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Rituximab for the Treatment of Myasthenia Gravis: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

ab	antibody
AChR	acetylcholine receptor
AChR MG	Acetylcholine receptor antibody positive myasthenia gravis
CI	confidence interval
DRG-MG	Diagnosis Related Group score of hospital admissions related to myasthenia gravis
FVC	forced vital capacity
IVIg	Intravenous immunoglobulin
MG	myasthenia gravis
MG-ADL	MG related activities of daily living
MGCS	MG composite scale
MGFA	Myasthenia Gravis Foundation of America
MGFA-PIS	Myasthenia Gravis Foundation of America post-intervention status
MGSTI	Myasthenia Gravis Status and Treatment Intensity
MM	minimal manifestation
MMS	myasthenic muscle score
MMT	manual muscle testing
MuSK	muscle specific tyrosine kinase
MuSK MG	Muscle specific tyrosine kinase antibody positive myasthenia gravis
PEX	plasmapheresis or plasma exchange
PIS	post-intervention status
PIS-m	post-intervention status modified
QMG	Quantitative myasthenia gravis
QoL	Quality of life

Context and Policy Issues

Myasthenia gravis (MG) is an antibody mediated chronic autoimmune disorder affecting the neuromuscular junction.[1-3] MG is characterized by muscle weakness that is aggravated after activity and is improved after rest; however, after onset, MG symptoms progress over time.[4] In MG, muscles that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often affected, and muscles that control breathing, neck and limb movements may also be affected[1,2]. Antibodies to acetylcholine receptor (AchR) are detected in the majority (up to 90%) of patients with MG, whereas antibodies to muscle-specific tyrosine kinase (MuSK) and antibodies to low-density lipoprotein receptor-related protein 4 are detected in a minority of MG patients.[5] MuSK antibody positive MG occurs in approximately 7% of MG patients.[6]

An epidemiological study conducted in Ontario, Canada, demonstrated that the crude prevalence of MG increased over time, from 16.6 cases per 100,000 in 1996 to 32.0 cases per 100,000 in 2013. However, the crude incidence remained almost unchanged at 2.7 per 100,000 in 1996, and 2.8 per 100,000 in 2013.[3] These findings may be reflective of patients living longer.[3] MG is associated with direct healthcare costs resulting from long-term treatment requirements and periodic hospitalization, as well as indirect costs such as income loss and reduced caregiver productivity[3]. According to a US study, the estimated annual cost associated with MG is $15,675 per patient.[3]

About 80% to 85% of MG patients respond well to available immunosuppressive treatment options which include steroids, azathioprine, mycophenolate mofetil, cyclosporine, intravenous immunoglobulin (IVIG), plasma exchange (PEX), or tacrolimus.[7] The remaining 15% to 20% of MG patients are refractory to treatment, as indicated by sub-optimal responses with multiple immunosuppressive therapies, intermittent requirement for IVIG infusions or PEX, or inability to reduce steroid dose without relapse.[7] Refractory MG decreases quality of life, may require hospitalization for potentially lethal exacerbations, and is associated with a considerable financial burden.[8] Hence, other treatment options are sought for these refractory patients. A previous CADTH report[9] which included a single health technology assessment report, reported that, based on small case series studies, rituximab appeared to be a feasible option for treating patients with MuSK MG who are refractory to standard treatment. Rituximab is a chimeric mouse/human monoclonal antibody that binds to CD20 B lymphocytes.[6]

In Canada, rituximab is approved for treatment of non-Hodgkin lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, and granulomatosis with polyangiitis.[10]. The evidence pertaining to rituximab therapy for patients with MG would be useful for healthcare decision makers to decide on the optimal treatment pathway.

The purpose of this report is to review the clinical effectiveness and cost-effectiveness of rituximab therapy for the treatment of MG. Additionally, this report aims to review the evidence-based guidelines regarding the use of rituximab for the treatment of MG. This report updates a previous CADTH report[9] and in addition has a broader scope.

Research Questions

1. What is the clinical effectiveness of rituximab induction therapy for the treatment of myasthenia gravis for those who are refractory to standard therapy?
2. What is the clinical effectiveness of rituximab re-treatment for the treatment of myasthenia gravis?
3. What is the clinical effectiveness of rituximab maintenance therapy for the treatment of myasthenia gravis?
4. What is the cost-effectiveness of rituximab therapy versus other therapies for the treatment of myasthenia gravis?
5. What are the evidence-based guidelines regarding rituximab for the treatment of myasthenia gravis?

