmapheresis.

sive weakness or as a chronic maintenance therapy when all other treatment modalities have failed or are contraindicated. The clinical response to i.v. IgG is similar to, but slower than, the response to plasma exchange, but it offers an alternative in myasthenic crisis when therapeutic plasmapheresis is contraindicated or not available, or when vascular access is problematic.

In the first randomized trial of patients with severe myasthenic exacerbation, i.v. IgG treatment showed slightly weaker efficacy but was better tolerated than plasmapheresis.²⁴ In a subsequent trial, 1 g/kg body weight of i.v. IgG was similarly effective as 2 g/kg body weight for the treatment of myasthenia gravis exacerbation.²⁵ Fifty-one patients were randomized to infusion with 2 g/kg body weight i.v. IgG or placebo and scored with the quantitative myasthenia gravis score at baseline and at days 14 and 28 after therapy.²⁶ In i.v. IgG-treated patients, a significant improvement in muscle strength was observed at both time points. The highest benefit occurred in patients with more pronounced muscle weakness.

If patients respond, the onset is usually within four to five days. The effect lasts for several weeks. Once i.v. IgG is given, patients should also receive immunosuppressive medication simultaneously. Adverse reactions occur in less than 10% of patients and include headache, fluid overload, aseptic meningitis, and—rarely with replacement of osmotic stabilizers in modern i.v. IgG brands—renal failure. Patients with selective IgA deficiency (about one in 300) can develop anti-IgA antibodies, causing anaphylactic reaction on repeated treatment.

Disadvantages of i.v. IgG therapy are the inconsistency of the response, lack of long-term studies in MG, high cost, and shortage of supplies.

Plasmapheresis

There are two techniques for therapeutic plasmapheresis: plasma separation by a cell separator (centrifuge) or by membrane filtration. A typical plasmapheresis protocol uses four to five exchanges of 40 to 50 mL/kg body weight each, over one week or longer, until the patient shows satisfactory improvement.

Plasmapheresis aims at the removal of pathogenic antibodies and cytokines.²⁷ In MG, early clinical effects of plasmapheresis are occasionally observed in less than 24 hours. Such immediate improvement is probably due to the removal of a minor fraction of autoantibodies that have a direct blocking effect on the ACh receptor.²⁸ Often, the effects of plasmapheresis are more delayed and become apparent only after two or more days. This delayed improvement is usually due to the removal of antibodies that act indirectly; for example, by increased receptor turnover or by complement-mediated lysis of the postsynaptic membrane.

Although there is now practically no age limit for this treatment, it is the elderly patient with multi-organ disease who carries an increased risk for developing severe complications: cardiovascular systemic reactions, electrolyte disturbances, sepsis, thrombosis and thrombophlebitis, pulmonary embolism, and subacute bacterial endocarditis have been observed. In order to increase the efficiency and selectivity of plasmapheresis, standard

Table 1. Treatment of MG (modified from Schneider-Gold and Toyka¹⁰)

1. Ach-Esterase-Inhibitors
Pyridostigmine 60 mg every 4 h orally, optional 180 mg of a time-span (slow release form) at bedtime* (Evidence class 1)
2. Glucocorticosteroids
60–100 mg methylprednisolone per day orally (or prednisone/prednisolone); caveat initial deterioration; optional slowly increasing doses; after reaching near remission: gradual dose reduction (Evidence class 1)[†]
3. Long-term Immunosuppressive Treatment
Azathioprine, 2–4 doses of 50 mg per day (2–3 mg per kg body weight)[‡] (initially combined with glucocorticosteroids; Evidence class 1)[†]
Cyclosporin A, 100–200 mg per day[§] (Evidence class 1)[†]
4. Off-label options (for nonresponders or in very severe MG, or for those with intolerable side effects from treatments 1, 2, or 3)
Mycophenolate mofetil, 1000–2000 mg per day orally^{||} (Evidence class 2 or 3)
Methotrexate, 7.5–15 mg per week orally^{||} (Evidence class 2 or 3)
Cyclophosphamide, 500 mg per m² every 4–12 weeks i.v. or 1–2 mg per kg BW per day orally^{||#} (Evidence class 2 or 3)
Tacrolimus, 2–5 mg twice per day orally** (Evidence class 2 or 3)
Rituximab (Mabthera®)** (Evidence class 3)

*Late evening time-span preparations indicated only with marked myasthenic weakness in the morning.

[†]Treatment trials designed as class 1 studies but with limited power due to early termination and small numbers of patients.

[‡]An initial trial dose of 50 mg once a day may help to discover primary hypersensitivity. Divided daily doses are better tolerated than single doses.

[§]Monitored by measuring blood trough levels available. Off-label status despite Evidence class 1 study.

^{||}Off-label, well-documented single case studies available.

