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Emerging therapies for autoimmune myasthenia gravis: Towards treatment without corticosteroids

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Abstract

Myasthenia gravis is an autoimmune disease characterized by dysfunction of the neuromuscular junction. Current treatment is based on lifestyle advice, symptomatic treatment, immunosuppressive drugs and thymectomy. Corticosteroids remain the cornerstone of treatment beside symptomatic medication due to their low cost, wide availability and fast mode of action. However, long term steroid use carries substantial risks of severe adverse side effects. Therefore, non-steroidal immunosuppressive drugs are commonly added to the treatment. Unfortunately, they have a delayed-onset effect and evidence of their efficacy appears to be difficult to obtain. Several trials using drugs that have had clear positive results in other immunological disorders have failed in myasthenia. This failure may in part be related to difficulties in the design of clinical trial for myasthenia, which has a fluctuating disease course involving weakness that may be difficult to assess quantitively. This problem is exacerbated by the tendency of most clinical trials to select patients with a stable, but severe disease. Future trials should: select patients with weakness and fatigability that is completely explained by their myasthenia gravis, use a design that avoids the exclusion of patients with recent changes in medication, and explore the possibilities to completely avoid the use of corticosteroids.

Keywords: Myasthenia gravis; Treatment; Emerging therapies; Corticosteroids.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease characterized by dysfunction of the neuromuscular junction [1,2]. It has an overall prevalence of 150–250 cases per million, with an estimated annual incidence of 8−10 cases per million [3]. It is considered to be a model of organ-specific autoimmune disease, due to the known and thoroughly characterized autoantigens. The diagnosis is usually based on a combination of clinically confirmed fluctuating muscle weakness and the presence of serum autoantibodies, which are most frequently directed at the acetylcholine receptor (AChR), muscle-specific kinase (MuSK) or lipoprotein-related peptide 4 (LRP4) [2]. Antibodies cannot be detected in a substantial proportion of patients, particularly in those with isolated ocular symptoms. In these patients, the diagnosis is usually supported by electrophysiological testing: the presence of an abnormal decrement during low-frequency repetitive nerve stimulation, or an increased jitter in single-fiber EMG testing are considered to be indicative of an impairment in neuromuscular transmission.

In recent years, a wide range of drugs to treat autoimmune MG have become available. However, approximately 15% of patients still have refractory MG, defined as a post-intervention status that is unchanged or worse after corticosteroids and at least 2 other IS agents, used in adequate doses for an adequate duration of at least 18 months, with persistent symptoms or side effects that limit functioning, as defined by patient and physician [4,5]. Importantly, corticosteroids remain indispensable and the most effective drug for treating MG [6,7]. New drugs with a more favorable safety profile would be very welcome, but in recent years several promising candidate drugs unexpectedly failed to prove efficacy in clinical trials [8–12]. To test

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new drugs, well designed clinical trials are necessary with sensitive and validated outcome measures. After clinical remission is achieved, in most patients the dose of the immunosuppressive drugs can be gradually diminished. The reduction of the dose is currently purely based on the clinical course of disease. Although AChR antibody titers generally correspond to disease severity in individual patients [13], there is still considerable intra-individual variation and quick, reliable titration of AChR antibody titers is not commonly available. Therefore, it is not practically feasible to use these titers to predict an exacerbation or guide immune suppressant treatment. Sensitive biomarkers that reliably predict exacerbation of the disease would be helpful to better time the reduction of immune suppressive treatment in MG. Thus, the treatment for autoimmune MG can still be improved significantly. The main priorities for improvement are (1) to reduce or completely avoid the need for corticosteroids in the treatment of autoimmune MG, (2) an optimal trial design that closely takes into account the current clinical treatment strategies and fluctuating course of disease, and (3) markers that reliably predict exacerbation and allow early modification of therapy in order to avoid unnecessary treatment or the relapse of disease.

