HHS Public Access

Author manuscript

Expert Rev Neurother. Author manuscript; available in PMC 2019 July 04.

Published in final edited form as:

Expert Rev Neurother. 2018 July ; 18(7): 573–588. doi:10.1080/14737175.2018.1491310.

Advances in autoimmune myasthenia gravis management

Shuhui Wang[1], **Iva Breskovska**[1], **Shreya Gandhy**[1], **Anna Rostedt Punga**[2], **Jeffery T. Guptill**[3], and **Henry J. Kaminski**[1]

[1]Department of Neurology, George Washington University, Washington DC 20008

[2]Department of Neuroscience, Clinical Neurophysiology, Uppsala University, Uppsala, Sweden

[3]Department of Neurology, Duke University Medical Center, Durham, North Carolina, USA

Abstract

Introduction.—Myasthenia gravis (MG) is an autoimmune neuromuscular disorder with no cure and conventional treatments limited by significant adverse effects and variable benefit. In the last decade, therapeutic development has expanded based on improved understanding of autoimmunity and financial incentives for drug development in rare disease. Clinical subtypes exist based on age, gender, thymic pathology, autoantibody profile, and other poorly defined factors, such as genetics, complicate development of specific therapies.

Areas covered.—Clinical presentation and pathology vary considerably among patients with some having weakness limited to the ocular muscles and others having profound generalized weakness leading to respiratory insufficiency. MG is an antibody-mediated disorder dependent on autoreactive B cells which require T cell support. Treatments focus on elimination of circulating autoantibodies or inhibition of effector mechanisms by a broad spectrum of approaches from plasmapheresis to B cell elimination to complement inhibition.

Expert Commentary.—Standard therapies and those under development are disease modifying and not curative. As a rare disease, clinical trials are challenged in patient recruitment. The great interest in development of treatments specific for MG is welcome, but decisions will need to be made to focus on those that offer significant benefits to patients.

Keywords

myasthenia gravis; clinical trials; mycophenolate; tacrolimus; prednisone; eculizumab; rituximab; interleukins; plasma cells; acetylcholine receptor antibody; muscle specific kinase

Corresponding author: Henry J. Kaminski, Department of Neurology, GW-Medical Faculty Associates, 2150 Pennsylvania Avenue, Washington DC, 20008 USA, HKaminski@mfa.gwu.edu.

Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

1. Introduction

Myasthenia gravis (MG) is an autoimmune, neuromuscular disease with antibodies directed against the skeletal muscle nicotinic acetylcholine receptor (AChR), the muscle specific kinase (MuSK), and likely other proteins concentrated at the neuromuscular junctions. Great advances have been made in understanding the pathogenesis as well as therapeutic development, but a third of patients still experience MG exacerbations and respond poorly to standard therapy, which require hospitalization, and disease- and treatment-related morbidity remains high [1, 2]. Non-immunosuppressive treatments often do not relieve symptoms, and immune-suppressive and –modulators may have poor side effect profiles with variable benefit. MG has been a target for new drug development because of improved understanding of the pathophysiology of MG, a clear unmet need for better therapeutics, and its rare disease status, which has financial incentives for pharmaceutical investment. The review will provide a broad review of the clinical presentation of MG, pathophysiology, and conventional therapies. We will then review the extremely broad array of drug development initiatives ranging from pre-clinical to early phase clinical trials occurring in MG.

2. Clinical presentation

The clinical hallmark of MG is the reduction of muscle strength with repetitive activity. The severity of weakness (Table 1) also varies over time based on fluctuations of underlying disease severity, hormonal fluctuations, treatments, infections, and unknown factors. The spectrum and course of the disease is highly variable with rare spontaneous remissions as well as sudden exacerbations that may produce respiratory insufficiency requiring intubation with mechanical ventilation. Typically, the initial symptoms in over half of patients are ptosis and diplopia. Ptosis may be unilateral or bilateral and will fluctuate in severity throughout the day. Involvement of extraocular muscles produces varying degrees of diplopia, which may be vertical, horizontal, or diagonal. Upwards of twenty percent will remain with weakness limited to these muscle, so-called ocular myasthenia [3–5].

Generalized weakness involves all skeletal muscles to varying degrees of severity with a distinct subgroup of patients having clinical weakness isolated to the bulbar muscles, producing dysphagia and dysarthria. Facial muscle weakness occurs compromising emotional expression producing a dour appearance. Obicularis oculi weakness impairs eye closure and is often present among patients with purely ocular myasthenia. Limb muscles are affected in a predominantly proximal pattern, with arms more often affected than legs. Neck extension weakness occurs, which may be so severe as to compromise the airway and swallowing [6, 7]. At times remarkably, focal weakness of neck, respiratory, or limb muscles may occur leading to confusion with peripheral nerve injury [2, 8] Patients with MuSK antibodies tend to have a preponderance of bulbar manifestations and individuals with long-standing disease develop muscle atrophy [9]. Fatiguing weakness often is less prominent and the course may mimic a progressive myopathy [10].

3. Diagnosis

Once the clinical presentation is recognized as consistent with MG, there are "bedside" tests that can be performed to assist in confirmation of the diagnosis. The classic edrophonium test involves administration of the acetylcholinesterase inhibitor and monitoring for objective improvement in a weak muscle, usually an ocular muscle. The sensitivity of the test is upwards of ninety percent but false positives do occur [11]. The ice pack test employs the principle of improved neuromuscular transmission at low muscle temperatures and is used to externally cool the levator palpebrea with observation of improved lid elevation. The test is helpful when unequivocally positive, but the predictive value of the test has been poorly defined [11].

Serologic testing is of critical importance for diagnosis. 74 to 88 percent of generalized MG patients will be positive for AChR antibodies, while at most 50–60 percent of ocular MG patients are seropositive [12]. The most sensitive and specific AChR antibody is the binding antibody assay which is a radioimmunoassay that uses human AChR. The modulating and blocking antibodies are of limited diagnostic value. MuSK-Ab are present in 38–50% of those testing negative for AChR-antibodies and are uncommon in ocular MG [10]. As will be described, autoantibodies to low density lipoprotein receptor-related protein (LRP)-4 are detected in some patients without antibodies to the other autoantigens and account for two to three percent of patients. Such patients appear to have a similar phenotype to AChR-positive patients.[13] Upwards of eight percent of patients with MG will not have detectable autoantibodies.

Electrodiagnostic studies assist in differentiation from other conditions and confirmation of the clinical diagnosis in those patients have no identified autoantibodies. Repetitive nerve stimulation leading to a decremental response in the compound muscle action potential is observed in at most 75 percent of patients [14]. Single-fiber electromyography, which involves recording of action potentials activated at single muscle fibers, may identify asynchronous activation of potentials (jitter). Increased jitter is not specific for MG and may be observed in neuropathies and motor neuron diseases [11]; however, these usually can be easily distinguished on clinical grounds. When performed by experts, single-fiber electromyography is highly sensitive and may correlate with treatment response [15, 16]. However, the method is dependent on the skill of the performer and therefore, published reports of its sensitivity of 99% are not likely to be generalize to common clinical practice and a normal single fiber exam does not rule out MG [17, 18].

4. Pathophysiology

In 1973 Patrick and Lindstrom identified the skeletal muscle acetylcholine receptor AChR as the likely autoantigen causing MG [19]. After their publication, supportive work rapidly demonstrated MG fulfilled strict criteria for autoimmunity [20]. 1) Antibody is present at the site of pathology, the neuromuscular junction. 2) AChR antibody from patients when injected into experimental animals will induce disease. 3) Immunization of animals with purified AChR will produce manifestations similar to the human disease and 4) plasma exchange, which removes AChR antibodies, improves patient symptoms. In 2001 the muscle

specific kinase (MuSK) was identified as another autoantigen for patients [21], who had no detectable antibodies towards the AChR and since then MuSK-associated MG has fulfilled criteria for autoimmunity. Recently, antibodies towards the lipoprotein receptor like protein-4 (LRP4) have been found in patients with MG, but thus far their pathogenicity has not been unequivocally established. Still a significant minority of patients do not have detectable circulating autoantibodies [13, 22–24]. Using cell-based assays which present the complex pentameric, membrane bound AChR in a more native state, AChR antibodies can be found among seronegative patients [25]. Antibodies directed against several other muscle proteins have been identified, including cortactin, agrin. potassium channels, and the ryanodine receptor [26–28]. Some of these patients do not have other autoantibodies, but in others multiple autoantibodies may be detected. The following sections will discuss the basis of the neuromuscular transmission defect, the autoantibodies producing this defect, and the cellular autoimmune mechanisms involved in disease generation. Each of these areas are targets for therapy.

4.1 Neuromuscular transmission defect

Regardless of the autoantibody type the underlying physiological abnormality leading to skeletal muscle weakness is the reduction of the safety factor for neuromuscular transmission [29, 30]. The safety factor is the difference in the endplate potential and the threshold potential required to generate an action potential, which will then trigger contraction of the muscle fiber. Whether there are AChR, MuSK, or no other autoantibody presently detected, the reduction of AChR is the primary contributor to a reduced endplate potential. Loss of synaptic folds and post-synaptic sodium channels serve to reduce the safety factor further. This tenuous situation of low safety factors among neuromuscular junctions across all skeletal muscle in a patient leads to the variability in weakness depending on the level of activity, degree of damage, temperature, and unknown factors produces the characteristic fatigable weakness that patients experience. Repetitive neuronal activity leads to a small reduction in release of acetylcholine, which under normal conditions is unimportant, but at the myasthenic junction can reduce the endplate potential that is required for action potential generation with consequent reduced muscle force generation and weakness. The basal lamina of the synaptic cleft is concentrated with acetylcholinesterase (AChE), which serves to terminate the activity of acetylcholine released from the presynaptic nerve terminal. AChE inhibition increases the available acetylcholine for binding to the AChR thereby increasing the endplate potential and improving a compromise of the safety factor.

4.2 Autoantibodies in MG

Antibodies to the skeletal muscle nicotinic AChR are the most commonly identified autoantibodies among MG patients. The AChR consists of five homologous subunits two α and single β, ε and δ in adults with a γ subunit replacing the ε-subunit in fetal mammalian tissue and at some neuromuscular junctions of extraocular muscle [31–33]. Antibodies may be directed against any of the subunits but a main immunogenic region is present on the α-subunit where the majority of pathogenic antibodies bind [31, 34]. AChR antibodies, primarily of the IgG1 and IgG3 subclass, are polyclonal IgGs pathogenic through three mechanisms. First, AChR antibodies activate the complement cascade leading to injury of

the post-synaptic muscle surface. Complement-mediated injury of the post-synaptic surface is likely the primary mechanism of injury [35–37]. Second, the divalent AChR antibodies crosslink the tightly packed AChRs resulting in enhanced endocytosis and subsequent degradation [38, 39]. This process is referred to as antigenic modulation. Third, AChR antibodies may inhibit activation of the AChR through blocking of the ACh binding site or inhibition of ion channel opening [40, 41]. There is little correlation between serum AChR antibodies concentration and clinical severity [42, 43]. This is likely due to variations in binding affinity, specific location of binding, and IgG subclass.

Antibodies towards MuSK have been demonstrated to be pathogenic through cell culture systems, passive transfer, and active immunization [44, 45]. MuSK is involved in agrin-induced clustering of AChR at the NMJ to promote efficient neuromuscular transmission [46]. In contrast to AChR antibodies, MuSK antibodies primarily belong to the IgG4 subclass, which cannot activate complement, but rather directly bind to the extracellular N-terminal Ig-like domains of the MuSK. This binding interferes with MuSK signaling to induce AChR clustering and ultimately leads to a deficiency of AChR on the post-synaptic surface [47–49].

LRP4 antibodies are primarily reported in MG patients without AChR or MuSK antibodies [13]; however this is not always the case and patients with amyotrophic lateral sclerosis have also been identified with LRP4 antibodies [50]. Antibodies to LRP4 are predominantly IgG1 and appear to induce weakness by disrupting the interaction between LRP4-agrin signaling and by complement-activation [51]. Antibodies to LRP-4 have been detected in about 18% of patients without AChR and MuSK antibodies in a large multicenter analysis from Europe [13], while a study from China indicated a frequency of 4% [52]. At present the LRP-4 antibodies have not been fully validated as pathogenic.

Other autoantibodies target skeletal muscle proteins, including agrin, collagen Q, cortactin, titin, the ryanodine receptor (RyR) and the voltage-gated potassium channel Kv1.4 [26, 53] but their pathogenicity is not well-established. Serum from some patients with no detectable circulating antibodies may induce transmission defects, when injected into mice [54]. This suggest that antibody-mediated disease mechanisms are also in play in these MG patients.

