

Guidelines for the treatment of autoimmune neuromuscular transmission disorders

G. O. Skeie^a, S. Apostolski^b, A. Evoli^c, N. E. Gilhus^d, I. K. Hart^e, L. Harms^f, D. Hilton-Jones^g, A. Melms^h, J. Verschuurenⁱ and H. W. Horge^j

^aDepartment of Neurology, University of Bergen, Bergen, Norway; ^bInstitute of Neurology, School of Medicine, University of Belgrade, Serbia and Montenegro; ^cNeuroscience Department, Catholic University, Rome, Italy; ^dDepartment of Neurology, University of Bergen, Bergen, Norway; ^eUniversity Department of Neurological Science, Walton Centre for Neurology and Neurosurgery, Liverpool, UK; ^fUniversitätsmedizin Berlin Charité, Neurologische Klinik Berlin, Germany; ^gRadcliffe Infirmary, Oxford, UK; ^hNeurologische Klinik, Universität Tübingen, Germany; ⁱDepartment of Neurology, LUMC, Leiden, The Netherlands; and ^jPatient advocate, The Norwegian Muscularly Disorders Association, Norway

Keywords:

Lambert–Eaton myasthenic syndrome, myasthenia gravis, neuromuscular transmission disorders, neuromyotonia

Received 8 November 2005

Accepted 21 November 2005

Important progress has been made in our understanding of the cellular and molecular processes underlying the autoimmune neuromuscular transmission (NMT) disorders; myasthenia gravis (MG), Lambert–Eaton myasthenic syndrome (LEMS) and neuromyotonia (peripheral nerve hyperexcitability; Isaacs syndrome). To prepare consensus guidelines for the treatment of the autoimmune NMT disorders. References retrieved from MEDLINE, EMBASE and the Cochrane Library were considered and statements prepared and agreed on by disease experts and a patient representative. The proposed practical treatment guidelines are agreed upon by the Task Force: (i) Anticholinesterase drugs should be the first drug to be given in the management of MG (good practice point). (ii) Plasma exchange is recommended as a short-term treatment in MG, especially in severe cases to induce remission and in preparation for surgery (level B recommendation). (iii) Intravenous immunoglobulin (IvIg) and plasma exchange are equally effective for the treatment of MG exacerbations (level A Recommendation). (iv) For patients with non-thymomatous autoimmune MG, thymectomy (TE) is recommended as an option to increase the probability of remission or improvement (level B recommendation). (v) Once thymoma is diagnosed TE is indicated irrespective of the severity of MG (level A recommendation). (vi) Oral corticosteroids is a first choice drug when immunosuppressive drugs are necessary in MG (good practice point). (vii) In patients where long-term immunosuppression is necessary, azathioprine is recommended together with steroids to allow tapering the steroids to the lowest possible dose whilst maintaining azathioprine (level A recommendation). (viii) 3,4-diaminopyridine is recommended as symptomatic treatment and IvIg has a positive short-term effect in LEMS (good practice point). (ix) All neuromyotonia patients should be treated symptomatically with an anti-epileptic drug that reduces peripheral nerve hyperexcitability (good practice point). (x) Definitive management of paraneoplastic neuromyotonia and LEMS is treatment of the underlying tumour (good practice point). (xi) For immunosuppressive treatment of LEMS and NMT it is reasonable to adopt treatment procedures by analogy with MG (good practice point).

Background and objectives

The autoimmune neuromuscular transmission (NMT) disorders are relatively rare, but often debilitating diseases. Myasthenia gravis (MG) is caused by autoantibodies against the acetylcholine receptor (AChR) at the neuromuscular junction. The autoimmune attack at the

muscle endplate leads to NMT failure and muscle weakness. Lambert–Eaton myasthenic syndrome (LEMS) is caused by antibodies against the voltage-gated calcium channels (VGCC) at the pre-synaptic side of the muscle endplate. The antibodies inhibit acetylcholine (ACh) release and cause NMT failure and muscle weakness. Neuromyotonia (peripheral nerve hyperexcitability; Isaacs syndrome) is caused by antibodies to nerve voltage-gated potassium channels (VGKC) that produce nerve hyperexcitability and spontaneous and continuous skeletal muscle

Correspondence: Dr Geir Olve Skeie, Department of Neurology, Haukeland University Hospital, 5021 Bergen, Norway (tel.: +47 55 97 5000; fax: +47 55 97 5165; e-mail: geir.olve.skeie@helse-bergen.no).

overactivity presenting as twitching and painful cramps and stiffness.

Our increased understanding of the basic mechanisms of NMT and autoimmunity has led to the development of novel treatment strategies. NMT disorders are now amenable to treatment and their prognoses are good. Treatment developed for other and more common antibody-mediated autoimmune disorders with similar pathogenetic processes have been applied also for NMT disorders. However, although present treatment strategies are increasingly underpinned by scientific evidence, they are still based partly on clinical experience. In this paper we have reviewed the available literature on treatment for the autoimmune NMT disorders and give evidence-based guidelines.

Materials and methods

Search strategy

MEDLINE 1966–2004 and EMBASE 1966–2004 were examined with appropriate MESH and free subject terms: 1. Myasthenia, 2. Myasthenia gravis, 3. Lambert–Eaton, 4. Lambert–Eaton myasthenic syndrome/LEMS, 5. Neuromyotonia, 6. Isaacs syndrome.

The terms 1–6 were combined with the terms: 7. Treatment, 8. Medication, 9. Therapy, 10. Controlled clinical trial, 11. Randomized controlled trial, 12. Clinical trial, 13. Multicenter study, 14. Meta analysis, 15. Cross-over studies, 16. Thymectomy, 17. Immunosuppression.

