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[Intervention Protocol]

Complement inhibitors for myasthenia gravis in adults

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To evaluate the benefits and harms of complement inhibitors for treating myasthenia gravis in adults compared with control treatment (placebo or standard care).

BACKGROUND

Description of the condition

Myasthenia gravis is an autoimmune disease whereby the person's immune system produces antibodies against components of the neuromuscular junction, where the nerves controlling muscle movement meet the muscles [1]. Myasthenia gravis is the most commonly acquired disorder affecting the neuromuscular junction, with an incidence of around 15.7 cases per million person-years and a prevalence of 20 to 475 cases per million person-years [2]. The incidence and prevalence of myasthenia gravis are increasing, particularly in older people [3]. People with myasthenia gravis present with weakness that gets progressively worse the more the muscle is used (known as fatigability), and it commonly affects the ocular (eye), bulbar (swallowing and speech), respiratory (breathing), and proximal limb muscles (those closest to the centre of the body, specifically in the shoulders, upper arms, hips, and thighs). The clinical severity of myasthenia gravis can vary greatly; ranging from mild ocular symptoms, such as double vision (diplopia) and drooping of the eyelids (ptosis), to frequent and severe bulbar and respiratory crises requiring hospital admission [4].

The disordered physiological processes (pathophysiology) of myasthenia gravis involve the development of antibodies that mistakenly target components of the postsynaptic cell membrane of the neuromuscular junction (autoantibodies) [1]. Most of the affected people (around 85%) have antibodies to the acetylcholine receptor (AChR), while other antibody targets include muscle-specific kinase (MuSK) (5% of affected people) and lipoprotein-related protein 4 (LRP4) (2% of affected people) [5]. The remaining 5% to 7% of people with myasthenia gravis have no identifiable autoantibody and are classified as seronegative myasthenia gravis. In around 15% of people, the development of myasthenia gravis is associated with a tumour of the thymus gland (known as a thymoma); in these cases, removal of the thymoma is recommended and can sometimes result in disease remission [6, 7]. AChR antibodies are known to activate the complement system (part of the immune system of the body), which can lead to deposition of the membrane attack complex (MAC) on the muscle endplate (a specialised region on the muscle fibre's membrane where the neuromuscular junction forms a connection with a motor neuron), causing disruption to the functioning of the neuromuscular junction and resulting in the symptoms of myasthenia gravis [8]. Although complement deposition has also been seen in people who are seronegative, MuSK antibodies do not activate the complement system [9].

Disease classification

Myasthenia gravis can be classified by disease onset (early versus late), although there is considerable clinical overlap between the two categories [5, 10]. Early-onset disease (people under 45 years of age) is more common in women. It is thought to result from an overactive immune system, and these people typically have thymic hyperplasia (enlargement of the thymus). Late-onset disease (people over 45 years of age) is more common in men. The mechanism of autoantibody development is thought to differ from early-onset disease, with loss of immune tolerance, resulting in a loss of the ability of the immune system to recognise molecules of the body as self [5, 10].

Myasthenia gravis can also be classified by clinical phenotype; these are the observable characteristics of a disease, such as the symptoms experienced by the affected people, or the clinical signs observed by the clinician when they examine the patient, or both. Myasthenia gravis presents as either an ocular or generalised disease. In ocular myasthenia gravis, muscle weakness is limited to the eyelids and the extraocular muscles (muscles around the eyes) [5, 10]. In generalised myasthenia gravis, the weakness involves a variety of different muscle groups, including ocular, bulbar, respiratory, and limb muscles. While most people with ocular myasthenia gravis eventually develop generalised myasthenia gravis, some people have a milder disease form that remains restricted to the ocular muscles [5, 10]. Although the disease process is similar between ocular and generalised myasthenia gravis, the two phenotypes (sets of observable characteristics or traits of an organism) can vary in their sensitivity to diagnostic tests and response to treatment.

Diagnosis of myasthenia gravis

The diagnosis of myasthenia gravis involves assessment of the clinical phenotype, serological (blood) testing for autoantibodies, and neurophysiology testing (nerve tests). All people with suspected myasthenia gravis will also require a computed tomography (CT) scan of the chest to look for a thymoma [11]. Clinical assessment will involve obtaining a typical history of fatigable weakness and demonstrating this on examination, such as progressive ptosis while the affected person is looking upwards, or proximal muscle weakness following repetitive exercises. Serological testing includes AChR and MuSK autoantibodies, while neurophysiology can demonstrate a progressive reduction in muscle response following repetitive nerve stimulation and jitter on single fibre electromyography. In people who have negative serology and neurophysiology tests, further investigations may be required to rule out other causes of muscle weakness; for example, magnetic resonance imaging (MRI) of the head to rule out a brain disorder [11].

Management of myasthenia gravis

Initial management of myasthenia gravis depends on the clinical severity of the disease at presentation. Myasthenia gravis crises typically present with severe bulbar or respiratory involvement, or rapidly progressive disease; these are managed as inpatient cases, with intravenous immunoglobulin (IVIg; antibodies taken from the blood of healthy donors) or plasma exchange (removal of the affected person's plasma, which is the part of the blood that contains antibodies, and replacing it with donated plasma), along with respiratory support in the hospital intensive care unit if required [12]. Management of myasthenia gravis in people who are not in crisis can be initiated in the outpatient setting. The initial treatment of choice is typically a medication called pyridostigmine, with the addition of oral prednisolone (a type of steroid treatment) if the person remains symptomatic [11, 13]. Immunosuppression is generally reserved for those who do not achieve remission on prednisolone therapy, or who experience relapse (return of their myasthenia gravis symptoms) on prednisolone withdrawal [11, 13]. Azathioprine is typically used as the first-line immunosuppressive agent, while other options include mycophenolate mofetil, methotrexate, and ciclosporin. In difficult-to-treat cases, a medication called rituximab can be used, which acts to deplete the cells of the immune system that produce antibodies (known as B cells). Response to rituximab is better in

people with MuSK antibody-positive myasthenia gravis compared with those with AChR antibody-positive myasthenia gravis [14], and a randomised controlled trial (RCT) of rituximab as an add-on therapy to prednisolone treatment for myasthenia gravis did not demonstrate a clinically meaningful steroid-sparing effect at 12 months compared with prednisolone plus placebo [15]. If imaging shows evidence of a thymoma, it should be removed as this can result in spontaneous remission of myasthenia gravis (complete resolution of the symptoms of myasthenia gravis). Additionally, in people without a thymoma who are under 65 years and AChR antibody-positive, there is evidence that thymus removal can reduce their myasthenia gravis medication requirements [16].