2. Current treatment

The current treatment of autoimmune MG is based on a combination of lifestyle advice, including exercise, symptomatic treatment, immunosuppressive drugs and interventions, and thymectomy.

2.1. General recommendations

Physical exercise should be encouraged in all MG patients as it carries no risk. In addition, a sedentary lifestyle is likely to increase the risk of comorbid pathologies and cardiovascular side-effects of corticosteroid treatment. Although specific studies are sparse, recent observations have reported good tolerance, improved quality of life, and better muscle strength in patients with mild disease undergoing supervised training [14,15]. A multicenter randomized controlled trial (the Benefits and Tolerance of Exercise in Patients With Generalized and Stabilized Myasthenia Gravis (MGEX) trial) is ongoing [16].

Several drugs have been associated with worsening of MG. Such drugs should be used with caution in MG, and only if they are clearly necessary. Association of drug use and MG exacerbation can be causal or by chance. MG patients starting a new drug should always be warned about the possibility for side-effects including MG exacerbation. This especially applies to patients with active disease and clear signs of bulbar or respiratory weakness. However, most patients with minimal disease activity or complete remission will tolerate most of these drugs quite well, especially during short-term treatment.

Vaccinations are generally recommended, including against influenza [17]. Influenza vaccination is safe and effective in MG patients, regardless of the use immunosuppressive medication, and does not lead to immunological or clinical exacerbation [18]. Patients taking high doses of immune-suppressant medication should not receive live-attenuated vaccines.

Sleep apnea has a high frequency in MG patients and should be actively investigated and treated [19].

2.2. Symptomatic treatment

Acetylcholinesterase inhibitors enhance the bioavailability of acetylcholine at the synaptic cleft. Pyridostigmine bromide is usually the first-line treatment and may be sufficient as stand-alone treatment in patients with mild or moderate MG. Ambenonium chloride is an alternative drug, but is rarely used.

3,4-diaminopyridine increases presynaptic acetylcholine (ACh) release by blocking pre-synaptic K+ channels and is commonly used as a symptomatic treatment of Lambert–Eaton myasthenic syndrome or congenital MG [20]. Several small studies suggest that 3,4-diaminopyridine improves neuromuscular transmission [21] and alleviates symptoms in auto-immune myasthenia gravis with MuSK antibodies as well [22,23].

Salbutamol, a selective B2-adrenergic agonist, is an effective treatment for patients with congenital myasthenic syndrome (CMS), including those with AChR deficiency syndromes [24] and patients with DOK7 mutations [25]. It may also have beneficial effects on muscle strength in patients with auto-immune MG [26]. Ephedrine is another sympathomimetic agent which mainly affects adrenergic receptors. Its mechanism of action in MG has been investigated, but is not well understood. Ephedrine appears to have a beneficial effect in patients with CMS [24,27]. In a recent series of randomized controlled n-of-1 trials, treatment with ephedrine resulted in a small but consistent reduction of symptoms and weakness [28]

3. Immunosuppressive treatment

3.1. Corticosteroids

Corticosteroid treatment, usually by means of oral prednisone, is currently the mainstay of immunosuppressive treatment. Although prednisone has been in use as a treatment for MG for several decades, there is limited evidence of its efficacy from controlled studies. In patients with ocular MG, the EPITOME trial showed a clear superiority of prednisone over placebo [29], but similar trials have not been performed for generalized MG. In large, retrospective studies, the mean response rate to glucocorticoids in monotherapy was 74% on average [30]. A major advantage of prednisone, which is readily available worldwide at low cost, is its relatively rapid effect, which is especially important in severely affected patients. High-dose treatment is associated with a quick clinical response, with an onset of clinical improvement within 2–4 weeks [31,32]. The response rate is higher in

Table 1
Overview of recent trials on new drugs for MG.