4.3 Thymus pathology

Abnormalities of the thymus are often found in MG patients and correlate with clinical subtypes with circulating AChR antibody [55, 56]. Early-onset MG (EOMG) has a poorly characterized age cut-off. Late onset MG (LOMG) patients are more commonly men with thymic atrophy. About 10% of patients have a thymoma and more commonly are men. Normal thymus is responsible for the differentiation of T cells and the establishment of central tolerance [57]. In the thymic cortex immature CD4+/8+ T cells interact with major histocompatibility complex (MHC) molecules displayed on thymic epithelial cells (TEC) via T cell receptors (TCRs). Through the process of positive selection, only a small number of T cells survive for the further differentiation through TCR interactions with MHC molecules [58]. In the thymic medulla, negative selection occurs with apoptosis of thymocytes through high affinity interactions between TCR and MHC. Medullary TEC express tissue-specific antigens under the control of the autoimmune regulator (AIRE) to present to T cells [58, 59].

Dysregulation of positive and negative selection has the consequence of producing an immune response towards the AChR and other skeletal muscle proteins including the titin and ryanodine receptor which are expressed on TECs [53].

4.3.1 Thymoma—In approximately ten percent of patients with MG a paraneoplastic process occurs related to an underlying thymoma, a neoplasm of the TEC [60]. Most thymomas retain the ability to generate and positively select T cells that preferentially recognize AChR and other muscle antigens. Positive selection is likely supported by a deficiency of the autoimmune regulator AIRE, which is observed in the majority of thymomas. The loss of AIRE expression would lead to inappropriate expression of self-antigen [61]. Negative selection of autoreactive T cells and generation of regulatory T cells is also impaired. Neoplastic epithelial cells contain muscle-specific antigens and can present these peptides to T cells in the thymoma leading to the production of autoreactive T cells, specific for muscle-specific antigens [62, 63]. These can then be exported to the periphery where they are maintained through unknown mechanisms. Once triggered by the tumor, the autoimmune reaction often persists despite removal of the tumor and surrounding thymus [64].

4.3.2 Thymic follicular hyperplasia—Lymphoid follicular hyperplasia with germinal centers is the hallmark pathology observed in EOMG patients [65]. The perivascular spaces are swollen with lymphoid tissue that resembles peripheral immune organs; and active germinal centers are present, similar to the secondary lymph follicles of peripheral lymph nodes. The thymus expresses AChR-like proteins and contains antigen presenting cells. Hyperplastic MG thymus contains significant numbers of mature immune cells including anti-AChR T and B cells, which are capable of mounting a pathogenic AChR antibody response. An inflammatory response resulting from infection in the thymus could cause professional antigen presenting cells to present epitopes derived from the thymus AChR-like proteins. This would activate potentially autoreactive anti-AChR T cells and initiate the autoimmune reaction of MG [66–69]. Several cytokines, including CXCL12, CCL17, CCL21, CXCL13, APRIL and BAFF, are over expressed in the hyperplastic thymus [70, 71]. These cytokines support recruitment of B-cells and dendritic cells to the thymus. Interferon (IFN)-β is overexpressed in MG thymuses. IFN-β might play central role in the pathophysiology of EOMG by triggering the overexpression of α-AChR, inducing thymic dendritic cell autosensitization [72], the abnormal recruitment of peripheral cells, and GC formation. The trigger for thymic inflammation is not known.

4.3.3 Atrophic thymus—The thymus is usually found to be atrophic in LOMG. Morphometric analysis does not reveal significant differences between LOMG and normal thymus from age matched controls. The epithelial cells are steadily substituted with fat over time and the number of myoid cells and AIRE positive cells decline with age [55]. A diversity of autoantibodies, including anti-titin and anti-RyR, are found in the circulation of LOMG patients [73]. The pathogenesis of LOMG and thymoma-associated MG share similarities in the clinical preponderance of men and autoantibodies to several skeletal muscle proteins [68].

4.4 Defects of immune system

MG is a T cell-dependent, B cell-mediated autoimmune disorder [20, 74]. When naive B cells react with the antigens and receive the help of CD4+T-cell in lymph nodes, they differentiate into memory B cells, antibody-secreting short-lived plasmablasts and long-lived plasma cells [74]. AChR autobody-producing B cells can be found in thymus, circulation, lymph nodes and bone marrow. As discussed above, immune-cell infiltrates and ectopic germinal centers are found in the thymus of EOMG patients, but in MuSK MG this pathology is rarely observed suggesting MuSK antibody generation occurs primarily outside the thymus [75]. Regulatory B cells (Bregs) are a rare B-cell subset, which promote immune tolerance [76]. The frequency of B10 cells (B cells that produce Il-10 and moderate inflammation) in AChR and MuSK MG is lower than in healthy controls, which is consistent with MG patients having impaired immune tolerance [77].

The production of autoantibodies in AChR MG requires the support of CD4+ T cells which have T helper (Th) lymphocyte function. They secrete inflammatory cytokines to induce autoimmune reactions to self-antigen and activate B-cells [78]. In MG patients there are several abnormalities in T cells subsets. AChR MG had higher frequency of AChR-specific Th1 and Th17 cells with increased production of interferon (IFN) γ and IL-17 [79]. The critical role of IL-17 secreting Th17 cells in MG pathogenesis has been confirmed in AChR induced EAMG [80]. CD4+CD25+ forkhead box P3 (FoxP3)+ regulatory T (Treg) cells control the immune response through inhibition of autoreactive T lymphocytes. Thymic and peripheral Treg quantitative defects are reported in MG patients compared with healthy controls [81, 82]. Follicular Th (Tfh) cells that promote B-cell maturation and Ab production in germinal centers, and their counterpart of follicular Treg (Tfr) cells with suppressive function, have been investigated in MG patients. MG patients have high ratios of Tfh /Tfr cells and lower frequency of Tfr cells, which indicates that there are immune tolerance failure in MG [83].

A balance of apoptosis and cell proliferation plays an important role in the development and homeostasis of the immune system and emerging evidence indicates apoptotic elimination of autoreactive immune cells is defective in many autoimmune disorders[84],[85, 86] Autoimmunity and cancer share several features: uncontrolled replication of “misprogrammed” cells, the inability of these pathological cells to undergo cell death, a breakdown in normal control mechanisms, and abnormal cell migration. Expression of anti-apoptotic factors is common among many forms of cancer and is associated with resistance to treatment. They also influence nuclear factor kappa B transcription factors and therefore provide a link to inflammation and possibly autoimmunity. The continued expression of autoreactive lymphocytes in the thymus or circulation of patients with MG may be supported by the expression of anti-apoptotic factors [87–89].

5. Standard treatments

From the description of the pathology of MG, there are several points that would be logical to target treatment. The following sections discuss presently used therapies and their disadvantages (Table 2). Several groups have established guidelines for treatment of patients, which will not be discussed in this review [90–92].

5.1 Acetylcholinesterase (AChE) inhibitors

AChE inhibitors (pyridostigmine bromide) retard the hydrolysis of acetylcholine at the neuromuscular junction and thereby increase the chance of activation of existing AChRs at the damaged myasthenic junction. For mild to moderate weakness, these are usually the initial treatment [93, 94] and for rare patients cholinesterase inhibitor therapy may be the only therapy required [93]. Often when immunotherapies are optimized AChE inhibitors may be discontinued and can be restarted, if symptoms develop again. Adverse effects, in particular nausea, bloating, and diarrhea, limit the use of AChE inhibitors. Excessive sweating is a common complaint of some patients. Respiratory secretions may be increased, which complicates treatment of patients with pulmonary diseases and may actually worsen breathing.

5.2 Thymectomy

Removal of the thymus has been a treatment for MG since the middle of the last century, but only recently was thymectomy found in a randomized, controlled trial to reduce corticosteroid dose over time, particularly the first six months of surgery, and limit weakness for patients with AChR antibodies between the ages of 18 and 65 [95]. Removal of the thymus reduces AChR antibody levels, but not to zero, and thymectomy is usually not considered a cure [96]. Therefore, there continues to be a stimulus for autoantibody after thymectomy. Similarly, in thymoma-associated MG, the removal of the tumor and surrounding thymus does not lead to remission, but removal of the tumor and surrounding thymus is required as a treatment. There is insufficient evidence to determine whether MuSK antibody and seronegative patients benefit from thymectomy, but the procedure is not commonly performed on this population [75, 97].

5.3 Corticosteroids

High doses of oral corticosteroids given for months followed by low doses often for years are the first-line immunotherapy recommended for patients who experience functionally limiting ocular or generalized weakness and cannot be adequately improved by AChE inhibitors [98–101]. Corticosteroids are the most effective treatment for MG but are compromised by numerous adverse effects. The optimal dosing of corticosteroids is not known, and expert opinion and investigations vary considerably [73]. International consensus guidelines provide options that either begin with a high dose or a low dose escalating to a high dose [92]. Each followed by slow tapers. Also, there is a possibly up to 30 percent of patients being poorly responsive to corticosteroids based on a lack of improvement or intolerance [102–104]. Treatment resistance is likely to be more a function of individual differences in corticosteroid responsiveness than severity of disease per see [103–106]. Corticosteroids impact autoimmune mechanisms in several ways. Corticosteroids act by binding the glucocorticoid receptor and thereby influence transcription of a number of pathways that ultimately suppress autoimmune responses by glucocorticoid receptor-mediated apoptosis of autoreactive cells and suppression of proinflammatory cytokines [107]. Lymphocytes vary in their susceptibility to corticosteroid induced apoptosis and therefore treatment-resistance is not only dependent on severity of disease but the host's

sensitivity to treatment. Polymorphisms in the glucocorticoid receptor gene are associated with differential response to glucocorticoid treatment of patients with MG [104].

5.4 Azathioprine

Azathioprine (AZA) was the first immunosuppressive used for MG either alone or as an agent to limit corticosteroid use [108]. A single, randomized trial indicated that efficacy takes 12–18 months as assessed by a reduction of corticosteroid requirement [109]. Purine synthesis is inhibited by azathioprine leading to inhibition of rapidly dividing cells, including lymphocytes involved in the autoimmune response [110, 111]. An increased risk of neoplasm, particularly lymphoma, has been observed among patients with long term use of azathioprinl [112, 113]. Azathioprine has the potential for significant hepatotoxicity and myelosuppression [114]. A consensus guideline has judged azathioprine not to have significant teratogenic potential [115]. Assessment for thiopurine S-methyltransferase enzyme activity prior to initiation of azathioprine therapy may identify patients at risk for severe reactions.

5.5 Mycophenolate mofetil

Although small, retrospective studies suggested that mycophenolate reduces severity of MG, [116–119] two large, randomized, controlled studies failed to meet their primary outcome measures [120, 121]. However, each were compromised by their short duration [122]. Mycophenolate selectively inhibits proliferation of T and B lymphocytes, which exclusively use the de novo pathway for purine synthesis [123]. The depletion of autoreactive lymphocytes would be expected to take several months. Mycophenolate is well-tolerated, although significant leukopenia may occur and rarely severe infections including progressive multi-focal leukoencephalopathy may develop [124]. Mycophenolate is a teratogen [125] and may increase the risk of malignancy [126–128]

5.6 Tacrolimus

Tacrolimus is a macrolide similar in action to cyclosporine, which has been used for MG but has a milder nephrotoxic profile, and is used for corticosteroid sparing [129–131]. One study showed that prednisone was withdrawn in 95% of patients with pharmacologic remission or complete remission achieved by >85% of patients [132]. Tacrolimus is calcineurin inhibitor which provides an immunosuppressive effect by modulation of T cell activity and support of antibody production in B cells. It may also enhance T regulatory cell function. Tacrolimus also enhances muscle contraction rapidly by modulation of intracellular calcium-release channels, thereby providing a rapid onset of improvement in some patient. Adverse effects include hyperglycemia and hypomagnesemia. Tremor and paresthesias may also occur and generally resolve after dose adjustment.

5.7 Cyclosporine

Cyclosporine has been used alone or as a steroid-sparing agent since the 1980s for patients with treatment-resistant disease [133–136] but has significant downside of renal toxicity and hypertension with five percent of patients unable to tolerate the medication in one study [134]. Cyclosporine increases risk of osteoporosis [137]. Monitoring trough levels and

creatinine must be performed to limit toxicity. The primary adverse effects of cyclosporine are renal insufficiency and hypertension. Cyclosporine has many drug interactions, which may reduce or elevate serum levels of cyclosporine. Cyclosporine is a highly specific inhibitor of T cell activation [131, 138]. Cyclosporine inhibits the phosphatase activity of calcineurin leading to modulation of the nuclear factor of activated T cell transcription factor. Also, cyclosporine blocks the activation of JNK and p38 signaling pathways, which are triggered by antigen recognition.

5.8 Methotrexate

Methotrexate inhibits de novo pyrimidine and purine syntheses necessary for DNA and RNA syntheses, and would therefore would inhibit cellular proliferation of autoreactive lymphocytes. [139]. A randomized, controlled trial of methotrexate did not find a steroid-sparing effect after 1 year of treatment [140], while a single-blind comparison study against azathioprine found both drugs to have similar steroid-sparing effects [141]. As a relatively inexpensive generic drug, methotrexate may be considered as an option for treatment. Methotrexate has significant adverse effects of hepatoxicity and anemia. Most patients develop hair loss, which is reversible.

