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

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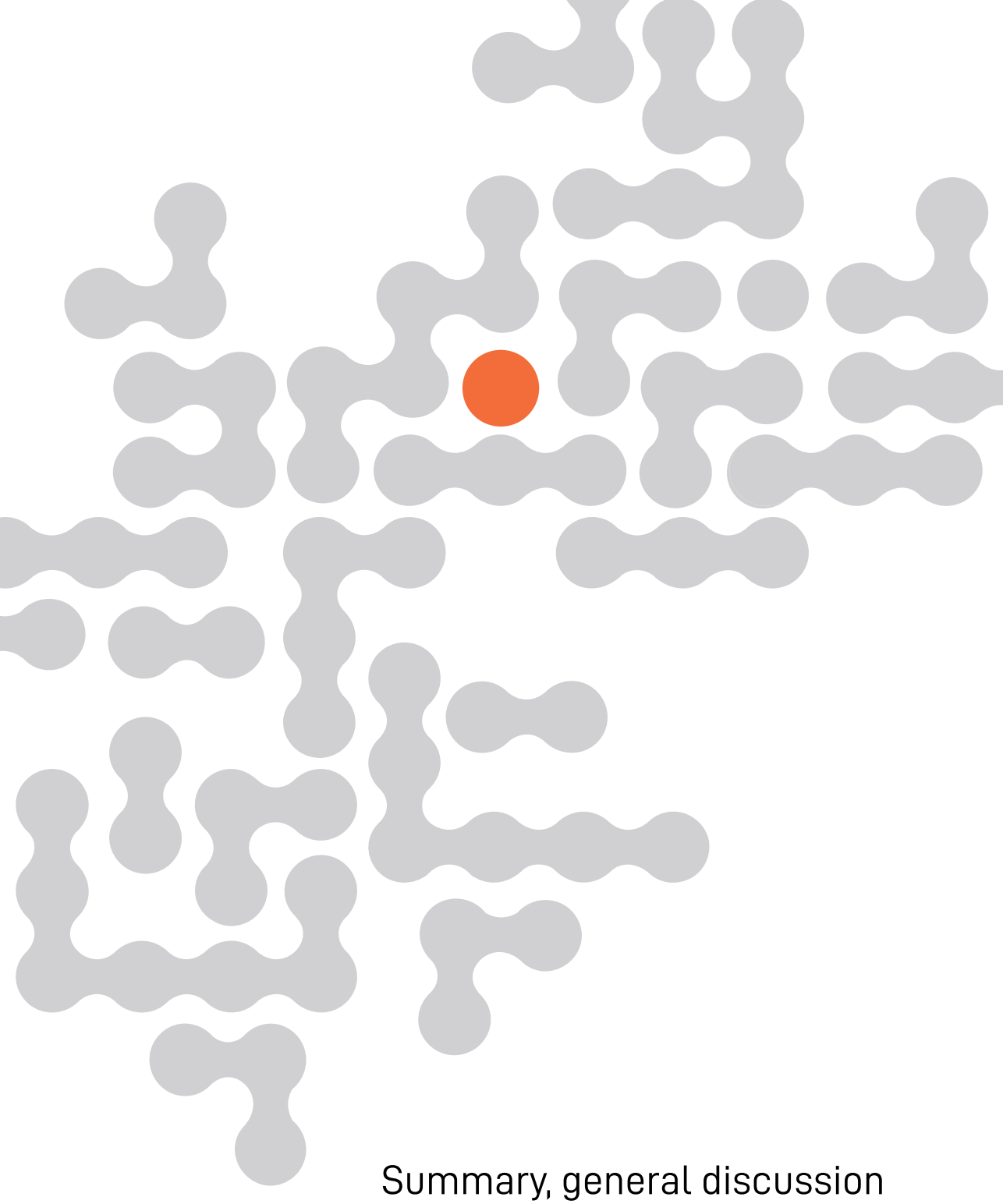
CHAPTER

8



Summary, general discussion and future perspectives

Summary

The aim of this thesis was to provide an overview of the therapeutic landscape for patients with myasthenia gravis (MG), with Part I focusing on existing and emerging symptomatic treatment strategies, and Part II on immunomodulatory therapies and their current use in clinical practice.

