

Comparing Safety and Efficacy of Rituximab and Eculizumab in Treating Refractory Myasthenia Gravis: A Systematic Review

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Abbreviations

MG: Myasthenia Gravis
MG-ADL: Myasthenia Gravis Activities of Daily Living Scale
QMG: Quantitative Myasthenia Gravis score
MG-QOL: Myasthenia Gravis- Quality of Life score
MMS: Minimal Manifestation Status
Neuro-QoL Fatigue: Quality of Life in Neurological Disorders Fatigue scale
AChR: Acetylcholine receptor
MuSK: Muscle-specific tyrosine kinase
IVIG: Intravenous Immunoglobulin

Abstract

Introduction: Myasthenia gravis is a common autoimmune disease in which patients experience weakness primarily in the ocular, respiratory, bulbar, and limb muscles. Although the symptoms of most patients with myasthenia gravis are well controlled with conventional immunotherapies, about 15% of them experience a refractory disease. This systematic review will focus on the safety and efficacy of monoclonal antibodies, specifically rituximab and eculizumab, in treating myasthenia gravis.

Methods: A thorough search for relevant research papers was conducted utilizing PubMed and Google Scholar. A comparative investigation of published research studies was carried out, with only articles published in the last five years being selected. The primary terms that were chosen were "myasthenia gravis, monoclonal antibodies, rituximab, eculizumab, and refractory myasthenia gravis" as keywords and medical subject headings (MeSH). A total of 11 papers were selected for inclusion in this review, with the primary outcomes focusing on the safety and efficacy of rituximab and eculizumab, as subjectively and objectively noted in various scales used to quantify improvement or deterioration.

Results: Eleven studies that were either systematic reviews, meta-analyses, or randomized control trials

were selected for this study. They analyzed the effect of rituximab, eculizumab, or both on patients with refractory generalized myasthenia gravis. Each study concluded that both drugs showed improvement in patients via their MG-ADL, MG-QOL, MMS, or QMG scores. Adverse events were seen in both groups of patients, with discrepancies between studies regarding which drug caused more. Multiple studies determined that the development of myasthenia crisis in both groups was insignificant. In terms of the safety profile of rituximab it is important to note that infusion reactions, infection, immunosuppression, and cardiovascular events have been seen to occur. For eculizumab, infections including meningococcal, hypertension and infusion related injuries have also been seen to occur.

Conclusion: Many patients with myasthenia gravis experience a refractory disease that requires additional or conjunctive treatment. Monoclonal antibodies have been used for these cases, and there is an ongoing investigation as to which one is most safe and most effective. There are many discrepancies in current research on whether rituximab or eculizumab is superior, and there are still many unanswered questions. Both therapies successfully improve clinical manifestations of the disease objectively and subjectively. Rituximab, in particular, was seen to have a safer safety profile in some studies; however, it remains to potentially cause a life-threatening disease known as progressive multifocal leukoencephalopathy (PML) in a meniscal number of patients.

Introduction and Background

Myasthenia gravis is a chronic autoimmune disorder of the neuromuscular junction that weakens and exhausts skeletal muscle by targeting different parts of the postsynaptic membrane with immune system-produced antibodies (1). Most patients with myasthenia gravis develop auto-antibodies against postsynaptic acetylcholine receptors at the neuromuscular junction end plates. The remaining individuals with this disease either have antibodies against muscle-specific tyrosine kinase (MuSK), against related proteins, including agrin and LDL receptor-related proteins, or are seronegative (1). The classic symptoms that patients exhibit are a

variable weakness of the ocular, bulbar, limb, and respiratory muscles. This presents as blurry vision, drooping of eyelids, dysphagia, dysarthria, dyspnea, and fatigue in the muscles of the face, neck, and extremities (2). This disease presents very similar to Lambert-Eaton syndrome but is distinguished by the fact that the condition improves with rest.

