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REVIEW ARTICLE

Italian recommendations for the diagnosis and treatment of myasthenia gravis

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Abstract

Myasthenia gravis is a well-treatable disease, in which a prompt diagnosis and an adequate management can achieve satisfactory control of symptoms in the great majority of patients. Improved knowledge of the disease pathogenesis has led to recognition of patient subgroups, according to associated antibodies, age at onset and thymus pathology, and to a more personalized treatment. When myasthenia gravis is suspected on clinical grounds, diagnostic confirmation relies mainly on the detection of specific antibodies. Neurophysiological studies and, to a lesser extent, clinical response to cholinesterase inhibitors support the diagnosis in seronegative patients. In these cases, the differentiation from congenital myasthenia can be challenging. Treatment planning must consider weakness extension and severity, disease subtype, thymus pathology, together with patient characteristics and comorbidities. Since most subjects with myasthenia gravis require long-term immunosuppressive therapy, surveillance of expected and potential adverse events is critical. For patients refractory to conventional immunosuppression, the use of biologic agents is highly promising. These recommendations are addressed to non-experts on neuromuscular transmission disorders. The diagnostic procedures and therapeutic approaches hereafter described are largely accessible in Italy.

Keywords Myasthenia gravis · Thymectomy · Immunosuppressive therapy · Plasma exchange · Rituximab

This document takes into consideration recent advances in the field and international guidelines. It represents an update of diagnostic procedures and therapeutic approaches used in Italian neurological departments with experience in neuromuscular transmission (NMT) disorders.

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Epidemiologic and pathogenic aspects

Myasthenia gravis (MG) is the most frequent disorder of the NMT with a prevalence approaching 150/million [1]. IgG antibodies (Abs) against proteins expressed at the neuromuscular junction cause acetylcholine receptor (AChR) loss and postsynaptic dysfunction [2].

Anti-AChR Abs are detected in approximately 85% of MG patients and act through three mechanisms: (1) complement-mediated destruction of postsynaptic membrane; (2) increased AChR degradation through formation of antigen-Ab complexes that are internalized and destroyed inside the muscle fiber; (3) block of the ACh binding site [2]. MG with anti-AChR Abs (AChR-MG) is associated with thymus follicular hyperplasia or thymoma both contributing in the disease pathogenesis [3]. According to age at presentation, gender bias, and thymus pathology, generalized AChR-MG is subdivided in early-onset, late-onset (age of onset ≥ 50 years), and thymoma-associated disease [2]. Early-onset AChR-MG is highly prevalent in females and strongly associated with thymus follicular hyperplasia, which is thought to be the site of sensitization against the AChR and a relevant source of specific Abs [3]. On the other hand, male predominance characterizes the late-onset subgroup; only minor inflammatory changes can be detected in thymus specimens from these subjects. AChR-MG is associated with thymoma in 10–15% of patients, with no gender bias and a peak age at onset around 50 years. A defective intra-tumorous thymocyte selection with the export of autoreactive T lymphocytes is thought to be responsible for MG development in these patients [3].

Around 5–8% of patients have Abs to the muscle-specific tyrosine-kinase (MuSK). MuSK is activated by neural agrin through its co-receptor, the lipoprotein-related receptor 4 (LRP4). MuSK activation triggers an intracellular pathway leading to AChR clustering [4]. The main effect of anti-MuSK Abs is a block of MuSK-LRP4 binding [5]. MuSK-MG has a striking prevalence in women with a peak age of onset in the fourth decade [6].

Abs to LRP4 and agrin have been reported in some anti-AChR/MuSK negative cases [2]. This still leaves a proportion of patients who are seronegative, i.e., without detectable Abs.

Clinical aspects

The clinical hallmark of MG is fluctuating muscle weakness that worsens with exertion and improves with rest. Clinical presentation is typical in most cases with broad variability in symptom severity.

Weakness of extrinsic ocular muscles (EOM) is responsible for ptosis and binocular diplopia. Ptosis is generally asymmetrical and may be alternating. Diplopia may be due to paresis of a single eye muscle, but multiple pareses are common. Although ocular symptoms are very frequent at presentation, only in 15–20% of patients MG remains confined to EOM, as generally within 2 years from onset, weakness spreads to other muscle groups [7].

Reduced strength of the orbicularis oculi muscle is responsible for weak eyelid closure. Weakness of lower facial muscles causes difficulty in blowing out cheeks and accounts for a characteristic vertical smile. Fatigability of the masseter results in progressive difficulty in chewing through the meal. “Bulbar” symptoms are related to muscles innervated by motor-neurons in the medulla oblongata. Dysphagia is more relevant for liquids and hot food, and when severe, requires feeding through a nasogastric tube. Dysarthria can be apparent on prolonged talking, but speech may become unintelligible in severely affected cases. Tongue weakness contributes to speaking and eating difficulties and may evolve into a characteristic atrophy with one median and two lateral furrows (triple furrowed tongue). Weakness of neck extensors may cause a “dropped head.”

In the limbs, proximal muscles are prevalently involved; weakness is bilateral, although its severity may be asymmetrical. Among distal muscles, finger extensors are more commonly affected; weakness of foot extensors occurs rarely. Reduced strength of pelvic floor muscles in MG women and of the external urethral sphincter in men can be responsible for urinary stress incontinence [7].

Respiratory failure (myasthenic crisis) occurs in 15–20% of patients, more frequently in the first 2 years from onset [8, 9]. Ventilation failure is caused by weakness of the diaphragm and intercostal muscles together with upper airway obstruction by bronchial secretions and saliva aspiration. Crises are most often precipitated by respiratory infections. Other potential triggers are surgery, sedation, drugs interfering with NMT (see Table 1), withdrawal/overmedication of cholinesterase inhibitors, initiation of steroid treatment [8].

MuSK-MG is characterized by predominant involvement of bulbar and axial muscles, with dysarthria, dysphagia, weakness of facial and neck muscles, and frequent respiratory crises; ocular symptoms are mild and often transient; limb muscles can be totally spared [6].

Patients with anti-LRP4 Abs are mostly affected by mild generalized or ocular MG [13].

MG scoring measures

The Osserman classification has been applied for many years [14]; since 2000, the MG Foundation of America (MGFA) scale has been mostly used in clinical practice [15]. These classifications distinguish ocular from generalized myasthenia, and, in the latter, differentiate mild, moderate, and severe forms. They describe a patient’s status at a certain point of his/her disease, do not quantify

Table 1 Drugs to be avoided in myasthenia gravis

Classes	Drug	Topics
Drugs acting on the immune system	**Interferon alpha** **Immune check point inhibitors**	Can induce myasthenia gravis and can worsen myasthenic symptoms (see also ref. [10, 11])
	D-penicillamine	
	Steroids	Can induce early exacerbation (see text)
General anesthetics Neuromuscular blocking agents (NMBA) Inhalational agents	**Atracurium** **Rocuronium** **Pancuronium** **Vecuronium** **Succinylcholine** **Mivacurium** *Enflurane* *Halothane* *Isoflurane*	NMBA should be avoided unless absolutely necessary. If they must be used, reversal of neuromuscular block with sugammadex rather than with prostigmine is recommended (see ref. [12]) Though inhalation anesthetics decrease neuromuscular transmission, they are better tolerated than NMBA. Intravenous anesthesia with propofol has the advantage of rapid onset, short duration, and no effect on neuromuscular transmission.
Local anesthetics	*Esters* *Amides*	Amide local anesthetics (ropivacaine, lidocaine) should be used rather than esters.
Antibiotics	**Ciprofloxacin** **Gentamicin** **Neomycin** **Colistin** **Kanamycin** **Amikacin** **Netilmicin** *Streptomycin* *Tobramycin* *Norfloxacin* *Ofloxacin* *Clindamycin* *Lincomycin* *Vancomycin* *Ampicillin* *Telithromycin* *Sulfonamides* *Doxycycline* *Azithromycin* *Erythromycin* *Clarithromycin* *Imipenem*	Several classes of antibiotics impair neuromuscular transmission and can worsen weakness. Such effect appears to be dose-dependent. As a principle, the antibiotic choice should secure the most effective treatment for a given infection. The effect on neuromuscular transmission depends on the grade of disease control. In patients without optimal control of their disease, second-line antibiotic treatment is justified. Aminoglycosides, macrolide, and fluoroquinolones should be avoided, as far as possible, in patients with history of myasthenia gravis.
Cardiovascular drugs	**Verapamil** **Procainamide**	Inhibition of acetylcholine release Bretylium blocks acetylcholine receptors.
	Bretylium	
	Quinine **Quinidine**	Inhibition of acetylcholine release Quinine blocks acetylcholine receptors.
	Magnesium (injectable)	Inhibition of acetylcholine release Block of calcium entry at the motor nerve terminal Potentiation of neuromuscular blocking agents
	Propanolol *Oxprenolon* *Timolol* *Atenolol* *Labetolol* *Metoprolol*	Specific mechanisms unclear. The effect on neuromuscular transmission is greater with propranolol than atenolol. The negative effect on myasthenia gravis is dependent on the grade of disease control. In patients with uncontrolled disease, second-line treatment is justified.

