Pharmacological treatment of Lambert-Eaton Myasthenic Syndrome

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ABSTRACT

Lambert-Eaton myasthenic syndrome (LEMS) is a very rare antibody-mediated autoimmune disease of the neuromuscular junction. Therapy can be divided in symptomatic treatment and immunosuppressive treatment. Symptomatic treatment with amifampridine is the only therapy currently authorized for use in LEMS patients. In the Netherlands the first-choice drug is amifampridine base in an extended-release formulation instead of the currently authorized immediate release amifampridine phosphate. The extended-release formulation has lower costs and is possibly safer due to lower peak concentrations. Other therapy used in LEMS patients is prescribed off-label and is based on experience in patients with myasthenia gravis. In many cases pyridostigmine is added as symptomatic treatment. In almost half of patients immunosuppressive therapy is started, mostly corticosteroids with or without azathioprine. Intravenous immunoglobulins and plasma exchange are used as emergency treatment.

Currently no randomized clinical trials with new therapies are ongoing or announced in patients with LEMS, although multiple new therapies for myasthenia gravis are being investigated. These future therapies can be differentiated in symptomatic and immunomodulating drugs. The immunomodulating drugs can be further differentiated in early-stage drugs which target the B-cell, later stage drugs which target the circulating autoantibodies and targeted therapy which have a disease-specific target. Some early and later stage immunomodulating drugs show promising results in myasthenia gravis although high cost and uncertain long-term safety may be limiting for incorporating these drugs in LEMS treatment guidelines.

Clinical trials in LEMS patients are lacking due to the rarity of the disease and we suggest the following requirements for future trials of potential new treatments: Sufficient power by performing multicenter or N-of-1 trials when appropriate, a cross-over design to reduce the number of patients and using a LEMS-specific quantitative primary outcome measure like the Triple Timed-Up-and-Go (3TUG) score.

Key words: Lambert-Eaton Myasthenic Syndrome, amifampridine

Introduction

Lambert-Eaton myasthenic syndrome (LEMS) is an autoantibody-mediated immune disease of the neuromuscular junction. LEMS is a very rare disease with a point prevalence between 2.3 and 3.5 per million (1-3). Autoantibodies to P/Q-type voltage-gated calcium channels (VGCC) can be detected in 90% of patients (4, 5). Autoantibodies against presynaptic VGCCs inhibit the release of the neurotransmitter acetylcholine in the neuromuscular junction (6) causing muscle weakness and autonomic dysfunction (3). In approximately 60% of patients, LEMS is associated with a malignancy, in most cases small cell lung cancer (SCLC) (3). It is believed that autoantibodies directed against VGCCs expressed on the tumor surface cross-react with the VGCCs expressed on the presynaptic nerve terminal at the neuromuscular junction (7). LEMS is often compared to myasthenia gravis (MG), since they are both associated with muscle weakness due to pathology in the neuromuscular junction, however autoantibodies in MG are directed at the postsynaptic membrane and the symptoms differ. Ocular and bulbar muscle weakness causing ptosis, diplopia, difficulties in swallowing and talking is usually rather mild compared to MG patients, and mostly not present as presenting symptoms (3). In contrast, proximal leg weakness is almost invariably present in the early phase of LEMS and relatively rare in MG. Furthermore, patients with LEMS are less likely to be hospitalized due to disease specific symptoms than patients with MG (8), probably because respiratory muscles are less likely to be affected.

Therapy for LEMS can be divided into symptomatic treatment and immune-directed treatment (9). Amifampridine has been the symptomatic drug of choice since 1983 (10) and is the only drug currently authorized at the FDA and EMA for the treatment of LEMS. Since its approval by the FDA, multiple review articles have been published to highlight amifampridine as the first drug of choice in the symptomatic treatment of LEMS (11-14). Other therapies used in the treatment of LEMS are prescribed off-label. Due to the low prevalence of LEMS, clinical trials needed for the regulatory approval of new therapies are difficult to carry out and have not been done. In addition, older clinical trials in LEMS patients often used outcome parameters developed for MG, making it difficult to assess the efficacy of the investigated therapies. The Triple

