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Autoimmune Neuromuscular Junction Disorders 3

Advances and ongoing research in the treatment of autoimmune neuromuscular junction disorders

Jan JGM Verschuuren, Jacqueline Palace, Hiroyuki Murai, Martijn R Tannemaat, Henry J Kaminski, Vera Bril

Myasthenia gravis and Lambert-Eaton myasthenic syndrome are antibody-mediated autoimmune diseases of the neuromuscular junction that usually present with weakness in ocular muscles and in proximal muscles of the limb and trunk. Prognosis regarding muscle strength, functional abilities, quality of life, and survival is generally good. However, some patients do not respond to treatment. Symptomatic drugs, corticosteroids, and steroid-sparing immunosuppressive drugs remain the cornerstone of treatment. In the past few years, new biological agents against complement, the FcRn receptor, or B-cell antigens have been tested in clinical trials. These new therapies extend the possibilities for targeted immunotherapies and promise exciting new options with a relatively rapid mode of action. Challenges in their use might occur, with barriers due to an increase in cost of care and additional considerations in the choice of drugs, and potential consequences of infection and vaccination due to the COVID-19 pandemic.

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This is the third in a **Series** of three papers about autoimmune neuromuscular junction disorders

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Introduction

Myasthenia gravis and Lambert-Eaton myasthenic syndrome are antibody-mediated autoimmune diseases of the neuromuscular junction. Most patients with myasthenia gravis have antibodies against the acetylcholine receptor, whereas a low percentage of patients have antibodies against muscle-specific tyrosine kinase (MuSK).[1] In even smaller groups of patients with myasthenia gravis, serum antibodies against low-density lipoprotein receptor-related protein 4, agrin, or cortactin have been found.[2] The majority of patients with Lambert-Eaton myasthenic syndrome have antibodies against voltage-gated calcium channels (VGCCs). Drugs that enhance neuromuscular transmission, including pyridostigmine, salbutamol, or amifampridine, are used in autoimmune myasthenia gravis or Lambert-Eaton myasthenic syndrome, but the mainstay is targeting the immunological pathway via thymectomy, or immunosuppressive or immunomodulatory medication. For a large group of patients, the treatment of generalised myasthenia gravis or Lambert-Eaton myasthenic syndrome heavily depends on the use of corticosteroids, with potential severe side-effects, such as infections, osteoporosis, diabetes, glaucoma, hypertension, psychiatric disturbances (eg, depression and psychosis), and negative effects on quality of life. Steroid-sparing immunosuppressive drugs have not been able to completely avoid the need for long-term use of corticosteroids and have their own potential side-effects, such as liver or renal toxic effects.

New drugs with different modes of action might reduce the need for chronic corticosteroid-based treatments and hopefully contribute to an overall improvement of the quality of life of patients with myasthenia gravis or Lambert-Eaton myasthenic syndrome. Progress in the understanding of the autoimmune pathology, including the role of complement and molecules involved in the T cell-driven synthesis of autoantibodies by B cells, have provided a rationale for testing new drugs in several clinical trials. So far, these new drugs have been developed for multiple antibody-mediated diseases, and not solely for myasthenia gravis or Lambert-Eaton myasthenic syndrome. The new developments offer increasing possibilities to personalise treatment for patients with autoimmune disorders of the neuromuscular synapse, although the COVID-19 pandemic has posed challenges for the use of immunosuppressive drugs and their effect on vaccine efficacy.[3]

This Series paper gives an overview of the latest findings on the treatment of autoimmune neuromuscular junction disorders and the new drugs that have been introduced in the past decade or might become available soon for treatment of patients with myasthenia gravis and Lambert-Eaton myasthenic syndrome. We first present the new drugs that are available now, then discuss the drugs that are being assessed in clinical trials. Drugs designed to restore tolerance or specifically target solely the autoimmune reaction in myasthenia gravis or Lambert-Eaton myasthenic syndrome are still in preclinical phases of development and will not be discussed here.[4] This paper is the third in a Series of three. The first paper discusses the disease mechanisms of autoimmune neuromuscular junction disorders[2] and the second paper discusses the epidemiology, biomarkers, and diagnostic procedures.[5]

General aspects of treatment

The goal of treatment is to induce remission of the disease, to remove or diminish the limitations that are faced by the patients in their daily activities, and to avoid a myasthenic crisis (ie, a serious, life-threatening, rapid worsening of the disease and potential airway compromise from ventilatory or bulbar dysfunction).[6] The Myasthenia Gravis Foundation of America postintervention status can be used to assess the clinical state of patients with myasthenia gravis at any time after institution of treatment.[7]

Figure 1: **Timeline of drug studies in acetylcholine receptor antibody-positive myasthenia gravis**
An overview of 62 clinical studies is provided. An increase in the number of trials and the number of different classes of drugs that have been tested for autoimmune myasthenia gravis can be seen over time. The class of drugs is indicated in the figure for each group. Current immunosuppressants are the group of drugs that is most frequently used in daily practice, and include azathioprine, mycophenolate mofetil, ciclosporin, tacrolimus, methotrexate, and cyclophosphamide. The new drugs include all drugs that are currently being tested in different phases of clinical development (appendix). Filled circles represent randomised clinical trials with a positive outcome. Open circles represent all other randomised and non-randomised trials or cohort studies with no significant treatment effect.

See Online for appendix

The options for treatment of autoimmune myasthenia gravis or Lambert-Eaton myasthenic syndrome have substantially increased in the past 5 years.[8–11] Figure 1 shows a timeline for drug development in myasthenia gravis. One group of drugs or interventions has clinical effect in hours, days, or weeks, whereas the other groups have an effect in months (figure 2). Treatments with short-term onset of clinical effect consist of symptomatic treatment, advice on exercise, intravenous immunoglobulin, or plasmapheresis. Therapies with long-term onset of clinical effect are immunosuppressive drugs, thymectomy, or treatment of associated tumours. We discuss the existing therapies followed by treatments that are likely to become available soon (table).

Treatment with short-term onset of clinical effect

Symptomatic treatment

Acetylcholinesteras inhibitors, such as pyridostigmine, are the initial treatment in most patients with myasthenia gravis and can be sufficient (ie, no other drugs are needed) for patients with ocular or mild generalised symptoms.[6] In 2018, almost 90 years after the introduction of this drug, the first randomised study (NCT03510546) was initiated. This trial is an ongoing crossover phase 4 study evaluating the effect of pyridostigmine in newly diagnosed, treatment-naive patients with myasthenia gravis, and patients with myasthenia gravis on stable medication; the results have not yet been reported.

Amifampridine, a potassium channel blocker, is commonly used as an approved symptomatic treatment in Lambert-Eaton myasthenic syndrome.[20] Several small observational case studies suggest that amifampridine might also alleviate symptoms in MuSK-positive myasthenia gravis.[21,22]

A trial of salbutamol, a β2-adrenergic agonist, investigating the efficacy and tolerability as adjuvant therapy in adult patients with generalised myasthenia gravis on stable medications with residual symptoms is ongoing (EU Clinical Trials Register number 2019-000895-40). Ephedrine is an alternative β1-adrenergic agonist, but is not readily available in all countries. In a small series of randomised controlled n-of-1 trials in patients with acetylcholine receptor antibody-positive myasthenia gravis, treatment with ephedrine caused a statistically and clinically significant reduction of symptoms, although the observed effect was below the predefined minimal clinically important difference.[23]

Exercise

Exercise can help combat weight gain from immunosuppressive treatment with corticosteroids, can limit

inactivity-induced muscle wasting, and possibly improve fatigue in neuromuscular diseases.[24] Exercise appears to be safe for patients.[24] Moderate to high intensity aerobic training and progressive resistance training are feasible for most patients with mild myasthenia gravis, and maximal strength and functional capacity improve with progressive resistance training.[25–27]

Human immunoglobulin

Immunomodulation therapy with intravenous immunoglobulin for myasthenia gravis is useful in myasthenic crises,[28] as preoperative preparation in patients with inadequate disease control,[29] and for treatment of exacerbations of symptoms.[6,30,31] Intravenous immunoglobulin has shown clinical improvement on specific myasthenia gravis muscle fatigue scales within a similar timeframe as plasmapheresis.[32] The usual treatment consists of a total dose of 2 g/kg administered over the course of 2–5 days. Improvement generally starts in the first few weeks after treatment has commenced, and lasts 4–8 weeks.

Chronic immunoglobulin therapy, including with subcutaneous immunoglobulin, has shown safety and efficacy in clinical practice in reducing myasthenia gravis impairments, improving overall myasthenia gravis status, reducing the dose of immunosuppressant agents, such as corticosteroids, and reducing the dose of acetylcholinesterase inhibitors.[33] This clinical experience supports the use of subcutaneous immunoglobulin as a maintenance therapy, and chronic intravenous immunoglobulin or subcutaneous immunoglobulin can be considered in patients with refractory myasthenia gravis,[6] although a prospective controlled double-blind clinical trial is needed.