Key Findings

Evidence from two systematic reviews of non-randomized studies, and 11 non-randomized studies suggests that rituximab treatment offers some clinical benefit to adult patients with refractory myasthenia gravis (MG). The MuSK MG subgroup appeared to experience greater clinical benefit compared to the AChR MG subgroup. Quality of life was reported in a few studies and there was suggestion of improvement with rituximab treatment. Rituximab treatment resulted in reduction in prednisone use. Antibody levels were reduced after rituximab treatment. Generally, side effects with rituximab were few and were not serious. Findings need to be interpreted in the light of limitations — particularly the low quality of the studies, and small sample sizes.

No relevant studies were identified that exclusively examined rituximab retreatment for the treatment of MG.

No relevant studies were identified that exclusively examined rituximab maintenance therapy for the treatment of MG.

No relevant study on the cost-effectiveness of rituximab therapy versus other therapies for the treatment of MG was identified.

One evidence-based guideline regarding management of MG mentioned rituximab therapy as a treatment option; however, authors of the guideline cautioned readers as to the uncertainty of the evidence which prevented a formal consensus on the recommendations presented.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases and a focused Internet search. No methodological filters were applied to limit retrieval by publication type. The search was limited to English language documents published between January 1, 1998 and July 11, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with myasthenia gravis (regardless of clinical or autoantibody subtype) who are/were refractory to standard therapy or who are unable to tolerate standard therapy.
Intervention	Q1. Rituximab induction therapy (i.e., an initial course of rituximab) Q2. Rituximab retreatment in case of flares Q3. Rituximab, given as regularly scheduled treatment (i.e., maintenance therapy) irrespective of initial response); this would generally only be given to those who have had an initial response or remission Q4. Rituximab as induction therapy, retreatment, or maintenance therapy Q4. Rituximab, any regimen
Comparator	Q1. Standard therapy (e.g. plasma exchange, corticosteroids, IVIg, cholinesterase inhibitors, steroid sparing agents such as azathioprine, thymectomy, methotrexate, cyclophosphamide, cyclosporine, tacrolimus, mycophenolate) OR no comparator Q2. Standard therapy (e.g. plasma exchange, corticosteroids, IVIg, cholinesterase inhibitors, steroid sparing agents such as azathioprine, thymectomy, methotrexate, cyclophosphamide, cyclosporine, tacrolimus, mycophenolate) OR no comparator Q3. Retreatment with rituximab upon disease flare/relapse OR standard therapy upon disease flare/relapse OR no comparator Q4. Any comparator for the treatment of myasthenia gravis Q5. No comparator
Outcomes	Q1, Q2, Q3: clinical effectiveness and safety Remission is the treatment goal Clinical response reduction in need for steroids, plasmapheresis, and immunotherapy, quality of life, laboratory parameters Q4. Cost-effectiveness Q5 Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic studies, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published prior to 1998. Studies that were included within eligible systematic reviews were excluded. Publications on case reports were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR 2 tool,[11] non-randomized studies were critically appraised using the Downs and Black checklist,[12] and guidelines were assessed with the AGREE II instrument.[13] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 204 citations were identified in the literature search. Following screening of titles and abstracts, 179 citations were excluded and 25 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search. Of these 28 potentially relevant articles, 12 publications were excluded for various reasons, while 16 publications[5,6,8,14-26] met the inclusion criteria and were included in this report. These comprise one health technology assessment,[23] two systematic reviews,[5,6] 11 non-randomized studies,[8,14-21,24,25] and one guideline published in two reports.[22,26] No randomized controlled trials, or cost-effectiveness studies were identified. Appendix 1 presents the PRISMA flowchart of the study selection.

The health technology assessment report by Sinclair et al.[23] has been described in detail in a previous CADTH report,[9] and will not be presented here; though, findings from the report will briefly be described.

Summary of Study Characteristics

Study characteristics are summarized below and details are available in Appendix 2, Tables 2 to 6.