The Cochrane Central Register of Controlled Trials (CENTRAL) was also sought. Articles in English that contained data which could be rated according to the guidance statement for neurological management guidelines of EFNS were included [1].

Information from patient and other voluntary organizations and existing guidelines including those from the American Academy of Neurology was reviewed and validated according to the above criteria. Finished and ongoing Cochrane data based projects on LEMS treatment, immunosuppressive MG treatment, IvIg for MG, plasmapheresis for MG and corticosteroids for MG in addition to TE for MG were reviewed.

Methods for reaching consensus

Four members of the task force prepared parts of the manuscript and draft statements about the treatment of MG, LEMS and neuromyotonia. Evidence was classified as class I to IV and recommendations as level A to C according to the scheme agreed for EFNS guidelines [1]. When only class IV evidence was available but

consensus could be reached the Task force has offered advice as good practice points [1]. The statements were revised and collated into a single document, which was then revised iteratively until consensus was reached.

Conflicts of interest

None of the Task force members reported any conflicts of interest.

Myasthenia gravis

Myasthenia gravis is characterized by a fluctuating weakness of skeletal muscle with remissions and exacerbations [2]. In 85% of MG patients, the disease is caused by antibodies against the AChR at the post-synaptic side of the neuromuscular junction that cause transmission failure and produce destruction of the endplate. Of the 15% of generalized MG patients without AChR antibodies, 20–50% have antibodies against another synaptic antigen, muscle-specific tyrosine kinase (MuSK) [3]. The remaining patients probably have antibodies against unknown antigens at the neuromuscular junction. MG is closely associated with thymic pathology. Fifteen percent of MG patients have a thymoma and often have antibodies against additional striated muscle antigens such as titin [4] and ryanodine receptors [5]. These antibodies are more common in thymoma and severe MG and are considered as useful markers for these conditions [6,7]. A hypertrophic thymus is found in 60% of MG patients, typically young females, whilst most patients with debut after 50 years of age, have a normal or atrophic thymus.

Myasthenia gravis often used to cause chronic, severe disability and had a high mortality. However, improved treatment allied with advances in critical care have transformed the long-term prognosis and life expectancy is now near normal [8].

Symptomatic treatment

Acetylcholine esterase inhibitors (of which pyridostigmine is the most widely used) inhibit the breakdown of ACh at the neuromuscular junction. This increases the availability of ACh to stimulate AChR and facilitates muscle activation and contraction. These drugs are symptomatic treatments and most helpful when used as initial therapy in newly diagnosed MG patients, and as sole long-term treatment of milder, especially ocular, disease.

These drugs are usually well tolerated at standard doses of up to 60 mg five times per day. Adverse effects are caused by the increased concentration of ACh at

both nicotinic and muscarinic synapses. The common muscarinic effects are gut hypermotility (stomach cramps, diarrhoea), increased sweating, excessive respiratory and gastrointestinal secretions [9,10] and bradycardia. The main nicotinic adverse effects are muscle fasciculations, and sometimes, cramps.

There are no placebo controlled randomized studies of these drugs, but case reports, case series and daily clinical experience demonstrate an objective and marked clinical effect (class IV evidence). Although there is inadequate evidence for a formal recommendation, the Task force agreed that an anticholinesterase drug should be the first-line treatment for all forms of MG (class IV evidence, good practice point).

The optimal dose is determined by the balance between clinical improvement and adverse effects, and can vary over time and with concomitant treatment. There is one report of additional effect of intranasally administered pyridostigmine, although this is not commercially available [11] (class III evidence).

Another symptomatic agent, ephedrine, increases ACh release. It has probably both less effect and more severe side-effects than pyridostigmine [12] (class III evidence). Pyridostigmine should be preferred to ephedrine in the symptomatic treatment of MG (level C recommendation).

3,4-diaminopyridine releases ACh from nerve terminals and is used as a treatment for LEMS. In a double-blind, placebo-controlled trial the drug seemed effective in congenital (hereditary and non-immune) myasthenia patients. Juvenile MG patients did not respond [13] (class III evidence). The drug is not recommended in autoimmune MG although it may prove useful in some forms of congenital myasthenia (level C recommendation).

Immune-directed treatment

Definitive MG treatments target the autoimmune response by suppressing the production of pathogenic antibodies or the damage induced by the antibodies. The aim of immunotherapy is to induce and then maintain remission. MG patients with a thymoma and other patients with anti-titin and anti-RyR antibodies usually have a severe disease [6,14] (class III evidence), thus, suggesting that more aggressive treatment strategies should be considered in these patients (level C recommendation).

Most MG treatment studies are insufficient. There is no consideration of whether patients have had TE and it is not possible to extract from the data how many patients of a treatment arm have had TE and how many have not. In non-operated patients, it is unknown how many of them had thymoma. In studies conducted

before 1980, the percentage of patients with and without AChR antibodies is not known, and the MuSK antibodies were detected very recently. There are no controlled or prospective trials of immunosuppressive treatment in children and adolescents. Evidence suggests that each immunological subtype of MG may be associated with a different spectrum of clinical phenotypes and thymus pathologies that should be considered when designing optimum treatment strategies.

