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Symptomatic treatment of myasthenia gravis and its role in the era of emerging immunomodulatory treatments

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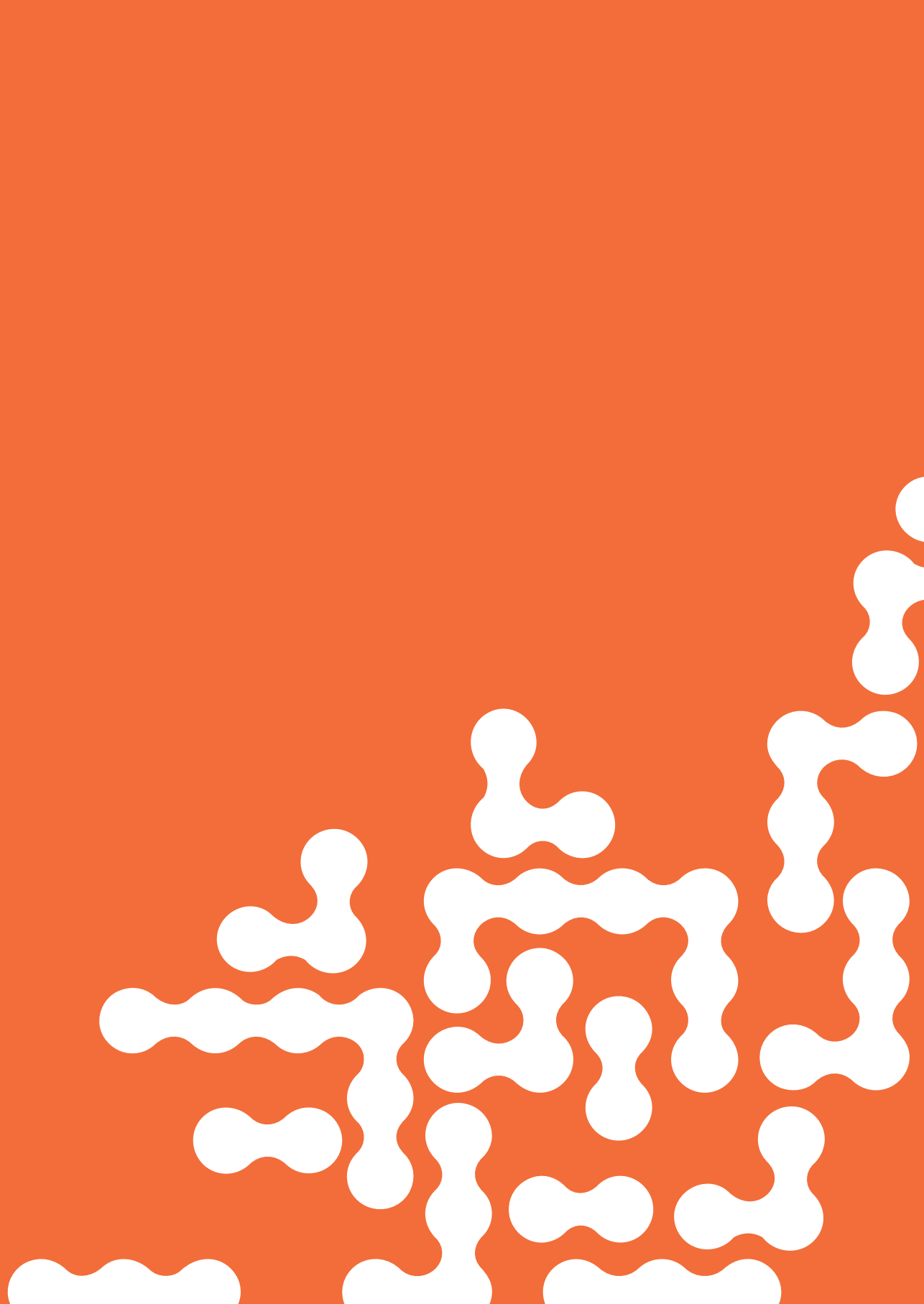
