MEDS Chinese Medicine (2024)
Clausius Scientific Press, Canada

DOI: 10.23977/medcm.2024.060320
ISSN 2616-1753 Vol. 6 Num. 3

Research progress in the combined treatment of traditional Chinese and Western medicine for myasthenia gravis

Wenfeng Chen

First Clinical College of Integrative Medicine, Hubei University of Chinese Medicine, Wuhan, Hubei, 430000, China

Keywords: Myasthenia gravis, modern medicine, Integrated Traditional Chinese and Western Medicine, Treatment progress

Abstract: Myasthenia gravis (MG) is a common neurological disease and one of the incurable diseases to date. With the development of medical technology this year, there have been more treatment methods. This article reviews the progress in the treatment of MG with Western medicine and the combination of Chinese and Western medicine in recent years.

Myasthenia gravis (MG) is an acquired autoimmune disease primarily triggered by acetylcholine receptor (AChR) antibodies, involving cellular immune mechanisms and complemented by the complement system. It is characterized by impaired acetylcholine transmission at the neuromuscular junction. The main symptom is muscle weakness, which tends to be lighter in the morning and worsens in the evening, with aggravation after exercise and relief after rest. In Western medicine treatment strategies, targeted interventions are developed based on the patient's clinical classification. In traditional Chinese medicine (TCM), treatment focuses on identifying the patient's specific syndrome and selecting appropriate prescriptions and medications accordingly. This paper aims to provide a comprehensive review of the latest advancements in Western medical treatment for myasthenia gravis (MG) and the practice of integrated traditional Chinese and Western medicine therapies.

1. Western Medicine Treatment

1.1 Cholinesterase inhibitors

Cholinesterase inhibitors are the first-line treatment for various myasthenic syndromes, particularly suitable for the initial treatment of patients newly diagnosed with myasthenia gravis and those with ocular myasthenia syndrome. Commonly used drugs in clinical practice include pyridostigmine bromide, pyridostigmine, and neostigmine. These drugs work by inhibiting the action of acetylcholinesterase, which leads to an increase in acetylcholine levels in the synaptic cleft, thereby improving neuromuscular junction dysfunction and alleviating patients' symptoms [1]. However, long-term and large-dose use of these drugs may reduce patients' sensitivity to them, requiring increased doses and leading to diminishing efficacy, while also exhibiting significant side effects. Therefore, prolonged and high-dose use of these drugs is not recommended to avoid inducing cholinergic crisis.

1.2 Corticosteroids

Corticosteroids are the preferred drugs for treating MG, effectively improving symptoms in about 70% to 80% of patients. They are widely used in clinical practice, demonstrating rapid onset and stable efficacy. Common drugs include prednisolone acetate, methylprednisolone, and methylprednisolone sodium succinate. Clinically, treatment typically involves high-dose acute therapy, gradual tapering to maintenance doses, medium-dose intensive therapy, low-dose ongoing management, and long-term microdose administration[2]. During glucocorticoid treatment, supplementary therapies such as calcium and vitamins should be considered to reduce potential side effects.

1.3 Azathioprine

Azathioprine is a first-line drug for the treatment of generalized myasthenia gravis (MG) in adults. It can also be used as an adjunct to corticosteroid therapy for MG to reduce steroid dosage or even serve as an alternative treatment. Regular monitoring of blood counts and liver function is required during its use.

1.4 Cyclophosphamide

Cyclophosphamide is commonly used to treat refractory MG. When used in combination with high-dose glucocorticoids, it can reduce the required dose of glucocorticoids in MG treatment [3]-[4]. It has immunosuppressive effects on both cellular and humoral immunity, with its primary mechanism varying depending on the dosage, mainly inhibiting cell proliferation. Cyclophosphamide is thought to modulate the number of CD3+, CD4+, and CD8+ cells, helping to correct the imbalance in T lymphocyte subpopulations [5].

1.5 Mycophenolate mofetil

Mycophenolate mofetil is a novel metabolic immunomodulator. Its mechanism of action is to specifically inhibit the proliferation of T and B lymphocytes by suppressing the production of guanine nucleotides. Its side effects are similar to those of azathioprine, and regular monitoring of liver and kidney function, as well as blood counts, is required during its use [6].

