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Review Article

Myasthenia gravis: Historical achievements and the "golden age" of clinical trials

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ABSTRACT

Since the death of Chief Opechankanough >350 years ago, the myasthenia gravis (MG) community has gained extensive knowledge about MG and how to treat it. This review highlights key milestones in the history of treatment and discusses the current "golden age" of clinical trials. Although originally thought by many clinicians to be a disorder of hysteria and fluctuating weakness without observable cause, MG is one the most understood autoimmune neurologic disorders. However, studying it in clinical trials has been challenging due to the fluctuating nature of the medical condition which impacts MG clinical outcomes. Clinical trials must also account for the possibility of a placebo effect. Because MG is a rare incurable autoimmune disorder, it limits the number of potential patients available to participate in clinical trials. In the last 15 years, however, significant progress has been made with MG randomized clinical trials, resulting in a new drug (eculizumab) for physicians' treatment repertoire and an old technique (thymectomy) confirmed effective for MG. Some of the therapies (eg, thymectomy, corticosteroids, plasma exchange, and intravenous immunoglobulin [IVIg]) have survived the test of time. Others (eg, eculizumab and neonatal Fc receptor inhibitor) are novel and hold promise.

1. Introduction

Myasthenia gravis (MG) is one of the oldest afflictions recorded in medical history and the most understood autoimmune neurologic disorder, yet clinical trials remain challenging despite greater knowledge of pathophysiology. The most exciting acceleration in clinical trials has been happening throughout the last 15 years. This review will recount the key milestones in the history of MG treatment and discuss the current "golden age" of clinical trials in MG.

Myasthenia gravis is a rare incurable autoimmune disease with widely ranging epidemiological estimates. In a 2010 meta-analysis of 55 studies conducted from 1950 through 2007 [1], the estimated global incidence rate ranged from 1.7 to 21.3 per million person-years, and the observed prevalence rate ranged from 15 to 179 per million persons. More recently in 2015, an analysis of 24 studies performed from 1990 through 2014 [2] reported an incidence rate of 3 to 28 per million person-years and prevalence rate of 54 to 350 per million persons. It is unclear whether the incidence of MG is increasing over time, or whether the seemingly increased frequency is due to greater awareness of MG, better application of diagnostic testing, and better quality of epidemiologic studies. And while MG affects people of all ages, all races, and both sexes, age and sex appear to influence disease occurrence [1,3,4]. The incidence rates for both males and females generally rise with increasing age, peaking around age 60–80 years and having more males in the older age groups (late-onset MG). In some populations, MG presents in a bimodal pattern, with more females having early-onset MG at roughly 20–40 years old, followed by another peak around 60–80 years old [3,5–12].

Although we have not yet identified all driver(s) for the MG disease course, recent advances in therapy have been accomplished due to a clearer understanding of the molecular pathophysiology of MG. Myasthenia gravis is a disorder of signal transmission at the neuromuscular junction (Fig. 1.1) [13], resulting in fluctuating muscle weakness and fatigability due to autoantibodies targeting molecular components at the neuromuscular junction. The predominant auto-antibodies in MG are those against acetylcholine receptors (AChRs), muscle-specific kinase (MuSK), and low-density lipoprotein receptor-related protein 4 (LRP4). Other associated auto-antibodies of potential pathological significance are those against titin, ryanodine receptors (RyRs), cortactin, agrin, collagen Q, and voltage-gated potassium channel 1.4 (K_V1.4). We will not describe the molecular pathology of MG in detail here, as others have done this extensively elsewhere

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[13–15]. However, it is important to note that auto-antibodies against specific proteins in the neuromuscular junction and muscle fiber may play key roles in disease presentation. For instance, the majority (~80%) of patients with MG have antibodies against AChR, which cause AChR loss and postsynaptic membrane damage via complement activation. Patients with anti-AChR antibodies can present with early- or late-onset MG in generalized or ocular form. In contrast, auto-antibodies against titin, a large intracellular protein providing scaffolding and muscle elasticity [16] found less frequently in ~30% of patients seropositive for anti-AChR antibodies, are associated with

