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Review

Update in immunosuppressive therapy of myasthenia gravis

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ABSTRACT

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction. Immunosuppressive treatments are part of the therapeutic armamentarium in MG. Long-term systemic steroid administration carry considerable risks and adverse events. Consequently, steroid-free immunosuppressive therapy is necessary to reduce the dose or discontinue steroids. First immunosuppressive drug trials in MG were performed in the mid-60s using standard and nonspecific immunosuppression. Since then, only few randomized controlled clinical trials were conducted in MG and assesed drug efficacy in terms of its steroid-sparing capacity and the ability to reduce myasthenic signs and symptoms. Treatment strategy in MG is quite challenging, mainly due to the disease heterogeneity in terms of clinical presentation, immunopathogenesis and drug response. To solve this dilemma, emerging treatment are based on biological drugs and use new targets of the immune pathway.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease which is caused by autoantibodies directed against the neuromuscular junction, leading to muscle weakness and fatigability. Therapy in MG comprises symptomatic treatment (acetylcholinesterase inhibitors), thymectomy, first-line immunomodulation [plasma exchange (PLEX) and subcutaneous or intravenous immunoglobulins (IVIg)] and long-term immunosuppressive drugs. Immunosuppressive therapy should be promptly initiated in severe and generalized forms of MG since symptomatic drug monotherapy is usually insufficient to achieve disease control.

The most frequently used immunosuppressive non-steroidal therapy in MG includes azathioprine (AZA), mycophenolate mofetil (MMF), methotrexate (MTX), cyclosporine (CsA), and tacrolimus (TAC). Many centres apply cyclophosphamide (CYC) in severe forms [1] and rituximab (RTX) in refractory cases or in MG associated with muscle-specific tyrosine kinase (MuSK) antibodies [2,3]. Complement modulation treatment and monoclonal antibody therapies are used in refractory MG. The latter is defined as either drug-resistant or presenting a contraindication to "conventional" immunosuppressive therapies [4].

Treatment goal in MG was recently defined by the Task Force appointed by the Myasthenia Gravis Foundation of America (MGFA). Optimal MG therapy should aim at achieving complete remission or minimal manifestation status -MMS- (i.e. asymptomatic and no functional limitation due to the disease) while causing only mild side effects [5]. The concept of "disease freedom" has been applied to other autoimmune diseases in the past and has been proposed as a surrogate for treatment response and decision making [6]. This approach would lead to a change in MG treatment paradigm, since initial trials assessed treatment success in terms of their steroid-sparing capacity [7–10].

As the arsenal of MG immunosuppressive therapies increases, choosing a treatment that is targeted to the individual patient becomes more difficult. For that reason, appropriate understanding of the purpose of MG therapy is required. Current treatment targets B and T cells, complement cascade, neonatal crystallizable fragment of immunoglobulins G antibodies (FcRn) and cytokines which are associated with antibody production.

In this review we will discuss the different immunosuppressive therapies that are currently available in the market and the ongoing clinical trials. We will not tackle the chronic use of immunomodulators (PLEX and immunoglobulins), symptomatic treatment or thymectomy.

2. Steroidal therapy

Since the past 60 years, intravenous and oral steroidal therapy is being administered to about two-thirds of MG patients with a favourable clinical response [11]. Steroidal therapy has a broad effect on the immune system and has shown to be efficient in all subtypes.

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Observational studies showed a slowing in the conversion rate from an ocular to a generalized form [12–14]. In addition, the use of prednisone led to a regression of symptoms at a median period of 14 weeks and at a median dose of 15 mg q.d. in 5/6 patients with ocular MG (EPITOME study) [15]. Despite the encouraging results, the study has several limitations: its unblinded nature, the small number of patients and the fact that long-term safety was not assessed. Another limitation is the lack of randomized placebo-controlled trials, especially in the generalized forms of MG. Nonetheless, it would probably be unethical to withhold steroidal therapy from MG patients in a clinical trial for research purposes.

Even though steroids are meant to be a short-term treatment, this drug is not usually discontinued. Prednisone is usually initiated at 1 mg/kg/day and, once optimal clinical status is achieved, the drug is tapered down to the lowest effective dose. Adverse effects of chronic steroidal therapy are one of the main concerns, which eventually leads to the administration of steroid-sparing agents. International recommendations propose nonsteroidal immunosuppressive drugs if the clinical response to steroids is insufficient within the first year or if the dosage cannot be reduced due to symptom relapse [16,17].