Plasma exchange

Antibodies are removed from patient sera by membrane filtration or centrifugation. The onset of improvement is within the first week and the effect lasts for 1–3 months. Short-term benefits of plasma exchange have been reviewed by Gajdos *et al.* (Cochrane review) [15] who conclude: 'There are no adequate randomized controlled trials, but many case series report short-term benefit from plasma exchange in MG, especially in myasthenic crisis'. Numerous reports have shown this [16–18] (all class IV). The NIH consensus of 1986 states: 'the panel is persuaded that plasma exchange can be useful in strengthening patients with MG before TE and during the postoperative period. It can also be valuable in lessening symptoms during initiation of immunosuppressive drug therapy and during an acute crisis' (class IV evidence). Therefore, sham controlled trials would be unethical. Plasma exchange is recommended as a short-term treatment in MG, especially in severe cases to induce remission and in preparation for surgery (level B recommendation).

There is one report on the use of repeated plasma exchange over a long period in refractory MG. It failed to show any cumulative long-term benefit of plasma exchange in combination with immunosuppressive drugs over immunosuppressive treatment alone [19] (class II evidence). A Cochrane review concludes that: 'There are no adequate randomized controlled trials to determine whether plasma exchange improves the long-term outcome from MG' [15] (class I evidence). Repeated plasma exchange is, thus, not recommended as a treatment to obtain a continuous and lasting immunosuppression in MG (level B recommendation).

Intravenous immunoglobulin

Intravenous immunoglobulin had a positive effect in several open studies especially in the acute phase of MG [20] (class IV evidence). It has been used for the same indications as plasma exchange; rapidly progressive disease, preparation of weak patients for surgery including TE, and as an adjuvant to minimize long-term side-effects of oral immunosuppressive therapy [21]. A

recent Cochrane review compared the efficacy of IvIg compared with plasma exchange, other treatments, or placebo. It concluded the only randomized controlled trial examining early treatment effects did not show a significant difference between IvIg and plasma exchange for the treatment of MG exacerbations. Non-randomized evidence consistently favours the interpretation that they are equally effective in this situation [22] (class I evidence) (level A recommendation). Two multicentre randomized controlled studies suggest that, although efficacy is equal, side-effects of IvIg may be fewer and less severe. Thus, IvIg may be the preferred option [23] (class I evidence). However, the controlled study by Gajdos *et al.* [23] used a lower volume of plasma exchange than usual for the treatment of MG crisis, and the end-point was improvement at a time-point set too late to allow proper assessment of whether one therapy worked quicker than the other. There are published abstracts but no papers suggesting that plasma exchange work faster in MG crisis.

In mild or moderate MG, no significant difference in efficacy of IvIg and placebo was found after 6 weeks. In moderate exacerbations of MG no statistically significant difference in efficacy was found between IvIg and methylprednisolone. Randomized controlled trials have not shown evidence of improved functional outcome or steroid-sparing effect with the repeated use of IvIg in moderate or severe stable MG [22] (class I evidence).

Clinical experience does, however, suggest that IvIg can be helpful in patients with severe MG who fail to respond to maximal tolerated doses of corticosteroids and/or immunosuppressive agents.

Thymectomy

There are several surgical approaches to TE: full or partial sternotomy, transcervical and thoracoscopic. There are no randomized controlled studies for TE in MG. It is difficult to compare the outcomes of the different operative techniques (confounding factors influenced both the controlled and the uncontrolled studies). Despite the absence of randomized, well-controlled studies, TE in MG patients with and without thymoma is widely practised. Postoperative improvement can take months or years to appear, making it difficult to distinguish TE effects from those of immunosuppressive drugs, which are often used concomitantly. In a controlled study, a 34% remission and a 32% improvement rate were achieved after TE compared with 8% and 16% for matched patients without the operation [24] (class III evidence). As TE is an elective intervention, the patient should be in a clinically stable condition. The perioperative morbidity is very low and consists in wound healing disorders,

bronchopneumonia, phrenic nerve damage and, sternum instability with transsternal procedures.

The Quality Standard Subcommittee of the American Academy of Neurology [25,26] analysed 28 articles written 1953–1998 describing outcomes in 21 MG cohorts with or without TE (class II evidence). Most series used the transsternal approach and the follow-up ranged from 3 to 28 years. There are a number of methodological problems in the studies including the definition of remission, the selection criteria, the medical therapy applied in both groups, and data on antibody status. However, 18 of the 21 cohorts showed improvement in MG patients who underwent TE compared with those who did not. The authors used median relative outcome rates and found that MG patients undergoing TE were twice as probably to attain medication-free remission, 1.6 times as probably to become asymptomatic, and 1.7 times as probably to improve. No study found a significant negative influence of TE on the outcome. A sub-group analysis after controlling for different single confounding variables yielded additional results: Patients with purely ocular manifestations did not benefit from TE. The outcome for younger TE patients was not significantly different from the total MG group. Mild MG (Ossermann grade 1–2) did not profit from surgery, whilst more severe cases (Ossermann grade 2b–4) were 3.7 times as probably to achieve remission after TE than those without surgery ($P < 0.0077$).

The widespread opinion that an early TE in the course of MG improves the chance of a quick remission is based on observations that lack detailed information and cannot be verified by meta-analysis. However, from pathogenic considerations it is tempting to assume that early TE should be preferred to TE after many years.

Gronseth *et al.* asserted unequivocally that 'for patients with non-thymomatous autoimmune MG, TE is recommended as an option to increase the probability of remission or improvement'. Their recommendation is supported by this Task force with the specification that patients with generalized MG and AChR antibodies are the group most probably to benefit (level B recommendation).

A future randomized trial to assess the efficacy of TE in the different clinical and immunological subgroups of MG patients is needed. The indication for TE in AChR antibody negative MG patients is controversial. A retrospective cohort study displayed a similar postoperative course in AChR antibody negative and AChR antibody positive patients with a follow-up of at least 3 years [27]. Remission or improvement after TE occurred in 57% of AChR antibody negative patients and in 51% of AChR antibody positive patients. Another study [28] could not prove any effect of TE in

15 MuSK antibody positive patients, but the data do not permit any recommendations at present regarding TE in MG without AChR antibodies.