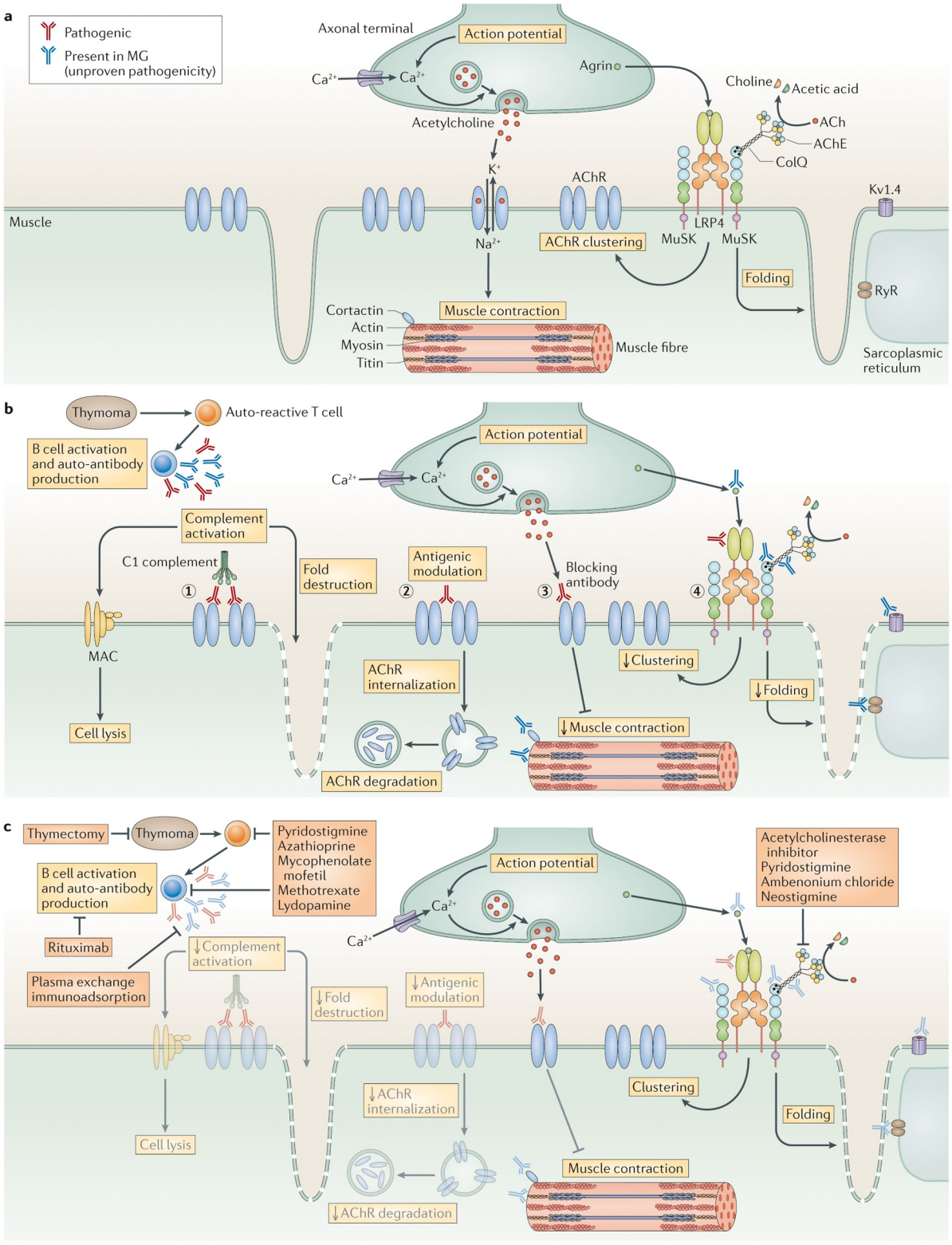

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Fig. 1. Structural changes at the neuromuscular junction and how treatment may alleviate MG symptoms. Image republished with copyright permission from Gilhus et al. 2016. [13] Image republished with copyright permission from Gilhus et al. 2016. [13] a) Normal neuromuscular junction with major MG-related components. Voltage-dependent Ca^{2+} channel opening due to action potential at the presynaptic nerve terminal triggers release of acetylcholine and agrin into the synaptic cleft. When acetylcholine binds to acetylcholine receptors (AChRs), sodium channels open, leading to muscle contraction. Acetylcholine receptor (AChR) clustering is required for maintenance of the postsynaptic structures of the neuromuscular junction, and the binding of agrin to the complex formed by low-density lipoprotein receptor-related protein 4 (LRP4) and muscle-specific kinase (MuSK) causes AChR clustering. b) Major pathogenic mechanisms of the AChR antibodies, with known pathogenic involvement in MG shown in red. (1) Complement activation at the neuromuscular junction causes destruction of the typical folds in the sarcolemma and formation of membrane attack complexes (MACs) on the muscle membrane. (2) Antigenic modulation results in internalization and degradation of surface AChRs. (3) Binding of AChR antibodies at the AChR ligand binding site could directly block acetylcholine binding and channel opening. (4) Anti-MuSK and anti-LRP4 antibodies could block intermolecular interactions of MuSK or LRP4, consequently inhibiting the normal function of the neuromuscular junction. c) Restoring function of the neuromuscular junction can be done by increasing acetylcholine availability (acetylcholinesterase inhibitors; green) for improved signal transduction, or by decreasing the concentration of autoantibodies (immunosuppressive drugs, plasma exchange/immunoadsorption, B-cell-targeting therapies; red) to alleviate the pathogenic mechanisms in panel (b). The mechanism of action for IVIg therapy has not been clearly elucidated, but it is speculated to have multifactorial effects on the major pathogenic mechanisms described in panel (b). IVIg, intravenous immunoglobulin; $K_V1.4$, voltage-gated potassium channel 1.4; RyR, ryanodine receptor.

thymomatous and late-onset MG [11,17–20]. Anti-RyR antibodies are also found in late-onset MG and in up to 70% of patients with MG and thymoma [19,20]. The presence of titin and RyR auto-antibodies in a young patient with MG suggests possible involvement of a thymoma, and patients with these striational antibodies tend to have more severe disease and worse prognosis [19,21–23]. Therefore, the classification of MG into subgroups based on specific antibodies, biomarkers, and clinical presentations (ie, age of onset, involvement of ocular muscles, the absence or presence of thymoma, severity of symptoms) guides therapeutic regimens for individual patients.

For the purpose of this review, we will focus on the historical clinical milestones and the current explosion of clinical trials in MG.

2. Historical achievements in myasthenia gravis

The name “myasthenia gravis,” a combination of Greek and Latin, means grave weakness. The observation that symptoms worsened with repetitive movement and warm temperatures suggested early treatment regimens of rest and icing of muscles. As X-ray imaging techniques became available and advances in anesthesia and sterile surgical techniques were realized, the role of the thymus and beneficial effects of thymectomy were explored. The first clues to definitive drug treatment came from an appreciation for the analogy of episodic MG symptoms with curare poisoning, when the application of the antidote showed remarkable results (Fig. 2). With additional understanding of MG as an autoimmune disorder, various immunosuppressive and immunomodulator treatments arose. Currently, specific molecular components of the immune system may be targeted with modern drug therapies that promote quality of life.

2.1. Early clinical reports (17th–19th century)

The first recorded case of MG was most probably Native-American Indian Chief Opechankanough in the early 17th century [24]. Chief Opechankanough, whose niece was the famous Pocahontas, reportedly developed severe generalized muscle weakness that “wrecked his constitutions.” Known for his vigor before the early Jamestown encounters, Chief Opechankanough later became so weak that his warriors had to carry him into battle, and his eyes became so droopy that his attendants had to prop them open for him to see. Although he could not walk during the last phase of this life, Chief Opechankanough was able to stand after a period of inactivity while being imprisoned in Jamestown, Virginia for leading a deadly attack on English settlers. Opechankanough's clinical presentation is considered to be consistent with MG: his symptoms manifested in adulthood, his severe weakness improved with rest, and other family members did not suffer similar problems.

In 1672, Thomas Willis documented the “the habitual and spurious palsies” in his book, *De Anima Brutorum* [25], which was later translated into English in 1683 [26]. Willis theorized that “the spurious palsies” might “depend upon the fault of the explosive Copula suffused everywhere from the blood into the moving fibres.” Now, we appreciate MG as an autoimmune disorder of neurotransmission, and the “fault of the explosive Copula…from the blood” foreshadows later discoveries of autoantibodies against AChR that block, alter, or destroy AChRs at the neuromuscular junction [27,28].

