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The Management of Generalized Myasthenia Gravis in Adults: New Biological Therapies

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Abstract

Myasthenia Gravis is an autoimmune disorder caused by autoantibodies against acetylcholine receptors in the neuromuscular junction. It is characterized by fluctuating weakness involving the eyes, throat, and extremities muscles. First-line treatment agents include peripheral AChE inhibitors (pyridostigmine and neostigmine) and immunosuppressors (prednisone). To avoid long-term corticosteroid therapy-related risks, non-steroidal immunotherapy (azathioprine or mycophenolate mofetil) is usually advised. Current treatment alternatives for patients with refractory disease include cyclosporine, cyclophosphamide, and surgical management with thymectomy. Despite the wide variety of available treatment options, a significant number of patients continue to be unable to respond to current medical interventions. In recent years, monoclonal antibodies (rituximab, ravulizumab, eculizumab) have acquired wide acceptance in the medical community, and their use has become essential for the optimal management of certain MG patients. This review aims to provide a comprehensive understanding of current and emerging therapies in the management of adults with generalized myasthenia gravis.

Keywords: Myasthenia gravis; Generalized myasthenia gravis; Monoclonal antibodies therapy; New biological therapies

Abbreviations: MG: Myasthenia Gravis; NMJ: Neuromuscular Junction; Achrs: Acetylcholine Receptors; Musk: Muscle-Specific Kinase; Lrp4: Low-Density Lipoprotein Receptor-Related Protein 4; MAC: Membrane Attack Complex; FDA: Food and Drug Administration; Ach: Acetylcholine; 6-MP: Mercaptopurine; 6-TGN: Thioguanine; HPRT: Hypoxanthine-Guanine Phosphoribosyl Transferase; TPMT: Thiopurine Methyltransferase; GI: Gastrointestinal; AZA: Azathioprine; MMF: Mycophenolate Mofetil; NF-AT: Nuclear Factor of Activated T Cells; GVHD: Graft-Versus-Host Disease; RA: Rheumatoid Arthritis; CBC: Complete Blood Count.

Introduction

Myasthenia gravis (MG) is an autoimmune disorder affecting the skeletal muscles' neuromuscular junction (NMJ). Most patients with MG have autoantibodies against the acetylcholine receptors (AChRs). Less commonly identified autoantibodies include those targeted to muscle-specific kinase (MuSK), low-density

lipoprotein receptor-related protein 4 (Lrp4), and AGRN/Agrin. These autoantibodies disrupt cholinergic transmission between nerve terminals and muscle fibers by causing downregulation, destruction, functional blocking of AChRs, or disrupting the clustering of AChRs in the postsynaptic membrane [1]. Myasthenia gravis has a prevalence of 20 per 100,000 population in the US. It exhibits a female predominance in those less than 40 years of age and a male predominance in those greater than 50 years of age. The incidence is estimated to be 4.1 to 30 cases per million person-years. The current mortality rate is around 4.47%. Morbidity results from intermittent muscle weakness leading to aspiration pneumonia and the adverse effects of medications [1-3]. Myasthenia gravis affecting multiple muscle groups throughout the body is called generalized myasthenia gravis. Generalized MG (gMG) accounts for 85% of patients with MG [3]. The classic clinical presentation is a fluctuating weakness that is more prominent in the afternoon. It usually involves muscles of the eyes, throat, and extremities (ptosis, double or blurred vision, slurred speech, drooling, trouble chewing and swallowing) [2].

The diagnosis of MG is primarily clinical. Among the assessments that can be useful are serologic tests (especially anti-AChR antibody test), electrophysiology tests (relevant in patients who have positive antibodies), edrophonium tests (a short-acting acetylcholinesterase inhibitor that increases the availability of ACh in the NMJ), and imaging (chest CT or MRI to assess for thymoma). Several treatment options can be used to manage MG. It has been found that the most effective therapies include ravulizumab, rituximab, eculizumab, pyridostigmine, neostigmine, prednisone, azathioprine, mycophenolate, cyclosporine, and cyclophosphamide. This review aims to identify when to use these options, with a particular emphasis on biological medications, to provide a more comprehensive understanding of these emerging treatments.