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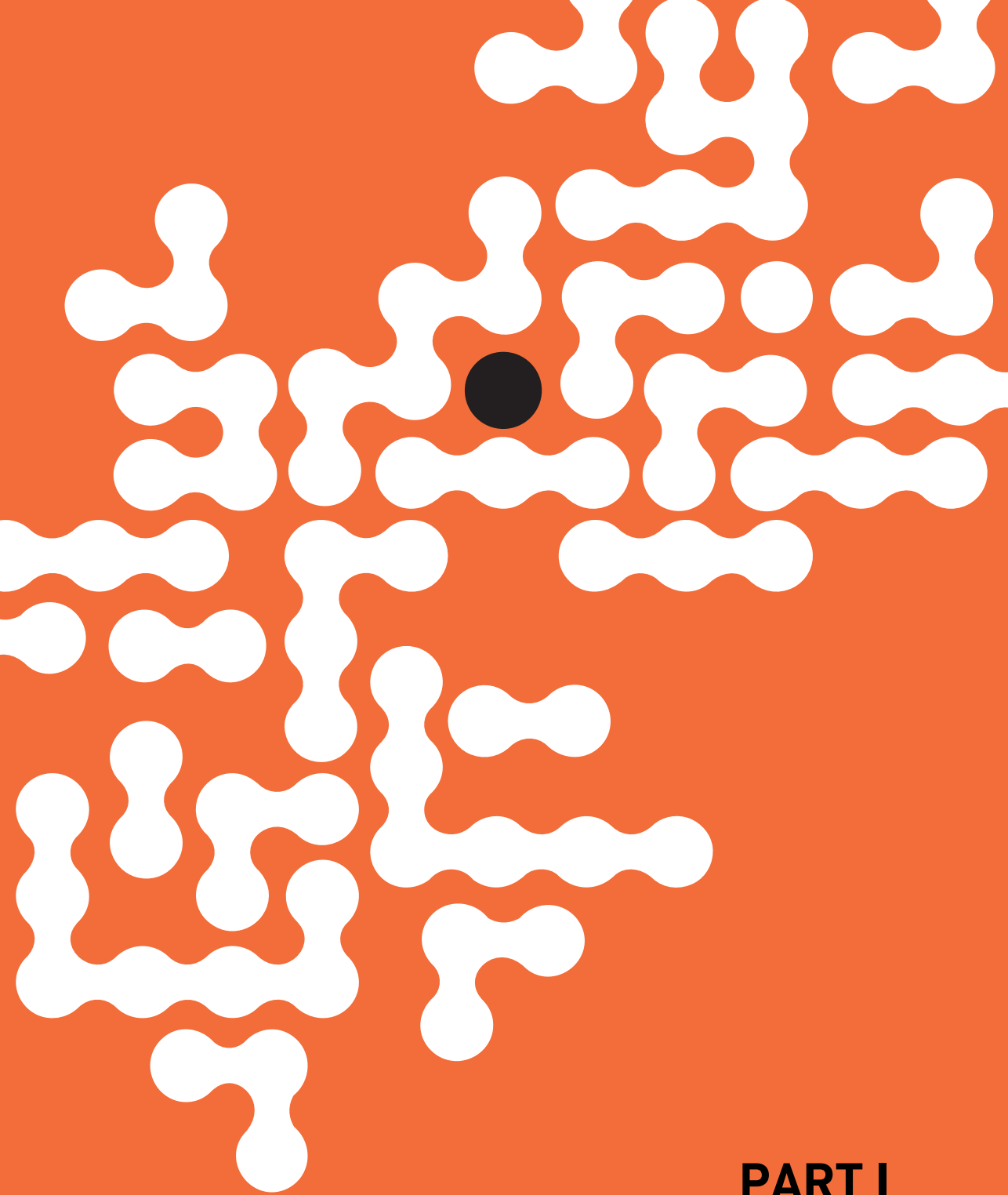
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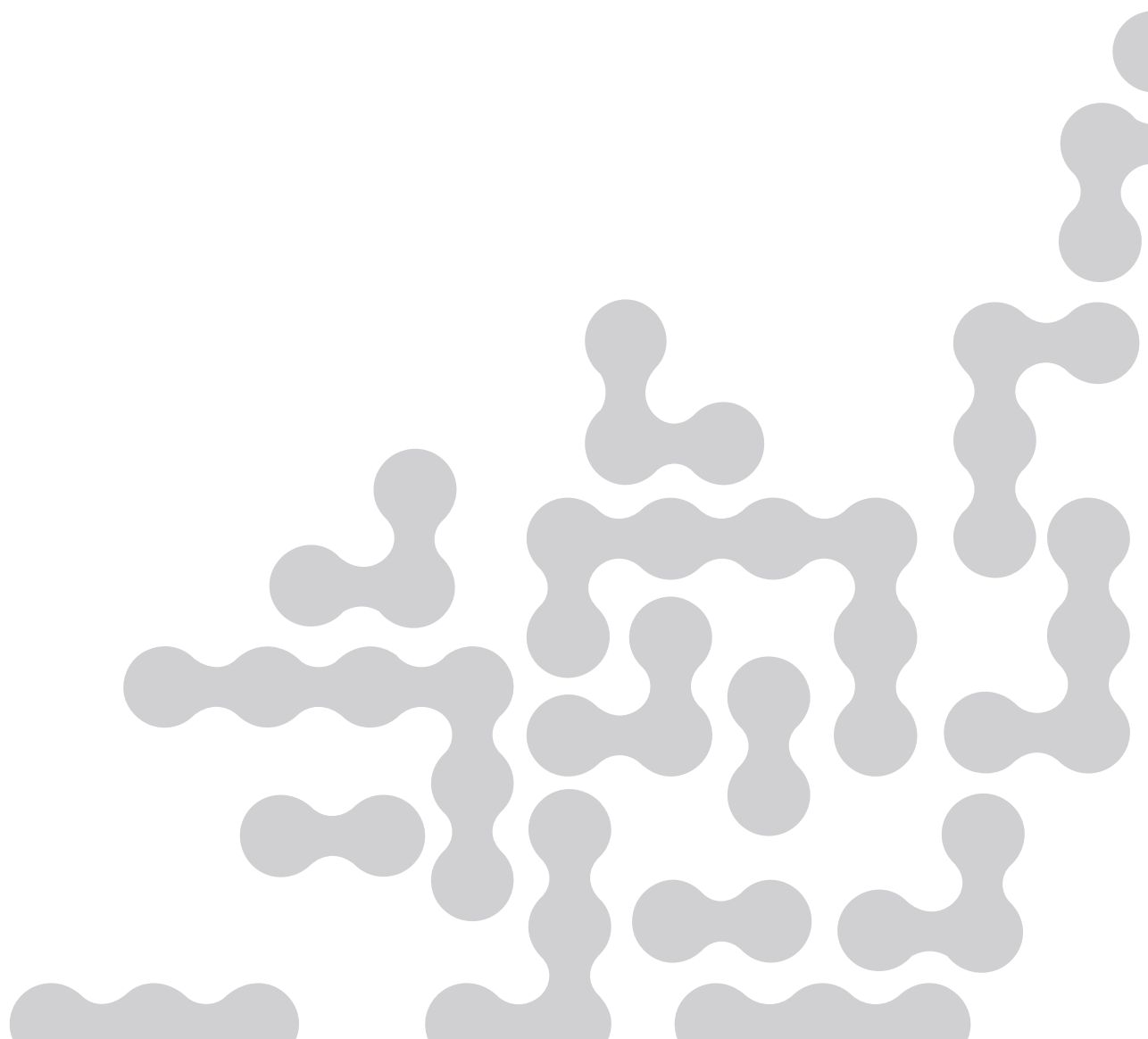