The disease in most patients is controlled using standard therapies, including cholinesterase inhibitors, immunosuppressants, and immunomodulatory treatments such as azathioprine, IV immunoglobulin (IVIG), and plasma exchange (PLEX) (3). However, in a small percentage of cases, these conventional therapies are ineffective, or patients experience serious adverse events known as "refractory myasthenia gravis." Therefore, monoclonal antibodies such as rituximab and eculizumab have been approved for use. To understand how these therapies work, it is vital to understand the pathophysiology of the disease. The autoantibodies that are formed in myasthenia gravis cause the complement cascade to be activated by binding to complement factors and inducing the formation of membrane attack complexes (MAC), the neurotransmitter acetylcholine's ability to attach to its receptor to be diminished, and the acetylcholine receptors (AChRs) to degrade at a faster rate (2). The activation of the complement cascade is one of the primary causes of impaired neurotransmission, leading to muscular symptoms in patients with myasthenia gravis.

Eculizumab is a humanized monoclonal IgG2/4K antibody that inhibits complement activation by binding to complement protein C5. It is being used for several diseases, including paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome, but it has recently been approved for use in patients with anti-AChR antibody-positive MG (4). Rituximab is another monoclonal antibody utilized in patients experiencing refractory myasthenia gravis. It targets and attaches to CD20 found on B-lymphocytes, subsequently triggering apoptosis in both normal and abnormal B lymphocytes (4). Additionally, antibody-dependent and complement-dependent cytotoxicity are involved in the action mechanism.

Refractory Myasthenia Gravis

There are many definitions of what is considered refractory myasthenia gravis; currently, not one has been unanimously agreed upon. In the most general sense, these patients experience an unsatisfactory response to traditional therapies used for the disease. This includes inadequate objective and subjective results from using the highest dose of steroids without compromising safety, along with at least one immunosuppressive medication (5). Another way it is defined is as failure to decrease immunosuppressive therapy minus a clinical reversion or requirement for additional treatment such as intravenous immunoglobulin (IVIG) or plasma exchange. Although individuals may initially have positive results, the length of these therapies must be limited due to the risk of serious

adverse events associated with long-term usage, particularly corticosteroids (6). An additional part of the criteria used in defining refractory myasthenia gravis is the development of serious or unendurable side effects from conventional therapy. Patients with comorbid conditions preventing them from taking traditional therapies and those experiencing repeated myasthenia crises while on therapy are also described as having refractory myasthenia gravis (6). This narrative review's primary focus was on comparing rituximab and eculizumab in the treatment of refractory myasthenia gravis. The paper used studies analyzing patients with myasthenia gravis that have at least one of these criteria.

Methods

We conducted a thorough literature search via PubMed, PMC, Medline and Google Scholar for the relevant published studies. We used "myasthenia gravis, monoclonal antibodies, rituximab, and eculizumab as keywords and medical subject headings (MeSH), excluding eculizumab which did not yield any results for MeSH. Research papers that were selected included those published in the last five years. This duration of time was chosen because there are continual studies being performed on these medications and we wanted to ensure that the latest and most recent data and facts were extracted. Out of the papers found, 25 papers were chosen centered on the applicability of the title, with 15 being subsequently qualified after reviewing the abstracts. The inclusion and exclusion criteria were applied, duplicated papers were eliminated, and only full-text papers in English were selected. Ultimately, 11 articles were included in this review.

Table 1
Keyword search results breakdown by database

KEYWORDS	PubMed/PMC/Medline	Google Scholar
Myasthenia Gravis	368	7,080
Rituximab	1,700	18,600
Eculizumab	34	3,550
Myasthenia Gravis and Rituximab	280	1,700
Myasthenia Gravis and Eculizumab	130	592