5.9 Cyclophosphamide

Intravenous and oral cyclophosphamide has been used for treatment-resistant patients and one study found half of patients at one year to be asymptomatic [136, 142]. High-dose cyclophosphamide alone is not myeloablative, which allows a patient's endogenous stem cells to repopulate the hematopoietic/immune systems. Such an approach has been applied to patients with treatment-resistant autoimmune diseases, including MG [143]. Autologous hematopoietic stem cell transplantation has been used in combination with cyclophosphamide in a limited number of patients [144]. Cyclophosphamide therapy may have severe complications including alopecia, diarrhea, nausea, vomiting, and hemorrhagic cystitis. The drug has carcinogenic, teratogenic potential, and a likelihood of producing infertility. Rarely, interstitial pneumonitis and hepatic injury occur. Cyclophosphamide inhibits lymphocyte replication but also has more broader immunomodulatory effects including modulation of Th2/Th1 ratios, altered cytokine production, and enhanced proliferation and survival of certain lymphocyte populations, and modulation of dendritic cell activity [145].

5.10 Intravenous Immunoglobulin (IVIG)

IVIG is used in the setting of life-threatening weakness or manifestations that significantly compromise activities of daily living. IVIG may be administered at total dose of 2 grams per kg over 2–5 days [146, 147]. IVIG has also been used as a maintenance therapy to limit prolonged corticosteroid use while other immunosuppressive agents are initiated. IVIG presumably has multiple mechanisms of action in autoimmune MG. IVIG causes inhibition of cytokines, competition with autoantibodies, inhibition of complement deposition, interference with Fc receptor binding on macrophages or binding of immunoglobulins on B cells, and interference with antigen recognition by sensitized T cells [147]. Response to IVIG therapy may be seen within days of initiation but on average at three weeks. When compared to plasma exchange, IVIG therapy may have fewer complications and similar

overall efficacy [146, 148, 149]. Headache including severe migraine, occurs in a large minority of patients at the time of infusion or days after; chills, myalgia, or chest discomfort may also occur. Flu-like symptoms, urticarial, and petechiae may occur within days of treatment and resolve over weeks to months. Pre-treatment with diphenhydramine and acetaminophen may limit some of these reactions. Rare anaphylactic reactions are noted in patient with IgA deficiency. Rarely, deep venous thrombosis, pulmonary emboli, cerebral infraction or myocardial infarction may occur [150].

5.11 Plasma exchange

Plasma exchange was identified as an effective acute treatment for severe MG in 1976 and often produces rapid improvement in severe weakness. Indications include myasthenic crisis and optimization of muscle function prior to surgery, including thymectomy [148, 151, 152]. Plasma exchange is done three times per week for up to six exchanges, with limited evidence for benefit with more exchanges. The exchange is performed with resins that remove proteins of certain molecular weights, particularly aimed at removal of circulating antibodies [149]. Benefit may be seen within hours but typically over days. Plasma exchange may be used as a chronic therapy in rare patients. However, plasma exchange is limited by its restriction to major medical centers and frequent need for large bore intravenous catheters. Adverse reactions include rebound symptoms in weeks following initial exchanges, which may be mitigated with the use of concomitant immunosuppressive treatments. During the exchanges paresthesia may occur. Hypotension, nausea and vomiting may occur due to fluid shifts and electrolyte alterations during plasma exchange. The most significant complications are infections and thrombotic complications related to need for intravenous catheters. The risk of exchange may be decreased by use of peripheral catheters, which is possible in upwards of 75 percent of patients [152].

5.12 Eculizumab

Eculizumab is a monoclonal antibody directed against the C5 component of complement. Preclinical testing found it to be highly effective for moderation of experimental MG in rodents [153] and its efficacy confirmed in a phase 3 trial for AChR antibody positive patients who had failed immunosuppressive treatment [154]. The Food and Drug Administration of the United States approved its use for AChR antibody positive, generalized MG in 2017. The authors expect eculizumab will be used for treatment resistant patients and possibly as acute management of severe disease. It is important to appreciate that eculizumab should only be used for AChR antibody positive patients because complement activation is the primary driver of neuromuscular junction injury. Despite the potential risk of infection with capsulated bacterium particularly meningococcus, with appropriate pre-treatment vaccination, eculizumab thus far has shown good safety and tolerability [155, 156]. A deficiency of eculizumab is its inactivity among patients with a genetic variant of the C5 epitope to which it binds [157, 158], and its general complement inhibition in an immunosuppressed population. Also, eculizumab is an extremely expensive drug, which will likely cost several hundred thousand dollars per year in the United States for care of MG patients.

6. Therapies under development

As should be appreciated from the discussion thus far, current therapeutics for MG do not cure the disease, most are non-specific, and all have the potential for significant adverse effects. Although great advances have been made in understanding of disease pathogenesis and in therapy, more than a third of patients experience MG exacerbations, which require hospitalization, and disease- and treatment-related morbidity remains high. Non-immunosuppressive treatments often do not completely relieve symptoms, and immune system targeted treatments have poor side effect profiles with variable benefit. There is also a concern for increased frequency of neoplasia for several of the drugs. Although mortality of MG patients has improved over the decades, MG remains a disease with high morbidity and at times, mortality. From the description of standard therapies, it should be appreciated that there is great unmet need. Presently, no investigators are claiming a cure may be at hand, but therapeutic development is focused on moderating symptom severity or reduction of corticosteroid dose. More rationale targeting of MG specific pathology is needed. Below we describe therapies that are in pre-clinical or early phase clinical trials.

6.1 Enhanced muscle contraction

The oldest effective treatment for MG is inhibition of ChE. No fundamental change in this approach has occurred in over eight decades. A potentially promising treatment was assessed in Phase 1b open-label trial with oral EN101 with patient reported and objective measures showing improvement [159]. Additionally, improvement was maintained for greater than 24 hours, which would be a great improvement over pyridostigmine. EN101 is an antisense oligodeoxynucleotide that acts at the mRNA level and selectively reduces the enzymatic isoform of AChE-R, which is generated with injury to the NMJ produced by MG [160, 161]. Despite its promise no commercial interests have moved development forward. There is some interest in improving pyridostigmine by limiting its adverse effect profile or improving the pharmacokinetic profile, but none have moved to phase 2 development. Also, a potassium channel inhibitor, amifampridine phosphate, is under Phase 3 evaluation. The agent appears to improve acetylcholine release and muscle contraction. Tirasemtiv is a troponin activator, which enhances the force generation of muscle contraction, is in Phase 2 assessment. The question is whether these latter two compounds will be significant improvements compared to cholinesterase inhibitors.

6.2 Moderation of autoantibody levels

Several approaches have been taken to remove pathogenic antibody. In order to improve conventional plasma exchange, protein A based absorption to bind immunoglobulin, and thereby limit removal of other plasma proteins have been evaluated [162–164]. Unfortunately, trials have failed to find improved safety or efficacy [165]. Resins with bound AChR or peptides with the extracellular domains of the AChR subunits have been constructed and assessed in preclinical studies. The expectation is such resins would enhance efficacy of plasma exchange [166–168].

Another antibody specific approach involves enhancement of IgG removal from circulation. Normally, IgG molecules moving through the circulation undergo endocytosis by endothelial

cells and the endocytosed IgG interacts with the neonatal Fc receptor (FcRn), which are then returned to the circulation but with a significantly extended half-life [169, 170]. Neonatal Fc receptor (FcRn) monoclonal antibodies are currently in clinical trials in MG and other autoimmune diseases (Table 3). The disruption of FcRn-IgG interaction results in IgG catabolism and lowering of serum IgG levels. The expectation is that such an approach would be used in a similar fashion as plasma exchange or IV IG for significant exacerbations or potentially as a maintenance therapy by chronically maintaining IgG levels (and presumably autoantibodies) below a threshold associated with clinical symptoms.

6.3 Complement inhibition

With eculizumab validating complement inhibition as a therapy for AChR-positive MG, interest has increased in improving the approach and efficacy of complement targeted therapeutics [36, 37, 171, 172]. RA101495 is a small molecule inhibitor of C5 that is administered as a daily subcutaneous injection is in phase 2 testing (NCT03315130). Akari Pharmaceuticals has a small recombinant protein (Coversin), which has been used successfully for treatment of paroxysmal nocturnal hemaglobinuria and is being contemplated for use in MG after successful preclinical evaluation [173, 174]. Alnylam Pharmaceuticals has developed small interfering RNAs to suppress the synthesis of liver-derived C5, which have moderated severity of animal models of MG (unpublished data HK and Alnylam Pharmaceuticals). Preclinical studies of C1q and Factor B inhibition have shown some efficacy but have yet to move to human studies [175, 176]

Thus far all the emerging treatments discussed do not address the underlying processes that generate pathogenic antibody. The following sections discuss approaches that attempt to reestablish tolerance, eliminate key pathogenic cells, or moderate signaling molecules.

6.4 Induction of tolerance [177]

The first attempts to induce tolerance involved administration of denatured *Torpedo* AChR, which reduced severity of EAMG in rabbits and rodents.[178–181] However, the use of *Torpedo* AChR is compromised by its immunogenicity and quantity required. Recently, bacterially-expressed human AChR cytoplasmic domains have been successful in reversing established weakness in animal models [182, 183]. These experiments found that AChR antibody production continues to be produced but is directed primarily towards cytoplasmic domains, which are not pathogenic. Presently, there are no clinical trials planned to assess this approach. If successful, such a treatment has the potential to be curative.

A phase 1b study in patient with MG is ongoing with CV-MG-101. CV-MG01 is a combination of two synthetic peptides designed to complement the structure of the main immunogenic region of the AChR. The expectation is that the administration of exogenous peptide will induce anti-idiotype and anti-clonotypic responses against binding sites of antigen receptors on autoreactive lymphocytes. This will then reduce AChR-specific T cell help and anergize autoreactive B cells [184–186]. A vaccination with the peptide in dogs with spontaneously occurring MG reduced weakness and antibodies more rapidly to historical controls [187]. However, canine MG has high rates of spontaneous remissions limiting firm conclusions to be drawn about efficacy [188].

6.5 Cytokine targeted therapies

Dysregulated cytokine signaling is observed in MG and despite cytokine inhibitors in therapeutic development, there has been limited application to MG. Patients have increased numbers of transcripts of tumour necrosis factor alfa (TNF-α) expressing mononuclear cells in the blood compared to normal individuals and T cells from MG patients have significantly greater TNF-α receptors [189, 190]. TNF-α is involved in the generation of AChR-specific T and B cell responses during the development of EAMG and etanercept, a TNF-receptor blocker, can suppress established EAMG without inducing significant immunosuppression [191]. In a small group of patients, etanercept, reduced steroid requirements [192, 193]. However, there are case reports suggesting TNF-α agents may exacerbate MG and therapeutic development has not been pursued [194].

In MG patients, B cell activating factor (BAFF) cytokine levels are increased in the serum, while expression of BAFF and its receptors have been identified in MG thymus [195–197]. BAFF promotes the survival, growth, and maturation of B-cells, including autoreactive B-cells and rescue B-cells from apoptosis [198]. Associations have been found between EOMG and BAFF gene polymorphisms [199]. Using a conjugate of BAFF receptor specific-monoclonal antibody and short interference RNA, EAMG was treated with a high-dose regimen, which resulted in accumulation of Fas expressing CD19+/B220+ cells and concurrent expression of type 1 interferon in lymph nodes. In contrast a low-dose of conjugate did not induce FAS expression but caused marked BAFF receptor deficiency in lymph nodes that was associated with improved MG manifestations. Surprisingly, despite inhibition of BAFF receptor in PBMCs the treatment did not reduce the AChR antibody titer. The results indicate a dose-dependent, immunomodulatory distant effect resulting from BAFF receptor specific mAb-siRNA conjugate treatment of EAMG [200]. A clinical trial has been completed of belimumab, an antibody directed towards BAFF but results are yet to be published (NCT01480596).

6.6 Immune cell-targeted therapy

B cells are an obvious target for an MG therapeutic. Rituxan is a chimeric IgG1 monoclonal antibody that targets CD20 present on a large number of B cells and by activation of complement-mediated or antibody-dependent cell-mediated cytotoxicity eliminates CD20 positive cells [201]. Rituximab is now commonly used in clinical practice but is not approved by the US Federal Drug Administration for MG. A phase II trial for patients with AChR antibody-positive MG has been completed enrollment with results pending (NCT02110706). In MuSK antibody-positive patients, rituximab also reduces prednisone dose and induces withdrawal of concomitant immunosuppressants along with clinical improvement and significant decrease in the MuSK antibody titers [202].

Rituximab depletes CD20 positive B cells but does not affect autoantibody producing plasmablasts or plasma cells (see below) that do not express CD20. Thus, these cell subsets are not directly affected and the dramatic effects observed in some MG patients receiving rituximab is likely accounted for by either indirect modulation of plasma cell populations (i.e., cell signaling) or by depleting plasma cell precursors, such as activated B cells.

