Journal of Biosciences and Medicines, 2023, 11, 106-119
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

New Progress in the Treatment of Myasthenia Gravis

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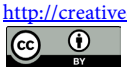
How to cite this paper: Sun, Y.P. and Cheng, X.L. (2023) New Progress in the Treatment of Myasthenia Gravis. *Journal of Biosciences and Medicines*, **11**, 106-119.
https://doi.org/10.4236/jbm.2023.1112010

Received: October 10, 2023
Accepted: December 5, 2023
Published: December 8, 2023



Abstract

In recent decades, the treatment of myasthenia gravis has been extensively developed, but a standardized standard still needs to be used. Its treatment strategy is associated with patient prognosis, economic costs, and complications. This article reviews the pathogenesis, treatment methods, and complications of myasthenia gravis, providing new ideas for diagnosing and treating myasthenia gravis and fully embodies the principle of safety and precision.

Keywords

Myasthenia Gravis, Thymusectomy, Immunosuppressive Drug, Biological Drug

1. Introduction

Myasthenia Gravis (MG) is a disease that targets neuromuscular joints and postsynaptic membrane antibodies. Its clinical feature involves skeletal muscles becoming tired and weak, with varying degrees of severity [1]. The annual incidence of this disease ranges from 4.1 to 30 cases per million people, while the yearly prevalence rate is 150 to 200 cases per million people [2]. Due to immune attacks on the postsynaptic membrane of neuromuscular joints, the typical symptoms are fluctuating weakness and fatigue, affecting their eye muscles, spinal cord function, limbs, and respiratory muscles. MG is one of the treatable neurological diseases. Currently, the main clinical treatments for this disease are drug treatment, surgical treatment, and traditional Chinese medicine. [3] Significant progress has been made in developing innovative treatment methods in recent decades. Yet, there still needs to be standardized and uniform treatment standards, and the traditional treatment methods have some deficiencies. Hence, opting for a rational diagnosis and treatment strategy is crucial. A review of MG's

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latest biological treatment strategies is presented to garner greater clinical attention towards this rare neurological disease and enable more patients to access optimal care.

2. Traditional Treatment Strategies and Their Shortcomings

2.1. Anticholinesterase Drugs

Neurodegenerative diseases are a group of disorders characterized by the progressive loss of structure or function of neurons, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Acetylcholinesterase (AChE) plays a crucial role in the pathogenesis of these disorders by influencing inflammatory responses, cell apoptosis, oxidative stress, and aggregation of pathological proteins. Initially, neostigmine and physostigmine were identified by Scottish doctors as drugs that transiently improved skeletal muscle in patients with myasthenia gravis (MG) and were called the "Mary Walke effect" [4]. Once the diagnosis of MG is established, treatment should be to control the symptoms promptly. Acetylcholinesterase inhibitors (AChEI), such as pyridostigmine bromide, are the most common symptomatic treatment drugs, and their clinical efficacy has been confirmed by electrophysiological measurements [5]. Good clinical practice has supported their widespread use in the treatment of MG [6]. These drugs improve the structure and functional defects of the neuromuscular junction (NMJ) in patients with MG by prolonging the release of acetylcholine into the synaptic cleft. However, the use of AChEI can lead to excessive accumulation of acetylcholine at the NMJ and synapses, resulting in symptoms of muscarinic and nicotinic toxicity. In a study by Remijn-Nelissen *et al.* [7], all patients treated with pyridostigmine for MG reported side effects (55% in the control group). The most common side effects were gastrointestinal gas, urinary urgency, muscle spasms, blurred vision, and hyperhidrosis, with 26% of patients discontinuing treatment due to intolerance. The study found that the most common reason for stopping pyridostigmine was diarrhea, abdominal cramps, and muscle cramps. Currently, AChEIs are commonly used for the clinical diagnosis of MG. In addition to using AChEIs alone to improve symptoms in early generalized MG treatment, other cases require combined medication. However, the combined pill has many adverse reactions and is difficult to control. Due to the many adverse reactions of AChEIs and to fully embody the concept of individualized precision medicine and maximize patient benefits, seeking new treatment strategies or developing new AChEI drugs at appropriate times is necessary.

