

Treatment of myasthenia gravis^{1, 2}

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Summary

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Myasthenia gravis is a prototypic antibody-mediated neurological autoimmune disorder. Its pathogenesis is much better understood than that of multiple sclerosis or immune neuropathies. Currently two targets in the endplate membrane are considered as autoantigens, the acetylcholine receptor (in up to 90%) and the muscle-specific kinase (MuSK, in about 5%).

Fortunately, substantial therapeutic progress has been made even before the era of molecular and translational medicine. In this review we characterise modern treatment algorithms that are adapted to disease severity and introduce the principle of escalating treatment strategies for myasthenia gravis. In mild cases and ocular forms of myasthenia gravis treatment with acetylcholine esterase inhibitors may be sufficient, at least temporarily. In generalised myasthenia gravis a wide array of immunosuppressive treatments have been established but most have never been tested in a full-size prospective randomised trial. Up to 10% of patients with myasthenia gravis are associated with a thymoma, i.e. of paraneoplastic origin, and this has to be looked for by CAT scan or MRI. In non-thymoma patients younger than about 50 years of age and with generalised weakness a complete early (but not urgent) thymectomy is considered as state of the art based on circumstantial evidence and expert opinion; the best type of procedure is still under debate. Usually, pretreatment with immunosuppressive medication or plasmapheresis is recommended.

Myasthenic crisis is best treated by plasmapheresis, mostly combined with immunoadsorption techniques. Intravenous immunoglobulins are a reasonable therapeutic alternative, but a shortage in supply and high prices limit its use.

With regard to immunosuppression azathioprine is still the standard base-line treatment, often combined with initial corticosteroids. In rare patients with inborn hepatic enzyme deficiency of thiomethylation azathioprine it is not well tolerated and may be substituted by mycophenolate mofetil. Severe cases may profit from combined immunosuppression with corticosteroids, cyclosporine A and even moderate doses of methotrexate or cyclophosphamide. Tacrolimus is under investigation. All such combination therapies need to be supervised by an experienced academic neuroimmunological centre. Serial measurements of anti-acetylcholine receptor antibodies, once these are elevated, or MuSK antibodies are a useful adjunct for monitoring treatment success.

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2 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 any drug (on-label or off-label) before prescribing treatments described in this manuscript.

All drug dosages have been double-checked but readers should be aware that they are liable to check the numerical values before actually treating patients.

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In escalating therapy for very severe cases one may employ monoclonal anti-CD 20 antibodies (rituximab). In highly refractory cases also immunoadsorption via high-dose cyclophosphamide, followed by trophic factors such as G-CSF has been suggested.

Keywords: *myasthenia gravis; immunosuppression; i.v. immunoglobulins; plasmapheresis; immunoadsorption; acetylcholine receptor; muscle-specific kinase; thymoma*

Definition

Myasthenia gravis is a disease that affects the neuromuscular junction. In autoimmune myasthenia gravis autoantibodies reduce the number of available postsynaptic nicotinic acetylcholine receptors (AChR) and thereby impair neuromuscular transmission. The cardinal features of myasthenia gravis are weakness and fatigability of skeletal muscles, usually in a characteristic distribution. The weakness increases with activity and improves with rest [2].

Pathogenesis and clinical testing

The basic defect in the most common form of acquired autoimmune myasthenia gravis is a loss of available postsynaptic AChRs at the neuromuscular junction. The pathogenetic cascades that

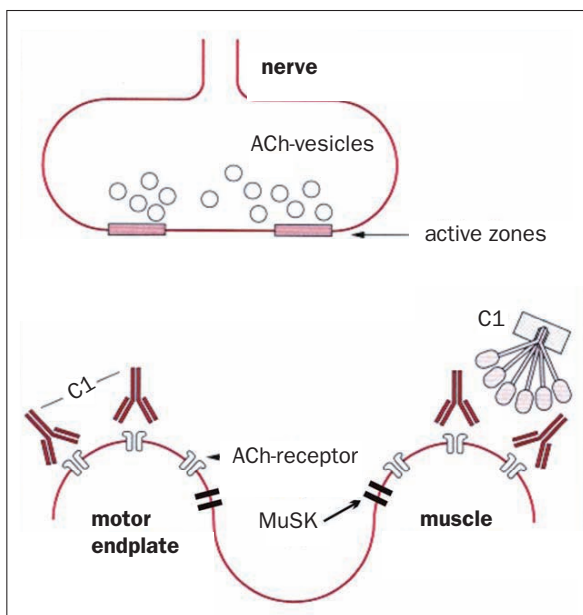
lead to impairment of neuromuscular transmission are well understood [3, 4]. Circulating anti-AChR autoantibodies impair AChR function by three different mechanisms: (1) antibody binding and cross-linking of receptors, which accelerates internalisation and degradation of AChR; (2) local activation of the complement cascade, eventually leading to complement-mediated destruction of the folds of the postsynaptic membrane; (3) blocking of the binding site for acetylcholine [5]. The thymus that contains all the elements required to initiate and sustain an autoimmune response against the AChRs is profoundly involved in the pathogenesis of myasthenia gravis [4, 6, 7].