MeSH	PubMed/PMC/Medline
("Myasthenia Gravis/complications"[Majr] OR "Myasthenia Gravis/drug therapy"[Majr] OR "Myasthenia Gravis/prevention and control"[Majr] OR "Myasthenia Gravis/therapy"[Majr])	100
("Rituximab/drug effects"[Majr] OR "Rituximab/therapeutic use"[Majr] OR "Rituximab/toxicity"[Majr])	190
("Antibodies, Monoclonal, Humanized/administration and dosage"[Majr] OR "Antibodies, Monoclonal, Humanized/adverse effects"[Majr] OR "Antibodies, Monoclonal, Humanized/drug effects"[Majr] OR "Antibodies, Monoclonal, Humanized/pharmacokinetics"[Majr] OR "Antibodies, Monoclonal, Humanized/pharmacology"[Majr] OR "Antibodies, Monoclonal, Humanized/therapeutic use"[Majr] OR "Antibodies, Monoclonal, Humanized/toxicity"[Majr])	2,716
("Myasthenia Gravis/complications"[Majr] OR "Myasthenia Gravis/drug therapy"[Majr] OR "Myasthenia Gravis/prevention and control"[Majr] OR "Myasthenia Gravis/therapy"[Majr]) AND "Rituximab/therapeutic use"[Majr] OR "Rituximab/toxicity"[Majr] OR ("Antibodies, Monoclonal, Humanized/administration and dosage"[Majr] OR "Antibodies, Monoclonal, Humanized/adverse effects"[Majr] OR "Antibodies, Monoclonal, Humanized/drug effects"[Majr] OR "Antibodies, Monoclonal, Humanized/pharmacokinetics"[Majr] OR "Antibodies, Monoclonal, Humanized/pharmacology"[Majr] OR "Antibodies, Monoclonal, Humanized/therapeutic use"[Majr] OR "Antibodies, Monoclonal, Humanized/toxicity"[Majr])	2,700

Inclusion and exclusion criteria

Systematic Reviews, Meta-Analysis, Retrospective Observational studies, and Randomized Control Trials published in the last five years were chosen for reviews. Initially, included studies were filtered based on the title and abstract. Following that, appropriateness for inclusion was assessed via a full-text screen. The primary focus of these studies was on the safety and efficacy of rituximab and eculizumab in treating myasthenia gravis. Editorials, papers not published in English, gray literature and papers including ICU, juvenile, CKD patients and pregnant patients were excluded from this study. Additionally, studies with patients that were not treated with either rituximab or eculizumab were omitted. In randomized control trials, only papers that included patients with a confirmed diagnosis of myasthenia gravis in accordance with national guidelines were included.

Results

Among the 11 chosen research papers, three were randomized control trials (RCTs), two were systematic reviews and meta-analyses, four were retrospective studies, one was a systematic review, and one meta-analysis. The selected three RCTs assessed the role of eculizumab in the treatment of refractory generalized myasthenia gravis. One of the systematic reviews and meta-analyses compared the safety and efficacy of rituximab and eculizumab, while the other selected one

solely evaluated the effect of rituximab. A detailed review of the screening and study selection is represented in Figure 1. In each of the studies selected for this paper, the most general criteria for refractory myasthenia gravis was used, meaning that the individuals were proven to have an unsatisfactory response to traditional therapies, as noted by several scaling tools. Several of the studies chosen for this paper included refractory myasthenia gravis patients with either the anti-MuSK -ab positive or anti-AChR-ab positive subtypes. However, the majority of the selected studies only included those with the anti-AChR-ab positive subtype, as it is much more common. Only patients with this subtype were administered eculizumab because as mentioned earlier, it was proven that complement activation is involved in damaging the neuromuscular junction (NMJ) due to MAC deposits (4).

In the main clinical trial done for eculizumab known as the REGAIN trial, an initial dose of 900 mg/week, which was ultimately increased to 1200 mg after four weeks, and then 1200mg every two weeks thereafter was utilized as the treatment plan for patients enrolled in the trial. This served as the standard protocol for dosages for patients receiving eculizumab in all studies selected. Rituximab, on the other hand, was observed to be administered at different doses and times across studies, with some utilizing induction doses. More precise doses and the effects of them observed in the studies selected are elaborated on in the discussion section.