Eculizumab

Eculizumab effects are produced by a complement cascade blockade, preventing membrane attack complex (MAC) formation. Therefore, preventing the destruction of postsynaptic NMJ structure in MG [4]. The FDA has approved this medication for the treatment of MG, making it the first targeted complement inhibitor to be approved for its use on complement-mediated diseases. A series of 98 patients with gMG treated with eculizumab as salvage therapy after receiving first-line therapy (cholinesterase inhibitors, oral corticosteroids, or other immunosuppressive treatments) revealed remission in most patients by week 12 of eculizumab treatment [5]. Moreover, Renato et al. analyzed patients with refractory anti-AChR-Abpositive gMG. With eculizumab treatment, patients experienced rapid improvements in all four domain scores of both the MG-ADL and QMG scales. These therapeutic effects were sustained for 2 years [5]. Both publications highlighted that eculizumab treatment elicited rapid and sustained improvements in muscle strength and quality of life in patients with MG. However, the REGAIN study of patients with anti-AChR antibody-positive refractory generalized myasthenia gravis found no statistically significant difference between eculizumab and placebo. A limitation of this study was its use of a worst-rank analytical approach since the results from the secondary and sensitivity analyses were not consistent with the primary endpoint [4]. In refractory gMG, defined as the use of ≥2 immunosuppressants for ≥12 months without symptom control, or ≥1 immunosuppressant for ≥12 months with IVIg or plasma exchange given ≥4 times/year without symptom control, eculizumab was administered at an induction dose of 900 mg per week for 4 weeks, followed by 1200 mg every 2 weeks after that, as per the prescribing information for the product. Results showed a gradual reduction in all patients' MG-ADL total scores after 12 months [5].

A retrospective study has shown that headache is the most common adverse event with eculizumab, followed by nasopharyngitis. Other side effects reported include diarrhea, upper respiratory infection, and arthritis. Notably, no cases of meningococcal infection were reported, possibly due to vaccination prior to enrollment in the study [6]. The therapies administered to patients at the beginning of eculizumab administration were IVIg, prednisone, pyridostigmine, mycophenolate, and azathioprine. Twelve months after initiating eculizumab, all patients underwent reductions in concomitant medications. Additionally, eculizumab seemed to present a favorable benefit-risk profile in pregnant patients and no adverse reactions in either the patient or the infant. Notably, a few patients were recruited, and the findings should be considered cautiously [6,7].

Ravulizumab

Ravulizumab inhibits the C5 protein in the terminal complement cascade, a component of the body's immune system. In response to an activation of the complement cascade, the body attacks its healthy cells [8]. As a result of the short half-life and frequent dosing schedule associated with eculizumab therapy, the development of ravulizumab was intended to address those limitations [9]. As a result, four unique amino acid substitutions have been made to the heavy chain of eculizumab to design ravulizumab. Consequently, ravulizumab has a longer half-life of serum terminal elimination and a longer duration of pharmacological activity when compared with eculizumab [9,10]. Adult patients receive this medication intravenously every eight weeks following a loading dose [8,10]. This dose ranges between 2400 to 3000mg IV. Additionally, IV maintenance doses vary according to weight and are given at 3,000mg IV, 3,300mg IV, and 3,600mg IV every eight weeks, respectively [11].

The FDA approved this medication to treat adults with generalized myasthenia gravis who are AChR antibody positive. Several factors contributed to the approval of this medicine, including its efficacy and safety profile. Currently, this is the only long-acting C5 complement inhibitor approved for the treatment of gMG [8]. The most common side effects of the treatment are

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upper respiratory tract infections, headaches, nausea, and diarrhea [8,9,12]. In rare cases, ravulizumab-treated patients may develop severe but nonfatal infections, such as Neisseria meningitis [9,12]. Therefore, vaccination is recommended no more than two weeks before starting ravulizumab therapy to prevent meningococcal disease. If this medication must be initiated immediately, it is suggested that an antibacterial medication be administered prophylactically for two weeks. Furthermore, it is contraindicated in patients with unresolved Neisseria meningitides infection [11].