Plasmapheresis

Plasmapheresis includes plasma exchange, double filtration plasmapheresis, and immunoadsorption plasmapheresis. Due to loss of albumins, double filtration plasmapheresis is not used as frequently as immunoadsorption plasmapheresis. The number of exchanges and the volume of plasma to be exchanged has not been established. A typical schedule consists of five sessions on alternate days. International consensus guidelines recommend plasma exchange as a short-term treatment in patients with life-threatening weakness and before surgery. When other treatments are ineffective, chronic plasma exchange might be considered in refractory myasthenia gravis.[6] German guidelines support immunoadsorption plasmapheresis for myasthenia gravis crisis and as maintenance therapy for patients with refractory myasthenia gravis.[34] In Japan, intravenous immunoglobulin and plasmapheresis are used for treatment of disease exacerbations, treatment of myasthenic crisis, induction therapy, and as maintenance therapy.[35,36]

Plasma exchange rapidly lowers all immunoglobulins, including acetylcholine receptor antibodies, and levels of most immunoglobulins remain low for about 3 weeks.[37]

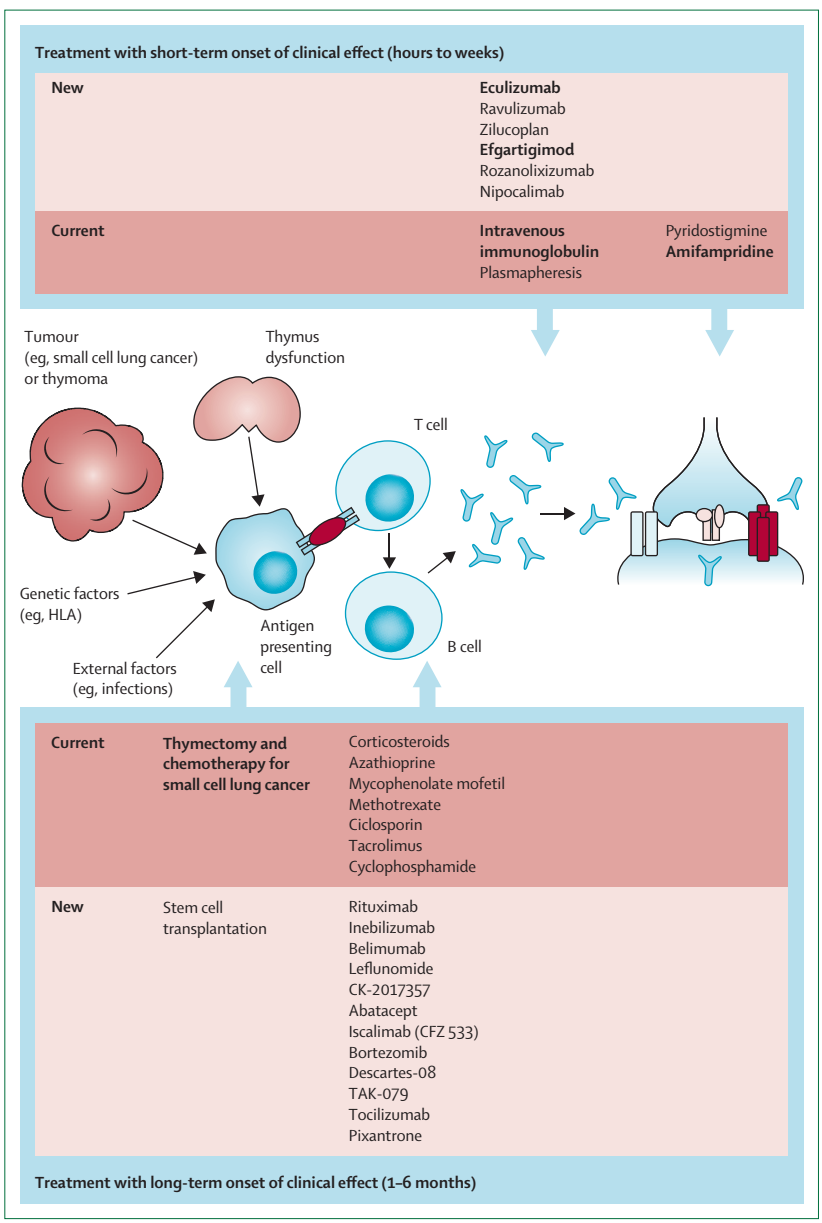

Figure 2: **Treatment and time-to-onset of clinical effect**
The new (recently introduced treatments or therapies that are still being tested in clinical trials) and current drugs in the upper part of the figure are treatments that have a short-term onset of clinical effect, whereas the new and current drugs in the lower part are therapies with a long-term onset of clinical effect. Drugs in bold indicate positive results in a controlled clinical trial. Except for amifampridine, all trials have been done with patients with acetylcholine receptor antibody-positive myasthenia gravis. The diagram in the middle shows the stages of the immune response at which the different groups of drugs have their effect. See appendix for more details on the drugs mentioned here.

To maintain long-term remission, additional immunosuppressive treatments are often needed. Plasma exchange is safe and generally well tolerated in patients with myasthenia gravis.[38] The effectiveness of plasmapheresis and intravenous immunoglobulin are comparable,[32,39,40] as are improvements in quality of life with the two approaches;[41] safety was not a specified outcome measure.

	Active drug or intervention	Control	Participants	Duration	Primary outcome	NCT number	EudraCT number	Result	Publication
Acetylcholine receptor antibody-positive myasthenia gravis									
Symptomatic treatment									
2017	Pyridostigmine	Placebo	32	12 weeks	Change on clinical rating scales	..	2017-002599-15	Ongoing	..
2018	Pyridostigmine	Placebo	44	12 weeks	QMG score	NCT03510546	..	Ongoing	..
2019	Salbutamol	Placebo	30	Not available	MG-QoL-15	..	2019-000895-40	Ongoing	..
Anti-metabolites									
2016	Methotrexate	Placebo	50	36 weeks	Prednisone dose	NCT00814138	..	No significant difference	Pasnoor et al (2012)[12]
Immunoglobulin or plasma exchange									
2017	Subcutaneous immunoglobulin	None	23	12 weeks	QMG score	NCT02100969	..	Completed	..
Complement inhibition									
2017	Zilucoplan	Placebo	44	12 weeks	QMG score	NCT03315130	..	Significant results	Howard et al (2020)[13]
2019	Zilucoplan	Placebo	130	12 weeks	MG-ADL score	NCT04115293	2019-001564-30	Ongoing	..
2020	Zilucoplan	None (open label extension study)	200	Ongoing	Multiple	..	2019-001565-33	Ongoing	..
2019	Ravulizumab	Placebo	175	26 weeks	MG-ADL	NCT03920293	2018-003243-39	Ongoing	..
2020	Eculizumab	None (open label extension study)	17	26 weeks	QMG score	..	2016-001384-37	Ongoing	..
FcRn blocking									
2016	Efgartigimod	Placebo	24	11 weeks	Treatment emergent adverse events	NCT02965573	2016-002938-73	A significant increase in treatment emergent adverse events with the intervention	Howard et al (2019)[14]
2017	Rozanolixizumab	Placebo	43	4 weeks	QMG score	NCT03052751	2016-002698-36	No significant difference	Bril et al (2021)[15]
2019	Nipocalimab (M-281)	..	68	16 or 8 weeks	Adverse events and MG-ADL	NCT03772587	2018-002247-28	Not available	..
2020	Efgartigimod	Placebo	167	5 weeks	MG-ADL	NCT03669588	..	Significant results	Howard et al (2021)[16]
Anti-CD19 or anti-CD20 monoclonal antibodies									
2016	Rituximab	Placebo	47	16 weeks	QMG score	NCT02950155	..	Ongoing	..
2016	Rituximab	Placebo	60	16 weeks	QMG score plus prednisone dose	..	2015-005749-30	Ongoing	..
2020	Inebilizumab	Placebo	252	52 weeks	MG-ADL	NCT04524273	2020-000949-14	Ongoing	..
CTLA-4 checkpoint inhibitors									
2017	Abatacept	None	6	..	Subjective score of myasthenia gravis severity	NCT03059888	..	Inconclusive	..

(Table continues on next page)

Treatment with long-term onset of clinical effect

Immunosuppressive treatment

The effect of pyridostigmine can be assessed within hours, but it does not target the autoantibody attack itself. Some researchers suggest that a delay in the start of immunosuppressive treatment might result in resistant weakness, particularly of extra ocular muscles, or a greater risk of generalisation in those with ocular onset.[42] However, the risk factors for conversion to generalised myasthenia gravis and the protective effect of immunosuppressive treatment are controversial. A 2020 retrospective study in 62 adults with myasthenia gravis showed a high rate of conversion during the first 2 years of progression, and a strong association with female sex and with the presence of acetylcholine receptor antibodies.[43]

Corticosteroid treatment is generally accepted as first-line immunosuppressive treatment in all autoimmune neuromuscular junction disorders. The conventional policy of aiming for remission by using high daily doses of 60 mg prednisolone, and then reducing to a low maintenance dose, is still the most frequently used schedule globally. Japanese observational studies suggest

	Active drug or intervention	Control	Participants	Duration	Primary outcome	NCT number	EudraCT number	Result	Publication
(Continued from previous page)									
Anti-CD40									
2019	Iscalimab (CFZ 533)	Placebo	44	25 weeks	QMG score	NCT02565576	2015-000097-35	No significant difference	··
CAR T-cell therapy									
2019	Descartes-08	Open label	18	4 weeks	Maximum tolerated dose	NCT04146051	··	Ongoing	··
Anti-CD38 monoclonal antibodies									
2019	TAK-079	Placebo	36	36 weeks	Treatment emergent adverse events	NCT04159805	2019-003383-47	Ongoing	··
Anti-IL-6 monoclonal antibodies									
2016	Tocilizumab	Case reports of individual patients	2	72 weeks	QMG score	··	Not available	Favourable outcomes	Jonsson et al (2017)[17]
Vaccinations for influenza or tetanus									
2016	Influenza vaccine	Placebo	50	4 weeks	Influenza antibody titre	··	2016-003138-26	Development of protective antibody titre	Strijbos et al (2019)[18]
MuSK-positive myasthenia gravis									
Potassium channel blocker									
2017	Amifampridine	Placebo	70	1 and 5 weeks	MG-ADL	NCT03304054	··	Not available	··
Lambert-Eaton myasthenic syndrome									
Symptomatic treatment									
2016	Amifampridine	Placebo	26	4 days	QMG score and subject global impression	NCT02970162	··	Significant difference	Maher et al (1986)[19]

Symptomatic drugs are shown, followed by several classes of immunosuppressive drugs. The order of drugs within one class is based on the year of the first study that is presented and does not reflect any preference for one or another drug within the same class. A complete overview of all clinical studies is available in the appendix. MG-ADL=myasthenia gravis activities of daily living. MG-QoL-15=myasthenia gravis quality of life 15 question score. FcRn=neonatal Fc receptors. QMG=quantitative myasthenia gravis.