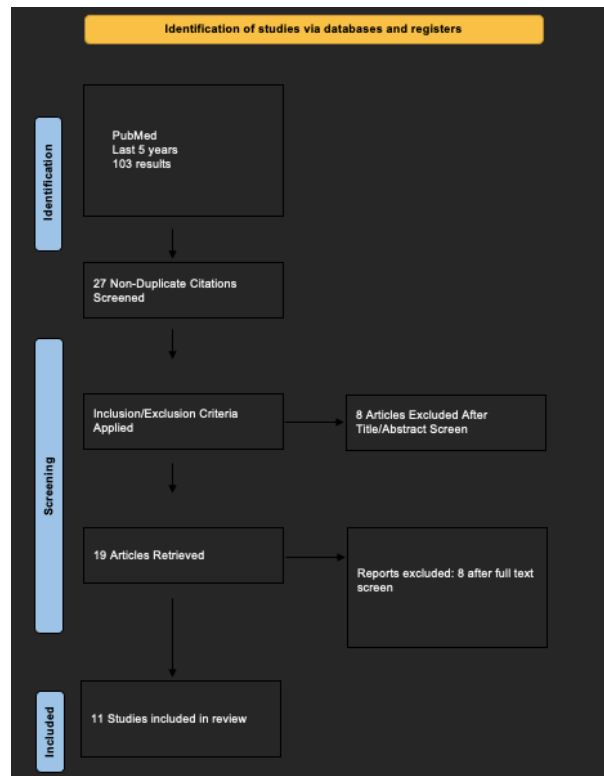


Figure 1: PRISMA diagram illustrating the selection of data
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses

Table 2
Several studies selected for inclusion in the review

RCT: Randomized Controlled Trial; MG: Myasthenia Gravis; QMG: Quantitative Myasthenia Gravis Score

Study	Location	Study Type	Drugs Used/Patient Groups	Result	Conclusion
Vissing et al. (2)	USA	RCT analysis	Eculizumab in patients with ACh antibody-positive refractory generalized MG	Eculizumab use showed minimal symptom expression	The REGAIN study proved a prompt and persistent reaction to eculizumab in patients with refractory generalized MG that is effective for long-term periods.
Anderson et al. (7)	USA	RCT	Eculizumab in patients with ACh antibody-positive refractory generalized MG	Utilizing Neuro-QoL, it was seen that the use of eculizumab improved fatigue in comparison to placebo in patients with refractory MG	Eculizumab improved fatigue in patients who received it for the first time and those who completed the REGAIN trial.
Brauner et al. (6)	Sweden	Retrospective Cohort Study	Comparing rituximab in patients with new onset MG, excluding MuSK + patients, on conventional immunotherapy versus rituximab in refractory disease.	The average time to remission was less for new-onset disease vs. refractory disease, with a 7-month vs. 11-month difference. The percentage of treatment cessation due to side effects was inferior to those of immunosuppressants, with 3% vs. 46%, with P<.001 being noted.	Treatment with rituximab is more favorable when started early after diagnosis and showed shorter times to remission.
Nelke et al. (9)	Germany	Retrospective Observational Study	57 rituximab-treated generalized refractory anti-ACh MG patients and 20 eculizumab-treated generalized refractory anti-ACh MG patients	Based on QMG scores, eculizumab exhibited a considerably superior benefit compared to rituximab, with scores of 11.2 for rituximab and 8.4 for eculizumab at 12 months, with a p score of .021. At 24 months, a greater benefit was seen with a QMG score of 11.2 for rituximab and 9.6 for eculizumab, with a p score <.001.	Eculizumab was shown to be more successful in improving MG severity compared to rituximab. Both treatments decreased average prednisone doses; however, the risk of myasthenia crisis remained similar.
Zhao et al. (12)	China	Single arm Meta-Analysis	Analyzed the safety and efficacy of rituximab by evaluating 24 studies done on 417 patients (112 male and 305 female)	It was discovered that patients with the MuSK-MG subtype attained MMS at a higher rate than the AChR-MG subtype group.	In this study group, patients with mild to moderate disease showed significantly more improvement when treated with rituximab than patients with severe myasthenia gravis.

