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The Past, Present and Future

Myasthenia Gravis and Its Immunotherapies

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Abstract

Autoimmune myasthenia gravis (MG), a rare disorder of the neuromuscular transmission with resulting increased muscular fatigue, often significantly impairs the quality of life in affected patients. With better understanding of its underlying pathophysiology in recent years, a growing number of therapies can be used to lessen the disease burden in patients. This review summarizes the current understanding of clinically important pathophysiological aspects of MG. We highlight the historical journey from the first therapeutic attempts with acetylcholine esterase inhibitors by Mary Walker in the 1930s to the development of targeted monoclonal antibodies or fragments in recent years. This review covers the standard therapy regimen, but also aims to provide an outlook on new classes of therapeutics currently in the pipeline and available in clinical practice in the near future.

Keywords: Myasthenia gravis; pathophysiology; immunotherapy; adverse events

Introduction: Pathophysiology of Myasthenia Gravis at the Neuromuscular Junction

In the past few decades, there has been an increase in myasthenia gravis (MG) incidence and prevalence, partially explained by improved diagnostic techniques and an aging population [1]. Autoimmune MG, with its main symptom of increased skeletal muscle fatigability, is caused by disturbed transmission at the neuromuscular junction by various antibodies. In recent years, novel insights into disease pathophysiology across different MG subtypes and autoantibodies have increased the spectrum of therapeutics to treat MG patients [2]. In this article, we give a short update on current information on MG pathophysiology, before reviewing and summarizing standard therapeutic regimens and immune treatments in the pipeline for autoimmune MG.

MG subtypes and autoantibodies: In acetylcholine receptor (AChR)-antibody mediated MG (approximately 85% of patients), three main effector mechanisms are thought to lead to a reduced endplate potential. A direct functional blockade of acetylcholine docking to AChRs, cross-linking of AChRs and their internalization (antigenic modulation), and complement-mediated damage of the muscle membrane. AChR-antibodies are primarily of the IgG1 and IgG3 subclasses and are therefore able to activate the complement cascade [3]. Autoantibodies against muscle-specific tyrosine kinase (MuSK) are found among 30–60% of patients that do not have AChR-autoantibodies. MuSK-directed antibodies prevent the interaction between MuSK and low-density lipoprotein receptor-related protein (LRP) 4 which is essential for MuSK phosphorylation and effective clustering of AChR at the neuromuscular junction [4]. MuSK-directed autoantibodies are largely of the non-complement binding IgG4 subclass. They can also block the interaction between MuSK and collagen Q, leading to reduced acetylcholinesterase (AChE) concentrations at the neuromuscular junction. This could explain clinical signs of cholinergic hyperactivity (e.g., muscle cramps) and neurophysiological correlates in MuSK-antibody mediated MG, as suggested by a recent study [2, 5]. Autoantibodies against LRP 4 and the LRP 4 ligand agrin were initially described in variable proportions of seronegative patients without AChR- or MuSK-directed antibodies [6, 7]. Since then, AChR/LRP 4, MuSK/LRP 4 and AChR/agrin double-positive antibody constellations have been observed frequently in MG patients [8, 9], while AChR- and MuSK-autoantibodies rarely occur together in the same patient [10]. Antibodies against LRP 4 belong to the complement-activating IgG isotypes IgG1 and IgG3 and there is some data supporting their functional relevance, while the role of agrin-autoantibodies is less clear [8, 11]. The clinical utility of LRP 4-antibody testing for MG diagnosis is debated [2, 12, 13]. In a recent histopathological study of muscle biopsies in 13 "triple seronegative", mostly treatment-refractory MG patients, IgG1 and complement deposits at endplates stained positive [14]. However, the targeted autoantigen at the neuromuscular junction of such seronegative MG patients has not been discovered yet. Besides, it has not been fully excluded that low-level AChR-antibodies could be detected using more sensitive tests such as cell-based assays [15].