In MG patients with a thymoma the main aim of TE is to treat the tumour rather than for any effect on the MG. Once thymoma is diagnosed, TE is indicated irrespective of the severity of MG (good practice point). Thymoma is a slow-growing tumour and TE should be performed only after stabilization of the MG. After TE, the AChR-antibody titre usually falls less in patients with thymoma than in those with thymic hyperplasia [29]. The prognosis depends on early and complete tumour resection [30].

Corticosteroids

In observational studies, remission or marked improvement is seen in 70–80% of MG patients treated with oral corticosteroids, usually prednisolone [31] (class IV evidence), but the efficacy has not been studied in double-blind, placebo-controlled trials. Steroids have side-effects including weight gain, fluid retention, hypertension, diabetes, anxiety/depression/insomnia/psychosis, glaucoma, cataract, gastrointestinal haemorrhage and perforations, myopathy, increased susceptibility to infections and avascular joint necrosis. The risk of osteoporosis is reduced by giving bisphosphonate [32] (class IV evidence), and antacids may prevent gastrointestinal complications. The Task force agreed that oral prednisolone should be a first choice drug when immunosuppressive drugs are necessary in MG (good practice point). Some patients have a temporary worsening of MG if prednisolone is started at high dose. This steroid dip occurs after 4–10 days and sometimes can precipitate a MG crisis. Thus, we recommend starting treatment at low dose, 10–25 mg on alternate days increasing the dose gradually (10 mg per dose) to 60–80 mg on alternate days. If the patient is critically ill one should start on a high dose every day and use additional short-time treatments to overcome the temporary worsening. When remission occurs, usually after 4–16 weeks, the dose should be slowly reduced to the minimum effective dose given on alternate days (good practice point).

Azathioprine

Azathioprine is in extensive use as an immunosuppressant. It is metabolized to 6-mercaptopurine, which inhibits DNA and RNA synthesis and interferes with T-cell function. The onset of therapeutic response may be delayed for 4–12 months, and maximal effect is obtained after 6–24 months. Azathioprine is usually well tolerated but idiosyncratic flu-like symptoms or

gastrointestinal disturbances including pancreatitis occur in 10%, usually within the first few days of treatment. Some patients develop hepatitis with elevations of liver enzymes. Leucopenia, anaemia, thrombocytopenia or pancytopenia usually respond to drug withdrawal. Blood cell effects and hepatitis often do not recur after cautious reintroduction of the drug. Careful monitoring of full blood cell count and liver enzymes is mandatory and the dosage should be adjusted according to the results. About 11% of the population are heterozygous and 0.3% homozygous for mutations of the thiopurine methyltransferase gene and have an increased risk of azathioprine-induced myelosuppression.

One large double-blind randomized study has demonstrated the efficacy of azathioprine as a steroid sparing agent with a better outcome in patients on a combination of azathioprine and steroids than in patients treated with steroids alone [33] (class I evidence). It has an immunosuppressive effect when used alone without steroids [34] (class III evidence). In a small randomized study, prednisone was associated with better and more predictable early improvement in muscle strength than azathioprine [35] (class III evidence). In patients where long-term immunosuppression is necessary, we recommend starting azathioprine together with steroids to allow tapering the steroids to the lowest dose possible, whilst maintaining azathioprine (level A recommendation).

Methotrexate

Methotrexate should be used in selected MG patients who do not respond to first choice immunosuppressive drugs (good practice point). It is well studied in other autoimmune disorders, but there is no evidence of sufficient quality published for MG.

Cyclophosphamide

Cyclophosphamide is an alkylating agent with immunosuppressive properties. It is a strong suppressor of B-lymphocyte activity and antibody synthesis and at high doses it also affects T-cells. In a randomized, double-blind, placebo-controlled study including 23 MG patients, those on treatment had significantly improved muscle strength and a lower steroid dose compared with the placebo group. Intravenous pulses of cyclophosphamide allowed reduction of systemic steroids without deterioration of muscle strength or serious side-effects [36] (class II evidence). However, the relative high risk of toxicity including bone marrow suppression, opportunistic infections, bladder toxicity, sterility and neoplasms, limits the use of this medication to MG patients intolerant or unresponsive to steroids plus

zathioprine, methotrexate, ciclosporin or mycophenolate mofetil (level B recommendation).

Ciclosporin

Ciclosporin has an immunosuppressive effect in both organ transplantation and autoimmune disorders. It is an inhibitor of T-cell function through inhibition of calcineurin signalling [37]. Tindall *et al.* conducted a placebo-controlled double blind randomized study in 20 patients for 6 months with an open extension [38] (class II evidence) [39,40] (class III evidence). The ciclosporin group had significantly improved strength and reduction in AChR antibody titre compared with the placebo group. Two open trials of 1 and 2 years treatment and one retrospective study all support the beneficial effect of ciclosporin [41–44] (class III evidence). Ciclosporin is effective in MG, has significant side-effects of nephrotoxicity and hypertension and should be considered only in patients intolerant or unresponsive to azathioprine (level B recommendation).

Mycophenolate mofetil

Mycophenolate mofetil's active metabolite, mycophenolic acid, is an inhibitor of purine nucleotide synthesis and impairs lymphocyte proliferation selectively. A few studies including a small double-blind placebo controlled study of 14 patients have shown that mycophenolate mofetil is effective in patients with poorly controlled MG and as a steroid sparing medication [45–51] (class III, class IV evidence). Mycophenolate mofetil should be tried in patients intolerant or unresponsive to azathioprine (level B recommendation).