Discussion

Myasthenia gravis is one of the most common autoimmune diseases that affect millions of individuals around the world. Several treatments are currently available for the generalized condition; however, many patients experience a refractory disease. Also, many patients on immunosuppressants develop serious adverse events, and therefore newer therapies have been explored in the treatment of myasthenia gravis, with studies showing decreased risks of side effects. Currently, there are several mechanisms to measure outcomes of improvement of the disease. Myasthenia Gravis Activities of Daily Living Scale (MG-ADL) is the primary outcome score utilized in the selected studies for this review. This is a subjective 8-item patient-reported outcome measure, with a total score ranging from 0 to 24, that evaluates MG symptoms and functional activities linked to activities of daily life (10). Higher scores reflect more severe symptoms. The MG-ADL includes questions that measure patients' functional limitations as a result of ocular (2 questions), bulbar (3 questions), respiratory (1 item), and gross motor or limb impairment (2 items) (11). Another test that was assessed in several studies was the ability of MG patients to successfully attain Minimal Manifestation Status (MMS), described as the patient having no symptoms or functional restrictions from MG but having weakness on the physical examination of certain muscles (12). Additionally, several objective outcomes were measured based on physical examination and evaluation, including Quantitative Myasthenia Gravis (QMG) score, Myasthenia Gravis Quality of Life (MG-QoL), Quality of Life in Neurological Disorders Fatigue Scale (Neuro-QoL Fatigue) scores as well as the proportion of patients that were able to discontinue oral immunosuppressants were also used as outcomes in a few studies that were selected. In this study, the

primary outcome analyzed is the QMG score, with secondary outcomes including MG-ADL score, MMS, and reduction in conventional therapies.

Traditional Therapies for MG

Myasthenia gravis currently has no cure to rid the disease. Therefore, treatment aims to manage symptoms and control immune system activity. The symptoms of myasthenia gravis have been treated traditionally with several different medications. However, depending on the individual's subtype of the disease, different therapies may be indicated. These include cholinesterase inhibitors such as pyridostigmine, immunosuppressive agents such as glucocorticoids, antimetabolites such as azathioprine, pyridines, and IV immunoglobulins (IVIG) (13).

The mainstay of treatment for patients with the anti-AChR-ab-positive subtype of myasthenia gravis patients are the cholinesterase inhibitors (AChE inhibitors). However, they only treat symptomatic patients, are unable to stop disease progression, and are frequently resistant to treatment; therefore, it is not advised for long-term use. The side effects observed are due to the parasympathetic effects on the nervous system, including diarrhea, increased urination, miosis with lacrimation, and sweating.

Azathioprine has historically been used to treat MG since the late 1960s, with proven improvement in the disease seen within several months. When used supplementally with steroids, it has been effective in promptly treating flare-ups of the disease. A major unfavorable result of treatment is the development of bone marrow suppression in certain patients with the TPMY genotype (13). This immunosuppressant, along with cyclosporine and tacrolimus, has been shown to be effective against the anti-MuSK-ab-positive subtype of MG.

The use of immunosuppressive agents such as glucocorticoids has been highly effective in treating symptomatic disease and allowing many patients with both subtypes to attain remission. This therapy has an indolent process and has well-known side effects, both short and long-term, including increased risk of infection, osteoporosis, and cardiovascular disorders.

IVIG is one of the most successful therapies to treat patients with severe myasthenia gravis. It has been noted to have scarce adverse events, with improvement being seen in under a week, making it an ideal choice of therapy. An additional therapy for myasthenia gravis, almost equivalent in efficacy to IVIG, is plasma exchange (PLEX). It is reserved for those with highly refractory disease and has been indicated for patients experiencing myasthenia crisis or impending crisis (14).