Table: **Overview of clinical studies in acetylcholine receptor antibody-positive myasthenia gravis, MuSK-positive myasthenia gravis, and Lambert-Eaton myasthenic syndrome that began from 2016 onwards**

that lower doses, with a maximum of 20 mg per day, with the early addition of non-steroid immunosuppressive agents, might be sufficient to induce remission; however, higher doses are more likely to result in complete stable remission and less likely to lead to worsening or an exacerbation.[44] Additionally, as non-randomised observational studies cannot completely adjust for indication bias, there could be racial differences that might make these observations less widely applicable. Low-dose corticosteroid regimens of a daily dose of 15 mg might be suitable in patients with ocular myasthenia gravis.[45,46]

Adjunctive therapy is indicated when there are contraindications or side-effects, and corticosteroids alone are ineffective or cannot be reduced to a low enough maintenance dose without relapse.[6] There is much variation between countries in the use of immunosuppressive agents due to a scarcity of comparative studies; however, azathioprine appears to be most commonly used, partly because of relative safety for women planning to have children. Several studies (table) and an international consensus guideline also support the use of mycophenolate mofetil, methotrexate, cyclosporine, and tacrolimus for patients with acetylcholine receptor antibody-positive myasthenia gravis.[6] The oral immunosuppressive treatment options do not differ according to the antibody status; however, patients who are MuSK positive might need more or longer prednisolone, and rituximab should be considered earlier in the treatment pathway than for patients who are acetylcholine receptor antibody-positive.[6,45]

A single-blind study comparing azathioprine with methotrexate in 24 adults with myasthenia gravis showed similar steroid sparing effects over 10–12 months,[47] but a steroid sparing effect was not seen with methotrexate in a subsequent double-blind placebo-controlled study in 50 adults with myasthenia gravis after a period of 12 months.[12,48] Longer follow up times might have been needed.

The aggressiveness of treatment (eg, the use of a higher dose or combining multiple immunosuppressive drugs) might need to be adjusted according to age. Patients with late-onset myasthenia gravis have less refractory disease and less requirement for multiple immunosuppressive drugs, and are therefore more likely than patients younger than 50 years to achieve remission despite presenting with more life threatening events.[30,49] In contrast, complete drug-free remission in children, particularly those with ocular myasthenia gravis and

Panel 1: Treatment consideration for pregnancy and lactation and in children

Prospective studies of pregnancy outcomes in myasthenia gravis have not been done, although multiple retrospective reports indicate that worsening of myasthenia gravis occurs in about 50% of women, either during pregnancy or in the post-partum period, and is more frequent in those within the first 2 years of myasthenia gravis onset.[51] Myasthenia gravis might first manifest during pregnancy or the post-partum period.[52] Recommendations on management during pregnancy have varied over the years,[53] but abrupt withdrawal of immunosuppressant medication can lead to worsening and even myasthenic crisis.[51] Azathioprine and corticosteroids are safe during pregnancy, but other drugs such as mycophenolate mofetil, methotrexate, and cyclophosphamide should not be used.[54] Scarce use of cyclosporine or tacrolimus in patients with rheumatic disease indicate that these drugs are probably safe during pregnancy or breastfeeding.[55] The fetal risks vary by geographic location, perhaps due to genetic factors.[56] The prevalence of transient neonatal myasthenia gravis also varies among centres, perhaps due to differences in management practices, including recommendation of early thymectomy to young women soon after diagnosis, which could lead to better outcomes.[51] Specific medications (eg, pyridostigmine, corticosteroids, and azathioprine) are found in low concentrations in breast milk but are not considered as contraindications to breastfeeding, whereas other medications (eg, mycophenolate mofetil, methotrexate, and cyclophosphamide) should not be used by breastfeeding mothers.[56]

For children, the potential for amblyopia when ophthalmoplegia is not adequately treated, and growth failure and weight gain, need to be considered in treatment decisions. Concerns about growth failure and weight gain suggest a lower threshold for using regular intravenous immunoglobulin in children. Additional issues regarding immunisation are more important in children: the risk of infection when immunosuppressed is greater (eg, varicella zoster), the inability to have live vaccines, and the potential for reduced vaccine efficacy when on immunosuppression might delay the initiation of immunosuppressive therapy until after vaccination and might reduce early control of symptoms.[6,57] Long-term malignancy risks with immunosuppression are also a greater concern in paediatric populations.[58]

Referral to an expert on myasthenia gravis in refractory cases is recommended to assure optimisation of treatment options and more extensive assessment of the reasons for non-response to treatment.

Panel 2: Perioperative care

Thymectomy is not an emergency procedure and thus careful assessment should be done to determine whether a patient requires preoperative treatment with rapid acting treatments. Especially in patients with bulbar or respiratory weakness, treatment of myasthenia gravis by using immunosuppressive drugs should be considered first, to avoid postoperative complications. However, the routine use of preventive intravenous immunoglobulin in patients with well controlled myasthenia gravis is not recommended.[62] For patients with unstable myasthenia gravis requiring any surgery, including thymectomy, preoperative treatment with intravenous immunoglobulin was comparable to plasma exchange treatment with respect to avoiding exacerbations.[29] A 2017 randomised study suggests that intravenous immunoglobulin might be more effective than plasma exchange in the preoperative preparation of patients for thymectomy.[63] In this study of 24 patients undergoing thymectomy, the plasma exchange group had greater duration of hospitalisation and length of stay in the intensive care unit after surgery than the intravenous immunoglobulin group.

detectable acetylcholine receptor antibodies on cell based assays, is more common than in adults.[50] These observations might affect decisions on long-term treatments, such as thymectomy, and reduce concerns regarding drugs contraindicated in pregnancy (panel 1), in patients with a high chance of complete stable remission.

Thymectomy in acetylcholine receptor antibody-positive myasthenia gravis

The 2016 MGTX study, a randomised, single-blind trial, showed efficacy of thymectomy plus prednisolone (versus prednisolone only) for patients who were acetylcholine receptor antibody-positive, with regard to a reduction in the need for prednisolone and an improvement in weakness over the 3-year observation time.[59] Extension studies have shown persistent effects for an additional 2 years. The MGTX trial enrolled patients aged 18–65 years, but some studies recommend limitation of thymectomy to early-onset myasthenia gravis for patients younger than 50 years at the time of surgery, despite no difference in endpoints between patients (whether younger or older than 50 years) who have had a thymectomy and those who have not; however, the number of patients older than 50 years was small.[60] Therapeutic benefit has not been shown among patients with acetylcholine receptor antibody-negative myasthenia gravis. Although the MGTX trial used only the transsternal surgical approach, an international consensus guideline suggests that there is general agreement that videoscopic approaches, which remove the maximal amount of thymic tissue, would have the same benefit.[45] One study in 2015 compared thymectomy in 108 patients with myasthenia gravis with 1040 patients without myasthenia gravis who had hyperparathyroidism or neoplasm of the thyroid gland of thymus.[61] Although patients with myasthenia gravis had a greater preoperative morbidity and a higher frequency of reintubation compared with the control group, thymectomy was found to be a safe procedure overall (panel 2).

Tumour screening and treatment in Lambert-Eaton myasthenic syndrome

Screening for small cell lung cancer is mandatory in patients presenting with Lambert-Eaton myasthenic syndrome. The Dutch-English Lambert-Eaton myasthenic syndrome Tumour Association Prediction (DELTA-P) score can be used to estimate the risk for the presence of a small cell lung cancer at the moment of diagnosis of Lambert-Eaton myasthenic syndrome.[64] A 2020 study confirmed the sensitivity and specificity of the DELTA-P score for cancer prediction in a prospective cohort of 87 patients with newly diagnosed Lambert-Eaton

myasthenic syndrome in a real-world setting.[65] Weight loss of 5% or more, tobacco use at onset of Lambert-Eaton myasthenic syndrome, and age of 50 years or more at onset were independent predictors for the development of small cell lung cancer in a multivariable analysis.[65] Median DELTA-P scores were significantly higher in patients with small cell lung cancer and Lambert-Eaton myasthenic syndrome compared with non-tumour Lambert-Eaton myasthenic syndrome.[65] Treatment of small cell lung cancer mainly consists of chemotherapy. In 81 patients with Lambert-Eaton myasthenic syndrome with associated small cell lung cancer, survival was significantly longer compared with more than 34 000 patients from the Netherlands Cancer Registry with small cell lung cancer and without Lambert-Eaton myasthenic syndrome (median survival 17 months *vs* 7 months, $p<0\cdot0001$).[66]

New or future treatment options

Anti-CD20 and anti-CD19 monoclonal antibodies

Rituximab is a monoclonal antibody directed at the cell surface marker CD20, expressed on B cells, except for pre-B cells and late-stage plasma cells. A systematic review described a meta-analysis of 24 studies involving 417 patients with acetylcholine receptor antibody-positive and MuSK-positive myasthenia gravis. The meta-analysis indicated a positive treatment response, assessed as the proportion of patients achieving minimal manifestation status or improved quantitative myasthenia gravis (QMG) score.[67] A multicentre, blinded, prospective observational study, comparing 24 of 55 anti-MuSK-positive patients with myasthenia gravis treated with rituximab to the other 31 patients not treated with rituximab, indicated benefit in terms of a myasthenia gravis status and treatment intensity score of equal or less than 2.[68] However, the BeatMG phase 2 trial (NCT02110706) failed to meet its efficacy measure of corticosteroid-sparing effect in acetylcholine receptor antibody-positive myasthenia gravis. The available data suggest that patients with MuSK-positive myasthenia gravis might respond better to rituximab than patients with acetylcholine receptor antibody-positive myasthenia gravis. Other anti-CD20 antibodies are in development for the treatment of several autoimmune diseases but have not yet been applied to myasthenia gravis. Ofatumumab and ocrelizumab have shown efficacy in patients with multiple sclerosis.[69,70] Obinutuzumab removes anti-CD20 cells by direct cell death, but whether this mechanism of action is superior to the use of rituximab for treatment of myasthenia gravis cannot be predicted. Veltuzumab is a subcutaneously administered anti-CD20-directed monoclonal antibody, but has been used rarely for autoimmune diseases, including a case report of refractory pemphigus vulgaris[71] and relapsed immune thrombocytopenia.[72] Inebilizumab is a anti-CD19 monoclonal antibody approved for treatment of neuromyelitis optica, but has not been assessed for myasthenia gravis.[73] CD38 is expressed on plasma cells;[74] Tocil-079, a high-affinity antibody directed against CD38,[75] is being considered as a potential intervention for MuSK-positive and acetylcholine receptor antibody-positive myasthenia gravis.