Table 1 (continued)

Classes	Drug	Topics
	Nadolol	
	Acebutolol	
	Propafenone	Block of sodium channels
	Felodipine *Nifedipine*	Block of L-type calcium channels
Anti-rheumatic drugs	**D-penicillamine**	Reduction of acetylcholine binding properties
	Chloroquine	Reduction of membrane excitability
Anti-epileptic drugs	*Phenytoin* *Levetiracetam*	Most anti-epileptic drugs act presynaptically, reducing acetylcholine release. As all these agents have been associated with myasthenia gravis worsening or unmasking in case reports, their use should be cautious in these patients.
	Carbamazepine	
	Gabapentin	
	Barbiturates	
Analgesic drugs	*Codeine* *Morphine*	Because of their tendency to produce respiratory depression, these agents should be used with caution.
	Hydromorphone	
	Fentanyl	
	Meperidine	
Ophthalmic drugs	*Timolol* *Betaxol*	
	Carbachol	
	Tropicamide	Muscarinic antagonist
Psychiatric drugs	**Lithium**	Reduction of acetylcholine synthesis and release Increased rate of acetylcholine receptor turnover
	Promazine *Chlorpromazine*	Neuromuscular transmission impairment
	Amitriptyline *Droperidol*	Neuromuscular transmission impairment
	Haloperidol	
	Imipramine	
	Paraldeide	
	Amphetamines	
	Benzodiazepines	Because of respiratory depression, they should be used with caution.
Radiographic contrast	**Iodinate contrast**	As it may worsen myasthenic weakness, its administration should be avoided in patients with uncontrolled disease.
Muscle relaxants	**Dantrolene** **Baclofen**	Neuromuscular transmission block
	Thiocolchicoside	
Anticholinergic drugs	*Trihexyphenidyl* *Hyoscine*	Neuromuscular transmission block
	Otilonium	
Miscellaneous drugs	**Botulinum toxin**	Weakness in the region of local injection
	Amantadine	Possible weakness after administration

Bold entries are associated with more common or more severe adverse event. Italics are associated with less common or less severe adverse events

weakness and should not be used to evaluate treatment-related changes in individual patients [15].

Quantitative scores, based on the evaluation of selected muscle groups, are available as outcome measures. The MGFA quantitative MG (QMG) scoring includes 13 test items and, together with outcome measures as "post-intervention status" (PIS), is largely used in clinical practice and in therapeutic trials [15]. Other quantitative systems, such as the MG composite [16], the manual muscle test for MG [17], and the Besta Neurological Institute MG scale [18], are available.

Clinicians may choose among these systems provided they are consistent during patient follow-up.

MG activities of daily living (MG-ADL) is a patient-reported assessment of the disease impact on daily activities [19]. Other quality of life (QOL) measures, including the Italian versions of SF-36 [20] and MG-QOL15 [21], are available. The use of patient-oriented measures in clinical practice is recommended.

Diagnosis

MG is easily suspected in patients presenting with a typical pattern of fatigable muscle weakness. As symptoms and signs may be evident only after exertion, maneuvers that fatigue-specific muscle groups can be useful. Facial, ocular, oropharyngeal, axial, and limb muscles should be tested. Tendon reflexes are normal; pain and autonomic signs are absent.

The clinical diagnosis of MG is confirmed by electromyography (EMG) studies, pharmacologic testing, and serum Ab assay. Positive results on EMG confirm a postsynaptic defect of the NMT, the clinical response to cholinesterase inhibitors (ChE-Is) supports MG diagnosis, and detection of specific Abs confirms MG and identify Ab-related subgroups. In patients with neither AChR nor MuSK Abs on standard assay, EMG confirmation is crucial.

EMG studies

Repetitive nerve stimulation

Repetitive nerve stimulation (RNS) protocol includes 1–2 baseline trains of supramaximal nerve stimuli at low frequency (2–5 Hz) followed by isometric contraction of the muscle for 15–20 s, and, within 10 s after muscle contraction, by another train of low-frequency stimuli, which aims at recording facilitation. Three trains of stimuli are then given at 1, 3, and 5 min after muscle contraction to document post-activation exhaustion followed by gradual recovery.

The compound muscle action potential (CMAP) amplitude depends on the number of activated muscle fibers. In MG, the first stimulus evokes a normal CMAP unless weakness is very severe. RNS at low frequency is typically associated with a CMAP decrement greater than 10% between the first and fourth response, followed by a partial decrement repair producing a "U-shaped" curve [22]. Such "decremental response" is the neurophysiological equivalent of muscle fatigability.

In MG, post-activation facilitation (i.e., CMAP amplitude increment after a brief voluntary contraction) is between 10 and 25% and rarely reaches 50%. Post-activation exhaustion, i.e., a further CMAP decrement, is usually seen 1–3 min after muscle contraction [22].

RNS sensitivity depends on testing weak muscles and is increased by muscle warming at 32–34 °C. Cholinesterase inhibitors (ChE-Is) should be withdrawn, when possible, 12 h before testing.

RNS of hand muscles is well tolerated. Examination of proximal muscles increases diagnostic yield but is more painful and associated with movement artifacts. Stimulation of the accessory nerve is well tolerated and should be performed when RNS in distal muscles is negative [23]. Examination of cranial muscles (nasalis, orbicularis oculi, masseter) increases RNS sensitivity in patients with ocular symptoms and in MuSK-MG [24].

A decremental response on low-rate RNS is present in other primary disorders of NMT and, less frequently, in amyotrophic lateral sclerosis (ALS) and radiculopathy. Most congenital myasthenic syndromes (CMSs) have the same pattern as MG on the above RNS/activation protocol. On the other hand, Lambert-Eaton myasthenic syndrome (LEMS) and botulism are characterized by low amplitude of the first CMAP, further CMAP decrement during low-rate RNS and CMAP amplitude restoration (potentiation) during high-rate RNS or immediately after a brief maximal muscle contraction [22].

Single-fiber electromyography

Single-fiber electromyography (SF-EMG) measures the neuromuscular jitter, i.e., the latency variability in the depolarization of muscle fibers belonging to the same motor unit. In MG, the reduced EPP amplitude prolongs the time to reach the firing threshold (increased jitter) and muscle fiber AP can be blocked [22].

SF-EMG is generally performed during voluntary muscle contraction. In non-cooperative patients (as in children), APs can be elicited by axon stimulation; in this case, jitter measures the interval variations between the stimulus and the AP of single muscle fibers. Jitter is expressed as mean consecutive difference of inter-potential intervals [25]. The extensor communis digitorum muscle is generally tested first; in case of negative results, the study is extended to facial muscles.

SF-EMG is the most sensitive test for MG diagnosis, and, when limb and facial muscles are examined, positive results are recorded in > 90% of cases [26, 27]. SF-EMG of cranial muscles has a high diagnostic yield in patients with ocular myasthenia [27] or MuSK-MG [6]. However, an increased jitter is not specific as, apart from other diseases of NMT, it can be found in neurogenic and myopathic conditions [27].

Pharmacological testing

ChE-Is prolongs ACh half-life at the synaptic cleft and, in MG, improve NMT as ACh can repeatedly bind the remaining AChRs. A positive response to ChE-Is, as *unequivocal*

clinical improvement, although not specific, strongly supports the diagnosis of MG.

Parenterally given short-acting agents, as edrophonium and neostigmine, are used for diagnostic purposes. Clinical response should be evaluated on symptomatic muscles and compared with that obtained from a previous placebo (or atropine) injection [7]. Edrophonium (formerly called Tensilon®) test starts with the injection of a 2 mg dose; in the absence of response and adverse effects (AEs), after 1 min, another 2–5 mg are given; clinical reaction is evident within 10–60 s and lasts for 1.5 to 10 min. Edrophonium injection is associated with lacrimation, sweating, and fasciculation. As bronchoconstriction and severe bradycardia may occur, atropine should always be kept at reach. In the atropine-neostigmine test, 1–2 mg of neostigmine is given intramuscularly after subcutaneous administration of 0.5 mg of atropine; clinical effect appears 15–30 min after the second injection. The response to ChE-Is can be evaluated 45–60 min after the oral administration of pyridostigmine 60 mg. Currently, neostigmine and pyridostigmine have largely replaced edrophonium in clinical practice.

In MG, the rate of positive responses to ChE-Is is around 90%. In patients with MuSK Abs, ChE-I injection is often ineffective, elicits cholinergic side effects, and may even induce clinical deterioration [6].