PART I

Symptomatic treatment

CHAPTER

2





Symptomatic pharmacological treatment

Symptomatic, pharmacological treatment of myasthenia gravis

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Abstract

Myasthenia gravis (MG) is a chronic antibody-mediated autoimmune disease. The most frequent form is MG with antibodies directed against the acetylcholine receptor on the postsynaptic membrane. The first step in the treatment of autoimmune myasthenia gravis consists of symptomatic therapy. If this is insufficiently effective, the next step is to start immunosuppressive treatment with corticosteroids, usually prednisolone. A corticoid-sparing agent is often added because of the long long-term side effects of high doses of corticosteroids. Emerging immunomodulatory therapies targeting B and T cells, the complement cascade, the neonatal Fc receptor and cytokines associated with antibody production, are currently expected to be limited to patients with severe refractory MG. It is therefore likely that symptomatic treatment will remain the cornerstone in the management of patients with MG in the foreseeable future. In this review, we provide an overview of currently available symptomatic treatments and recent advances in this field.

Pyridostigmine, an acetylcholinesterase inhibitor, is the most commonly used symptomatic drug for MG. Acetylcholinesterase inhibitors prolong and enhance the effect of acetylcholine on the muscarinic and nicotinic receptors. In addition, there is evidence that pyridostigmine may also have an anti-inflammatory effect. Pyridostigmine is moderately effective and side effects are frequently reported by patients. Other therapies include amifampridine and sympathomimetics such as ephedrine, salbutamol and terbutaline. At present, there is insufficient evidence for the use of amifampridine as monotherapy or as add-on therapy to pyridostigmine. The addition of β 2-adrenergic agonists to pyridostigmine may possibly be beneficial in some patients, however, well-designed randomized trials are needed to establish their efficacy. Emerging symptomatic therapies include CIC-channel blockers, fast-skeletal muscle troponin activators and antisense oligodeoxynucleotides. These therapies appear to be promising, with fewer side effects than pyridostigmine. However, phase III clinical trials are needed to assess their effectiveness and determine their place in the symptomatic treatment of MG patients.