Part I: Symptomatic treatment

Chapter 2 presents an extensive literature review on symptomatic therapies for MG. These therapies target the neuromuscular junction directly, although for certain drugs like sympathomimetics, their precise mode of action remains unclear.
Three main groups of currently available therapies are described; acetylcholinesterase inhibitors, potassium channel blockers, and sympathomimetic agents. Acetylcholinesterase inhibitors like pyridostigmine and ambenonium chloride, enhance cholinergic transmission by inhibiting the breakdown of acetylcholine in the synaptic cleft. According to national and international guidelines, pyridostigmine is widely accepted as the cornerstone of symptomatic treatment for MG. This is based on observational studies, the earliest of which date back to the mid-1930s, as well as decades of clinical experience. However, no randomized clinical trial has quantified its effect size, and systematic evaluation of its side effect burden is lacking. As a result, it remains challenging to position pyridostigmine relative to other symptomatic therapies. The role of short-acting potassium channel blockers (e.g., amifampridine), which enhance acetylcholine release by prolonging the presynaptic action potential, as well as sympathomimetic agents (e.g., ephedrine, salbutamol, terbutaline), remains unclear due to a lack of robust comparative studies.
In addition to currently available treatments, three experimental compounds are discussed: CLC-1 chloride channel inhibitors, fast-skeletal muscle troponin activators, and antisense oligodeoxynucleotides. The latter two are no longer under active development, limiting their future clinical applicability. CLC-1 chloride channel inhibitors appear to be promising with potentially fewer side effects than the current standard. Hopefully, phase III trials will provide greater insight into their efficacy and help clarify their role in the symptomatic treatment of MG patients.

In **chapter 3** we characterized the effectiveness and side effects of pyridostigmine in a cross-sectional study. Data were collected from 410 out of 642 invited patients participating in the Dutch-Belgian myasthenia patient registry. In a dynamic, for this study developed questionnaire, effectiveness, side effects and net benefit were evaluated. Almost all patients

reported to have used pyridostigmine at some point during the course of their disease, with approximately two thirds (62%) continuing its use. The reported net benefit and effectiveness were moderate with frequently reported side effects. Out of all patients currently using pyridostigmine, 91% reported at least one side effect compared to 54% in the control group. The most frequently reported side effects included gastro-intestinal symptoms (flatulence, diarrhea, and abdominal cramps), urinary urgency, muscle cramps, blurred vision, hyperhidrosis, increased salivation, light-headedness and flu-like symptoms. Side effects were cited as the primary reason for discontinuation by 26% of respondents. Factors associated with discontinuation of pyridostigmine were male sex and the presence of MuSK antibodies.

In **chapter 4** and **chapter 5** we describe the results of IMPACT-MG, a randomized double-blinded, placebo controlled crossover trial that evaluated the efficacy and cost-effectiveness of pyridostigmine (part one), followed by a second randomization to assess the efficacy and safety of amifampridine in combination with pyridostigmine (part two) in patients with AChR MG.

The findings of part one of IMPACT-MG are described in **chapter 4**. Nineteen participants were assigned to two five-day treatment periods separated by a two-day washout. Participants received pyridostigmine followed by placebo, or vice versa. All participants had been using pyridostigmine chronically before enrollment, and their trial dose was identical to their usual pre-study dose.

The primary endpoint was the within-patient difference in MGII score, a validated score measuring MG disease severity, during pyridostigmine use compared to placebo. Secondary outcome measures included the MG-ADL and QMG, evaluating efficacy; the MG-QoL15r, evaluating quality of life; and the TSQM-9, evaluating treatment satisfaction. Adverse events were systematically recorded, and an economic evaluation was performed from both societal and healthcare perspectives.