FK506 (tacrolimus)

Tacrolimus (FK506) is a macrolide molecule of the same immunosuppressant class as ciclosporin. It inhibits the proliferation of activated T cells via the calcium-calcineurin pathway. FK506 also acts on ryanodine receptor mediated calcium release from sarcoplasmic reticulum to potentiate excitation-contraction coupling in skeletal muscle [52]. Case reports and a small open trial all showed a useful improvement of MG with minor side-effects [53–56] (class III evidence). Interestingly, patients with anti-RyR antibodies (and potential excitation-contraction coupling dysfunction) had a rapid response to treatment indicating a symptomatic effect on muscle strength in addition to the immunosuppression [53]. FK506 should be tried in MG patients with poorly controlled disease, especially in RyR antibody positive patients (level C recommendation).

Antibodies against leucocyte antigens

There are case reports of improvement of refractory MG with monoclonal antibodies against different lymphocyte subsets such as anti-CD20 (rituximab) (B-cell inhibitor) [57] (class IV evidence), and anti-CD4 (T-cell inhibitor) [58] (class IV evidence), both reporting good clinical outcome. These treatment strategies are promising, but more evidence is needed before any recommendations can be given.

Training, weight control and lifestyle modifications

The importance of reducing weight and modification of activities of daily living has been suggested, but there is no hard scientific evidence to support this. There are reports that show some benefit of respiratory muscle training in MG [59] (class III evidence) and strength training in mild MG [60] (class III evidence). Physical training can be carried out safely in mild MG and produces some improvement of muscle force (level C recommendation).

Myasthenia gravis is associated with a slightly increased rate of complications during birth and more frequent need of operative interventions [61] (class II evidence). Transient neonatal MG occurs in 10–20% of children born to MG mothers. Maternal MG is also a rare cause of arthrogryphosis congenita and of recurrent miscarriages [62]. Acetylcholine esterase inhibitors and immunosuppressive drugs should be continued during pregnancy when necessary for the MG, except for methotrexate, and also mycophenolate mofetil and other new drugs where no safety data are available [63] (good practice point). Effective immunosuppression can improve severe fetal MG-related conditions (class III evidence). Women with MG should not be discouraged from conceiving, and pregnancy does not worsen the long-term outcome of MG [64] (class II evidence).

Recommendations for myasthenia gravis

After the diagnosis of MG is established an acetylcholine esterase inhibitor should be introduced. Thymoma patients should have TE. AChR-antibody positive early-onset patients with generalized MG and insufficient response to pyridostigmine therapy should be considered for TE, ideally within 1 year of disease onset. Immunosuppressive medication should be considered in all patients with progressive MG symptoms. We recommend starting with prednisolone covered by bisphosphonate and antacid. If long-term treatment with steroids is expected, a steroid-sparing agent, usually azathioprine should be introduced. Non-responders or patients intolerant to this regime should be

considered for treatment with one of the other recommended immunosuppressive drugs. Recommendation levels are generally B, C or good practice points.

Lambert–Eaton myasthenic syndrome

Antibodies to peripheral nerve P/Q-type VGCC antibodies are present in the serum of at least 85% of LEMS patients [65]. The disease is characterized by ascending muscle weakness that usually starts in the proximal lower limb muscles and is associated with sensory symptoms and autonomic dysfunction. Ptosis and ophthalmoplegia tend to be milder than in MG [66]. LEMS rarely causes respiratory failure [66]. In half of the patients LEMS is a paraneoplastic disease and a small cell lung carcinoma (SCLC) will be found [67].

Symptomatic and immune-directed treatment

Evidence from small, randomized, controlled trials showed that both 3,4-diaminopyridine and IvIg improved muscle strength scores and compound muscle action potential amplitudes in LEMS patients [68] (Cochrane Review) (class I evidence).

Firstline treatment is 3,4-diaminopyridine [69]. An additional therapeutic effect may be obtained if combined with pyridostigmine. If symptomatic treatment is insufficient immunosuppressive therapy should be started, usually with a combination of prednisone and azathioprine. By analogy to MG, other drugs like ciclosporin or mycophenolate can be used, although evidence of benefit is limited to case series reports (class IV evidence) (level C recommendation).

For patients with a paraneoplastic LEMS it is essential to treat the tumour. Chemotherapy is the first choice in SCLC and this will have an additional immunosuppressive effect. The presence of LEMS in a patient with SCLC improves tumour survival [70]. For a more detailed description of LEMS consult the Guidelines for the Management of Paraneoplastic Disorders (EFNS guidelines).

Neuromyotonia (peripheral nerve hyperexcitability)/Isaacs syndrome

This commonest acquired form of generalized peripheral nerve hyperexcitability is autoimmune and caused by antibodies to nerve VGKC [71], although the only generally available assay detects these antibodies in only 30–50% of all patients [71]. Neuromyotonia is paraneoplastic in up to 25% of patients and can predate the detection of neoplasia, usually thymus or lung, by up to 4 years [72]. The clinical hallmark is spontaneous and continuous skeletal muscle overactivity presenting

as twitching and painful cramps and often accompanied by stiffness, pseudomyotonia, pseudotetany, and weakness [73]. One-third of patients also have sensory features and up to 50% have hyperhidrosis suggesting autonomic involvement. Central nervous system features can occur (Morvan's syndrome). [72,74]

Symptomatic and immune-directed treatment

Neuromyotonia usually improves with symptomatic treatment [73], although evidence is case reports and case series (class IV evidence). Carbamazepine, phenytoin, lamotrigine and sodium valproate can be used, if necessary in combination.