1.6 Methotrexate

Methotrexate is a selective inhibitor of dihydrofolate reductase, and its core mechanism of action involves interfering with the initial steps of purine and pyrimidine synthesis, while also inhibiting lymphocyte division. Common side effects include gastrointestinal discomfort, liver damage, anemia, bleeding, and infections [7]. However, some experts point out that current research on methotrexate primarily relies on the personal experience of clinicians, with limited empirical evidence, especially lacking support from randomized controlled trials. In 2014, the European Academy of Neurology [8]officially listed methotrexate as a second-line recommended drug. By 2020, China's guidelines included it for the first time, categorizing it as a third-line drug, and it is generally not considered a standard treatment option. According to international consensus [9] methotrexate is recommended as a corticosteroid-sparing agent for patients with myasthenia gravis (MG), particularly for those who do not respond well to or are intolerant of other corticosteroid-sparing therapies. This recommendation is supported by randomized controlled trial (RCT) evidence. However, the guidelines do not cover thymoma-associated myasthenia gravis. Moreover, both the 2020 Chinese

guidelines and the 2016 international guidelines indicate that methotrexate poses teratogenic risks, making it contraindicated for use in women during pregnancy and the pre-pregnancy phase. Currently, research on methotrexate in the treatment of multiple sclerosis (MG) remains relatively scarce. Studies abroad suggest that methotrexate has some therapeutic effects, but domestic studies are limited, and existing evidence is insufficient to provide conclusive proof of efficacy.

1.7 Tacrolimus

Tacrolimus is a novel immunomodulator and is recommended as a second-line treatment for MG. It mainly includes two types, rituximab and eculizumab, which are gradually becoming highly effective immunotherapies for refractory MG. This therapeutic strategy focuses on B-cell-targeted treatments and the use of complement inhibitors. According to Chinese clinical practice guidelines, due to the high cost of these drugs, their use is recommended mainly for patients with moderate to severe MG that is difficult to control with conventional treatments, especially adult patients with AChR-GMG. International guidelines, in consensus proposals, emphasize that before administering eculizumab, reference should be made to the Advisory Committee on Immunization Practices (ACIP) or relevant regional guidelines for vaccination against meningococcal meningitis.

1.8 Rituximab

Rituximab (RTX) Rituximab is suitable for MuSK-MG patients who show poor responses to initial immunotherapy. It effectively reduces corticosteroid requirements, decreases relapse rates, and prevents the occurrence of myasthenic crises, while also displaying good safety characteristics. In the study by Zhao Sijia et al. [10], it was found that small to moderate doses of rituximab could help patients reduce their use of immunosuppressants, and in some cases, even achieve medication discontinuation. Additionally, it helps lower antibody levels and restore normal electromyography (EMG) results, significantly improving the clinical manifestations of patients. This reveals that for treatment-resistant MG, this method is not only safe but can also bring positive benefits. A prospective study [11] followed 22 patients with refractory AChR-MG, MuSK-MG, and seronegative MG after rituximab treatment and found significant improvements in Manual Muscle Testing (MMT) scores. A multicenter, blinded, prospective study [12] revealed that 58% of MuSK-MG patients treated with rituximab achieved minimal manifestation status (MMS). Although subsequent evaluation criteria differed, most patients experienced significant clinical relief. For refractory MG , Chinese guidelines recommend that this drug shows significant efficacy for refractory GMG cases that are unresponsive to immunosuppressants and steroids, and it is also effective for certain AChR-MG cases. However, global guidelines suggest that the efficacy of this drug in treating refractory AChR-MG remains uncertain. Nevertheless, for patients who do not respond well to other immunosuppressants or cannot tolerate their side effects, this therapy could be a viable option. There is an urgent need for additional randomized controlled trials to assess the effectiveness of RTX in treating refractory MG and to identify characteristics of patient groups that may respond positively to RTX.