Treatment with pyridostigmine improved the MGII score by -5.3 points compared with placebo. All secondary endpoints also favored pyridostigmine (QMG -1.4 points, MG-ADL -1.2 points, MG-QoL15r -2 points, and TSQM-9 7.2 points). Adverse events occurred more frequently during pyridostigmine use than during placebo, with fatigue and flatulence being the most commonly reported events. In the cost-utility analysis, pyridostigmine treatment showed lower annual healthcare and societal costs, and annual improved QALYs, compared to treatment without pyridostigmine. In addition, the probability of cost-effectiveness at a willingness-to-pay threshold of €20,000 per QALY was high (>99%), from both societal and healthcare perspectives.

Chapter 5 presents the findings from the second part of IMPACT-MG, which evaluated the addition of amifampridine to treatment with pyridostigmine. Amifampridine is a presynaptic potassium channel blocker that prolongs the action potential and thereby enhances acetylcholine release in the synaptic cleft. It is primarily used in patients with Lambert-Eaton myasthenic syndrome and congenital myasthenic syndrome, while its use in AChR MG has been hypothesized but has not previously been studied in randomized controlled trials.
To be eligible for participation in part two, patients had either completed part one of the study or failed to complete the two-day washout period prior to randomization in part. A total of twenty patients were randomized to one of three treatment sequences, each consisting of three treatment periods of five days, separated by a two-day washout period. During these periods, patients received either 30 mg amifampridine, 60 mg amifampridine, or placebo. The primary and secondary efficacy and safety outcomes were identical to those used in part one. An additional pharmacokinetic/pharmacodynamic (PK/PD) substudy was conducted to assess PK parameters and evaluate potential dose-response relationships.
For the primary outcome, measured by the MGII score, the mean treatment difference compared with placebo was -1 point for amifampridine 30 mg and -1.7 points for amifampridine 60 mg. Similar to the primary outcome, no statistically significant differences were observed across any of the secondary efficacy endpoints. In contrast, adverse events occurred more frequently during treatment with amifampridine. The most commonly reported events included paresthesia, fatigue, numbness, dizziness, and sleep disturbances. In three cases, treatment-emergent adverse events were severe enough to necessitate discontinuation of amifampridine. Within the PK/PD substudy, no associations were found between mean steady-state AUCτ, and C_{max} and the primary outcome measure.

Part II: Immunomodulatory therapies

In **chapter 6**, we provide an overview of current treatment patterns in the Netherlands across different subgroups of MG patients throughout the disease course. We analyzed longitudinal data from adult patients enrolled in the Dutch-Belgian Myasthenia Registry, stratifying them by age at disease onset (≤50 years as early-onset MG [EOMG], and >50 years as late-onset MG [LOMG]) and antibody status (AChR, MuSK, and seronegative). Within the first year after diagnosis, the majority patients initiated pyridostigmine (93%), and after five years, approximately two-thirds continued its use. Furthermore, this study demonstrates that a substantial proportion of patients remains dependent on corticosteroids ten years after disease onset (30-40%). In addition, about one third of patients reported the use of intravenous immunoglobulin therapy at some point during the course of the disease, and 16% of patient reported treatment with plasma exchange.

In **chapter 7** we describe our clinical experience with sixteen patients with refractory MG treated with efgartigimod, an FcRn blocker, in a retrospective cohort study. A favorable outcome was defined as either a clinically meaningful improvement on at least two outcome measures (MG-ADL, QMG, or MGC) or discontinuation of prednisolone, a prednisolone dose reduction of >10 mg per day, or discontinuation of chronic plasma exchange or IVIg, without the use of rescue medication. A favorable outcome was observed in 56% of patients at the last assessment. Moreover, in 80% of patients, MG-related treatments (prednisolone, azathioprine, plasma exchange, and IVIg) were reduced compared with treatment prior to efgartigimod. All patients had discontinued the treatment regimen as used in the pivotal ADAPT-trial (one infusion per week for four weeks, followed by a variable interval before the next treatment cycle) to administration intervals of 1, 2, or 3 weeks.