After Willis' initial publications, the field remained silent for 200 years before a series of deaths due to respiratory paralysis without central nervous system abnormalities began to appear in Germany in the late 18th century. The puzzling nature of these deaths revived curiosity into what physicians thought were mysterious cases of bulbar palsy. We will discuss several of these cases.

In 1877, Samuel Wilks, an English physician at Guy's Hospital in London, was the first to describe a girl who he thought had bulbar palsy and died of respiratory paralysis; however, no abnormalities could be found in her medulla oblongata upon very careful examination with the naked eye and the microscope [29]. Wilks noted that the healthy-appearing girl came to the hospital for general weakness; she manifested limited mobility, slow speech, mild crossed eyes, and great difficulty swallowing, but no limb paralysis was observed. Interestingly, Wilks also noted that her symptoms changed throughout the course of a day and that the house-physician was “inclined to regard this case as one of hysteria.”

Then 10 years later, Eisenlohr reported treating an 18-year-old girl with progressive external ophthalmoplegia and bulbar paralysis resulting in death but without brainstem pathology upon postmortem examination [30]. As Willis and Wilks previously reported, Eisenlohr noted that his patient had significant variations in her condition throughout the day. Additionally, she had ptosis, poor performance of extra-ocular muscles and was able to regain some mobility on an intermittent basis. She developed the first occurrence of ptosis around the same time as the appearance of migraine attacks, although it was not clear whether the two events were linked. This patient ultimately died of diaphragmatic respiratory paralysis and gradual “cardiac paralysis.”

A possible case of MG in a patient with “an enlarged mediastinal gland” was reported by Lauriston Shaw who published the first report of artificial respiration use in a 37-year-old baker to prolong his life. The patient subsequently died of respiratory paralysis, also without observed cause on autopsy [31]. In February 1887, this previously healthy patient presented with progressive weakness and general wasting of the body, which began six months prior to the hospital admission. The patient suffered greater arm than leg weakness, with symptoms worsening as the day progressed. He could stand and walk short distances without assistance but fell often and required help undressing. He also experienced difficulty speaking, chewing, and swallowing. Memory and other mental capacities appeared normal. Upon arrival at the hospital, his condition did not require immediate attention, but he was admitted for monitoring. The following evening, he suddenly suffered a dyspnea attack for which artificial respiration was attempted with initial success. Unfortunately, subsequent attacks increased in frequency and severity, and the patient died within a few hours. Upon close postmortem examination, Shaw found that “beyond some pus in the smaller bronchial tubes and an enlarged mediastinal

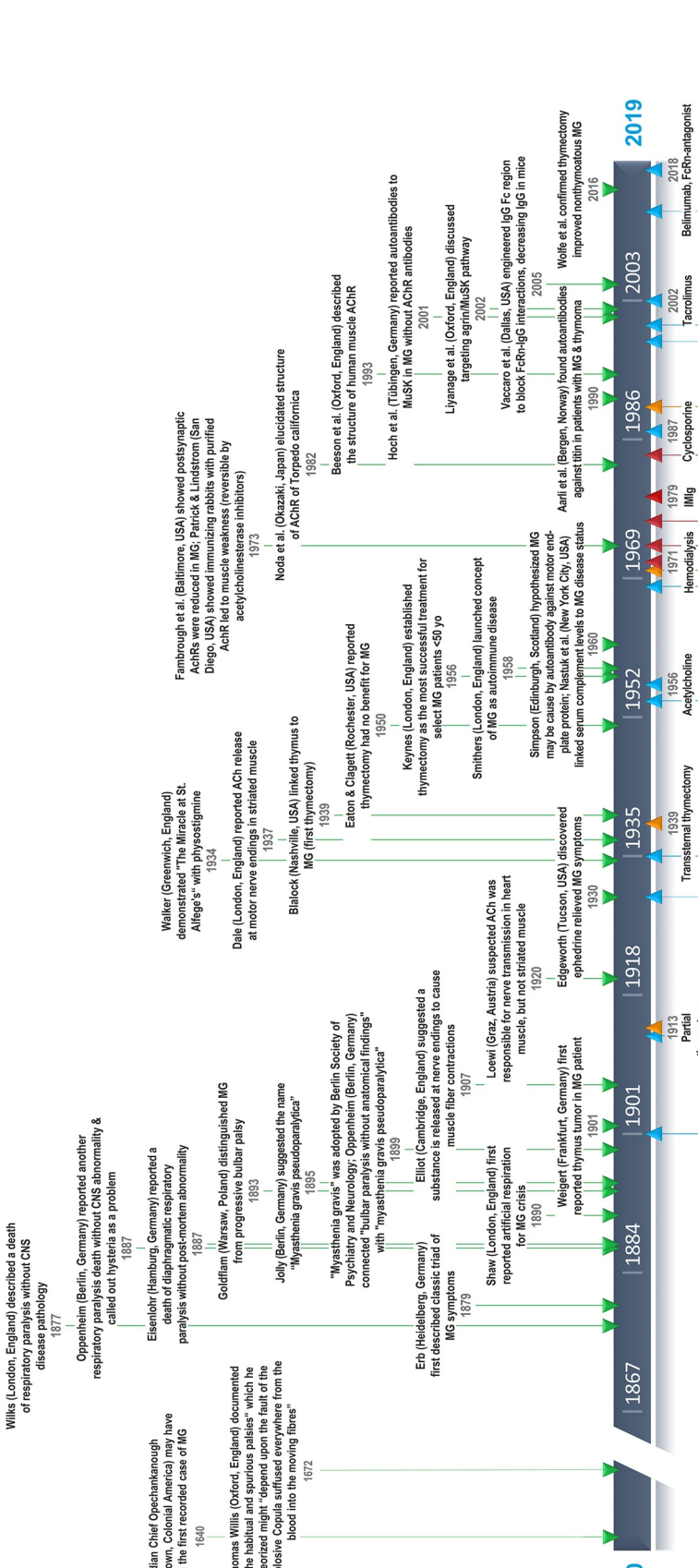

Fig. 2. Historical achievements and therapeutic approaches used to treat MG. Above the timeline are the major clinical and scientific discoveries (green) in MG [24,25,27–34,36,37,44,46,49,52,53,55,56,58,62,63,68,79,82,90–92]. Below the timeline, surgical (orange) [46,67,93–95], pharmaceutical/biological (blue) [32,33,41,43,56,58,66,81,96–104], and blood-derived (red) [71,105–108] therapeutic approaches for MG are shown as they were reported in the literature. Literature searches were performed in the Scopus search engine using the topics of the therapeutic approaches AND all forms of the word "myasthenia gravis."

gland, every organ in the body was normal." There were no signs of prior syphilis infection, no abnormalities in the central nervous system (CNS), and no microscopic abnormalities in any of the cells, fibers, vessels, and tissues examined. Shaw had suspected that the constellation of defects involving respiration, swallowing, speaking, and chewing would lead to a logical explanation of some disease in the medulla. However, no such pathology could be found. Thus, this case was added to the growing collection of mysterious deaths.