	n	Disease duration (m)	Age (y)	QMG	MGFA I (n)	MGFA II (n)	MGFA III (n)	MGFA IV (n)	Study duration (m)
Positive trials									
IVIG[67]	51	56	56	12,3	n/a	n/a	n/a	n/a	0,5
Prednisone[27]*	11	7,5	64	6,5*	n/a	n/a	n/a	n/a	4
Eculizumab[68]	125	119	47,5	17,3	0	37%	53%	10%	6
Ciclosporin[69]	39	n/a	56,1	11,5	n/a	n/a	n/a	n/a	6
Azathioprine[70]	34	28	58,5	n/a	n/a	n/a	n/a	n/a	36
Thymectomy[46]	126	13	32	11,4	0	65%	32%	3%	36
Negative trials									
Mycophenol, International Study[41]	176	35	49	11,3	0	39%	42%	19%	9
Mycophenol, Muscle Study Group[71]	80	24	57,1	13,3	0	46%	54%	0	3
Belimumab[10]	40	104	52,7	12	0	89%	11%	0	6
Methotrexate[72]	50	n/a	66,5	10,5	0	92%	8%	0	12
Rituximab[50]	52	n/a	53,2	11	0	60%	36%	4%	12

N: total number of participants, including placebo group; n/a: not available. The column "MGFA" indicates the number of patients of each MGFA class included in the treatment arm of the study.
* only patients with ocular MG were included.

patients older than sixty years than in younger patients [33]. In up to 42% of patients a temporary, paradoxical MG exacerbation has been observed in the first weeks of treatment, followed by improvement [34]. However, steroid treatment is associated with several adverse effects, both short-term, including insomnia, mood changes, or impaired glucose tolerance and long-term. Some of these long-term side effects, such as osteoporosis, skin atrophy, glaucoma, and increased risk of infection are well-known and will usually be easily recognized by the prescribing physician. The cardiovascular risk associated with corticosteroid use is perhaps less well-known, but equally important: in a large population-based study, patients who received glucocorticoid doses higher than 7.5 mg/day were 2.5 times more likely than control subjects to experience a cardiovascular event (defined as myocardial infarction, angina, coronary revascularization, hospitalization for heart failure, transient ischemic attack, or stroke), even after adjustment of known covariates [35].

Whether early treatment with prednisone can prevent generalization in patients with ocular MG is the subject of debate. By definition, symptoms in patients with pure ocular MG are limited to ptosis and diplopia. These symptoms are often considered insufficiently debilitating to warrant the potentially severe risks of treatment with corticosteroids and immunosuppressant therapy is often withheld until patients show signs of generalized weakness. Patients with pure ocular MG are excluded from participation in most clinical trials (Table 1), while fluctuating diplopia clearly is an invalidating condition causing important restrictions in daily life. Several small, retrospective studies suggest that ocular patients are less likely to convert to generalized MG when treated early with corticosteroids [36–38]. Although the difference in generalization rate in these studies is consistently lower by a considerable margin in patients who were treated early with corticosteroids, all studies suffer from a number of methodological flaws: they are all retrospective in nature, describe small numbers of patients, and have major differences in baseline variables between the treated and untreated groups. Definitive proof of the efficacy of early corticosteroid treatment in preventing secondary generalization will have to come from a prospective, placebo-controlled double-blind study. To our knowledge, there are currently no plans to perform such a trial.

3.2. Non-steroidal immunosuppressive drugs

Non-steroidal immunosuppressive drugs are commonly added to the treatment regimen with a dual aim: to enhance the effect of prednisone on MG symptoms and to allow the tapering of corticosteroids to a minimum with the aim of reducing long term side effects. Surprisingly, firm evidence of efficacy with regards to both aims from randomized trials appears to be difficult to obtain (Table 1). Several trials using drugs that have had clear positive results in clinical trials for other immunological disorders failed in MG. Positive trials have been reported using mycophenolate mofetil for kidney transplantation [39], methotrexate for rheumatoid arthritis [40], belimumab in systemic lupus erythematosus [41] and rituximab for rheumatoid arthritis [42], but in autoimmune MG all trials investigating these drugs were negative [10,11,43].