Although initial treatment with conventional therapy for myasthenia gravis improves symptoms in many people, few people achieve disease remission [17], and many have ongoing symptoms despite maximal therapy [18]. Long-term exposure to non-targeted immunosuppressive medications comes with several systemic (throughout the body) side effects, such as opportunistic infections and an increased risk of malignancy (cancer). Prolonged treatment with steroids also provides a myriad of undesirable side effects, such as weight gain and an increased risk of developing type 2 diabetes mellitus. Furthermore, there is a subset of people with myasthenia gravis (around 15%) who do not achieve remission with current treatment and are classified as treatment refractory [19]. These people have frequent exacerbations of their myasthenia gravis, requiring inpatient management. As a result, there is high morbidity associated with myasthenia gravis, including time lost from work, impact on family dynamics, frequent hospitalisations, and reduced quality of life. There are also implications for the wider community, as myasthenia gravis care involves substantial healthcare utilisation and economic costs [17]. Therefore, strategies are needed to improve the management of myasthenia gravis in people. Strategies such as the early use of fast-acting therapy or early use of rituximab have shown benefit [20, 21], and new therapeutic targets have been developed. These include inhibitors of the neonatal Fc receptor (FcRn) [22], and complement inhibitors [23].

Description of the intervention and how it might work

Complement system

Complement inhibitors are therapeutic molecules directed against components of the complement system, which form part of the body's immune system. The complement system comprises a set of proteins that are activated by three different mechanisms, known as the classical, lectin, and alternative pathways [24]. Activation of these separate pathways results in a cascade of reactions with a common convergence into a single pathway resulting in the production of the enzyme C3 convertase. C3 convertase activity causes another cascade of reactions, including production of a C5 convertase, and ultimately MAC production. The MAC is required for the lysis (killing) of certain bacteria in the body, such as meningococcus which can cause meningitis [24]. Additionally, the MAC has an important role in lysis of the postsynaptic cell membrane in AChR antibody-mediated myasthenia gravis [8]. MAC deposition has been shown in muscle biopsies in people with myasthenia gravis [9]. Although levels of circulating complement proteins C3, C4, and C5a were similar in people with myasthenia gravis compared with healthy controls, C5a levels showed a positive correlation with disease severity, with higher levels in people with more severe myasthenia gravis [25].

Complement inhibitors

If the complement cascade can be interrupted or inhibited, this can prevent MAC formation and the resulting damage to the postsynaptic membrane of the neuromuscular junction in people with AChR antibody-positive myasthenia gravis. This should lead to an improvement in neuromuscular transmission at the neuromuscular junction, and therefore reduce fatigable muscle weakness. This would improve disease severity and quality of life and allow reduced use of other therapies, such as prednisolone or IVIg, that have a high side-effect burden. Improved disease treatment would also reduce relapses, and therefore hospital admissions. Complement inhibitor therapies are not likely to have any utility in people with MuSK antibody-positive myasthenia gravis, as MuSK antibodies do not activate complement; however, they may have benefits in people who are seronegative.

In recent years, several complement inhibitors have been developed for treating myasthenia gravis. They have been proposed for use as 'add-on' therapies for people with myasthenia gravis who have ongoing symptoms despite standard treatment. They may therefore be thought of as comparable to B cell depletion, FcRn inhibition, or regular IVIg or therapeutic plasma exchange (PLEX); all of which are also considered 'add-on' therapies to standard care. Use of these therapies varies between countries due to the high cost. The different complement inhibitors target different aspects of the complement pathway. The most common target to date is C5 convertase [24]. C5 convertase inhibitors include eculizumab, ravulizumab, zilucoplan, and pozelimab.

Eculizumab

Eculizumab is a humanised monoclonal antibody inhibitor that acts against C5 convertase, preventing further propagation of the complement pathway. Eculizumab is administered intravenously (into a vein), with an induction regimen of 900 mg intravenously weekly for four weeks, followed by 1200 mg intravenous maintenance every four weeks [24]. It was licenced initially for treating the haematological disorders paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uraemia syndrome (HUS). More recently, its use has been expanded to treating neuromyelitis optica spectrum disorder with antibodies to aquaporin 4, which is an inflammatory disorder of the central nervous system similar to multiple sclerosis. In 2017, eculizumab was approved in the USA for treating people with AChR antibody-positive generalised myasthenia gravis [26], and in the European Union (EU) for people with AChR antibody-positive refractory generalised myasthenia gravis. In 2023, the EU licence was expanded to include children and adolescents aged 6 to 17 years with AChR antibody-positive refractory generalised myasthenia gravis [27]. Eculizumab is not available for use in the UK, as the company did not provide the required information to the UK National Institute for Health and Care Excellence (NICE).

Ravulizumab

Ravulizumab has a similar mechanism of action to eculizumab, but has a longer half-life, thereby requiring less frequent intravenous infusions [24]. Similar to eculizumab, ravulizumab was first licenced for use in people with PNH and atypical HUS. In 2022, ravulizumab was approved in the USA for treating AChR antibody-positive generalised myasthenia gravis [28], and approved in the EU for AChR antibody-positive refractory generalised myasthenia gravis [29]. It is delivered intravenously at a weight-based dose, with a

single loading dose followed by maintenance doses every eight weeks. The company withdrew from the NICE technology appraisal, and therefore ravulizumab is not currently in use in the UK.

Zilucoplan

Zilucoplan is a small peptide molecule that binds and inhibits the activity of both C5 convertase and one of the C5 cleavage products, C5b [24]. Zilucoplan is administered as a subcutaneous (into the skin) injection, at a dose of 0.3 mg/kg. Zilucoplan was approved in the USA in 2023 for treating people with AChR antibody-positive generalised myasthenia gravis [30].

Pozelimab

Pozelimab is a human monoclonal antibody against C5 convertase and is given with cemdisiran, which is a synthetic small interfering RNA that suppresses C5 production in the liver [24]. Pozelimab is typically given as a one-off intravenous loading dose followed by subcutaneous maintenance, while cemdisiran is given subcutaneously. Although this combination is not yet approved for use in people with myasthenia gravis, a phase 3 RCT is ongoing to assess the efficacy and safety of pozelimumab plus cemdisiran in people with generalised myasthenia gravis [31].

Other complement inhibitor therapies

Additional complement inhibitor therapies, targeting other components of the complement pathway, that are currently being evaluated in clinical trials for myasthenia gravis include vemircopan and gefurulamib. Vemircopan is an orally administered inhibitor of the complement protein Factor D and is being compared with placebo in an ongoing phase 2 trial [32]. Gefurulamib is an anti-C5 convertase antibody that is administered subcutaneously once weekly; it is currently being evaluated in a phase 3 trial compared with placebo [33].