Anti-CD40 monoclonal antibodies

Iscalimab is an anti-CD40 monoclonal antibody[76] that reduces T-cell-dependent antibody responses and impairs germinal cell formation. Preclinical studies of anti-CD40 monoclonal antibodies in experimental autoimmune myasthenia gravis in rats indicate a reduced severity of weakness and reduction of proinflammatory cytokines.[77] Preliminary reports of a phase 2 study (NCT02565576) of acetylcholine receptor antibody-positive myasthenia gravis or MuSK-positive myasthenia gravis showed safety but no difference in clinical outcome measures.

Anti-CTLA-4 checkpoint inhibitors

Abatacept is a fusion protein consisting of CTLA-4 and IgG. T-cell activation is moderated by blocking the CD80 pathway or the CD86 and CD28 costimulatory pathway. Abatacept is approved for treatment of rheumatoid arthritis. Some patients with myasthenia gravis have polymorphisms in the *CTLA4* gene and checkpoint inhibitors targeting CTLA-4 might activate myasthenia gravis. These observations suggest abatacept could be beneficial for myasthenia gravis treatment. A pilot study (NCT03059888) of generalised patients with myasthenia gravis was terminated for logistical reasons.

Anti-B-lymphocyte stimulator and anti-B-cell activating factor monoclonal antibodies

Belimumab is a humanised IgG1 monoclonal antibody that is directed against B-cell activating factor, also named B-lymphocyte stimulator. The drug is already licensed for the treatment of systemic lupus erythematosus. The results from a phase 2, randomised, double-blind trial in 39 patients with autoimmune myasthenia gravis (37 with acetylcholine receptor antibodies and two with MuSK antibodies) comparing belimumab with placebo did show a difference in the QMG score in favour of belimumab but did not reach a statistically significant difference at 24 weeks of treatment.[78]

Proteasome inhibitors

Selective inhibition of plasma cells that produce pathogenic antibodies could potentially be an effective treatment for myasthenia gravis or Lambert-Eaton myasthenic syndrome. Plasma cells have a high protein turnover due to their high rate of immunoglobulin production. The ubiquitin–proteosome pathway has a major role in clearing intracellular proteins, and inhibition of proteasomes has shown to be an effective therapy for multiple myeloma.[79] An open label trial testing the use of bortezomib in treatment of multiple refractory autoimmune diseases, including myasthenia gravis, was terminated early due to recruitment issues.[79] Proteasome inhibitors are promising, but more studies are needed. Sensory neuropathy, a frequent side-effect of these therapies, is likely to be an

important limiting factor in the treatment of myasthenia gravis or Lambert-Eaton myasthenic syndrome.[80]

Anti-IL-6 monoclonal antibodies

IL-6 is a cytokine involved in autoantibody production. Tocilizumab and satralizumab are humanised anti-IL-6 receptor monoclonal antibodies that prevent the pro-inflammatory activity of IL-6. Tocilizumab has been approved for the treatment of rheumatoid arthritis, and satralizumab for the treatment of neuromyelitis optica.[81] Case reports of two female patients with acetylcholine receptor antibody-positive myasthenia gravis that responded favourably to treatment in terms of the QMG score with tocilizumab suggest possible efficacy in myasthenia gravis,[17] but no clinical trial in myasthenia gravis or Lambert-Eaton myasthenic syndrome has been completed yet.

Complement inhibitors

Complement plays a pivotal part in the pathogenesis of acetylcholine receptor antibody-positive myasthenia gravis.[82] The terminal components of complement have been detected at the neuromuscular junction in patients with myasthenia gravis.[83] There are several complement (ie, C5) inhibitors already approved or in clinical studies for myasthenia gravis. Targeting C5 preserves proximal cascade effects including C3b-mediated opsonization, C3a inflammatory response, and immune complex clearance.

Eculizumab is a humanised monoclonal antibody binding the terminal complement protein C5. This binding inhibits cleavage of C5 to C5a and C5b, preventing the formation of the C5b-induced membrane attack complex. Eculizumab is currently approved for the treatment of paroxysmal nocturnal haemoglobinuria, atypical haemolytic uremic syndrome, and neuromyelitis optica spectrum disorder, and is the only complement inhibitor that is approved for the treatment of generalised acetylcholine receptor antibody-positive myasthenia gravis. Benefit in terms of myasthenia gravis activities of daily living (MG-ADL) score has been shown in a randomised, double-blind, placebo-controlled phase 2 study in 125 adult patients with refractory generalised acetylcholine receptor antibody-positive myasthenia gravis and within a duration of 26 weeks.[84] Long-term safety and sustained efficacy with regard to MG-ADL score were shown in REGAIN and its open label extension study in 117 patients with acetylcholine receptor antibody-positive myasthenia gravis with refractory generalised disease.[85] Improvements in clinical parameters assessing activities of daily living and quality of life in REGAIN were maintained for 3 years; the safety profile of eculizumab was consistent and there were no cases of meningococcal infection during the interim analysis period.[85] Eculizumab was effective with regard to MG-ADL for patients who received chronic intravenous immunoglobulin before REGAIN, implying treatment-refractory generalised acetylcholine receptor antibody-positive myasthenia gravis might benefit from this component.[86] In real-world practice, eculizumab has been used in various settings, including myasthenic crisis and thymoma-associated myasthenia gravis.[87] Although responders to eculizumab generally show improvement in MG-ADL within a few weeks, late responders have been reported.[88] Eculizumab is ineffective for patients harbouring rare C5 mutations, which are carried by 3·5% of the healthy people in the Japanese population.[89]

Ravulizumab is a humanised monoclonal antibody that specifically binds to human terminal complement protein C5 and was developed for paroxysmal nocturnal haemoglobinuria and atypical haemolytic uremic syndrome.[90] The drug is a version of eculizumab modified to attain prolonged complement inhibition to allow less frequent dosing.[91] In paroxysmal nocturnal haemoglobinuria, safety and efficacy were similar between eculizumab and ravulizumab in a non-inferiority RCT.[92] A phase 3, randomised, double-blind, placebo-controlled study (NCT03920293) in 175 patients with acetylcholine receptor antibody-positive myasthenia gravis and a minimal MG-ADL score of six was completed. In July, 2021, the sponsor, Alexion, reported in a press release a significant difference for the primary endpoint of change from baseline in the MG-ADL total score at week 26.

Zilucoplan is a small (3·5 kDa), 15-amino acid macrocyclic peptide that binds to C5 with high affinity and specificity. This binding prevents the cleavage of C5 into complement components C5a and C5b. Zilucoplan also binds to the domain of C5 that corresponds to C5b to block interaction with C6.[93] Zilucoplan is a self-administered daily subcutaneous injection. Zilucoplan showed rapid and sustained improvements in the QMG score over 12 weeks in moderate to severe generalised myasthenia gravis in a phase 2 study.[13] Safety and tolerability profiles were favourable. The drug is in phase 3 development (RAISE; NCT04115293), and zilucoplan might benefit patients refractory to other immunomodulatory treatments and those harbouring C5 mutations.

FcRn blockers

The neonatal Fc receptors (FcRns) were first detected on neonatal intestinal epithelial cells and found to be responsible for transport of maternal IgG to the fetal circulation, but FcRns are also involved in maintaining serum IgG levels. In the past few years, FcRns became an important target for new therapies in several antibody mediated autoimmune diseases. FcRn blockers inhibit the binding of IgG to the FcRn.[94,95] This inhibition results in increased IgG catabolism and subsequent reduction in serum IgG. The results of the intervention are analogous to plasma exchange, which effectively lowers circulating blood IgG, including the pathogenic antibodies. Five sessions of plasma exchange can lower autoantibody levels by about 75%.[37] Similarly, saturation of FcRn is the

main mechanism that underlies the therapeutic effect of intravenous IgG in antibody-mediated autoimmune diseases.[96] A study in rats showed that dexamethasone decreases the expression of the FcRn alpha subunit, and therefore the beneficial effect of corticosteroids might relate to FcRn regulation.[96]

FcRn inhibitors that are in clinical development for myasthenia gravis and for other autoimmune diseases include rozanolixizumab, nipocalimab, batoclimab, orilanolimab, bivalent antibody mimetics (eg, ABY-039), and Fc fragments (eg, efgartigimod and CSL730 [M230]). Efgartigimod, rozanolixizumab, nipocalimab (table), and batoclimab (under investigation only in China) are in clinical trials for myasthenia gravis.