MG and the Thymus: In 70% of early-onset MG patient (before turning 50) with AChR-directed antibodies inflammatory changes of the thymus (thymitis, lymphofollicular hyperplasia) can be detected. Germinal centers indicate an active inflammatory pro-

cess underlying intrathymic AChR-autoantibody production [16]. AChR-autoantibody positive MG patients over 60 years usually show age-appropriate thymic involution (fatty atrophy), and the pathogenic relevance of the thymus is less clear [17]. However, there are exceptions with histopathological evidence of thymic hyperplasia in late-onset MG patients [18]. In about 15% of MG patients, MG occurs as a paraneoplastic syndrome resulting from a thymoma. In thymoma-associated MG, AChR-autoantibodies are almost always present. In more than 50% of cases, they are found together with titin-directed antibodies [9, 19]. The use of anti-titin and other anti-striational antibodies for predicting malignancy or neurological phenotypes has been recently questioned, pointing out, that a positive result may tempt to over utilize computer tomography imaging [20]. MG with MuSK- or LRP 4-antibodies are usually not linked to thymoma [21, 22]. In thymoma patients, parameters that have been associated with MG development are: seropositivity for AChR-autoantibodies, B1 or B2 histological subtypes, presence of ectopic germinal centers in the adjacent tissue of thymoma, local invasiveness, and being a woman under 50 years of age [23].

Treatments for Myasthenia Gravis: Historical Overview

The first description of the disease was documented in 1672 by Thomas Willis, an English physician, who observed a female patient with muscle weakness of her limbs and tongue, that was exacerbated by effort. In the early 20th century, several surgeons observed improvement of myasthenic symptoms after the removal of a thymoma. Thymectomy remains an important part in the treatment of several patient groups. In 1921, Loewi and Dale were able to demonstrate that neuromuscular transmission depends on the release of acetylcholine from the motor nerve axon. However, it was Mary Walker, a young physician who drew conclusions about the analogies between the effect of the arrow poison curare and symptoms of MG, and made the first therapeutic attempt with physostigmine. She observed a rapid improvement of muscle weakness in the patient. The short-lasting clinical improvement soon led to the use of long-acting AChE inhibitors. In 1960, Simpson was the first to propose that MG is an autoimmune disease caused by antibodies against a specific protein causing the loss of AChRs from the neuromuscular junction [24]. Built on the hypothesis of an autoimmune disease etiology, new pharmacological treatments, such as corticosteroids and non-steroidal immune therapies emerged. By the 1980s, plasma exchange (PEX) and intravenous immunoglobulin (IVIg) were considered established treatment methods in the management of myasthenic crises [25]. Treatment approaches with leukocytotoxic substances, originally used against lymphomas, including azathioprine, methotrexate (MTX) and cyclophosphamide followed. In the 1990s, physicians started to make use of additional immunosuppressive agents, such as cyclosporine and mycophenolate due to partly positive results in ongoing clinical trials [25]. Founded on the increasing knowledge of MG pathogenesis and in successfully conducting randomized controlled MG treatment trials, more targeted treatments are being developed and brought into the clinic.