6.7 Plasma cell therapeutics

Elimination of plasma cells responsible for synthesis of autoantibodies would be expected to be a highly effective therapy [203]. The first therapy to become available is bortezomib [204]. Bortezomib is a proteasome inhibitor used for treatment of mantle cell lymphoma and multiple myeloma, which causes accumulation of nondegraded, misfolded proteins within plasma cells leading to apoptosis. Bortezomib treatment of EAMG animals reduces disease severity and *in vitro* studies of MG patient thymus cultures treated with bortezomib demonstrated plasma cell depletion [205]. In EAMG studies, reduced AChR antibody production, reduced postsynaptic muscle membrane damage, and clinical improvement have been observed [206]. Clinical trials of bortezomib to treat MG are currently underway and other proteasome inhibitors are under development for multiple myeloma and could be considered as a treatment for MG. Unfortunately, upwards of 35% of bortezomib treated patients with cancer develop a painful neuropathy [207]. This level and severity of toxicity would not be suitable for patients with MG who are otherwise relatively healthy and have many other treatment options. Next generation proteasome inhibitors are under development with the expectation that they will have fewer adverse effects [208]. Given the prime role of plasma cells in autoantibody production a therapeutic that selectively targets autoreactive plasma cells and overcomes the current limitations of existing therapies should be a focus for therapeutic development in MG.

The monoclonal antibody daratumumab targeting CD38 expressed on plasmablasts has been approved for treatment of refractory multiple myeloma offering another agent which may be effective for MG [209]. However, significant limitations are being identified. An effect of daratumumab observed in multiple myeloma patients is depletion of immune suppressive CD38 expressing regulatory T cells and expansion of helper and cytotoxic T cell populations [210]. Dysfunctional regulatory T cells and abnormal activation of T cell populations are present in MG and therefore daratumumab may exacerbate the disease [79, 211].

6.8 Targeting T cells

Despite the well appreciated role of T cells in the pathogenesis of MG there are limited therapeutics to modulate their activity. Strategies aimed at reducing T cell activation, improving regulatory T cell (Treg) function, and inhibiting stimulatory interactions between activated T cells and B cells hold promise for MG therapy.

Studies have demonstrated strong Th1 and Th17 cell involvement in both AChR and MuSK positive MG. Th17 cells represent a subset of CD4+ T cells characterized by the production of inflammatory cytokines interleukin-17 (IL-17) and IL-21 [212–215]. MG patients show upregulation of Th17 genes in PBMCs and increased peripheral IL-17A levels [216–218]. Increased frequencies of Th17 cells are found in MuSK+ MG patients compared with controls following polyclonal T cell stimulation and AChR antibody positive MG patients demonstrate a memory response with high IL-17 production [79, 219]. These findings strongly suggest that MG patients are primed for proinflammatory IL-17 responses. This makes Th17 a likely target for therapy. Multiple subcutaneously administered monoclonal antibodies are in development that target the inflammatory cytokine IL-17 or its receptor and may have applications to MG. The IL-17 receptor A is targeted by brodalumab and approved

for the treatment of adults with moderate to severe plaque psoriasis. Two approved monoclonal antibodies target the IL-17A cytokine itself. Ixekizumab is also moderate to severe plaque psoriasis, while secukinumab has additional indications for psoriatic arthritis and ankylosing spondylitis.

A pilot clinical trial is ongoing in MG (NCT03059888) with the fusion protein Abatacept, consisting of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and a modified Fc region of human immunoglobulin G1. It blocks the required co-stimulatory signal to activate T cells that is mediated by CD80/CD86 (also known as B7–1 and B7–2) on antigen presenting cells. Abatacept inhibits T cell activation, resulting in reduced levels of proinflammatory cytokines that are implicated in MG, such as TNF-α, interferon-γ, and IL-2. Abatacept has failed in clinical trials in multiple sclerosis and ulcerative colitis.

Monoclonal antibodies targeting the CD40 – CD40L interaction are currently in clinical testing in MG (NCT02565576). Antigen presenting cells, including B cells, macrophages and dendritic cells, constitutively express CD40 on their surface. Activated CD4+ T cells interact with CD40 through CD40L (CD154) leading to dendritic cell activation, production of proinflammatory cytokines, and enhanced humoral immune responses [220, 221] Studies in EAMG demonstrated clinical improvement in established disease following delivery of anti-CD40L monoclonal antibodies and a reduction in Th1 related inflammatory cytokines [222].

Multiple studies have shown regulatory T cell (Treg) dysfunction in both the thymus and periphery [211, 217, 223]. EAMG studies and a single case report in MG suggest that granulocyte-macrophage colony-stimulating factor (GM-CSF) can increase Treg frequencies and function and ameliorate disease [224–227]. Methods for selectively improving Treg function are currently under development, but are still several years away.

6.9 Stem cell transplant

Allogenic hematopoietic stem cell transplantation led to resolution of symptoms and discontinuation of all MG medications in one MG patient [228]. A case series of seven patients and a report of one patient treated with autologous haematopoietic stem cell transplantation (AHSCT) for MG found all patients achieved durable MGFA complete stable remission [144, 229]. Compared to allogenic HSCT, AHSCT does not require a compatible donor and does not result in graft-versus-host disease. Significant treatment related morbidity and mortality of AHSCT must be taken into account when considering this treatment. Nevertheless, based on these few reports, autologous hematopoietic stem cell transplantation can be an effective therapeutic option for carefully selected patients with severe, treatment refractory MG [229].

7. Expert Commentary

MG is a chronic, autoimmune neuromuscular disorder caused by antibodies directed towards proteins concentrated at the neuromuscular junction.

The characteristic clinical feature of MG is weakness which fatigues and may involve any voluntary muscle. The ocular muscle are preferentially involved leading to ptosis or diplopia in nearly all patients at some point in their illness.

Antibodies are primarily directed against the skeletal muscle AChR and a small population of patients with antibodies to MuSK. LRP-4 is likely a new antigenic target but has not been fully validated. AChR-antibodies induce injury of the neuromuscular junction primarily by activation of complement.

Regardless of autoantibody, a compromise of neuromuscular transmission occurs through the reduction of AChR on the post-synaptic surface leading to a compromised safety factor for neuromuscular transmission.

MG is a clinically and biologically heterogeneous condition with subgroups based on age of onset, autoantibody, thymic pathology, and disease severity. Thymic hyperplasia with germinal center formation is the hallmark pathology observed in AChR-antibody positive early-onset MG with women being predominantly effected. Approximately ten percent of patients have a thymoma, a tumor of thymic epithelial cells. Although removal of the tumor is required, it does not reduce the clinical severity of MG.

MG is a T cell-dependent, B cell-mediated autoimmune disorder. AChR autobody-producing B cells can be found in thymus, circulation, lymph nodes and bone marrow. MuSK MG this pathology is rarely observed suggesting MuSK antibody generation occurs primarily outside the thymus.

Thymectomy has been demonstrated by a randomized, evaluator-blinded clinical trial to reduce the severity and corticosteroid use of patients with AChR antibody positive patients with predominantly early-onset MG.

Cholinesterase inhibition and corticosteroids are the most common initial therapies and effective in the majority of patients.

Because of the significant adverse effects of corticosteroids and treatment resistance, many patients will require additional therapy the immunosuppressives, such as azathioprine, mycophenolate, or tacrolimus.

Eculizumab has been approved for use in Europe, Japan, and the United States for generalized, AChR-antibody positive MG.

Guidelines for treatment have been issued by a panel with international national representation as well as Japanese and British neurological associations.

Large pharmaceutical corporations, biotech companies, and academics in the last decade have taken an interest in development of agents that target specific mechanisms of MG disease pathology. These therapies range for enhancers of muscle contraction to reduction of circulating autoantibodies or autoreactive cells.

Thus far, there is no promising approach that will lead to a sustained return to tolerance to the autoantigen inciting the disease and there is limited understanding of the initial trigger, which produces MG.

8. Five-year view

A tremendous amount of late stage preclinical work and clinical trials at various stages is being done for MG. This is surprising given the slow pace of therapeutic development in the late 1900's and first decade of this century [108]. We suspect the reasons for this are a combination of its relatively well-defined pathophysiology, advances in understanding of autoimmunity, and financial advantages that exist for drug development for rare diseases. MG now has the advantage of a community of clinicians and scientists who have established strong collaborations and rigorous assessments for human trials [230]. A situation that was not present 20 years ago. All these forces will bring an explosion of data to drive further refinement of treatments. Since clinical trials are expensive and trial patients are few, a major concern for the field is how clinicians and drug developers will be able to prioritize their efforts to improve therapeutics. Leaders in MG, be they clinicians, scientists, patient advocacy, or the pharmaceutical industry will need to come to consensus as to how to expend limited resources.

Acknowledgments

Funding

This manuscript was supported by the Muscular Dystrophy Association (Grant No: 508240) and the National Institutes of Health (K23NS085049; HHSN27100001).

HJ Kaminski is supported by Muscular Dystrophy Association (Grant No: 508240), serves on the editorial board of Experimental Neurology, is co-editor of *Neuromuscular Disorders in Clinical Practice* and *Myasthenia Gravis and Related Disorders*. He has received monetary compensation for serving on data and safety monitoring committees for Novartis and NeuroNext. He consults for Alnylam, UCB Pharma, RA Pharmaceuticals, Momenta Therapeutics, and GT Biopharma. He has received research funding from the National Institutes of Health, the Myasthenia Gravis Foundation of Illinois, Akari Therapeutics, and the Neumann Professorship. He has patent US 8,961,981 issues. J Guptill receives research support from National Institute of Neurological Disorders and Stroke (K23NS085049; HHSN27100001), the Myasthenia Gravis Foundation of America, Ra Pharmaceuticals, Bioverativ and the Jose Antonio Grifols Lucas Foundation.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

1. Sonkar KK, Bhoi SK, Dubey D, et al. Direct and indirect cost of myasthenia gravis: A prospective study from a tertiary care teaching hospital in India. J Clin Neurosci 2017;38:114–17 [PubMed: 27887977]

2. Alshekhlee A, Miles JD, Katirji B, et al. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospitals. Neurology 2009;72:1548–1554 [PubMed: 19414721]

3•. Gilhus NE. Myasthenia Gravis. N Engl J Med 2017;376:e25

Excellent focused review of all aspects of the disease

4•. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. Muscle Nerve 2008;37:141–49

Large longitudinal study of MG patients

[PubMed: 18059039]

5. Mazzoli M, Ariatti A, Valzania F, et al. Factors affecting outcome in ocular myasthenia gravis. Int J Neurosci 2018;128:15–24 [PubMed: 28625092]

6. Sih M, Soliven B, Mathenia N, et al. Head-drop: A frequent feature of late-onset myasthenia gravis. Muscle Nerve 2017;56:441–44 [PubMed: 28000322]

7. Romano AE, Al-Qudah Z, Kaminski HJ, et al. Concurrent Paraspinous Myopathy and Myasthenia Gravis. J Clin Neuromuscul Dis 2017;18:218–22 [PubMed: 28538252]

8. Bershad EM, Feen ES, Suarez JI. Myasthenia gravis crisis. South Med J 2008;101:63–69 [PubMed: 18176295]

9•. Evoli A, Tonali PA, Padua L, et al. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. Brain 2003;126:2304–11

Describes unique phenotype of MuSK-antibody MG

[PubMed: 12821509]

10. Guptill JT, Sanders DB, Evoli A. Anti-MuSK antibody myasthenia gravis: clinical findings and response to treatment in two large cohorts. Muscle Nerve 2011;44:36–40 [PubMed: 21674519]

11. Benatar M A systematic review of diagnostic studies in myasthenia gravis. Neuromuscul Disord 2006;16:459–67 [PubMed: 16793269]

12. Phillips WD, Vincent A. Pathogenesis of myasthenia gravis: update on disease types, models, and mechanisms. F1000Res 2016;5

13•. Zisimopoulou P, Evangelakou P, Tzartos J, et al. A comprehensive analysis of the epidemiology and clinical characteristics of anti-LRP4 in myasthenia gravis. J Autoimmun 2014;52:139–45

Characterization of LRP-4 antibody related MG

[PubMed: 24373505]

14. Seybold ME. Diagnosis of myasthenia gravis In: Engel AG, ed. Myasthenia gravis and myasthenic disorders. New York: Oxford University Press, 1999: 146–66

15. Meriggioli MN, Rowin J. Single fiber EMG as an outcome measure in myasthenia gravis: results from a double-blind, placebo-controlled trial. J Clin Neurophysiol 2003;20:382–85 [PubMed: 14702000]

16. Juel VC, Sanders DB, Hobson-Webb LD, et al. Marked clinical and jitter improvement after eculizumab in refractory myasthenia. Muscle Nerve 2017;56:E16–E18 [PubMed: 28214342]