2.2. Thymectomy

The thymus has been recognized as the primary site of auto-sensitization in patients with AChR-MG, with most of these patients exhibiting thymus abnormalities, including follicular hyperplasia and thymoma [8]. The reported thymic hyperplasia in about 70% of patients with early-onset MG represents the ratio-

nale behind thymectomy as a therapeutic strategy to modify the natural course of MG. The underlying concept is to remove the site of the autoimmune attack that is responsible for self-sensitization [9]. Wolfe *et al.* [10] conducted a multi-center, randomized trial comparing the efficacy of thymectomy plus prednisone versus prednisone alone in patients with MG. The results showed that patients who underwent thymectomy had a lower time-weighted average severe quantitative muscle weakness score over three years compared to patients who received prednisone alone (6.15 vs. 8.99, $p < 0.001$). The thymectomy group also had a lower average requirement for prednisone (44 mg vs. 60 mg, $p < 0.001$). There were fewer patients in the thymectomy group compared to the prednisone-alone group who required azathioprine immunosuppression (17% vs. 48%, $p < 0.001$) or were hospitalized due to acute exacerbations (9% vs. 37%, $p < 0.001$). The two groups had no significant difference in the number of patients with treatment-related complications ($p = 0.73$). Still, the thymectomy group had fewer treatment-related symptoms related to immunosuppression ($p < 0.001$) and lower symptom-related distress ($p = 0.003$). This confirms the beneficial effect of thymectomy in patients with hyperplastic thymus and supports using thymectomy as a therapeutic strategy to modify the natural course of MG, particularly in non-thymoma MG patients. However, the significance of thymectomy in the treatment of non-thymoma MG has remained controversial until recent times. Zhang *et al.* [11] proposed that thymectomy applies to almost all patients with thymoma and severe myasthenia gravis patients with acetylcholine receptor antibodies. This includes patients with severe myasthenia gravis, especially young female patients; patients who are refractory to or intolerant of medical therapy; patients with thymic tumors or thymic enlargement; and patients with thymic inflammation or other severe comorbidities. It is particularly suitable for patients with acetylcholine receptor antibodies, severe myasthenia gravis, symptoms not limited to ocular myasthenia gravis, age < 50 years, and short duration of severe myasthenia gravis. A study has shown [12] that among 46 patients with severe myasthenia gravis undergoing thymectomy, thymoma (23.96%) was more common in elderly patients (53 ± 20 years old compared to 33 ± 24 years old) and males (54.5% compared to 18.8%). One year after thymectomy, 28.2% of patients had a poor prognosis, while 54.3% of patients had a good prognosis. Thymectomy in patients with MG can have a wide range of histological findings, from normal thymus to thymoma, with a preference for cortical phenotype. Still, there may be some errors in pathological specimens [13]. The incidence and prevalence of MG patients with thymoma are relatively low, and the inconsistent results of various studies and the need for long-term observation of treatment efficacy make it challenging to generate compelling data. A comprehensive analysis suggests that thymectomy can be beneficial under certain conditions, as it can significantly reduce the medication dosage required by postoperative MG patients. For MG patients with thymoma, the risk of surgery should be jointly considered by thoracic surgeons and neurologists, often under stable conditions, to reduce the incidence of postoperative crisis. However, sur-

gery may not significantly improve MG symptoms in patients with malignant thymoma, as it primarily aims to treat the thymoma itself.