Even with this multitude of therapies, about 10-15% of patients experience refractory or worsening disease.

Mechanism of Action of Rituximab and Eculizumab

Rituximab and eculizumab are both drugs that belong to the family of monoclonal antibodies; however, they each have separate mechanisms of action. The anti-CD20 antibody derived from mice was used to create the chimeric human/mouse antibody known as rituximab. Rituximab strongly binds to the CD20 antigen, expressed in normal B cells, precursor B cells, mature B cells, and most cancerous B cells. It is not expressed on stem cells and progenitor B-cells which is why rituximab has been utilized for many cancers, including non-Hodgkin's lymphoma, CLL, and other B cell lymphomas. After binding to the antibody, the B-cells undergo cell death via several different means, including apoptosis, antibody-dependent-cell-mediated-cytotoxicity, and complement-dependent cytotoxicity. The primary reason rituximab is effective in myasthenia gravis is that it causes a decline in the new plasma cell synthesis rate (14). It is important to understand that CD20 is not present in plasma cells; therefore, they would not be affected by the drug. Besides cancer, rituximab has also been approved for use in many autoimmune diseases, including ANCA-positive vasculitis, SLE, ITP, and Anti-phospholipid syndrome.

The mechanism of action for eculizumab primarily deals with a major component of the innate immune system known as the complement system. Several different pathways exist in the system, such as the classical, lectin, and alternative pathways. They are activated by various immune system constituents, including antibodies, IgM, or IgG, freed following subjection to a pathogen or mannose-comprising sugars on microbe surfaces or are freely activated and elicited via microbe surface molecules (4). In summary, once the pathway is activated, it generates an enzyme called C3 convertase, which cleaves C3 into C3a and C3b. Each of these has its unique functions; however, for this discussion, we will mention how they are involved in this system. C3b then generates C5 convertase, which acts similarly to C3 convertase by cleaving C5 into C5a and C5b. These two proteins then advance and bind to specific complement proteins, C6, C7, C8, and C9. Combined, these proteins form a complex known as the membrane attack complex (MAC). It is theorized that MAC is involved in the destruction of acetylcholine receptors, ultimately leading to the clinical manifestations of myasthenia gravis. A great deal of research is still required to define the degree to which complement fosters disease outcomes (15).

Following the REGAIN study, eculizumab was approved for use in patients with refractory myasthenia gravis.

Side effects and Safety of Eculizumab

A phase III study known as the REGAIN study, in which a total of 125 patients with anti-AChR-Ab-positive refractory generalized myasthenia gravis were either administered eculizumab (62) with an initial dose of 900 mg, which was ultimately increased to 1200 mg after

four weeks or a placebo (63) for 26 weeks, had a primary outcome of MG-ADL scores (16). The study demonstrated that there was no substantial disparity seen between the two treatment groups. However, the study did prove that eculizumab successfully alleviated symptoms of the disease and was well endured, even moderately lessening the progression of the disease in patients. The same 26-week REGAIN study showed the effectiveness and durability of eculizumab in treating patients with anti-AChR-positive refractory generalized myasthenia gravis, with partakers reporting clinically significant improvements in various actions of daily living, muscular strength, functional ability, and quality of life. The REGAIN open-label extension (OLE) experiment showed eculizumab's continued efficacy and long-term safety (17). In a responder study analysis on the REGAIN study performed by Howard et al., it was reported that a bulk of the patients enrolled in the trial displayed a positive response, noted as a reduction in QMG score of greater than 3, to eculizumab in the first 12 weeks of being treated. The remaining participants achieved reductions in QMG between 12 weeks and the end of the trial, with few discontinuing due to no clinical or subjective improvement, claiming that despite initial response by week 12, extended treatment can show more promising results (18).