Rituximab

In treating MG, the most used anti-B cell therapy is rituximab. In terms of its mechanism of action, it has been described as an "anti-human" monoclonal antibody that depletes B cells by binding to their CD20 and causing complement-dependent cytolysis or antibody-dependent cell-mediated cytotoxicity [13]. It is important to note that this mechanism does not impair the recovery of cell B or the production or secretion of antibodies. Efficacy data in MG may vary across subgroups, although it has been described in several studies as a favorable outcome for patients with MuSK MG having impressive success. In a blinded prospective review, 58% (14/24) of rituximab-receiving patients reached the primary outcome vs. 16% (5/31) of controls after a median follow-up of 3.5 years [13]. Nevertheless, a retrospective study of rituximab-treated patients with non-MuSK+ gMG suggested that initiation of therapy early after diagnosis could be associated with improved outcomes. Patients treated with rituximab entered clinical remission significantly faster than those in the control group receiving other conventional immunotherapies [14]. As is well known, MG has a bimodal distribution, which means that older patients can achieve positive outcomes with this therapy. An analysis of 7 patients with AChR MG, where the mean age was 66, has shown that all were treated with rituximab with significant improvement. No adverse reactions, myasthenic crises, or hospitalizations were observed [15].

While the FDA does not fully approve rituximab for MG (currently in phase II) [16], it has shown benefits in previous studies when used in patients who fail to respond to standard therapy, who are poorly controlled, who have MuSK MG, and those who are positive for AChR. This treatment has been successful in treating seronegative MG in adolescents and children. Standard dosages have not been fully described, but the most common doses include 375mg/m^2 once a week for four weeks, or 2g (divided into two, 1 g each, biweekly infusions), which is effective in 50-70% of patients with MG. In a study, AChR antibodies decreased by 33% after cycle 1 of rituximab, 20% after cycle 2 (compared with cycle 1), and 17% after cycle 3 (compared with cycle 2) [13]. Infusion-related side effects include severe mucocutaneous reactions, polymorphous light eruption (PMLE), myelosuppression, and hepatitis B virus or tuberculosis reactivation. Following prolonged exposure to the treatment, severe hypogammaglobulinemia has been observed. Evidence recommends CBC pre-treatment and CD19/CD20 post-treatment 1 month later and before the next cycle to ensure appropriate drug surveillance [17]. The FDA issued a contraindication in 2013 regarding patients with prior Hepatitis B virus (HBV) infection due to the possibility of reactivation using this therapy [18]. Therefore, it is recommended that patients with prior HBV infection undergo screening and monitoring before and throughout treatment with rituximab. Nonetheless, there is evidence that patients should be screened for hepatitis C infection and tuberculosis (TB) before beginning treatment and closely monitored during treatment for infusion reactions, particularly with the first dose. The American College of Rheumatology reported that the cost of infusions per cycle is approximately $8,988 [19]. Although rituximab is more expensive than other possible treatments previously disclosed, clear benefits have been demonstrated in patients with refractory MG. A new approach to targeted immunotherapy has demonstrated promising and sustained results in MG and many other autoimmune diseases.

Pyridostigmine and Neostigmine

Pyridostigmine and neostigmine are peripherally acting AChE inhibitors used as symptomatic treatments for temporally alleviating muscle weakness in MG patients. They act by reversibly inhibiting the action of AChE, preventing the breakdown of acetylcholine (ACh). Thus, increasing the amount of ACh available at the NMJ binds postsynaptic ACh receptors [20,21]. The first AChE in use was physostigmine, which subsequently has been replaced by pyridostigmine and neostigmine. These remain the first-line agents for symptomatic treatment of MG. Several formulations, such as oral sustained-release preparations, syrup for pediatric use, and injectables for parenteral administration, have been proven to have significant benefits [21]. Pyridostigmine can reach peak plasma levels 1 to 2 hours after an oral dose, with clinical effects starting in 0.5 hours and wearing off in 3-4h due to plasma cholinesterase activity [21]. Clinical response to AChE inhibitors may vary between individuals or muscles involved. For example, patients with ocular MG may have better alleviation of the ptosis than diplopia [1]. It is suggested to discontinue AChE inhibitors in patients with MG crisis requiring mechanical ventilation support due to concerns of increased bronchial secretion and bronchospasm, to restart them during the waning process or after extubating. The side effects are either due to stimulation of the ACh muscarinic receptors, which include gastrointestinal disturbances (abdominal cramps, diarrhea, nausea, increased salivation), bronchial secretions, lacrimation, hyperhidrosis, and bradycardia; or stimulation of nicotinic receptors, including muscle cramps, and fasciculations. Muscarinic side effects may be mitigated with the use of loperamide or glycopyrrolate. AChE inhibitors may be stopped once clinical remission is achieved or if patients develop incapacitating side effects. Paradoxical weakness (MG crisis) may occur with remarkably high doses of AChE inhibitors [20,21].