Safety of complement inhibitor therapies

The main safety consideration with complement inhibitor therapies is the risk of infection, particularly meningococcal infection. Data from people with PNH treated with eculizumab demonstrate a 75- to greater than 4000-fold increase in risk compared to normal background risk, despite vaccination [34]. Therefore, vaccination against meningococcus is required at least two weeks prior to starting treatment. If complement inhibitor therapy is to be started earlier than two weeks postvaccination, then prophylactic (preventative) antibiotics are required. Other less serious infections reported with complement inhibitors include upper respiratory tract infections and nasopharyngitis (inflammation of the nasal passages and the throat). Another common side effect seen with subcutaneously-administered therapies, such as zilucoplan, is bruising at the injection site. The main contraindications to complement inhibitor use are active systemic infection (infection that has spread into the bloodstream and throughout the body) [26, 27, 28, 29, 30]. Live vaccines, such as Bacillus Calmette-Guérin (BCG), influenza, and measles, mumps, and rubella (MMR), are also not recommended during treatment due to the risk of generalised infection. People who already have a high immunosuppression burden may be at higher risk of infection.

Additional considerations include pregnancy, breastfeeding, and contraception. The manufacturers currently advise the use of complement inhibitors in pregnancy only if benefit outweighs risk. Eculizumab has been used in pregnancy in those with haematological disorders that can threaten pregnancies, with good outcomes [35]. The manufacturer also advises people to avoid breastfeeding and to use effective contraception during and up to eight months after treatment [26, 27, 28, 29, 30]. It is unknown if response to complement inhibitor treatment would differ between children and adults.

Why it is important to do this review

Complement inhibitors are a rapidly expanding research area in the treatment of myasthenia gravis in people. In the last five years, three complement inhibitors have been approved for myasthenia gravis in the USA [26, 28, 30], and two approved in the EU [27, 29], with three additional agents currently in clinical trials [31, 32, 33]. Despite this, we do not yet have consensus on the long-term efficacy and safety profiles of these agents, or the optimum dosing regimen and duration of treatment [13]. Furthermore, we do not know which groups of people are most likely to benefit from treatment with complement inhibitors. Alongside the recent progress in complement inhibitor therapy, new myasthenia gravis agents have been developed that have other targets, such as FcRn inhibitors. This Cochrane systematic review will support a better understanding of where complement inhibitors fit in the rapidly expanding landscape of myasthenia gravis treatment.

OBJECTIVES

To evaluate the benefits and harms of complement inhibitors for treating myasthenia gravis in adults compared with control treatment (placebo or standard care).

METHODS

Criteria for considering studies for this review

We will follow the Methodological Expectations of Cochrane Intervention Reviews (MECIR) when conducting the review [36], and PRISMA 2020 for the reporting [37].

Types of studies

We will include RCTs, cross-over RCTs, and quasi-RCTs. Quasi-RCTs are trials that allocate participants to a treatment group by a systematic approach that is not truly random; for example, alternate participants in an alphabetical list. We will exclude any studies that are not randomised or quasi-randomised, to reduce the risk of allocation bias. We will exclude cluster-RCTs, as the unit of analysis for this review will be the individual participant. Cross-over design studies will be included provided there is random sequence allocation to the treatment group, and a washout period of at least three months prior to the randomisation timeframe. We chose this washout period as the half-life of eculizumab is 11 to 15 days, and the clinical elimination of a drug from the body is considered to require five half-lives [26, 27].

We will include studies published in full text and those published as abstracts only. We will also include unpublished data, such as data available on clinical trial registries or data obtained directly from researchers. We will include studies that involve adult participants (aged 18 years and older). There will be no language restrictions on the included studies.

Types of participants

We will include participants with myasthenia gravis that fulfil all the following eligibility criteria.

- **Disease severity:** we will include participants with any classification of disease severity, as per the Myasthenia Gravis Foundation of America (MGFA) clinical system [38].
- **Antibody status:** we will include participants with any antibody status. Where possible, we will perform subgroup analyses by antibody status.
- **Time of onset:** we will include participants at any time of disease onset (early versus late). Subgroup analyses will be performed according to time of onset (early versus late) if data are available.
- **Localisation of disease:** we will include participants with any disease phenotype (ocular or generalised). Where possible, we will perform subgroup analyses by disease localisation.
- **Thymoma status:** we will include participants with any thymoma status (thymoma-associated disease versus non-thymomatous disease).
- **Previous treatments:** we will include participants who have received any previous immunomodulatory treatment for myasthenia gravis other than a complement inhibitor.
- **Disease duration:** we will include participants with any disease duration. Subgroup analyses will be performed if data are available.

We will exclude participants that fulfil one or more of the following exclusion criteria.

- **Age under 18 years:** we will exclude participants with juvenile-onset myasthenia gravis. Juvenile myasthenia gravis is very rare and has a different disease trajectory to adult myasthenia gravis, and participants will likely have received different prior management. Therefore, their response to complement inhibitors will likely be different to participants with adult-onset disease.
- **Previous treatment with a complement inhibitor:** we will exclude participants previously treated with a complement inhibitor.

For identified studies that have only a subset of eligible participants, initially we will attempt to obtain individual participant data (IPD). If this is not possible, we will include the study if over half of the participants meet the review eligibility criteria.

Types of interventions

We will include studies that utilise any therapy designed primarily to inhibit component(s) of the complement pathway (e.g. not IVIg, as although this treatment likely has beneficial effects on the complement cascade, it is not the primary target of the treatment), administered according to any dosing regimen by any administration route. We shall group by dose, if appropriate.

Comparisons (considered individually) will include:

- placebo; or
- no treatment; or
- an alternative complement inhibitor; or
- an alternative immunomodulatory therapy (including thymectomy, i.e. surgical removal of the thymus gland).

We will include co-interventions (e.g. prednisolone) if they are allocated to each treatment group equally.

Outcome measures

We have listed the outcomes of interest for this review below. We will still include trials that do not report these outcomes.

Given the variability in study lengths, we will include studies that report follow-up of any duration. Complement inhibitors appear to have a rapid onset of activity, with significant benefit in functional status seen within the first four weeks, and sustained benefit observed weeks to months later [39]. We will divide the trials into subgroups according to follow-up time for analysis; that is, short term (0 to 2 months), medium term (2 to 9 months), and long term (> 9 months). Outcome data at all follow-up intervals will be considered and included for analysis. We will use the last time point available within each timeframe.

As complement inhibitors are intended as an add-on maintenance treatment for myasthenia gravis, rather than a rescue therapy, we will define short term as 0 to 2 months. In preliminary studies, the initial treatment regimen with eculizumab was five weeks, followed by a maintenance dose every two weeks for a further three months. Following the initial five-week treatment with eculizumab, preliminary studies showed that quantitative myasthenia gravis (QMG) scores (a measurement of functional ability in people with myasthenia gravis) rapidly improved in the first four weeks, before achieving a steady state from about 6 to 8 weeks [40]. Therefore, early improvements in functional ability may be detected in the initial two-month period following the start of complement inhibitor treatment.