In many instances, the duration of the study may have been too short to show a prednisone sparing effect (Fig. 1). This has been suggested as an explanation for the failure of demonstrating a prednisone sparing effect in the ciclosporin trial [44] and both trials with mycophenolate mofetil (MMF) [9]. The duration of treatment in the ciclosporin trial was six months, and in the MMF trials three or nine months. Results from open label studies and retrospective reviews most likely suggested a too optimistic perspective by reporting

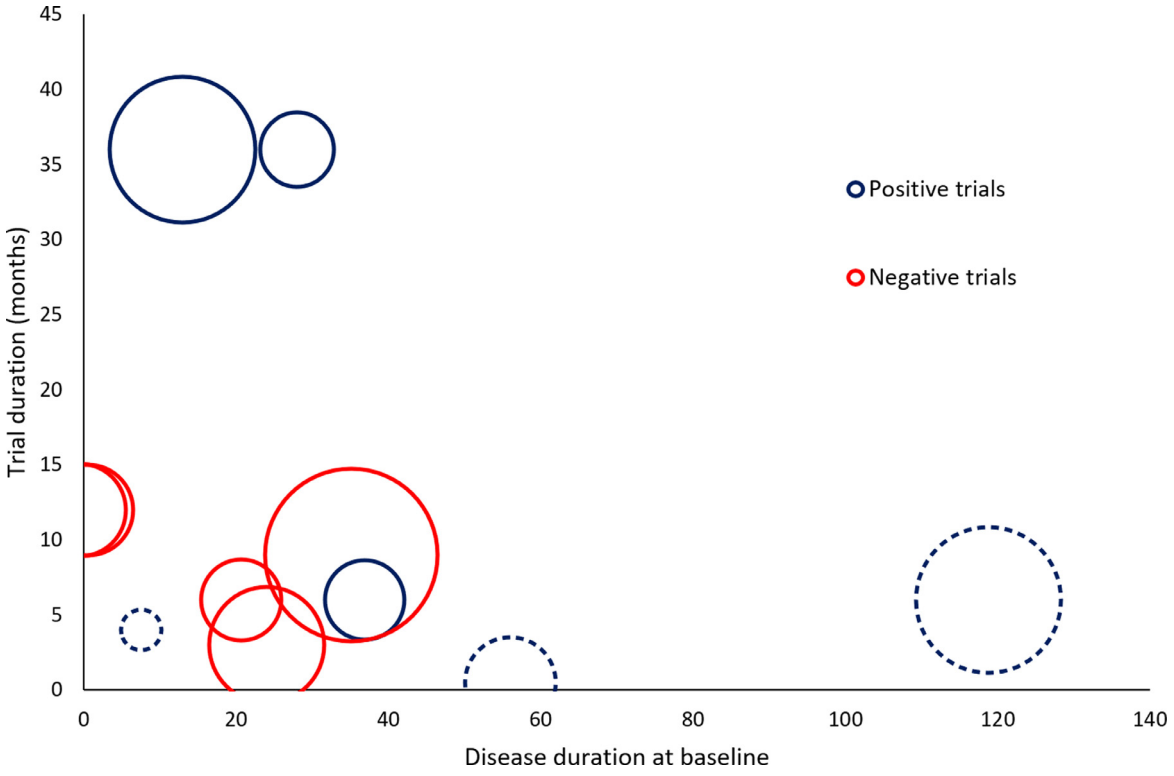

Fig. 1. Overview of medication trials in myasthenia gravis. Relation between disease duration at the start of the trial (x-axis), trial duration (y-axis), study size (bubble area) for positive (blue) and negative (red) trials. Trials on fast-acting medication (prednisone, IVIg and Eculizumab) are indicated by a dotted line. Information on disease duration was unavailable for the trials on methotrexate and rituximab: these trials are plotted on the y-axis. See table 1 for details on trials. When trials on fast-acting medication are excluded, longer trials appear to be more likely to be successful than shorter trials.

a clinical improvement within two months in 90% of the responders [9,45,46]. This view is supported by the results of the azathioprine trial [5]. This drug has a similar mode of action and this trial did not show a significant difference in prednisone sparing after one year either. In fact, a significant difference was found only after three years of treatment.