A positive reaction to ChE-Is is observed in CMS and, to a lesser extent, in LEMS. False responses have been reported in ALS, Guillain-Barrè syndrome [28], and in single patients with brainstem lesions [29].

Antibody assays

Anti-AChR and -MuSK Abs are routinely tested by a radioimmunoprecipitation assay (RIPA). Quality controls for these assays have been promoted by the Italian Association of Neuroimmunology, and specific guidelines have been published [30].

When MG is suspected on clinical ground, anti-AChR Abs are the first to be tested. Anti-MuSK should be assayed in all AChR-negative cases. As Abs can be undetectable at onset and become positive afterwards, negative results on RIPA should be confirmed in two subsequent assays, 6 months apart.

Anti-AChR and anti-MuSK are very specific, and, in practice, their detection in patients with congruous symptoms confirms the diagnosis. The diagnostic accuracy of anti-AChR RIPA ranges 97–99% [26] as positive results may rarely be found in ALS [31] and in association with thymoma (these patients are at risk of developing MG) [32]. Abs to MuSK have never been reported outside MG [33].

In patients negative on standard RIPA, MG-specific Abs to AChR or MuSK expressed on cell membrane can be detected on cell-based assays (CBA), more commonly in children and in patients with mild disease [34, 35]. Anti-LRP4 and anti-agrin Abs have been reported at different rates in dSN-MG [2, 13]. Commercial assays for these Abs are not available.

A diagnostic algorithm is shown in Fig. 1.

Additional diagnosing testing

The ice-pack test can be helpful in patients with ptosis. It is performed by applying an iced pack across the eyelid for 2 min; ptosis modification is evaluated 5–10 s after ice removal. A palpebral fissure increase > 2 mm is considered a positive response [36]. The ice-pack test has a high negative predictable value (94%) [36] and is a useful bed-side test provided the final diagnosis is based on Ab assay and EMG studies.

Abs to the intracellular muscle proteins, titin and ryanodine receptor (RyR), can be detected in AChR-MG, strongly associated with thymoma (anti-titin Abs in 95% and anti-RyR in 70% of thymoma patients) and to a lesser extent with late-onset disease. These Abs are useful markers of thymoma in early-onset AChR-MG [33].

Upon MG diagnosis, all patients (especially those with AChR-MG) should undergo a radiological study of the mediastinum through computed tomography or magnetic resonance imaging.

Given MG high-rate association with thyroid disease, specific Abs and hormones should be tested. Screening for medical conditions, such as diabetes, arterial hypertension, osteoporosis, and active infections, which could complicate management, is recommended.

Differential diagnosis

In seronegative patients, MG must first be distinguished from other disorders of NMT. The differential diagnosis with CMS should be undertaken by referral centers [37].

ALS with prevalent bulbar symptoms can be misdiagnosed as MG. Of note, in these patients, ChE-Is may induce mild improvement, RNS and SF-EMG can show NMT defect, and anti-AChR [33] and anti-LRP4 Abs can be detected [38]. However, EMG studies can clarify the diagnosis.

In patients with symmetrical ophthalmoparesis, a mitochondrial disorder should be considered. Miller-Fisher syndrome may be confused with MG when ataxia and pupillary changes are not evident; in these patients, SF-EMG often shows abnormal NMT [39].

Treatment

Treatment is aimed at achieving satisfactory control of symptoms minimizing the risk for adverse events (AEs). This goal can be achieved through individualized therapeutic choices.

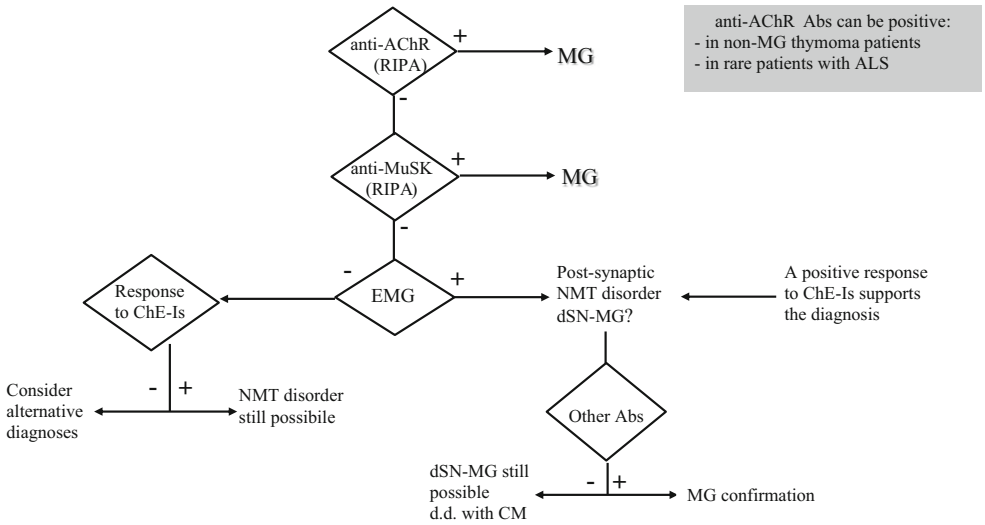

Fig. 1 Algorithm for the diagnosis of MG. Ab: antibody; AChR: acetylcholine receptor; ALS: amyotrophic lateral sclerosis; ChE-Is: cholinesterase inhibitors; CM: congenital myasthenia; d.d.: differential diagnosis; dSN-MG: double seronegative myasthenia gravis; EMG: electromyography; MG: myasthenia gravis; MuSK: muscle-specific tyrosine-kinase; NMT: neuromuscular transmission; RIPA: radio-immunoprecipitation assay

Symptomatic treatment

It is based on ChE-Is, with pyridostigmine (Mestinon®) being the agent for oral treatment in Italy.

The great majority of MG patients respond, to some extent, to Mestinon with inter-individual variability in tolerance. Treatment is started at 30 mg three to four times daily. If well tolerated, it can be increased to 60 mg (1 tablet) four times daily, and, when needed, up to 90 mg five times daily. Higher doses are associated with little benefit and AEs. For infants and children, dosage is based on body weight starting at 1 mg/kg. Pyridostigmine affect peaks 1–1.5 h after ingestion and wears off in 3.5–4 h [40]. A sustained-release preparation (Mestinon-Timespan® 180 mg) can be prescribed at bedtime for patients symptomatic early in the morning or during the night. AEs mostly consist of gut hyperactivity, diarrhea, hyperhidrosis, and fasciculations and can usually be controlled by dose adjusting. Cholinergic crisis with severe clinical deterioration is currently a rare event, as early immunosuppression has reduced the need for high doses of symptomatic therapy. In MuSK-MG, ChE-Is should not be used as generally ineffective and associated with AEs [6].

Immunosuppressive therapy

Immunosuppression is used in all patients with disabling symptoms not adequately controlled with ChE-Is. Steroids are generally first-line therapy because of their rapid effect; steroid-sparing agents are commonly associated in long-term treatment.

Steroids

Oral prednisone is generally used because of its strong immunosuppressive activity and relatively short half-life [40]. The initial dose in generalized MG is 0.75–1 mg/kg/day. Clinical response is usually observed within 2–3 weeks and maximal improvement within 2–3 months. Treatment can also be started at low doses (5–10 mg) with an increasing schedule (i.e., 5 mg every 5–7 days) [41, 42] .

MG worsening can occur in the initial phase of steroid administration [7, 41, 42]. As this "early deterioration" can be severe and progress to respiratory failure, patients with bulbar weakness should be hospitalized for treatment initiation and carefully monitored; plasma exchange or intravenous immunoglobulin (IVIg) is recommended for severely affected patients.

Patients with ocular or mild symptoms can start prednisone as outpatients, at lower doses [43]. Once stable improvement is achieved, treatment is usually shifted to alternate-day administration and gradually tapered to the minimum effective dose [40–42].

Steroid AEs include osteoporosis, cataract, diabetes, hypertension, glaucoma, weight gain, and skin disorders. Adequate prevention (salt and sugar dietary restriction, proton pump inhibitors) and treatment (i.e., diphosphonates for osteoporosis) as well as specialist monitoring should be planned.

Immunosuppressants

All these agents have a longer latency of effect than prednisone. Immunosuppressants are mostly used as "steroid-sparing agents," can replace steroids in long-term treatment, and can be used in monotherapy in patients with mild non-progressive MG.

Before treatment, active infections, particularly viral hepatitis and tuberculosis, must be excluded.