1.9 Eculizumab

Eculizumab is a humanized monoclonal antibody whose main function is to inhibit C5 activity by preventing the cleavage of C5 into C5a and C5b, and by inhibiting the formation of the membrane attack complex (MAC), thus reducing the damage caused by AChR antibodies bound to complement[13]. A preliminary Phase II study conducted in 2013 on eculizumab in the treatment of refractory AChR-GMG indicated clinically significant improvement in these patients[14]. Furthermore, a Phase III randomized, double-blind, controlled, multi-center study (REGAIN) conducted in 2017

demonstrated an advantage for the eculizumab group. Specifically, after 26 weeks of treatment, individuals treated with eculizumab experienced only half the rate of exacerbations and hospitalizations compared to the control group[15]. In summary, eculizumab shows potential positive effects in the treatment of AChR-GMG patients. Results from the open-label extension of the REGAIN study revealed that patients receiving continuous eculizumab treatment experienced sustained improvements in daily activities, muscle strength, functional performance, and quality of life for up to three years[16]. This strongly supports the long-term efficacy of eculizumab in alleviating disease symptoms and maintaining complement system inhibition. The above data suggest that eculizumab should be considered for refractory MG patients, especially when other immunotherapy trials have not yielded expected results.

1.10 Thymectomy

Thymectomy Research indicates that thymic activity may trigger an autoimmune response loop involving AChR, and removal of the thymus can significantly reduce the production of pathogenic AChR antibodies. For MG patients with thymoma, thymectomy is often considered the preferred treatment[17]. However, for MG cases without thymoma, whether to perform thymectomy remains a topic of debate in both international and domestic academic circles, and the mechanism of action is not fully understood. It is hypothesized that the removal of TH cells within the thymus reduces the expression of key cytokines that activate B cells, leading to a gradual decline in AChR-Ab levels, thereby improving the clinical symptoms of patients[18]. Regarding whether to perform thymectomy on non-thymoma AChR-GMG patients, some domestic and international guidelines reference the first global multicenter randomized controlled trial[19], which advocates for early thymectomy to optimize clinical outcomes, significantly reduce the need for immunosuppressants, and lower the likelihood of hospitalization due to disease exacerbation. A retrospective study showed that of 110 MG patients who underwent thymectomy, 84.6% of the cases were effective. Among them, 105 were non-thymoma patients, of which 49 (46.7%) achieved complete remission, while 5 were thymoma patients, of which 3 (60.0%) achieved complete remission[20] ·However, this trial did not monitor antibody levels. A comprehensive evaluation based on 26 collected articles found that the symptoms of non-thymoma MG patients did improve after thymectomy. However, it is noteworthy that only six articles mentioned serum antibodies, which is insufficient to clearly indicate differences in postoperative treatment effects among various pathogenic antibodies[21]. Research by SHRAGER et al[22], involving 151 MG patients who underwent transcervical thymectomy, revealed that after five years, remission rates for Osserman class I (60%) were significantly better than for generalized MG (45%, 26%, 22%), providing support for surgical treatment. In MINEO et al.'s[23]study exploring the feasibility of thymectomy in MG patients, although the proportion of AChR antibody-positive patients was not specifically reported, an analysis of the clinical attributes of the patients showed that most had positive antibody test results. Although these studies consistently recognized the feasibility of thymectomy for non-thymoma MG patients, none addressed information regarding patients' antibodies. Fan Zhimin et al.'s research[24]revealed that symptom improvement in postoperative MG patients was associated with factors such as age, gender, disease duration, and pathological classification, and they observed that some patients experienced disease exacerbation after surgery.

1.11 Intravenous Immunoglobulin

Intravenous Immunoglobulin (IVIG) IVIG is commonly used in cases of MG crises, situations where venous access cannot be established, hemodynamic instability, or when plasmapheresis or oral corticosteroid therapy is unsuitable. The mechanism of action centers on the activation, differentiation, and recognition abilities of T and B cells[25]. The effective duration of this therapy typically lasts 1 to

2 months, and it is favored for its ability to enhance the immune system. Due to the demonstrated safety of both IVIG and subcutaneous immunoglobulin (SCIG), they have gradually been incorporated as part of chronic treatment regimens. A retrospective study explored the response to long-term treatment with low-dose IVIG. After treatment, 92.5% of patients maintained clinical stability, and 61.47% showed improvement by at least one MGFA grade. Additionally, patients continued to experience significant and sustained steroid-sparing effects for up to three years after treatment[26]. IVIG treatment is not feasible for patients with renal impairment.