Introduction

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction in which autoantibodies bind to the acetylcholine receptor (AChR) or associated structures on the postsynaptic membrane, resulting in impairment of neuromuscular transmission.⁵ Clinical features are fluctuating weakness in ocular, bulbar, limb and respiratory muscles. Typically patients experience an increase in weakness with exercise and an improvement after rest of the involved muscles.^{3,66} Antibodies are found against the AChR in approximately 80% of the patients with generalized MG.³ Less commonly, antibodies against muscle specific kinase (MuSK) or low-density lipoprotein receptor-related protein 4 (LRP4) are formed,² resulting in different clinical features including an altered response to pharmacologic treatment.⁶⁷ First line pharmacological treatment consists of symptomatic treatment.²⁵ Patients who do not meet treatment goals with symptomatic drugs, are advised to start corticosteroids often in combination with nonsteroidal immunosuppressive drugs. In recent years, advances in the understanding of the pathophysiology of MG have led to the development of new immunomodulatory therapies, acting at many different sites of the immune system, including IL-6, CD19, CD20, CD38, CD40, CTLA-4, FcRn and the complement pathway.³⁹ Although these novel therapies appear to be effective in reducing MG related muscle weakness, there are some drawbacks: they are associated with high costs and most of them require intravenous administration, for which hospitalization or infusion in day care setting is often necessary. Furthermore, little is known about their long-term safety and treatment therefore requires more intensive monitoring. In contrast, the long term risks associated with symptomatic drugs are probably negligible, they are relatively cheap and can be used “as needed” allowing the patient a greater degree of control over the management of their disease.

It is therefore likely that symptomatic treatment will remain one of the cornerstones in the treatment of patients with MG. However, despite this fact, only limited high-quality data is available regarding their efficacy and safety. In this review, we aim to provide an overview of currently available symptomatic treatments and recent advances in this field (**Figure 2.1**).

Existing therapies

Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors increase the amount of acetylcholine in the synaptic cleft by blocking the enzyme acetylcholinesterase, resulting in enhanced neuromuscular transmission. Their beneficial effects in patients with autoimmune MG have long been recognized; the first application of an acetylcholinesterase inhibitor dates from April 1934

when dr. Mary Broadfoot Walker treated a patient with physostigmine with dramatic results.⁶⁸ A year later, neostigmine was introduced and this remained the primary drug for the treatment of MG until the first case reports with pyridostigmine were published in 1947.⁶⁹⁻⁷² Neostigmine was known to have significant response fluctuations due to a short half-life, which led to patients taking neostigmine frequently throughout the day resulting in high cumulative doses. Furthermore, neostigmine had pronounced side effects, both muscarinic (such as gastrointestinal symptoms, increased salivation and a marked increase in bronchial secretions) and nicotinic (such as skeletal muscle cramps). These side effects remained and were difficult to control, even with the use of atropine. Pyridostigmine, which had a longer duration of action and had fewer side effects, was developed by Hoffmann-La Roche as a superior alternative.⁶⁹⁻⁷³ Since then, pyridostigmine has been the first choice in the symptomatic treatment of myasthenia gravis.²⁵ Other acetylcholinesterase inhibitors include ambenonium chloride, which is used less frequently than pyridostigmine due to a less favorable side effect profile, and hydrophonium or edrophonium, which is only used in the diagnosis of seronegative MG due to a brief duration of action.⁷⁴

Mouse models suggest that long-term anticholinesterase therapy may have an adverse effect on neuromuscular transmission and motor end-plate structure,^{75,76} resulting in a potential decrease in efficacy over time and an increased risk of cholinergic side effects.⁷⁷ Neurotransmission itself has a dispersal effect on AChR clusters and postsynaptic structures, which is counteracted by the agrin/muscle-specific kinase pathway (i.e. the AChR-clustering pathway). An increase of neurotransmission, through a pharmacological intervention such as acetylcholinesterase inhibitors, will therefore lead to an amplification of the disruption of the postsynaptic structures, especially in diseases in which the counteracting AChR agrin/muscle-specific kinase pathway is affected.⁷⁸ However, in patients with MG, no correlation has been found between the perceived efficacy and age or diseases duration, nor between the number and severity of side effects and age or disease duration.⁷⁹

In addition to the direct effect of acetylcholinesterase inhibitors on the neuromuscular junction, there is evidence that pyridostigmine may also have an anti-inflammatory effect,^{80,81} through the cholinergic anti-inflammatory pathway. This pathway can modulate the activity of immune cells through activation of nicotinic acetylcholine receptors on macrophages, dendritic cells, monocytes and T and B lymphocytes. Furthermore, it can inhibit cell proliferation and differentiation, as well as suppress cytokine release.⁸² The exact role of acetylcholinesterase inhibitors and their interaction with the cholinergic pathway and inflammatory reactions in MG has not been established.