Without any obvious signs of disease pathology, it remained a mystery how these strange afflictions could rob patients of their mobility and speech upon exertion and then show improvement with rest—a hallmark of the fluctuating manifestations of MG. Physicians of that time were inclined to diagnose these patients as having "hysteria" at some point during their disease course and the minimal treatment available was often delayed, because the patients had a difficult time convincing physicians that something was truly wrong.

2.2. Myasthenia gravis: evolution of the name

The term "myasthenia gravis" evolved over time. Earlier names included "bulbar paralysis without anatomical findings" and "asthenic bulbar palsy." When it was first established as a unique disease entity, MG was also known as the "Erb-Goldflam Symptom-Complex," named after two hallmark publications distinguishing key features of MG.

Wilhelm Heinrich Erb and Samuel Goldflam were credited for describing the classic MG features and distinguishing MG from true progressive bulbar palsy. In his 1879 landmark publication [32], Erb meticulously described three cases with the triad of symptoms rare to CNS disorders: bilateral and isolated ptosis, paresis of the masticatory muscles, and paresis of the neck muscles. This peculiar symptom complex was highlighted as the primary affliction, while weakness of the tongue, extraocular muscles and extremities were of less importance. In addition, Erb noted that these three cases possessed nuances that suggested a new condition yet to be described. He could not pinpoint precisely the origin of the symptom complex, but he was convinced that the pathological processes localized in the brain. In 1893, Goldflam reinforced Erb's suspicions for this new peculiar disease by detailing three of his own cases of bulbar paralysis with extremity involvement, distinguished by periods of recovery and relapse [33]. Like Erb, Goldflam appreciated the severity of this affliction. All three patients were of similar age (25, 27, and 22 years) when the disease developed over the course of a few weeks to two months. Muscle weakness was dominated by early bulbar symptoms. One of the earliest and most salient symptoms was the impairment of the tongue and masticatory muscles. Ptosis and facial palsy were present in all cases; however, atrophy, muscle spasms, and changes in electrical excitability were generally absent. Muscles in the extremities and trunk, notably the respiratory, cervical and abdominal muscles, were all affected. All three cases showed the same characteristic rapid fatigue and decline down to zero function—with daily fluctuations and frequent remissions and exacerbations lasting for up to several days. Goldflam called for this unique condition to be positioned as its own distinct disease. Many consider that Goldflam's manuscript provided the first clear and comprehensive description of MG as a distinct disease entity.

Friedrich Jolly was the first to suggest the name "Myasthenia gravis pseudoparalytica" in 1895 [34] when describing two teenage boys with similar clinical presentation to those described by Erb [32] and Goldflam [33]. Both boys were healthy until the onset of their illness, which was characterized by intermittent paresis upon exertion that recovered with periods of inactivity and significant weakness of the neck muscles, masticatory muscles, and lips. The first boy had severe problems chewing and spent one month in a mental hospital. Jolly noticed that when the second boy exhausted one group of voluntary muscles, other groups of muscles also became weak. This phenomenon was later known as the "Walker Effect," named after Mary Walker who described it again in 1938 [35]. Jolly used the word "pseudoparalytica" to indicate the lack of structural changes.

2.3. Myasthenia gravis: a unique entity (20th century)

It was not until November 1899 that the current term, "*myasthenia gravis,*" was officially adopted at a meeting of the Berlin Society of Psychiatry and Neurology [36]. Herman Oppenheim connected the two concepts of "bulbar paralysis without anatomical findings" with that of "myasthenia gravis pseudoparalytica" in his 1899 publication [37]. In America, Wharton Sinkler used the term "Asthenic bulbar paralysis" to describe a patient in his journal article published in 1899 [38], and William Osler used the term "Asthenic (Bulbar) Paralysis" in his 1899 textbook, *The Principles and Practice of Medicine* [39]. However, he updated the term to "Myasthenia Gravis" in the following edition in 1901 [40].

There was no specific treatment for MG at the time. [41]. Treatment consisted of rest, and in severe cases, bed confinement. Patients were to avoid doing anything that could lead to muscle fatigue (ie, "excitement of every sort," cold temperature and cold baths, and chewing food that had not been chopped carefully) [41]. There was not much in the way of drug treatments. Tonics of various compounds, such as iron and arsenic [41], calcium lactate [42], iodide of potassium and mercury [32,33], and even strychnine injections [43], had been tried without effect [41]. Electrical muscle stimulation (ie, galvanism, faradism) and massage also had been tried without good results.

2.4. What's the thymus got to do with it?

After Herman Oppenheim [37] and Carl Weigert [44] reported incidental findings of thymus tumors in patients with MG, physicians started to target the thymus gland for treatment of MG. Organic extracts of various tissues, including the pituitary gland, parathyroid gland, and thyroid gland were tried but also failed [42].

In 1913, Schumacher and Roth [45] reported on a case from Zurich, in which Sauerbruch (Director of the Surgical and Medical Clinic) accidentally discovered that partial removal of the thymus to treat hyperthyroidism in a 21-year-old female patient with both hyperthyroidism and MG actually improved her MG symptoms. Fourteen days after the partial thymectomy, slight improvements of MG began to emerge. She was able to chew soft food, experienced less rapid fatigue of speech, and was able to sit up with less trouble. Subsequently, interest in the relationship between the thymus and MG increased, but it was not until 1939 that Alfred Blalock established a clear connection between the thymus and MG by becoming the first to remove a thymic tumor from a 19-year-old female patient to treat MG specifically, and reported that the patient had a favorable outcome [46]. In contrast to her previous four years of incapacitation, in the three years after her surgery, the patient had only one mild MG recurrence, lasting a few days. Two years later, Blalock reported six patients with MG treated by total thymectomy [47]. Five of the six patients had definite hyperplasia in the thymic tissue, but no adenomas were found. Microscopic sections of several patients had "germinal centers," which we now know is a common characteristic of MG.