1.12 Plasmapheresis

Plasmapheresis is mainly used for patients who do not respond well to cholinesterase inhibitors and immunosuppressive treatments, for MG crises, and for preoperative management of MG patients undergoing thymectomy. By removing AChR-Ab, immune complexes, and other pathogens from the circulatory system, and replacing the patient's plasma filled with pathological components, it reduces antibody concentrations in the plasma, thereby achieving rapid and effective symptom relief. This method is relatively costly and requires precise and essential protective measures during implementation. Moreover, due to the limited dosage used in plasma exchange, some beneficial components may be lost, presenting certain challenges in clinical practice.

Intravenous immunoglobulin (IVIG) and plasma exchange should not be performed concurrently. It is recommended to consider plasma exchange, if necessary, four weeks after the administration of immunoglobulin.

2. Integrated Traditional Chinese and Western Medicine Treatment

Currently, in the treatment of myasthenia gravis (MG), the application of traditional Chinese medicine (TCM) mainly lies in its combined use with Western medications such as cholinesterase inhibitors, corticosteroids, or thymectomy. TCM treatments are often administered through herbal decoctions or proprietary Chinese medicines as an adjunct therapy. However, clinical studies on the independent use of TCM for MG treatment are relatively scarce, with few clinical data and case reports available for reference. The core of TCM therapy for MG focuses on harmonizing the body's immune system and alleviating immune imbalance. When used in combination with Western medications, it shows significant advantages in promoting faster symptom relief and enhancing the longevity of therapeutic effects. Compared to the use of Western medicine alone, TCM can more effectively reduce the side effects associated with Western treatments. TCM treatment strategies mainly follow the principle of syndrome differentiation and treatment in traditional Chinese medicine, often targeting organ functions such as the lungs, spleen, liver, and kidneys, or are based on specific prescriptions formed through accumulated clinical experience.

2.1 Strengthening the spleen and stomach

Treating MG from the Perspective of the Lung and Spleen Professor Liu Fengbin[27]points out that if the spleen and stomach functions are weak, over time, the accumulated deficiency will affect the kidneys, leading to an imbalance in the relationships among the five elements, which will subsequently affect the liver, heart, and lungs, triggering corresponding pathological changes. Based on the strategy of tonifying the spleen, benefiting qi, and raising the yang to lift prolapse, Professor Deng Tietao developed Qiangji Jianli Oral Liquid, which has shown certain efficacy in treating MG patients with spleen and stomach weakness[28]. Studies have indicated[29]that the TCM intervention group using spleen-tonifying and qi-benefiting therapy showed better results compared to the control group taking oral corticosteroids, confirming the clear clinical benefits of treating myasthenia gravis

(MG) with the method of tonifying the spleen and benefiting qi.

2.2 Tonifying liver and kidney

Combining modern medical understanding of MG, TCM treatment aims to regulate the overall balance of the body and promote smooth circulation of qi and blood, thus achieving therapeutic effects and enhancing physical constitution. Professor Zhou Shaohua[30]indicates that this condition arises from the dysfunction of the liver, spleen, and kidneys, with a core issue being the deficiency of kidney essence and qi. Limited innate essence, coupled with improper diet and excessive fatigue affecting the spleen and stomach, leads to physical weakness over time, presenting symptoms such as eyelid lifting weakness and muscle weakness. Professor Yang Wenming suggests[31]that the imbalance of the spleen, stomach, liver, and kidneys is particularly pronounced, with spleen and stomach deficiency and insufficient liver and kidney qi being notable. The liver governs the fascia and stores blood, with the eyes being its orifice; the kidneys store essence, which is the foundation of life, and essence and blood are interconnected. If liver and kidney functions decline, it can lead to decreased vision, limb weakness, and sluggish mobility of muscles and bones. The spleen and stomach are the foundation of postnatal life, responsible for generating and supplying nutrients. If prolonged illness affects the liver and kidneys, it can result in insufficient nutritional sources, leading to symptoms such as blurred vision. Reports indicate that astragalus compound preparations can adjust the abnormal immune response in MG and regulate the body's immunity[32]. Professor Li Geng's [33] strong muscle formula, based on the principle of tonifying the spleen and kidneys, has been shown to adjust the production of cytokines, demonstrating positive effects in treating MG.