The annual incidence of myasthenia gravis is 1 to 2 per 100 000 while the prevalence can be as high as 20 to over 50 per 100 000 in the population, with higher figures in countries where all modern treatments are available and hence patients live longer with the disease. The distribution is age- and sex-related with the first peak in the second and third decades affecting mostly women, and a second peak in the sixth and seventh decades affecting more men. It is rare in children less than 10 years of age. Recently, another type of autoimmune myasthenia gravis has been described that is characterised by antibodies to a muscle serine kinase MuSK [8]; this subgroup forms about half of the hitherto “seronegative” myasthenia-gravis patients (fig. 1).

The clinical diagnosis is based on typical clinical findings including fluctuating weakness and fatigue of extraocular muscles, producing ptosis and diplopia (table 1; these quantitative scores may also be used for follow-up examination during ongoing therapy); this is termed *pure ocular myasthenia gravis* if presenting in isolation for more than 12 months. *Generalised myasthenia gravis* shows widespread skeletal muscle weakness with, or rarely without, ocular signs. If weakness of respiration or swallowing becomes so severe as to require mechanical support, the patient is in ‘myasthenic crisis’. The variety of clinical and electrophysiological tests which is available to establish a diagnosis of myasthenia gravis is not discussed here except for the pharmacological testing because it immediately bears on symptomatic treatment [2, 3].

As a diagnostic test, edrophonium chloride is used as a short-acting cholinesterase inhibitor (duration 3 to 10 min). Atropine (1–2 mg) should be available to antagonise possible muscarinic side effects. The rapid action after intravenous administration allows repeated interaction between ACh and AChR, and partially compensates for the functional deficit of receptors. This test

Figure 1 Neuromuscular junction in myasthenia gravis and Lambert Eaton myasthenic syndrome: schematic drawing of a motor endplate and a nerve terminal (MuSK: muscle-specific kinase [9]; ACh: acetylcholine; active zones indicate arrays of voltage-gated calcium channels).



should be carried out with objective assessment (scoring) of myasthenic weakness in muscle groups that are unequivocally affected. A useful alternative or addition to the edrophonium test is the oral pyridostigmine test (Mestinon® or other brands). The patient receives 30 or 60 mg p.o. and reports back after 60 and 90 minutes for quantitative testing. The edrophonium test is not entirely specific for myasthenia gravis, and equivocal or falsely positive responses, especially of ocular symptoms, have been observed in a variety of disorders in-

cluding brain-stem glioma or vascular malformations, cranial neuropathies and orbital tumours.

Based on the clinical presentation and prognostic factors, different classifications have been proposed (table 2). Further evidence for disease heterogeneity is based on differences in age at onset (<45 or >45 years), thymic abnormalities, immunological parameters (HLA-association, AChR-antibody titre or other targets such as MuSK [8]) and response to therapy. Before any invasive treatment is started, one needs to con-

Table 1 Myasthenia score modified after Besinger und Toyka¹.

	no weakness (0)	mild weakness (1)	moderate weakness (2)	marked weakness (3)
arm outstretched time ²	>180 s	60–180 s	10–60 s	<10 s
leg outstretched time ³	>45 s	30–45 s	5–30 s	<5 s
head-holding time ⁴	>90 s	30–90 s	5–30 s	<5 s
vital capacity ⁵	>4.0 L (♂)	2.5–4.0 L (♂)	1.5–2.5 L (♂)	<1.5 L (♂)
	>3.0 L (♀)	2.0–3.0 L (♀)	1.2–2.0 L (♀)	<1.2 L (♀)
FEV1	>90 %	60–90%	40–60%	<40%
chewing/swallowing	normal	fatiguing (with solid food)	soft foods only	gastrostomy needed
facial expression	normal	lid closure weak	incomplete lid closing	no facial expression
diplopia	>60 s	10–60 s	>0–10 s	spontaneous diplopia
ptosis	>60 s	10–60 s	>0–10 s	spontaneous ptosis

¹ This original score has been adapted and extended for clinical trials by the MGFA.

² Dominant arm, outstretched horizontally during sitting; semi-prone, severely ill patients lift arm by about 30–45° (the outstretched times are only approximate measures).

³ Supine, dominant leg lifted 45°.

⁴ Supine, head lifted 45°.

⁵ Vital capacity measured while seated; FEV1 = forced expiratory volume at one second.

Table 2 Osserman und Genkins classification of myasthenia gravis, modified by the MGFA/Task Force (modified after [1]).

class	clinical form(s)	signs
I*/MGFA I	ocular form	ptosis and diplopia
II a*/MGFA II	mild generalised form	mild generalised weakness
II b*/MGFA IIb	faciopharyngeal form	IIa and bulbar weakness
III*	severe acute generalised form	acute and severe general weakness and bulbar symptoms and respiratory insufficiency
MGFA III	medium severity generalised form	medium severity generalised weakness with involvement of the extremities/trunk muscles
MGFA IIIa		more than the faciopharyngeal musculature
MGFA IIIb		faciopharyngeal/respiratory musculature more than extremities/trunk musculature
IV*	severe chronic generalised form	severe, often progressive generalised weakness
MGFA IV	severe generalised form	
MGFA IVa		extremities/trunk musculature more than faciopharyngeal musculature
MGFA IVb		faciopharyngeal/respiratory musculature more than extremities/trunk musculature
V*	myasthenia with severe residual deficits	severe chronic form with muscle atrophy
MGFA V	severe myasthenia gravis requiring intubation	

MGFA = Myasthenia Gravis Foundation Association; the entries marked with * refer to the Osserman and Genkins classification.

sider myasthenia gravis in the differential diagnosis of a variety of disorders presenting with muscle weakness.