In the years between 1949 and 1956, there was significant controversy regarding the role of thymectomy for the treatment of MG. Inspired by Blalock's work, Sir Geoffrey Keynes was the first to perform thymectomy in England in 1942 [48]. The 31-year-old female patient had very severe MG symptoms. As she also had mild thyrotoxicosis, partial thyroidectomy was performed with thymectomy. She recovered almost completely within 10 days after surgery and resumed her occupation as a land-worker. From 1942 to 1949, Keynes and his colleagues operated on 155 patients with MG [48]. Of the 120 patients without thymic tumors who survived the thymectomy, 65% (79 of 120) had a complete or almost complete remission. While Keynes et al. were collecting data supporting the benefits of thymectomy for MG, another group of surgeons in the United States came to a different conclusion. In

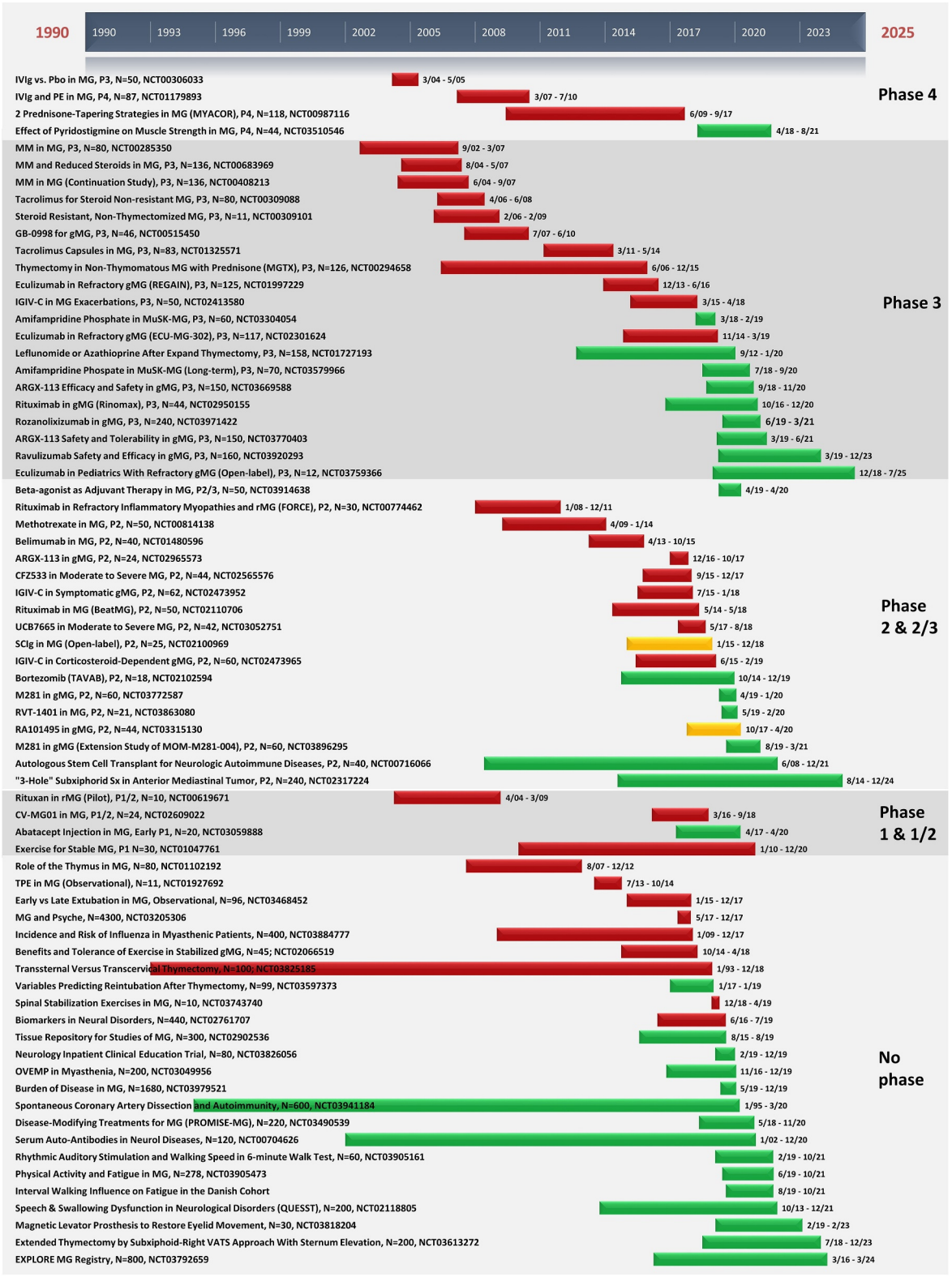

Fig. 3. Completed and on-going clinical trials registered on ClinicalTrials.gov as of August 2019. Clinical trial information retrieved from ClinicalTrials.gov using key word "myasthenia gravis". Results shown are trials with status as "completed" (red bar), "active not recruiting" (yellow bar), and "recruiting/enrolling by invitation/ not yet recruiting" (green). The trials are categorized by phases 1 through 4 in descending order. The "No phase" category includes trials without phase designation. Within each category, the trials are listed in chronological order by end date. Trials that were labeled as "terminated" or "unknown status" were not included in this figure. Two entries were excluded from this figure due to irrelevance: Translation, Cross-cultural Adaptation and Validation of the MGQOL-15-F (NCT02470364), and Rare Disease Patient Registry & Natural History Study - Coordination of Rare Diseases at Sanford (CoRDS, NCT01793168).

1950, Lee Eaton and Theron Clagett of the Mayo Clinic in Rochester, Minnesota concluded that thymectomy yielded no benefit for MG [49]. Their study compared results from 72 surgical MG cases to 142 non-surgical (control) cases. They found the percentage of surgical cases that achieved complete remissions was comparable to the percentage of nonsurgical (control) cases (6.9% of 72 surgical cases vs 7.7% of 142 control cases had complete remission). When matched for age and severity of symptoms, 8.1% of 62 surgical cases vs 8.9% of 56 control cases had complete remission. Thus, in this retrospective analysis, the chance of improvement was the same with or without thymectomy (35.5% vs 28.5%, respectively). Subsequently, thymectomy treatment for MG was met with significant skepticism and criticism worldwide. However, Keynes's group noticed early on that thymic tumors existed in about 12% of their MG patients and that these patients were generally more seriously ill and responded more poorly to thymectomy [48]. Therefore, they drew their conclusions of the benefit of thymectomy based on the nontumor majority of cases. In contrast, Eaton and Clagett had performed most of their thymectomies on patients with tumor and came to the opposite conclusion [49]. Despite the controversy, by the time Keynes retired in 1956, he had operated on 281 patients with MG, collecting the largest series of data on thymectomy of that time and continued to advocate for thymectomy as the best hope for a select subgroup of younger MG patients who were <50 years old [36]. It was not until the 21st century that the benefits of thymectomy were clearly proven in a prospective, randomized, controlled clinical trial.