[#]Off-label, available for most severely affected and treatment refractory patients. “Immune ablation” with higher doses and subsequent G-CSF rescue is also available.

**Off-label, very limited experience.

plasmapheresis techniques have been combined with (semi-)selective immunoadsorption to tryptophan-linked polyvinylalcohol gels or protein-A-columns.^{29,30} These more selective procedures seem to be at least as effective as standard plasmapheresis. Because there is negligible adsorption of albumin with immunoadsorption columns, protein substitution is not required. In a large series, 72 patients with MG crisis were treated by plasmapheresis, immunoadsorption, or a combination of both. Immunoadsorption, given alone or in combination, was associated with faster improvement of patients with myasthenic crisis, a shorter stay in hospital, and it was better tolerated (Gold, Toyka, in preparation).

Monoclonal antibodies

In recent years, B-cell-dependent effector mechanisms with antibody and complement mediated demyelination have become of interest not only in multiple sclerosis (MS)³¹ but also in MG, thus opening the way for B-cell-directed therapies.

Rituximab is a chimeric monoclonal antibody against the CD20 antigen, which is present on pre-B cells and B cells, but not on antibody-producing plasma cells or stem cells in the bone marrow. Rituximab results in depletion of CD20-positive cells via multiple mechanisms.³² After one treatment cycle, circulating B cells are reduced to 1% or less for six to nine months. Rituximab is currently used mainly in hematologic indications for non-Hodgkin's lymphoma. Since the first published MS case reports, two subsequent infusions with an absolute dose of 1000 mg and an interval of two weeks have been the basis for therapeutic application in the latest MS studies.³¹

We administered anti-CD20 in a patient with highly active MG.³³ She stabilized immediately after the first treatment cycle, needed "boosts" 15 and 19 months later, and since then has experienced no further relapses. Interestingly, anti-AChR antibody titers remained high, suggesting that either affinity/pathogenicity of anti-AChR antibodies is modulated, or treatment acts via modulation of cellular immune functions (FIG. 1). Further case studies on rituximab in MG are available.^{34,35}

Further B-cell-directed approaches include a completely humanized anti-CD20 antibody (ofatumumab) or inhibition of B-cell survival factors with atacicept. Atacicept is a tumor necrosis factor family receptor transmembrane activator and calcium-modulator and cyclophilin ligand interactor (Ig fusion protein [TACI-Ig]) that sequesters the B-cell survival factors APRIL (a proliferation-inducing Ligand) and BLys (B-lymphocyte stimulator of the tumor necrosis factor family) and thus inhibits later stages of B-cell development. At present, a Phase II trial (sponsor: Merck Serono) is testing atacicept *versus* placebo in relapsing-remitting MS.

Acknowledgments: Parts of this article have been adapted from previously published review articles and book chapters by the same group of authors. There is no conflict of interest in relation to the writing of this article.