For the subgroup of myasthenia gravis with antibodies to MuSK, it has been proposed that the clinical type and severity differs from the predominant type of myasthenia gravis with antibodies to AChR in that MuSK-positive cases more often have a bulbar distribution with atrophy of the respective muscles [10], treatment modalities may be less effective (see below) and the typical thymic abnormalities are absent or less pronounced [11].

Table 3 Treatment of myasthenia gravis (modified after [1]).

1 ACh-esterase inhibitors	
pyridostigmine 60 mg every 4 hours orally, optionally 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; optionally 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 BW)**	
(initially combined with glucocorticosteroids; evidence class 1)+	
cyclosporine A, 100–200 mg per day ***	
(evidence class 1)+	
4 off-label options (for non-responders, in very severe cases or with intolerable side effects)	
mycophenolate mofetil, 1000–2000 mg per day orally ****	
methotrexate, 7.5 mg to 15 mg per week orally ****	
cyclophosphamide, 500 mg per m ² every 4 to 12 weeks i.v. or 1–2 mg per kg BW per day orally ****, §	
tacrolimus 2 × 2–5 mg per day orally §§	
(each evidence class 2 or 3)	
rituximab (Mabthera®) §§	
(evidence class 3)	
+	Treatment trials designed as class-1 studies but with limited power due to early termination and small numbers of patients.
*	Late-evening time-span preparations indicated only with marked myasthenic weakness in the morning.
**	An initial trial dose of 1 × 50 mg may help to discover primary hypersensitivity. Divided daily doses are better tolerated than single doses.
***	Monitoring 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.

Treatment principles

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 myasthenia gravis. Malignant thymic tumours occur in 10 to 15% of patients [12]. A thyroid disorder occurs in 3 to 8% of myasthenic patients, and either hyper- or hypothyroidism may aggravate myasthenic weakness. Tests for thyroid function and thyroid autoantibodies should be obtained routinely. Disorders that may interfere with immunosuppressive therapy include unsuspected infections such as tuberculosis, diabetes, peptic ulcer, occult gastrointestinal bleeding, renal disease, hypertension and occult malignancies.

With the treatment options available today, the great majority of patients can lead essentially normal lives (table 3). However, most patients must take immunosuppressive medication for many years or even indefinitely, despite of the risk of adverse effects. Sudden deterioration with respiratory failure (myasthenic crisis) is now rare (less than 2%) in patients treated with long-term immunosuppression and monitored by trained experts. In thymoma patients the prognosis is related to the course and histological stage of the tumour.

Anti-cholinesterase agents are the basic symptomatic treatment, which partially compensate for the reduced safety margin at the neuromuscular junction. Rarely this may be sufficient in cases of mild myasthenia gravis and purely ocular involvement [1]. In patients with generalised autoimmune myasthenia gravis immunosuppression with steroids, azathioprine or other immunosuppressive drugs is usually required. Immediate removal of autoantibodies by plasma exchange or immunoadsorption (semiselective columns [13] or protein-A adsorption columns [14]) is generally very effective as a short-term treatment in crisis, in cases with rapid deterioration or in unstable patients before thymectomy. Following the guidelines below, among various therapeutic options the best available therapy has to be selected for the individual patient.

Anticholinesterase agents

The clinically useful anticholinesterase reagents inhibit the synaptic acetylcholine esterase (AChE) reversibly. Drugs like pyridostigmine and neostigmine are hydrolysed by AChE, but much more slowly than is ACh. In vivo, the duration of inhibi-

tion by these carbamylating agents is in the range of hours.

In general, the toxic side effects of anti-AChE drugs are caused by excess of ACh and actions on muscarinic AChR. These adverse reactions may affect the gastrointestinal system (abdominal cramps, diarrhoea, anorexia, nausea, vomiting), the respiratory system (bronchoconstriction and increased bronchial secretion), the eyes (miosis, conjunctival congestion), glandular secretion (lacrimation, salivation, profuse sweating) and the heart (bradycardia, hypotension). Atropine effectively antagonises these muscarinic side effects, but is ineffective at the neuromuscular junction and therefore has no influence on the muscle weakness due to excessive ACh.

Large doses of anti-AChE drugs lead to failure of neuromuscular transmission due to excess and prolonged action of ACh and, if given for longer periods of time, may alter the fine structure of the motor endplate. Generalised fasciculations or cramps can be observed with overdose, and AChRs are desensitised, resulting in increased weakness, fatigability, eventually leading to 'cholinergic crisis' with excessive overdoses.

Immunosuppressive and immunomodulating treatments

All long-term treatments usually include a combination of drugs, i.e. glucocorticosteroids and one immunosuppressive agent, as the foremost azathioprine [2, 15].