4. Surgical treatment

In a recent, well-controlled trial comparing thymectomy plus prednisone with prednisone alone in non-thymoma generalized AChR MG, showed that thymectomy leads to significant improvements both in primary end-points (lower average QMG score and lower alternate-day prednisone requirement) and in several secondary outcomes in patients up to 65 years of age with a disease duration of less than five years [47]. Although thymectomy has been a common treatment for MG for decades, the Level 1 evidence obtained through this trial will aid the inclusion of thymectomy as a standard in international guidelines, constituting an important step towards the reduction of long-term corticosteroid treatment, as 67% of patients achieved minimal manifestation status at month 36 (vs 47% in the control group). However, thymectomy remains controversial in older patients and patients with a longer disease duration, highlighting the need for alternative treatment options.

4.1. Emerging therapies

Currently, a number of new drugs for MG are being developed. These novel therapeutic interventions can be divided in treatment aimed at weakening the autoimmune response, at strengthening the neuromuscular synapse, or a combination of both strategies.

Rituximab, an anti-CD20 monoclonal immunoglobulin has been used to treat rheumatoid arthritis successfully for several decades. For several years, retrospective reports have suggested that it may be particularly effective in the treatment of MuSK myasthenia gravis [48,49]. In a recently published multicenter blinded prospective review study, treatment of MuSK MG with rituximab was associated with an improvement on the primary end point, which consisted of a combination of severity of clinical symptoms and treatment intensity [50]. However, the evidence for the efficacy of rituximab in the treatment of AChR MG is far less compelling. The results of a recent clinical trial, although not yet published, are available at clinicaltrials.gov and appear to be negative [51].

The proteasome inhibitor bortezomib is highly effective at depleting short-lived and long-lived B-cells and may have potential as a novel treatment for MG [52], although its side effects, including sensorimotor polyneuropathy, may limit its clinical use.

Complement is thought to play a crucial role in the pathophysiology of AChR MG. Recently, eculizumab, an inhibitor of complement activation through inhibiting C5 protein, was approved for use in MG in both the US and Europe after a randomized, double-blind, placebo-controlled, multicenter study. It showed significant effects on a number of relevant secondary end points [53]. However, similar to several previous trials using corticosteroid - sparing immunosuppressive agents, as discussed above, the treatment with eculizumab did not result in a significant improvement on the primary end-point either. Inhibition of C5 is a therapeutic target with a strong biological rationale for AChR-antibody positive gMG. Indeed, several other complement inhibitors are currently being tested for use in MG. Ravulizumab is currently under investigation in a phase III clinical trial. Like eculizumab, ravulizumab binds the complement protein C5, but has a longer half-life [54]. Zilucoplan (RA101495), a subcutaneously-administered macrocyclic peptide, binds C5 and inhibits its cleavage into C5a and C5b, preventing the production of MAC [55]. Phase 2 trials on Zilucoplan for the treatment of MG have been completed. A preliminary report suggest possible favorable results [56,57]. A third complement inhibitor, an RNAi molecule, ALN-CC5 has been tested in preclinical models of MG [58].