3. Summary

Currently, Western medicine has not achieved an ideal state in the treatment of myasthenia gravis (MG). The existing clinical drugs generally place a significant burden on liver and kidney function, and the effects of symptom control can fluctuate easily. Some of the latest treatment methods and medications still require more clinical trials to verify their effectiveness. In contrast, the integration of traditional Chinese and Western medicine shows advantages in improving patient symptoms and can effectively reduce adverse reactions. However, there is still a need for improvement in the standardization of treatment systems, the sample size of clinical trials, and whether to employ double-blind randomized controlled trials. By further conducting in-depth research and addressing these issues, the goal is to achieve a more mature and optimized treatment plan.

References

[1] Feng Xia. Progress in the treatment of myasthenia gravis[J]. Chinese Medical Guide, 2014, 9(11): 911.
[2] Yang Mingshan, Fang Siyu, Ruan Xuzhong. Diagnosis and treatment of neurological emergencies[M]. Wuhan: Hubei Science and Technology Press, 1995: 403-416.
[3] Fan Weinu, Hong Wenke. Observation of the efficacy of cyclophosphamide or azathioprine in steroid-resistant myasthenia gravis [J]. Modern Practical Medicine, 2009, 21(5): 463-465.
[4] Xiong Xiaoping, Yu Feng, Wang Weiqiang, et al. Clinical observation of high-dose cyclophosphamide intermittent pulse therapy for generalized myasthenia gravis[J]. Shandong Medical Journal, 2009, 49(44): 92-93.
[5] Li Xiuhua, Cheng Yan, Yang Li, et al. The effect of immunosuppressants on T lymphocyte subsets in myasthenia gravis patients [J]. Chinese Journal of Practical Neurological Diseases, 2008, 11(5): 1-4.
[6] Hu Qing, Jiang Haiwei, Ge Lintong, et al. Clinical observation of mycophenolate mofetil in the treatment of 28 cases of myasthenia gravis[J]. Clinical Internal Medicine Journal, 2014, 31(6): 407-409.
[7] Dong Mengqi, Guo Junhong, Zhang Jin. Management of refractory myasthenia gravis[J]. International Journal of Immunology, 2017, 40(2): 216-220.
[8] Kerty E, Elsais A, Argov Z, et al. EFNS/ENS guidelines for the treatment of ocular myasthenia[J]. Eur J Neurol, 2014,