Glucocorticosteroids

The anti-inflammatory and immunosuppressive effects of glucocorticosteroids have several different components. A gradual effect of prednisone (or equivalent glucocorticosteroids) is expected which starts after a few days but is usually obvious after two weeks, and the maximum benefit may take months [2]. Short courses of large intravenous doses (1–2 grams) were employed with good results to manage exacerbations [16], but high doses carry a considerable risk of steroid-induced worsening and are not generally recommended. The few published trials of prednisone versus placebo or in combination with other drugs all support their therapeutic efficacy [17].

Up to 10% of patients may show a transient glucocorticosteroids-induced worsening of myasthenic weakness. This adverse effect may come from a direct action on neuromuscular transmis-

sion. This may be avoided by gradually increasing the dose of the steroid medication over the course of weeks. Alternatively, in more severe myasthenia gravis, plasma exchange may reduce the likelihood of early steroid-induced exacerbation.

Side effects of long-term treatment with glucocorticosteroids 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, occasional opportunistic infections and serum electrolyte derangement (in particular potassium loss). Regular slit-lamp examinations (every 6 months) help to detect glucocorticosteroids-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⁺-ATPase inhibitors such as omeprazole (Antra®) may be given.

In order to minimise steroid-induced osteoporosis, the single most effective measure is reduction of dosage and, eventually, complete discontinuation of glucocorticosteroids. All patients, especially the elderly, should be given calcium supplements and vitamin D (50 000 units 1–2 × per week), based on the level of urinary calcium excretion. Bisphosphonate agents appear to be useful for the treatment and prevention of steroid-induced osteoporosis. In postmenopausal women oestrogens may be given to reduce the risk of fractures. Potassium replacement is necessary only in patients who are known to develop hypokalaemia.

Immunosuppressive drugs

Azathioprine (*Imurek*®, *Imuran*®) acts as a purine analogue primarily on proliferating lymphocytes and induces both B- and T-cell lymphopenia. Antigen- and mitogen-induced in vitro proliferative responses of T cells are less inhibited in azathioprine-treated patients than in patients treated with cytotoxic drugs such as cyclophosphamide. Azathioprine also has mild anti-inflammatory properties probably due to the inhibition of promonocyte cell division.

Azathioprine 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. It is one of the best tolerated therapeutic agents to use but two aspects should be considered. *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 which can be analysed in peripheral blood cells (see review in [18]). Yet, heterozygote individuals often show borderline enzyme values, and tolerability can best be tested by slow tapering of azathioprine to tolerable doses. In the situation of severe gastrointestinal symptoms the drug should be discontinued immediately. *Second*, its beneficial effects in myasthenia gravis begin slowly, requiring many months up to one year for an adequate trial.

In a randomised, placebo-controlled double-blind study, azathioprine in combination with prednisone was tested versus azathioprine and placebo [19]. None of this and other long-term trials had a placebo arm because this was felt to be unethical [17].

The incidence of serious side effects of azathioprine is surprisingly low, although it has to be continued as long-term treatment in many patients [20]. In one study the most frequent adverse reactions encountered were in decreasing order of frequency: reversible bone marrow depression with leukopenia, gastrointestinal complications, infections and transient elevation of liver enzymes [21]. The most serious long-term adverse effect is the development of a lymphoma. Mild intestinal discomfort can usually be alleviated by splitting the dose into three or more divided doses, taking the drug after meals, starting treatment with a first 50 mg bedtime dose and reducing the dose temporarily. Elevation of liver enzymes up to three times baseline is also common and may be tolerated since it is usually reversible after the dose has been reduced. By contrast to what might be expected, serious infections are rarely a problem. Azathioprine 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. Data available from mothers treated with azathioprine for kidney transplant or autoimmune disorders have not shown an increased rate of birth defects in their children, but no data on the actual risk are available (see review in [18]).

Patients should be monitored carefully for side effects during treatment. Complete blood counts should be obtained at least weekly 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

the WBC around 4000/ μ l and lymphocyte counts ranging between 800 and 1000/ μ l. However, it is not certain whether the immunosuppressive efficacy of azathioprine therapy in autoimmune diseases is directly correlated to the WBC or lymphocyte count.

In patients receiving azathioprine and steroids in combination the total WBC is usually elevated because of steroid-induced neutrophilia (see above). Therefore, the above suggestions for monitoring treatment by total WBC do not apply. It is thus recommended to adjust the dose according to a WBC at 6000 to 8000/ μ l as the lower range during combined treatment.

An important drug interaction occurs with allopurinol. The inhibition of xanthine oxidase by allopurinol impairs the conversion of azathioprine to 6-thiouric acid which accumulates and eventually leads to potentially deleterious bone marrow suppression. If allopurinol must be administered concurrently, the dose of azathioprine must be reduced to 25% or less of the regular dose (approximately 0.5 mg per kg body weight) and the WBC should be closely monitored. In case of pronounced leucopenia or of other intolerable side effects of azathioprine, the drug should be replaced by another immunosuppressive compound like mycophenolate mofetil (see below) or the daily dose needs to be reduced to 10–25% or less of the recommended regular dose.

Cyclosporine A (*Sandimmune®*) 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. Cyclosporine A was the first effective drug in myasthenia gravis to be studied in a prospective, double-blind and placebo-controlled trial. It is about as effective as azathioprine, but its onset of action is more like the glucocorticosteroids (2–4 weeks).