2.3. Immunosuppressive Drugs

Immunosuppression is a common clinical approach for treating MG, including "broad-spectrum" immunosuppressive therapy using drugs such as corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, ciclosporin, tacrolimus, etc. In 1935, Simon [14] reported the effectiveness of using pituitary extracts to treat MG. This may be the first description of the therapeutic effect of corticosteroids on MG. However, there is currently no standard oral corticosteroid dosing regimen in guidelines. Glucocorticoids (GC) are the preferred treatment for MG, based on their rapid onset of action, low cost, and high efficiency, which can improve the condition of 80% - 95% of patients. Once the symptoms are relieved, the corticosteroid dose should be reduced or stopped to minimize long-term side effects [15]. With their widespread use, the side effects of corticosteroids have been extensively studied, including side effects ranging from mild to severe, affecting multiple bodily systems, including musculoskeletal (such as osteoporosis and muscle disease), metabolic and endocrine (such as hyperglycemia, Cushing's syndrome, weight gain, and hirsutism), immunological (such as infection), cardiovascular (such as hypertension and arrhythmia), gastrointestinal (such as gastric ulcer and bleeding), neuropsychiatric (such as mood changes and psychosis), ocular (such as glaucoma and cataracts), and laboratory abnormalities (such as hypokalemia) [16]. Menon D [17] *et al.* believe that this type of treatment has many drawbacks, such as increasing the risk of life-threatening infections, widespread systemic side effects, delayed onset of action, and an apparent increase in the risk of malignancies and drug toxicity. In clinical practice, most patients experience significant side effects after long-term use of immunosuppressants. At the same time, reducing the dosage of immunosuppressants is associated with a risk of recurrence. If the reduction is too rapid, the risk of recurrence increases even more. Therefore, GC is generally used as a first-line rescue treatment for MG patients experiencing side effects when using AChEI.

2.3.1. Azathioprine

Azathioprine is a purine analog whose metabolism produces the active compounds 6-mercaptopurine and 6-thioguanine triphosphate. These metabolites inhibit cell synthesis and replication by incorporating into DNA and RNA, thus limiting lymphocyte proliferation [18]. As early as 150 years ago, azathioprine was successfully used to treat MG at 200 - 1969 mg/d [19]. A prospective randomized study included three MG patients and compared prednisolone + azathioprine with prednisolone + placebo, finding that maintenance remission rates were significantly lower in the prednisolone group compared with the placebo group, with a lower recurrence rate in the azathioprine group [20]. Another prospective randomized study showed that using azathioprine reduced predni-

solone dosing rapidly [21]. In clinical practice, azathioprine is one of the preferred steroid-sparing agents for patients who cannot receive corticosteroids or are taking corticosteroids but cannot tolerate the side effects. It is initiated at a dose of 50 mg daily for two weeks, then gradually increased to the total amount of 2 - 3 mg/kg/day, rarely causing idiosyncratic reactions but requiring regular monitoring of peripheral blood cell count and liver enzymes, with good tolerability and low incidence of side effects.

2.3.2. Tacrolimus

Tacrolimus (FK 506) is a macrolide antibiotic that functions similarly to cyclosporine A (CsA). By binding with immunophilin, calmodulin was inhibited, interleukin synthesis, nitric oxide synthase activation, and cell degranulation, and the effect of glucocorticoid was enhanced. [22]. A systematic review of prospective clinical trials from 1947 to 2014 showed that tacrolimus reduced QMG scores and corticosteroid burden in patients with refractory and newly diagnosed MG [23]. The starting dose of tacrolimus is 4 mg/d or 8 - 10 mg/kg/d administered twice daily, with a target trough concentration of 81.90 - 91 ng/mL [24]. Side effects include hyperglycemia, hypomagnesemia, hypertension, headache, tremors, diarrhea, nausea, and sensory abnormalities [25].

2.3.3. Cyclosporine

CsA is a lipophilic cyclic peptide derived from fungi that inhibits T-cell activation by blocking the transcription of cytokine genes [22]. Cyclosporine is effective in patients with MG who are refractory to standard first-line agents or dependent on IVIG or PLEX for a long time. A study evaluated CsA treatment in 52 patients with severe generalized MG whose disease was not controlled by anti-cholinesterase drugs, thymectomy, corticosteroids, and azathioprine. This study showed that CsA is an effective and safe treatment for severe and refractory forms of MG [26]. It is initiated at a dose of 3 mg/kg/d and increased to 6 mg/kg/d, titrated based on clinical response, therapeutic drug monitoring (400 - 600 ng/mL), or serum creatinine levels [27]. Possible side effects include influenza-like symptoms, myalgia, nephrotoxicity, hypertension, gingival hyperplasia, hypertrichosis, postural tremors, headache, sensory abnormalities, and optic neuropathy [26].