Standard Immunotherapy and Current Guidelines

To maintain disease stability, most patients with generalized MG require immunotherapy in addition to cholinesterase inhibitors due to the underlying autoimmune reaction. According to international consensus guidelines from 2016, corticosteroids or immunosuppressive therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine [26]. The more recently revised guidelines of the German Neurological Society (DGN) with Swiss participation emphasize that – as a principle – MG patients should be offered a "disease-modifying" (immuno-) therapy in addition to the symptomatic treatment [59]. Due to long- and short-term side effects of corticosteroids, "steroid-sparing" immunotherapies, such as azathioprine, mycophenolate, cyclosporine, methotrexate, or tacrolimus are preferably applied as maintenance therapy. Regarding the best choice of drug, the different MG subtypes and disease manifestations should be taken into consideration. Because clear evidence from randomized controlled MG therapeutic trials is still lacking for some of these agents, the implementation of treatment varies worldwide [27]. Expert consensus and some randomized controlled trials suggest the use of azathioprine as first line therapy [26, 59]. There is a double-blind randomized controlled trial that compared MG patients who received prednisolone plus placebo versus prednisolone plus azathioprine (2.5 mg/kg daily) over a period of three years [28]. The maintenance dose of prednisolone was lower after two years in the azathioprine group. Furthermore, azathioprine was associated with fewer treatment failures and longer remissions. After the first year of treatment, there was no significant difference between the patient groups, suggesting that there is a long latency period for azathioprine to become beneficial. There is no clear evidence of efficacy based on two randomized controlled trials for the use of mycophenolate mofetil in MG [29, 30]. However, several study limitations have been discussed as possible explanation for the negative results, including a too brief study duration (three or nine months) or unexpectedly good response in patients receiving prednisone alone [31]. A more recent multicenter prospective observational comparative effectiveness study conducted in the United States showed meaningful improvements in MG patients receiving either azathioprine or mycophenolate mofetil [32]. Accordingly, mycophenolate mofetil is recommended in several national treatment guidelines. Despite supporting evidence from randomized controlled trials, the long-term use of cyclosporine is limited due to potential serious adverse effects, such as nephrotoxicity [26]. There are varying outcomes reported for the use of MTX in studies. A randomized controlled trial did not show a significant steroid sparing benefit in patients treated with 20 mg MTX per os, compared to placebo over twelve months of treatment [33]. In addition, a small single-blinded trial compared MG patient groups treated with either MTX 17.5 mg weekly, or azathioprine 2.5 mg/kg daily. At two years, the average prednisolone dose required to achieve and maintain minimal manifestation status was reduced but did not differ in both treatment groups [34]. Therefore, the use of MTX may still be considered if patients do not respond to or develop adverse reactions from other steroid-sparing agents, or if they have concomitant rheumatologic diseases [27].

Earlier observational studies have suggested a benefit of rituximab (RTX) particularly in patients with MuSK-autoantibody positive MG and patient groups with longer disease duration (e.g., refractory patients) [35, 36]. According to current treatment guidelines, RTX should therefore be considered an early therapeutic option in patients with MuSK positive MG with rather poor response to treatment [27, 59].

The recently published Swedish RINOMAX trial investigated patients that developed generalized MG symptoms within twelve months or less. Prior non-corticosteroid immunosuppressants or high doses of corticosteroids were exclusion criteria. Participants received a single intravenous infusion of 500 mg RTX compared to placebo. RTX was associated with greater probability of minimal MG manifestations and reduced need of rescue medications compared to the control group [37]. In contrast, results of a randomized phase II trial (BeatMG) of RTX in patients with generalized AChR-autoantibody positive

MG did not reach the primary outcome represented by steroid-sparing effect without exacerbation of MG at one year [38]. There are important differences to the RINOMAX trial that could account for this discrepancy. For example, most patients in the BeatMG study did not have newly diagnosed MG and they had mild generalized disease that responded to concomitant treatments alone. In addition, the BeatMG study used prednisone dose as a primary outcome measure, whereas in recent years, positive MG treatment trials have used other clinical outcome measures, such as MG Activities of Daily Living (MG-ADL) scores [39]. Furthermore, the number of study participants was relatively small.

Thymectomy was one of the first therapeutic attempts in the history of MG and still plays an important role in present treatment recommendations. The MGTX trial demonstrated that thymectomy combined with prednisolone improves clinical outcomes of patients with non-thymomatous AChR-autoantibody positive MG over a three year period compared to prednisolone alone [40]. In the follow-up extension trial, patients continued to benefit from thymectomy after five years [41], which is reflected in current treatment guidelines. The indication for purely ocular MG or seronegative MG is less clear. According to guidelines, thymectomy may be considered in patients with seronegative generalized MG with insufficient treatment response after an adequate trial of immunotherapy. In patients with MuSK, LRP 4, or agrin autoantibodies, thymectomy is currently not recommended [27].

More rapidly acting therapies, such as therapeutic PEX or IVIg are mainly used for acute MG exacerbation, imminent MG crisis with neuromuscular respiratory failure or to "bridge" slower-acting therapies and to minimize glucocorticoid use [42, 43]. Plasmapheresis is thought to act primarily by removing AChR-autoantibodies from the circulation. However, their levels rebound within weeks, and the beneficial clinical effects typically lasts only up to six weeks, making plasmapheresis less useful as a long-term maintenance therapy.