The more serious potential side effects of cyclosporine include dose-dependent nephrotoxicity and hepatic disorders. In addition, cyclosporine can affect other organs such as the pancreas, central nervous system, bone and skeletal muscle. 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 (best in the morning). The starting dose is 5 mg per kg body weight. 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 azathioprine. With overt malignancy including thymic carcinoma cyclosporine 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 like cyclosporine, yet with a higher efficacy and lower side effects [22].

Other immunosuppressive drugs

Cyclophosphamide and *methotrexate* are potentially useful in very severe myasthenia gravis not responding to the basic treatments but have serious side effects in the long run. They may have a place in treatment-resistant patients after all other options have been tried (treatment escalation).

The most recent drug evaluated for refractory myasthenia gravis in open trials is the much less toxic compound mycophenolate mofetil (*CellCept*®) [23]. Like azathioprine mycophenolate mofetil is an immunosuppressive agent acting on DNA metabolism. In transplantation medicine mycophenolate mofetil has proved useful and seems more effective than azathioprine. In patients with neuroimmunological disease, e.g. myasthenia gravis, mycophenolate mofetil has been used as an alternative to azathioprine. 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 reported adverse effects include gastrointestinal symptoms, gastrointestinal haemorrhage, leucopenia and infection. Compared to azathioprine, its hepatotoxicity is low, but its risk of secondary lymphoma may be slightly higher. In contrast to azathioprine, the combination of mycophenolate mofetil and allopurinol is not problematic. Thus far, a number of case reports [23] and open trials indicate that mycophenolate mofetil is beneficial in myasthenia gravis suggesting that at least 50% of the patients improved to some degree. Results from prospective randomised trials are pending. In general, clinical benefit from mycophenolate mofetil occurs as late as 3 to 12 months, or even more. Since it is not cytotoxic, but only prevents

proliferation of lymphocytes, the pre-existing populations of AChR-reactive lymphocytes must gradually die off before a beneficial clinical effect is apparent. Overall, mycophenolate mofetil seems to be an effective alternative immunosuppressant in severe refractory myasthenia gravis.

Immunomodulating and antibody-depletion treatments

Intravenous immunoglobulins

The potential mechanisms of action include, amongst others, interactions with inhibitory Fc receptors on phagocytic and antigen presenting cells. Moreover, they can directly neutralise the blocking effects of AChR antibodies. There is now convincing evidence that i.v. immunoglobulin treatment is effective in myasthenia gravis [24]. IgG has a potential role as an acute intervention in rapidly progressive 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 when vascular access is problematic.

In the only randomised trial in patients with severe myasthenic exacerbation i.v. IgG treatment showed slightly weaker efficacy but was better tolerated than plasmapheresis [24]. The usual total dose is 2 grams per kg body weight given in divided doses on 3 to 5 consecutive days. If patients respond, the onset is usually within 4 to 5 days. The effect lasts for several weeks. Once i.v. IgG is needed, 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, renal failure. Patients with selective IgA deficiency (about 1 in 300) can develop anti-IgA antibodies causing anaphylactic reaction on repeated treatment. Disadvantages of intravenous immunoglobulin therapy are the inconsistency of the response, high cost and shortage of supplies. In a recent study Gajdos et al. showed therapeutic equivalence of 1 gram vs 2 grams per kg body weight given as rescue therapy in myasthenic crisis [25].

Plasmapheresis

There are two techniques of therapeutic plasmapheresis: plasma separation by a cell separator

(centrifuge) or by membrane filtration. A typical plasmapheresis protocol employs 4 to 5 exchanges of one or 1.5 plasma volumes over one week or longer until the patient shows satisfactory improvement. Usually, plasma exchange therapy is combined with immunosuppressive treatments, most commonly a combination of corticosteroids and azathioprine.

Plasmapheresis aims at the removal of circulating autoantibodies, inflammatory mediators or both. In myasthenia gravis 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 [5]. Often the effects of plasmapheresis are more delayed and become apparent only after 2 or more days. This delayed improvement is usually due to the removal of antibodies that act indirectly, for example by increased receptor turnover or 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, particularly in patients who have had arteriovenous shunts or grafts placed for vascular access. In order to increase the efficiency and selectivity of plasmapheresis, standard plasmapheresis techniques have been combined with (semi-)selective immunoadsorption to tryptophan-linked polyvinylalcohol gels or protein-A columns [13, 14]. These more selective procedures seem to be at least as effective as standard plasmapheresis. Since there is negligible adsorption of albumin with immunoadsorption columns, protein substitution is not required.

Thymectomy

Thymectomy has not yet been investigated in a prospective randomised controlled clinical trial in myasthenia gravis. However, this form of treatment has been found useful empirically and is widely applied. Thymectomy is recommended for patients with non-thymomatous autoimmune myasthenia gravis as an *option* to increase the probability of remission or improvement [26]. Most studies report better responses when thymectomy is performed early in the disease and a transsternal surgical approach is preferred.