3. Antimetabolites

3.1. Azathioprine (AZA)

AZA is a prodrug that is rapidly converted, via a non-enzymatic process, to the active metabolites 6-mercaptopurine and 6-thioinosinic acid. It acts as a purine mimic antimetabolite which inhibits purine synthesis (DNA, RNA and proteins) and interferes with T cell lymphocyte function.

Currently, AZA remains the drug of choice to sustain steroid-free remission in MG. On the one hand, AZA is often administered in women of childbearing age (see treatment limitations below). AZA and steroids have not been associated with drug-induced congenital malformations during pregnancy. Studies performed on pregnancy in a kidney transplant recipient did not show higher rate of congenital anomalies in the treated group with AZA versus the general population [18]. International task force on MG therapy did not achieve general consensus on the safety profile of AZA in pregnancy; while European experts support its use, American specialists prefer to avoid it [5]. On the other hand, AZA has the disadvantage that clinical efficacy is achieved at six to twelve months after treatment onset.

Concerning treatment efficacy, a double-blind, randomized, prospective study by Palace and collaborators showed a steroid sparing effect in the AZA + prednisolone ($n = 15$) versus placebo + prednisolone ($n = 19$) at 36 months [8]. About 60% of the patients belonging to the AZA arm did not require retreatment with steroids. In addition, treatment failure, measured in terms of number of relapses, was lower in the AZA group presenting only three relapses versus twelve in the placebo group. This study has certain limitations mainly due to the missing data (ten dropouts and six deceased), the presence of two patients with thymoma in the placebo group and the lack of quantitative MG-specific parameters of disease outcome.

3.2. Mycophenolate mofetil (MMF)

MMF is a prodrug of mycophenolic acid which inhibits inosine-5′-monophosphate dehydrogenase. This results in the depletion of guanosine nucleotides (*de novo* pathway), preferentially in T and B lymphocytes and selectively inhibits their proliferation. MMF was initially designed for renal allograft recipients, but increasing evidence is accumulating in other systemic autoimmune disorders. MMF is usually applied as an alternative drug whenever AZA is not well tolerated. However, it should be kept in mind that MMF is teratogenic and its use is contraindicated during pregnancy.

The first report suggesting a beneficial use of MMF was published in 1998 in a teenager with refractory MG [19]. Further observational studies validated this finding, showing improvement of the functional status, muscle strength and/or steroidal therapy sparing effect on about 63–73% of patients [20–22]. However, these results were not confirmed in two multicentric, prospective, double-blind and placebo-controlled studies receiving MMF + prednisone ($n = 80$) versus placebo + prednisone ($n = 176$) [23,24]. No significant differences were observed between the study groups at 12–36 weeks and MMF showed a good safety profile. Study limitations of methodological nature were postulated by the authors: short observation period, high prednisone dose at treatment onset, more severe disease course in the study group and the lack of strict quantitative outcome parameters [25].

3.3. Methotrexate (MTX)

MTX is an antagonist of folate metabolism which inhibits the synthesis of the purines and pyrimidine, thus, interfering with DNA synthesis and cellular replication. MTX is widely used in several autoimmune diseases with a good safety profile. However, its use in MG has been widely debated.

A single-blind study showed similar efficacy to AZA at 10 months in terms of prednisone dosing [7]. In addition, safety profile and clinical response were relatively similar in both groups. The main motivation of this study was the cost related to MTX which is cheaper than AZA, resulting in an interesting choice in developing nations. However, a recent randomized, double-blind, and placebo-controlled trial conducted for 12 months showed no steroid-sparing effect in the MTX treated group [26]. Authors postulate that the initial steroid dose was lower in their cohort and, thus, no significant decrease could be detected. It was argued that the follow-up period was too short.

Despite the controversial results, European guidelines propose to limit the use of MTX to patients who do not respond to the above-mentioned therapies [17].

3.4. Cyclophosphamide (CYC)

CYC is an alkylating prodrug which acts as a cytostatic and antiproliferative agent. CYC inhibits B lymphocyte activity and antibody synthesis, and at high doses it can also affect the T cells. It is widely used in oncology, tissue transplantation and autoimmune diseases. Lung and renal toxicity, and bone marrow suppression are one of the main drawbacks. To limit potential toxic effects, several centres propose an initial induction protocol with pulsed intravenous CYC (i.e. monthly infusion for six months), followed by an oral immunosuppressor as maintenance therapy. A recently published retrospective case series showed that MMS was achieved in 4/8 (50%) of patients under maintenance therapy at 15–49 months [27].