One of the major symptoms that patients with myasthenia gravis exhibit are fatigue, both muscular and subjective. In a study done by Anderson et al., it was observed how eculizumab affected patients perceived generalized fatigue using the Neuro-QOL fatigue subscale. Analyzing the patients enrolled in the REGAIN study, it was reported that patients receiving eculizumab had significantly more fatigue enhancements than patients receiving a placebo with a p-value < 0.05 (7).

Several adverse events have been reported associated with the use of eculizumab. In a study done by Vissing et al. analyzing the REGAIN study, the most common unfavorable events were nasopharyngitis and headache. Nausea, myalgia, upper respiratory tract infection, and diarrhea were adverse events reported in order of most to least common, respectively (2). Notably, being a complement inhibitor, many patients treated with eculizumab required meningococcal vaccination to prevent serious infectious complications. However, there has been a small percentage of reported cases. A review of the 26-week REGAIN study performed by Dhillon et al. analyzed that there was no significant difference in the number of adverse events experienced by patients taking eculizumab and for those taking a placebo. It was also reported that the patients exhibited similar adverse events in groups taking the drug long-term (>52 weeks) and short-term (6).

In a meta-analysis performed by Song et al., it was reported that although eculizumab was effective in decreasing QMG and MG-ADL scores, it did not show any significant difference in safety profile compared to placebo. Granted, the study population was small and

included just six studies. It is important to note that only patients with anti-AChR-Ab-positive refractory generalized myasthenia gravis who were administered eculizumab were analyzed, excluding patients with the MuSK subtype. Currently, eculizumab is only approved for myasthenia gravis, specifically with this subtype.

Side effects and Safety of Rituximab

In one retrospective cohort study done on a randomized clinical trial with 72 participants with Ach + autoantibodies that began taking rituximab at different times, the primary outcome was the time to remission and the need for rescue treatments or supplementary treatments immunotherapies as secondary outcomes. Results demonstrated that rituximab was more favorable in new-onset generalized MG than in long-term disease and displayed improvement in disease compared to conventional therapies (8).

A single-arm meta-analysis and systemic review by Zhao et al. analyzed the safety and efficacy of rituximab by evaluating 24 studies done on 417 patients (112 male and 305 female) with refractory MG. The studies included AChR-IgG positive patients, MuSK-IgG positive and double negative MG patients. Doses with time intervals that were administered differed between studies, with some groups receiving 375 mg/m² weekly for four weeks, some receiving low induction doses, some getting 600 mg, and some receiving either 375 mg/m² twice with a two-week interval or 1 g within two weeks apart (19). MG-ADL was not a primary outcome. However, results revealed that rituximab successfully decreases the symptoms of myasthenia gravis, reduces QMG score, and lowers the dosages of corticosteroids and immunosuppressive agents in patients with refractory disease. Also, it was discovered that patients with the MuSK-MG subtype attained MMS at a higher rate than the AChR-MG subtype group. In this study group, patients with mild to moderate disease showed significantly more improvement than patients with severe myasthenia gravis. Notably, it is still a mystery as to which group of patients with myasthenia gravis benefits the most from treatment with rituximab, as many studies were small.

In a review performed by Feng et al., a comparison of dosages of rituximab administered was performed, with the low dose being defined as lower than 375 mg/m² twice a month and anything higher being classified as a high dosage. It was reported that higher doses were associated with slightly higher minimal manifestation status (MSS). However, a somewhat larger number of adverse events were also seen (12% compared to 9%) (20). In the observational retrospective cross-sectional study performed by Cortes-Vicente, it was seen that patients with the MuSK subtype refractory myasthenia gravis reacted more positively to rituximab than any other immunosuppressant agent. One patient in the study had anti-AChR-antibody and anti-MuSK-positive antibodies and responded positively to rituximab (21). Several adverse events were reported in patients that received rituximab, the most common being infusion