General discussion

Treatment of myasthenia gravis (MG) consists of two main therapeutic approaches: symptomatic therapy with pyridostigmine on the one hand, and immunomodulatory treatments on the other, including agents such as prednisolone, non-steroidal immunosuppressive agents, intravenous immunoglobulin (IVIg), and plasma exchange. As these treatments target different aspects of MG pathophysiology, they are often used in combination to achieve disease control.
As described in chapter 6, nearly all patients (93%) initiate treatment with pyridostigmine, and approximately two-thirds continue its use later in the disease course, either as monotherapy or in combination with immunomodulatory therapy. It is therefore noteworthy that, prior to the studies presented in this thesis, despite the widespread and long-standing use of pyridostigmine, systematic literature on its efficacy and adverse effects was scarce. This is of particular relevance, as information on the use of pyridostigmine not only helps to inform patients about the expected effects and side effects, but also provides a basis for comparing new symptomatic treatments with the current standard.

When considering the effect size of pyridostigmine, many (myasthenia) experts may recall cases with remarkable responses to a single dose of an acetylcholinesterase inhibitor. However, chapter 3 shows that only a small minority of patients reported experiencing a very good effect on ocular, bulbar or generalized symptoms, indicating that such remarkable responses are at least uncommon.
In chapter 4, we quantified the effect size of pyridostigmine on outcomes reflecting myasthenia severity (MGII, MG-ADL and QMG), quality of life (MG-QoL15r), and treatment

satisfaction (TSQM-9) in a randomized double-blinded, placebo-controlled crossover trial. All measures demonstrated statistically significant, yet rather small, improvements compared with placebo. When comparing these results to the predefined thresholds for clinically meaningful improvement, the cutoff value for the primary outcome measure (MGII) was found to lie within the 95% confidence interval. This implies that a clinically meaningful effect cannot be excluded. For the secondary outcome measures, the MG-ADL and the QMG, the predefined thresholds for clinically meaningful change fell outside the corresponding 95% confidence intervals. This raises the question of whether this simply indicates that pyridostigmine does not produce a clinically meaningful improvement (on our secondary outcome measures) within this specific population, or whether the established cutoff values may not be truly appropriate within this therapeutic context with a symptomatic treatment such as pyridostigmine. To address this question, it is useful to provide some background on how a Minimal Clinically Important Difference (MCID) is determined. Two main approaches can be distinguished: anchor-based and distribution-based methods. In the anchor-based approach, the change in the outcome measure is linked to an external reference, such as a global rating of change or a clinical outcome measure. This method is therefore highly dependent on the choice of reference. In the distribution-based approach, the MCID is derived from the statistical distribution of the measurements, for example by using 0.5 standard deviation as an approximation of a clinically meaningful improvement. While this method is more objective, it does not capture the subjective perception of clinical benefit. For both approaches, the values obtained are strongly influenced by the study population and the treatment under investigation. For the MGII, for example, the MCID was established in a population receiving prednisone, IVIg, and PLEX.[156] The nature of these treatments is fundamentally different from that of pyridostigmine, as they are more invasive and often associated with more (severe) adverse effects. Consequently, a clinically meaningful improvement with these treatments would be expected to be larger than with a symptomatic treatment like pyridostigmine. This should be taken into account when interpreting the results; rather than considering the MCID as a gold standard, it should be viewed in the context of the specific study population and the treatment under investigation.

When comparing our study population with other MG-trials, patients enrolled in IMPACT-MG had milder symptoms, as expected for a symptomatic treatment rather than an immunomodulatory therapy. However, this implies that the potential for improvement in IMPACT-MG was smaller than in populations with a higher disease burden, which likely contributed to the observed small effect size. This anticipated limitation was one of the reasons why the MGII was chosen as the primary endpoint rather than the more commonly used MG-ADL or QMG, as the MGII is known to have minimal floor effects compared with other outcome measures.[163]

This may explain why a clinically meaningful improvement could not be excluded for the MGII (as the cut-off value for a clinically meaningful difference fell within the 95% confidence interval of the mean difference between pyridostigmine and placebo) and, in contrast, could not be demonstrated for the MG-ADL and the QMG (for which the cut-off value fell outside the 95% confidence interval).