Beneficial outcome in terms of muscle strength (specially bulbar and oculomotor muscle improvement) and lower steroid dose were observed in a randomized double blind and placebo-controlled study using high-dose CYC infusions ($n = 23$) [9]. However, effects of CYC were generally short-lived and most of the patients presented with clinical relapse and required escalation therapy [9,28]. Time-to-improvement ranged from one to three months after treatment onset.

Given its teratogenic effect, CYC should be avoided in patients of childbearing age. Due to the high risk of toxicity, the task force recommends that this medication should be reserved to refractory MG patients, who are not responding to conventional therapies [17]. It is sought that 10–15% of patients fall into this category [29]. However, definition of refractory MG is not uniform and varies according to the clinical trial.

4. Calcineurin inhibitors

4.1. Cyclosporine A (CsA)

CsA is a potent immunosuppressor that inhibits T-cell function (transcription of cytokine genes, specifically IL-2) through action via calcineurin signalling. It is used to suppress the immune response in transplant patients and prevent organ rejection. In MG, CsA is rarely used as a first-choice drug due to its unwanted side effects, notably nephrotoxicity, requiring frequent monitoring of renal function and blood count. It was suggested that a lower dosage might be sufficient to control the disease and minimize adverse effects [30,31].

CsA showed a beneficial effect in several controlled studies after a short and a long-term period of assessment [30–32]. In a retrospective study, clinical improvement was observed between one and three months, with a maximum peak at seven months in 22/75 (30%) of patients who reached MMS and in 7/38 (18%) of patients in whom steroids were discontinued [30].

4.2. Tacrolimus (TAC)

As with CsA, TAC blocks IL-2 transcription and has an effect in the cell-mediated immune system and, potentially, the humoral immunity. Its main advantage over CsA is the lower incidence of nephrotoxic effects at low-dose [33].

TAC is widely used in Japan and is approved in MG patients who underwent thymectomy and with either a poor response or adverse events after administration of steroidal therapy. Several case reports and small case series showed clinical improvement in different forms of MG, including thymomatous patients, while using low-dose TAC [34–36]. Treatment efficacy was also assessed after CsA failure in an unblinded and unrandomized study including 79 MG patients during a period of three years [37]. In this study, steroids were discontinued in 77/79 patients.

A placebo-controlled study showed no steroid sparing effect at 12 weeks nor changes in the muscle strength assessed by a quantitative MG scoring system at the end of the trial ($n = 80$) [10]. According to the authors the results can be explained by the inclusion of patients with ocular MG or with a long disease duration (average of 7.5 years), thus, being more “vulnerable” to steroidal therapy dose reduction.

Different studies showed a good short-term and long-term safety and tolerability profile [10,35,38]. Noteworthy, lymphopenia is amongst one of the most common adverse events, which usually does not lead to treatment discontinuation. Other side effects include renal insufficiency, neuropathy, hypomagnesemia, etc.

In practice, calcineurin inhibitors are usually prescribed in severe forms of MG, and whenever the association of prednisone with AZA or MMF is ineffective [39]. Nonetheless, given their adverse effects, their prescription should be considered in the light of biological drugs which are currently used as off-label (RTX) or FDA approved (eculizumab) treatments in refractory MG.

5. Biologic drugs

5.1. Rituximab (RTX)

RTX is a chimeric monoclonal antibody to CD-20, which leads to B lymphocyte depletion by cell-mediated or complement-dependent toxicity.

Initial case series showed favourable results in MG using four weekly doses of 375 mg/m^2, followed by a dose every two months [40–44]. Lebrun and collaborators showed that steroids were stopped and anticholinesterase inhibitors could be tapered off in all patients with refractory MG ($n = 6$) at 2 years [41]. Based on reports from haematology, a therapeutic dose of 1 g was used in a retrospective study showing clinical improvement at 12 months in 11/14 MG patients and complete remission in 3/14, all three anti-MuSK+ [45]. A Canadian prospective study showed similar effects between the two infusion protocols: 375 mg/m^2 weekly for 1 month and then once every month for two additional infusion, versus 1 g given twice with two weeks between infusion [2]. Interestingly, the peak of the clinical response was observed at 20.7 +/− 12 weeks and time-to-relapse was 17.1 +/− 5.5. months (range: 9–23 months) after the first infusion; showing a relatively fast efficacy and treatment durability. These results were confirmed by a second retrospective case series, in which 56% of MG patients presented with a clinical relapse during a mean follow-up of 36 months and a 33% decrease in relapse rate after the first infusion [46].