reactions, infection due to B-cell depletion (upper respiratory most commonly), and hematological disorders. Some infrequent side effects that were seen were psychiatric illness, alopecia areata, paroxysmal atrial fibrillation, and progressive multifocal leukoencephalopathy (PML), which is one of the most feared adverse effects of the drug (19). Herpes zoster infection, along with enteritis, were other rare adverse events that were seen in a small percentage of patients. In an observational retrospective cross-sectional study performed by Cortes-Vicente in which 990 patients from 15 hospitals were enrolled, 40 patients were administered rituximab. Thirty-five of them withdrew from the drug over an average of 9.8 years. They were followed either due to inefficacy, side effects, or achieving remission. Adverse events that were seen were exacerbation of psoriasis in one patient and PML in another (21).

Comparison between Rituximab and Eculizumab in the treatment of MG

A retrospective observational study by Nelke et al. compared the use of eculizumab versus rituximab in treating myasthenia gravis, analyzing 77 patients treated with one or neither. Both groups had similar demographics, were treated with the same immunosuppressive therapy, and had analogous disease severity with QMG scores of 10.7 for rituximab and 13.25 for eculizumab. The primary outcome measured was the QMG score following one year of treatment, with secondary outcomes including the rate of myasthenia crisis occurring, the development of minimal manifestation status (MMS), and the reduction in average steroid use. It was seen that patients treated with eculizumab exhibited a considerably superior benefit from therapy compared to those treated with rituximab (9). Similar QMG results were also seen following two years of therapy. In terms of developing a myasthenia crisis, some patients developed it in both groups; however, no statistical significance was reached.

Additionally, the duration of its development was similar in both treatment groups, with the primary cause being infection. Both rituximab and eculizumab allowed a reduction in average prednisone usage. In another study comparing both drugs performed by Feng et al., it was seen that the incidence of MG exacerbation was 0.178 per year for patients on rituximab and 0.218 per year for patients on eculizumab. However, the approximate incidence rate for MC was about .5X less for patients on eculizumab (20). Both therapies were effective and had similar changes in decreasing QMG and MG-ADL. However, rituximab showed a roughly 18% increase in MMS. It was reported that rituximab had a greater safety profile than eculizumab, with fewer adverse events reports.

Conclusion and Recommendations

While conventional immunotherapies have shown efficacy in treating a significant proportion of myasthenia gravis patients, a prominent number still

deal with unresponsive symptoms. Both rituximab and eculizumab have shown efficacy in addressing generalized MG, however the uncertainty regarding their safety and effectiveness remains a question in treating refractory cases.

Limited patient cohorts, often centered around the specific Anti-Ach antibody subtype, have been the primary focus of majority of studies. For eculizumab, thorough monitoring of patient complement levels is required prior to treatment and vaccination to avoid potential life-threatening consequences. Although the occurrence is rare, those undergoing treatment with rituximab must undergo continuous monitoring to detect the onset of PML. Nonetheless, the safety profiles of both therapies exhibit minimal discrepancy when compared to placebo and other immunosuppressive agents.

Both rituximab and eculizumab have been seen to decrease QMG and MG-ADL scores and increase MMS scores, among others, justifying that both cause objective and subjective improvement in patients. Administering these therapies reduces patients' burden on taking steroids known to cause serious side effects.

The discrepancies observed in many of the studies included in this review portray the difficulty in choosing which is superior. The emergence of monoclonal antibodies has been promising; however, more research and clinical studies must be performed to ensure that rituximab and eculizumab, along with other monoclonal antibodies, are acting as safe and successful treatment of refractory myasthenia gravis.

Limitations and Recommendations

Sample Size and heterogeneity: This paper was limited by only using research papers that were published in the last five years. Only papers published in the English language were used. Many studies that were included only had limited sample sizes with patient populations often having varying characteristics. This could have led to potential biases impacting the findings. Finding studies with more diverse patient populations would add more value to the efficacy of rituximab and eculizumab in refractory MG.

Finding more data directly comparing rituximab and eculizumab in the treatment of refractory MG would provide a more comprehensive understanding of their clinical utility.

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