Only limited research has been conducted on alternative symptomatic therapies, but in line with our study findings, the (small) trials that are available demonstrate modest effect sizes. In a double-blind, placebo-controlled, crossover pilot study, the short-term efficacy of terbutaline, a β2-adrenergic agonist, was assessed in eight patients with generalized MG.[112] The primary efficacy endpoint, a ≥3-point reduction in QMG score, was achieved in 63% of patients, with estimated mean improvements of approximately 3 points compared to placebo treatment. Similarly, in a randomized, double-blind, n-of-1 trial, four patients were treated with ephedrine, an adrenergic agonist, or placebo as add-on therapy to pyridostigmine.[31] All included patients had mild residual symptoms that did not warrant immunosuppressive therapy but were inadequately controlled by pyridostigmine monotherapy. Ephedrine produced a modest mean improvement of 1.0 points on the QMG score compared to placebo. More recently, a randomized, double-blind, placebo-controlled crossover trial evaluated the ClC-1 inhibitor NMD670 in 12 patients.[166] Two single doses of NMD670 showed statistically significant improvements in QMG scores compared to placebo, with least square mean changes of -1.5 and -1.0 points for the lower and higher doses, respectively. While these three trials demonstrate consistent statistical significance, the improvements in efficacy outcome scores with all symptomatic therapies remain modest (ranging from 1.0 to 3.0 points on the QMG score), comparable to the changes observed in our study (1.4 points).

Another important consideration is that, in our study, the observed effect reflects the difference relative to placebo rather than the change from baseline. In most clinical trials, and also in the determination of the MCID, outcomes are typically assessed as a change over time, that is, relative to baseline. Given the presence of a placebo effect, the change from baseline is likely to be larger than the change relative to placebo. This may have influenced the observed effect size and contributed to the smaller effects seen in IMPACT-MG compared with those reported in previous clinical trials. **Table 8.1** provides an overview of the most recent MG-trials investigating immunomodulatory treatments, and it presents the effect sizes relative to placebo for both the MG-ADL and the QMG. Although it is interesting to compare these differences side by side, it is important to recognize that the study populations in the newer trials and the pyridostigmine trial were not the same. Patients in the latter generally had milder symptoms, whereas those in the more recent trials were more often refractory to previous treatments. Direct comparisons of treatment

effects should therefore be made with caution. Nevertheless, it is noteworthy that when the effect size is presented relative to placebo rather than to baseline measurements, treatments such as ravulizumab and nipocalimab, for example, do not exceed the threshold for a clinically meaningful difference (≥3 for the QMG and ≥2 for the MG-ADL). This raises the question of whether a clinically relevant improvement should be assessed in relation to baseline measurements alone, or whether the placebo effect should also be taken into account.

Table 8.1 Effect sizes in phase 3 MG research relative to placebo measurements

	QMG			MG-ADL		
	Treatment	**Placebo**	**Difference**	**Treatment**	**Placebo**	**Difference**
Eculizumab[57]	-4.6	-1.7	2.9	-4.1	-2.3	1.8
Ravulizumab[59]	-2.8	-0.8	2.0	-3.1	-1.4	1.7
Zilucoplan[60]	-6.2	-3.3	2.9	-4.4	-2.3	2.1
Efgartigimod#[62]	-6.2	-1.0	5.2	-4.6	-1.8	2.8
Rozanolixizumab[64]						
7 mg/kg	-5.4	-1.9	3.5	-3.4	-0.8	2.6
10 mg/kg	-6.7	-1.9	4.8	-3.4	-0.8	2.6
Nipocalimab[65]	-4.9	-2.1	2.8	-4.7	-3.3	1.5
Pyridostigmine			1.2			1.4

Approximate values were derived from published figures, as the original numerical data were not available in the text.
QMG, Quantitative Myasthenia Gravis; MG-ADL, Myasthenia Gravis-Activities of Daily Living

One of the main strengths of IMPACT-MG is that it included a cost-effectiveness analysis. At baseline, we collected data on healthcare and productivity costs over the preceding year, along with corresponding MGII scores and utility values. Using these baseline measures, we were able to estimate how changes in MGII and utility during the two treatment periods in part one of the trial, translated into total societal costs of pyridostigmine after one year. In addition to improving quality-adjusted life years after one year, pyridostigmine was also associated with a reduction in societal costs of €6565 per patient per year. While its cost-effectiveness cannot be directly compared with that of novel treatments, our data can serve as a benchmark for evaluating the cost-effectiveness of newer therapies, which is particularly important in an era of rising healthcare costs.