Azathioprine is the first-choice immunosuppressant in MG. It proved effective as steroid-sparing agent in a randomized controlled trial (RCT) [44]. Treatment is started at 50 mg (1 tablet) once a day, increasing of 50 mg/week up to 2.5 mg/kg/day. This dosage is maintained for 10–12 months, then is

gradually tapered to 1 mg/kg daily [42]. Few patients may be intolerant of azathioprine developing a flu-like syndrome with fever, malaise, and vomiting in the first 2 weeks of treatment.

Liver function and complete blood count should be evaluated each week for 1 month, then every 2 months. Increased serum levels of liver enzymes usually normalize with dose tapering; persistent hepatic or pancreatic dysfunction requires azathioprine withdrawal.

Azathioprine should be reduced when white blood count (WBC) falls below 4×10^9/l and must be withheld if WBC reaches 3×10^9/l. Mild macrocytic anemia is a common AE [42].

Individuals carrying nonfunctional alleles of thiopurine S-methyltransferase (TPMT), the enzyme that inactivates azathioprine, may experience severe myelosuppression when receiving azathioprine at conventional doses [45]. TPMT functional and genetic assays have not yet entered the routine practice.

Although two RCTs (severely limited by the protocol design) did not demonstrate additional benefit of mycophenolate mofetil (MMF) over prednisone [46], several studies support MMF efficacy in MG patients, including those with refractory disease [47]. MMF is initiated at 500 mg/day with an escalating regimen up to 1.5–2 g/daily. Improvement has been reported after 2–3 months, with maximum benefit after 6–18 months. AEs include gastrointestinal discomfort, leucopenia, and infection; liver toxicity is less common than with azathioprine [48].

Cyclosporine effectiveness in MG has been proved in a RCT [49], not followed, however, by further reports on large series. Treatment is started at 4–5 mg/kg/day in two divided doses. Improvement is usually evident after 2 months, with a peak after 3–4 months. In chronic treatment, dosages of 2–3 mg/kg/day are often adequate.

Periodic controls of WBC and liver enzymes are necessary. Renal function should be monitored, titrating cyclosporine to keep creatinine level < 150% of pretreatment value [42]. As chronic administration entails the risk of severe AEs (nephrotoxicity, hypertension, skin malignancy, tremor, hypertrichosis, and gingival hypertrophy), cyclosporine is usually considered after failure of other agents.

Tacrolimus proved effective in retrospective studies and two RCTs [50]. A dose of 3 mg/day is generally accepted for MG treatment. Its safety profile is like that of cyclosporine, but it was shown to be less nephrotoxic at low doses (0.1 mg/kg/day) [51].

Measuring cyclosporine and tacrolimus concentrations in blood is helpful, especially in the early stages of treatment.

RCTs investigating the steroid-sparing effect of methotrexate yielded conflicting results [52, 53]. This agent is not expensive and generally well tolerated but has had limited use in MG so far.

Oral treatment with cyclophosphamide is limited by severe AEs as alopecia, leukopenia, nausea, vomiting, hemorrhagic cystitis, sterility, increased risk for infection and malignancy, and is restricted to patients who have failed less toxic agents including rituximab [54]. Pulse intravenous treatment (500 mg/m^2/monthly) is better tolerated and proved effective in refractory disease [55].

Rituximab (Mabthera®) is an anti-CD20 monoclonal Ab which depletes circulating B cells. From retrospective observations and meta-analyses, rituximab appears to be effective in all forms of MG, especially in MuSK-MG [56, 57]. The results of a RCT in AChR-MG [ClinicalTrials.gov Identifier: NCT02110706] have not yet been published. Rituximab is predominantly used in patients refractory to conventional immunosuppression [54], with two regimens: 375 mg/m^2/week for four consecutive weeks and 1000 mg on day 1 and day 15. Most patients need more than one treatment cycle. In the absence of an established protocol, the decision to repeat rituximab should be based on clinical observation and on circulating B cell subpopulations. Rituximab is well tolerated with a low rate of severe AEs [57]. Progressive multifocal leukoencephalopathy has been reported in two MG patients previously treated with other immunosuppressants [56, 58].

A recent RCT showed no significant benefit of belimumab, a mAb targeting the B cell activating factor (BAFF), in generalized AChR-MG [59].

Eculizumab (Soliris®) binds to the protein C5 preventing complement activation. This agent has been approved for refractory AChR-MG, in view of the results a RCT mostly favoring eculizumab over placebo, in association with conventional immunosuppression [60].

Short-term treatments

Plasma exchange and IVIg have a rapid albeit short-lived effect, and additional immunosuppression is usually needed. Plasma-exchange standard protocol consists of 3–6 exchanges of 1–1.5 plasma volumes on alternate days; IVIg is usually administered at 1–2 g/kg over 2–5 days. They are mainly used in treating disease exacerbations, in preventing MG deterioration at the start of steroid therapy and in preparation for surgery in selected cases. IVIg can be used as periodic treatment in patients intolerant of immunosuppressants [40, 54].

Plasma exchange and IVIg were found to have comparable efficacy in the treatment of respiratory crisis [61] and moderate to severe MG [62]. Plasma-exchange AEs are mainly related to central venous catheters; IVIg administration can be complicated by allergic reaction, hemolysis, and thrombosis. The choice between these options is based on patient's comorbidities, procedure's risks, and medical facilities. In patients with life-threatening symptoms, plasma exchange is preferred because of its more rapid effect, while for outpatients, IVIg is more suitable [63].

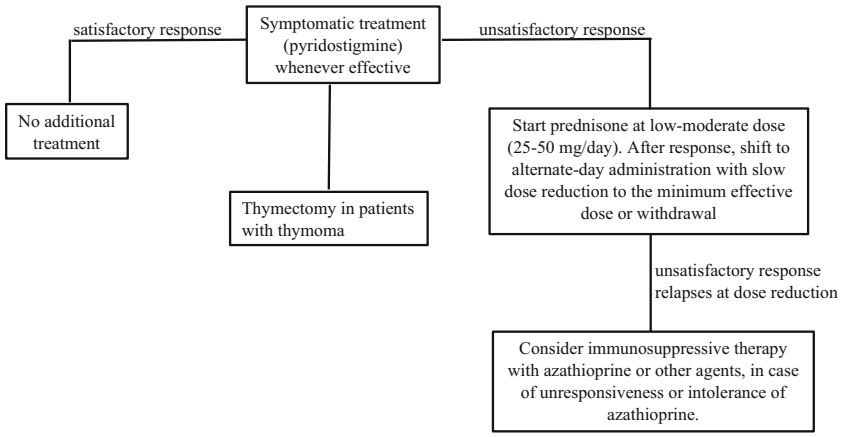

Fig. 2 Treatment flow chart: ocular myasthenia

Semi-selective immunoadsorption, which removes IgG leaving other plasma components unaltered, represents a valuable alternative in patients requiring intensive plasma-exchange protocols [64].

Subcutaneous IgG may be a practical option in chronic management of MG. It proved effective and well tolerated in uncontrolled observations [65].

Thymectomy

The rational for therapeutic thymectomy, i.e., thymectomy in non-thymoma patients to improve the disease course, relies on the pathogenic role of the thymus in MG. Its efficacy in generalized AChR-MG was assessed in a RCT comparing transsternal thymectomy plus prednisone with

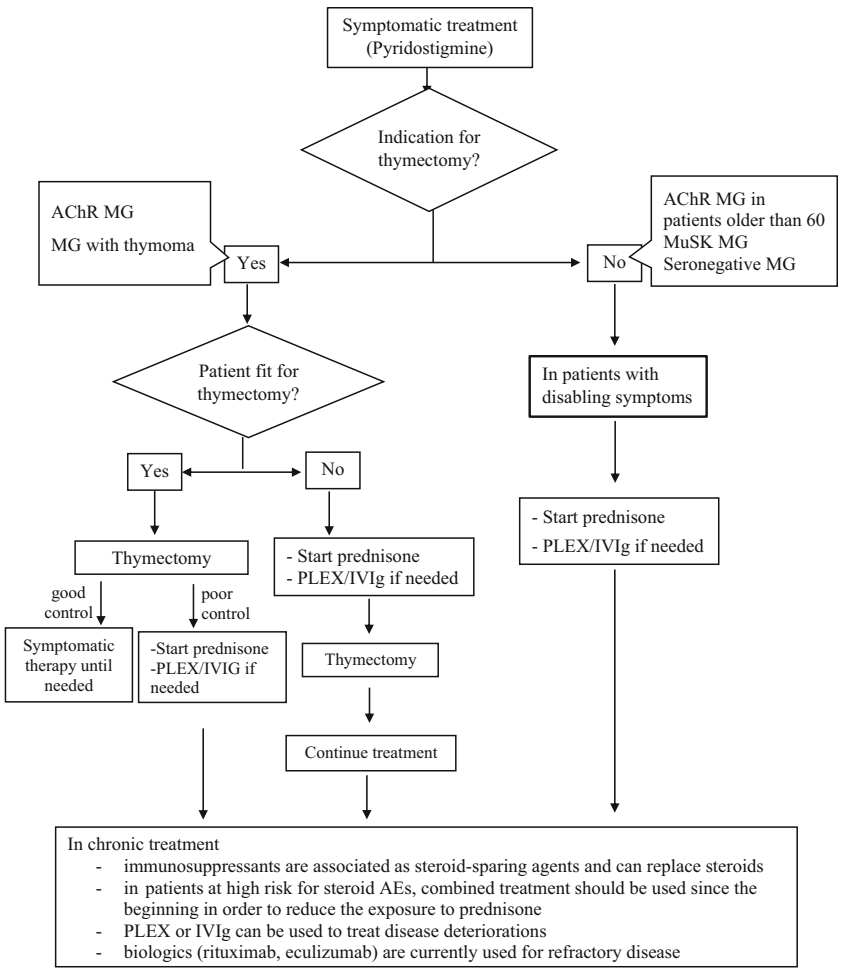

Fig. 3 Treatment flow chart: generalized myasthenia. AChR-MG: acetylcholine receptor antibody-positive myasthenia gravis; AEs: adverse events; MuSK-MG: muscle-specific kinase antibody-positive myasthenia gravis; PLEX: plasma exchange; IVIg: intravenous immunoglobulin