Although such treatments have significantly improved patients' survival rates, MG patients' quality of life still needs improvement. Introducing new alternative treatment options is the key to changing the clinical treatment pattern of MG. Current biologics can specifically eliminate abnormal antibodies, reducing attacks on the neuromuscular system and improving MG symptoms, and may become potential alternative treatment options to immunosuppressants for treating MG.

2.4. Venous Plasma Replacement and Immunoglobulin Therapy

Plasma exchange has been widely used in autoimmune neurological diseases and

is the standard treatment for myasthenic crisis and Guillain-Barre syndrome (GBS) [28]. Currently, plasma exchange (PE) is commonly used for patients with acute exacerbation of MG. Safa *et al.* [29] suggested that patients receiving intravenous immunoglobulin (IVIG) or plasma exchange (PLEX) as first-line treatment have better outcomes in improving MG symptoms compared to patients receiving steroid treatment alone (95% vs 63%, p = 0.011). Nagayasu *et al.* [30] conducted a study that showed preoperative plasma exchange may help improve the prognosis of MG patients after thymectomy. In early observational reports [31], IVIG was effective in nearly 70% - 75% of MG patients. Peng *et al.* [32] believed that PE combined with IVIG could effectively enhance the immune function of MG patients and promote the prognosis, ensuring treatment safety. Japanese researchers have shown that PE can be applied to various neurological diseases to recognize immune involvement [33]. The most common illnesses treated by PE are MG, followed by autoimmune encephalitis/encephalopathy, multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), chronic inflammatory demyelinating polyneuropathy (CIDP), and GBS. Current MG guidelines recommend intravenous immunoglobulin or PE during the myasthenic crisis. Still, intravenous immunoglobulin or PE is expensive and often unavailable in developing countries, and there is a risk of blood-borne infections during plasma exchange therapy.

3. New Treatments with Biological Drugs

Some MG patients either do not respond adequately or have poor tolerance to existing drugs, thus necessitating new treatments. This paper describes the latest situation of three categories of targeted biological agents in chronic management, with complement inhibitors, FcRn cells, and B cells as the focus for treating MG.

3.1. FcRn Cell Therapy Strategy

A study by Nair SS [34] *et al.* found that FcRn blockers and B cell depletion agents have shown promising efficacy in MG treatment regimens. Such drugs are most valuable for refractory MG patients, and their use in early severe patients may alleviate symptoms. Neonatal Fc receptor (nFcR) antagonists are a new class of drugs first used in MG [35]. The neonatal Fc receptor (FcRn) functions as the intracellular protective receptor for IgG [36]. Antagonizing FcRn to prevent its binding with IgG can accelerate the latter's catabolism, reducing IgG levels, including pathogenic autoantibodies, thereby achieving therapeutic effects [37]. The ability of these drugs to rapidly reduce circulating Igs provides a new therapeutic option for antibody-mediated diseases; if proven effective, nFcR could become an alternative to intravenous immunoglobulin or plasma exchange, overcoming the increasing demand for human plasma or the feasibility of single donation in patients with poor vascular access [38]. Keller *et al.* [39] are developing therapeutic strategies that utilize FcRn function to enhance endogenous

IgG degradation or increase the serum half-life of therapeutic Abs, which could significantly improve the treatment management of MG.