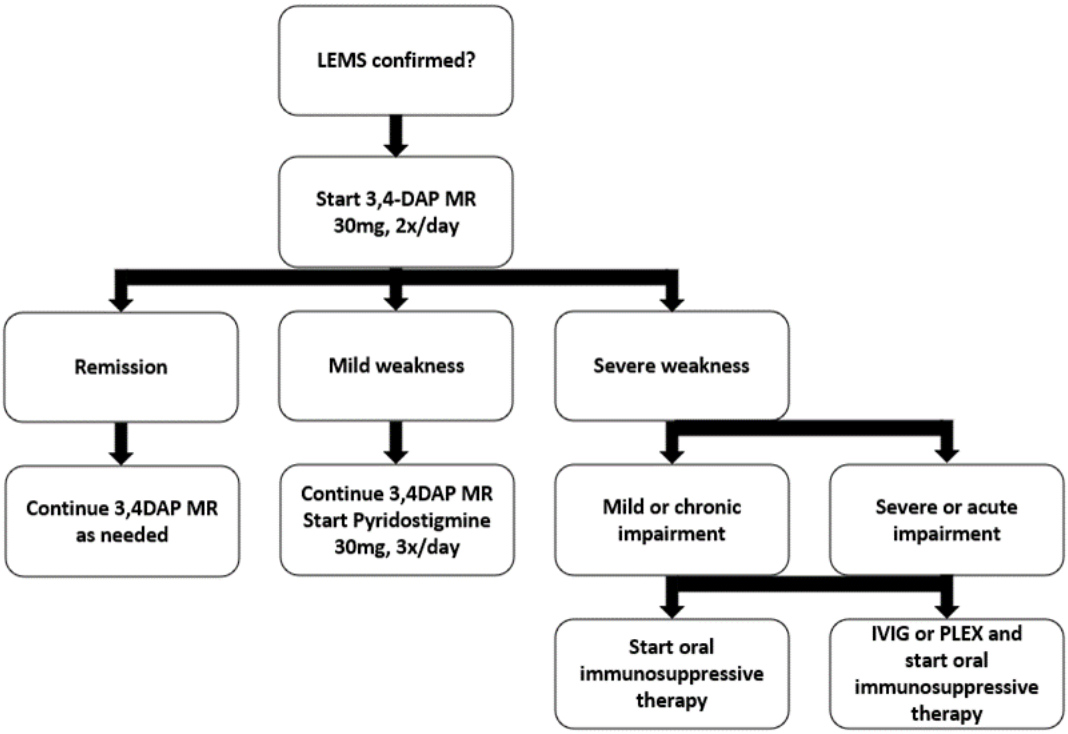

Figure 1: Treatment scheme for LEMS used in the Netherlands. 3,4-DAP MR = 3,4-diaminopyridine base modified release tablets. Illustration of a decision tree for the therapeutic options for patients with confirmed LEMS. This decision tree is based on data collected between 1998 and 2015 in the Netherlands and Belgium (4). Ninety-five percent of patients used amifampridine and 68% used pyridostigmine; 40% used immunosuppressive treatment of whom 29% used the combination azathioprine and prednisolone and 14% used prednisolone alone; intravenous immunoglobulins and plasma exchange were used as emergency treatment and were used in 26% of patients. Based on the Dutch registry for disorders of the neuromuscular junction, the use of immunosuppressive treatment in patients with LEMS is lower than in patients with MG, 49% and 69% respectively (8).

Timed-Up-and-Go (3TUG) score, a more disease-specific measure with a better representation of the functional disability of LEMS has been validated and introduced in most recent clinical trials in LEMS patients (15-17). As MG and LEMS show some similarities in pathogenesis and pathology, most therapeutic decisions in LEMS are based on experience with these treatments in MG patients. Several emerging treatments in MG may be useful in LEMS patients as well. In this article, the most applied therapeutic options for LEMS are reviewed. Treatment directed at the primary tumor is outside the scope of this review. Finally, potential future therapies will be discussed.

Existing therapies

Amifampridine

Most patients with confirmed LEMS start with amifampridine. Amifampridine is the International Nonproprietary Name (INN) of 3,4-diaminopyridine (3,4-DAP). Use of the name amifampridine may refer to 3,4-DAP phosphate (Firdapse) or 3,4-DAP base. Amifampridine blocks the efflux of potassium ions in the presynaptic nerve by blocking the presynaptic voltage gated potassium channel. This prolongs the duration of depolarization in the presynaptic nerve which then increases the calcium influx, thereby improving the efflux of acetylcholine in the synaptic cleft (2).