Efgartigimod is a human IgG1-derived Fc fragment and was the first of the FcRn drugs that completed a phase 3 trial. In a phase 2 randomised controlled trial, intravenous administration of efgartigimod in 24 patients with myasthenia gravis was safe and well tolerated.[14] Adverse effects included headache (33% with efgartigimod *vs* 25% with placebo), myalgia, and asymptomatic reduction of total serum lymphocytes and monocytes. Secondary endpoints of the QMG score, MG-ADL, and the revised 15 question myasthenia gravis quality of life score showed significant improvement at one or more timepoints during the trial. Of the patients treated with efgartigimod, 75% had a clinically meaningful and statistically significant improvement in MG-ADL score (≥2) for at least 6 consecutive weeks, versus 25% of patients on placebo. A maximal reduction of serum IgG of 70% was reached after subsequent doses. IgG concentrations remained reduced by 50% or more for approximately 3 weeks. A phase 3 clinical trial (ADAPT; NCT03669588) in patients with autoimmune myasthenia gravis (with mostly acetylcholine receptors, but also MuSK and seronegative myasthenia gravis) showed a clinically significant positive effect; 44 of 65 participants in the efgartigimod group were MG-ADL responders versus 19 of 64 participants in the placebo group (odds ratio 4·95, 95% CI 2·21–11·53, $p<0·0001$).[16]

Rozanolixizumab is a humanised IgG4 anti-FcRn monoclonal antibody provided subcutaneously. A phase 2 study with two treatment periods in 43 patients with myasthenia gravis showed no significant difference in the QMG score.[15] On day 29, responder rates were higher for the QMG score, MG-ADL, and Myasthenia Gravis Composite scale; although the primary endpoint, the change in the QMG score from baseline to day 29, did not show a significant difference compared with the placebo group. The maximal reduction in serum IgG in period one was 61%, and 40% for acetylcholine receptor antibodies. In period 2 after six treatments, a maximal reduction of serum IgG of 68% was reached. A higher frequency of headache (57%) occurred with drug compared with placebo (14%) and led to withdrawal from the trial of three patients. A phase 3 study (NCT03971422) has been initiated in patients with acetylcholine receptor or MuSK antibodies.

Nipocalimab (M281) is a fully human deglycosylated IgG1 anti-FcRn monoclonal antibody.[72] A phase 1 study in healthy volunteers with multiple weekly doses of 15 mg/kg or 30 mg/kg showed mean IgG reductions of 85% from baseline and IgG reductions were maintained at 75% from baseline for up to 24 days.[72] A phase 2 study (NCT03772587) in myasthenia gravis has been completed with positive results reported by the company.

Batoclimab (RVT-1401) is a human recombinant anti-FcRn monoclonal antibody. A randomised controlled trial with weekly, subcutaneous doses of 340 mg or 680 mg for 6 weeks in generalised patients with acetylcholine receptor antibody-positive myasthenia gravis was completed, followed by an open label extension study (NCT03863080). The company released a positive press release, but no results have been published.

Autologous haematopoietic stem cell transplantation

Autologous haematopoietic stem cell transplantation has occasionally been used in a clinical setting to treat refractory myasthenia gravis.[97–99] Seven patients with refractory myasthenia gravis underwent stem cell mobilisation with cyclophosphamide and granulocyte colony-stimulating factor. Stem cell grafts were harvested and purified using anti-CD34 monoclonal antibodies. High dose chemotherapy was used for immune ablation before stem cell graft infusion.[99] All seven patients have a postintervention status of complete stable remission after haematopoietic stem cell transplantation.[99] To date, there is no prospective study of haematopoietic stem cell transplantation in patients with myasthenia gravis.

Consequences of the COVID-19 pandemic

The COVID-19 pandemic remains rampant across the world. COVID-19 is caused by SARS-CoV-2, and can lead to pneumonia and acute respiratory distress. However, associations with various neurological manifestations, including stroke, encephalitis, anosmia, ageusia, and Guillain-Barré syndrome, have been reported.[100] Myasthenia gravis exacerbations are reported with COVID-19.[101–105] A study interviewing 162 patients with myasthenia gravis showed that the risk of acquiring COVID-19 was no higher than that of the general population, regardless of immunosuppressive therapies. In this cohort, COVID-19 infection barely affected the myasthenia gravis disease course.[106] In contrast, another cohort study of 93 patients with myasthenia gravis infected with COVID-19 identified that the most important predictors of severe COVID-19 were a lower forced vital capacity, previous long-term corticosteroid treatment especially at higher doses, older age, the presence of cancer, and rituximab treatment.[107] One case study reported that one patient developed MuSK-positive myasthenia gravis after SARS-CoV-2 infection, suggesting the virus might act as a trigger of myasthenia gravis development.[108]

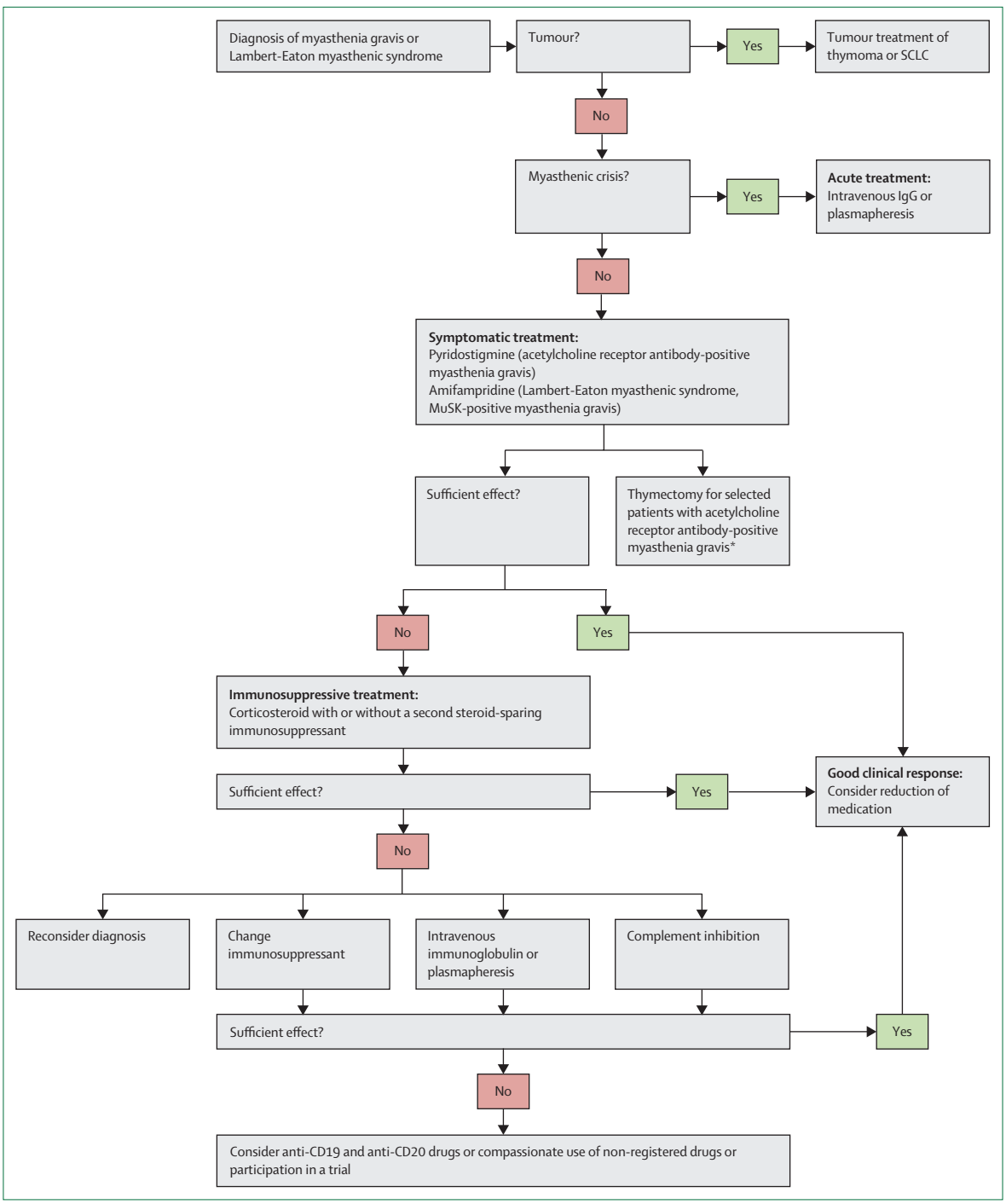

Figure 3: **Proposed treatment algorithm for acetylcholine receptor antibody-positive myasthenia gravis, MuSK-positive myasthenia gravis, or Lambert-Eaton myasthenic syndrome**

The proposed algorithm is based on consensus among the authors and two consensus guidelines.[6,45] The process starts with a definite diagnosis of myasthenia gravis or Lambert-Eaton myasthenic syndrome. The next step is the identification of a myasthenic crisis (ie, a serious, life-threatening, rapid worsening of myasthenia gravis and potential airway compromise from ventilatory or bulbar dysfunction). If myasthenic crisis is not present, the first line of treatment is the use of a symptomatic drug. If these drugs do not work, the next step is the use of corticosteroids with or without the addition of steroid-sparing immunosuppressant drugs. If this step does not work, there are several options to continue treatment, including revision of the diagnosis, changing the choice of immunosuppressive drug, starting intravenous immunoglobulin or plasmapheresis, or using complement inhibition. If all conventional drugs that are available and registered or reimbursed fail, immunosuppressive drugs that are not yet registered can be considered. These options include anti-CD19 or anti-CD20 drugs, compassionate use programmes on the FcRn blocking drugs, or the new complement inhibitors. Alternatively, depending on the clinical condition of the patient, participation in a clinical trial could be considered. *Thymectomy is a procedure for a selected group of patients aged 18–65 years.

Guidance for the management of myasthenia gravis during the COVID-19 pandemic has been published by the International Myasthenia Gravis and COVID-19 Working Group.[109] Patients are advised to continue their current treatment and not to stop any existing medications. Four vaccines—BNT162b2 mRNA (Pfizer–BioNTech), mRNA1273 (Moderna), ChAdOx1 nCoV-19 (Vaxzevria, AstraZeneca), and Ad26.COV2.S (Janssen–Johnson & Johnson)—have obtained emergency use authorisation.[110] All four approved COVID-19 vaccines are not live-attenuated vaccines and are not contraindicated for immunosuppressed patients. BNT162b2 mRNA and mRNA1273 are lipid nanoparticle-formulated, nucleoside-modified RNA vaccines that encode SARS-CoV-2 full-length spike protein. ChAdOx1 nCoV-19 and Ad26.COV2.S are recombinant, replication-incompetent adenoviruses, which express the SARS-CoV-2 spike protein. Regarding B-cell depleting therapy, the risk of ineffective vaccinations and benefit should be discussed between the physician and the patient. It might be advisable to delay initiation of therapy until the peak of the outbreak is over in their region, but the rate of vaccination and the prevalence of infected people highly varies per region, resulting in a rapid change of recommendations.