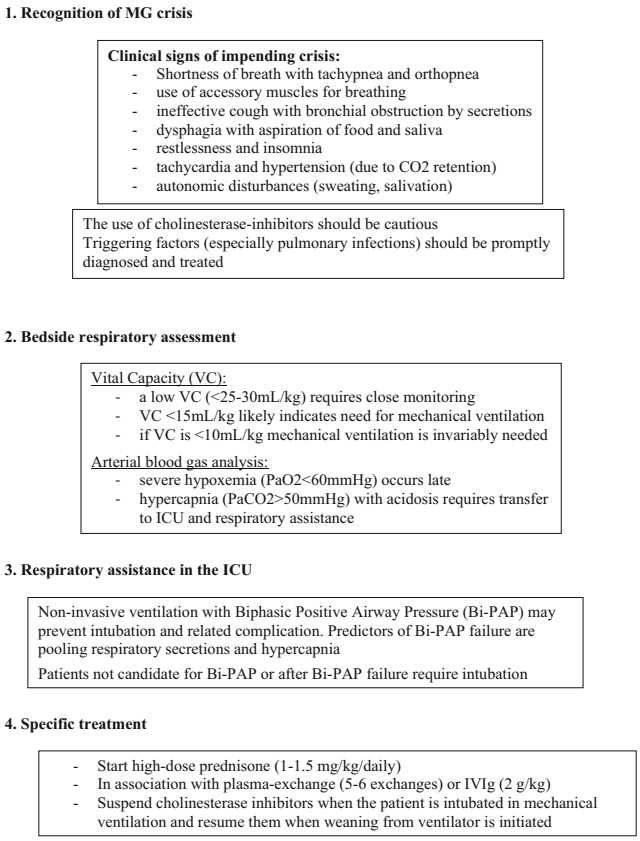

Fig. 4 Management of respiratory crisis (see also ref. nos. 8–9). ICU: intensive care unit; IVIg: intravenous immunoglobulin

prednisone alone. Thymectomy proved effective in primary end-points (the average QMG score and prednisone requirement were significantly lower in the thymectomy group) as well as in several secondary outcomes [66], although the benefit of thymectomy in patients older than 50 years of age remains undetermined [66].

Less invasive surgical approaches have been applied with increasing frequency. In Italy, considerable experience has been reached with video-assisted [67, 68] and robotic thymectomy [69], which proved effective and safe in MG patients. The indication for thymectomy in ocular MG is controversial. There is no evidence of a pathogenic link between the thymus and MG with Abs other than anti-AChR [3].

Radiologic evidence of a thymoma is an obvious indication to surgery. As additional treatment may be required, patients with thymoma should be managed by a multidisciplinary team. Even in thymoma patients, thymectomy should never be an emergency treatment but should be performed once a stable control of MG has been achieved.

Treatment flow charts are summarized in Figs. 2, 3, and 4.

Medications with contraindications in MG are listed in Table 1.

MG treatment in pregnancy

Pyridostigmine is safe during pregnancy and lactation [54]. Prednisone is the immunosuppressant of choice during pregnancy [54] but should be avoided during lactation for daily doses > 10 mg [70]. Azathioprine and cyclosporine do not increase the risk for teratogenicity, whereas MMF, methotrexate, and cyclophosphamide must be avoided before conception (both in female and male patients) and during pregnancy [54, 71]. Plasma exchange and IVIg can be used weighing maternal/fetal risks [54]. Rituximab administration temporarily depletes B cell in the child [72].

In the management of eclampsia, injectable magnesium should be avoided or, at least, serum magnesium levels should be monitored (concentrations ranging 3.5–7 mEq/l are considered safe) [73]. Methyldopa and hydralazine should be preferred in treating hypertension; phenytoin and levetiracetam are relatively safe in seizure prevention and treatment [74].

Transient neonatal MG occurs in 15–20% of babies born to myasthenic mothers and may require symptomatic treatment as well as nutritional and respiratory assistance [54].

Myasthenia gravis and vaccination

The main concern with vaccination in MG is that immunosuppression may prevent a sustained specific Ab response. Live attenuated vaccines are contraindicated, whereas inactivated vaccines, such as influenza and pneumococcal vaccines, are safe [75]. Annual flu vaccination is well tolerated and can prevent MG deterioration related to respiratory complications [76].

Compliance with ethical standards

Conflict of interest Amelia Evoli served on an advisory board for Alexion and as jury member for research grant award for Grifols.

Giovanni Antonini received conference honoraries from Kedrion, Sanofi-Genzyme and travel grants from Kedrion, Sanofi-Genzyme, Pfizer, Almylan.

Carlo Antozzi has no conflicts of interest to disclose.

Antonio Di Muzio has no conflicts of interest to disclose.

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Maurizio Inghilleri has no conflicts of interest to disclose.

Rocco Liguori served on advisory boards for Biogen, Sanofi-Genzyme, Argon Healthcare s.r.l., Editree Eventi s.r.l., received Lecture fees from Dynamicom Education, SIMG Service, Adnkronos Salute unipersonale s.r.l., DOC Congress s.r.l., First Class s.r.l., and is a consultant for Alfasigma and Amicus Therapeutics s.r.l.

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Elena Pegoraro reports personal fees from PTC Therapeutics, Santhera, Roche and Sanofi-Genzyme.

Roberta Ricciardi has no conflicts of interest to disclose.

Carmelo Rodolico has no conflicts of interest to disclose.