Pyridostigmine

All international guidelines recommend pyridostigmine as the first step in the pharmacological treatment of MG.^{25,83-85} In a recent study involving participants of the Dutch national

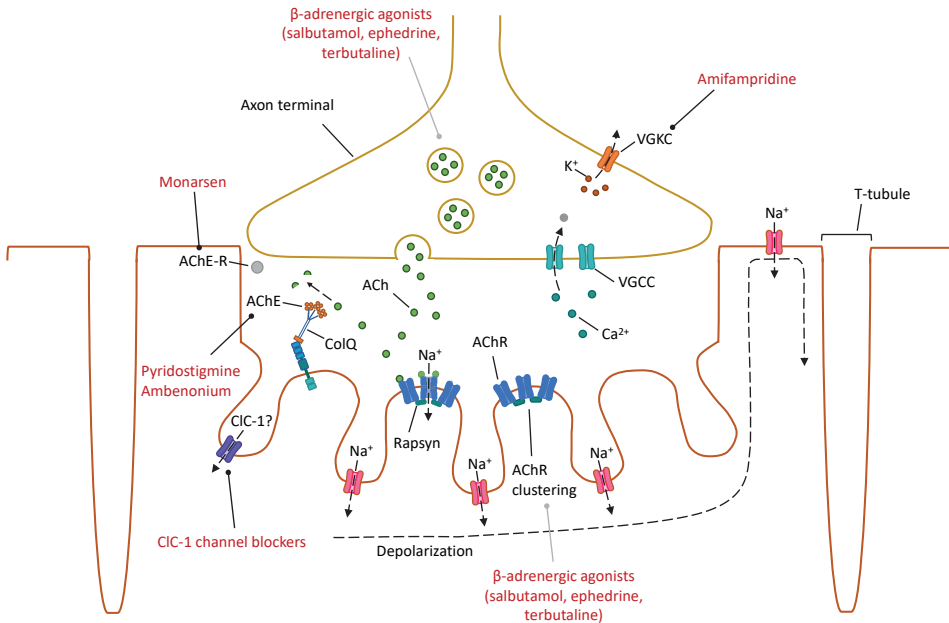


Figure 2.1 (Assumed) mechanism of action of different drugs in the symptomatic treatment of patients with myasthenia gravis

Pyridostigmine and ambenonium, both acetylcholinesterase inhibitors, block the enzyme acetylcholinesterase and thereby increase the amount of acetylcholine in the synaptic cleft. Amifampridine blocks potassium efflux which results in a prolonged action potential of the presynaptic nerve terminal and thereby enhances the release of acetylcholine into the synaptic cleft. The mechanism of action of β -adrenergic agonists (salbutamol, ephedrine and terbutaline) is not fully understood. There is evidence that β -adrenergic agonists affect post-synaptic AChR clustering. Furthermore, it is hypothesized that β -adrenergic agonists play a role in the regulation of quantal acetylcholine content. CIC-1 channel blockers reduce the inhibitory currents that counteract neuromuscular transmission. The precise localization of this channels at the neuromuscular junction is unknown. Monarsen is an antisense oligodeoxynucleotide which inhibits the expression of AChE-R, a isoform of AChE mainly found in patients with myasthenia gravis. Not shown: Fast-skeletal muscle troponin activators (tirasemtiv, reldesemtiv). Abbreviations: ACh Acetylcholine. AChE Acetylcholinesterase. VGCC Voltage-gated calcium channel. VGKC Voltage-gated potassium channel.

MG registry, 74% reported using pyridostigmine.⁸⁶ Unfortunately, no precise data are available on its effect, as no randomized controlled studies have ever been performed since the first published case-studies.³⁰ However, in a large-scale cross-sectional study on 410 MG patients; 61% reported that they currently used pyridostigmine, 36% had discontinued pyridostigmine and 2% reported to never have used pyridostigmine. On a scale of 0 (no effect at all) to 100 (maximum effect), patients currently using pyridostigmine reported a median effectiveness of 60 (IQR 28-78) and net benefit of 65 (IQR 45-84). In the group of patients who discontinued pyridostigmine, side effects were the reason for discontinuation in 26%. Pyridostigmine monotherapy is used in 22-66% percent of all patients,⁸⁶⁻⁸⁸ suggesting that it is sufficiently effective to prevent the use of immune suppressant medication in

patients with relatively mild symptoms. In 2018, the first randomized controlled trial started recruiting patients to evaluate the effect of pyridostigmine in two groups: 1) newly diagnosed, treatment-naïve patients treated with 60 mg pyridostigmine administered twice in four hours and 2) patients with MG on stable anti-myasthenic medication treated with the patient's usual dosage also administered twice in four hours (NCT03510546). In 2023, in our center a randomized controlled withdrawal trial will start, comparing the efficacy of pyridostigmine versus placebo over a 5-day period.