REFERENCES

1. Drachman DB. Myasthenia gravis. *N Engl J Med* 1994;330:1797–1810.
2. Hohnfeldt R, Wekerle H. The immunopathogenesis of myasthenia gravis. In: Engel AG, editor. *Myasthenia gravis and myasthenic syndromes*. Oxford: Oxford University Press;1999. pp. 87–110.
3. Vincent A, Bowen J, Newsom-Davis J, McConville J. Seronegative generalised myasthenia gravis: clinical features, antibodies and their targets. *Lancet Neurol* 2003;2:99–106.
4. Hohnfeldt R, Melms A, Schneider C, Toyka KV, Drachman DB. Therapy of myasthenia gravis and myasthenic syndromes. In: Brandt T, Caplan LR, Dichgans J, Diener HC, Kennard C, editors. *Neurological disorders: course and treatment*. Philadelphia: Elsevier; 2003. pp. 1341–1362.
5. Wekerle H, Ketelsen UP. Intrathymic pathogenesis and dual genetic control of myasthenia gravis. *Lancet* 1977;1:678–680.
6. Kirchner T, Schalke B, Melms A, von Kugelgen T, Muller-Hermelink HK. Immunohistological patterns of non-neoplastic changes in the thymus in Myasthenia gravis. *Virchows Arch B Cell Pathol Incl Mol Pathol* 1986;52:237–257.
7. Farrugia ME, Robson MD, Clover L, et al. MRI and clinical studies of facial and bulbar muscle involvement in MuSK antibody-associated myasthenia gravis. *Brain* 2006;129:1481–1492.
8. Leite MI, Strobel P, Jones M, et al. Fewer thymic changes in MuSK antibody-positive than in MuSK antibody-negative MG. *Ann Neurol* 2005;57:444–448.
9. Strobel P, Bauer A, Puppe B, et al. Tumor recurrence and survival in patients treated for thymomas and thymic squamous cell carcinomas: a retrospective analysis. *J Clin Oncol* 2004;22:1501–1509.
10. Schneider-Gold C, Toyka KV. Myasthenia gravis: pathogenesis and immunotherapy (English). *Dtsch Arzteblatt* 2007;104:A420–A426.
11. Gold R, Dalakas MC, Toyka KV. Immunotherapy in autoimmune neuromuscular disorders. *Lancet Neurol* 2003;2:22–32.
12. Muller-Hermelink HK, Marx A. Thymoma. *Curr Opin Oncol* 2000;12:426–433.
13. Schneider-Gold C, Gajdos P, Toyka KV, Hohnfeldt RR. Corticosteroids for myasthenia gravis. *Cochrane Database Syst Rev* 2005; CD002828.
14. Gronseth GS, Barohn RJ. Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review)-Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000;55:7–15.
15. Mertens HG, Hertel G, Reuther P, Ricker K. Effect of immunosuppressive drugs (azathioprine). *Ann N Y Acad Sci* 1981;377: 691–699.
16. Palace J, Newsom-Davis J, Lecky B; Myasthenia Gravis Study Group. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. *Neurology* 1998;50:1778–1783.
17. Gold R, Toyka KV. *Immunotherapie neurologischer Erkrankungen*. UniMed Verlag; Bremen: 2006.
18. Hohnfeldt R, Toyka KV, Besinger UA, Gerhold B, Heininger K. Myasthenia gravis: reactivation of clinical disease and of autoimmune factors after discontinuation of long-term azathioprine. *Ann Neurol* 1985;17:238–242.
19. Schneider-Gold C, Hartung HP, Gold R. Mycophenolate mofetil and tacrolimus: new therapeutic options in neuroimmunological diseases. *Muscle & Nerve* 2006;34:284–291.
20. Benatar M, Rowland LP. The muddle of mycophenolate mofetil in myasthenia. *Neurology* 2008;71:390–391.
21. Schneider C, Gold R, Reiners K, Toyka KV. Mycophenolate mofetil in the therapy of severe myasthenia gravis. *Eur Neurol* 2001;46:79–82.
22. Sanders DB, Hart IK, Mantegazza R, et al. An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. *Neurology* 2008;71:400–406.

23. Gold R, Stangel M, Dalakas MC. Drug insight: the use of intravenous immunoglobulin in neurology-therapeutic considerations and practical issues. *Nat Clin Pract Neurol* 2007;3:36–44.
24. Gajdos P, Chevret S, Clair B, Tranchant C, Chastang C. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. *Ann Neurol* 1997;41:789–796.
25. Gajdos P, Tranchant C, Clair B, et al. Treatment of myasthenia gravis exacerbation with intravenous immunoglobulin-a randomized double-blind clinical trial. *Arch Neurol* 2005;62:1689–1693.
26. Zinman L, Ng E, Bril V. IV immunoglobulin in patients with myasthenia gravis-a randomized controlled trial. *Neurology* 2007;68:837–841.
27. Lehmann HC, Hartung HP, Hetzel GR, Stuve O, Kieseier BC. Plasma exchange in neuroimmunological disorders: part 2. Treatment of neuromuscular disorders. *Arch Neurol* 2006;63:1066–1071.
28. Bufler J, Kahler S, Tzartos S, Toyka KV, Maelicke A, Franke C. Activation and blockade of mouse muscle nicotinic channels by antibodies directed against the binding site of the acetylcholine receptor. *J Physiol (Lond)* 1996;492:107–114.
29. Heininger K, Hartung H-P, Toyka KV, Gaczkowski A, Borberg H. Therapeutic plasma exchange in myasthenia gravis: semiselective adsorption of Anti-AChR autoantibodies with tryptophane-linked polyvinylalcohol gels. *Ann N Y Acad Sci* 1987;505:898–900.
30. Flachenecker P, Taleghani BM, Gold R, Grossmann R, Wiebecke D, Toyka KV. Treatment of severe myasthenia gravis with protein A immunoadsorption and cyclophosphamide. *Transfus Sci* 1998;19(Suppl):43–46.
31. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med* 2008;358:676–688.
32. Martin F, Chan AC. B cell immunobiology in disease: evolving concepts from the clinic. *Annu Rev Immunol* 2006;24:467–496.
33. Chan A, Lee DH, Linker R, Mohr A, Toyka KV, Gold R. Rescue therapy with anti-CD20 treatment in neuroimmunologic breakthrough disease. *J Neurol* 2007;254:1604–1606.
34. Thakre M, Inshasi J, Marashi M. Rituximab in refractory MuSK antibody myasthenia gravis. *J Neurol* 2007;254:968–969.
35. Hain B, Jordan K, Deschauer M, Zierz S. Successful treatment of musk antibody-positive myasthenia gravis with rituximab. *Muscle & Nerve* 2006;33:575–580.