The formulation of amifampridine currently approved at EMA and FDA for LEMS is 3,4-DAP phosphate in an immediate release formulation. The approval of amifampridine by the EMA has been based on two pivotal studies performed with another formulation, 3,4-DAP base, which confirmed a positive risk-benefit balance (18, 19). The market authorization holder assessed the bioequivalence in a relative bioavailability trial of 3,4-DAP phosphate and 3,4-DAP base to include these studies in the application for marketing authorization. For the approval of amifampridine (as phosphate and as base) by the FDA, more recent randomized clinical trials (RCTs) have been performed using a withdrawal design (15, 16, 20). In a withdrawal trial, patients who already use a stable dose of amifampridine are included in the trial and, after randomization, either receive a tapered withdrawal using a placebo or receive their usual dose of amifampridine. Combining these RCTs a total of 168 patients were included of whom 93 patients received amifampridine. A summary of the main trial findings is shown in Table 1.

Table 1: Summary of main trial results of RCTs with amifampridine.

Study	Study drug	Trial type	Number of Patients	Outcome	Main trial findings	Serious drug reactions
McEvoy 1989(19)	Amifampridine base capsules	Double blind placebo-controlled crossover	12	NDS Isometric muscle strength Autonomic function CMAP amplitude	Significant improvement in all outcome measures	1 patient had a seizure when 3,4DAP was increasing from 90-100mg and pyridostigmine from 120mg-240mg
Sanders 1993(21)	Amifampridine base capsules	Double blind placebo-controlled crossover trial	18 (10 with LEMS)	QMG	significant lower QMG scores	2 patients had seizures who took 100mg 3,4DAP per day, 1 had toxic levels of theophylline, no seizures recurred after theophylline was discontinued, 1 had no seizures after dose reduction to 40mg per day
Sanders 2000(18)	Amifampridine base capsules	Double blind placebo- controlled parallel	26 (12 3,4-DAP)	QMG score change	Significant lower QMG scores	No serious drug reactions
Oh 2009(22)	Amifampridine tablets	Double blind placebo-controlled crossover	7	SS score LEMS classification MRC QMG CMAP amplitude	Significant improvement in all outcome measures	1 patient withdrew due to chills, weakness, shortness of breath, wooziness in the stomach and difficulty sleeping
Wirtz 2009(23)	Amifampridine base IV, pyridostigmine IV, placebo or combination	Double blind placebo-controlled crossover	9	Isometric muscle strength CMAP amplitude	Significant improvement in both outcome measures in amifampridine or combination treatment, no improvement in pyridostimine or placebo, no additive effect of combination therapy	2 patients withdrew due to pain in upper arm into which medication was administered
Oh 2016(20)	amifampridine phosphate tablets (Firdapse)	Double blind placebo-controlled parallel withdrawal trial	38 (16 3,4-DAPP)	Primary endpoints: QMG and SGI	Significant improvement in both primary endpoints	No serious drug reactions
Sanders 2018(16)	Amifampridine base tablets	Double blind placebo-controlled parallel withdrawal trial	32 (14 3,4-DAP)	Primary endpoint: 3TUG score	Significant change in 3TUG scores	No serious drug reactions
Shieh 2019(15)	Amifampridine phosphate tablets (Firdapse)	Double blind placebo-controlled parallel withdrawal trial	26 (13 3,4-DAPP)	Primary endpoints: SGI and QMG	Significant improvement in both primary endpoints	No serious drug reactions

NDS: Neurologic Disability Score, QMG: Quantitative Myasthenia Gravis score, SS score: Subjective Symptoms score, MRC: Medical Research Council score, SGI: Subject Global Impression of Improvement, 3,4-DAP: 3,4-diaminopyridine, 3,4-DAPP: 3,4-diaminopyridine phosphate.