3.2. FcRn Therapeutics

Efgartigimod is an Fc fragment, while rozanolixizumab, batoclimab, nipocalimab, and olisoxib are monoclonal antibodies against FcRn. Efgartigimod has been FDA-approved for managing refractory generalized myasthenia gravis (gMG) and is currently undergoing phase III trials for nipocalimab and batoclimab [40]. Studies have shown that efgartigimod improves health-related quality of life in gMG patients, with significant and rapid improvement in HRQoL observed up to 2 weeks after the first infusion of TC 8 and TC 1 [41]. In critical clinical trials of gMG patients, efgartigimod α rapidly reduced disease symptoms and improved quality of life [42]. Rozanolixizumab is also being developed to mitigate pathogenic IgG in autoimmune and alloimmune diseases [43]. In various phase I, II, and III trials to date, phase I trials have assessed the drug's safety, tolerability, pharmacokinetics, and pharmacodynamics on circulating IgG concentrations. Pharmacokinetics showed nonlinear increases with dose, and serum IgG concentrations (IV and SC rozanolixizumab) had sustained dose-dependent reductions [44]. Phase II trials have investigated clinical efficacy and safety in gMG patients, with data suggesting that rozanolixizumab may provide clinical benefits to gMG patients, usually with good tolerability [45]. Compared to FcRn-targeted therapies, the regulation of classic FcγR function or signaling has been less studied in MG, and further research is needed to understand their biology and potential pathogenic role in MG. FcγR modulation may benefit several Ab-mediated autoimmune diseases [39]. This year, efgartigimod has been officially launched in China and approved by the National Medical Products Administration to be used in combination with conventional therapeutic drugs for the treatment of adult generalized myasthenia gravis patients with acetylcholine receptor (AChR) antibody positivity. This marks a milestone in helping MG patients improve muscle strength and quality of life.

3.3. Targeted B-Cell Therapeutic Strategies and Drugs

B-cells are a vital element in the immunopathogenesis of MG, and drugs that selectively target these cells may be therapeutically relevant. Therefore, therapeutic approaches that target critical molecules of B-cells (primarily CD19 and CD20) are expected to be effective in treating MG [46]. CD20 plays a crucial role in B-cell growth and differentiation into plasma cells. Rituximab, a chimeric monoclonal antibody against the B-cell surface antigen CD20, depletes CD20-positive B-cells for 6 - 12 months, primarily through cell apoptosis and receptor downregulation. Its immune effects include reducing antigen presentation, reducing cytokine production, T-cell and macrophage activation, and upregulating Treg cells [47]. Compared to rituximab, epratuzumab is a humanized IgGκa monoclonal antibody that targets the CD19 surface antigen on B-cells. A placebo-controlled

trial for NMO spectrum disorders showed that the treatment group had a lower recurrence rate, indicating that epratuzumab may also be a targeted B-cell therapy option for MG [48]. In addition, inflammatory cytokines initiate and activate dendritic cells, antigen-specific helper T-cells, and B-cells, inducing pathogenic differentiation and development of plasma cells. Therefore, drugs that inhibit cytokine/chemokine activity represent an effective potential therapeutic strategy [49]. Studies have shown that abnormal proportions and functions of Breg cells can cause harmful effects in MG patients and trigger autoimmunity [50]. A better understanding of the interactions between human Breg and other immune cells, especially in the thymus of MG patients, is worth pursuing to develop new therapeutic strategies. Non-controlled studies have shown that the use of rituximab can significantly reduce or discontinue the use of steroids and other immunosuppressants [51]. Compared to acetylcholine receptor antibodies (AChR Ab+), rituximab is more effective in MuSK Ab+ MG [52]. However, side effects include infusion reactions (itching, redness, shortness of breath, and chills), infections, hematological disorders, alopecia, and atrial fibrillation [53]. In addition, drugs that inhibit cytokine/chemokine activity represent an effective potential therapeutic strategy [52]. Studies have shown that abnormal proportions and functions of Breg cells can cause harmful effects in MG patients and trigger autoimmunity [53]. A better understanding of the interactions between human Breg and other immune cells, especially in the thymus of MG patients, is worth pursuing to develop new therapeutic strategies.