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Prednisone

The most commonly used immunosuppressive treatment for MG is corticosteroids [22,23]. For many years, this has been considered one of the most effective first-line immunotherapies for MG, particularly when symptoms fail to improve in response to AChE inhibitors [18-20]. The exact mechanism by which corticosteroids cause remission or improvement in MG is unknown. The most important explanation is its ability to inhibit the immune system by decreasing the production of inflammatory cytokines and reducing leukocyte adhesion to endothelial cells, which suppresses the autoimmune response [22,23]. Multiple studies have reported that initial improvements are seen within the first 2 weeks and with the greatest benefits in the first 6 months. However, a paradoxical and temporal worsening of weakness within the first 2 weeks of starting corticosteroids may be experienced by some patients, especially in patients starting with high doses, in early-onset or thymoma-associated MG, and older patients [22,24]. There are 2 therapeutic regimens of prednisone for MG, a high dose with fast induction and a low dose with a slow titration approach. The latter regimen has been correlated with decreased risk of the paradoxical and temporal worsening of weakness [22,24]. High-dose prednisone (1.0-1.5mg/kg/day; not >100mg/day) is recommended in patients with severe myasthenic crisis. When patients show improvement, a subsequent slow decrease of dose (by 5-10mg a month) may be started [22]. On the other hand, low-dose prednisone (starting with 10mg/day and gradually increasing dose to 10mg every 5-7 days; up to 100mg) is recommended in patients with mild dysfunction, together with ocular MG, or in mild to moderate MG [22,24]. Prednisone is effective for ocular MG compared to placebo and should be considered in patients that lack response to AChE inhibitors [22]. Numerous studies have demonstrated that corticosteroids are effective immunotherapy for managing MG symptoms. However, the clinical use of corticosteroids in patients with MG may be limited due to several adverse reactions [22,23]. Long-term corticosteroid use's most important adverse reactions are diabetes, hypertension, weight gain, accelerated bone demineralization, cataract, gastric and peptic ulcers, neuropsychiatric disturbances, and opportunistic infection [22,24]. Therefore, some tests are recommended, including a test for tuberculosis (before initiating treatment), an annual bone density test, and an ophthalmologic examination. Furthermore, patients should be advised about changes in diet, such as a low calorie, low carbohydrate, and low salt diet. Calcium and vitamin D supplements and proton pump inhibitors are also suggested [22,24].

Azathioprine

Azathioprine (AZA) is an immunosuppressive medication that has been used as a treatment for MG since 1967 [25]. As a purine analog, this drug is converted to its active metabolites, mercaptopurine (6-MP) and thioguanine (6-TGN), through the action of hypoxanthine-guanine phosphoribosyl transferase (HPRT) and thiopurine methyltransferase (TPMT). The metabolites of AZA are incorporated into the replicating DNA, halting cellular division, and producing toxic and immunosuppressive effects. This medication has a liver metabolism and kidney excretion and does not penetrate the blood-brain barrier [26]. Only a few clinical trials have investigated the efficacy of azathioprine in treating myasthenia gravis, but the drug has been used successfully for decades. Treating MG patients with azathioprine alone or in combination with corticosteroids usually results in a satisfactory response in approximately 70% of cases [27].