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 as compared with the natural course of myasthenia gravis. Thymectomy is usually recommended in patients between 10 and 50 years of age with relatively recent onset of myasthenia gravis, i.e. within 3–5 years after the first manifestation. Between ages 6 and 10 the indication for thymectomy is controversial. It is usually not recommended to operate on pure ocular myasthenia although this may be an effective treatment [2]. Patients older than 60–65 years are usually not thymectomised, except for thymoma (see section on thymoma). If the severity of myasthenia gravis is marked or severe, pretreatment with immunosuppressive drugs or plasmapheresis is recommended. Minimally invasive, endoscopically guided thymectomy is now advocated by some surgeons but its benefits are not established. Thymectomy is not recommended in patients with seronegative myasthenia gravis and also not in patients with antibodies to MuSK, because retrospective analyses indicate a lack of the typical thymus pathology [11] which is clearly different from the more common type of myasthenia gravis, but formal clinical trials are lacking. A malignant thymoma is generally considered as an absolute indication for thymectomy at any age.

When properly performed, thymectomy has a low mortality rate that is essentially that of any operation with general anaesthesia. However, it should be performed in a centre with extensive experience and a neuromuscular consultant available. In patients with stable disease and after appropriate preparation severe perioperative complications are very uncommon (less than 1%). There is no need to discontinue azathioprine before or after surgery. During the immediate pre- and postoperative period oral pyridostigmine can be replaced by continuous flow i.v. prostigmine.

Practical treatment recommendations for myasthenia gravis subtypes

Generalised myasthenia gravis

Therapy should aim at complete or nearly complete remission which can be achieved in over 90% of patients. A gradual (stepwise) treatment regimen is recommended with *gradual escalation* according to disease severity and treatment effects (table 3). Restrictions by national health authorities may exist for off-label treatments.

All patients should first be treated with an AChE-inhibiting drug, usually pyridostigmine or, alternatively, ambenonium chloride. The optimum dose of any of these drugs and the timing of repeated doses must be determined for each patient. The patient is advised to use a monitoring flow sheet every 4–5 hours where the major items of the Clinical Myasthenia Gravis Score [27] or the MGFA/Task Force Score [26] is listed repeatedly.

Especially when treatment is initiated, patients should be carefully observed for side effects. In adult patients treatment begins with 30–60 mg pyridostigmine every 4 hours during the daytime and should not exceed 90 mg per dose. The action of pyridostigmine begins about 30 min after ingestion and lasts for about 4–6 hours, although the half-life is much longer. In infants and children the starting oral dose is 0.5–1.0 mg/kg pyridostigmine. The need for a steady increase in the dose of AChE inhibitors indicates progressive disease and should alert the physician to the possibility that myasthenic crisis may be imminent and additional treatment modalities, such as plasma-exchange treatment, must be considered.

The most common side effects (see above) are gastrointestinal symptoms. Persistent diarrhoea can be treated with atropine, 0.125–0.25 mg (rarely 0.5 mg); probanthine, 7.5–15 mg; or other analogues, occasionally with every dose of Mestinon®, if the AChE inhibitor cannot be reduced. Anti-muscarinic agents should not be given routinely from the start.

If the remaining symptoms are mild, thymectomy can be planned (see above). For patients with moderate or severe myasthenia gravis surgery should be postponed until the symptoms, especially pulmonary function and swallowing, are controlled by medical treatment, plasma exchange or i.v. IgG.

Immunosuppressive treatment is advised in patients whose symptoms persist for more than 3–6 months after thymectomy (1), in those who deteriorate after thymectomy (2) or in patients for whom thymectomy is rejected because of high surgical risk or older age (>50 years) (3). If symptoms are not disabling but sufficiently severe to interfere significantly with daily activities, it seems justified to offer the possibility of treatment with glucocorticosteroids alone for a few months after thymectomy in young patients and women who wish to have children, but the combination with azathioprine is preferred in all other patients.

Immunosuppression may be initiated either (a) with corticosteroids alone, followed later with azathioprine as needed, or (b) with a combination of corticosteroids and azathioprine from the beginning. The rationale for (a) is that it permits

evaluation of the beneficial and adverse effects of each drug separately. The use of combined immunosuppression (b) takes advantage of the more rapid clinical benefit of corticosteroids, while allowing extra time for azathioprine to take effect. It may be possible to taper the steroids somewhat earlier with this regimen. There are two different approaches to initiate glucocorticosteroids treatment:

1) If glucocorticosteroids are used alone to initiate treatment, the beginning daily dose is usually 15 to 20 mg of prednisone, as recommended by Drachman [28]. It is increased by about 5 mg every 2 to 3 days, while observing the patient closely. The rate of increase should be guided by the patient's clinical response, and the end point is either a satisfactory clinical response or a maximum dose of 50 to 60 mg/day (whichever occurs first). This slowly increasing dose regimen can be recommended in the outpatient situation. Azathioprine may be added to the treatment regimen after steroid-induced improvement is established. A test dose of azathioprine (50 mg/day) is given for one or up to several days. If tolerated, it is increased to 2 to 3 mg/kg/day.

2) If the patient's condition is mild to moderate and stable, or after plasmapheresis has been carried out to rapidly improve the clinical status, the prednisone dosage may be started at a higher level (40–80 mg/day). If the patient tolerates a test dose (50 mg/day) of azathioprine, this drug may be added to the regimen at a dosage of 3 mg/kg body weight/day with subsequent tapering to 2 or 2.5 mg/kg once remission has been achieved.