We will define medium term as 2 to 9 months, as we hope to assess the effect of complement inhibitor therapy on relapse rates and steroid-sparing effect. These outcomes are likely to be most clinically meaningful at 2 to 9 months post-treatment, as prednisolone treatment typically takes 4 to 6 weeks to achieve clinical benefit, and is usually given for a minimum of 2 to 3 months before consideration of weaning [11], with an aim to wean over the subsequent 4 to 6 months.

We will define long term as more than 9 months, as this is the earliest time point at which a patient will typically be established on a stable maintenance immunosuppressive regimen, with an initial three months of steroid treatment followed by approximately six months of immunosuppressive therapy before clinical effect is evident. This time point should therefore reflect the utility of complement inhibitors as a long-term maintenance treatment.

Critical outcomes

The main critical outcome of this review will be as follows.

- **Improvement in functional ability or severity of symptoms with treatment in the short term (0 to 2 months)**. There are several validated ways that functional ability may be measured in different trials, and we will include the following as indicators of the main critical outcome:
  - **Myasthenia Gravis Activities of Daily Living (MG-ADL) score:** this scoring system focusses on limitations of daily

functioning due to myasthenia gravis [41]. We will measure and analyse the MG-ADL data as continuous data by mean change in score from baseline;
    - **QMG score:** the QMG includes a wide range of muscle strength measures, and is the most widely used validated measure in clinical trials in people with myasthenia gravis [42]. We will measure and analyse the QMG data as continuous data by mean change in score from baseline.

Additional critical outcomes will be the following.

- **Reduction in the burden of alternative treatment in the medium term (2 to 9 months).** We will report the following measures independently if data is available:
    - **steroid-sparing effect:** this outcome will be measured and analysed as a risk ratio (RR) of dichotomous data, and whether an average dose of prednisolone ≤ 10 mg/day is achieved, which is considered a clinically meaningful target. Assessment of this outcome may require obtaining IPD, but if this is not possible, we will perform a narrative synthesis;
    - **relapse requiring rescue therapy (including IVIg and PLEX)**: we will compare the rates of requirement for rescue therapy to treat worsening myasthenia gravis, measured and analysed as a rate ratio.
- **Serious adverse events** (SAEs; those that are sentinel events i.e. fatal, life-threatening, or result in prolonged hospitalisation) will also be considered in order to assess the safety of treatment. We will assess SAEs by the proportion of participants experiencing any SAE in the intervention group compared with the control group at any time during the treatment period, analysed as a RR.

Important outcomes

The important outcomes of the review will be as follows.

- **Improvement in functional ability or severity of symptoms with treatment** (as described in Critical outcomes) in the medium term (2 to 9 months) and long term (> 9 months). If reports provide appropriate data, we will also analyse the data dichotomously, to assess whether a clinically significant improvement is seen at the short-, medium-, and long-term time points. This will allow us to evaluate the proportion of responders, as well as the degree of response.
- **A clinically significant improvement in MG-ADL score:** a clinical improvement is indicated by a 2-point improvement in score from baseline to postcomplement inhibitor treatment [43]. This will be analysed dichotomously, to assess whether a clinically significant improvement is seen. We will assess this outcome in the short term (0 to 2 months), medium term (2 to 9 months), and long term (> 9 months).
- **A clinically significant improvement in QMG score:** a clinically significant improvement is shown by a ≥ 2-point reduction in mean score between baseline and postcomplement inhibitor treatment in mild-to-moderate disease (QMG 0 to 16), or a ≥ 3-point reduction in severe myasthenia gravis (QMG > 16) [44]. We will analyse this outcome dichotomously to determine whether there is a clinically significant improvement. We will assess this outcome in the short term (0 to 2 months), medium term (2 to 9 months), and long term (> 9 months).
- **Myasthenia Gravis Composite (MGC) score:** this score combines clinical examination with participant-reported measures [45]. We will measure and analyse this outcome as continuous data by mean change in score from baseline. We will assess this outcome in the short term (0 to 2 months), medium term (2 to 9 months), and long term (> 9 months).
- **A clinically significant improvement in MGC score:** a clinically significant improvement is defined as a ≥ 3-point reduction in mean change in the MGC score, compared between baseline and postcomplement inhibitor treatment [46]. This will be analysed dichotomously, to assess whether a clinically significant improvement is seen. We will assess this outcome in the short term (0 to 2 months), medium term (2 to 9 months), and long term (> 9 months).
- **Reduction in burden of alternative treatment:** (as described in Critical outcomes) in the short term (0 to 2 months) and long term (over 9 months).
- **Quality of life:** assessed by the Myasthenia Gravis Quality of Life 15 (MG-QoL-15) score [47]. We will measure this as a change in score from baseline to the end of the follow-up period. We will exclude other measures of quality of life from the review.
- **Hospital admissions:** assessed as a comparison of the rate of hospitalisation pre- and post-treatment with the complement inhibitor, compared with the control group and analysed as a RR.
- **Adverse effects**: comparison of the proportion of participants experiencing any adverse effects in the complement inhibitor-treated group versus the control group at any time after the introduction of treatment. We will collect data regarding the type of adverse effect, timing in relation to complement inhibitor treatment, and potential causality if available. We will analyse adverse effects as RRs at any time after the introduction of treatment, and categorise as follows:
    - any adverse effect;
    - treatment (complement inhibitor or placebo)-related adverse effects; and
    - adverse effects that lead to discontinuation of treatment.
- **Antibody titre:** assessed by the change in titre from baseline to the end of the follow-up period.

We will only use the outcome methods specified above in the review.

Search methods for identification of studies

Electronic searches

The Information Specialist (KS) will search the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Library;
- MEDLINE (1946 to present);
- Embase (1974 to present).

All databases will be searched from their inception to the present day. There will be no language restrictions. We have included a draft search strategy in Supplementary material 1.

The Information Specialist (KS) will design and quality check the search strategy, help to translate it to other databases, and perform the searches. If the search yield is very high, we will consider the use of the Cochrane-validated RCT search filters to achieve a more precise search.

We will also search the following clinical trials databases for studies currently in progress:

- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (https://who.int/clinical-trials-registry-platform).

Searching other resources

We will review the reference lists of all included primary studies for additional studies not identified in the above searches. Where required, we will contact trial authors for information on any ongoing or unpublished trial data.

We will search for any postpublication amendments published on included or eligible studies. Postpublication amendments include expressions of concern, errata, corrigenda, and retractions.

Data collection and analysis

We will summarise data using the standard methodologies outlined in Chapter 5 of the *Cochrane Handbook for Systematic Reviews of Interventions* [48].