Adding to the challenge of identifying the pathophysiology of MG was the recognition that a different form of fluctuating muscle weakness sometimes occurred in patients with bronchogenic carcinoma. In 1957, Eaton briefly characterized this new condition called “myasthenic syndrome sometimes associated with bronchogenic carcinoma.” [50] The new paraneoplastic condition he described later became known as “Lambert-Eaton Myasthenic Syndrome.” [51]

2.5. Developments in molecular pathology and treatments for MG

In parallel with discovering the connection between the thymus and MG, the medical field began to investigate the molecular pathology of MG during the first four decades of the 20th century. With a better understanding of the disease process, physicians started to test drug treatments for MG based on their mechanism of action and the evolving understanding of the pathophysiology of MG.

In 1907, Thomas Renton Elliott suggested that a chemical substance might be released at the nerve endings to cause muscle contractions [52]. In the 1920s, Otto Loewi described two different substances (most likely acetylcholine [ACh] and epinephrine) that might facilitate neurotransmission in cardiac muscles [53,54]. Loewi himself did not believe the same mechanism could exist in striated muscles [55]. Finally in the 1930s, Dale and other researchers demonstrated that ACh was indeed released at the motor nerve end plates to induce striated muscle contraction, and such effects were inhibited by the enzyme cholinesterase [55].

It is worth noting here that two physicians made crucial contributions to our understanding of MG: Harriet Edgeworth and Mary Broadfoot Walker. Their breakthrough discoveries in the treatment of MG arose from their astute medical intuition.

Harriet Edgeworth was an American who earned her PhD degree in chemistry and developed MG herself in her 4th year of medical school [51]. In her case report, Edgeworth described herself as a healthy and robust person before an “influenzal pneumonia” attack in December 1918 [56]. Based on her research of the literature and new awareness of the hormone ephedrine [51], Edgeworth thought that ephedrine could be effective for treating her own MG symptoms, but she was not able to convince her doctors to prescribe it for her. By 1928, Edgeworth had deteriorated severely, and in 1929 while taking a combination of 0.1 g amidoprine and 8 mg ephedrine for menstrual cramps, Edgeworth noticed a degree of muscle improvement that had not happened in many months. She reported these findings in 1930 [56] and confirmed her continued improvements with 48 mg ephedrine sulphate or ephedrine hydrochloride in a subsequent report in 1933 [57].

Ephedrine became a secondary drug for MG for many years. Edgeworth herself continued to benefit from ephedrine for 18 years [51]. It was later discovered that ephedrine boosted the effect of physostigmine.

Mary B. Walker is credited for the most significant event in MG history, “The Miracle at St. Alfege's” in 1934 [58]. As Oppenheim did in 1901, Walker recognized the similarities between symptoms of curare poisoning and MG, so she tried the antidote for curare poisoning, physostigmine, on a 56-year-old female patient with MG. The hypodermic injections of physostigmine salicylate began working within an hour and the positive effects wore off gradually over 2 to 4 h. The patient had significant improvements in her eyelid opening, stronger arm movements, less jaw dropping, and improved swallowing. The patient received 26 injections with varying degrees of effectiveness and felt better after the physostigmine treatments began. Walker suspected that physostigmine inhibited the enzyme at the neuromuscular junction (NMJ) that destroyed acetylcholine, which we now know is acetylcholinesterase. Years later, Walker demonstrated that neostigmine, another acetylcholinesterase inhibitor, worked well with fewer side effects than physostigmine.

In 1941 Harvey and Richard Masland demonstrated that the muscles of myasthenic patients responded to repetitive nerve stimulation similarly to muscles that had been partially curarized [59]. Curare poisoning was thought to be a result of curare competing with ACh at the muscle endplate, thus blocking ACh's ability to stimulate muscle contraction. With the commercial availability of the electron microscope in the 1950s and more sophisticated techniques for electrophysiological investigations, researchers were able to visualize the subcellular structure of the nerve terminal and clinically evaluate function of the muscle endplate [60,61]. Being able to visualize these endplates and conduct quantitative testing via electrodiagnostic testing catapulted our fundamental understanding of neurotransmission at the molecular level.

It was not until 1958 that D. W. Smithers first suggested MG may be a result of autoimmune dysregulation [62,63]. Two years later, John Simpson associated MG with thymus abnormalities and other autoimmune diseases (ie, hyperthyroidism, lupus, rheumatoid arthritis, sarcoidosis) [63]. Simpson hypothesized that an autoantibody against proteins at the motor end plate may be blocking nerve signaling in MG patients. In addition, Nastuk and colleagues linked changes in serum complement levels to MG disease status [64,65]. Corticosteroids were introduced in the 1950s but were not used widely in MG due to observations of exacerbation of weakness leading to MG crisis (respiratory compromise requiring ventilator support) in some patients after starting corticosteroids. It took 2 decades for steroids to become a mainstay of treatment in the 1970's, when it was observed that a proportion of patients experienced subsequent improvements in weakness after an initial transient deterioration with corticosteroids [66,67].

Also in the 1970s, researchers discovered that ACh receptors (AChR) were the target of the autoimmune antibodies in MG [68] and that AChR-immunized rabbits experienced myasthenic-like weakness, which was treatable with acetylcholinesterase inhibitors [69,70]. Various therapies were used in the 1960s aiming to remove possible pathologic components from the circulation. Hemodialysis and lymph duct drainage were attempted without much promise, but in the 1970's clinicians began using plasma exchange (PLEX) to remove, and thus reduce, autoantibodies at the neuromuscular junction. In 1979, Gabriel Genkins used intramuscular injections of pooled gammaglobulin to “block” pathologic antibodies [71]. Then in the mid-1980s intravenous immunoglobulin (IVIg) was found to have rapid effectiveness for transient improvement of MG [72,73].

Plasma exchange and IVIg are still recommended as short-term treatment options for myasthenic patients with life-threatening

Table 1
Current treatment options for MG [89].