Very few studies have reported on the side effects of pyridostigmine. Current knowledge is mainly based on years of clinical experience. Side effects are due to overstimulation of the muscarinic receptor causing symptoms such as abdominal cramping, diarrhoea, hyperhidrosis, increased salivation, sweating, lacrimation and bradycardia. Nicotinic side effects have also been reported due to overdosage of pyridostigmine and include muscle cramps, fasciculations and muscle weakness.⁸⁹ Side effects are frequently reported by patients using pyridostigmine.^{77,79} Most frequently reported side effects are gastro-intestinal symptoms (flatulence, diarrhea and abdominal cramps), urinary urgency, muscle cramps, blurred vision, hyperhidrosis, increased salivation, light-headedness and flu-like symptoms. Diarrhea, abdominal cramps and muscle twitching are the most frequently cited reasons to discontinue pyridostigmine.⁷⁹ Cumulative side-effects after long-term treatment have not been reported.³ Many patients with MuSK-MG respond poorly to acetylcholinesterase inhibitors with less effect and frequent side effects compared to patients with anti-AChR antibodies.⁹⁰

Muscarinic side effects of pyridostigmine can be controlled by the addition of muscarinic antagonists such as atropine,³ glycopyrronium bromide,³ propantheline,⁹¹ or hyoscyamine.⁹² Loperamide can be used to treat persistent diarrhea.³ There have been no studies comparing these agents in patients with MG. Their use in clinical practice is therefore based on single case reports, personal experience and expert opinion. In 2021, a phase II trial started to evaluate the effect of combined therapy of pyridostigmine and ondansetron, an anti-emetic drug which selectively blocks the serotonin 5-HT₃-receptor, in patients experiencing pyridostigmine-related gastrointestinal adverse events (NCT04226170).

Amibenonium chloride

The first use of amibenonium in patients with MG was reported in 1955. Out of fifty patients treated with oral amibenonium, 41 patients experienced more benefit from it than from neostigmine or pyridostigmine with the main advantages being its longer duration of action and fewer side effects.⁹³ In a later study, patients experienced more side effects with amibenonium than with pyridostigmine, although the duration of action of amibenonium was longer.⁹⁴ Amibenonium has an unpredictable pattern of bioavailability in MG patients, with a greater risk of accumulation and overdosage, possibly because pharmacokinetics showed no correlation between the daily dose and the area under the curve.⁹⁵ In current

clinical practice, ambenonium is rarely used, although it may be a good alternative for patients for whom pyridostigmine is contra-indicated.

Amifampridine

Amifampridine is a well-known treatment for other diseases of the neuromuscular junction such as Lambert Eaton Myasthenic Syndrome and congenital myasthenic syndromes. It is a short-acting potassium channel blocker, which blocks potassium efflux presynaptically. This results in a prolonged action potential of the presynaptic nerve terminal, which enhances the release of acetylcholine into the synaptic cleft by an increase in calcium influx into the nerve terminal.⁹⁶

A preliminary report of a double-blind, placebo-controlled crossover study noted an improvement of at least 3 points on the QMG scale in two of eight MG patients on amifampridine. However, only a limited description of methods and results of this study is available.⁹⁷ Another randomized controlled crossover trial showed an improvement of 6.9 points on the QMG scale and 5.7 points on the MG-ADL in 7 patients treated with amifampridine monotherapy with MuSK-MG.³²

Amifampridine and pyridostigmine act on different parts of the neuromuscular junction and it is hypothesized that they work in synergy to enhance neuromuscular transmission. Indeed, in a study on LEMS patients, the combination of amifampridine and pyridostigmine did have an effect on some pharmacokinetic parameters: pharmacokinetics of amifampridine were not significantly affected by cotreatment with pyridostigmine, whereas amifampridine caused an increase in the average pyridostigmine serum concentration. However, the average plasma concentrations of pyridostigmine corresponded with clinically therapeutic levels in both the co-treatment and the stand-alone treatment arm.⁹⁸ The combined use of pyridostigmine and amifampridine in clinical practice is not uncommon in patients with LEMS; 71% of all patients in the Dutch LEMS registry reported using a combination of pyridostigmine and amifampridine.⁸⁶ The efficacy and tolerability in patient with MG in clinical practice has only been described in a limited number of studies. Two small case studies and one case report provide anecdotal evidence that patients may benefit from the use of amifampridine as add-on in MG.^{33,34,99}

A phase II trial provided evidence that amifampridine phosphate was effective in patients with MuSK-MG.³² However, results were not replicated in a phase III trial evaluating the efficacy and long term safety of amifampridine in 55 patients with MuSK MG and 15 patients with AChR MG (NCT03304054). Results have yet to be published.