Limited data on the cost-effectiveness of novel therapies are available, and the existing studies mostly estimate utilities using proxy measures, such as QMG scores, rather than directly observed values. This complicates the development of rational and cost-effective treatment strategies, and it is important to be transparent and to include cost-effectiveness data, such as utilities, when reporting efficacy outcomes.

Before extrapolating our findings to the general MG population, it is important to recognize that IMPACT-MG included a specific subset of MG patients. As noted earlier, we enrolled patients with relatively mild disease, but in addition, all participants were required to be able to temporarily discontinue pyridostigmine. Consequently, patients who experienced substantial symptomatic benefit from pyridostigmine were less likely to participate in the study or discontinued during the washout phase prior to randomization (which occurred in two patients). In an ideal scenario during the study design phase, we would have selected MG patients who had been recently diagnosed and had never received any treatment. However, we deliberately decided against this approach due to feasibility concerns, as recruiting a sufficient number of patients would likely have required a multicenter, and potentially even multinational, trial. Nevertheless, this limitation regarding patient inclusion should be considered when interpreting the observed effect size.

In chapters 3 and 4 we characterized the side effects of pyridostigmine. We showed in chapter 3 that a notable 91% of patients currently using pyridostigmine reported experiencing at least one side effect. It should be noted, however, that in this study side effects were actively queried, and patients were presented with a symptom checklist based on the Summary of Product Characteristics for pyridostigmine. It is well established that this method of actively querying side effects leads to higher reporting rates compared to spontaneous reporting.[134] Nevertheless, the 91% prevalence is substantially higher than the 54% reported in the control group, which consisted of patients not using pyridostigmine at the time of completing the questionnaire.

In chapter 3, we also showed that patients with MuSK antibodies were more likely to discontinue pyridostigmine, consistent with previous studies indicating that acetylcholinesterase inhibitors are less effective in these patients and that they experience more side effects.[126-128] In addition, female patients reported side effects more frequently than males, in line with literature showing that women are 50 to 75% more likely to experience an adverse drug reaction than men,[132] likely due to sex-based differences in pharmacokinetics and pharmacodynamics.[133]

In addition to identifying the most commonly reported side effects, which in this cross-sectional study

were gastrointestinal symptoms (flatulence, diarrhea, and abdominal cramps), urinary urgency, muscle cramps, blurred vision, hyperhidrosis, increased salivation, light-headedness, and flu-like symptoms, it is also important to consider the severity of these side effects. Patients who discontinued pyridostigmine experienced considerable discomfort from gastrointestinal symptoms, and these side effects were often reason for discontinuation or dose reduction, as has been widely recognized. Notably, hyperhidrosis was reported as particularly bothersome in both current users and those who had discontinued treatment, highlighting the importance of addressing this side effect in clinical practice.

In patients discontinuing pyridostigmine, approximately one-quarter of patients cited side effects as reason for discontinuation. This reflects a substantial subgroup of patients who do not tolerate the only registered and guideline-recommended symptomatic treatment in national and international protocols. Consequently, there appears to be a need for alternative symptomatic treatment options.