Selection of studies

Two review authors (from LMW, RYSK, or KCD) will use Covidence to screen and assess the title and abstracts of all identified studies independently for inclusion [49]. Each review author will code each study as either 'retrieve' (appears suitable for inclusion or not clear) or 'do not retrieve' (clearly unsuitable for inclusion), and provide a reason for inclusion or exclusion. The two review authors will compare the list of codes for the identified studies, and will resolve any disagreements through discussion or involving a third review author (JBL, JSu, or JSp). For the included studies, we will retrieve the full-text publications and two review authors will assess each independently. The two review authors will code the studies as either 'include' or 'do not include', providing a rationale for inclusion or exclusion. They will resolve any disagreements by discussion or by involving a third review author (JBL, JSu, or JSp).

If it is unclear from the full-text manuscript whether a study is eligible for inclusion, we will contact the study authors for any missing information required for the review author team to determine study eligibility.

Duplicate publications will be identified and removed. We will collate multiple publications pertaining to the same study, so that we can express the results by study rather than by publication.

We will record the selection process in detail to facilitate completion of a PRISMA diagram [37], and a Characteristics of excluded studies table.

Data extraction and management

We will record study characteristics and outcome data using Covidence [49]. One review author (LMW) will extract the following data from one of the included studies as a pilot test for the Covidence data extraction tool:

- study design and setting;
- baseline characteristics of the participants (e.g. age, sex, ethnicity, disease severity, comorbidities);
- inclusion and exclusion criteria;
- details of the intervention;
- details of the control;
- outcomes assessed;
- details of any funding contributions;
- conflicts of interest (if any).

A second review author (KCD or RYSK) will check and verify the included data. Once satisfied with the data extraction process, the two review authors will independently extract the outcome data from the remaining studies. If any outcome data is not reported in a way that we can use (as defined by the critical and important outcomes), we will describe the data narratively in the Characteristics of included studies table. Any disagreements will be resolved by discussion or by involving a third review author (JBL, JSu, or JSp). One review author (LMW) will transfer the data to Review Manager (RevMan) [50], and a second review author (KCD or RYSK) will check and verify data entries.

For any non-English language publications, either:

- a translator will directly extract the data from the text; or
- a study author (LMW) will extract the data from the translated version.

A second review author (KCD or RYSK) will check and verify the numerical data collected.

Risk of bias assessment in included studies

Two review authors (from LMW, RYSK, or KCD) will independently assess the risk of bias of the included studies, using the criteria as described in Chapter 8 of the *Cochrane Handbook for the Systematic Review of Interventions* [51]. They will resolve any disagreements through discussion or involving a third review author (JBL, JSu, or JSp).

We will assess the risk of bias across the following categories, as per the Cochrane risk of bias tool RoB 2 [52]:

- bias arising from the randomisation process;
- bias due to deviation from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

We will use the RoB 2 Excel tool to implement RoB 2. Each potential source of bias will be assessed as either 'high', 'low', or 'unclear'. A justification for the grading (including any quotes from the study reports if indicated) will be provided in the risk of bias tables. We will provide a grading for each of the above five domains for each included study. If it is unclear from the full-text manuscript what the grade should be for a potential domain, we will contact the study authors for any missing information that we require to determine the bias grading. If the study authors are unable to provide sufficient information, we will grade the potential source of bias as unclear.

For each study, we will attempt to find the study protocol, to help gauge the risk of selective outcome reporting. We will use the Outcome Reporting Bias in Trials (ORBIT) as a framework for this assessment [53].

We will document in the risk of bias table any bias that may arise from unpublished data, or from information we receive from the trial authors.

For each of the critical outcomes listed below (and detailed in Critical outcomes), we will consider the risk of bias for all studies that contribute data to that outcome. The risk of bias will be considered within and across studies for each outcome and documented in the risk of bias table.

- Change in MG-ADL score in the short term (0 to 2 months).
- Change in QMG score in the short term (0 to 2 months).
- Steroid-sparing effect (whether an average dose of prednisolone ≤ 10 mg/day was achieved) in the medium term (2 to 9 months).
- Relapse that requires rescue therapy (including IVIg and PLEX) rate in the medium term (2 to 9 months).
- SAEs, as assessed by the proportion of participants experiencing any SAE in the intervention group compared with the control group at any time during the treatment period.

We will use the intention-to-treat (ITT) population for all the outcomes assessed in RoB 2, as we wish to assess the effect of assignment to the interventions at baseline, regardless of whether the interventions are received as intended.

We will follow the guidance outlined in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* to assess the risk of bias in cross-over trials [54]. We will use the variant available in RoB 2 that allows for two intervention periods. As already described in the protocol, we will only include cross-over trials that have a washout period of at least three months to minimise the effect of carry-over. If unequal numbers of participants are randomised to the different intervention sequences, we will include period effects in the RoB 2 analysis to avoid randomisation bias.

We will establish an overall risk of bias judgement using the guidance as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* [51]. In brief, if we judge all domains to have a low risk of bias, the overall risk of bias will be low. If there are one or more bias domains that raise concerns, but none are felt to have a high risk of bias, we will label the overall risk of bias as 'some concerns'. If one or more of the bias assessment domains are felt to have a high risk of bias, or if there are some concerns about multiple domains that substantially lower confidence in the result, we will judge the overall risk of bias as high.

We will perform the systematic review in accordance with this protocol. Where any differences arise, we will document these in the 'Differences between protocol and review' section of the published systematic review.

We will exclude any review authors involved in an included RCT from the risk of bias assessments for that study.

Measures of treatment effect

We will use the ITT population for the primary analysis. For dichotomous outcomes (outcomes with one of two potential values, e.g. hospitalisation, disease relapse, or death), our preferred measure of treatment effect will be the Mantel-Haenszel RR with 95% confidence intervals (CIs). For continuous variables (e.g. changes in MG-ADL, QMG, MGC, or QoL scores), we will analyse the data as a mean difference along with 95% CIs.

Although different studies may use different scores to measure the treatment effect for the main critical outcome (i.e. MG-ADL, or QMG), we do not anticipate combining results for outcomes that use different measurement scales. Where possible, we will report pooled data for each individual scale provided the heterogeneity between studies is low and, thus, would produce a clinically meaningful output.

Unit of analysis issues

The unit of analysis for the review will be the individual randomised participant.

For trials with multiple intervention arms, we will analyse each arm as a separate comparison with the control treatment. We will not attempt to pool the treatment arms or split the control group. If two different drug interventions from the same trial are combined in the same meta-analysis, we will use the methods detailed in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* to avoid double counting of the participants in the control arm [54].

We will analyse any trials that compare different complement inhibitors to each other with no control arm as a separate comparison.

For trials that use different doses of the same intervention, we will pool the dose intervention arms using the methods described in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* [54].