17. Benatar M, Hammad M, Doss-Riney H. Concentric-needle single-fiber electromyography for the diagnosis of myasthenia gravis. Muscle Nerve 2006;34:163–68 [PubMed: 16642500]

18. Stalberg E, Sanders DB, Kouyoumdjian JA. Pitfalls and errors in measuring jitter. Clin Neurophysiol 2017;128:2233–41 [PubMed: 29017138]

19••. Patrick J, Lindstrom J. Autoimmune response to acetylcholine receptor. Science 1973;180:871–72

Among the most important papers in the field

[PubMed: 4706680]

20. Le Panse R, Berrih-Aknin S. Autoimmune myasthenia gravis: autoantibody mechanisms and new developments on immune regulation. Curr Opin Neurol 2013;26:569–576 [PubMed: 23995274]

21•. Hoch W, McConville J, Helms S, et al. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. Nat Med 2001;7:365–68

Demonstrates MuSK as a new autoantigen

[PubMed: 11231638]

22•. Higuchi O, Hamuro J, Motomura M, Yamanashi Y. Autoantibodies to low-density lipoprotein receptor-related protein 4 in myasthenia gravis. Ann Neurol 2011;69:418–22

Suggest LRP-4 as a new autoantigen

[PubMed: 21387385]

23. Pevzner A, Schoser B, Peters K, et al. Anti-LRP4 autoantibodies in AChR- and MuSK-antibody-negative myasthenia gravis. J Neurol 2012;259:427–35 [PubMed: 21814823]

24. Zhang B, Tzartos JS, Belimezi M, et al. Autoantibodies to lipoprotein-related protein 4 in patients with double-seronegative myasthenia gravis. Arch Neurol 2012;69:445–51 [PubMed: 22158716]

25. Rodriguez Cruz PM, Al-Hajjar M, Huda S, et al. Clinical Features and Diagnostic Usefulness of Antibodies to Clustered Acetylcholine Receptors in the Diagnosis of Seronegative Myasthenia Gravis. JAMA Neurol 2015;72:642–9. [PubMed: 25894002]

26. Gilhus NE, Skeie GO, Romi F, et al. Myasthenia gravis - autoantibody characteristics and their implications for therapy. Nat Rev Neurol 2016;12:259–268 [PubMed: 27103470]

27. Cortes-Vicente E, Gallardo E, Martinez MA, et al. Clinical Characteristics of Patients With Double-Seronegative Myasthenia Gravis and Antibodies to Cortactin. JAMA Neurol 2016;73:1099–104 [PubMed: 27379450]

28. Gallardo E, Martinez-Hernandez E, Titulaer MJ, et al. Cortactin autoantibodies in myasthenia gravis. Autoimmun Rev 2014;13:1003–7 [PubMed: 25193850]

29. Verschuuren JJ, Palace J, Gilhus NE. Clinical aspects of myasthenia explained. Autoimmunity 2010;43:344–52 [PubMed: 20380587]

30. Lindstrom J Acetylcholine receptors and myasthenia. Muscle Nerve 2000;23:453–477. [PubMed: 10716755]

31. Luo J, Lindstrom J. Myasthenogenicity of the main immunogenic region and endogenous muscle nicotinic acetylcholine receptors. Autoimmunity 2011;45:245–52 [PubMed: 21950318]

32. Kaminski HJ, Kusner LL, Nash KV, Ruff RL. The gamma-subunit of the acetylcholine receptor is not expressed in the levator palpebrae superioris. Neurology 1995;45:516–18 [PubMed: 7898708]

33. Bouzat C, Sine SM. Nicotinic acetylcholine receptors at the single-channel level. Br J Pharmacol 2018;175:1789–1804 [PubMed: 28261794]

34. Kordas G, Lagoumintzis G, Sideris S, et al. Direct proof of the in vivo pathogenic role of the AChR autoantibodies from myasthenia gravis patients. PLoS One 2014;9:e108327 [PubMed: 25259739]

35. Engel AG, Lambert EH, Howard FM. Immune complexes (IgG and C3) at the motor end-plate in myasthenia gravis: ultrastructural and light microscopic localization and electrophysiologic correlations. Mayo Clin Proc 1977;52:267–80 [PubMed: 870771]

36. Kusner LL, Sengupta M, Kaminski HJ. Acetylcholine receptor antibody-mediated animal models of myasthenia gravis and the role of complement. Ann N Y Acad Sci 2018;1413:136–42

Summarizes research standards for preclinical MG studies

[PubMed: 29356015]

37•. Howard JF, Jr, Myasthenia gravis: the role of complement at the neuromuscular junction. Ann N Y Acad Sci 2018;1412:113–28

Nice review of complement mechanisms in MG

[PubMed: 29266249]

38. Loutrari H, Kokla A, Tzartos SJ. Passive transfer of experimental myasthenia gravis via antigenic modulation of acetylcholine receptor. Eur J Immunol 1992;22:2449–52 [PubMed: 1516631]

39. Drachman DB, Angus CW, Adams RN, Michelson JD, Hoffman GJ. Myasthenic antibodies cross-link acetylcholine receptors to accelerate degradation. N Engl J Med 1978;298:1116–22 [PubMed: 643030]

40. Gomez CM, Richman DP. Anti-acetylcholine receptor antibodies directed against the alpha-bungarotoxin binding site induce a unique form of experimental myasthenia. Proc Natl Acad Sci U S A 1983;80:4089–93 [PubMed: 6575398]

41. Hara H, Hayashi K, Ohta K, et al. Detection and characterization of blocking-type anti-acetylcholine receptor antibodies in sera from patients with myasthenia gravis. Clin Chem 1993;39:2053–57 [PubMed: 8403390]

42. Heldal AT, Eide GE, Romi F, et al. Repeated acetylcholine receptor antibody-concentrations and association to clinical myasthenia gravis development. PLoS One 2014;9:e114060 [PubMed: 25464006]

43. Sanders DB, Burns TM, Cutter GR, et al. Does change in AChR antibody level correlate with clinical change in MG? Muscle Nerve 2013;49:30–4 [PubMed: 23625360]

44. Punga AR, Lin S, Oliveri F, et al. Muscle-selective synaptic disassembly and reorganization in MuSK antibody positive MG mice. Exp Neurol 2011;230:207–217 [PubMed: 21565192]

45. Klooster R, Plomp JJ, Huijbers MG, et al. Muscle-specific kinase myasthenia gravis IgG4 autoantibodies cause severe neuromuscular junction dysfunction in mice. Brain 2012;135:1081–1101 [PubMed: 22396395]

46. Messeant J, Dobbertin A, Girard E, et al. MuSK frizzled-like domain is critical for mammalian neuromuscular junction formation and maintenance. J Neurosci 2015;35:4926–4941 [PubMed: 25810523]

47. Plomp JJ, Huijbers MG, van der Maarel SM, Verschuuren JJ. Pathogenic IgG4 subclass autoantibodies in MuSK myasthenia gravis. Ann N Y Acad Sci 2012;1275:114–22 [PubMed: 23278586]

48. Huijbers MG, Vink AF, Niks EH, et al. Longitudinal epitope mapping in MuSK myasthenia gravis: implications for disease severity. J Neuroimmunol 2016;291:82–8. [PubMed: 26857500]

49. Deymeer F, Gungor-Tuncer O, Yilmaz V, et al. Clinical comparison of anti-MuSK- vs anti-AChR-positive and seronegative myasthenia gravis. Neurology 2007;68:609–11. [PubMed: 17310034]

50. Tzartos JS, Zisimopoulou P, Rentzos M, et al. LRP4 antibodies in serum and CSF from amyotrophic lateral sclerosis patients. Ann Clin Transl Neurol 2014;1:80–7 [PubMed: 25356387]

51. Shen C, Lu Y, Zhang B, et al. Antibodies against low-density lipoprotein receptor-related protein 4 induce myasthenia gravis. J Clin Invest 2013;123:5190–5202 [PubMed: 24200689]

52. Li Y, Zhang Y, Cai G, et al. Anti-LRP4 autoantibodies in Chinese patients with myasthenia gravis. Muscle Nerve 2017;56:938–942 [PubMed: 28120340]

53. Romi F, Hong Y, Gilhus NE. Pathophysiology and immunological profile of myasthenia gravis and its subgroups. Curr Opin Immunol 2017;49:9–13 [PubMed: 28780294]

54. Leite MI, Jacob S, Viegas S, et al. IgG1 antibodies to acetylcholine receptors in 'seronegative' myasthenia gravis. Brain 2008;131:1940–1952 [PubMed: 18515870]

55. Marx A, Pfister F, Schalke B, Saruhan-Direskeneli G, Melms A, Strobel P. The different roles of the thymus in the pathogenesis of the various myasthenia gravis subtypes. Autoimmun Rev 2013;12:875–884 [PubMed: 23535159]

56•. Truffault F, de Montpreville V, Eymard B, Sharshar T, Le Panse R, Berrih-Aknin S. Thymic Germinal Centers and Corticosteroids in Myasthenia Gravis: an Immunopathological Study in 1035 Cases and a Critical Review. Clin Rev Allergy Immunol 2017;52:108–24

Extensive review of thymus pathology

[PubMed: 27273086]

57. Hogquist KA, Baldwin TA, Jameson SC. Central tolerance: learning self-control in the thymus. Nat Rev Immunol 2005;5:772–82 [PubMed: 16200080]

58. Klein L, Kyewski B, Allen PM, Hogquist KA. Positive and negative selection of the T cell repertoire: what thymocytes see (and don't see). Nat Rev Immunol 2014;14:377–91 [PubMed: 24830344]

59. Anderson MS, Venanzi ES, Klein L, et al. Projection of an immunological self shadow within the thymus by the aire protein. Science 2002;298:1395–1440 [PubMed: 12376594]

60. Fujii Y Thymus, thymoma and myasthenia gravis. Surg Today 2013;43:461–66 [PubMed: 22948665]

61. Strobel P, Murumagi A, Klein R, et al. Deficiency of the autoimmune regulator AIRE in thymomas is insufficient to elicit autoimmune polyendocrinopathy syndrome type 1 (APS-1). J Pathol 2007;211:563–71 [PubMed: 17334980]

62. Marx A, Porubsky S, Belharazem D, et al. Thymoma related myasthenia gravis in humans and potential animal models. Exp Neurol 2015;270:55–65 [PubMed: 25700911]
63. Marx A, Willcox N, Leite MI, et al. Thymoma and paraneoplastic myasthenia gravis. Autoimmunity 2010;43:413–427 [PubMed: 20380583]
64. Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol 2015;14:1023–36 [PubMed: 26376969]
65. Cron MA, Maillard S, Villegas J, et al. Thymus involvement in early-onset myasthenia gravis. Ann N Y Acad Sci 2018;1412:137–45 [PubMed: 29125185]
66. Conti-Fine BM, Milani M, Kaminski HJ. Myasthenia gravis: past, present, and future. J Clin Invest 2006;116:2843–54 [PubMed: 17080188]
67. Lang B, Vincent A. Autoimmune disorders of the neuromuscular junction. Curr Opin Pharmacol 2009;9:336–40 [PubMed: 19428298]
68. Willcox N, Leite MI, Kadota Y, et al. Autoimmunizing mechanisms in thymoma and thymus. Ann N Y Acad Sci 2008;1132:163–73 [PubMed: 18567866]
69. Conti-Fine BM, Diethelm-Okita B, Ostlie N, et al. Immunopathogenesis of myasthenia gravis In: Kaminski HJ, ed. Myasthenia and Related Disorders. New York: Humana Press, 2009: 43–70
70. Poea-Guyon S, Christadoss P, Le Panse R, et al. Effects of cytokines on acetylcholine receptor expression: implications for myasthenia gravis. J Immunol 2005;174:5941–49 [PubMed: 15879086]
71. Le Panse R, Bismuth J, Cizeron-Clairac G, et al. Thymic remodeling associated with hyperplasia in myasthenia gravis. Autoimmunity 2010;43:401–12 [PubMed: 20402580]
72. Cufi P, Dragin N, Ruhlmann N, et al. Central role of interferon-beta in thymic events leading to myasthenia gravis. J Autoimmun 2014;52:44–52 [PubMed: 24393484]
73. Gilhus NE. Myasthenia Gravis. N Engl J Med 2016;375:2570–81 [PubMed: 28029925]
74. Yi JS, Guptill JT, Stathopoulos P, et al. B cells in the pathophysiology of myasthenia gravis. Muscle Nerve 2018;57:172–84 [PubMed: 28940642]
75. Leite MI, Strobel P, Jones M, et al. Fewer thymic changes in MuSK antibody-positive than in MuSK antibody-negative MG. Ann Neurol 2005;57:444–8 [PubMed: 15732104]
76. Han J, Sun L, Fan X, et al. Role of regulatory b cells in neuroimmunologic disorders. J Neurosci Res 2016;94:693–701 [PubMed: 27112131]
77. Sun F, Ladha SS, Yang L, et al. Interleukin-10 producing-B cells and their association with responsiveness to rituximab in myasthenia gravis. Muscle Nerve 2014;49:487–94. [PubMed: 23868194]
78. Fan X, Lin C, Han J, et al. Follicular Helper CD4+ T Cells in Human Neuroautoimmune Diseases and Their Animal Models. Mediators Inflamm 2015;2015:638968. [PubMed: 26300592]
79. Cao Y, Amezquita RA, Kleinstein SH, Stathopoulos P, et al. Autoreactive T Cells from Patients with Myasthenia Gravis Are Characterized by Elevated IL-17, IFN-gamma, and GM-CSF and Diminished IL-10 Production. J Immunol 2016;196:2075–84 [PubMed: 26826242]
80. Schaffert H, Pelz A, Saxena A, et al. IL-17-producing CD4(+) T cells contribute to the loss of B-cell tolerance in experimental autoimmune myasthenia gravis. Eur J Immunol 2015;45:1339–47 [PubMed: 25676041]
81. Alahgholi-Hajibehzad M, Kasapoglu P, Jafari R, Rezaei N. The role of T regulatory cells in immunopathogenesis of myasthenia gravis: implications for therapeutics. Expert Rev Clin Immunol 2015;11:859–70 [PubMed: 25973691]
82. Alahgholi-Hajibehzad M, Oflazer P, Aysal F, et al. Regulatory function of CD4+CD25++ T cells in patients with myasthenia gravis is associated with phenotypic changes and STAT5 signaling: 1,25-Dihydroxyvitamin D3 modulates the suppressor activity. J Neuroimmunol 2015;281:51–60 [PubMed: 25867468]
83. Wen Y, Yang B, Lu J, Zhang J, Yang H, Li J. Imbalance of circulating CD4(+)CXCR5(+)FOXP3(+) Tfr-like cells and CD4(+)CXCR5(+)FOXP3(−) Tfh-like cells in myasthenia gravis. Neurosci Lett 2016;630:176–82 [PubMed: 27473945]
84. Portt L, Norman G, Clapp C, Greenwood M, Greenwood MT. Anti-apoptosis and cell survival: a review. Biochim Biophys Acta 2011;1813:238–59 [PubMed: 20969895]