In chapter 2, we evaluated existing and emerging symptomatic therapies. The only symptomatic therapy currently under active investigation is the ClC-1 channel blocker NMD670. Other treatments, such as tirasemtiv, a fast-skeletal muscle troponin activator, and monarsen, an antisense oligodeoxynucleotide, have shown modest improvements in phase II trials; however, no plans have been announced to further develop these therapies. In chapter 5, we studied the effect of amifampridine, a well-established therapy for myasthenic disorders such as Lambert-Eaton myasthenic syndrome (LEMS) and congenital myasthenic syndromes. The use of amifampridine in patients with MG has been described, and it is occasionally prescribed off-label as an alternative to, or in addition to, pyridostigmine. Through a randomized, double-blind, placebo-controlled crossover trial, conducted immediately following the study described in chapter 4, we evaluated whether the addition of amifampridine to pyridostigmine provided added benefit.
We found no significant benefit of amifampridine compared to placebo on both primary and secondary outcome measures, while it was accompanied by an unfavorable safety profile, with a higher frequency of adverse events which led to treatment discontinuation in some patients. In addition, no association was found between pharmacokinetic parameters and the primary outcome measure.
Although several factors in the design of this part of the IMPACT-MG study may have influenced the observed outcomes, it seems unlikely that these factors played a decisive role in demonstrating the efficacy of amifampridine in addition to pyridostigmine. Even with a larger sample size, the small effect size of amifampridine (1.7 points on the MGII) raises questions about the clinical relevance of such a difference, regardless of statistical significance. Nevertheless, a few design elements are worth considering in relation to these outcomes.

- Patients were assigned a fixed dose of amifampridine (either 15 mg or 30 mg twice daily). During the trial, it became apparent that some patients preferred the lower dose, while others experienced greater benefit from the higher dose. A dose-titration phase prior to randomization was initially considered during the study design phase. However, it was ultimately decided against in order to minimize the risk that patients would become familiar with the medication and its potential side effects, which could have compromised blinding. Furthermore, PK/PD data demonstrated no correlation between drug concentrations and the primary outcome, suggesting that even with a dose-titration phase,

there would likely still have been no meaningful difference between placebo and amifampridine.

- Our power calculation was based on detecting an improvement of 8 points. However, the observed effect in the pyridostigmine study was "only" 5.3 points. Given clinical experience with amifampridine in MG, it seems unlikely that its effect size would exceed that of pyridostigmine. This would imply that we would have needed to include significantly more patients in the trial. For example, if we had aimed to demonstrate a difference of 3 points compared to placebo, a similar study design would have required over 140 patients, and to detect a difference of 1.7 points (the observed effect size in the trial), more than 435 patients would have been needed. This suggests that a substantially larger sample size might have led to a statistically significant difference; however, one could question whether such a small effect size would be clinically relevant, even for a symptomatic treatment.
- The baseline symptom severity at treatment initiation was higher in the first part of the study evaluating pyridostigmine compared to the second part evaluating amifampridine, with a baseline MGII score of 32.0 in the first part and 26.6 in the second part. This difference in baseline severity likely contributed to the small effect size found for amifampridine, as there were approximately six more points available for improvement during treatment with pyridostigmine than during treatment with amifampridine. It is possible that including patients with more severe MG symptoms could have resulted in a greater effect of amifampridine. However, one could question whether this would be the appropriate patient population for this treatment in a clinical setting.

It is noteworthy that two treatments, both of which increase the amount of acetylcholine in the synaptic cleft, show different effects in MG and LEMS. This raises questions about our understanding of the pathomechanism at the synaptic level. To understand why one treatment is more effective in MG (pyridostigmine) and the other in LEMS (amifampridine), it is important to recognize that presynaptic acetylcholine efflux from synaptic vesicles occurs directly opposite a cluster of acetylcholine receptors.[193] Although many graphic representations in textbooks suggest that acetylcholine diffuses freely across the synaptic cleft, the released acetylcholine in the synaptic cleft diffuses exclusively within a cluster of acetylcholine receptors, a "functional unit." Consequently, if a functional unit contains a sufficient number of acetylcholine receptors (as in LEMS), increasing local acetylcholine availability may have only limited benefit. In this situation, it is more effective to activate additional functional units.

In MG, an additional factor comes into play: due to the reduced number of acetylcholine receptors, acetylcholine efflux into the synaptic cleft is upregulated through cleaved LRP4 which binds to an as-yet unidentified presynaptic receptor.[16] The action of amifampridine

effectively mimics this mechanism, suggesting that amifampridine will only be effective in patients in whom this compensatory upregulation is insufficient.