The use of azathioprine has been found to be beneficial in patients with gMG who are still experiencing symptoms despite taking corticosteroids, in patients who have relative contraindications to corticosteroids (hypertension, diabetes, and osteoporosis), and in those who experience severe side effects from corticosteroids. AZA is administered at a starting dose of 50mg/day, with a dose increase of 50mg every two to four weeks (up to a goal dose of 2 to 3mg/kg/day). A baseline blood count and liver function test should be conducted and monitored monthly. An important monitoring parameter of bone marrow suppression is the WBC count and leukopenia. Others include liver function evaluation (alanine aminotransferase, aspartate aminotransferase). If the WBC count falls below 3000-4000mm^3, or if liver function enzymes rise, the dose is either decreased or discontinued. Azathioprine has been linked to an increased risk of malignancy in rheumatic diseases and post-transplant patients, but this phenomenon has not been described in patients with MG. Despite evidence from the transplant literature suggesting that azathioprine use in pregnancy is not associated with adverse outcomes, it is contraindicated in this population. It is estimated that 10% to 20% of patients prescribed azathioprine will experience an idiosyncratic drug reaction which may manifest as a flulike syndrome accompanied by fever, malaise, and appetite loss. Typically, this phenomenon occurs within the first two weeks following the start of the drug. If this occurs, azathioprine should be discontinued immediately, and the symptoms will subside within a few days [28]. Immunosuppressive medications, including AZA, may increase the risk of lymphoma and other malignancies, particularly skin cancers. These patients should wear protective clothing and use sunscreen with a high protection factor to limit their exposure to sunlight [29]. On average, a 30-tablet (50mg) of AZA costs $58.55 [30].

Mycophenolate

Mycophenolate mofetil (MMF) is one of the steroid-sparing medications used to treat myasthenia gravis. It blocks the de novo synthesis of purine nucleotides by inhibiting the enzyme inosine monophosphate dehydrogenase, inhibiting the proliferation of T and B lymphocytes [31]. In medical practice, the substances administered are mycophenolate sodium or mycophenolate mofetil (prodrug), which release mycophenolic acid, the active substance. The dose used is 1gr twice a day, and studies have reported that its greater efficacy is notable after the first six

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months of treatment. Its effectiveness is comparable to a once-a-week methotrexate dose. The first case where MMF's benefits were observed in 1998 in a young woman with myasthenia refractory to treatment, and subsequent studies have confirmed its effectiveness in improving muscle strength and functional status, as well as reducing the use of corticosteroids in up to 73% of patients [32].

Immunotherapy with MMF is indicated for patients who remain symptomatic or develop symptoms after a period of response to pyridostigmine treatment. This immunotherapy begins with glucocorticoids, but later it is necessary to add AZA or MMF (the best option when the patient does not tolerate AZA well). MMF, especially mycophenolic acid, is well tolerated by patients, with only a small number of adverse reactions, including dizziness and insomnia. This medication is contraindicated during pregnancy due to its teratogenic nature and in patients with fungal or viral infections, malignancies, and liver disease [33].

Cyclosporine

Cyclosporine is a calcineurin inhibitor that interferes with T cell activation. When cyclosporine binds to the receptor cyclophilin-1 inside cells, a complex known as cyclosporine-cyclophilin is formed. This complex subsequently inhibits calcineurin, which stops the dephosphorylation and the activation of the nuclear factor of activated T cells (NF-AT) that generally cause inflammatory reactions. NF-AT is a transcription factor that promotes the production of cytokines such as IL-2. The inhibition of IL-2, which is necessary for T cell activation or proliferation, is believed to be responsible for cyclosporine's immunosuppressive actions [34]. Cyclosporine suppresses the immune response responsible for MG's fluctuating and fatigable muscle weakness. Some MG patients taking cyclosporine may notice a gradual improvement in their symptoms after 2 to 3 months. Others may take longer to see a response [35]. The half-life of cyclosporine is biphasic and very variable in different conditions, but it generally lasts 19 hours [36]. Cyclosporine is approved for a variety of conditions other than MG: prophylaxis of transplant rejection, graft-versus-host disease (GVHD), severe active RA nonresponsive to methotrexate alone, severe psoriasis, keratoconjunctivitis sicca and in steroid-resistant nephrotic syndrome due to glomerular diseases.