Sympathomimetics

The effects of sympathomimetics on the (myasthenic) neuromuscular junction are complex and insufficiently understood. Therapies acting on the sympathetic nervous system, such

as the β 2-adrenergic agonist salbutamol and the α - and β -adrenergic agonist ephedrine, have a well-documented effect in subtypes of congenital myasthenic syndromes; a diverse range of genetic disorders in which neuromuscular transmission is impaired at the motor endplate.¹⁰⁰ However, the molecular mechanisms underlying the therapeutic effect of sympathomimetics are not understood. It is hypothesized that β 2-adrenergic agonists directly influence synaptic organization and the therapeutic effect may therefore be through morphological restoration of the neuromuscular junction.¹⁰¹ In vitro studies have shown that β -adrenergic agonists affect postsynaptic AChR clustering.¹⁰² This hypothesis is supported by observations in clinical practice that β -adrenergic agonists are particularly beneficial in disorders in which the endplate structure is disrupted such as DOK7 and COLQ CMS.¹⁰³ Furthermore, there is evidence that sympathomimetics regulate quantal acetylcholine content and influence the probability of quantal release at the neuromuscular junction.¹⁰⁴ Pharmacological stimulation of adrenoceptors, as well as sympathectomy, can affect acetylcholine release from motor nerve terminals.¹⁰⁵ Notably, it is uncertain whether the observed effects in these animal studies are relevant for the understanding of the observed effect in clinical practice since the concentrations of the adrenergic agonists used in animal studies were much higher than those reached in patients. Considerable ambiguities therefore remain regarding the mode of action of sympathomimetics. In addition to their action at the neuromuscular junction, catecholamines play a role in several immune parameters: they affect lymphocyte proliferation and modulate cytokine production and the functional activity of different lymphoid cells.^{106,107} However, the role of sympathomimetics on the immune system in MG patients is currently not fully understood.

Ephedrine

Ephedrine is a sympathomimetic drug with a stimulating effect on both α - and β -adrenergic receptors.¹⁰⁸ The use of ephedrine in patients with MG was first described in 1930 by Edgeworth, who serendipitously found that the ephedrine she was taking for menstrual cramps was effective for her myasthenic symptoms.¹⁰⁹ In a small series of randomized controlled n-of-1 trials with ephedrine as add-on treatment to pyridostigmine or prednisone in MG patients, a small reduction of MG symptoms was seen in both the primary outcome measure (QMG) and the secondary outcome measures (MG-ADL, MGC and VAS-score). This effect was statistically significant, but below the previously defined cut-off value for a clinically relevant difference.³¹

Salbutamol

Salbutamol is a selective β 2-adrenergic agonist and is mainly used in patients with CMS. As described above, pyridostigmine may have a long-term adverse effect on the motor endplate structure and thus on neuromuscular transmission. The addition of salbutamol to

pyridostigmine might be beneficial to counteract the long term adverse effects of pyridostigmine use because of the supposed mechanism of β 2-adrenergic agonists to morphologically restore the neuromuscular junction. The functional effect of this combination therapy was explored in acetylcholine receptor deficiency syndrome, the most common form of CMS, in a small long-term cohort of CMS patients and in a mouse model.¹¹⁰ In the cohort of eleven patients with severe AChR deficiency, a sustained response on QMG score was seen: after 4 years of combination therapy with pyridostigmine plus salbutamol, the mean QMG score improved from 17.7 (95% CI 13.25-22.2) at baseline to 12.3 (95% CI 9.1-15.6), although this effect did not reach statistical significance. Mouse models showed improvement of muscle fatigue which became apparent shortly after starting salbutamol addition. Furthermore, improved neuromuscular transmission and improved synaptic structure was seen. Whether the addition of salbutamol is useful in patients with MG as well is investigated in an ongoing randomized, controlled cross-over trial to study the efficacy and tolerability of oral salbutamol as adjuvant therapy in patients with MG. This study started in 2019 (NCT03914638).

Terbutaline

Like salbutamol, terbutaline is a β 2-adrenergic agonist. In a mouse model, clinical symptoms were suppressed after treatment with terbutaline and electrophysiological studies showed a significantly larger first compound muscle action potential.¹¹¹ In a phase II cross over study in eight patients with generalized MG, treated with terbutaline or placebo during two weeks, a significant improvement was seen on the QMG score. Five out of eight patients (63%) had a clinically relevant improvement on the QMG score of 3.0 or greater. Pyridostigmine was withheld for at least eight hours before each visit. Terbutaline was well-tolerated in all patients.¹¹²