New Targeted Immunotherapies

In addition to monoclonal antibodies against B-cell molecules, other targeted immunotherapies that are currently being developed include inhibitors of components of the complement system as well as blockers of neonatal Fc receptors (FcRn) [44].

Complement activation at the neuromuscular junction is thought to play a crucial part in the pathogenesis of AChR-autoantibody positive MG. The formation of the terminal complement complex (membrane attack complex) leads to damage of the postsynaptic membrane. Eculizumab is a terminal complement inhibitor that is currently approved for the treatment of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, and neuromyelitis optica spectrum disorder [45]. Although the REGAIN trial failed to meet the primary endpoint of change in MG-ADL, it demonstrated safety and clinical improvement in refractory AChR-autoantibody positive MG under the treatment with eculizumab. Furthermore, it was associated with fewer exacerbations and rescue therapies

Table 1: Selection of ongoing or recently completed studies on B cell- and T cell-directed therapies in generalized myasthenia gravis (MG)

Substance: *mode of action*	**Target**	**Inclusion criteria**	**Primary outcome measure**	**Status, NCT trial number**
Inebilizumab (Humanized IgGK mAb): *target cell depleting*	CD19: B cells, plasmablasts, some plasma cells	AChR- or MuSK-Ab + gMG. MG-ADL ≥6, QMG ≥11	Change in MG-ADL	Phase 3. Ongoing, NCT04524273
TAK-079 /Mezagitamab (IgG1 mAb): *target cell depleting*	CD38: plasma cells, T cells, NK cells	AChR- or MuSK-Ab + gMG. MG-ADL ≥6	% of patients with treatment emergent AE	Phase 2. Completed, NCT04159805
Telitacicept (IgG Fc Fusion protein): *inhibitor*	Blys and APRIL	AChR- or MuSK-Ab + gMG. QMG ≥6	Change in QMG	Phase 2. Ongoing, NCT04302103
Tolebrutinib: *inhibitor*	BTK enzyme	AChR- or MuSK-Ab + or seronegative gMG. MG-ADL ≥6	Change in MG-ADL	Phase 3. Ongoing*, NCT04302103
CAR-T-Cell Therapy (Autologous T cells with chimeric Ag receptor): *target cell depleting*	Cells expressing BCMA *(independent of antigen-specificity)*	gMG (seronegative MG included)	MG-ADL, safety	Phase 2. Ongoing, NCT04146051
MuSK-CART (Autologous T cells with chimeric Ag receptor): *target cell depleting*	B cells expressing anti-MuSK *(autoantigen-specific)*	MuSK-Ab + MG	AE	Phase 1. Ongoing, NCT05451212
Tocilizumab (Humanized IgG1 mAb): *inhibitor*	Il-6 receptor	AChR-Ab + gMG. MG-ADL ≥5, QMG ≥11	Change in QMG	Phase 2. Ongoing. NCT05067348
Satralizumab (Humanized IgG2 mAb): *inhibitor*	Il-6 receptor	AChR- or MuSK- or LRP4-Ab + gMG. MG-ADL ≥5.	Change in MG-ADL (AChR-Ab+)	Phase 3. Ongoing NCT04963270

Abbreviations: Ab, antibody. AE, adverse event. APRIL, a proliferation inducing ligand. BCMA, B Cell Maturation antigen. BLys, B lymphocyte stimulator (also called B-cell activation factor, BAFF). BTK, Bruton`s tyrosine kinase. gMG, generalized MG. Il, interleukin. mAb, monoclonal antibody. MG-ADL, Activities of Daily Living Score. MuSK, muscle-specific tyrosine kinase. QMG, Quantitative MG Score. NCT, clinicalTrials.gov Identifier number. * Recruitment paused in 8/2022, based on a limited number of cases of drug-induced liver injury.

compared to the placebo group [46]. There have been several publications from the REGAIN cohort as it was followed longitudinally that confirmed positive treatments effects. A following randomized controlled trial investigated the efficiency of ravulizumab, a longer-acting inhibitor of terminal complement protein C5, in AChR-autoantibody positive MG. Compared to placebo, ravulizumab demonstrated rapid and sustained clinical improvements measured by a significant difference in MG-ADL and Quantitative Myasthenia Gravis (QMG) response after 26 weeks [47]. The complement inhibitor eculizumab is approved in Switzerland for the treatment of severe refractory AChR-autoantibody positive, generalized MG. Ravulizumab has just been approved in the United States, Europe and in Switzerland for MG. Because the complement system is critical to fight of encapsulated bacteria, such as meningococci, the vaccination and/ or prophylactic antibiotic treatment is mandatory.