Conclusion and future directions

Mortality due to myasthenia gravis has been reduced from 70% around 1930 to only 2% in 2000.[111,112] Yet, approximately 10% of patients with myasthenia gravis fail to respond adequately to the current therapies. Several definitions have been used for treatment-refractory myasthenia gravis and include patients who do not respond to conventional therapies or who cannot reduce immunosuppression to a safe level without clinical relapse. Also, patients with severe or intolerable adverse effects on current treatment or comorbid conditions that restrict the use of conventional therapies can be considered refractory.[111] Given the increased prevalence of myasthenia gravis over the past two to three decades, a considerable proportion of patients need more effective treatments. Three new classes of drug, including complement inhibitors, FcRn blockers, and monoclonal antibodies against CD19 or CD20, are already available or are likely to become available for the treatment of autoimmune myasthenia gravis, and might profoundly change the current treatment algorithms. These new drugs could possibly also be used for the treatment of Lambert-Eaton myasthenic syndrome; however, due to the low prevalence of this disease, drugs trials might not be done. The major concerns about the new therapies are excessive costs and unknown long-term safety of complement inhibitors or FcRn blockers. Case reports of opportunistic viral, bacterial, or fungal infections have been reported with the use of conventional immunosuppressants.[113,114]

These new drugs—complement inhibitors, FcRn blockers, and monoclonal antibodies against CD19 or CD20—might substantially improve quality of life and diminish the adverse effects of long-term corticosteroids or the bone-marrow toxicity of current immunosuppressive drugs, but in several countries high costs are prohibitive. A 2020 Canadian pharmacoeconomic report on eculizumab concluded that, despite several limitations in the analysis, eculizumab could not be considered cost-effective without considerable price reduction.[115] Furthermore, none of these new drugs is designed specifically for myasthenia gravis or Lambert-Eaton myasthenic syndrome, nor are they able to selectively suppress the acetylcholine receptor, VGCC, or MuSK autoantibody response. Overall, the balance of risk to safety ratio should be viewed in the context of all the available treatment options and quality of life of the patient. To limit costs and to avoid possible long-term side-effects, these new drugs could be restricted to refractory patients. These drugs could be also used for a restricted time period to bring the patient into remission before switching to conventional immunosuppressive agents to prevent exacerbations (figure 3). Complement or FcRn inhibition early in the disease should be feasible given the relatively fast onset of clinical improvement that has been reported. Early treatment might offer an opportunity to reduce or even avoid corticosteroids and their side-effects, and could offer the possibility of personalised drug treatment based on age, associated antibody (acetylcholine receptor, MuSK of VGCC), or comorbidity of the patient. New, robust, and readily available immunological or genetic biomarkers would be helpful to select the most effective therapy for a patient. Overall, the new and more focussed immunotherapies have the potential for greater treatment options with a fast mode of onset, avoiding high doses of corticosteroids, fewer side-effects, and improved quality of life.

Search strategy and selection criteria

References were identified by searches of PubMed between Jan 1, 2000, and July 1, 2021, and from relevant articles. The search terms "myasthenia" "myasthenic" or "Lambert Eaton" and "immunosuppressant", "corticosteroid", "monoclonal", "thymoma", "intravenous immunoglobulin", "plasmapheresis", "plasma absorption", or "therapy" were used. There were no language restrictions. The final reference list was generated on the basis of relevance to the topics covered in this Series paper. We have included only phase 2 or 3 randomised or controlled clinical trials that provide evidence of efficacy for drugs with the highest chance of becoming available for routine clinical use.

Contributors

All authors contributed to the main conceptual idea and wrote parts of the first draft of the manuscript. JJGMV did the final editing before submission and created the figures and table. All authors reviewed the last version and provided essential modifications to the text of the manuscript.

Declaration of interests
JJGMV has been involved in myasthenia gravis research sponsored by the Prinses Beatrix Fonds and Health Holland; reports consultancies for Argenx, Alexion Pharmaceuticals, Ra Pharmaceuticals, and NMD Pharma, with reimbursements received by Leiden University Medical Center; is the coinventor of patent applications for MuSK-related research, with Leiden University Medical Center receiving royalties for MuSK antibody assays; and is a member of the European Reference Network for Rare Neuromuscular Diseases. JP is partly funded by highly specialised services to run a national congenital myasthenia service; has received support for scientific meetings and honorariums for advisory work from Novartis, Chugai Pharmaceutical, Bayer Schering, Alexion Pharmaceuticals, Roche, Genzyme, Abide, Argenx, Union Chimique Belge (UCB), and Viela Bio; reports grants from Merck Serono, Novartis, Abide, MedImmune, Genzyme, Chugai Pharmaceutical, and Alexion Pharmaceuticals; reports research grants from the Multiple Sclerosis Society UK, Guthy Jackson Foundation, National Institute of Health Research, John Fell, Myaware, and Amplo; and holds shares in AstraZeneca. HM has served as a consultant for Alexion Pharmaceuticals, Argenx, UCB, and Sanofi; has received speaker honoraria from Japan Blood Products Organization and Chugai Pharmaceutical; and reports research support from the Ministry of Health, Labour and Welfare, Japan. MRT has been involved in myasthenia gravis research sponsored by Argenx, Alexion Pharmaceuticals, and NMD Pharma, with all reimbursements received by Leiden University Medical Center. HJK is a consultant for Roche, Cabeletta Bio, Takeda Pharmaceutical, and UCB Pharmaceuticals; is the CEO and CMO of ARC Biotechnology based on US Patent 8 961 98; is the principal investigator of the Rare Disease Network for Myasthenia Gravis National Institute of Neurological Disorders & Stroke (U54 NS115054), and Targeted Therapy for Myasthenia Gravis (R41 NS110331-01) to ARC Biotechnology. VB is a consultant for Grifols, Commonwealth Serum Laboratories (CSL), UCB, Argenx, Takeda Pharmaceutical, Alnylam Pharmaceuticals, Octapharma, Pfizer, Powell Mansfield, Akcea Therapeutics, Ionis Immunovant, Sanofi, Momenta, Roche, Janssen Pharmaceuticals, Alexion, and NovoNordisk; reports research support from Alexion, Grifols, CSL, UCB, Argenx, Takeda Pharmaceutical, Octapharma Plasma, Akcea Therapeutics, Momenta, Immunovant, Ionis Pharmaceuticals.

References

1 Gilhus NE, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren JJGM. Myasthenia gravis. *Nat Rev Dis Primers* 2019; **5:** 30.
2 Huijbers MG, Marx A, Plomp JJ, Le Panse R, Phillips WD. Advances in the understanding of disease mechanisms of autoimmune neuromuscular junction disorders. *Lancet Neurol* 2022; **21:** 163–75.
3 Zhou Q, Zhou R, Yang H, Yang H. To be or not to be vaccinated: that is a question in myasthenia gravis. *Front Immunol* 2021; **12:** 733418.
4 Luo J, Lindstrom J. Acetylcholine receptor-specific immunosuppressive therapy of experimental autoimmune myasthenia gravis and myasthenia gravis. *Ann N Y Acad Sci* 2018; **1413:** 76–81.
5 Punga AR, Maddison P, Heckmann JM, Guptill JT, Evoli A. Epidemiology, diagnostics, and biomarkers of autoimmune neuromuscular junction disorders. *Lancet Neurol* 2022; **21:** 176–88.
6 Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: executive summary. *Neurology* 2016; **87:** 419–25.
7 Jaretzki A 3rd, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. *Ann Thorac Surg* 2000; **70:** 327–34.
8 Habib AA, Ahmadi Jazi G, Mozaffar T. Update on immune-mediated therapies for myasthenia gravis. *Muscle Nerve* 2020; **62:** 579–92.
9 Menon D, Barnett C, Bril V. Novel treatments in myasthenia gravis. *Front Neurol* 2020; **11:** 538.
10 Alabbad S, AlGaeed M, Sikorski P, Kaminski HJ. Monoclonal antibody-based therapies for myasthenia gravis. *BioDrugs* 2020; **34:** 557–66.
11 Dalakas MC. Progress in the therapy of myasthenia gravis: getting closer to effective targeted immunotherapies. *Curr Opin Neurol* 2020; **33:** 545–52.
12 Pasnoor M, He J, Herbelin L, Dimachkie M, Barohn RJ. Phase II trial of methotrexate in myasthenia gravis. *Ann N Y Acad Sci* 2012; **1275:** 23–28.
13 Howard JF Jr, Nowak RJ, Wolfe GI, et al. Clinical effects of the self-administered subcutaneous complement inhibitor zilucoplan in patients with moderate to severe generalized myasthenia gravis: results of a phase 2 randomized, double-blind, placebo-controlled, multicenter clinical trial. *JAMA Neurol* 2020; **77:** 582–92.
14 Howard JF Jr, Bril V, Burns TM, et al. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis. *Neurology* 2019; **92:** e2661–73.
15 Bril V, Benatar M, Andersen H, et al. Efficacy and safety of rozanolixizumab in moderate to severe generalized myasthenia gravis: a phase 2 randomized control trial. *Neurology* 2021; **96:** e853–65.
16 Howard JF Jr, Bril V, Vu T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2021; **20:** 526–36.
17 Jonsson DI, Pirskanen R, Piehl F. Beneficial effect of tocilizumab in myasthenia gravis refractory to rituximab. *Neuromuscul Disord* 2017; **27:** 565–68.
18 Strijbos E, Tannemaat MR, Alleman I, et al. A prospective, double-blind, randomized, placebo-controlled study on the efficacy and safety of influenza vaccination in myasthenia gravis. *Vaccine* 2019; **37:** 919–25.
19 Maher ER, Brown EA, Curtis JR, Phillips ME, Sampson B. Accumulation of aluminium in chronic renal failure due to administration of albumin replacement solutions. *BMJ* 1986; **292:** 306.
20 Lee M, Beeson D, Palace J. Therapeutic strategies for congenital myasthenic syndromes. *Ann N Y Acad Sci* 2018; **1412:** 129–36.
21 Lee MK, Sunwoo IN, Kim SM. 3,4-Diaminopyridine for the treatment of myasthenia gravis with electrophysiological patterns of Lambert-Eaton myasthenic syndrome. *J Clin Neurosci* 2018; **50:** 194–98.
22 Evoli A, Alboini PE, Damato V, Iorio R. 3,4-Diaminopyridine may improve myasthenia gravis with MuSK antibodies. *Neurology* 2016; **86:** 1070–71.
23 Lipka AF, Vrinten C, van Zwet EW, et al. Ephedrine treatment for autoimmune myasthenia gravis. *Neuromuscul Disord* 2017; **27:** 259–65.
24 Voet NB, van der Kooi EL, van Engelen BG, Geurts AC. Strength training and aerobic exercise training for muscle disease. *Cochrane Database Syst Rev* 2019; **12:** CD003907.
25 Rahbek MA, Mikkelsen EE, Overgaard K, Vinge L, Andersen H, Dalgas U. Exercise in myasthenia gravis: a feasibility study of aerobic and resistance training. *Muscle Nerve* 2017; **56:** 700–09.
26 Westerberg E, Molin CJ, Lindblad I, Emtner M, Punga AR. Physical exercise in myasthenia gravis is safe and improves neuromuscular parameters and physical performance-based measures: a pilot study. *Muscle Nerve* 2017; **56:** 207–14.
27 Westerberg E, Molin CJ, Spörndly Nees S, Widenfalk J, Punga AR. The impact of physical exercise on neuromuscular function in myasthenia gravis patients: a single-subject design study. *Medicine (Baltimore)* 2018; **97:** e11510.
28 Karelis G, Balasa R, De Bleecker JL, et al. A phase 3 multicenter, prospective, open-label efficacy and safety study of immune globulin (human) 10% caprylate/chromatography purified in patients with myasthenia gravis exacerbations. *Eur Neurol* 2019; **81:** 223–30.
29 Jensen P, Bril V. A comparison of the effectiveness of intravenous immunoglobulin and plasma exchange as preoperative therapy of myasthenia gravis. *J Clin Neuromuscul Dis* 2008; **9:** 352–55.
30 Barnett C, Tabasinejad R, Bril V. Current pharmacotherapeutic options for myasthenia gravis. *Expert Opin Pharmacother* 2019; **20:** 2295–303.
31 Zinman L, Ng E, Bril V. IV immunoglobulin in patients with myasthenia gravis: a randomized controlled trial. *Neurology* 2007; **68:** 837–41.
32 Ortiz-Salas P, Velez-Van-Meerbeke A, Galvis-Gomez CA, Rodriguez Q JH. Human immunoglobulin versus plasmapheresis in Guillain-Barre syndrome and myasthenia gravis: a meta-analysis. *J Clin Neuromuscul Dis* 2016; **18:** 1–11.
33 Alcantara M, Sarpong E, Barnett C, Katzberg H, Bril V. Chronic immunoglobulin maintenance therapy in myasthenia gravis. *Eur J Neurol* 2021; **28:** 639–46.