References

1. Andersen JB, Heldal AT, Engeland A, Gihlus NE (2014) Myasthenia gravis epidemiology in a national cohort; combining multiple disease registries. Acta Neurol Scand Suppl 198:26–31
2. Gihlus NE, Verschuuren JJ (2015) Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol 14:1023–1036
3. Marx A, Pfister F, Schalke B, Saruhan-Direskeneli G, Melms A, Ströbel P (2013) The different roles of the thymus in the pathogenesis of the various myasthenia gravis subtypes. Autoimmun Rev 12:875–884
4. Burden SJ, Yumoto N, Zhang W (2013) The role of MuSK in synapse formation and neuromuscular disease. Cold Spring Harb Perspect Biol 5:009167
5. Huijbers MG, Zhang W, Klooster R, Niks EH, Friese MB, Straasheijm KR, Thijssen PE, Vrolijk H, Plomp JJ, Vogels P, Losen M, van der Maarel SM, Burden SJ, Verschuuren JJ (2013) MuSK IgG4 autoantibodies cause myasthenia gravis by inhibiting binding between MuSK and Lrp4. Proc Natl Acad Sci U S A 110:20783–20788
6. Evoli A, Padua L (2013) Diagnosis and therapy of myasthenia gravis with antibodies to muscle-specific kinase. Autoimmun Rev 12:931–935
7. Keesey JC (2004) Clinical evaluation and management of myasthenia gravis. Muscle Nerve 29:484–505
8. Wendell LC, Levine JM (2011) Myasthenic crisis. Neurohospitalist 1:16–22
9. Rabinstein AA (2015) Acute neuromuscular respiratory failure. Continuum (Minneap Minn) 21:1324–1345
10. Mehrizi M, Fontem RF, Gearhart TR, Pascuzzi RM (2012) Medications and myasthenia gravis (a reference for health care professionals). Myasthenia Gravis Foundation of America. http://www.myasthenia.org/portals/0/draft_medications_and_myasthenia_gravis_for_MGFA_website. Published Summer 2015
11. Makarious D, Horwood K, Coward JIG (2017) Myasthenia gravis: an emerging toxicity of immune checkpoint inhibitors. Eur J Cancer 82:128–136
12. Schaller SF, Fink H (2013) Sugammadex as a reversal agent for neuromuscular block: an evidence-based review. Core Evid 8:57–67
13. Zisimopoulou P, Evangelakou P, Tzartos J, Lazaridis K, Zouvelou V, Mantegazza R, Antozzi C, Andreetta F, Evoli A, Deymeer F, Saruhan-Direskeneli G, Durmus H, Brenner T, Vaknin A, Berrih-Aknin S, Frenkian Cuvelier M, Stojkovic T, DeBaets M, Losen M, Martinez-Martinez P, Kleopa KA, Zamba-Papanicolaou E, Kyriakides T, Kostera-Pruszczyk A, Szczudlik P, Szyluk B, Lavrnic D, Basta I, Peric S, Tallaksen C, Maniaol A, Tzartos SJ (2014) A comprehensive analysis of the epidemiology and clinical characteristics of anti-LRP4 in myasthenia gravis. J Autoimmun 52:139–145
14. Osserman KE, Genkins G (1971) Studies in myasthenia gravis: review of a twenty-year experience in over 1200 patients. Mt Sinai J Med 38:497–537
15. Jaretzki A 3rd, Barohn RJ, Ernstoff RM et al (2000) Myasthenia gravis: recommendations for clinical research standards. Task force of the medical scientific advisory Board of the Myasthenia Gravis Foundation of America. Neurology 5:16–23
16. Burns TM (2012) The MG composite: an outcome measure for MG for use in clinical trials and everyday practice. Ann N Y Acad Sci 1274:99–106
17. Sanders DB, Tucker-Lipscomb B, Massey JM (2003) A simple manual muscle test for myasthenia gravis. Validation ad comparison with the QMG score. Ann N Y Acad Sci 998:440–444
18. Antozzi C, Brenna G, Baggi F, Camera G, Maggi L, Rezzani C, Montomoli C, Mantegazza R (2016) Validation of the Besta Neurological Institute rating scale for myasthenia gravis. Muscle Nerve 53:32–37
19. Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ (1999) Myasthenia gravis activities of daily living profile. Neurology 52:1487–1489
20. Padua L, Evoli A, Aprile I, Caliandro P, D'Amico P, Rabini A, Tonali P (2002) Quality of life in patients with myasthenia gravis. Muscle Nerve 25:466–467
21. Raggi A, Leonardi M, Ayadi R, Antozzi C, Maggi L, Baggi F, Mantegazza R (2017) Validation of the Italian version of the 15-item myasthenia gravis quality-of-life questionnaire. Muscle Nerve 56:716–720
22. Howard JF Jr (2013) Electrodiagnosis of disorders of neuromuscular transmission. Phys Med Rehabil Clin N Am 24:169–192
23. Shumm F, Stohr M (1984) Accessory nerve stimulation in the assessment of myasthenia gravis. Muscle Nerve 7:147–151
24. Oh SJ, Hatanaka Y, Hemmi S, Young AM, Scheufele ML, Nations SP, Lu L, Claussen GC, Wolfe GI (2006) Repetitive nerve stimulation of facial muscles in MuSK antibody-positive myasthenia gravis. Muscle Nerve 33:500–504
25. Sanders DB, Stålberg EV (1996) AAEM Minimonograph #25: single-fiber electromyography. Muscle Nerve 19:1069–1083
26. Benatar M (2006) A systematic revue of diagnostic studies in myasthenia gravis. Neuromuscul Disord 16:459–467
27. Sanders DB (2002) The clinical impact of single-fiber electromyography. Muscle Nerve 11:S15–S20
28. Oh SJ, Cho HK (1990) Edrophonium responsiveness not necessarily diagnostic of myasthenia gravis. Muscle Nerve 13:187–191
29. Dirr LY, Donofrio PD, Patton JF, Troost BT (1989) A false-positive edrophonium test in a patient with a brainstem glioma. Neurology 39:865–867
30. Andreetta F, Rinaldi E, Bartoccioni E et al (2017) Diagnostics of myasthenic syndromes: detection of anti-AChR and anti-MuSK antibodies. Neurol Sci 38(Suppl 2):S253–S257
31. Mehanna R, Patton EL Jr, Phan CL et al (2012) Amyotrophic lateral sclerosis with positive anti-acetylcholine receptor antibodies. Case report and review of the literature. J Clin Neuromuscul Dis 14:82–85
32. Vernino S, Lennon VA (2004) Autoantibody profiles and neurological correlations of thymoma. Clin Cancer Res 10:7270–7275
33. Meriggioli MN, Sanders DB (2012) Muscle autoantibodies in myasthenia gravis: beyond diagnosis? Expert Rev Clin Immunol 8:427–438
34. Rodríguez Cruz PM, Al-Hajjar M, Huda S et al (2015) Clinical features and diagnostic usefulness of antibodies to clustered acetylcholine receptors in the diagnosis of seronegative myasthenia gravis. JAMA Neurol 72:642–649
35. Huda S, Waters P, Woodhall M, Leite MI, Jacobson L, de Rosa A, Maestri M, Ricciardi R, Heckmann JM, Maniaol A, Evoli A, Cossins J, Hilton-Jones D, Vincent A (2017) IgG-specific cell-based assay detects potentially pathogenic MuSK-Abs in seronegative MG. Neurol Neuroimmunol Neuroinflamm 4:e357