The group of neonatal Fc-receptor (FcRn) antagonists form another group of promising new drugs. Three drugs, efgartigimod [59], UCB7665 [60] and M281 [61] have been developed to block this receptor, thereby shortening IgG half-life. Multiple dosing of efgartigimod resulted in a 75% drop of IgG serum concentration in healthy volunteers. Similar to intravenous IgG and plasmapheresis, these molecules rapidly lower pathogenic IgG and may have a beneficial effect in antibody-mediated diseases such as MG. Another new therapeutic agent, imlifidase, based on an immunoglobulin G-degrading enzyme of Streptococcus pyogenes, specifically cleaves IgG and has been tested in patients after renal transplantation [62]. This drug may be also suitable for the treatment of MG, although its immunogenicity is likely to limit repeated use [63].

4.2. Limitations of the current therapeutical approach

In summary, the current pharmacological treatment of MG encompasses a large array of options, that differ in efficacy, time scale in which they are effective and the level of evidence and experience with that particular drug in the treatment of MG.

In clinical practice, corticosteroids are still the cornerstone of treatment beside symptomatic medication due to their low cost, wide availability, relatively fast mode of action and the experience gained over decades. Corticosteroids feature prominently in published consensus statements on the treatment of MG [4,64]. Consequentially, almost half of more than 500 patients participating in the Dutch-Belgian Myasthenia Registry reported using prednisone at the time of questioning [65]. Thymectomy, although safe and effective, is at present not an option for older patients or those with a longer disease duration [65]. IVIg and plasma exchange are effective, but short-lived and relatively costly. Non-steroidal immunosuppressants such as azathioprine and cyclosporine probably have a better long term safety profile than corticosteroids. However, they have a delayed-onset effect, up to several months for azathioprine and at least two months for cyclosporine [30] rendering them less suitable as monotherapy for severely affected patients. The indication of eculizumab, a relatively new addition to the therapeutic toolbox, is currently limited to patients with refractory MG. Usage in a larger group of MG patients might be advantageous, but is not likely to become common practice because of its prohibitive cost.

4.3. Limitations in the design of clinical trials

The selection of subjects participating in MG trials is probably the most important source of potential bias. All trials include patients with a MGFA score of 2–4, as they aim to include patients with clear, generalized symptoms in order to be able to see an improvement of symptoms during the trial (Table 1 and Fig. 2). However, at the same time the inclusion and exclusion criteria of almost all trials require that patients are on a stable dose of their medication of at least 4 weeks for prednisone, and several months for other immunosuppressive drugs such as azathioprine, MMF and cyclosporine, while treatment with a short term effect, such as intravenous IgG or plasmapheresis should not have been used for 1 or 2 months. This creates a clinical paradox. The trials ask for patients with clear signs and symptoms of MG, while on the other hand we do not allow a change in medication for several months. In daily practice almost all patients with an MGFA score of 2,3 or 4 would be treated by adjusting their dose of prednisone or other immunosuppressive treatment or by providing them with a course of IVIg. Thus, the majority of MG patients that have an active disease, which clearly responds to changes in drug dosing, will not be able to participate in a clinical trial, because the period of stable drug dosing does not comply with the trial inclusion criteria. Still, a subset of MG patients with rather mild disease may be able or willing to delay the change of medication in order to fulfill the trial criteria. This is probably the reason that a large proportion of patients participating in trials have an MGFA score of 2, ranging from 37% [8] to 92% [10] in the actively treated groups. On the other hand, there is a group of MG patients that have clear symptoms of MG, while at the same time there are several reasons for not adapting their immunosuppressive treatment. Some patients have developed constant fixed weakness, that no longer responds well to treatment and rather choose to use no or less immunosuppressive medication, as the burden of the side effects is larger than the beneficial effect of the drug on the course of MG. Other patients have other diseases besides MG, including joint problems, other age-related problems, or problems with coping or other psychological conditions that interfere with the objective assessment of muscle weakness or