Glucocorticosteroids may be tapered very slowly after reaching (near) remission. AChR-antibody levels are monitored bimonthly in the beginning. The majority of patients require continued immunosuppression at some level for many years. The goal of tapering the dose is to find the minimum effective amounts required for maintenance of a satisfactory clinical status. After clinical remission has been achieved for more than 6 months, an attempt may be made to taper and eventually discontinue azathioprine over 6–12 months in patients if they have shown stable antibody titres for about one year. After withdrawal of azathioprine patients are monitored monthly for the first 6 months and every 2–3 months thereafter, for rising antibody titres and signs of clinical relapse. If there are signs of clinical deterioration while off any drug, immunosuppressive treatment is reinstituted immediately [20].

Ptosis responds to AChE inhibitors (30–60 mg per dose) much more favourably than does diplopia. If AChE inhibitors do not correct the symptoms at moderate to high doses, they should be discontinued at that time but may become more effective after successful immunosuppressive treatment. If AChE inhibitors fail, various mechanical devices may be considered. Occlusion of one eye with an adhesive patch applied to a spectacle may be helpful as a means to relieve transient diplopia. In an occasional patient the diplopia may be sufficiently stable so that prisms may restore binocular vision. Self-adhesive plastic prisms are relatively inexpensive and may be helpful. Ptosis may be relieved by a custom-made lid “crutch” soldered to the inner side of the spectacle frame or by the use of a strip of transparent adhesive tape. If AChE inhibitors fail and if mechanical devices are either insufficient or not acceptable to the patient (driving, professional activities), glucocorticosteroids should be tried. Often, a relatively low dose of glucocorticosteroids results in resolution of ptosis and diplopia [2].

The indication for azathioprine in ocular myasthenia is controversial. However, azathioprine or cyclosporine A may be considered for patients who have permanent ocular symptoms interfering with their professional activities despite maintenance of glucocorticosteroids or if glucocorticosteroids at low doses are not tolerated.

Neonatal transient myasthenia

All children born to a mother with myasthenia gravis should be watched carefully for myasthenic signs during the first 3 to 6 days of life. If no symptoms have occurred by then, they are unlikely to occur later. Myasthenic weakness develops in about 10–20% of infants born to myasthenic mothers. Neither the mother’s anti-AChR antibody titre nor her clinical state is predictive of neonatal myasthenia gravis. Usually, the symptoms last for 2–4 weeks but elimination of maternal IgG antibodies may take months. Patients should be advised to schedule delivery in a specialised centre with experience with this condition. In affected children myasthenic symptoms usually become apparent 3 to 72 hours after birth. Apart from acute problems in the first week the prognosis of neonatal myasthenia gravis is excellent. Recovery is usually complete within 2–4 months after birth. When symptoms are mild, small feedings and careful surveillance are sufficient. When symptoms

are more severe, with weakness of suckling and swallowing, a feeble cry, general muscle hypotonia or respiratory difficulties, neostigmine methylsulfate should be given by subcutaneous or intramuscular injection (usually 0.04–0.05 mg/kg), or neostigmine bromide can be given orally through a nasogastric tube (0.5 mg/kg). Alternatively, pyridostigmine bromide intramuscularly (0.05–0.15 mg/kg) or orally (1–2 mg/kg) may be used. In case of severe respiratory problems due to neonatal myasthenia, exchange transfusion or discontinuous plasma exchange may be considered.

Myasthenic crisis

Myasthenic crisis is defined as the inability to maintain adequate respiratory function, swallowing or to keep airways patent and free of secretions. Precipitating factors are often infections, surgery, emotional distress, insufficient long-term treatment or too rapid tapering of medication. Myasthenic crisis is a neurological emergency requiring prompt treatment. The warning signs of an imminent crisis include: shortness of breath and slurred speech, swallowing difficulties, progressive respiratory and neck weakness with orthopnoea, pale or cyanotic skin, and sweating. Blood gases show rising CO₂ and falling oxygen levels. “*Cholinergic crisis*” results from excessive doses of AChE inhibitors (usually more than 600 mg pyridostigmine per day, see above) inappropriately given to a myasthenic patient with progressive disease, but this is now rare. If deterioration of muscle strength cannot be improved by an adjusted dose of AChE inhibitors, patients are prone to sudden deterioration, and crisis management should be anticipated (see treatment section).

Patients in crisis should be hospitalised in an intensive care unit. Ventilatory support must be available during transfer. If the situation cannot be drastically improved by administration of AChE inhibitors (e.g. by i.v. injection of 0.5 to 1 mg neostigmine or 1 to 3 mg pyridostigmine, combined with 0.5 mg of atropine i.v.), the need for long-term ventilation is imminent. After the respiratory problems are under control, the cause of the crisis should be investigated.

Respiratory assistance should be provided if the forced vital capacity is less than 15 ml/kg body weight, the tidal volume drops to below 5–6 ml/kg body weight or if arterial oxygen decreases to less than 85 mm Hg and carbon dioxide increases to more than 45 mm Hg. It should be noted that arterial blood gas determinations may give a false assurance and cannot substitute for close and care-

ful clinical observation of the patient. Patients in myasthenic crisis receive the same respiratory support as do patients with other neuromuscular respiratory disorders.

During assisted ventilation, AChE inhibitors may be maintained by continuous i.v. infusion, e.g. 0.15 to 0.5 mg neostigmine per hour, i.e. a total maximal dose of 16–20 mg per day. Along with improvement AChE may be reduced temporarily in order to judge the clinical response to immunologic therapy.