21(5): 687-693.
[9] Wang Ke, Xu Peng, Zhang Ying, et al. Comparison and analysis of domestic and foreign guidelines for the treatment of myasthenia gravis [J]. Journal of Practical Medicine, 2022, 38(08): 917-922.
[10] Sanders D B, Wolfe G I, Benatar M, et al. International consensus guidance for the management of myasthenia gravis: Executive summary[J]. Neurology, 2016, 87(4): 419-425.
[11] Beecher G, Anderson D, Siddiqi Z A. Rituximab in refractory myasthenia gravis: Extended prospective study results [J]. Muscle Nerve, 2018, 58(3): 452-455.
[12] Hehir M K, Hobson-Webb L D, Benatar M, et al. Rituximab as treatment for anti-MuSK myasthenia gravis: Multi-center blinded prospective review [J]. Neurology, 2017, 89: 10-100.
[13] Rother R P, Rollins S A, Mojcik C F, et al. Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria[J]. Nat Biotechnol, 2007, 25(11): 1256-1264.
[14] Howard J F Jr, Barohn R J, Cutter G R, et al. A randomized, double-blind, placebo-controlled phase II study of eculizumab in patients with refractory generalized myasthenia gravis [J]. Muscle Nerve, 2013, 48(1): 76-84.
[15] Howard J F Jr, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis (REGAIN): A phase 3, randomized, double-blind, placebo-controlled, multicenter study[J]. Lancet Neurol, 2017, 16(12): 976-986.
[16] Muppidi S, Utsugisawa K, Benatar M, et al. Long-term safety and efficacy of eculizumab in generalized myasthenia gravis [J]. Muscle Nerve, 2019, 60(1): 14-24.
[17] He Lifeng, Shen Shuang, Yang Xiangyan, et al. Surgical treatment of 45 cases of myasthenia gravis with thymic abnormalities[J]. Journal of Practical Medicine, 2021, 37(7): 962-964.
[18] Gong Taiqian, Jiang Yaoguang, Wang Ruwen. The immunological mechanism of thymectomy in the treatment of myasthenia gravis [J]. Journal of Immunology, 2002, 18(z1): 221-223.
[19] Wolfe G I, Kaminski H J, Aban I B, et al. Randomized trial of thymectomy in myasthenia gravis[J]. N Engl J Med, 2016, 375(6): 511-522.
[20] Liu Z, Feng H, Yeung S C, et al. Extended transcervical thymectomy for the treatment of ocular myasthenia gravis[J]. Ann Thorac Surg, 2011, 92(6): 1993-1999.
[21] Zhu K, Li J X, Huang X, et al. Thymectomy is a beneficial therapy for patients with non-thymomatous ocular myasthenia gravis: A systematic review and meta-analysis [J]. Neurol Sci, 2017, 38(10): 1753-1760.
[22] Shrager J B, Nathan D, Brinster C J, et al. Outcomes after 151 extended transcervical thymectomies for myasthenia gravis [J]. Ann Thorac Surg, 2006, 82(5): 1863-1869.
[23] Mineo T C, Ambrogi V. Outcomes after thymectomy in class I myasthenia gravis[J]. Thorac Cardiovasc Surg, 2015, 145(5): 1319-1324.
[24] Fan Zhiming, Wen Guoqiang, Zhang Zhenhe. The value of thymectomy in the treatment of myasthenia gravis[J]. Chinese Medical Journal, 1998, 78(5): 363-365.
[25] Luo Weiting. Observation of the efficacy of high-dose intravenous immunoglobulin in severe myasthenia gravis[J]. Contemporary Medicine, 2012, 18(19): 11-13.
[26] Wilf-Yarkoni A, Lotan I, Steiner I, et al. Chronic low-dose intravenous immunoglobulins as steroid-sparing therapy in myasthenia gravis [J]. J Neurol, 2021, 268(10): 3871-3877.
[27] He Guoliang, Wu Keqing, Ye Yun, Cai Donghui. Advances in the understanding of myasthenia gravis and treatment strategies [J]. Chinese Journal of Neurology, 2016, 49(6): 371-376.
[28] Chen Hui, Huang Yu, Chen Chao, et al. The application of stem cell therapy in myasthenia gravis[J]. Chinese Journal of Practical Neurology, 2018, 21(4): 325-329.
[29] Wang Y, Liu Y, Zhang Z, et al. Advances in research on the pathogenesis of myasthenia gravis[J]. Journal of Clinical Neuroscience, 2015, 22(3): 479-483.
[30] Ma Jianhua, Zhang Jianzhong. Myasthenia gravis in children: Clinical characteristics and treatment strategies[J]. Chinese Journal of Pediatrics, 2019, 57(4): 272-277.
[31] Li Xin, Wu Xin, Li Shuguang. The relationship between thyroid disease and myasthenia gravis[J]. Journal of Clinical Endocrinology and Metabolism, 2014, 30(12): 1303-1308.
[32] Zhang Yi, Wang Shaohua. An analysis of risk factors for myasthenia gravis and its complications[J]. Journal of Modern Medicine, 2020, 28(1): 105-110.
[33] Wang Jianjun, Zhan Jun. The impact of psychological factors on the quality of life of patients with myasthenia gravis [J]. Chinese Journal of Psychological Medicine, 2017, 50(4): 281-285.