FcRn inhibition is another novel therapeutic strategy in autoimmune diseases mediated by IgG autoantibodies, such as MG. FcRn physiologically binds to the Fc portion of IgGs and protects them from intracellular breakdown increasing IgG circulation level and half-life. FcRn binding also allows IgG transport across endothelial or (gut) epithelial cell layers, which is, amongst others, important for IgG transfer from mother's milk to their offspring [48]. FcRn antagonists, such as efgartigimod, inhibit functional FcRn expression resulting in an increased lysosomal degradation of IgG and reduced circulating IgG levels. According to the literature, IgG reduction is typically about 70–90% more effective than with PEX [44] The phase III ADAPT study, a randomized controlled trial, included 167 patients with generalized MG who were treated with either efgartigimod, an antagonistic humanized anti-FcRn-IgG1 Fc fragment, or matched placebo. During continuous treatment with efgartigimod, a reduction of serum IgG and AChR-autoantibodies by a maximum of 75% was obtained, correlating with significant improvement in strength and quality of life in patients measured in response of MG-ADL score compared to placebo [49]. Efgartigimod is approved in the United States and Europe for MG, the approval in Switzerland is currently pending.

Additional complement inhibitors and other anti-FcRn blockers (intravenous and subcutaneous) are currently in the clinical development for MG [50].

Outlook: What Is on the Horizon

Several drugs (besides terminal complement C5 inhibitors and FcRn inhibitors), are in development for the treatment of MG (https://clinicaltrials.gov). These include, amongst others, next generation B cell depleting agents such as inebilizumab (anti-CD19), T cell and cytokine-based therapies, and chimeric antigen receptor (CAR) T-cell therapy. A selection of ongoing or recently completed immunotherapy trials in generalized MG are listed in table 1.

Monitoring Adverse Events and Preventive Measures

There is an increasing awareness of the negative impact of treatment-related adverse events on MG patients' quality of life. As new MG immunotherapies are approved, it is important to understand differences among drugs and to implement tools to measure adverse event burden that are currently being developed [51].

Knowledge of adverse events and drug interactions of azathioprine, mycophenolate mofetil, and new biologics is highly relevant for clinical practice as it may guide safety monitoring and therapy choices [52].

Infections include reactivation of latent infections under immunosuppression (e.g., by herpes viruses; John Cunningham virus associated progressive multifocal leukoencephalopathy) [53, 54]. Eculizumab is known to particularly increase the danger of infections with encapsulated bacteria such as meningococci, and despite vaccinations and/or microbial prophylaxis, heightened awareness and monitoring are important [55]. Vaccinations should be carried out according to "Bundesamt für Gesundheit" (BAG) recommendations (https://www.bag.admin.ch). Live vaccinations should not be used during immunosuppressive therapies. If time permits, the required vaccinations should be completed no later than four weeks before the start of immunotherapy. Vaccinations should be given one month before a planned infusion of RTX or at least one month after or before the next dose (https://dgn.org).

MG and COVID-19: Physician-reported registry (COVID-19 associated risks and effects in myasthenia gravis; with the limitation of a potential bias towards poor outcome reporting) and electronic health record data indicate that MG patients infected with Sars-CoV2 are at increased risk of hospitalization, intensive care unit stay, intubation and higher mortality than the general population with COVID-19 [56, 57]. A recent longitudinal study by Reyes-Leiva and colleagues provided reassurance, that patients with MG receiving mRNA-based COVID-19 vaccines showed no MG exacerbations and mostly achieved good humoral and cellular anti-Sars-CoV2 responses [58]. For MG patients on immunosuppressive medications, BAG recommendations on COVID-19 prophylaxis and treatment (https://www.bag.admin.ch) are updated regularly.

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