34 Melzer N, Ruck T, Fuhr P, et al. Clinical features, pathogenesis, and treatment of myasthenia gravis: a supplement to the Guidelines of the German Neurological Society. *J Neurol* 2016; **263:** 1473–94.

35 Utsugisawa K, Nagane Y, Akaishi T, et al. Early fast-acting treatment strategy against generalized myasthenia gravis. *Muscle Nerve* 2017; **55:** 794–801.

36 Murai H. Japanese clinical guidelines for myasthenia gravis: putting into practice. *Clin Exp Neuroimmunol* 2015; **6:** 21–31.

37 Guptill JT, Juel VC, Massey JM, et al. Effect of therapeutic plasma exchange on immunoglobulins in myasthenia gravis. *Autoimmunity* 2016; **49:** 472–79.

38 Ebadi H, Barth D, Bril V. Safety of plasma exchange therapy in patients with myasthenia gravis. *Muscle Nerve* 2013; **47:** 510–14.

39 Barth D, Nabavi Nouri M, Ng E, Nwe P, Bril V. Comparison of IVIg and PLEX in patients with myasthenia gravis. *Neurology* 2011; **76:** 2017–23.

40 Bril V, Barnett-Tapia C, Barth D, Katzberg HD. IVIG and PLEX in the treatment of myasthenia gravis. *Ann N Y Acad Sci* 2012; **1275:** 1–6.

41 Barnett C, Wilson G, Barth D, Katzberg HD, Bril V. Changes in quality of life scores with intravenous immunoglobulin or plasmapheresis in patients with myasthenia gravis. *J Neurol Neurosurg Psychiatry* 2013; **84:** 94–97.

42 Li F, Hotter B, Swierzy M, Ismail M, Meisel A, Rückert JC. Generalization after ocular onset in myasthenia gravis: a case series in Germany. *J Neurol* 2018; **265:** 2773–82.

43 Díaz-Maroto I, García-García J, Sánchez-Ayaso PA, et al. Ocular myasthenia gravis and risk factors for developing a secondary generalisation: description of a Spanish series. *Neurologia (Engl Ed)* 2020; 30300–05.

44 Imai T, Suzuki S, Nagane Y, Uzawa A, Murai H, Utsugisawa K. Reappraisal of oral steroid therapy for myasthenia gravis. *Front Neurol* 2020; **11:** 868.

45 Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: 2020 update. *Neurology* 2021; **96:** 114–22.

46 Benatar M, Mcdermott MP, Sanders DB, et al. Efficacy of prednisone for the treatment of ocular myasthenia (EPITOME): a randomized, controlled trial. *Muscle Nerve* 2016; **53:** 363–69.

47 Heckmann JM, Rawoot A, Bateman K, Renison R, Badri M. A single-blinded trial of methotrexate versus azathioprine as steroid-sparing agents in generalized myasthenia gravis. *BMC Neurol* 2011; **11:** 97.

48 Pasnoor M, He J, Herbelin L, et al. A randomized controlled trial of methotrexate for patients with generalized myasthenia gravis. *Neurology* 2016; **87:** 57–64.

49 Barnett C, Bril V. New insights into very-late-onset myasthenia gravis. *Nat Rev Neurol* 2020; **16:** 299–300.

50 Vecchio D, Ramdas S, Munot P, et al. Paediatric myasthenia gravis: prognostic factors for drug free remission. *Neuromuscul Disord* 2020; **30:** 120–27.

51 Alharbi M, Menon D, Barnett C, Katzberg H, Sermer M, Bril V. Myasthenia gravis and pregnancy: Toronto specialty center experience. *Can J Neurol Sci* 2021; published online Jan 12. https://doi.org/10.1017/cjn.2021.2.

52 Boldingh MI, Maniaol AH, Brunborg C, Weedon-Fekjær H, Verschuuren JJGM, Tallaksen CM. Increased risk for clinical onset of myasthenia gravis during the postpartum period. *Neurology* 2016; **87:** 2139–45.

53 Norwood F, Dhanjal M, Hill M, et al. Myasthenia in pregnancy: best practice guidelines from a U.K. multispecialty working group. *J Neurol Neurosurg Psychiatry* 2014; **85:** 538–43.

54 Ponticelli C, Moroni G. Fetal toxicity of immunosuppressive drugs in pregnancy. *J Clin Med* 2018; **7:** 552.

55 Levy RA, de Jesús GR, de Jesús NR, Klumb EM. Critical review of the current recommendations for the treatment of systemic inflammatory rheumatic diseases during pregnancy and lactation. *Autoimmun Rev* 2016; **15:** 955–63.

56 Gilhus NE, Hong Y. Maternal myasthenia gravis represents a risk for the child through autoantibody transfer, immunosuppressive therapy and genetic influence. *Eur J Neurol* 2018; **25:** 1402–09.

57 O'Connell K, Ramdas S, Palace J. Management of juvenile myasthenia gravis. *Front Neurol* 2020; **11:** 743.

58 Munot P, Robb SA, Niks EH, et al. 242nd ENMC international workshop: diagnosis and management of juvenile myasthenia gravis Hoofddorp, the Netherlands, 1–3 March 2019. *Neuromuscul Disord* 2020; **30:** 254–64.

59 Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med* 2016; **375:** 511–22.

60 Akaishi T, Motomura M, Aoki M, Utsugisawa K. MGTX extension study longitudinally favors early thymectomy in non-thymomatous young-adult patients with AChR antibody-positive myasthenia gravis. *Ann Transl Med* 2019; **7** (suppl 6)**:** S208.

61 Alshaikh JT, Amdur R, Sidawy A, Trachiotis G, Kaminski HJ. Thymectomy is safe for myasthenia gravis patients: analysis of the NSQIP database. *Muscle Nerve* 2016; **53:** 370–74.

62 Gamez J, Salvadó M, Carmona F, et al. Intravenous immunoglobulin to prevent myasthenic crisis after thymectomy and other procedures can be omitted in patients with well-controlled myasthenia gravis. *Ther Adv Neurol Disord* 2019; **12:** 1756286419864497.

63 Alipour-Faz A, Shojaei M, Peyvandi H, et al. A comparison between IVIG and plasma exchange as preparations before thymectomy in myasthenia gravis patients. *Acta Neurol Belg* 2017; **117:** 245–49.

64 Titulaer MJ, Maddison P, Sont JK, et al. Clinical Dutch-English Lambert-Eaton myasthenic syndrome (LEMS) tumor association prediction score accurately predicts small-cell lung cancer in the LEMS. *J Clin Oncol* 2011; **29:** 902–08.

65 Maddison P, Lipka AF, Gozzard P, et al. Lung cancer prediction in Lambert-Eaton myasthenic syndrome in a prospective cohort. *Sci Rep* 2020; **10:** 10546.