Neuromyotonia often improves and can remit after treatment of an underlying cancer [73]. In patients whose symptoms are debilitating or refractory to symptomatic therapy, immunomodulatory therapies should be tried [73,75]. Plasma exchange often produces useful clinical improvement lasting about 6 weeks accompanied by a reduction in EMG activity [73] and a fall in VGKC antibody titres [76]. Single case studies suggest that IvIg can also help [77]. There are no good trials of long-term oral immunosuppression. However, prednisolone, with or without azathioprine or methotrexate, has been useful in selected patients [78] (class IV evidence) (good practice point).

References

1. Brainin M, Barnes M, Baron JC, *et al.* Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. *European Journal of Neurology* 2004; **11**: 577–581.
2. Vincent A. Unravelling the pathogenesis of myasthenia gravis. *Nature Reviews. Immunology* 2002; **2**: 797–804.
3. Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. *Nature Medicine* 2001; **7**: 365–368.
4. Aarli JA, Stefansson K, Marton LS, Wollmann RL. Patients with myasthenia gravis and thymoma have in their sera IgG autoantibodies against titin. *Clinical and Experimental Immunology* 1990; **82**: 284–288.
5. Mygland A, Tysnes OB, Matre R, Volpe P, Aarli JA, Gilhus NE. Ryanodine receptor autoantibodies in myasthenia gravis patients with a thymoma. *Annals of Neurology* 1992; **32**: 589–591.
6. Skeie GO, Mygland A, Aarli JA, Gilhus NE. Titin antibodies in patients with late onset myasthenia gravis: clinical correlations. *Autoimmunity* 1995; **20**: 99–104.
7. Somnier FE, Skeie GO, Aarli JA, Trojaborg W. EMG evidence of myopathy and the occurrence of titin autoantibodies in patients with myasthenia gravis. *European Journal of Neurology* 1999; **6**: 555–563.
8. Gerber NL, Steinberg AD. Clinical use of immunosuppressive drugs: part II. *Drugs* 1976; **11**: 90–112.