Therapy	Possible mechanism(s)	Agent(s)
Thymectomy	Removal of thymoma or hyperplastic nonthymomatous thymus	–
Cholinesterase inhibitors	Reduce breakdown of ACh at NMJ	Mestinon (pyridostigmine), Neostigmine
Immunosuppressive agents	Reduce production of abnormal autoantibodies	Corticosteroids (eg, prednisone), azathioprine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide, cyclosporine
Plasmapharesis, referred to as PLEX	Removal of autoantibodies by plasma exchange	Exchange replacement fluid, albumin (human)
Intravenous immunoglobulin	Modulating the pathogenic autoantibody response likely by multiple complementary mechanisms	Immunoglobulin
Monoclonal antibodies	Differing mechanisms of action based on specific antibody target	Belimumab, eculizumab, rituximab

ACh, acetylcholine; MG, myasthenia gravis; NMJ, neuromuscular junction; PLEX, plasma exchange.

complications, prior to surgery, prior to corticosteroid initiation to avoid exacerbations, at times when response is needed rapidly, and when other treatments are not adequate [74]. For MG crisis, PLEX and IVIg are the main treatments. For refractory MG, chronic PLEX and chronic IVIg have been used in addition to other immunosuppressive treatments, and most recently the complement inhibitor eculizumab has shown good efficacy in this population.

3. Accelerated progress with clinical trials

In the last 50 years, numerous clinical trials have been conducted in search of better treatments for MG. Due to the fluctuating nature of the MG disease course, it has been difficult to establish conclusively the effectiveness of some treatments for MG. Various outcome measures have been developed. The Quantitative Myasthenia Gravis (QMG) Score, is the most comprehensive objective set of measurable assessments of MG physical functioning inclusive of bulbar and respiratory function (forced vital capacity) [75]. Other MG scoring systems utilized in clinical trials include the MG composite, and patient-reported outcomes such as MG activities of daily living (MG-ADL), and MG quality of life (MG-QOL).

Many of the currently recommended therapies used in MG lack Class I evidence. It is necessary to conduct prospectively designed clinical trials, even for existing treatments that have been in use in the field to establish definitive product effectiveness and safety. Past clinical trial failures may have been due to: 1) insufficient powering; 2) inadequate study duration; 3) improperly chosen endpoints; and 4) concomitant drugs that the patients were already taking.

The last 15 years have seen an acceleration of clinical trials. As of August 2019, 70 clinical studies have been completed or are on-going (Fig. 3). We searched ClinicalTrials.gov for studies with the key words "myasthenia gravis," excluding those that were suspended, terminated, withdrawn, or of unknown status. There were 72 entries total; 2 were excluded due to irrelevance (Translation, Cross-cultural Adaptation and Validation of the MGQOL-15-F (NCT02470364), and Rare Disease Patient Registry & Natural History Study - Coordination of Rare Diseases at Sanford (CoRDS, NCT01793168). The remaining 70 studies comprise 33 "completed" studies, 3 "active, not recruiting" studies, and 34 "recruiting/enrolling by invitation/not yet recruiting" studies. Due to space constraints, we will not discuss the details of each trial but rather wish to highlight some of the recent clinical trials of interest.

Through the years, some of the older treatments for MG have been replaced by newer treatment options. Treatment options being used by physicians today are summarized in Table 1, and are based on standard clinical practices and pragmatic medical approaches to MG management. Eculizumab (Alexion Pharmaceuticals, New Haven, CT, USA) has shown demonstrable efficacy in phase 3 clinical development and achieved regulatory approval with labeling specifically for MG [76–78]; and the value of thymectomy [79] has also been definitively demonstrated in a randomized clinical trial. However, Class 1 evidence is not universally available for all MG medications in the table.

After decades of controversial debates about the effectiveness of thymectomy for MG, the MGTX trial ($N = 126$), which studied thymectomy plus prednisone vs prednisone alone, finally gave us conclusive evidence that removal of the thymus does benefit patients with nonthymomatous MG and reduces the requirement for immunosuppressive medication [79]. Relative to the patients who took prednisone alone, patients who underwent thymectomy and took prednisone had a lower time-weighted average QMG score (6.15 vs 8.99, $P < .001$), which indicated clinically relevant improvement, and a lower average prednisone need (32 mg vs 54 mg, $P < .001$).

Eculizumab is the latest addition to the MG treatment repertoire. It is a complement inhibitor for the terminal portion of the complement cascade [77,80,81]. Based on data from the REGAIN study (ECU-MG-301) [76], the U.S. Food and Drug Administration (FDA) approved eculizumab for adult patients with generalized MG who are anti-AchR antibody-positive. Regulatory approval in Europe has also been achieved for eculizumab.

Future trials are anticipated for neonatal Fc receptor (FcRn) blocking agents (ie, ARGX-113 [argenx, Boston, MA, USA]) that may lower autoantibody. The Fc region of a human IgG was engineered to modulate endogenous IgG concentrations [82]. Encouraging results from the recent phase 2 randomized, double-blind, placebo-controlled, multicenter study conducted in 24 patients with generalized MG showed that ARGX-113 yielded improvement in MG-ADL scores through $\geq$6 weeks relative to 25% of patients on placebo [83]. Further studies are needed to determine whether this approach is as effective and safe as other treatments for patients with MG.

4. Clinical trials with immunoglobulin

For the purpose of streamlining this review, we focus on the four published clinical trials that tested IVIg products for the treatment of MG (Table 2), which were also evaluated in the most recent Cochrane Review [84]. As of August 2019, two (NCT00306033, NCT01179893) of the 70 clinical studies registered on ClinicalTrials.gov (Fig. 3) tested IVIg products (Talecris Biotherapeutics, currently known as Grifols Therapeutics, Research Triangle Park, NC, USA). The other two studies [85,86] that reported on IVIg products (LFB Laboratories, Les Ulis, France) will be discussed here but are not represented in Fig. 3, because they were not registered on ClinicalTrials.gov. And although listed on ClinicalTrials.gov as studies testing Ig, we will not discuss the unpublished studies on GB-0998 (pegylated form of IVIg, NCT00515450) from Mitsubishi Tanabe Pharma Corporation (formerly known as Benesis Corporation, Osaka, Japan), caprylate/chromatography-purified IVIg (NCT02413580, NCT02473952, NCT02473965) from Grifols Therapeutics (Research Triangle Park, NC, USA), and subcutaneous Ig (NCT02774239, NCT02100969) from CSL Behring (King of Prussia, PA, USA).