Regarding other MG forms, RTX increased probability of favourable outcome in patients with anti-MuSK MG [3]. Favourable clinical response, resulting in a dose decrease of other immunosuppressive therapies, was reported in 14/24 (58%) compared to 5/31 (15%) in the control group (NNT = 2.4). Efficacy of RTX was also observed in two cases of thymomatous MG [44], in 24 patients with recently diagnosed MG [47] and in seven patients with late-onset MG [48].

According to a recent meta-analysis including 169 MG patients and 47 publications, there was no correlation between treatment efficacy and age at onset, sex, disease duration, number of previous immunosuppressors, amount of pre-treatment relapses and total administered infusions [49]. The only independent factor predicting a favourable outcome was anti-MuSK antibody status. In addition, RTX showed a good safety profile since no side effects were mentioned in 86% of patients, even in association with other immune suppressive therapies. One major limitation of RTX is the fact that it remains unlicensed and unfunded in many countries.

5.2. Other therapeutic monoclonal antibodies

Ofatumumab is a full human anti-CD20 antibody, validated in treatment refractory rheumatoid arthritis. This treatment was used in a case of a 74-year-old woman with MG and a rheumatological disorder, who presented a hypersensitivity reaction after two infusions of RTX and haematological complications after MTX [50].

Iscalimab (CFZ533) is a fully human anti-CD40 monoclonal antibody, used in thyroid disease, and whose safety and tolerability were tested as an add-on therapy in moderate-to-severe MG with acetylcholine receptor antibody-positive (anti-AChR+) and anti-MuSK antibody status [51]. Results of this study are pending.

Belimumab is a human IgG1 λ recombinant monoclonal antibody that neutralizes B cell-activating factor and is used in lupus erythematosus. A phase III trial did not show a statistically significant improvement at 24 weeks in a cohort of 40 anti-AChR+ MG patients versus placebo [52].

Tocilizumab is a humanized recombinant monoclonal antibody targeting interleukin 6 receptor (IL6-R). A published case report showed clinical improvement in two patients with refractory MG after failure to respond to RTX [53].

Obinutuzumab is a humanized anti-CD20 monoclonal antibody administered in a case of severe MG and concurrent chronic lymphocytic leukaemia with complete disease remission [54].

5.3. Complement inhibitors

A role for complement and the membrane attack complex (MAC) has been suggested in the physiopathology of anti-AChR MG. Complement inhibitors (i.e. eculizumab, zilucoplan and ravulizumab), target the main immune mechanism involved in endplate destruction, and showed beneficial results in experimental autoimmune MG [55]. Since anti-MuSK autoantibodies lack the ability to activate the complement cascade, this MG subtype does not respond to complement inhibitors.

5.3.1. Eculizumab

Eculizumab is a humanized monoclonal antibody against the terminal complement protein C5. This drug was approved 10 years ago for nocturnal haemoglobunuria and atypical haemolytic ureamic syndrome. Currently, it is accepted in many countries as an add-on therapy in refractory MG with anti-AChR+.

A randomized and placebo-controlled clinical trial included patients with refractory MG, in whom two immunosuppressive treatments were already used, and with moderate/severe symptoms [4,56]. During the phase II trial, eculizumab showed an eight-point reduction on the quantitative MG score in 4/7 (57%) patients versus 1/7 (14%) in the placebo group over a period of 16 weeks [56]. Benefit of eculizumab over the placebo group was also observed in the phase III trial (REGAIN) including a larger number of patients ($n = 125$), an induction dose of 900 mg/week for four doses and a maintenance dose of 1200 mg/every two weeks, and an assessment period of 26 weeks; however, without reaching statistical significance [4]. Noteworthy, during the study, other immunosuppressive therapies were pursued, and rescue treatment was used at the investigator's discretion in 6/62 patients in the treated group versus 12/63 in the placebo group. Further analysis showed that, even if immunosuppressive therapies were removed from the analysis, results still favoured the eculizumab group.

Long-term safety and efficacy was assessed for a treatment duration of three years in the open-label study ($n = 117$) [57]. Clinical improvement was observed during the week following the first infusion, was maximal at three months and remained stable for over 30 months. At the end of the open-label study, 86/116 (74.1%) patients reported clinical improvement and 65/116 (56%) achieved MMS.

Concerning safety issues, the most common adverse event were headaches and nasopharyngitis in about 1/3 of the treated patients [57]. Since the inhibition of complement protein C5 increases the risk of *Neisseria meningitides* infection, vaccination should be administered prior to treatment onset. One case of meningococcal infection was reported after the study period, with a favourable outcome after antibiotic therapy.