Study Design

Both eligible systematic reviews[5,6] included primary studies of single or multiple cases; and countries where the cases were from were not reported. One systematic review[6] published in 2017 included 47 reports published between 2000 and 2015. The second systematic review[5] published in 2015 included 37 reports —15 of which were included in a meta-analysis and published between 2008 and 2013. Publication years for the remaining reports were not reported. Of the 11 non-randomized studies,,[8,14-21,24,25] four studies[14,16-18] were prospective and the number of patients ranged between eight and 55; and seven studies[8,15,19-21,24,25] were retrospective studies with patient numbers in the range 3 to 42. Of the four prospective studies, two were published in 2018[14,18] and two were published in 2017.[16,17] Of the seven retrospective studies, two were published in 2018,[15,19] four were published in 2017,[8,20,21,24] and one was published in 2016.[25]

The included evidence based guideline.[22,26] did not report conduct of a formal systematic literature search; rather, literature available in recent national and regional MG treatment guidelines was included, as well as additional literature used for formulating guidance statements. Recommendations were formulated based on voting and consensus using a modified Delphi process. The guideline was published in 2017.[22,26]

Country of Origin

Of the two included systematic reviews[5,6] one was from the USA,[6] and the other from Italy[5].

Of the 11 non-randomized studies, one study each was from Austria,[24] Canada,[14] China,[17] India,[25] Portugal,[20] and Spain;[15] two studies were from France,[8,18] and; three studies were from the USA .[16,19,21]

The included evidence based guideline was from the USA.[22,26]

Patient Population

One systematic review[6] included adult patients with MG. The second systematic review[5] included adult patients with MG; 85% of whom with refractory MG.

All of the 11 non-randomized studies included adult patients: patients with refractory MG,[14,17,24,25] patients with resistant MG,[8] patients with resistant MuSK MG,[15] patients with refractory AChR MG,[18,21] patients with MG,[19,20] and patients with MuSK MG.[16] Definitions of refractory or resistant MG used by the authors when available are presented in Appendix 2, Table 4. The number of patients varied between three and 55, and the proportion of female patients varied between 45% and 100%.The mean ages of patients in nine of the non-randomized studies varied between 35 years and 62 years. Of the two studies that did not report mean ages, one reported an age range of 22 to 55 years,[24] and; another reported a median age of 36 years.[25]

For the included evidence based guideline, the target population was patients with MG.[22,26]

Interventions and Comparators

Both systematic reviews[5,6] investigated rituximab with no comparator interventions. Rituximab doses and frequencies of treatment were variable. In most instances, each dose of rituximab was 375 mg/m^2 or 500 mg/m^2.

Of the 11 non-randomized studies, nine investigated rituximab with no comparator interventions;[8,14,17,18Memon, 2018 #16,20,21,24,25] one compared three different rituximab regimens;[15] and one compared rituximab with a control group of those not yet started on rituximab treatment.[16] Rituximab doses and frequencies of treatment were variable. In most instances, each dose of rituximab was 375 mg/m^2; other doses mentioned were 750 mg/m^2, 600 mg, and 1000mg.

The guideline included several treatment options for MG, among which rituximab was included.[22,26]

Outcomes

Outcomes included clinical efficacy, quality of life (QoL), laboratory parameters, relapse rates, changes in the need for other medications or procedures, adverse effects, and costs. Several outcome measures were used**;** however, details were rarely presented. Clinical outcome measures included: Diagnosis Related Group score of hospital admissions related to MG **(**DRG-MG),[24] forced vital capacity (FVC),[18] MG related activities of daily living (MG-ADL),[17] MG composite scale (MGCS**),** [20] myasthenia muscle score (MMS),[8,18] manual muscle testing (MMT),[14,17] MG Foundation of America post-intervention status (MGFA-PIS), [5,8,15,16 18 20] MG Status and Treatment Intensity (MGSTI),[16] post-intervention scale modified (PIS-m),[6] and quantitative MG (QMG)[6 17,18,24] quality of life (QoL) outcomes including MG quality of life (MG-QoL)**,**[17] QoL**,**[20] and the short form 36 (SF-36).[18] Relapse rates were reported in four articles.[6 14,15,21] Changes in requirements for other treatments or procedures were reported in nine articles.[8,14-18,20,24,25] Examples of other treatments and procedures used were prednisone, intravenous immunoglobulin (IVIg), and/or plasma exchange (PE). Laboratory parameters were reported in five articles.[6,17 18,21,25] Adverse effects were reported in 11 articles,[5 6,8,15 17,18 19-21,24,25] and cost of treatment before and after rituximab treatment was reported in one article.[20]

The included guideline.[22,26] presented recommendations for treatments for MG, including rituximab.