In aggregate, the four published studies compared IVIg to placebo or PLEX in a randomized, controlled manner with a short-term primary endpoint at either day 14 or day 15. One of these trials compared two

Table 2
Summary of clinical trials involving IVIg and/or PLEX in patients with MG.

	Trial design (number of patients)	Disease state	Intervention	Authors' overall conclusions
Gajdos et al. [85]	Prospective, randomized (N = 87)	MG exacerbation	• 3 PLEX sessions on alternate day, versus • IVIg at 0.4 g/kg/day for 3 days or for 5 days	• Improvement in MMS seen from randomization to day 15 for all treatment arms with no significant difference between IVIg and PLEX, or between the 2 regimens of IVIg • IVIg appeared to be better tolerated
Gajdos et al. [86]	Prospective, randomized, double-blind (N = 173)	MG exacerbation	• 1 g/kg/day IVIg on day 1, versus • 1 g/kg/day IVIg on day 1 and day 2	• Response in MMS seen from randomization to day 15 for both treatment arms with no significant difference between the 2 regimens of IVIg
Zinman et al. [87] NCT00306033	Prospective, placebo-controlled, randomized, double-blind (N = 51)	Worsening chronic MG	• 2 g/kg IVIg over 2 days • Placebo	• Significant improvement (P = .047) in QMG score from randomization to day 14 with IVIg (−2.54) relative to placebo (−0.89) • Moderate and severe MG subpopulations appeared to benefit more from IVIg • More severe MG subpopulation had clinically meaningful QMG score improvement of −4.1
Barth et al. 2007 [88] NCT01179893	Prospective, randomized, assessor-blinded (N = 84)	Moderate to severe MG and worsening weakness	• 1 g/kg/day IVIg for 2 consecutive days • 5 PLEX sessions every second day	• Improvements seen in QMG score from randomization to day 14 in both treatment groups • IVIg was noninferior to PLEX

ACh, acetylcholine; CS, corticosteroid; IGIV-C, immune globulin intravenous injection, caprylate/chromatography purified; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MMS, Myasthenic Muscular Score; NMJ, neuromuscular junction; PLEX, plasma exchange; QMG, Quantitative Myasthenia Gravis.

different dose levels of IVIg. Two of the four studies [87,88] were done in the setting of worsening (chronic) MG. The other two studies were undertaken in the setting of MG exacerbations [85,86]. All of these trials employed a loading dose divided over one to five days, and none evaluated multiple doses of IVIg given as maintenance treatment over a prolonged time period. These four studies are described below in chronological order of publication date.

Gajdos and colleagues (1997) prospectively randomized 87 participants experiencing an exacerbation of MG [85]. They received three sessions of alternate-day PLEX (1.5 volumes) versus IVIg (LFB, Les Ulis, France) at one of two doses: 0.4 g/kg/day for 3 days or for 5 days. The primary endpoint was the MMS change between randomization and day 15. There was improvement in the MMS in all treatment arms with no significant difference between IVIg and PLEX, or between the two dose regimens of IVIg. The authors reported that IVIg appeared to be better tolerated.

Gajdos et al. (2005) then conducted a prospective, randomized, double-blind trial comparing two different doses of IVIg (1 g/kg/day delivered on day 1, versus 1 g/kg/day delivered on both day 1 and day 2; LFB, Les Ulis, France) in 173 participants experiencing an exacerbation of MG [86]. The primary endpoint was change of the MMS between randomization and day 15. Both arms showed a treatment response, and there was no significant difference between the two IVIg doses.

Zinman and colleagues conducted a prospective, placebo-controlled, randomized and double-blind trial (NCT00306033) of IVIg 2 g/kg over two days (Grifols, formerly known as Talecris Biotherapeutics, Toronto, Canada) versus placebo in 51 participants with worsening chronic MG [87]. The primary endpoint was change in the QMG score from baseline through day 14. The study demonstrated a significant (P = .047) improvement in the QMG score with IVIg (−2.54) relative to placebo (−0.89). Notably, the subpopulation with moderate and severe MG appeared to benefit more from IVIg. Subjects with more severe disease who were treated with IVIg had a clinically meaningful improvement in the QMG score of −4.1, well above a target value of −3.5 for benefit. Overall, the mean change in score was −2.5 for the entire group given IVIg.

Barth and colleagues conducted a prospective, randomized, assessor-blinded trial (NCT01179893) of IVIg (Grifols, formerly known as Talecris Biotherapeutics, Mississauga, Canada) vs. PLEX in 84 participants with moderate to severe MG and worsening weakness [88]. Participants randomized to IVIg were dosed with 1 g/kg/day for two consecutive days, while PLEX participants received five plasma exchanges every second day. Participants in both groups exhibited improvements in the change in QMG score from randomization to day 14 (primary efficacy outcome); they were followed for a total of 60 days. Use of IVIg was found to be non-inferior to PLEX.

In the last 50 years, significant progress has been achieved in the development of treatment options via studies in patients with generalized MG and in the MG exacerbation setting. However, there is still progress to be made and clinical data need to be obtained to understand the effectiveness and safety of new products or existing products in this rare disease.

5. Conclusions

Since the documented illness of Chief Opechankanough >350 years ago, we have gained extensive knowledge about MG. With all of the advances in technology, outcome measures, and therapies on the market, we welcome the explosion of clinical trials that will hopefully provide more definitive data regarding how to treat MG. Some of the therapies (thymectomy, corticosteroids, PLEX, IVIg) have survived the test of time. Others are novel and hold promise. As we move into the modern era of personalized medicine, we look forward to seeing how new data from upcoming clinical trials will impact the MG patient population, and how different types of patients with MG may respond

to various therapies depending on their underlining molecular pathology.

Author's contributions

Tam Nguyen-Cao conducted the literature research, analyzed search results, and wrote the initial draft of this manuscript. Deborah Gelinas, Elsa Mondou, and Rhonda Griffin provided critical review and revision of the manuscript. All authors approved the final draft for submission.

Declaration of Competing Interest

All authors are employees of Grifols, a manufacturer of IVIg.

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ACh, acetylcholine; AChR, acetylcholine receptor; CNS, central nervous system; IgG, immunoglobulin G; IMIg, intramuscular immunoglobulin; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MuSK, muscle-specific kinase; PLEX, plasma exchange; USA, United States of America.

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