36. Fakiri MO, Tavy DL, Hama-Amin AD, Wirtz PW (2013) Accuracy of the ice test in the diagnosis of myasthenia gravis in patients with ptosis. Muscle Nerve 48:902–904
37. Maggi L, Bernasconi P, D'Amico A et al (2018) Italian recommendations for diagnosis and management of congenital myasthenic syndromes. Neurol Sci. https://doi.org/10.1007/s10072-018-3682-x
38. Tzartos JS, Zisimopoulou P, Rentzos M, Karandreas N, Zouvelou V, Evangelakou P, Tsonis A, Thomaidis T, Lauria G, Andreetta F, Mantegazza R, Tzartos SJ (2014) LRP4 antibodies in serum and CSF from amyotrophic lateral sclerosis patients. Ann Clin Transl Neurol 1:80–87
39. Lo YL, Chan LL, Pan A et al (2004) Acute ophthalmoparesis in the anti-GQ1b antibody syndrome: electrophysiological evidence of neuromuscular transmission defect in the orbicularis oculi. J Neurol Neurosurg Psychiatry 75:436–440
40. Mantegazza R, Bonanno S, Camera G et al (2011) Current and emerging therapies for the treatment of myasthenia gravis. Neuropsychiatr Dis Treat 7:151–160
41. Sghirlanzoni A, Peluchetti D, Mantegazza R, Fiacchino F, Cornelio F (1984) Myasthenia gravis: prolonged treatment with steroids. Neurology 34:170–174
42. Sanders DB, Evoli A (2010) Immunosuppressive therapies in myasthenia gravis. Autoimmunity 43:428–435
43. Kerty E, Elsais A, Argov Z, Evoli A, Gilhus NE (2014) EFNS/ENS guidelines for the treatment of ocular myasthenia. Eur J Neurol 21:687–693
44. Palace J, Newsom-Davis J, Lecky B (1998) A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. Neurology 50:1778–1783
45. Dean L (2012) Azathioprine therapy and TPMT genotype. In: Pratt V, McLeod H, Dean L, Malheiro A, Rubinstein W (eds) Source medical genetics summaries [Internet]. National Center for Biotechnology Information (US), Bethesda [updated 2016 May 3]
46. Sanders DB, Siddiqi ZA (2008) Lessons from two trials of mycophenolate mofetil in myasthenia gravis. Ann N Y Acad Sci 1132:249–255
47. Hehir MK, Burns TM, Alpers J, Conaway MR, Sawa M, Sanders DB (2010) Mycophenolate mofetil in AChR-antibody-positive myasthenia gravis: outcomes in 102 patients. Muscle Nerve 41:593–598
48. Gotterer L, Li Y (2016) Maintenance immunosuppression in myasthenia gravis. J Neurol Sci 369:294–302
49. Tindall RS, Phillips JT, Rollins JA et al (1993) A clinical therapeutic trial of cyclosporine in myasthenia gravis. Ann N Y Acad Sci 681:539–551
50. Cruz JL, Wolff ML, Vanderman AJ, Brown JN (2015) The emerging role of tacrolimus in myasthenia gravis. Ther Adv Neurol Disord 8:92–103
51. Nagane Y, Utsugisawa K, Obara D, Kondoh R, Terayama Y (2005) Efficacy of low-dose FK506 in the treatment of myasthenia gravis-a randomized pilot study. Eur Neurol 53:146–150
52. Heckmann JM, Rawoot A, Bateman K et al (2015) A single-blinded trial of methotrexate versus azathioprine as steroid-sparing agents in generalized myasthenia gravis. BMC Neurol 11:97
53. Pasnoor M, He J, Herbelin L, Burns TM, Nations S, Bril V, Wang AK, Elsheikh BH, Kissel JT, Saperstein D, Shaibani JA, Jackson C, Swenson A, Howard JF Jr, Goyal N, David W, Wicklund M, Pulley M, Becker M, Mozaffar T, Benatar M, Pazcuzzi R, Simpson E, Rosenfeld J, Dimachkie MM, Statland JM, Barohn RJ, The Methotrexate in MG Investigators of the Muscle Study Group (2016) A randomized controlled trial of methotrexate for patients with generalized myasthenia gravis. Neurology 87:57–64
54. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, Kuntz N, Massey JM, Melms A, Murai H, Nicolle M, Palace J, Richman DP, Verschuuren J, Narayanaswami P (2016) International consensus guidance for management of myasthenia gravis: executive summary. Neurology 87:419–425
55. de Feo LG, Schottlender J, Martelli NA, Molfino NA (2002) Use of intravenous pulsed cyclophosphamide in severe, generalized myasthenia gravis. Muscle Nerve 26:31–36
56. Afanasiev V, Demeret S, Bolgert F, Eymard B, Laforêt P, Benveniste O (2017) Resistant myasthenia gravis and rituximab: a monocentric retrospective study of 28 patients. Neuromuscul Disord 27:251–258
57. Tandan R, Hehir MK 2nd, Waheed W, Howard DB (2017) Rituximab treatment of myasthenia gravis: a systematic review. Muscle Nerve 56:185–196
58. Kanth KM, Solorzano GE, Goldman MD (2016) PML in a patient with myasthenia gravis treated with multiple immunosuppressing agents. Neurol Clin Pract 6:e17–e19
59. Hewett K, Sanders DB, Grove RA, Broderick CL, Rudo TJ, Bassiri A, Zvartau-Hind M, Bril V, On behalf of the BEL115123 Study Group (2018) Randomized study of adjunctive belimumab in participants with generalized myasthenia gravis. Neurology 90(16):e1425–e1434
60. Howard JF Jr, Utsugisawa K, Benatar M, Murai H, Barohn RJ, Illa I, Jacob S, Vissing J, Burns TM, Kissel JT, Muppidi S, Nowak RJ, O'Brien F, Wang JJ, Mantegazza R, Mazia CG, Wilken M, Ortea C, Saba J, Rugiero M, Bettini M, Vidal G, Garcia AD, Lamont P, Leong WK, Boterhoven H, Fyfe B, Roberts L, Jasinarachchi M, Willlems N, Wanschitz J, Löscher W, de Bleecker J, van den Abeele G, de Koning K, de Mey K, Mercelis R, Wagemaekers L, Mahieu D, van Damme P, Smetcoren C, Stevens O, Verjans S, D'Hondt A, Tilkin P, Alves de Siqueira Carvalho A, Hasan R, Dias Brockhausen I, Feder D, Ambrosio D, Melo AP, Rocha R, Rosa B, Veiga T, Augusto da Silva L, Gonçalves Geraldo J, da Penha Morita Ananias M, Nogueira Coelho E, Paiva G, Pozo M, Prando N, Dada Martineli Torres D, Fernanda Butinhao C, Coelho E, Renata Cubas Volpe L, Duran G, Gomes da Silva TC, Otavio Maia Gonçalves L, Pazetto LE, Souza Duca L, Suriane Fialho TA, Gheller Friedrich MA, Guerreiro A, Mohr H, Pereira Martins M, da Cruz Pacheco D, Macagnan AP, de Cassia Santos A, Bulle Oliveira AS, Amaral de Andrade AC, Annes M, Cavalcante Lino V, Pinto W, Miranda C, Carrara F, Souza I, Genge A, Massie R, Campbell N, Bril V, Katzberg H, Soltani M, Ng E, Siddiqi Z, Phan C, Blackmore D, Vohanka S, Bednarik J, Chmelikova M, Cierny M, Toncrova S, Junkerova J, Kurkova B, Reguliova K, Zapletalova O, Pitha J, Novakova I, Tyblova M, Wolfova M, Jurajdova I, Andersen H, Harbo T, Vinge L, Mogensen A, Højgaard J, Witting N, Autzen AM, Pedersen J, Färkkilä M, Atula S, Nyrhinen A, Erälinna JP, Laaksonen M, Oksaranta O, Eriksson J, Harrison T, Desnuelle C, Sacconi S, Soriani MH, Decressac S, Moutarde J, Lahaut P, Solé G, le Masson G, Wielanek-Bachelet AC, Gaboreau M, Moreau C, Wilson A, Vial C, Bouhour F, Gervais-Bernard H, Merle H, Hourquin C, Lacour A, Outteryck O, Vermersch P, Zephir H, Millois E, Deneve M, Deruelle F, Schoser B, Wenninger S, Stangel M, Alvermann S, Gingele S, Skripuletz T, Suehs KW, Trebst C, Fricke K, Papagiannopoulos S, Bostantzopoulou S, Vlaikidis N, Zampaki M, Papadopoulou N, Mitsikostas DD, Kasioti E, Mitropoulou E, Charalambous D, Rozsa C, Horvath M, Lovas G, Matolcsi J, Szabo G, Szabadosne B, Vecsei L, Dezsi L, Varga E, Konyane M, Gross B, Azrilin O, Greenbereg N, Bali Kuperman H, Antonini G, Garibaldi M, Morino S, Troili F, di Pasquale A, Filla A, Costabile T, Marano E, Sacca F, Marsil A, Puorro G, Maestri Tassoni M, de Rosa A, Bonanno S, Antozzi C, Maggi L, Campanella A, Angelini C, Cudia P, Pegoraro V, Pinzan E, Bevilacqua F, Orrico D, Bonifati DM, Evoli A, Alboini PE, D'Amato V, Iorio R, Inghilleri M, Fionda L, Frasca V, Giacomelli E, Gori M, Lopergolo D, Onesti E, Gabriele M, Patti F, Salvatore Caramma A, Messina S, Reggio E, Caserta C,