If there is a washout period within the study, the time from treatment will restart once the treatment is recommenced. For cross-over trials, we will use data if there is a washout period of at least three months. Analysis of continuous data from a two-intervention cross-over trial will be with a paired t-test, to evaluate the value of 'measurement on experimental intervention (E)' minus 'measurement on control intervention (C)' separately for each participant, with the effect estimate included using a generic inverse-variance approach.

Dealing with missing data

If we identify studies with unpublished data, we will contact the principal study authors to obtain the relevant data. Where possible, we will contact study authors to confirm missing data in a study article. Such missing data may include study design, participant characteristics, or outcome measures. If it is not possible to obtain this information, we will perform sensitivity analyses to assess the effect of the missing data on the validity of the overall results.

Reporting bias assessment

If 10 or more studies are included for an outcome measure, we will create a funnel plot to screen for potential reporting bias. We will inspect the funnel plots visually to assess the risk of bias. If there is any observed asymmetry in the funnel plot, we will formally assess the asymmetry using Egger's test [55, 56]. If there are fewer than 10 studies for an outcome measure, it will not be possible to assess reporting bias.

Synthesis methods

We will use the random-effects model available in RevMan [50], as this is considered to be a more conservative estimate. We will perform sensitivity analysis to determine whether a fixed-effect

model makes a difference to the conclusions drawn (see Sensitivity analysis).

If the analysis includes studies of substantially different population sizes, we will perform a sensitivity analysis to assess the effect of sample size on the results.

Comparisons of interest include:

- placebo; or
- no treatment; or
- an alternative complement inhibitor; or
- an alternative immunomodulatory therapy.

If a study reports more than one comparison and we are unable to combine the data, we will report each comparison separately. Additionally, if different studies use different comparators (e.g. placebo treatment, no treatment, or current standard-of-care therapy), we will collate each different comparator and report these separately.

If meta-analysis of effect estimates is not possible, then we will summarise effect estimates using the Synthesis Without Meta-analysis (SWiM) reporting guidance [57].

Investigation of heterogeneity and subgroup analysis

We will measure heterogeneity between the different trials using the I^2 and Chi^2 statistics [58]. We will use the interpretation guide for the I^2 statistic, as detailed in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions*, as a rough indicator of heterogeneity [59]. That is:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: may represent considerable heterogeneity.

However, the values above are not absolute cutoffs. We will consider each I^2 statistic result individually in relation to the size and direction of effects and strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or CI for I^2 statistic).

If we identify substantial or considerable heterogeneity, we will report this and explore the potential causes for this by subgroup analysis (as prespecified in the Investigation of heterogeneity and subgroup analysis section). We will consider the I^2 and Chi^2 statistic results alongside the size and direction of the observed effect.

We will assess methodological heterogeneity by comparing the study designs. We will assess clinical heterogeneity by reviewing participant characteristics between studies.

Where possible, we plan to perform the following subgroup analyses, using the same outcomes as prespecified for the primary analysis.

- **Disease subtypes** (as pathophysiology may vary):
  - early- (age < 45 years) versus late-onset myasthenia gravis (age > 45 years), as defined previously [60];
  - ocular versus generalised myasthenia gravis;
  - AChR antibody-positive versus LRP4 antibody-positive versus seronegative MG.
- **Disease duration** (as earlier treatment may be more effective): we will compare participants according to disease onset within the last two years versus more than two years ago.
- **Complement inhibitor** (as differing therapies may have different efficacies): we will compare participants according to the complement inhibitor received, e.g. eculizumab, ravulizumab, zilucoplan, or pozelimab.
- **Previous treatment**:
  - treatment-naive versus refractory myasthenia gravis;
  - thymectomy versus no thymectomy (non-thymoma-associated myasthenia gravis only);
  - steroid alone versus steroids and other immunosuppressive agent versus steroid-sparing immunosuppression alone.

We will perform subgroup comparisons using the formal test for subgroup differences in RevMan [50].

Equity-related assessment

We do not plan to investigate health inequities in this review, as this does not seem feasible within this topic.

Sensitivity analysis

We will perform sensitivity analyses to assess whether studies with a high overall risk of bias (high risk in one or more domains) and studies with missing data should be excluded from the overall analysis. We will report the sensitivity analyses in a summary table.

To assess the effect of study size on the outcomes, we will compare our random-effects model with a fixed-effect model, which we will weight according to the population size of each trial. We will also compare the use of the RR to the odds ratio.

Certainty of the evidence assessment

We will present all critical outcomes in a summary of findings table using the GRADEpro Guideline Development Tool (GDT) tool [61]. The overall risk of bias assessment (as detailed in Risk of bias assessment in included studies) will be used to assess the certainty of the evidence.

For our summary of findings table, we will focus on the comparison of 'any complement inhibitor versus placebo' for the outcomes as specified in the Critical outcomes section:

- change in MG-ADL score in the short term (0 to 2 months);
- change in QMG score in the short term (0 to 2 months);
- steroid-sparing effect (whether an average dose of prednisolone ≤ 10 mg/day is achieved) in the medium term (2 to 9 months);
- relapse that required rescue therapy (including IVIg and PLEX) in the medium term (2 to 9 months);
- SAEs, as assessed by the proportion of participants experiencing any SAE in the intervention group compared with the control group at any time during the treatment period.

If the study reports multiple time points within a time frame, we will report the latest time point that falls within each time frame and use this in the analysis.

Two review authors (from LMW, KCD, or RYSK) will independently assess the certainty of the evidence, and resolve any disagreements by discussion or consensus with a third author (JBL, JSu, or JSp) if needed. We will assess the certainty of the evidence for the critical

and important outcomes using the five GRADE criteria (risk of bias, inconsistency, imprecision, indirectness, and publication bias) and the recommendations in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* [62], and the GRADE Handbook [63]. We will classify the certainty of the evidence as either 'high', 'moderate', 'low', or 'very low', according to performance in relation to the five GRADE criteria listed above. We will document the rationale for each grading clearly in the summary of findings table.

We will exclude any member of the review author team involved in an included RCT from the certainty of the evidence assessments.

Consumer involvement

One review author (A-MF) is an experienced patient-author who will be involved from the conceptualisation of the review throughout the full review process. We sought their opinion at each stage of protocol development. In particular, they helped to identify which outcomes and time points are of the greatest importance to patients.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016098.

Supplementary material 1 Search strategies

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Colin Chalk, McGill University, Department of Neurology & Neurosurgery
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Justin Mann, Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Jessenia Hernandez, Central Editorial Service
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Contributions of authors

KCD conceived the idea for the review, and contributed to the design and co-ordination of the protocol.

LMW wrote the protocol, and contributed to the design and co-ordination of the protocol.

KS provided methodological input.

All authors (LMW, FJC, A-MF, RYSK, JBL, JSp, KS, JSu, KCD) reviewed the protocol, contributed to manuscript revisions, and approved the final version.

Declarations of interest

LMW: I do not have any interests to disclose at this time.