In a retrospective analysis of the use of cyclosporine in MG, the authors reviewed the records of patients with myasthenia gravis who took cyclosporine for at least 6 months between November 1987 and January 1999. Of 57 patients who took cyclosporine for an average of 3.5 years, 55 (96%) had clinical improvement. The median time to best clinical response was 7 months. Corticosteroids were discontinued or decreased in 95% of 38 patients taking them. Major side effects included elevated serum creatinine (28%) and malignancy (11%). Five percent could not afford or tolerate the drug. Prices range from $1.50/capsule up to $600 for a 50ml bottle of 100mg/ml solution [36,37]. Following FDA approval in 1983, other more effective and targeted treatments have been researched for MG. Although cyclosporine and related compounds represent an improvement over earlier immunosuppressive agents, they produce serious side effects that practitioners should be aware of. Hypertension is the most common side effect of cyclosporine and cyclosporine-induced functional nephrotoxicity due to preferential constriction of the afferent renal arteriole. Bacterial and fungal infections are less common with regimens of cyclosporine plus prednisone than with azathioprine plus prednisone. Nevertheless, cyclosporine-treated patients are vulnerable to viral infections [38]. Cyclosporine contraindications include known hypersensitivity to cyclosporine or any ingredient in the formulation, RA or psoriasis patients with abnormal renal function, uncontrolled hypertension or malignancies, concurrent therapy with methotrexate or other immunosuppressive agents, and radiation. Cyclosporine interactions include antibiotics, antifungals, gastric ulcers, gout medications, oral contraceptives, anticonvulsants, steroids, statins, grapefruit products, potassium-containing products, and St. John's Wort, to mention a few [39].

Cyclophosphamide

Cyclophosphamide is a non-phase-specific alkylating agent that modifies the guanine base of DNA, interfering with transcription and DNA replication [40-42]. It inhibits rapidly proliferating cells such as T and B lymphocytes, thus causing immunosuppression [40]. This medication is indicated in patients with life-threatening MG or refractory MG who fail to respond to conventional therapy, severe adverse effects, or frequent myasthenic crises while on therapy [42]. Treatment can be administered orally daily or intravenously monthly. However, studies have shown a better response and fewer adverse effects when administered monthly pulses [40,42]. Cyclophosphamide has shown to be effective in patients who failed multiple immunomodulatory therapies, with two-thirds of patients improving within the first month [40]. Another study showed a significant improvement in QMG score in patients given 500mg/m^2 intravenously monthly and a reduction of steroid dose at six and 12 months of therapy [41].

The recommended dosage for IV pulse therapy is 500-750mg/m^2 every 4-8 weeks, along with Mesna and antiemetics, until remission [43]. Cyclophosphamide has many adverse effects and must be closely monitored. Weekly CBC, as well as a urinalysis, are recommended to monitor neutrophil count and hemorrhagic cystitis (bladder prophylaxis and adequate hydration are strongly recommended) [43]. Other side effects include nausea, pancytopenia, infertility, alopecia, leukemia, lymphoma, bladder cancer, respiratory and mucocutaneous infections, gastrointestinal conditions, lung fibrosis, and cardiomyopathy [41-43]. Because cyclophosphamide is teratogenic and excreted in breast milk, it is contraindicated during pregnancy and breastfeeding [44].

Thymectomy

Multiple lines of evidence show that the thymus's primary function in MG pathophysiology provides the foundation for

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thymectomy as a therapy for these patients. Thymomas are uncommon tumors in the anterior mediastinum in 10% of patients with MG. Thymectomy is thought to be necessary to stop the spread of these tumors, and it is essential to guarantee the neoplasm's radical removal [45]. It has been reported that up to 70% of patients with MG exhibit hyperplastic thymic alterations that are not observed in healthy individuals. The possibility of thymectomy may be considered if a patient has not responded to a first immunotherapy treatment or has suffered severe side effects [46]. The patient's age influences thymectomy choice because of the high prevalence of thymic involution. It is believed that older people may not react well to thymectomy and that the hazards may outweigh any possible advantages. This is why most facilities will not operate on patients over the age of 60. However, some experts advise patients to undergo an individual risk and benefit analysis regardless of age [47]. Some factors are considered when deciding whether to perform a thymectomy, including the gender of the patient, the early onset of MG, the presence of a thymoma, the severity of MG symptoms, the presence of AchR antibodies or MuSK antibodies, and the development of seronegative myasthenia. It is still unclear how thymectomy affects people with double-seronegative MG. However, in these situations, most institutions advise thymectomy [47,48]. Thymectomy is advised for final tumor management and MG therapy to lessen long-term exposure to pharmacotherapy and enhance results [49]. The results of trans-sternal and video-assisted thoracoscopic thymectomy procedures are often comparable. In most cases, thymic neoplasia can be cured by radical removal of a thymoma. Nonetheless, not all patients get a fully stable remission after a thorough thymectomy, highlighting the necessity for ongoing management. When thymomas invade the pleura or the pericardium, which are surgically inaccessible, further oncological treatment is required [50,51]. The necessity for long-term mechanical breathing or the postoperative myasthenic crisis has been linked to many conditions. These include preoperative expiratory weakness, a vital capacity of less than 2.0L, bulbar symptoms, a history of a myasthenic crisis, a serum AChR antibodies level larger than 100nmol/L, and intraoperative hemorrhage of more than 1L. In the postoperative phase, patients with these poorer prognostic characteristics will require more outstanding care [47].