85. Nagata T, Onodera H, Ohuchi M, et al. Decreased expression of c-myc family genes in thymuses from myasthenia gravis patients. J Neuroimmunol 2001;115:199–202 [PubMed: 11282171]

86. Salakou S, Tsamandas AC, Bonikos DS, et al. The potential role of bcl-2, bax, and Ki67 expression in thymus of patients with myasthenia gravis, and their correlation with clinicopathologic parameters. Eur J Cardiothorac Surg 2001;20:712–21 [PubMed: 11574213]

87. Kusner LL, Ciesielski MJ, Marx A, et al. Survivin as a potential mediator to support autoreactive cell survival in myasthenia gravis: a human and animal model study. PLoS One 2014;9:e102231 [PubMed: 25050620]

88. Pedersen J, LaCasse EC, Seidelin JB, et al. Inhibitors of apoptosis (IAPs) regulate intestinal immunity and inflammatory bowel disease (IBD) inflammation. Trends Mol Med 2014;20:652–65 [PubMed: 25282548]

89. Gravina G, Wasen C, Garcia-Bonete MJ, et al. Survivin in autoimmune diseases. Autoimmun Rev 2017;16:845–55 [PubMed: 28564620]

90. Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. Myasthenia gravis: Association of British Neurologists' management guidelines. Pract Neurol 2015;15:199–206 [PubMed: 25977271]

91. Murai H Japanese clinical guidelines for myasthenia gravis: Putting into practice. Clin Exp Neuroimmunol 2015;2015:21–31

92. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. Neurology 2016;87:419–25 [PubMed: 27358333]

93. Maggi L, Mantegazza R. Treatment of myasthenia gravis: focus on pyridostigmine. Clin Drug Investig 2011;31:691–701

94. Mehndiratta MM, Pandey S, Kuntzer T. Acetylcholinesterase inhibitor treatment for myasthenia gravis. Cochrane Database Syst Rev 2014:CD006986

95•. Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized Trial of Thymectomy in Myasthenia Gravis. N Engl J Med 2016;375:511–22

Demonstrates that thymectomy provides therapeutic benefit in AChR-antibody positive MG

[PubMed: 27509100]

96. Okumura M, Ohta M, Takeuchi Y, et al. The immunologic role of thymectomy in the treatment of myasthenia gravis: implication of thymus-associated B-lymphocyte subset in reduction of the anti-acetylcholine receptor antibody titer. J Thorac Cardiovasc Surg 2003;126:1922–28 [PubMed: 14688707]

97. Evoli A, Bianchi MR, Riso R, et al. Response to therapy in myasthenia gravis with anti-MuSK antibodies. Ann N Y Acad Sci 2008;1132:76–83 [PubMed: 18567856]

98. Bedlack RS, Sanders DB. Steroids have an important role. Muscle Nerve 2002;25:117–121 [PubMed: 11754196]

99. Rivner MH. Steroids are overutilized. Muscle Nerve 2002;25:115–17 [PubMed: 11754195]

100. Schneider-Gold C, Gajdos P, Toyka KV, Hohlfeld RR. Corticosteroids for myasthenia gravis. Cochrane Database Syst Rev 2005:CD002828

101. Hoffmann S, Kohler S, Ziegler A, Meisel A. Glucocorticoids in myasthenia gravis - if, when, how, and how much? Acta Neurol Scand 2014;130:211–21 [PubMed: 25069701]

102. Evoli A, Batocchi AP, Palmisani MT, et al. Long-term results of corticosteroid therapy in patients with myasthenia gravis. Eur Neurol 1992;32:37–43 [PubMed: 1563453]

103. Xie Y, Li H-F, Sun L, et al. The Role of Osteopontin and its Gene on Glucorticoid Response in Myasthenia Gravis. Front Neurol 2017 doi: 10.3389/fneu

104. Xie Y, Meng Y, Li HF, et al. GR gene polymorphism is associated with inter-subject variability in response to glucocorticoids in patients with myasthenia gravis. Eur J Neurol 2016;23:1372–79 [PubMed: 27185333]

105. Imai T, Suzuki S, Tsuda E, et al. Oral corticosteroid therapy and present disease status in myasthenia gravis. Muscle Nerve 2015;51:692–6 [PubMed: 25155615]

106. Quax RA, Manenschijn L, Koper JW, et al. Glucocorticoid sensitivity in health and disease. Nat Rev Endocrinol 2013;9:670–86 [PubMed: 24080732]

107. Flammer JR, Rogatsky I. Minireview: Glucocorticoids in autoimmunity: unexpected targets and mechanisms. Mol Endocrinol 2011;25:1075–86 [PubMed: 21511881]

108. Kaminski HJ, Alnosair E, Algahtani RM. Clinical trials for myasthenia gravis: a historical perspective. Ann N Y Acad Sci 2018;1413:5–10 [PubMed: 29377153]

109. Palace J, Newsom-Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. Neurology 1998;50:1778–83 [PubMed: 9633727]

110. Pelin M, De Iudicibus S, Londero M, et al. Thiopurine Biotransformation and Pharmacological Effects: Contribution of Oxidative Stress. Curr Drug Metab 2016;17:542–9 [PubMed: 26935390]

111. Shin JY, Wey M, Umutesi HG, et al. Thiopurine Prodrugs Mediate Immunosuppressive Effects by Interfering with Rac1 Protein Function. J Biol Chem 2016;291:13699–714 [PubMed: 27189938]

112. Pedersen EG, Pottegard A, Hallas J, et al. Use of azathioprine for non-thymoma myasthenia and risk of cancer: a nationwide case-control study in Denmark. Eur J Neurol 2013;20:942–48 [PubMed: 23448676]

113. Machkhas H, Harati Y, Rolak LA. Clinical Pharmacology of Immunosuppressants: Guidelines for neuroimmunotherapy In: Rolak LA, Harati Y, eds. Neuroimmunology for the Clinician. Boston: Butterworth Heinemann, 1997: 77–104

114. Jack KL, Koopman WJ, Hulley D, Nicolle MW. A Review of Azathioprine-Associated Hepatotoxicity and Myelosuppression in Myasthenia Gravis. J Clin Neuromuscul Dis 2016;18:12–20 [PubMed: 27552384]

115. Norwood F, Dhanjal M, Hill M, et al. Myasthenia in pregnancy: best practice guidelines from a U.K. multispecialty working group. J Neurol Neurosurg Psychiatry 2014;85:538–43 [PubMed: 23757420]

116. Ciafaloni E, Massey JM, Tucker-Lipscomb B, Sanders DB. Mycophenolate mofetil for myasthenia gravis: an open-label pilot study. Neurology 2001;56:97–9 [PubMed: 11148243]

117. Chaudhry V, Cornblath DR, Griffin JW, et al. Mycophenolate mofetil: a safe and promising immunosuppressant in neuromuscular diseases. Neurology 2001;56:94–6 [PubMed: 11148242]

118. Meriggioli MN, Rowin J, Richman JG, Leurgans S. Mycophenolate mofetil for myasthenia gravis: a double-blind, placebo-controlled pilot study. Ann N Y Acad Sci 2003;998:494–9 [PubMed: 14592919]

119. Chan JW. Mycophenolate mofetil for ocular myasthenia. J Neurol 2008;255:510–13 [PubMed: 18299952]

120. Sanders DB, Hart IK, Mantegazza R, et al. An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. Neurology 2008;71:400–6 [PubMed: 18434638]

121. Muscle Study Group. A trial of mycophenolate mofetil with prednisone as initial immunotherapy in myasthenia gravis. Neurology 2008;71:394–99 [PubMed: 18434639]

122••. Benatar M, Rowland LP. The muddle of mycophenolate mofetil in myasthenia. Neurology 2008;71:390–91

Excellent summary of challenges in performing clinical trials in MG

[PubMed: 18678821]

123. Villarroel MC, Hidalgo M, Jimeno A. Mycophenolate mofetil: An update. Drugs Today (Barc) 2009;45:521–2 [PubMed: 19834629]

124. Termsarasab P, Katirji B. Opportunistic infections in myasthenia gravis treated with mycophenolate mofetil. J Neuroimmunol 2012;249:83–5 [PubMed: 22613699]

125. Coscia LA, Armenti DP, King RW, et al. Update on the Teratogenicity of Maternal Mycophenolate Mofetil. J Pediatr Genet 2015;4:42–55 [PubMed: 27617117]

126. Buell C, Koo J. Long-term safety of mycophenolate mofetil and cyclosporine: a review. J Drugs Dermatol 2008;7:741–48 [PubMed: 18720690]

127. O'Neill JO, Edwards LB, Taylor DO. Mycophenolate mofetil and risk of developing malignancy after orthotopic heart transplantation: analysis of the transplant registry of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2006;25:1186–91 [PubMed: 17045930]