In the Netherlands, 3,4-DAP base is available in a modified release tablet. The available strength of 3,4-DAP base is 30mg and patients usually start with 1 to 2 tablets a day. Based on the clinical response and side effects, the dosage can be increased to up to 3 tablets a day. Amifampridine is metabolized into the inactive metabolite 3-N-acetylated amifampridine by the enzyme N-acetyltransferase (NAT). Amifampridine and its metabolite are almost completely eliminated through the urine, resulting in an elimination half-life of approximately 2 hours (24). Patients with slow NAT phenotypes have a higher exposure to amifampridine than patients with a fast NAT phenotype (25). Pharmacogenetic testing is not recommended, because dosage is based on clinical response and amifampridine shows an immediate effect on clinical improvement of LEMS symptoms and side effects. The main side effects of amifampridine described in clinical trials are oral and digital paresthesia. Less frequently headache and gastrointestinal symptoms may occur (12). The most frequent serious side effect are seizures, which appear to be dose dependent. The occurrence of seizures is mainly described in patients with daily dosages of 100mg or more (19, 21). In addition, side effects are associated with high serum peak concentration of amifampridine (26). Of 93 LEMS patients who received amifampridine in RCTs, three patients had a seizure, of whom all received daily doses of 100mg amifampridine or more.

The modified release formulation will reduce the peak concentration of amifampridine, making it a safer option. Moreover, due to less frequent dosing it is more patient friendly. The market approval of amifampridine as the phosphate salt in Europe was based on efficacy data of the base and therefore the efficacy of amifampridine phosphate and base are comparable. Combined with the much lower price of the base and the possibly safer toxicity profile, the National Health Care Institute of the Netherlands concluded that 3,4-DAP modified release remains the first drug of choice in LEMS patients (27). A reason for using the market approved amifampridine mentioned in literature was that the base was not as stable as the phosphate salt, with a supposed maximum shelf life of 12 months (28). However, amifampridine base as a raw material as well as in the modified release formulation was found to have a shelf life of at least 36 months (personal observation by GMP licensed quality control laboratory).

Pyridostigmine

If the symptoms of LEMS are not adequately treated with amifampridine alone, pyridostigmine might be added, although there is limited evidence (19, 29). Pyridostigmine is an acetylcholine esterase inhibitor and increases the amount of acetylcholine by inhibiting the breakdown of acetylcholine in the synaptic cleft. Since amifampridine and pyridostigmine increase the amount of acetylcholine at the neuromuscular junction, but at a different site of action, they may have a synergistic effect. The only RCT to address the question whether the combination of amifampridine and pyridostigmine provides additional effect compared to amifampridine or pyridostigmine monotherapy, showed that the addition of pyridostigmine did not yield a significant benefit on isometric muscle strength and CMAP amplitude (23). In this randomized crossover trial, nine patients were treated with a single intravenous dose of amifampridine, pyridostigmine and the combination of these drugs. Nevertheless, in some cases pyridostigmine is still being used and in one study, 67% of patients noticed a subjective improvement due to pyridostigmine (4). The starting dose of pyridostigmine is usually 30mg 3 times a day and can be increased up to 6 times 60mg daily. The main side effects of pyridostigmine can be attributed to its cholinergic effects and include flatulence, urinary urgency, muscle cramps, blurred vision, hyperhidrosis, diarrhea, abdominal cramps, increased salivation, and light-headedness. Diarrhea has been reported to be the most frequent cause for treatment discontinuation or lowering the dose (30).

Immunosuppressive therapy

If symptoms are not adequately controlled with amifampridine and/or pyridostigmine, the introduction of immunosuppressive therapy can be considered, to inhibit the production of VGCC autoantibodies. There is little evidence, in terms of clinical trials, of its effect on the clinical severity of LEMS. The first-choice oral immunosuppressive treatment is a corticosteroid such as prednisolone, either with or without azathioprine. The use of the combination of these drugs is based on RCTs in patients with MG (31, 32). In one study of six patients with non-tumor related LEMS treated with the combination of prednisolone and azathioprine, three had sustained remission, while the other three improved. However two of the latter three were azathioprine intolerant (33). The corticoid sparing effect is another reason to add an immunosuppressive to prednisolone, in an attempt to avoid the serious side effects of prednisolone if high doses are needed for longer periods of time (34). Indeed, weight gain was less pronounced in patients using the combination of prednisolone and azathioprine compared to prednisolone alone and the overall dose of prednisolone was lower when combined with azathioprine (31).