Conclusion

Myasthenia Gravis (MG) is an autoimmune disorder of the neuromuscular junction of skeletal muscles. Symptom management is the primary thrust of the treatment of MG. Acetylcholinesterase Inhibitors such as Pyridostigmine or Neostigmine are used for temporally alleviating muscle weakness. However, these agents can produce side effects such as increased bronchial secretions and bronchospasm, making them impractical for patients requiring mechanical ventilation. Immunosuppressive therapy with steroids such as prednisone is recommended when symptoms fail to improve with Acetylcholinesterase Inhibitors. Still, its use might be limited due to significant adverse reactions such as diabetes, hypertension, weight gain, neuropsychiatric disturbances, and opportunistic infections. In those patients with generalized MG unresponsive to corticosteroids, patients with contraindications to corticosteroid treatment, or patients with toxicities of chronic glucocorticoid use, non-steroidal immunotherapy with azathioprine a purine analog that inhibits purine synthesis-might be indicated. The most common side effect encountered with azathioprine is a flulike illness and, less frequently, potential severe adverse effects such as hepatotoxicity, suppression of the white blood count, pancreatitis, and malignancy. Another steroid-sparing medication used to treat myasthenia gravis is Mycophenolate Mofetil, a drug that blocks the synthesis of purine nucleotides and inhibits the proliferation of lymphocytes. Mycophenolate is typically added to immunotherapy after glucocorticoids in patients that do not tolerate azathioprine but is contraindicated in pregnant patients and those with infections or malignancy. Ravulizumab is a long-acting C5 complement inhibitor for treating patients with generalized myasthenia gravis who are anti-acetylcholine receptor antibody positive. It has the advantage of allowing less frequent administrations (every 8 weeks). However, Ravulizumab has rarely been associated with an increased risk of infections such as SARS-CoV-2 and Neisseria meningitides. Cyclosporine, a calcineurin inhibitor that inhibits the function of T-cells, is also effective in suppressing the immune response causing the muscle weakness of Myasthenia Gravis but produces serious side effects that include hypertension, nephrotoxicity, viral infections, and drug interactions with many medications that affect the P-450 system. In patients with refractory disease, more aggressive treatment is required. Eculizumab, a targeted complement inhibitor, might be effective in gradually controlling the disease in patients with refractory anti-ACHR-Ab positive gMG with few adverse effects. Rituximab is a monoclonal antibody that targets CD20 on B lymphocytes, reduces relapses, and lessens the use of immunosuppressive agents. Cyclophosphamide is an alkylating agent that inhibits lymphocytes and causes immunosuppression, making it effective in patients with refractory Myasthenia Gravis. However, cyclophosphamide is associated with many adverse effects, including hemorrhagic cystitis, malignancy, infections, and cardiopathy, and is contraindicated in women of reproductive age due to teratogenicity. Lastly, thymectomy is recommended for all patients with thymomas, patients unresponsive to immunotherapy treatment, and to reduce long-term exposure to pharmacotherapy. Despite the myriad of current treatments, there are still unmet needs in managing myasthenia gravis. Some patients, such as those with refractory ocular myasthenia gravis or double-seronegative myasthenia gravis, are unresponsive to existing therapies, and other options are necessary. Additionally, further research should be focused on the safety of the drugs used for MG in pregnant patients and the pediatric population.

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