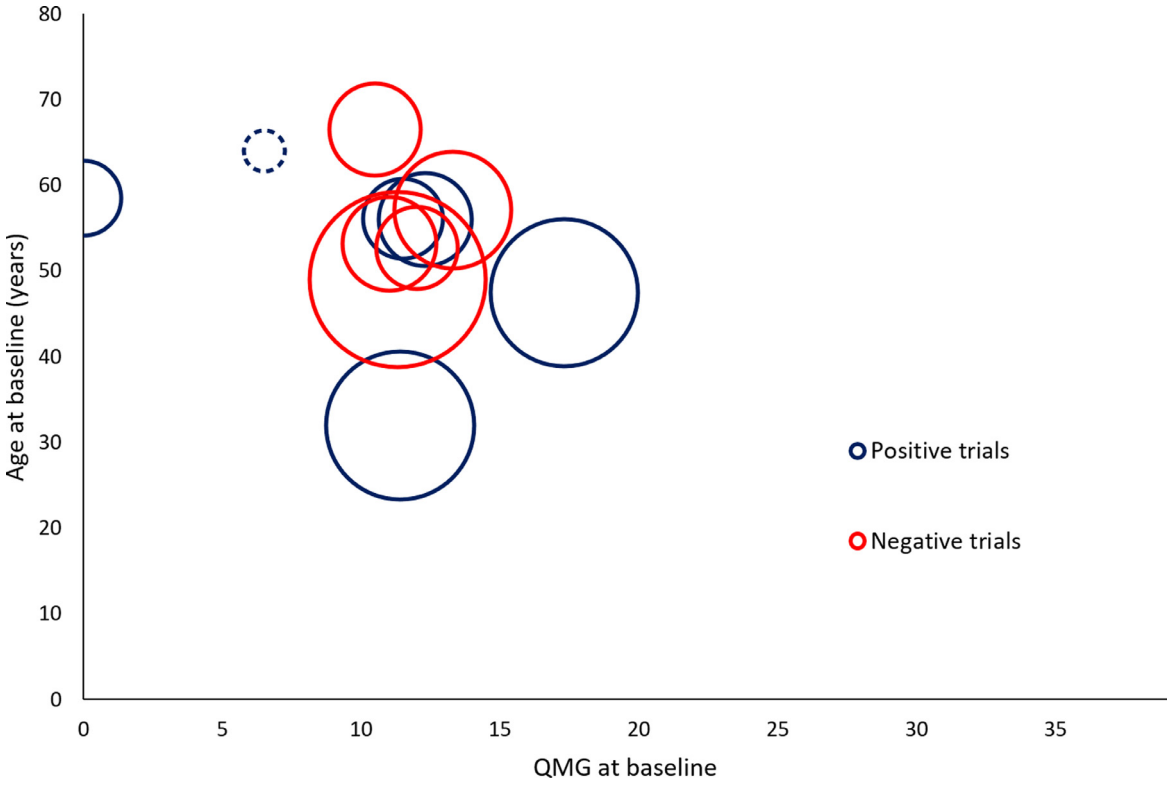

Fig. 2. Overview of medication trials in myasthenia gravis. Relation between QMG at the start of the trial (x-axis), age at baseline (y-axis), study size (bubble area) for positive (blue) and negative (red) trials. Dashed bubble: the prednisone trial only included patients with ocular MG and therefore a relatively low QMG score. Information on QMG score at baseline was unavailable for the trial on Azathioprine: this trial is plotted on the y-axis. See table 1 for details on trials. Almost all trials appear to involve relatively old patients with an average QMG score of 10-15.

fatigability. These patients can obtain relatively high scores on QMG or MG-ADL scales, while these results are not completely explained by true myasthenic weakness or for which it is difficult to separate true MG related weakness from dysfunction due to concomitant disease. It is clear that these patients will be less responsive to any form of immunomodulating or immunosuppressive treatment and should rather not be included in clinical trials investigating new immunosuppressive drugs.