The usual starting dose of prednisolone is 60mg after which the dose is tapered to a low maintenance dose. The standard daily dose of azathioprine is 2-3mg/

kg. Prednisolone can have major side effects including hyperglycemia, weight gain, opportunistic infections, hypertension, depression, and osteoporosis (34). Side effects of azathioprine include hepatotoxicity and myelosuppression. Because bone marrow toxicity is associated with the activity of thiopurine methyltransferase (TPMT), pharmacogenetic testing is recommended in patients in whom azathioprine is initiated (35). Another gene associated with azathioprine related toxicity is NUDT15. Patients who are homozygous for the inactive NUDT15-variant also need a dose reduction of azathioprine (36). Other corticosteroid sparing immunosuppressives can also be used, including tacrolimus, mycophenolate mofetil, cyclophosphamide and ciclosporin. Again, there is little evidence from RCTs, but the limited evidence in generalized MG does not show a clear difference in efficacy between these drugs, although the dose of the corticosteroid may be less when combined with other immunosuppressive drugs (37).

Intravenous Immunoglobulins (IVIG) or plasma exchange (PLEX) are used as a third line treatment when the disease is inadequately controlled by symptomatic treatment and immunosuppressive drugs. PLEX results in a rapid decrease in circulating antibodies (38). IVIG also leads to a reduced concentration of pathogenic autoantibodies, although the underlying mechanism is not fully understood. Possible explanations include neutralization by anti-idiotypic antibodies, downregulation of antibody production and accelerated autoantibody degradation by competing with the neonatal Fc receptor (39). One RCT in LEMS patients showed that IVIG therapy had a significant improvement on limb strength compared with placebo (40). Improvement in strength peaked at 2-4 weeks and declined after 8 weeks. Serum titers of VGCC autoantibodies declined significantly. Research in MG patients showed that IVIG and PLEX are comparable in effectiveness (41-43).

The usual dose of IVIG therapy is a total of 2 g/kg, divided over five daily doses of 0.4g/kg/day. Common side effects of IVIG therapy include headache, fever, chills, and nausea. However, side effects of IVIG therapy are subjectively less severe than PLEX (44). Reported side effects of PLEX are arterial bleeding, bleeding disorders, septicemia, and venous thrombosis. A typical PLEX schedule is performed by removing 1 plasma volume every other day in 5 sessions (45). The choice between PLEX and IVIG therapy depends on different factors. PLEX is considered when a rapid response is needed, but cannot be used in patients with sepsis, whereas IVIG treatment cannot be used in patients with renal failure (46).

Cost Of Therapy

The daily costs for a daily dose of 60mg of the licensed product with amifampridine phosphate are €130,80 in the Netherlands. This corresponds with annual costs of €47.742. In contrast, the daily costs of amifampridine base are €13,28, corresponding with annual costs of €4.847 (47). In the Netherlands, the total population of LEMS patients is estimated to be approximately 65 (4). If 95% of these use amifampridine, the estimated annual cost saving of using amifampridine base instead of amifampridine phosphate would be €42.895 per patient per year or €2.659.490 for the total estimated users of amifampridine. In particular in the United States, where amifampridine phosphate is priced in excess of $400.000 per patient per year, the annual savings achieved with a more affordable alternative would be immense. Licensing a medicinal product will increase its costs due to extra requirements, like post marketing pharmacovigilance. However, as the efforts undertaken by the pharmaceutical company that obtained marketing authorization at the time appear to be very limited, this enormous difference in drug pricing seems disproportionate (48).

The costs of pyridostigmine are €0,05 for the 10mg tablet and €0,20 for the 60mg tablet. With dose ranges between 3 times 30mg and 6 times 60mg the respective daily costs vary between €0,45 and €1,20 which corresponds with €164,25 to €438 per patient per year (49).

Prednisolone tablets are also relatively cheap with an estimated cost of €0,10 to €0,30 per patient per day and a respective yearly cost between €36,50 and €109,50 (50). However, the costs of prednisolone tablets do not provide an accurate representation of the total annual costs considering that these patients require monitoring and regular lab testing, bone density measurements and osteoporosis prophylaxis. In addition, the costs accrued through the occurrence of side effects of corticosteroids, including a 2.5-fold increased risk of cardiovascular events, are likely to be far higher.