9. Szathmary I, Magyar P, Szobor A. Air-flow limitation in myasthenia gravis. The effect of acetylcholinesterase inhibitor therapy on air-flow limitation. *The American Review of Respiratory Disease* 1984; **130**: 145.
10. Shale DJ, Lane DJ, Davis CJ. Air-flow limitation in myasthenia gravis. The effect of acetylcholinesterase inhibitor therapy on air-flow limitation. *The American Review of Respiratory Disease* 1983; **128**: 618–621.
11. Sghirlanzoni A, Pareyson D, Benvenuti C, *et al.* Efficacy of intranasal administration of neostigmine in myasthenic patients. *Journal of Neurology* 1992; **239**: 165–169.
12. Sieb JP, Engel AG. Ephedrine: effects on neuromuscular transmission. *Brain Research* 1993; **623**: 167–171.
13. Anlar B, Varli K, Ozdirim E, Ertan M. 3,4-diaminopyridine in childhood myasthenia: double-blind, placebo-controlled trial. *Journal of Child Neurology* 1996; **11**: 458–461.
14. Romi F, Skeie GO, Aarli JA, Gilhus NE. The severity of myasthenia gravis correlates with the serum concentration of titin and ryanodine receptor antibodies. *Archives of Neurology* 2000; **57**: 1596–1600.
15. Gajdos P, Chevret S, Toyka K. Plasma exchange for myasthenia gravis. *Cochrane Database of Systematic Reviews* 2002; **4**: CD002275.
16. Perlo VP, Shahani BT, Huggins CE, Hunt J, Kosinski K, Potts F. Effect of plasmapheresis in myasthenia gravis. *Annals of the New York Academy of Sciences* 1981; **377**: 709–724.
17. Dau PC. Plasmapheresis therapy in myasthenia gravis. *Muscle and Nerve* 1980; **3**: 468–482.
18. Olarte MR, Schoenfeldt RS, Penn AS, Lovelace RE, Rowland LP. Effect of plasmapheresis in myasthenia gravis 1978–1980. *Annals of the New York Academy of Sciences* 1981; **377**: 725–728.
19. Gajdos P, Simon N, de Rohan-Chabot P, Raphael JC, Goulon M. Long-term effects of plasma exchange in myasthenia. Results of a randomized study. *Presse Medicale* 1983; **12**: 939–942.
20. Fateh-Moghadam A, Wick M, Besinger U, Geursen RG. High-dose intravenous gammaglobulin for myasthenia gravis. *Lancet* 1984; **1**: 848–849.
21. Dalakas MC. Intravenous immunoglobulin in the treatment of autoimmune neuromuscular diseases: present status and practical therapeutic guidelines. *Muscle and Nerve* 1999; **22**: 1479–1497.
22. Gajdos P, Chevret S, Toyka K. Intravenous immunoglobulin for myasthenia gravis. *Cochrane Database of Systematic Reviews* 2003; **2**: CD002277.
23. Gajdos P, Chevret S, Clair B, Tranchant C, Chastang C. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Myasthenia Gravis Clinical Study Group. *Annals of Neurology* 1997; **41**: 789–796.
24. Buckingham JM, Howard FM Jr, Bernatz PE, *et al.* The value of thymectomy in myasthenia gravis: a computer-assisted matched study. *Annals of Surgery* 1976; **184**: 453–458.
25. Gronseth GS, Barohn RJ. Thymectomy for myasthenia gravis. *Current Treatment Options in Neurology* 2002; **4**: 203–209.
26. 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.
27. Guillermo GR, Tellez-Zenteno JF, Weder-Cisneros N, *et al.* Response of thymectomy: clinical and pathological characteristics among seronegative and seropositive myasthenia gravis patients. *Acta Neurologica Scandinavica* 2004; **109**: 217–221.
28. Evoli A, Tonali PA, Padua L, *et al.* Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. *Brain* 2003; **126**(Pt 10):2304–2311.
29. Reinhardt C, Melms A. Normalization of elevated CD4+/CD8- (double-negative) T cells after thymectomy parallels clinical remission in myasthenia gravis associated with thymic hyperplasia but not thymoma. *Annals of Neurology* 2000; **48**: 603–608.
30. Chen G, Marx A, Wen-Hu C, *et al.* New WHO histologic classification predicts prognosis of thymic epithelial tumors: a clinicopathologic study of 200 thymoma cases from China. *Cancer* 2002; **95**: 420–429.
31. Pascuzzi RM, Coslett HB, Johns TR. Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. *Annals of Neurology* 1984; **15**: 291–298.
32. Saag KG. Prevention of glucocorticoid-induced osteoporosis. *Southern Medical Journal* 2004; **97**: 555–558.
33. Palace J, Newsom-Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. *Neurology* 1998; **50**: 1778–1783.
34. Witte AS, Cornblath DR, Parry GJ, Lisak RP, Schatz NJ. Azathioprine in the treatment of myasthenia gravis. *Annals of Neurology* 1984; **15**: 602–605.
35. Bromberg MB, Wald JJ, Forshev DA, Feldman EL, Albers JW. Randomized trial of azathioprine or prednisone for initial immunosuppressive treatment of myasthenia gravis. *Journal of the Neurological Sciences* 1997; **150**: 59–62.
36. De Feo LG, Schottlender J, Martelli NA, Molfino NA. Use of intravenous pulsed cyclophosphamide in severe, generalized myasthenia gravis. *Muscle and Nerve* 2002; **26**: 31–36.
37. Matsuda S, Koyasu S. Mechanisms of action of cyclosporine. *Immunopharmacology* 2000; **47**: 119–125.
38. Tindall RS, Rollins JA, Phillips JT, Greenlee RG, Wells L, Belendiuk G. Preliminary results of a double-blind, randomized, placebo-controlled trial of cyclosporine in myasthenia gravis. *New England Journal of Medicine* 1987; **316**: 719–724.
39. Tindall RS. Immunointervention with cyclosporin A in autoimmune neurological disorders. *Journal of Autoimmunity* 1992; **5**(Suppl. A):301–313.
40. Tindall RS, Phillips JT, Rollins JA, Wells L, Hall K. A clinical therapeutic trial of cyclosporine in myasthenia gravis. *Annals of the New York Academy of Sciences* 1993; **681**: 539–551.
41. Goulon M, Elkharrat D, Gajdos P. Treatment of severe myasthenia gravis with cyclosporin. A 12-month open trial. *Presse Medicale* 1989; **18**: 341–346.
42. Goulon M, Elkharrat D, Lokiec F, Gajdos P. Results of a one-year open trial of cyclosporine in ten patients with severe myasthenia gravis. *Transplantation Proceedings* 1988; **20**(Suppl. 4):211–217.
43. Bonifati DM, Angelini C. Long-term cyclosporine treatment in a group of severe myasthenia gravis patients. *Journal of Neurology* 1997; **244**: 542–547.
44. Cialfoni E, Nikhar NK, Massey JM, Sanders DB. Retrospective analysis of the use of cyclosporine in myasthenia gravis. *Neurology* 2000; **55**: 448–450.