5.3.2. Zilucoplan

Zilucoplan (RA101495) is a synthetic macrocyclic peptide that binds to complement protein C5 and blocks cleavage into C5a and C5b, preventing MAC assembly. It also blocks binding between C5b and C6. As a matter of fact, zilucoplan has a different binding site than eculizumab, which could be useful in patients with missense C5 heterozygous mutation, considered as non-responders to eculizumab [58].

A multicentre, randomized, double-blind, placebo controlled study was performed in 44 patients with generalized anti-AChR+ and refractory MG. Patients were randomized in a 1:1:1 ratio to receive daily subcutaneous (SC) doses of 0.1 mg/kg, 0.3 mg/kg zilucoplan or placebo for 12 weeks [59]. Primary endpoint was met showing a 6-point change of the quantitative MG score in the 0.3 mg/kg treated group. Higher dose group showed earlier and more sustained results than the lower dose group. Clinical improvement was observed as early as 1 week after treatment onset. The proportion of patients achieving MMS was higher in the zilucoplan group (5/14 versus 2/15 patients in the placebo group), without attaining statistical significance. Phase 3 trial (RISE) is ongoing and will also include non-refractory patients.

Most adverse events reported during the phase II trial were considered as mild and there was no difference with the placebo arm. No serious adverse events were reported so far.

5.3.3. Ravulizumab

Ravulizumab (ALXN1210) is a monoclonal humanized antibody which, as eculizumab, binds to complement C5 protein [60]. Its half-life is much longer than eculizumab due to its antibody half-life extension technology. It can be administered every eight weeks, with a single loading dose on day one, followed by a maintenance dose on day 15. Ongoing phase III trial is being developed in patients who did not previously receive a complement inhibitor. Primary endpoint will assess baseline changes of the MG activity of daily living (MG-ADL) profile at 12 and 26 weeks.

5.4. FcRn antagonists

Another way to approach the immune pathway in MG patients is to limit the circulation of endogenous pathogenic antibodies. Since neonatal Fc-receptors allow for IgG recycling from lysosomal degradation, FcRn receptor antagonists accelerate removal of autoantibodies and shortens its half-life (for a review see Zuercher et al.) [61].

Ongoing trials are being held using different molecular structures: i) efgartigimod a humanized IgG1-derived Fc fragment, modified by biotechnology to increase Fc/FcRn binding, is currently in phase III [62,63], ii) rozanolixizumab, nipocalimab and batoclimab are monoclonal antibodies directed against FcRn. Rozanolixumab is a humanized IgG4 anti-FcRn monoclonal antibody [64], nipocalimab (M281) is a fully human deglycosylated IgG1 anti-FcRn monoclonal antibody with no effector function [65,66] and batoclimab (RVT-14-01) is a human IgG1 anti-FcRn monoclonal antibody [67]. To our knowledge, only nipocalimab will be tested in anti-MuSK+ MG. Noteworthy, preclinical data available on nipocalimab and batoclimab is currently limited.

5.4.1. Efgartigimod

A double-blind, placebo-controlled study performed in 24 anti-AChR+ MG patients were randomized to receive either placebo or four doses of 10 mg/kg intravenous efgartigimod over a three-week period, followed by an eight-week observation period [62]. Eligibility criteria included an MG-ADL score of at least 5 points, clinical stability under other immunosuppressive treatments and mild-to-severe MG forms (ocular MG were excluded). This study did not include seronegative generalised MG or MuSK-associated subgroups. The primary outcome was safety and the secondary outcome was efficacy. A phase III trial is currently ongoing to test treatment efficacy.

Administration of efgartigimod resulted in a drop of IgG serum concentration by 50% at week three, and levels returned to normal after the last dose. Maximal reduction of efficacy/strength scales (39–56% from baseline) and quality of life scores (31% from baseline) were achieved between one and two weeks after the last dose. This was concomitant to the period with lowest IgG serum concentration. In addition, statistically significant reduction of the quantitative MG score (−3 points) was achieved after the first infusion. Nonetheless, given the small number of patients a validation in a larger cohort is required.

Frequency and severity (generally mild) of adverse reactions were similar in both groups. In the treated arm, headache, myalgia, and reduced monocyte/lymphocyte count were observed. A single case of shingles was reported one week after infusion of efgartigimod.