128. Vernino S, Salomao DR, Habermann TM, O'Neill BP. Primary CNS lymphoma complicating treatment of myasthenia gravis with mycophenolate mofetil. Neurology 2005;65:639–41 [PubMed: 16116136]
129. Cruz JL, Wolff ML, Vanderman AJ, Brown JN. The emerging role of tacrolimus in myasthenia gravis. Ther Adv Neurol Disord 2015;8:92–103 [PubMed: 25922621]
130. Yagi Y, Sanjo N, Yokota T, Mizusawa H. Tacrolimus monotherapy: a promising option for ocular myasthenia gravis. Eur Neurol 2013;69:344–45 [PubMed: 23549260]
131. Azzi JR, Sayegh MH, Mallat SG. Calcineurin inhibitors: 40 years later, can't live without. J Immunol 2013;191:5785–91 [PubMed: 24319282]
132. Ponseti JM, Azem J, Fort JM, et al. Long-term results of tacrolimus in cyclosporine- and prednisone-dependent myasthenia gravis. Neurology 2005;64:1641–43 [PubMed: 15883336]
133. Tindall RSA, Phillips JT, Rollins JA, et al. A clinical therapeutic trial of cyclosporine in myasthenia gravis. Ann NY Acad Sci 1993;681:539–51 [PubMed: 8357194]
134. Ciafaloni E, Nikhar NK, Massey JM, Sanders DB. Retrospective analysis of the use of cyclosporine in myasthenia gravis. Neurology 2000;55:448–50 [PubMed: 10932288]
135. Lavrnic D, Vujic A, Rakocevic-Stojanovic V, et al. Cyclosporine in the treatment of myasthenia gravis. Acta Neurol Scand 2005;111:247–52 [PubMed: 15740576]
136. Hart IK, Sathasivam S, Sharshar T. Immunosuppressive agents for myasthenia gravis. Cochrane Database Syst Rev 2007:CD005224
137. Tamler R, Epstein S. Nonsteroid immune modulators and bone disease. Ann N Y Acad Sci 2006;1068:284–96 [PubMed: 16831929]
138. Marder W, McCune WJ. Advances in immunosuppressive therapy. Semin Respir Crit Care Med 2007;28:398–417 [PubMed: 17764058]
139. Wessels JA, Huizinga TW, Guchelaar HJ. Recent insights in the pharmacological actions of methotrexate in the treatment of rheumatoid arthritis. Rheumatology (Oxford) 2008;47:249–55 [PubMed: 18045808]
140. Pasnoor M, He J, Herbelin L, et al. A randomized controlled trial of methotrexate for patients with generalized myasthenia gravis. Neurology 2016;87:57–64 [PubMed: 27306628]
141. Heckmann JM, Rawoot A, Bateman K, et al. A single-blinded trial of methotrexate versus azathioprine as steroid-sparing agents in generalized myasthenia gravis. BMC Neurol 2011;11:97 [PubMed: 21819556]
142. Nagappa M, Netravathi M, Taly AB, et al. Long-term efficacy and limitations of cyclophosphamide in myasthenia gravis. J Clin Neurosci 2014;21:1909–14 [PubMed: 25043165]
143. Drachman DB, Brodsky RA. High-dose therapy for autoimmune neurologic diseases. Curr Opin Oncol 2005;17:83–8 [PubMed: 15725909]
144. Bryant A, Atkins H, Pringle CE, et al. Myasthenia Gravis Treated With Autologous Hematopoietic Stem Cell Transplantation. JAMA Neurol 2016;73:652–58 [PubMed: 27043206]
145. Sistigu A, Viaud S, Chaput N, et al. Immunomodulatory effects of cyclophosphamide and implementations for vaccine design. Semin Immunopathol 2011;33:369–83 [PubMed: 21611872]
146. Alabdali M, Barnett C, Katzberg H, et al. Intravenous immunoglobulin as treatment for myasthenia gravis: current evidence and outcomes. Expert Rev Clin Immunol 2014;10:1659–65 [PubMed: 25331319]
147. Lunemann JD, Nimmerjahn F, Dalakas MC. Intravenous immunoglobulin in neurology--mode of action and clinical efficacy. Nat Rev Neurol 2015;11:80–89 [PubMed: 25561275]
148. Bril V, Barnett-Tapia C, Barth D, Katzberg HD. IVIG and PLEX in the treatment of myasthenia gravis. Ann N Y Acad Sci 2012;1275:1–6 [PubMed: 23278570]
149. Barth D, Nabavi Nouri M, Ng E, et al. Comparison of IVIg and PLEX in patients with myasthenia gravis. Neurology 2011;76:2017–23 [PubMed: 21562253]
150. Nadeau JO, Bhibhatbhan A, McDougall D, Toth C. Identification and comparison of adverse events for preparations of IVIG in patients with neuromuscular diseases. Clin Neurol Neurosurg 2010;112:467–69 [PubMed: 20227821]
151. Pinching AJ, Peters DK, Newsom-Davis J. Remission of myasthenia gravis following plasma exchange. Lancet 1976;2:1373–76 [PubMed: 63848]

152. Guptill JT, Oakley D, Kuchibhatla M, et al. A retrospective study of complications of therapeutic plasma exchange in myasthenia. Muscle Nerve 2013;47:170–6 [PubMed: 23168720]
153. Zhou Y, Gong B, Lin F, et al. Anti-C5 antibody treatment ameliorates weakness in experimentally acquired myasthenia gravis. J Immunol 2007;179:8562–67 [PubMed: 18056404]
154. Howard JF, Jr, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. Lancet Neurol 2017;16:976–86 [PubMed: 29066163]
155. Licht C, Greenbaum LA, Muus P, et al. Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. Kidney Int 2015;87:1061–73 [PubMed: 25651368]
156. Ninomiya H, Obara N, Chiba S, et al. Interim analysis of post-marketing surveillance of eculizumab for paroxysmal nocturnal hemoglobinuria in Japan. Int J Hematol 2016;104:548–58 [PubMed: 27464489]
157. Nishimura J, Yamamoto M, Hayashi S, et al. Genetic variants in C5 and poor response to eculizumab. N Engl J Med 2014;370:632–39 [PubMed: 24521109]
158. Razzak M Anaemia: mutations in C5 explain eculizumab resistance. Nat Rev Nephrol 2014;10:182 [PubMed: 24566955]
159. Argov Z, McKee D, Agus S, et al. Treatment of human myasthenia gravis with oral antisense suppression of acetylcholinesterase. Neurology 2007;69:699–700 [PubMed: 17698793]
160. Boneva N, Hamra-Amitay Y, Wirguin I, Brenner T. Stimulated-single fiber electromyography monitoring of anti-sense induced changes in experimental autoimmune myasthenia gravis. Neurosci Res 2006;55:40–44 [PubMed: 16504322]
161. Brenner T, Hamra-Amitay Y, Evron T, et al. The role of readthrough acetylcholinesterase in the pathophysiology of myasthenia gravis. FASEB J 2003;17:214–22 [PubMed: 12554700]
162. Somnier FE, Langvad E. Plasma exchange with selective immunoadsorption of anti-acetylcholine receptor antibodies. J Neuroimmunol 1989;22:123–27 [PubMed: 2647782]
163. Ptak J Changes of plasma proteins after immunoadsorption using Ig-Adsopak columns in patients with myasthenia gravis. Transfus Apher Sci 2004;30:125–29 [PubMed: 15062750]
164. Antozzi C, Berta E, Confalonieri P, et al. Protein-A immunoadsorption in immunosuppression-resistant myasthenia gravis. Lancet 1994;343:124
165. Grob D, Simpson D, Mitsumoto H, et al. Treatment of myasthenia gravis by immunoadsorption of plasma. Neurology 1995;45:338–44 [PubMed: 7854536]
166. Lagoumintzis G, Zisimopoulou P, Kordas G, et al. Recent approaches to the development of antigen-specific immunotherapies for myasthenia gravis. Autoimmunity 2010;43:436–45 [PubMed: 20187712]
167. Lagoumintzis G, Zisimopoulou P, Trakas N, et al. Scale up and safety parameters of antigen specific immunoadsorption of human anti-acetylcholine receptor antibodies. J Neuroimmunol 2014;267:1–6 [PubMed: 24412396]
168. Lazaridis K, Evaggelakou P, Bentenidi E, et al. Specific adsorbents for myasthenia gravis autoantibodies using mutants of the muscle nicotinic acetylcholine receptor extracellular domains. J Neuroimmunol 2015;278:19–25 [PubMed: 25595248]
169. Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. Nat Rev Immunol 2007;7:715–25 [PubMed: 17703228]
170. Liu X, Ye L, Christianson GJ, Yang JQ, et al. NF-kappaB signaling regulates functional expression of the MHC class I-related neonatal Fc receptor for IgG via intronic binding sequences. J Immunol 2007;179:2999–3011 [PubMed: 17709515]
171. Kusner LL, Satija N, Cheng G, Kaminski HJ. Targeting therapy to the neuromuscular junction: proof of concept. Muscle Nerve 2014;49:749–756 [PubMed: 24037951]
172. Song C, Xu Z, Miao J, et al. Protective effect of scFv-DAF fusion protein on the complement attack to acetylcholine receptor: a possible option for treatment of myasthenia gravis. Muscle Nerve 2012;45:668–75 [PubMed: 22499093]

173. Fredslund F, Laursen NS, Roversi P, et al. Structure of and influence of a tick complement inhibitor on human complement component 5. Nat Immunol 2008;9:753–60 [PubMed: 18536718]
174. Soltys J, Kusner LL, Young A, et al. Novel complement inhibitor limits severity of experimentally myasthenia gravis. Ann Neurol 2009;65:67–75 [PubMed: 19194881]
175. Subias M, Tortajada A, Gastoldi S, et al. A novel antibody against human factor B that blocks formation of the C3bB proconvertase and inhibits complement activation in disease models. J Immunol 2014;193:5567–75 [PubMed: 25355917]
176. Huda R, Tuzun E, Christadoss P. Complement C2 siRNA mediated therapy of myasthenia gravis in mice. J Autoimmun 2013;42:94–104 [PubMed: 23410585]
177. Luo J, Lindstrom J. AChR-specific immunosuppressive therapy of myasthenia gravis. Biochem Pharmacol 2015;97:609–19 [PubMed: 26215875]
178. Bartfeld D, Fuchs S. Specific immunosuppression of experimental autoimmune myasthenia gravis by denatured acetylcholine receptor. Proc Natl Acad Sci U S A 1978;75:4006–10 [PubMed: 279016]
179. Ma CG, Zhang GX, Xiao BG, et al. Suppression of experimental autoimmune myasthenia gravis by nasal administration of acetylcholine receptor. J Neuroimmunol 1995;58:51–60 [PubMed: 7537280]
180. Okumura S, McIntosh K, Drachman DB. Oral administration of acetylcholine receptor: effects on experimental myasthenia gravis. Ann Neurol 1994;36:704–13 [PubMed: 7979216]
181. Wang ZY, Qiao J, Link H. Suppression of experimental autoimmune myasthenia gravis by oral administration of acetylcholine receptor. J Neuroimmunol 1993;44:209–14 [PubMed: 8505410]
182. Luo J, Kuryatov A, Lindstrom JM. Specific immunotherapy of experimental myasthenia gravis by a novel mechanism. Ann Neurol 2010;67:441–51 [PubMed: 20437579]
183. Luo J, Lindstrom J. Antigen-specific immunotherapeutic vaccine for experimental autoimmune myasthenia gravis. J Immunol 2014;193:5044–55 [PubMed: 25288571]
184. Araga S, Blalock JE. Use of complementary peptides and their antibodies in B-cell-mediated autoimmune disease: prevention of experimental autoimmune myasthenia gravis with a peptide vaccine. Immunomethods 1994;5:130–35 [PubMed: 7874437]
185. Araga S, LeBoeuf RD, Blalock JE. Prevention of experimental autoimmune myasthenia gravis by manipulation of the immune network with a complementary peptide for the acetylcholine receptor. Proc Natl Acad Sci U S A 1993;90:8747–51 [PubMed: 8378359]
186. Araga S, Xu L, Nakashima K, et al. A peptide vaccine that prevents experimental autoimmune myasthenia gravis by specifically blocking T cell help. FASEB J 2000;14:185–96 [PubMed: 10627293]
187. Galin FS, Chrisman CL, Cook JR, Jr., et al. Possible therapeutic vaccines for canine myasthenia gravis: implications for the human disease and associated fatigue. Brain Behav Immun 2007;21:323–31 [PubMed: 17113748]
188. Shelton GD, Lindstrom JM. Spontaneous remission in canine myasthenia gravis: implications for assessing human MG therapies. Neurology 2001;57:2139–41 [PubMed: 11739846]
189. Bongioanni P, Ricciardi R, Pellegrino D, Romano MR. T-cell tumor necrosis factor-alpha receptor binding in myasthenic patients. J Neuroimmunol 1999;93:203–7 [PubMed: 10378884]
190. Li H, Shi FD, Bai X, et al. Cytokine and chemokine mRNA expressing cells in muscle tissues of experimental autoimmune myasthenia gravis. J Neurol Sci 1998;161:40–6 [PubMed: 9879680]
191. Christadoss P, Goluszko E. Treatment of experimental autoimmune myasthenia gravis with recombinant human tumor necrosis factor receptor Fc protein. J Neuroimmunol 2002;122:186–90 [PubMed: 11777558]
192. Rowin J, Meriggioli MN, Tuzun E, et al. Etanercept treatment in corticosteroid-dependent myasthenia gravis. Neurology 2004;63:2390–2 [PubMed: 15623708]
193. Tuzun E, Meriggioli MN, Rowin J, et al. Myasthenia gravis patients with low plasma IL-6 and IFN-gamma benefit from etanercept treatment. J Autoimmun 2005;24:261–8 [PubMed: 15848049]
194. Fee DB, Kasarskis EJ. Myasthenia gravis associated with etanercept therapy. Muscle Nerve 2009;39:866–70 [PubMed: 19373885]