All recent clinical trials have tested new drugs while current treatment is continued. This dampens the fluctuating course of the disease, because exacerbations are less frequent and less severe. Older studies, dating before the period of the availability of many of the recent drugs, suggest that the course of disease of MG has the tendency to become less variable with increasing disease duration. The study of Osserman in 1200 MG patients indicated that generalization of MG occurs in the first 3 years of the disease [66]. Similarly, Oosterhuis describes a series of 432 MG patients and concludes that the disease becomes milder over the years [67]. Thus, fluctuations seem to be more pronounced in the first few years of the disease and after 3–5 years, the chance of a severe exacerbation becomes much smaller. These results were obtained in populations of MG patients that were only treated with acetylcholinesterase inhibitors, prednisone, azathioprine and thymectomy. As most recent trials include patients with relatively stable disease, the effect of new medication on the early, more fluctuating phase of the disease usually remains unclear (Table 2).

4.4. Conclusion and recommendations

The mainstay of immune suppressant treatment for MG is currently still prednisone, despite its major adverse effects on long term health, as effective, fast-acting alternatives are currently lacking. Thymectomy is a safe and effective treatment, but its application is limited to a subset of patients. In addition, a number of recent trials on non-steroidal immune suppressant drugs have failed, possibly in part due to difficulties in the design of clinical trials for MG, which has a fluctuating diseases course involving weakness that may be difficult to assess quantitively. This problem is exacerbated by the tendency of most clinical trials to select patients with a stable, but severe disease. Based on these facts, we recommend that future trials: (1) select patients with weakness and fatigability that is completely explained by their MG, (2) preferentially include patients with an onset of clinical disease of less than 5 years, (3) explore the possibilities of an induction therapy for autoimmune MG using newly available drugs, with a short-term onset of their beneficial effect, to completely avoid the use of corticosteroids and (4) use a design that allows the inclusion of patients with

Table 2
Time frame of the efficacy of various treatment options for MG.

Hours	Days	Weeks	Months	Years
Pyridostigmin 3,4-DAP				
	Intravenous IgG Plasmapheresis **Eculizumab** / *other complement inhibitors* *FcRn blocking*			
		Prednisone		
			Azathioprine MMF Methotrexate **Ciclosporine** Rituximab **Thymectomy**	

Faster-acting drugs may become alternatives to induction therapy with prednisone. Bold: positive result for AChR or MuSK MG in a randomized controlled trial. Emerging treatments are printed in italic.

recent exacerbation of their disease to avoid the exclusion of patients with recently adapted dosing of their medication. The inclusion of patients with a recent disease onset or a recent exacerbation may increase statistical uncertainty as this population is likely to experience more fluctuations in outcome measures, but this issue can be solved by increasing the sample size and duration of the trial. In addition, trials involving novel, fast-acting medication are less likely to be affected by these fluctuations. Finally, the expected effect of a treatment is likely to be higher in relatively treatment-naïve patients, rather than the chronic, stable population that is currently included in most trials.

Indeed, the emergence of complement inhibitors and FcRn blocking agents could create new possibilities for a novel treatment paradigm for autoimmune MG. These new drugs, may be used as a first step to rapidly block complement and quickly lower pathogenic antibody titers. This strategy would thus avoid the use of prednisone, as it is possible to quickly reduce the level of pathogenic autoantibodies, allow recovery or repair of damaged neuromuscular junctions, and prevent relapses by continuing the usual, long-term immunosuppressive agents to keep the level of antibodies at a lower level. This future perspective requires that ongoing trials deliver positive results and that the newly available drugs are priced at a level that allows use in a broad category of MG patients. Future clinical trials, especially those investigating drugs with a rapid onset in weeks, should try to take into account the relapsing-remitting nature of MG. The identification of biomarkers that allow a more precise prediction of remission or relapse of MG would be welcome additions to the armamentarium. All together these are exciting times for the MG community with an increasing number of new drugs to choose from, which hopefully will help to further optimize a personalized treatment advice for patients with MG.

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