Uzawa A, Kanai T, Mori M, Kaneko Y, Kanzaki A, Kobayashi E, Masaki K, Matsuse D, Matsushita T, Uehara T, Shimpo M, Jingu M, Kikutake K, Nakamura Y, Sano Y, Nagane Y, Kamegamori I, Fujii Y, Futono K, Tsuda T, Saito Y, Suzuki H, Morikawa M, Samukawa M, Kamakura S, Shiraishi H, Mitazaki T, Motomura M, Mukaino A, Yoshimura S, Asada S, Kobashikawa T, Koga M, Maeda Y, Takada K, Takada MT, Yamashita Y, Yoshida S, Suzuki Y, Akiyama T, Narikawa K, Tsukita K, Meguro F, Fukuda Y, Sato M, Matsuo H, Fukudome T, Gondo Y, Maeda Y, Nagaishi A, Nakane S, Okubo Y, Okumura M, Funaka S, Kawamura T, Makamori M, Takahashi M, Hasuike T, Higuchi E, Kobayashi H, Osakada K, Taichi N, Tsuda E, Hayashi T, Hisahara S, Imai T, Kawamata J, Murahara T, Saitoh M, Shimohama S, Suzuki S, Yamamoto D, Konno S, Imamura T, Inoue M, Murata M, Nakazora H, Nakayama R, Ikeda Y, Ogawa M, Shirane M, Kanda T, Kawai M, Koga M, Ogasawara J, Omoto M, Sano Y, Arima H, Fukui S, Shimose S, Shinozaki H, Watanabe M, Yoshikawa C, van der Kooi A, de Visser M, Gibson T, Maessen J, de Baets M, Faber C, Keijzers MJ, Miesen M, Kostera-Pruszczyk A, Kaminska A, Kim BJ, Lee CN, Koo YS, Seok HY, Kang HN, Ra HJ, Kim BJ, Cho EB, Lee HL, Min JH, Seok J, Koh DY, Kwon JY, Lee JE, Park SA, Hong YH, Lim JS, Kim MR, Kim SM, Kim YH, Lee HS, Shin HY, Hwang EB, Shin MJ, Sazonov D, Yarmoschuk A, Babenko L, Malkova N, Melnikova A, Korobko D, Kosykh E, Pokhabov D, Nesterova Y, Abramov V, Balyazin V, Casasnovas Pons C, Alberti Aguilo M, Homedes-Pedret C, Palacios NJ, Lazaro A, Diez Tejedor E, Fernandez-Fournier M, Lopez Ruiz P, Rodriguez de Rivera FJ, Salvado Figueras M, Gamez J, Salvado M, Cortes Vicente E, Diaz-Manera J, Querol Gutierrez L, Rojas Garcia R, Vidal N, Arribas-Ibar E, Piehl F, Hietala A, Bjarbo L, Lindberg C, Jons D, Andersson B, Sengun I, Ozcelik P, Tuga C, Ugur M, Boz C, Altiparmak D, Gazioglu S, Ozen Aydin C, Erdem-Ozdamar S, Bekircan-Kurt CE, Yilmaz E, Acar NP, Caliskan Y, Efendi H, Aydinlik S, Cavus H, Semiz C, Tun O, Terzi M, Dogan B, Onar MK, Sen S, Cavdar TK, Norwood F, Dimitriou A, Gollogly J, Mahdi-Rogers M, Seddigh A, Maier G, Sohail F, Sathasivam S, Arndt H, Davies D, Watling D, Rivner M, Hartmann JE, Quarles B, Smalley N, Amato A, Cochrane T, Salajegheh M, Roe K, Amato K, Toska S, Wolfe G, Silvestri N, Patrick K, Zakalik K, Katz J, Miller R, Engel M, Bravver E, Brooks B, Plevka S, Burdette M, Sanjak M, Kramer M, Nemeth J, Schommer C, Juel V, Guptill J, Hobson-Webb L, Beck K, Carnes D, Loor J, Anderson A, Lange D, Agopian E, Goldstein J, Manning E, Kaplan L, Holzberg S, Kassebaum N, Pascuzzi R, Bodkin C, Kincaid J, Snook R, Guinrich S, Micheels A, Chaudhry V, Corse A, Mosmiller B, Ho D, Srinivasan J, Vytopil M, Ventura N, Scala S, Carter C, Donahue C, Herbert C, Weiner E, McKinnon J, Haar L, McKinnon N, Alcon K, Daniels K, Sattar N, Jeffery D, McKenna K, Guidon A, David W, Dheel C, Levine-Weinberg M, Nigro C, Simpson E, Appel SH, Lai E, Lay L Jr, Pleitez M, Halton S, Faigle C, Thompson L, Sivak M, Shin S, Bratton J, Jacobs D, Brown G, Bandukwala I, Brown M, Kane J, Blount I, Freimer M, Hoyle JC, Agriesti J, Khoury J, Marburger T, Kaur H, Dimitrova D, Mellion M, Sachs G, Crabtree B, Keo R, Perez EK, Taber S, Gilchrist J, Andoin A, Darnell T, Goyal N, Sakamuri S, So YT, Welsh LW, Bhavaraju-Sanka R, Tobon Gonzalez A, Jones F, Saklad A, Nations S, Trivedi J, Hopkins S, Kazamel M, Alsharabati M, Lu L, Mumfrey-Thomas S, Woodall A, Richman D, Butters J, Lindsay M, Mozaffar T, Cash T, Goyal N, Roy G, Mathew V, Maqsood F, Minton B, Jones HJ, Rosenfeld J, Garcia R, Garcia S, Echevarria L, Pulley M, Aranke S, Berger AR, Shah J, Shabbir Y, Smith L, Varghese M, Gutmann L, Gutmann L, Swenson A, Olalde H, Hafer-Macko C, Kwan J, Zilliox L, Callison K, DiSanzo B, Naunton K, Bilsker M, Sharma K, Reyes E, Cooley A, Michon SC, Steele J, Karam CK, Chopra M, Bird S, Kaufman J, Gallatti N, Vu T, Katzin L, McClain T, Harvey B, Hart A, Huynh K, Beydoun S, Chilingaryan A, Droker B, Lin F, Shah A, Tran A, Akhter S, Malekniazi A, Tandan R, Hehir M, Waheed W, Lucy S, Weiss M, Distad J, Downing S, Strom S, Lisak R, Bernitsas E, Khan O, Kumar Sriwastava S, Tselis A, Jia K, Bertorini T, Arnold T, Henderson K, Pillai R, Liu Y, Wheeler L, Hewlett J, Vanderhook M, Dicapua D, Keung B, Kumar A, Patwa H, Robeson K, Nye J, Vu H (2017) Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. Lancet Neurol 16:976–986

61. Gajdos P, Chevret S, Clair B, Tranchant C, Chastang C, for the Myasthenia Gravis Clinical Study Group (1997) Clinical trial of plasma exchange and high-dose intravenous immunoglobulins in myasthenia gravis. Ann Neurol 41:789–796
62. Barth D, Nabavi Nouri M, Ng E, Nwe P, Bril V (2011) Comparison of IVIg and PLEX in patients with myasthenia gravis. Neurology 76:2017–2023
63. Dhawan PS, Goodman BP, Harper CM, Bosch PE, Hoffman-Snyder CR, Wellik KE, Wingerchuk DM, Demaerschalk BM (2015) IVIG versus PLEX in the treatment of worsening myasthenia gravis: what is the evidence? A critically appraised topic. Neurologist 19:145–148
64. Antozzi C (2013) Immunoadsorption in patients with autoimmune ion channel disorders of the peripheral nervous system. Atheroscler Suppl 14:219–222
65. Bourque PR, Pringle CE, Cameron W, Cowan J, Chardon JW (2016) Subcutaneous immunoglobulin therapy in the chronic management of myasthenia gravis: a retrospective cohort study. PLoS One 11:e0159993
66. Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, Ströbel P, Mazia C, Oger J, Cea JG, Heckmann JM, Evoli A, Nix W, Ciafaloni E, Antonini G, Witoonpanich R, King JO, Beydoun SR, Chalk CH, Barboi AC, Amato AA, Shaibani AI, Katirji B, Lecky BR, Buckley C, Vincent A, Dias-Tosta E, Yoshikawa H, Waddington-Cruz M, Pulley MT, Rivner MH, Kostera-Pruszczyk A, Pascuzzi RM, Jackson CE, Garcia Ramos GS, Verschuuren JJ, Massey JM, Kissel JT, Werneck LC, Benatar M, Barohn RJ, Tandan R, Mozaffar T, Conwit R, Odenkirchen J, Sonett JR, Jaretzki A 3rd, Newsom-Davis J, Cutter GR, MGTX Study Group (2016) Randomized trial of thymectomy in myasthenia gravis. N Engl J Med 375:511–522
67. Mantegazza R, Baggi F, Bernasconi P, Antozzi C, Confalonieri P, Novellino L, Spinelli L, Ferrò MT, Beghi E, Cornelio F (2003) Video-assisted thoracoscopic extended thymectomy and extended transsternal thymectomy (T-3b) in non-thymomatous myasthenia gravis patients: remission after 6 years of follow-up. J Neurol Sci 212:31–36
68. Ricciardi R, Melfi F, Maestri M, de Rosa A, Petsa A, Lucchi M, Mussi A (2016) Endoscopic thymectomy: a neurologist's perspective. Ann Cardiothorac Surg 5:38–44
69. Rea F, Schiavon M, Marulli G (2015) Robotic thymectomy for myasthenia gravis. Ann Cardiothorac Surg 4:558–560
70. Bandoli G, Palmsten K, Forbess Smith CJ, Chambers CD (2017) A review of systemic corticosteroid use in pregnancy and the risk of select pregnancy and birth outcomes. Rheum Dis Clin N Am 43: 489–502
71. Briggs GG, Freeman RK, Yaffe SJ (2015) Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Wolters Kluwer/Lippincott Williams & Wilkins Health, Philadelphia
72. Das G, Damotte V, Gelfand JM, Bevan C, Cree BAC, Do L, Green AJ, Hauser SL, Bove R (2018) Rituximab before and during pregnancy: a systematic review, and a case series in MS and NMOSD. Neurol Neuroimmunol Neuroinflamm 5:e453
73. Lake AJ, AI Khabbaz A, Keeney R (2017) Severe preeclampsia in the setting of myasthenia gravis. Case Rep Obstet Gynecol 2017: 9204930

74. Ozcan J, Balson IF, Dennis AT (2015) New diagnosis myasthenia gravis and preeclampsia in late pregnancy. BMJ Case Rep 2015: bcr2014208323. https://doi.org/10.1136/bcr-2014-208323
75. Esposito S, Bruno C, Berardinelli A, Filosto M, Mongini T, Morandi L, Musumeci O, Pegoraro E, Siciliano G, Tonin P, Marrosu G, Minetti C, Servida M, Fiorillo C, Conforti G, Scapolan S, Ansaldi F, Vianello A, Castaldi S, Principi N, Toscano A, Moggio M (2014) Vaccination recommendations for patients with neuromuscular disease. Vaccine 32:5893–5900
76. Seok HY, Shin HY, Kim JK et al (2017) The impacts of influenza infection and vaccination on exacerbation of myasthenia gravis. J Clin Neurol 14:325–330