3.4. Complement Inhibitor Therapeutic Strategies and Drugs

The main driver of the pathology of AChR antibody-positive MG is represented by complement activation. The role of the complement cascade has been widely demonstrated in patients and MG animal models [54]. The primary function of complement is to recognize and destroy invading microorganisms through the formation of the membrane attack complex (MAC) [55], and it also plays a crucial role in adaptive immunity by enhancing the antibody response. It is associated with clearing apoptotic cells and immune complexes [56]. Anti-C5 therapy has been used in patients with gMG and NMOSD, two neurological disorders driven by different pathogenic autoantibodies, which have become catalysts for developing complement inhibitors in this field [57]. Targeting the complement cascade represents a new strategy based on pathological mechanism principles. Therefore, compared with current conventional therapies, it has the potential for faster and better disease control with higher tolerance and safety. Zilucoplan is a C5 macrocyclic peptide inhibitor undergoing preclinical development, which can be self-administered via daily SC injection to rapidly and powerfully reduce complement activity and improve patient symptoms, demonstrating good safety and tolerability in Phase I and II studies [58]. Eculizumab, a monoclonal antibody, prevents the cleavage of C5 and inhibits complement-mediated membrane lysis [59]. It was approved by the FDA for AChR-positive MG patients in 2017

[60], becoming the first FDA-approved complement inhibition therapy for MG. For patients with antibodies that activate the complement cascade, this drug can effectively improve symptoms but requires a combination with immunosuppressive treatment, as eculizumab only inhibits terminal complement activation [61]. Ravulizumab is the next-generation eculizumab, a monoclonal antibody targeting complement C5. It is modified by four amino acid substitutions on the heavy chain of the drug, promoting the separation of C5 within the nuclear body. Changing the Fc fragment also increases ravulizumab's affinity for FcRn, avoiding intracellular degradation and prolonging its half-life in the blood [39]. Zilucoplan is a synthetic macrolide drug with a more extraordinary relationship for inhibiting C5 complement cleavage and also binds to preformed C5b, blocking its interaction with the C6 complement [58]. It was initially developed as a replacement for eculizumab-resistant patients with paroxysmal nocturnal hemoglobinuria (PNH), with the advantages of self-administration and rapid SC administration [17]. In summary, complement inhibitors are expected to become a new standard for treating generalized severe myasthenia gravis patients, providing earlier treatment for more patients. This will reduce dosing frequency and patient burden, increasing patient compliance with treatment.

4. Summary and Outlook

The treatment of MG requires consideration of multiple aspects, including symptom relief, disease control, prognosis improvement, and hospitalization cost reduction. Therefore, personalized and individualized treatment is necessary. For the treatment of MG, a comprehensive approach is essential, but it needs to be personalized based on each patient's specific situation. Different causes and mechanisms require other treatment plans, addressing the primary symptoms while also addressing the patient's primary symptoms. Each patient's psychological state, lifestyle, and economic conditions can also affect the treatment effect. Psychological counseling, guidance on lifestyle habits, and selecting appropriate treatment plans can achieve the best treatment effect.

Modern medicine has accumulated experience treating MG, providing clinicians with specific ideas and methods, but a suitable treatment plan still needs to be a standard. The ideal goal of MG treatment is to control and relieve symptoms while minimizing drug side effects. This goal currently requires more work to achieve. MG patients have significant genetic backgrounds, clinical manifestations, and drug reactions. Conventional treatment methods have certain defects for patients who are drug-resistant or cannot tolerate side effects. According to current clinical trials and evidence, new biological agent therapies may replace traditional treatment methods as the first choice for MG treatment and prognosis improvement due to their precise and safe characteristics. New natural agent therapies have brought more options and hope to patients. Better utilization of new treatment models can provide benefits and guidance for clinical practice, alleviate MG conditions and relapses, avoid crises, and improve the overall re-

search level of this disease.

Conflicts of Interest

The authors declare that this project has not received any funding support, so there is no conflict of interest.

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