It is a cardinal rule that infections in myasthenia gravis should be treated with antibiotics early and vigorously. A common error in the management of myasthenic crisis is to wait too long before initiating antibiotic therapy. Appropriate cultures should be obtained as quickly as possible and empirical antibiotic treatment started immediately, even before the results of these cultures are available. A good principle is to apply the antibiotic regimen that is used for immunocompromised oncology patients with acute infections. If indicated, third-generation cephalosporins can be given without adverse effect on myasthenic symptoms. Certain antibiotics, such as the aminoglycosides, may have adverse effects on neuromuscular transmission and are generally avoided. However, in an intensive care setting, the primary consideration is the successful treatment of the infection, while potential neuromuscular effects of antibiotics are clearly less important, especially if the patient is on a ventilator.

If the crisis cannot be controlled within a few hours or weakness further progresses, plasmapheresis is indicated. This is often combined with

corticosteroids, although the use of corticosteroids is controversial in patients with bacterial infection. High-dose i.v. IgG (up to 25 g per day) may be given immediately after an exchange treatment, both as an adjunct treatment modality and in order to substitute for losses during plasmapheresis. Azathioprine may be added to the regimen if long-term immunosuppressive therapy is indicated. This is usually the case in patients whose symptoms are severe enough to evolve into crisis. Bacterial respiratory tract infections are a common problem in myasthenic crisis. It is important to note that the removal of clotting factors during plasmapheresis, in particular fibrinogen, may result in impairment of haemostasis for about 24 hours. This should result in waiting for a day or two before the next plasmapheresis is done.

If there are contraindications to plasmapheresis, high-dose i.v. IgG are indicated instead, which may also be effective [24, 29].

Pregnancy and myasthenia gravis

The influence of pregnancy on myasthenic symptoms is variable and unpredictable. Frequent adjustments of the anti-AChE medications may be required. During pregnancy AChE inhibitors should not be given intravenously except in emergencies because they may cause uterine contractions. Infants born to mothers who have taken steroids during pregnancy should be monitored for adrenal insufficiency during the neonatal period. Also, since glucocorticosteroids are excreted in breast milk, inhibition of endogenous steroid production as well as growth suppression can occur in infants who are breastfed by mothers receiving glucocorticosteroids. Myasthenic crisis during pregnancy should be treated essentially as described for non-pregnant patients. Sedatives and narcotics may be given in half the usual doses used for non-myasthenics.

Drugs with adverse effects on neuromuscular transmission

Many drugs may compromise neuromuscular transmission and exacerbate myasthenic weakness. This is clinically relevant in all myasthenia-gravis patients once they have *marked* systemic weakness. The following agents should be used only if absolutely necessary and the patient should closely be monitored for any exacerbation of myasthenic symptoms: neuromuscular blocking agents (e.g. curare-like compounds); local anaesthetics

Table 4 Medications relatively contraindicated in myasthenia gravis¹.

substance group	examples
analgesics	morphine, flupirtine
antibiotics	aminoglycosides, macrolides, ketolides, gyrase inhibitors, sulphonamides, tetracyclines, penicillins (high doses)
antidepressants	tricyclics
rheumatological agents	D-penicillamine, chloroquine
beta-blockers	pindolol, propranolol, timolol
calcium antagonists	verapamil, diltiazem, nifedipine
magnesium	high-dose magnesium, e.g. in tocolysis
muscle relaxants	curare derivatives (max. 10–50% of the normal dose), succinyl choline

¹ These restrictions apply for patients with clinically visible signs, despite treatment with cholinesterase inhibitors; they may be used otherwise with observation during first treatment (table modified after [1]).

(prefer amide- over ester-type) and anti-arrhythmic drugs (quinine, quinidine, procainamide, verapamil); aminoglycosides, quinolone and macrolide antibiotics; beta-blockers; calcium-channel blocking agents (table 4). D-penicillamine must not be used in myasthenic patients because it can itself induce autoimmune myasthenia gravis which is completely reversible after the drug is discontinued. Many other drugs have been reported to produce worsening or unmasking of myasthenic symptoms. In general, all myasthenic patients should be observed for clinical worsening when any new medication is begun.

Thymoma and thymic carcinoma

Prior to surgery the patient's clinical status should be optimised, exactly as for thymectomy without thymoma (see above). After removal of the tumour the principles of treatment for myasthenia gravis, described above, also apply for patients with thymoma. Further treatment of the thymoma depends on the intraoperative staging of tumour invasion, the histopathological findings and the clinical response after surgery. The prognosis of medullary and mixed thymomas (A stages; benign thymoma) seems better than that of the other tumours [30, 31].

For non-invasive, encapsulated thymomas, radical thymectomy is considered curative. Nonetheless, patients should be followed with regular chest CT or MRI scans. Postoperative radiotherapy is usually not necessary in non-invasive thymomas. Patients with invasive thymomas are commonly treated with surgery, radiotherapy and chemotherapy in varying combinations and sequences. It should be noted that previous radiation may be a complicating factor if the tumour recurs and a second operation is needed. Several experimental protocols of adjuvant chemotherapy have been evaluated in invasively growing thymomas.

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