The estimated annual costs per patient of other oral immunosuppressive therapies are varying between €365 and €1.825 depending on the dose and choice of drug (51-53). The cost of PLEX and IVIG therapy are not directly available and depend on multiple variables including, but not limited to costs of personnel, costs of a hospital visit, insertion of a central line if needed, departmental and equipment costs. A cost-minimalization analysis has been performed in a neurological center in the UK comparing PLEX and IVIG, showing an estimated total cost-per course- of £4.432 for PLEX and £8.890 for IVIG (54), which is approximately €5.000 and €10.000 per course respectively.

Future Therapies

As mentioned before, the only therapy currently approved for the treatment of LEMS is amifampridine. New treatment modalities for LEMS are not yet in the clinical phase. As LEMS has a low prevalence, and thus low commercial value, it remains to be seen whether clinical trials will be eventually performed. Other off-label prescribed drugs used in the treatment of LEMS are mostly based on experiences with these drugs in MG. Therefore, it will be interesting to see which new treatment modalities are or will become available for MG and which of these drugs may be of added value in the treatment of LEMS. An overview of these new drug modalities tested in clinical trials is shown in Table 2.

Table 2: An overview of drugs being tested in clinical trials in myasthenia gravis (source clinicaltrials.gov and clinicaltrialsregister.eu).

Drug classes	Drug	Drugtarget
Symptomatic drugs	Tirasemtiv	troponin activator
	Salbutamol	beta 2 receptor agonist
	Ephedrine	beta 1 receptor agonist
Immunomodulating drugs		
target B cell / early stage	Inebilizumab	CD-19
	Rituximab	CD-20
	Mezagitamab	CD-38
	Iscalimab	CD-40
	Satralizumab	IL-6
	Tocilizumab	IL-6
	Descarted-08	BCMA (CAR-T)
	Telitacicept	BAFF and APRIL
	Tofacitinib	JAK inhibitor
	Tolebrutinib	BTK inhibitor
	Abatacept	CTLA-4 inhibitor
	Bortezomib	Proteasome inhibitor
target circulating autoantibodies/ later stage	Batoclimab	FcRn blocking
	Efgartigimod	FcRn blocking
	Nipocalimab	FcRn blocking
	Orilanolimab	FcRn blocking
	Rozanolixizumab	FcRn blocking
	Vemircopan	Complement pathway (factor D)
	Zilucoplan	Complement pathway (C5)
	Eculizumab	Complement pathway (C5)
	Gefurulimab	Complement pathway (C5)
	Pozelimab	Complement pathway (C5)
	Ravulizumab	Complement pathway (C5)
Targeted therapy	MuSK-CAART	Muscle specific tyrosine kinase chimeric autoantibody receptor T-cells
	CAR-T	RNA-engineered chimeric antigen receptor T-cell therapy targeting B-Cell Maturation Antigen (BCMA)

BCMA = B-Cell Maturation Antigen, BAFF = B-Cell Activation Factor, APRIL = Proliferation-Inducing Ligand, JAK = Janus Kinase, BTK = Bruton Tyrosine Kinase, FcRn = neonatal Fc Receptors.

In terms of symptomatic treatment, two types of drugs have been tested in randomized clinical trials in MG patients in the past decade. Tirasemtiv is a fast skeletal troponin activator, which has been tested in patients with acetylcholine receptor MG. This drug showed potential but not significant efficacy and had an acceptable safety profile (55). However, in the past decade, no new randomized clinical trials have been started or announced and the use of tirasemtiv in LEMS is not expected soon. Beta receptor agonists like salbutamol (beta 2) and ephedrine (beta 1) have shown some efficacy in MG and especially in congenital myasthenic syndrome (56, 57). In 2019 an RCT was started to study the effect of salbutamol as adjuvant therapy in MG, but no results are currently available. The mechanism of action is not clear, but researchers have hypothesized that beta agonists provide a compensatory mechanism to stabilize motor endplate structures. This is especially the case in patients treated with pyridostigmine, which has been suggested to have a destabilizing effect on the neuromuscular junction (56). A large effect of beta agonist in the symptomatic treatment of LEMS seems doubtful. However, one case report on the use of ephedrine in one patient with LEMS showed clinical improvement. The improvement was most marked with a combination of amifampridine and ephedrine, although potential cardiovascular side effects could limit its use (58).