In the second part of this thesis, we provide an overview of treatment patterns in the Netherlands over a period of nearly ten years (chapter 6). During this timeframe, the use of novel therapies, including complement inhibitors and FcRn blockers, remained limited in the Netherlands. A large proportion of patients relies on symptomatic treatment: the majority of patients initiate pyridostigmine within the first year after diagnosis (93%), and approximately two-thirds continues to use pyridostigmine in the long term. Furthermore, we show that a substantial proportion (30-40%) of patients remain dependent on corticosteroids ten years after disease onset. The latter is particularly undesirable, given the well-documented short- and long-term morbidity associated with corticosteroid use.[177,194] The key question is how these treatment patterns will shift with the introduction of complement inhibitors and FcRn blockers. In chapter 7, we describe our clinical experience with efgartigimod, an FcRn blocker, in sixteen patients with refractory MG. In this difficult-to-treat population, a considerable proportion of patients (80%) were able to reduce MG-related treatments, including prednisolone, azathioprine, plasma exchange, and IVIg.
It is highly likely that these novel therapies will substantially change current treatment patterns, leading to a reduction in corticosteroid use and, likely, the need for symptomatic treatments as well. At present, however, the use of novel treatments remains limited due to high costs. Over time, costs are expected to decrease, which may allow these therapies to be introduced earlier in the disease course. Nevertheless, even with these novel therapies, many patients do not achieve sustained disease control, and they are not effective in all patients. For example, approximately 30% of patients do not respond to complement inhibition.[19] This implies that, in the era of emerging immunomodulatory treatments, symptomatic treatment will continue to play an important role in the management of MG, and it is important that efforts to optimize symptomatic treatments are not overshadowed by advances in immune-targeted therapies.

Future perspectives

In the past decades, only 6% of all clinical trials have focused on symptomatic treatments.[39] At present, pyridostigmine remains the only symptomatic therapy recommended in national and international guidelines for MG. There is, however, as shown in this thesis need for alternative symptomatic treatments to improve efficacy, reduce side effects, and enhance ease of use.

Through the studies included in this thesis, we have gained insights into several considerations that need to be taken into account in future research on symptomatic treatments.

First, careful consideration is required when interpreting whether an observed change is clinically meaningful, rather than automatically applying the established cut-off values, which are likely not appropriate for symptomatic therapies. Ideally, these parameters should be redefined for the most relevant outcome measures (the MGII, MG-ADL, and QMG) in the context of symptomatic treatments in future research. Pyridostigmine could serve as a reference standard for this purpose, as it remains the only available symptomatic therapy.

Second, when selecting outcome measures, particular attention should be paid to the 'floor effect' of commonly used outcomes. The floor effect refers to an outcome measure's limited sensitivity to detect changes in patients presenting with mild symptoms. This is especially relevant for the MG-ADL, often chosen as a primary outcome measure, in which the floor effect is a well-known limitation.[191] For the MGII, the floor effect appears to play a more limited role, making this outcome measure preferable for assessing symptomatic treatments.[148]

Third, it is important to consider whether a treatment is intended to be used as an alternative to, or in addition to, pyridostigmine. In the latter case, several factors complicate the study design. For example, it must be considered how to account for the effect of pyridostigmine in the interpretation of the results. Given that pyridostigmine is fast-acting with a relatively short duration of action, the interval between its administration and the performance of the test affects the outcome. This is best approached by selecting an outcome measure that captures a longer period of time, since a single time-point assessment (such as the QMG or the examination items in the MGII) can be influenced by the timing of pyridostigmine administration. Furthermore, the study population should be selected with symptoms severe enough to adequately capture the expected treatment effects. Since these patients will often be those who would otherwise be eligible for immunosuppressive treatment, careful consideration must be given to ensure that patient safety is not compromised.

Finally, it is crucial that cost-effectiveness analyses are routinely included in clinical trials and that parameters relevant for determining the cost-effectiveness of new treatments are publicly accessible.

In a rapidly evolving field such as MG, these analyses are essential to ensure that long-term healthcare costs remain manageable.