45. Ciafaloni E, Massey JM, Tucker-Lipscomb B, Sanders DB. Mycophenolate mofetil for myasthenia gravis: an open-label pilot study. *Neurology* 2001; **56**: 97–99.
46. Chaudhry V, Cornblath DR, Griffin JW, O'Brien R, Drachman DB. Mycophenolate mofetil: a safe and promising immunosuppressant in neuromuscular diseases. *Neurology* 2001; **56**: 94–96.
47. Schneider C, Gold R, Reiners K, Toyka KV. Mycophenolate mofetil in the therapy of severe myasthenia gravis. *European Neurology* 2001; **46**: 79–82.
48. Hauser RA, Malek AR, Rosen R. Successful treatment of a patient with severe refractory myasthenia gravis using mycophenolate mofetil. *Neurology* 1998; **51**: 912–913.
49. Meriggioli MN, Rowin J. Single fiber EMG as an outcome measure in myasthenia gravis: results from a double-blind, placebo-controlled trial. *Journal of Clinical Neurophysiology* 2003; **20**: 382–385.
50. Meriggioli MN, Rowin J. Treatment of myasthenia gravis with mycophenolate mofetil: a case report. *Muscle and Nerve* 2000; **23**: 1287–1289.
51. Meriggioli MN, Ciafaloni E, Al-Hayk KA, et al. Mycophenolate mofetil for myasthenia gravis: an analysis of efficacy, safety, and tolerability. *Neurology* 2003; **61**: 1438–1440.
52. Timerman AP, Ogunbumni E, Freund E, Wiederrecht G, Marks AR, Fleischer S. The calcium release channel of sarcoplasmic reticulum is modulated by FK-506-binding protein. Dissociation and reconstitution of FKBP-12 to the calcium release channel of skeletal muscle sarcoplasmic reticulum. *Journal of Biological Chemistry* 1993; **268**: 22992–22999.
53. Takamori M, Motomura M, Kawaguchi N, et al. Anti-ryanodine receptor antibodies and FK506 in myasthenia gravis. *Neurology* 2004; **62**: 1894–1896.
54. Konishi T, Yoshiyama Y, Takamori M, Yagi K, Mukai E, Saida T. Clinical study of FK506 in patients with myasthenia gravis. *Muscle and Nerve* 2003; **28**: 570–574.
55. Yoshikawa H, Mabuchi K, Yasukawa Y, Takamori M, Yamada M. Low-dose tacrolimus for intractable myasthenia gravis. *Journal of Clinical Neuroscience* 2002; **9**: 627–628.
56. Evoli A, Di Schino C, Marsili F, Punzi C. Successful treatment of myasthenia gravis with tacrolimus. *Muscle and Nerve* 2002; **25**: 111–114.
57. Wylam ME, Anderson PM, Kuntz NL, Rodriguez V. Successful treatment of refractory myasthenia gravis using rituximab: a pediatric case report. *Journal of Pediatrics* 2003; **143**: 674–677.
58. Ahlberg R, Yi Q, Pirskanen R, et al. Treatment of myasthenia gravis with anti-CD4 antibody: improvement correlates to decreased T-cell autoreactivity. *Neurology* 1994; **44**: 1732–1737.
59. Weiner P, Gross D, Meiner Z, et al. Respiratory muscle training in patients with moderate to severe myasthenia gravis. *Canadian Journal of Neurological Sciences* 1998; **25**: 236–241.
60. Lohi EL, Lindberg C, Andersen O. Physical training effects in myasthenia gravis. *Archives of Physical Medicine and Rehabilitation* 1993; **74**: 1178–1180.
61. Hoff JM, Daltveit AK, Gilhus NE. Myasthenia gravis: consequences for pregnancy, delivery, and the newborn. *Neurology* 2003; **61**: 1362–1366.
62. Vincent A, Newland C, Brueton L, et al. Arthrogyrosis multiplex congenita with maternal autoantibodies specific for a fetal antigen. *Lancet* 1995; **346**: 24–25.
63. Ferrero S, Pretta S, Nicoletti A, Petrera P, Ragni N. Myasthenia gravis: management issues during pregnancy. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2005; **121**: 129–138.
64. Batocchi AP, Majolini L, Evoli A, Lino MM, Minisci C, Tonali P. Course and treatment of myasthenia gravis during pregnancy. *Neurology* 1999; **52**: 447–452.
65. Motomura M, Johnston I, Lang B, Vincent A, Newsom-Davis J. An improved diagnostic assay for Lambert-Eaton myasthenic syndrome. *Journal of Neurology, Neurosurgery and Psychiatry* 1995; **58**: 85–87.
66. Wirtz PW, Sotodeh M, Nijhuis M, et al. Difference in distribution of muscle weakness between myasthenia gravis and the Lambert-Eaton myasthenic syndrome. *Journal of Neurology, Neurosurgery and Psychiatry* 2002; **73**: 766–768.
67. Wirtz PW, Willcox N, van der Slik AR, et al. HLA and smoking in prediction and prognosis of small cell lung cancer in autoimmune Lambert-Eaton myasthenic syndrome. *Journal of Neuroimmunology* 2005; **159**: 230–237.
68. Maddison P, Newsom-Davis J. Treatment for Lambert-Eaton myasthenic syndrome. *Cochrane Database of Systematic Reviews* 2003; **2**: CD003279.
69. McEvoy KM, Windebank AJ, Daube JR, Low PA. 3,4-Diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome. *New England Journal of Medicine* 1989; **321**: 1567–1571.
70. Maddison P, Newsom-Davis J, Mills KR, Souhami RL. Favourable prognosis in Lambert-Eaton myasthenic syndrome and small-cell lung carcinoma. *Lancet* 1999; **353**: 117–118.
71. Hart IK, Maddison P, Newsom-Davis J, Vincent A, Mills KR. Phenotypic variants of autoimmune peripheral nerve hyperexcitability. *Brain* 2002; **125**(Pt 8): 1887–1895.
72. Hart IK, Waters C, Vincent A, et al. Autoantibodies detected to expressed K⁺ channels are implicated in neuromyotonia. *Annals of Neurology* 1997; **41**: 238–246.
73. Newsom-Davis J, Mills KR. Immunological associations of acquired neuromyotonia (Isaacs' syndrome). Report of five cases and literature review. *Brain* 1993; **116**(Pt 2):453–469.
74. Liguori R, Vincent A, Clover L, et al. Morvan's syndrome: peripheral and central nervous system and cardiac involvement with antibodies to voltage-gated potassium channels. *Brain* 2001; **124**(Pt 12):2417–2426.
75. Hayat GR, Kulkantrakorn K, Campbell WW, Giuliani MJ. Neuromyotonia: autoimmune pathogenesis and response to immune modulating therapy. *Journal of the Neurological Sciences* 2000; **181**: 38–43.
76. Shillito P, Molenaar PC, Vincent A, Leys K, Zheng W, van den Berg RJ, et al. Acquired neuromyotonia: evidence for autoantibodies directed against K⁺ channels of peripheral nerves. *Annals of Neurology* 1995; **38**: 714–722.
77. Alessi G, De Reuck J, De Blecker J, Vancayzeele S. Successful immunoglobulin treatment in a patient with neuromyotonia. *Clinical Neurology and Neurosurgery* 2000; **102**: 173–175.
78. Nakatsuji Y, Kaido M, Sugai F, et al. Isaacs' syndrome successfully treated by immunoadsorption plasmapheresis. *Acta Neurologica Scandinavica* 2000; **102**: 271–273.