Most new treatment modalities studied in MG have an immune modulating effect (59, 60). These new drugs are not specifically designed for MG but have their origin in other autoimmune diseases such as multiple sclerosis, ulcerative colitis, or systemic lupus erythematosus. Some of these new drugs exert their effect early in the immune response at the B-cell level and act by inhibiting the production of autoantibodies. Other drugs have their effect at a later stage in the immune response and act by diminishing the autoantibody levels. Of all immunomodulating drugs being tested in RCTs in MG, only rituximab has been mentioned in patients with LEMS in case reports. Three patients were treated with rituximab, of whom all three experienced improvements, but did not achieve remission (61, 62). Presumably, other new immunomodulating drugs have potential benefit in LEMS patients as well, although uncertainty on their long term safety, high cost and low level of evidence are barriers for incorporating these drugs in treatment guidelines of LEMS (63).

A drug specifically developed for MG is MuSK-CAART. This drug targets B cells that produce autoantibodies against muscle-specific kinase (MuSK) (64). By design this therapy is only effective in MuSK positive MG, but effectiveness of this therapy can accelerate the development of a comparable drug targeting VGCC autoantibody producing B-cells to treat LEMS. Another targeted therapy, CAR-T therapy, investigated in the Descartes-08 trial comprises of patients' own T-cells that have been modified ex-vivo with RNA to target B-cell maturation antigen (BCMA) (65). This therapy shows promising results in severe MG, however serious adverse reactions might prove a limitation of implementing CAR-T therapy in mild to moderate disease (42).

Towards Novel Treatment Options For Lems

Implementation of novel treatments for LEMS has been hampered by the rarity of the disease and relative paucity of data on valid outcome measures. Previous trials have sometimes used MG-specific outcome measures, which are not ideal for LEMS as they tend to be heavily tilted towards ocular and bulbar weakness, which is rarely the main limitation in LEMS patients.

We suggest the following requirements for a future trial on a potential novel treatment: 1) sufficient power (due to the rarity of the disease) by performing a multicenter trial or using an alternative trial design. 2) a cross-over design to reduce the number of patients required. 3) LEMS-specific but relevant and quantitative primary outcome measure. As a primary outcome measure, we would suggest the 3TUG (three Times Up and Go) test which has been used in the most recent RCTs (15, 16) in LEMS and which has been shown to have a high reliability (17). Potential secondary outcome measures could include neurophysiological outcome measures, the 15-item revised version of the Myasthenia Gravis Quality of Life (MG-QOL15r) questionnaire and muscle force dynamometry, which provides objective, reproducible measures of muscle force in arm and leg muscles. In addition to requirement 1, an alternative trial design can be an N-of-1 trial, in which the patient functions as its own control and can be entered in multiple treatment cycles. Evidence of these treatment cycles can be aggregated to produce population treatment effect estimates. An N-of-1 trial requires fewer patients to assess a meaningful treatment effect than a traditional RCT (66, 67). This trial design is suitable in LEMS because LEMS is a chronic or slowly progressive disease and symptoms are relatively stable and quantifiable. However, the use of N-of-1 trials is limited to treatments with a rapid response and few lasting carryover effects, so disease modifying therapy such as the new immunomodulating therapies tested in MG are not ideal candidates for an N-of-1 trial (66, 68).

Disclosures Of Conflicts Of Interest

LRN reports no disclosures relevant to the manuscript. WRB, KJMS and TvG are employed by the Department of Clinical Pharmacy and Toxicology which produces and

supplies the 3,4-diaminopyridine base modified release tablets to 40-50 users in the Netherlands. In the last 3 years TvG has received lecture fees and consulting fees from Roche Diagnostics, Thermo Fisher, Vitaeris, CSL Behring, Astellas and Aurinia Pharma. In all cases money has been transferred to hospital accounts, and none has been paid to his personal bank accounts. JJGMV has been involved in MG research sponsored by the Princes Beatrix Fonds, Health Holland and consultancies for Argenx, Alexion, and NMD Pharma. Reimbursements were received by the LUMC. He is coinventor on patent applications based on MuSK-related research. The LUMC receives royalties for MuSK antibody assays. He is a member of the Target-to-B! consortium. MRT reports trial support from Argenx and Alexion, consultancies for Argenx and UCB Pharma and research funding from NMD Pharma, with all reimbursements received by Leiden University Medical Center. LRN, JJGMV and MRT are members of the European Reference Network for Rare Neuromuscular Diseases (EURO-NMD).

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