5.4.2. Rozanolixizumab

A randomized, subject-blind and placebo-controlled trial was carried out in 43 anti-AChR+ MG patients with a moderate-to-severe disease form [68]. Subcutaneous infusions of rozanolixizumab 7 mg/kg or placebo were administered once weekly for the first 29 days and was re-randomized using either 7 mg/kg or 4 mg/kg once a week at day 29–43. Safety assessment was the main study aim and results showed that the treated group presented with a higher incidence of headache than the placebo group (57.1% vs. 13.6%) and three patients withdrew from the study. Improvement in all clinical scores were observed in the treated versus the placebo group at day 29, without reaching statistical significance ($p < .001$). However, improvement in the MG-ADL score (> three-point increase) reached 47.6% versus 13.6% in the placebo arm. Interestingly, patients belonging to the placebo group, and reassigned to rozanolixizumab in the second stage of the trial, showed clinical improvement.

6. Autologous hematopoietic stem cell transplantation (HSCT)

A Canadian retrospective case series on seven patients with severe MG (MGFA Class III-IV) suggests that HSCT may result in long-term remission [69]. It was hypothesized that HSCT might reset the immune system and avoid use of maintenance immunosuppressive treatment. In addition, no treatment-related death was reported.

7. Conclusion

Immunosuppressive therapies in MG aim at controlling disease-related symptoms/signs and achieving clinical remission or MMS. The way in which researchers measure "treatment success" in MG vary from trial to trial: initial studies used strength scores and steroid-sparing effect [8,9,23,30], while more recent publications used a three-point improvement of the MG-ADL score [4,59,62].

Heterogeneity in the assessment of treatment efficacity in phase III trials does not allow for adequate comparison between drugs. Different scores were developed to measure disability, signs/symptom severity and treatment response [70,71]. Interestingly, these measures were developed to evaluate efficacy in clinical trials and were often modified to suit the study purpose. Currently, more than ten different "disease-specific" scores are being used. In this sense, there is a clear need for scoring uniformization to evaluate clinical significance in MG trials. Currently there are no other reliable biomarkers allowing disease prognostication or follow-up. Antibody testing and electrophysiological exams are good diagnostic tools but are not correlated with disease activity nor they can assess treatment response in the individual patient [29].

Inclusion of different disease phenotypes and autoantibodies might explain the difficulty to reach the primary outcome in many clinical trials [10]. MG is caused by antibodies directed against AChR or other structural proteins of the neuromuscular junction (i.e. MuSK and low-density lipoprotein receptor-related protein 4). Antibodies directed towards other target antigens were described in triple seronegative patients (e.g. agrin, titin, cortactin, ryanodine, voltage gated Kv1). However, their clinical implication and pathogenic role in MG is currently unknown [72]. Treatment should be adapted to the individual patient and the antibody status should be kept in mind while selecting the proper immunosuppressive treatment. For instance, Hehir and collaborators showed a more favourable clinical response while administering RTX in anti-MuSK MG patients rather than in anti-AChR+ MG [3]. Other research focused in this antibody subtype includes chimeric antigen receptor (CAR) T cells which targets circulating B cells expressing anti-MuSK antibodies (Descartes-08; phase Ia-IIB) [73].

Certain MG forms are underrepresented due to their low incidence or difficulties in patient recruitment. Future studies should focus on patients with i) mild symptoms, ii) early-onset, and iii) unstable disease course. Indeed, most studies only included patients who were stable under other immunosuppressive treatments. Although this is logic from a pharmacological standpoint, and aims to assess the tested drug versus placebo, it does not usually fit the clinician's need nor it corresponds to real-life situations.

So far, no study has addressed the question of the long-term outcome of treatment decisions in people with MG. Short period of assessment has been criticized in many clinical trials. For instance, full efficacy of AZA of MMF is reached at 6 months of treatment onset, and most of these trials ended before that time frame [8,25]. Other factor that might limit the assessment of treatment response is the concomitant use of steroidal therapy. In many studies it was difficult to know if the response was related to the studied drug or the use of steroids [25]. Open-label extension studies should provide more light on treatment efficacy in a population in which steroids intake was either decreased or discontinued.

Given the number of emerging drugs in MG it is important to define each treatment's role: first-line, second-line, refractory MG, add-on therapy, patient with other autoimmune disease, etc. The proper place of FcRn antagonists also needs to be defined: are they suited to treat myasthenic crisis or as a long-term substitute for PLEX or IVIg? This indication needs to be weighted in terms of the financial cost. Although many questions remain unanswered, the emergence of new drugs will help to fuel further discussions.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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