FJC: I do not have any interests to disclose at this time.

A-MF: I do not have any interests to disclose at this time.

RYSK: received a travel and accommodation grant from CSL Behring for the Peripheral Nerve Society meeting, Baltimore, July 2018.

JBL: declares personal payments from Biogen (webinar host November 2021, booked but not attended), Sanofi (Travel and speakers fees for STEPS forwards meeting 2022; consultancy in collaboration with VOLV 2021; and speaker fees February 2020), Hoffman-La Roche (Participation in SMA HCRU Delphi Panel 2024; advisory meeting 2023, advisory board 2022), and Roche (advisory board 2020; writing support for a business case), neuromuscular study group (executive committee member (no fiduciary interest)), Myositis UK (attendance at global conference on myositis), British Myology Society (Vice chair (no fiduciary interest)), British Medical Association (production and update of an article for BMJ Best Practice).

JSp: declares speaker's fees and advisory board membership for Argenx, UCB, Johnson and Johnson, and Immunovant, as well as travel support from UCB, Johnson and Johnson, and Argenx. She is a PI for the ALXN1720 study.

KS: I do not have any interests to disclose at this time.

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Registration and protocol

Cochrane approved the proposal for this review in December 2023.

Data, code and other materials

Data sharing is not applicable to this article as it is a protocol, so no datasets were generated or analysed.

REFERENCES

1. Dresser L, Wlodarski R, Rezania K, Soliven B. Myasthenia gravis: epidemiology, pathophysiology and clinical manifestations. *Journal of Clinical Medicine* 2021;**10**(11):2235.

2. Sciancalepore F, Lombardi N, Valdiserra G, Bonaso M, Cappello E, Hyeraci G, et al. Prevalence, incidence, and mortality of myasthenia gravis and myasthenic syndromes: a systematic review. *Neuroepidemiology* 2024;**9**:1-24.

3. Binks S, Vincent A, Palace J. Myasthenia gravis: a clinical-immunological update. *Journal of Neurology* 2016;**263**(4):826-34.

4. Vincent A. Unravelling the pathogenesis of myasthenia gravis. *Nature Reviews Immunology* 2002;**2**(10):797-804.

5. Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. *Lancet Neurology* 2015;**14**(10):1023-36.

6. Mygland A, Vincent A, Newsom-Davis J, Kaminski H, Zorzato F, Agius M, et al. Autoantibodies in thymoma-associated myasthenia gravis with myositis or neuromyotonia. *Archives of Neurology* 2020;**57**:527-31.

7. Okumura M, Fujii Y, Shiono H, Inoue M, Minami M, Utsumi T, et al. Immunological function of thymoma and pathogenesis of paraneoplastic myasthenia gravis. *General Thoracic and Cardiovascular Surgery* 2008;**56**:143-50.

8. Morgan BP, Chamberlain-Banoub J, Neal JW, Song W, Mizuno M, Harris CL. The membrane attack pathway of complement drives pathology in passively induced experimental autoimmune myasthenia gravis in mice. *Clinical and Experimental Immunology* 2006;**146**(2):294-302.

9. Hoffmann S, Harms L, Schuelke M, Rückert J-C, Goebel H-H, Stenzel W, et al. Complement deposition at the neuromuscular junction in seronegative myasthenia gravis. *Acta Neuropathologica* 2020;**139**(6):1119-22.

10. Berrih-Aknin S, Frenkian-Cuvelier M, Eymard B. Diagnostic and clinical classification of autoimmune myasthenia gravis. *Journal of Autoimmunity* 2014;**48**:143-8.

11. Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. Myasthenia gravis: Association of British Neurologists' management guidelines. *Practical Neurology* 2015;**15**:199-206.

12. Claytor B, Cho SM, Li Y. Myasthenic crisis. *Muscle & Nerve* 2023;**68**(1):8-19.

13. Narayanaswami P, Sanders DB, Wolfe G, Benatar M, Cea G, Evoli A, et al. International consensus guidance for management of myasthenia gravis: 2020 update. *Neurology* 2021;**96**(3):114-22.

14. Tandan R, Hehir MK 2nd, Waheed W, Howard DB. Rituximab treatment of myasthenia gravis: a systematic review. *Muscle & Nerve* 2017;**56**(2):185-96.

15. Nowak RJ, Coffey CS, Goldstein JM, Dimachkie MM, Benatar M, Kissel JT, et al. Phase 2 trial of rituximab in acetylcholine receptor antibody-positive generalized myasthenia gravis: the BeatMG study. *Neurology* 2022;**98**(4):e376-89.

16. Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, et al; MGTX Study Group. Randomized trial of thymectomy in myasthenia gravis. *New England Journal of Medicine* 2016;**375**(6):511-22.

17. Saccà F, Salort-Campana E, Jacob S, Cortés-Vicente E, Schneider-Gold C. Refocusing generalized myasthenia gravis: patient burden, disease profiles, and the role of evolving therapy. *European Journal of Neurology* 2023;**20**:e16180.

18. Engel-Nitz NM, Boscoe A, Wolbeck R, Johnson J, Silvestri NJ. Burden of illness in patients with treatment refractory myasthenia gravis. *Muscle & Nerve* 2018;**58**(1):99-105.

19. Suh J, Goldstein JM, Nowak RJ. Clinical characteristics of refractory myasthenia gravis patients. *Yale Journal of Biology Medicine* 2013;**86**(2):255-60.

20. Uzawa A, Suzuki S, Kuwabara S, Akamine H, Onishi Y, Yasuda M, et al. Effectiveness of early cycles of fast-acting treatment in generalised myasthenia gravis. *Journal of Neurology, Neurosurgery and Psychiatry* 2023;**94**(6):467-73.

21. Piehl F, Eriksson-Dufva A, Budzianowska A, Feresiadou A, Hansson W, Hietala MA, et al. Efficacy and safety of rituximab for new-onset generalized myasthenia gravis: the RINOMAX randomized clinical trial. *JAMA Neurology* 2022;**79**(11):1105-12.

22. Bhandari V, Bril V. FcRN receptor antagonists in the management of myasthenia gravis. *Frontiers in Neurology* 2023;**14**:1229112.

23. Howard JF Jr. Myasthenia gravis: the role of complement at the neuromuscular junction. *Annals of the New York Academy of Sciences* 2018;**1412**(1):113-28.

24. Nair SS, Jacob S. Novel immunotherapies for myasthenia gravis. *Immunotargets and Therapy* 2023;**12**:25-45.

25. Aguirre F, Manin A, Fernandez VC, Justo ME, Leoni J, Paz ML, et al. C3, C5a and anti-acetylcholine receptor antibody as severity biomarkers in myasthenia gravis. *Therapeutic Advances in Neurological Disorders* 2020;**13**:1756286420935697.