Emerging therapies

CIC-1 channel blockers

In MG, due to the loss of AChR, the excitatory endplate currents are reduced. Skeletal muscle-specific CIC-1 chloride ion channels carry the inhibitory currents that counteract neuromuscular transmission. Inhibition of CIC-1 has been shown to reduce the inhibitory current, increasing muscle membrane excitability and strengthening of neuromuscular transmission.¹¹³ In 2020, a phase I/II randomized, controlled trial was initiated to assess safety and tolerability of NMD670, an inhibitor of the CIC-1 channel (NL8692). Results have yet to be published, although the company announced positive results in a press release.¹¹⁴

Fast-skeletal muscle troponin activators

Tirasemtiv is a highly selective activator of the troponin complex of fast skeletal muscles. It was developed to increase muscle strength in neuromuscular disease by amplifying the response of the muscle when neuromuscular input is diminished. Binding of tirasemtiv to the troponin complex slows the rate of calcium release from fast skeletal troponin and consequently sensitizes muscle fibers to calcium.¹¹⁵ In a phase II study, the efficacy, safety and tolerability of single doses of tirasemtiv in patients with AChR MG was investigated. This study showed small dose-related improvements in QMG with tirasemtiv. Furthermore, twice as many patients had clinically significant improvements in QMG (>3 points) at six hours after the 500 mg dose compared to placebo, but this difference did not reach significance due to the small sample size. Two single doses of tirasemtiv were well tolerated and no serious adverse events occurred.¹¹⁶ A phase III clinical trial in patients with amyotrophic lateral sclerosis did not meet primary or secondary endpoints. Poor tolerability after 48 weeks of double blind treatment may have contributed to this result: 34.2% of all patients treated with tirasemtiv stopped treatment before week 24 vs. 12.2% in the placebo group. Dizziness, fatigue, nausea, weight loss, and insomnia occurred more frequently on tirasemtiv.¹¹⁷ As a result, further development of tirasemtiv has ceased and the focus will be on reldesemtiv, a next-generation fast skeletal muscle troponin activator. Reldesemtiv advanced into clinical development for its potential to demonstrate increased efficacy relative to tirasemtiv as well as improved tolerability and less potential for drug-drug interactions.¹¹⁸ A phase III trial is initiated in patients with ALS in 2021 (NCT04944784). To our knowledge, no trials in MG are currently planned.

Antisense oligodeoxynucleotides

MG is associated with the production of a rare isoform of acetylcholinesterase which is referred to as the “read-through” transcript (AChE-R).^{119,120} This isoform is found in half of all patients with myasthenia gravis and not in healthy subjects.¹²¹ Monarsen (formerly EN101) is an antisense drug which inhibits the expression of AChE-R, potentially resulting in an increase of acetylcholine levels. In a phase II cross-over trial designed to compare three doses of monarsen, a decrease in QMG scores was found compared to baseline. All doses appeared to be effective, but no statistically significant difference between the three doses was found and the study did not include a placebo control group. Only preliminary results have been published.¹²² Currently, no plans have been announced to further develop monarsen.

Conclusion

Despite years of experience with symptomatic drugs in the treatment of MG patients, much remains unknown. This makes it challenging to make individually tailored treatment decisions. In the past decades, only 6% of all clinical trials have focused on the symptomatic treatment of MG,³⁹ while almost all patients initially start with symptomatic treatment and approximately two thirds of all patients continue using it throughout their disease.⁷⁹

Based on the available evidence, it is clear that pyridostigmine should remain the cornerstone of symptomatic treatment of MG patients. Many patients report a moderate effectiveness and a substantial number can be treated with pyridostigmine monotherapy without need for immunosuppressants. Nonetheless, pyridostigmine may cause considerable side effects, which can have substantial impact on quality of life. The addition of specific muscarinic antagonists such as atropine may alleviate side effects, but in our experience, the effect of atropine is often insufficient and it can be difficult to find a balance between adequate treatment of muscarinic side effects and inducing signs of overdosage of atropine.

The place of amifampridine and sympathomimetics such as ephedrine, salbutamol and terbutaline in the treatment of MG remains unclear. The addition of β_2 -adrenergic agonists to pyridostigmine may possibly be beneficial in some patients, however well-designed randomized trials are needed to establish the efficacy of these agents. At present, there is insufficient evidence for the addition of amifampridine to the standard symptomatic treatment with pyridostigmine. New emerging symptomatic therapies, especially the ClC-channel blockers and antisense oligodeoxynucleotides, appear to be promising therapies with fewer side effects than the current standard. Hopefully, phase III trials can shed more light on their effectiveness and determine their place in the symptomatic treatment of MG patients.

In the future, MG patients would greatly benefit from properly designed trials on symptomatic drugs for MG, as they are likely to remain an important element in achieving symptom relief for a large number of MG patients. Therefore, exciting developments involving drugs targeting the immune system should not overshadow efforts to improve the quality of life of MG patients by optimizing existing symptomatic treatment.