195. Kim JY, Yang Y, Moon JS, et al. Serum BAFF expression in patients with myasthenia gravis. J Neuroimmunol 2008;199:151–4 [PubMed: 18586330]
196. Ragheb S, Lisak R, Lewis R, et al. A potential role for B-cell activating factor in the pathogenesis of autoimmune myasthenia gravis. Arch Neurol 2008;65:1358–62 [PubMed: 18852352]
197. Ragheb S, Lisak RP. B-cell-activating factor and autoimmune myasthenia gravis. Autoimmune Dis 2011;2011:939520. [PubMed: 22235365]
198. Berrih-Aknin S, Ragheb S, Le Panse R, Lisak RP. Ectopic germinal centers, BAFF and anti-B-cell therapy in myasthenia gravis. Autoimmun Rev 2013;12:885–93 [PubMed: 23537509]
199. Avidan N, Le Panse R, Harbo HF, et al. VAV1 and BAFF, via NFkappaB pathway, are genetic risk factors for myasthenia gravis. Ann Clin Transl Neurol 2014;1:329–39 [PubMed: 25356403]
200. Ibtehaj N, Huda R. High-dose BAFF receptor specific mAb-siRNA conjugate generates Fas-expressing B cells in lymph nodes and high-affinity serum autoantibody in a myasthenia mouse model. Clin Immunol 2017;176:122–30 [PubMed: 28099879]
201. Monson NL, Cravens PD, Frohman EM, et al. Effect of rituximab on the peripheral blood and cerebrospinal fluid B cells in patients with primary progressive multiple sclerosis. Arch Neurol 2005;62:258–64 [PubMed: 15710854]
202. Diaz-Manera J, Martinez-Hernandez E, Querol L, et al. Long-lasting treatment effect of rituximab in MuSK myasthenia. Neurology 2012;78:189–93 [PubMed: 22218276]
203. Hiepe F, Radbruch A. Plasma cells as an innovative target in autoimmune disease with renal manifestations. Nat Rev Nephrol 2016;12:232–40 [PubMed: 26923204]
204. Kane RC, Farrell AT, Sridhara R, Pazdur R. United States Food and Drug Administration approval summary: bortezomib for the treatment of progressive multiple myeloma after one prior therapy. Clin Cancer Res 2006;12:2955–60 [PubMed: 16707588]
205. Gomez AM, Willcox N, Vrolix K, et al. Proteasome inhibition with bortezomib depletes plasma cells and specific autoantibody production in primary thymic cell cultures from early-onset myasthenia gravis patients. J Immunol 2014;193:1055–63 [PubMed: 24973445]
206. Gomez AM, Vrolix K, Martinez-Martinez P, et al. Proteasome inhibition with bortezomib depletes plasma cells and autoantibodies in experimental autoimmune myasthenia gravis. J Immunol 2011;186:2503–13 [PubMed: 21239719]
207. Arastu-Kapur S, Anderl JL, Kraus M, et al. Nonproteasomal targets of the proteasome inhibitors bortezomib and carfilzomib: a link to clinical adverse events. Clin Cancer Res 2011;17:2734–43 [PubMed: 21364033]
208. Gomez AM, Willcox N, Molenaar PC, et al. Targeting plasma cells with proteasome inhibitors: possible roles in treating myasthenia gravis? Ann N Y Acad Sci 2012;1274:48–59 [PubMed: 23252897]
209. Palumbo R, Gogliettino M, Cocca E, et al. APEH Inhibition Affects Osteosarcoma Cell Viability via Downregulation of the Proteasome. Int J Mol Sci 2016;17 E1614. doi: 10.3390/ijms17101614 [PubMed: 27669226]
210. Krejcik J, Casneuf T, Nijhof IS, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood 2016;128:384–94 [PubMed: 27222480]
211. Thiruppathi M, Rowin J, Ganesh B, Sheng JR, Prabhakar BS, Meriggioli MN. Impaired regulatory function in circulating CD4(+)CD25(high)CD127(low/-) T cells in patients with myasthenia gravis. Clin Immunol 2012;145:209–23 [PubMed: 23110942]
212. Harrington LE, Hatton RD, Mangan PR, et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. Nat Immunol 2005;6:1123–32 [PubMed: 16200070]
213. Park H, Li Z, Yang XO, et al. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. Nat Immunol 2005;6:1133–41 [PubMed: 16200068]
214. Waite JC, Skokos D. Th17 response and inflammatory autoimmune diseases. Int J Inflam 2012;2012:819467 [PubMed: 22229105]
215. Aguilo-Seara G, Xie Y, Sheehan J, et al. Ablation of IL-17 expression moderates experimental autoimmune myasthenia gravis disease severity. Cytokine 2017;96:279–85 [PubMed: 28599246]

216. Roche JC, Capablo JL, Larrad L, et al. Increased serum interleukin-17 levels in patients with myasthenia gravis. Muscle Nerve 2011;44:278–80 [PubMed: 21755509]

217. Gradolatto A, Nazzal D, Truffault F, et al. Both Treg cells and Tconv cells are defective in the Myasthenia gravis thymus: roles of IL-17 and TNF-alpha. J Autoimmun 2014;52:53–63 [PubMed: 24405842]

218. Xie Y, Li HF, Jiang B, et al. Elevated plasma interleukin-17A in a subgroup of Myasthenia Gravis patients. Cytokine 2016;78:44–6 [PubMed: 26618234]

219. Yi JS, Guidon A, Sparks S, et al. Characterization of CD4 and CD8 T cell responses in MuSK myasthenia gravis. J Autoimmun 2014;52:130–38 [PubMed: 24378287]

220. Pinelli DF, Wakeman BS, Wagener ME, et al. Rapamycin ameliorates the CTLA4-Ig-mediated defect in CD8(+) T cell immunity during gammaherpesvirus infection. Am J Transplant 2015;15:2576–87 [PubMed: 25989700]

221. Chen J, Yin H, Xu J, et al. Reversing endogenous alloreactive B cell GC responses with anti-CD154 or CTLA-4Ig. Am J Transplant 2013;13:2280–92 [PubMed: 23855587]

222. Im SH, Barchan D, Maiti PK, et al. Blockade of CD40 ligand suppresses chronic experimental myasthenia gravis by down-regulation of Th1 differentiation and up-regulation of CTLA-4. J Immunol 2001;166:6893–98 [PubMed: 11359850]

223. Balandina A, Lecart S, Dartevelle P,et al. Functional defect of regulatory CD4(+)CD25+ T cells in the thymus of patients with autoimmune myasthenia gravis. Blood 2005;105:735–41 [PubMed: 15454488]

224. Sheng JR, Li L, Ganesh BB, et al. Suppression of experimental autoimmune myasthenia gravis by granulocyte-macrophage colony-stimulating factor is associated with an expansion of FoxP3+ regulatory T cells. J Immunol 2006;177:5296–306 [PubMed: 17015715]

225. Sheng JR, Li LC, Ganesh BB, et al. Regulatory T cells induced by GM-CSF suppress ongoing experimental myasthenia gravis. Clin Immunol 2008;128:172–80 [PubMed: 18502693]

226. Sheng JR, Muthusamy T, Prabhakar BS, Meriggioli MN. GM-CSF-induced regulatory T cells selectively inhibit anti-acetylcholine receptor-specific immune responses in experimental myasthenia gravis. J Neuroimmunol 2011;240-241:65–73 [PubMed: 22099723]

227. Rowin J, Thiruppathi M, Arhebamen E, et al. Granulocyte macrophage colony-stimulating factor treatment of a patient in myasthenic crisis: effects on regulatory T cells. Muscle Nerve 2012;46:449–53 [PubMed: 22907239]

228. Strober J, Cowan MJ, Horn BN. Allogeneic hematopoietic cell transplantation for refractory myasthenia gravis. Arch Neurol 2009;66:659–61 [PubMed: 19433668]

229. Hakansson I, Sandstedt A, Lundin F, et al. Successful autologous haematopoietic stem cell transplantation for refractory myasthenia gravis - a case report. Neuromuscul Disord 2017;27:90–3 [PubMed: 27863874]

230. Benatar M, Sanders DB, Burns TM, et al. Recommendations for myasthenia gravis clinical trials. Muscle Nerve 2012;45:909–17 [PubMed: 22581550]

9. Key Issues

- MG remains a deadly disorder with a large minority of patients responding poorly to conventional treatments.
- MG is caused by antibodies directed towards proteins concentrated at the neuromuscular junction, primarily the acetylcholine receptor and the muscle specific kinase.
- The pathogenesis of MG varies based autoantibody, thymic pathology, age of onset, and gender. Targeted therapies will be needed to cure these subtypes.
- Conventional therapeutics are focused on moderating symptoms and reduction of corticosteroid use.
- Eculizumab, a complement inhibitor, was approved for use of acetylcholine receptor antibody-mediated MG and represents a fundamentally new class of drug for MG.
- Agents that target directly or indirectly target antibody production by B cells and plasma cells may offer therapies that produce long-term remission in all of MG subtypes.
- Induction of self-tolerance to the inciting autoantigen will be the key to potentially curing of MG but remains an elusive goal.
- With the plethora of therapies in development at various stages, there is a critical need for leaders from industry, patient advocacy, and researchers to prioritize therapeutic development.

Table 1.

Clinical Severity Based on MGFA Clinical Classification

Class I:	Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.
Class II:	Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
	IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
	IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
Class III:	Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
	IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
	IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
Class IV:	Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
	IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
	IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
Class V:	Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

Table 2.

Standard Therapies and Adverse Effects

Treatment	Major Adverse Effects
Cholinesterase Inhibition	Bloating, diarrhea, excess respiratory secretions, bradycardia
Prednisone	Osteoporosis, weight gain with central obesity, glaucoma, cataracts, hypertension, peripheral edema, psychiatric changes (depression, mania, personality alterations), sleep disturbance, easy bruising, glucose intolerance
Azathioprine	Idiosyncratic flu-like reaction, leukopenia, hepatotoxicity, alopecia, teratogen, possible risk of neoplasia
Cyclosporine	Renal insufficiency, hypertension, gingival hyperplasia, drug interactions
Mycophenolate	Anemia, leukopenia, gastrointestinal discomfort, diarrhea
Tacrolimus	Tremor, headache, diarrhea, hypertension, nausea, renal insufficiency, hyperkalemia, hypomagnesemia, drug interactions
Methotrexate	Hepatoxicity, anemia, hair loss
Cyclophospamide	alopecia, diarrhea, nausea, vomiting, hemorrhagic cystitis, carcinogenic, teratogenic potential, infertility, interstitial pneumonitis, hepatic toxicity
Eculizumab	Meningococcal and other infections, headache

Table 3.

Potential New Therapies for Myasthenia Gravis

Cholinesterase Inhibition		
EN101	Acetylcholinesterase inhibitor	• antisense oligodeoxynucleotide • acts at the mRNA level • selectively reduces the enzymatic isoform of AChE-R
Moderation of Autoantibody Levels		
Neonatal Fc receptor (FcRn) monoclonal antibodies	IgG endocytosis by endothelial cells	• disrupts of FcRn-IgG interaction • lowers the serum IgG levels • compounds under development by ArGEN-X, UCB, HanALL Biopharma
Complement inhibition		
RA101495	inhibits C5 complement	• daily subcutaneous injection • used for treatment of paroxysmal nocturnal hemoglobinuria
Induction of Tolerance		
Bacterially-expressed human AChR cytoplasmic domains	induces tolerance to antigen	• AChR antibody production continues primarily towards cytoplasmic domains, which are not pathogenic • no clinical trials planned • If effective, it has the potential to be curative
Cytokine Targeted Therapies		
Etanercept	TNF-receptor blocker	• can suppress established EAMG without inducing significant immunosuppression • TNF-α agents may exacerbate MG • therapeutic development has not been pursued
Belimumab	B cell activating factor (BAFF) Antibody	• results from the study yet to be published
Immune Cell-Targeted Therapy		
Rituxan	chimeric IgG1 monoclonal antibody that targets CD20	• eliminates CD20 positive cells by complement-mediated or antibody-dependent cell-mediated cytotoxicity • commonly used but not approved by the US Federal Drug Administration for MG • appears effective in MuSK+ MG patients • does not affect autoantibody producing plasmablasts or plasma cells that do not express CD20
Plasma cell therapeutics		
Bortezomib	proteasome inhibitor	• causes accumulation of nondegraded, misfolded proteins within plasma cells which leads to apoptosis • in EAMG reduced AChR antibody production and reduces postsynaptic muscle membrane damage • clinical trials currently in progress • significant side effect is a painful neuropathy
Daratumumab	targets CD38 expressed on plasmablasts	• depletion of immune suppressive CD38 expressing regulatory T cells and expansion of helper and cytotoxic T cell populations • may exacerbate MG

Targeting T cells		
IL-17 Antibodies	target the inflammatory cytokine IL-17 or its receptor	• MG patients are likely primed for proinflammatory IL-17 responses
Brodalumab	target the IL-17 receptor A	• approved for the treatment of moderate to severe plaque psoriasis
Ixekizumab	targets the IL-17A cytokine itself	• approved for the treatment of moderate to severe plaque psoriasis
Secukinumab	targets the IL-17A cytokine itself	• approved for the treatment of moderate to severe plaque psoriasis, and psoriatic arthritis and ankylosing spondylitis
Abatacept	blocks the required co-stimulatory signal to activate T cells that is mediated by CD80/CD86 on antigen presenting cells	• fusion protein, consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and a modified Fc region of human immunoglobulin G1 • inhibits T cell activation, resulting in reduced levels of pro-inflammatory cytokines • failed in clinical trials in multiple sclerosis and ulcerative colitis
Stem cell transplant		
Allogenic hematopoietic stem cell transplantation	stem cells	• One successful curative case
Autologous haematopoietic stem cell transplantation	stem cells	• Seven patients that achieved durable MGFA complete stable remission