66 Lipka AF, Boldingh MI, van Zwet EW, et al. Long-term follow-up, quality of life, and survival of patients with Lambert-Eaton myasthenic syndrome. *Neurology* 2020; **94:** e511–20.

67 Zhao C, Pu M, Chen D, et al. Effectiveness and safety of rituximab for refractory myasthenia gravis: a systematic review and single-arm meta-analysis. *Front Neurol* 2021; **12:** 736190.

68 Hehir MK, Hobson-Webb LD, Benatar M, et al. Rituximab as treatment for anti-MuSK myasthenia gravis. *Neurology* 2017; **89:** 1069–77.

69 Hauser SL, Belachew S, Kappos L. Ocrelizumab in primary progressive and relapsing multiple sclerosis. *N Engl J Med* 2017; **376:** 1694.

70 Sorensen PS, Lisby S, Grove R, et al. Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis: a phase 2 study. *Neurology* 2014; **82:** 573–81.

71 Ellebrecht CT, Choi EJ, Allman DM, et al. Subcutaneous veltuzumab, a humanized anti-CD20 antibody, in the treatment of refractory pemphigus vulgaris. *JAMA Dermatol* 2014; **150:** 1331–35.

72 Ling LE, Hillson JL, Tiessen RG, et al. M281, an anti-FcRn antibody: pharmacodynamics, pharmacokinetics, and safety across the full range of IgG reduction in a first-in-human study. *Clin Pharmacol Ther* 2018; **105:** 1031–39.

73 Chen D, Gallagher S, Monson NL, Herbst R, Wang Y. Inebilizumab, a B cell-depleting anti-cd19 antibody for the treatment of autoimmune neurological diseases: insights from preclinical studies. *J Clin Med* 2016; **5:** 107.

74 Morandi F, Airoldi I, Marimpietri D, Bracci C, Faini AC, Gramignoli R. CD38, a receptor with multifunctional activities: from modulatory functions on regulatory cell subsets and extracellular vesicles, to a target for therapeutic strategies. *Cells* 2019; **8:** 1527.

75 Fedyk ER, Zhao L, Koch A, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics of the anti-CD38 cytolytic antibody TAK-079 in healthy subjects. *Br J Clin Pharmacol* 2020; **86:** 1314–25.

76 Ristov J, Espie P, Ulrich P, et al. Characterization of the in vitro and in vivo properties of CFZ533, a blocking and non-depleting anti-CD40 monoclonal antibody. *Am J Transplant* 2018; **18:** 2895–904.

77 Im SH, Barchan D, Maiti PK, Fuchs S, Souroujon MC. Blockade of CD40 ligand suppresses chronic experimental myasthenia gravis by down-regulation of Th1 differentiation and up-regulation of CTLA-4. *J Immunol* 2001; **166:** 6893–98.

78 Hewett K, Sanders DB, Grove RA, et al. Randomized study of adjunctive belimumab in participants with generalized myasthenia gravis. *Neurology* 2018; **90:** e1425–34.

79 Kohler S, Märschenz S, Grittner U, Alexander T, Hiepe F, Meisel A. Bortezomib in antibody-mediated autoimmune diseases (TAVAB): study protocol for a unicentric, non-randomised, non-placebo controlled trial. *BMJ Open* 2019; **9:** e024523.

80 Yamamoto S, Egashira N. Pathological mechanisms of bortezomib-induced peripheral neuropathy. *Int J Mol Sci* 2021; **22:** 888.

81 Yamamura T, Kleiter I, Fujihara K, et al. Trial of satralizumab in neuromyelitis optica spectrum disorder. *N Engl J Med* 2019; **381:** 2114–24.

82 Howard JF Jr. Myasthenia gravis: the role of complement at the neuromuscular junction. *Ann N Y Acad Sci* 2018; **1412:** 113–28.

83 Tsujihata M, Yoshimura T, Satoh A, et al. Diagnostic significance of IgG, C3, and C9 at the limb muscle motor end-plate in minimal myasthenia gravis. *Neurology* 1989; **39:** 1359–63.

84 Howard JF Jr, Utsugisawa K, Benatar M, et al. 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* 2017; **16:** 976–86.

85 Muppidi S, Utsugisawa K, Benatar M, et al. Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. *Muscle Nerve* 2019; **60:** 14–24.

86 Jacob S, Murai H, Utsugisawa K, et al. Response to eculizumab in patients with myasthenia gravis recently treated with chronic IVIg: a subgroup analysis of REGAIN and its open-label extension study. *Ther Adv Neurol Disord* 2020; **13:** 1756286420911784.

87 Oyama M, Okada K, Masuda M, et al. Suitable indications of eculizumab for patients with refractory generalized myasthenia gravis. *Ther Adv Neurol Disord* 2020; **13:** 1756286420904207.

88 Mantegazza R, Wolfe GI, Muppidi S, et al. Post-intervention status in patients with refractory myasthenia gravis treated with eculizumab during REGAIN and its open-label extension. *Neurology* 2021; **96:** e610–18.

89 Nishimura J, Yamamoto M, Hayashi S, et al. Genetic variants in C5 and poor response to eculizumab. *N Engl J Med* 2014; **370:** 632–39.

90 McKeage K. Ravulizumab: first global approval. *Drugs* 2019; **79:** 347–52.

91 Sheridan D, Yu ZX, Zhang Y, et al. Design and preclinical characterization of ALXN1210: a novel anti-C5 antibody with extended duration of action. *PLoS One* 2018; **13:** e0195909.

92 Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. *Blood* 2019; **133:** 540–49.

93 Howard JF Jr, Vissing J, Gilhus NE, et al. Zilucoplan: an investigational complement C5 inhibitor for the treatment of acetylcholine receptor autoantibody-positive generalized myasthenia gravis. *Expert Opin Investig Drugs* 2021; **30:** 483–93.

94 Zuercher AW, Spirig R, Baz Morelli A, Rowe T, Käsermann F. Next-generation Fc receptor-targeting biologics for autoimmune diseases. *Autoimmun Rev* 2019; **18:** 102366.

95 Patel DD, Bussel JB. Neonatal Fc receptor in human immunity: function and role in therapeutic intervention. *J Allergy Clin Immunol* 2020; **146:** 467–78.

96 Sesarman A, Vidarsson G, Sitaru C. The neonatal Fc receptor as therapeutic target in IgG-mediated autoimmune diseases. *Cell Mol Life Sci* 2010; **67:** 2533–50.

97 Håkansson I, Sandstedt A, Lundin F, et al. Successful autologous haematopoietic stem cell transplantation for refractory myasthenia gravis—a case report. *Neuromuscul Disord* 2017; **27:** 90–93.

98 Sossa Melo CL, Peña AM, Salazar LA, et al. Autologous hematopoietic stem cell transplantation in a patient with refractory seropositive myasthenia gravis: a case report. *Neuromuscul Disord* 2019; **29:** 142–45.

99 Bryant A, Atkins H, Pringle CE, et al. Myasthenia gravis treated with autologous hematopoietic stem cell transplantation. *JAMA Neurol* 2016; **73:** 652–58.

100 Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. *Lancet Neurol* 2020; **19:** 767–83.

101 Kushlaf H. COVID-19 in muscle-specific kinase myasthenia gravis: a case report. *Muscle Nerve* 2020; **62:** E65–66.

102 Restivo DA, Centonze D, Alesina A, Marchese-Ragona R. Myasthenia gravis associated with SARS-CoV-2 infection. *Ann Intern Med* 2020; **173:** 1027–28.

103 Rein N, Haham N, Orenbuch-Harroch E, et al. Description of 3 patients with myasthenia gravis and COVID-19. *J Neurol Sci* 2020; **417:** 117053.

104 Hübers A, Lascano AM, Lalive PH. Management of patients with generalised myasthenia gravis and COVID-19: four case reports. *J Neurol Neurosurg Psychiatry* 2020; **91:** 1124–25.

105 Anand P, Slama MCC, Kaku M, et al. COVID-19 in patients with myasthenia gravis. *Muscle Nerve* 2020; **62:** 254–58.

106 Businaro P, Vaghi G, Marchioni E, et al. COVID-19 in patients with myasthenia gravis: epidemiology and disease course. *Muscle Nerve* 2021; **64:** 206–11.

107 Jakubikova M, Tyblova M, Tesar A, et al. Predictive factors for a severe course of COVID-19 infection in myasthenia gravis patients with an overall impact on myasthenic outcome status and survival. *Eur J Neurol* 2021; **28:** 3418–25.

108 Assini A, Gandoglia I, Damato V, Rikani K, Evoli A, Del Sette M. Myasthenia gravis associated with anti-MuSK antibodies developed after SARS-CoV-2 infection. *Eur J Neurol* 2021; **28:** 3537–39.

109 Jacob S, Muppidi S, Guidon A, et al. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. *J Neurol Sci* 2020; **412:** 116803.

110 Lai CC, Chen IT, Chao CM, Lee PI, Ko WC, Hsueh PR. COVID-19 vaccines: concerns beyond protective efficacy and safety. *Expert Rev Vaccines* 2021; **20:** 1013–25.

111 Mantegazza R, Antozzi C. When myasthenia gravis is deemed refractory: clinical signposts and treatment strategies. *Ther Adv Neurol Disord* 2018; **11:** 1756285617749134.

112 Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. *Muscle Nerve* 2008; **37:** 141–49.

113 Wang S, Jiang B, Li Y, Shang Y, Liu Z, Zhang Y. A case report of disseminated nocardiosis with ocular involvement in a myasthenia gravis patient and literature review. *BMC Neurol* 2019; **19:** 243.

114 Huong NTC, Altibi AMA, Hoa NM, et al. Progressive cutaneous Cryptococcosis complicated with meningitis in a myasthenia gravis patient on long-term immunosuppressive therapy—a case report. *BMC Infect Dis* 2017; **17:** 311.

115 Canadian Agency for Drugs and Technologies in Health. Pharmacoeconomic Report: Eculizumab (Soliris). Ottawa, ON: Canadian Agency for Drugs and Technologies in Health, 2020.

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