26. US Food and Drug Administration (FDA). Soliris® (eculizumab) concentrated solution for intravenous infusion. Available at www.accessdata.fda.gov/drugsatfda_docs/label/2011/125166s172lbl.pdf (accessed 14 May 2025).

27. European Medicines Agency. Soliris® summary of product characteristics. Available at ema.europa.eu/en/documents/product-information/soliris-epar-product-information_en.pdf (accessed 14 May 2025).

28. US Food and Drug Administration (FDA). Ultomiris® (ravulizumab-cwvz) concentrated solution for intraveouns infusion. Available at www.accessdata.fda.gov/drugsatfda_docs/label/2022/761108s023lbl.pdf (accessed 14 May 2025).

29. European Medicines Agency. Ultomiris® summary of product characteristics. Available at ema.europa.eu/en/documents/product-information/ultomiris-epar-product-information_en.pdf (accessed 14 May 2025).

30. US Food and Drug Administration (FDA). Zilbrysq (zilucoplan) injection, for subcutaneous use. Available at www.accessdata.fda.gov/drugsatfda_docs/label/2023/216834s000lbl.pdf (accessed 14 May 2025).

31. NCT05070858. A study to test how safe pozelimab and cemdisiran combination therapy and cemdisiran alone are and how well they work in adult patients with generalized myasthenia gravis (NIMBLE) [Efficacy and safety of pozelimab and cemdisiran combination therapy and cemdisiran monotherapy in patients with symptomatic generalized myasthenia gravis]. clinicaltrials.gov/study/NCT05070858 (first posted 27 September 2021).

32. NCT05218096. Study of ALXN2050 in adult participants with generalized myasthenia gravis [A Phase 2, randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of ALXN2050 in adult participants with generalized myasthenia gravis]. clinicaltrials.gov/study/NCT05218096 (first posted 28 January 2022).

33. NCT05556096. Safety and efficacy of ALXN1720 in adults with generalized myasthenia gravis [A Phase 3, randomized, double-blind, placebo-controlled, parallel, multicenter study to evaluate the safety and efficacy of ALXN1720 in adults with generalized myasthenia gravis]. clinicaltrials.gov/study/NCT05556096 (first posted 23 September 2022).

34. Barnum SR. Therapeutic inhibition of complement: well worth the risk. *Trends in Pharmacological Sciences* 2017;**38**(6):503-5.

35. Stefanovic V. The extended use of eculizumab in pregnancy and complement activation - associated diseases affecting maternal, fetal and neonatal kidneys - the future is now? *Journal of Clinical Medicine* 2019;**8**(3):407.

36. Higgins JP, Lasserson T, Thomas J, Flemyng E, Churchill R. Methodological Expectations of Cochrane Intervention Reviews (MECIR). Version August 2023. Cochrane, London. community.cochrane.org/mecir-manual.

37. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71. [DOI: 10.1136/bmj.n71]

38. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Neurology* 2000;**55**(1):16-23.

39. Howard JF Jr, Utsugisawa K, Benatar M, Murai H, Barohn RJ, Illa I, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. *Lancet Neurology* 2017;**16**:976-86.

40. Howard JF Jr, Barohn RJ, Cutter GR, Freimer M, Juel VC, Mozaffar T, et al. A randomized, double-blind, placebo-controlled phase II study of eculizumab in patients with refractory generalized myasthenia gravis. *Muscle & Nerve* 2013;**48**:76-84.

41. Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. *Neurology* 1999;**52**(7):1487-9.

42. Barohn RJ, McIntire D, Herbelin L, Wolfe GI, Nations S, Bryan WW. Reliability testing of the quantitative myasthenia gravis score. *Annals of the New York Academy of Sciences* 1998;**841**:769-72.

43. Muppidi S, Wolfe GI, Conaway M, Burns TM; MG composite and MG-QOL15 study group. MG ADL: still a relevant outcome measure. *Muscle & Nerve* 2011;**44**(5):727-31.

44. Katzberg HD, Barnett C, Merkies IS, Bril V. Minimal clinically important difference in myasthenia gravis: outcomes from a randomized trial. *Muscle & Nerve* 2014;**49**(5):661-5.

45. Burns TM, Conaway MR, Cutter GR, Sanders DB; Muscle Study Group. Construction of an efficient evaluative instrument for myasthenia gravis: the MG composite. *Muscle and Nerve* 2008;**38**(6):1553-62.

46. Burns TM, Conaway MR, Sanders DB; on behalf of the MG Composite and MG-QOL15 Study Group. The MG Composite: a valid and reliable tool for myasthenia gravis. *Neurology* 2010;**74**(18):1434-40.

47. Burns TM, Sadjadi R, Utsugisawa K, Gwathmey KG, Joshi A, Jones S, et al. International clinimetric evaluation of the MG-QOL15, resulting in slight revision and subsequent validation of the MG-QOL15r. *Muscle and Nerve* 2016;**54**(6):1015-22.

48. Li T, Higgins JP, Deeks JJ. Chapter 5: Collecting data (last updated October 2019). In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.5. Cochrane, 2024. Available from training.cochrane.org/handbook.

49. Covidence. Version accessed 8 January 2024. Melbourne, Australia: Veritas Health Innovation, 2024. Available at covidence.org.

50. Review Manager (RevMan). Version 9.2.1. The Cochrane Collaboration, 2025. Available at https://revman.cochrane.org.

51. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial (last updated October 2019). In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.5. Cochrane, 2024. Available from training.cochrane.org/handbook.

52. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.

53. Outcome Reporting Bias in Trials (ORBIT). Welcome to the ORBIT website. Available at outcome-reporting-bias.org.

54. Higgins JP, Eldridge S, Li T. Chapter 23: Including variants on randomized trials (last updated October 2019). In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.5. Cochrane, 2024. Available from training.cochrane.org/handbook.

55. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34.

56. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**:d4002.

57. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ* 2020;**368**:l6890.

58. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

59. Deeks JJ, Higgins JP, Altman DG, McKenzie JE, Veroniki AA. Chapter 10: Analysing data and undertaking meta-analyses (last updated November 2024). In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.5. Cochrane, 2024. Available from training.cochrane.org/handbook.

60. Akaishi T, Suzuki Y, Imai T, Tsuda E, Minami N, Nagane Y, et al. Response to treatment of myasthenia gravis according to clinical subtype. *BMC Neurology* 2016;**16**(1):225. [PMID: 27855632]

61. GRADEpro GDT. Version accessed 8 January 2024. Hamilton (ON): McMaster University (developed by Evidence Prime), 2024. Available at gradepro.org.

62. Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, Guyatt GH. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence (last updated May 2025). In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.5. Cochrane, 2024. Available from training.cochrane.org/handbook.

63. Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from https://gdt.gradepro.org/app/handbook/handbook.html.