Summary of Critical Appraisal

Critical appraisal of the studies is summarized below and details are presented in Appendix 3, Tables 7 to 9.

In both included systematic reviews,[5,6] the objective was clearly stated; literature search was conducted using a single database; data extraction was completed by one reviewer and checked by another reviewer, and; meta-analysis was undertaken. In the systematic reviews, the inclusion and exclusion criteria were not stated; study selection was not described; lists of excluded studies were not presented; characteristics of the individual studies were not presented (instead, a summary was presented); and it was unclear if quality assessment of the studies or tests for publication bias were conducted. In one systematic review[5] a partial list of included studies was provided and in one systematic review[6] the list of included studies was not presented. In both systematic reviews, conflicts of interest were declared; for one systematic review[5] the potential for bias was deemed to be unlikely, and in one systematic review[6] the potential for bias could not be definitively ascertained. Of note, the health technology assessment by Sinclair et al.[23] (which is not described in detail here for reasons previously explained) was deemed to have used a rigorous method; however, the authors mentioned that the findings need to be interpreted with caution, considering that the evidence was from case series or case reports involving small numbers of patients.

In all of the 11 included non-randomized studies, the objective and inclusion criteria were stated, and patient characteristics; interventions; and outcomes were described. However, in most of the studies, details describing the outcome measures were not presented. Four of the non-randomized studies[14,16-18] were prospective, and the remaining seven studies[8,15,19-21,24,25] were retrospective. These prospective and retrospective studies have potential for bias by virtue of their non-randomized designs. Sample size calculations were not reported in any of the non-randomized studies. Conflicts of interest for study authors were not reported in two studies, [8,17] whereas they were in the other nine studies; of these nine studies, there was no apparent potential for bias identified in six,[14,15,18,20,24,25] whereas potential for bias could not be ruled out in three.[16,19,21]

The included evidence-based guideline stated the purpose and scope, and the guideline development group included experts in the topic area. A systematic review of literature was not undertaken; instead, literature available in recent national and regional MG treatment guidelines, as well as additional literature was used for formulating guidance statements. Recommendations were not graded. Resource implications were not considered. It was unclear if patient input, or implementation barriers were considered; or if a policy was in place for updating the guideline. Conflicts of interest of the authors were mentioned and potential for bias could not be ruled out.

Summary of Findings

Findings are summarized below and details are available in Appendix 4, Table 10. The HTA report by Sinclair et al.[23] has been presented in the previous CADTH report;[9] hence it will briefly be presented here.

What is the clinical effectiveness of rituximab induction therapy for the treatment of myasthenia gravis for those who are refractory to standard therapy?

The HTA report by Sinclair et al.[23] reported that the majority of MG patients had improvement (based on outcome measures such as MGFA clinical classification and post-

intervention status, and QMG) with rituximab (RTX) treatment, particularly the MuSK antibody positive subgroup. It also reported reductions in use of intravenous immunoglobulin (IVIg) and/or plasmaphoresis (PEX) following RTX treatment from three included studies. Further, it mentioned that two patients were hospitalized due to infections, and one patient discontinued treatment due to an infusion reaction. Based on this HTA, the previous CADTH report[9] concluded that RTX appears to be a viable treatment option for refractory MuSK MG patients; however, it also noted that findings need to be interpreted with caution as the evidence was from case series or case reports with small sample sizes.

The systematic review by Iorio et al.[5] reported an overall response rate of 83.9% with RTX therapy for MG patients (the majority of whom had refractory MG). It also reported that adverse effects were observed in 4.2% of the patients (i.e., four patients had infection, two patients experienced prolonged B-cell depletion, and one patient had heart failure after the third RTX infusion).

The systematic review by Tandon et al. reported that, following RTX treatment, 44% of MG patients achieved minimal manifestation (MM) status or better, and 27% achieved combined chronic stable remission (CSR) and pharmacologic remission (PR) status as measured using the PIS-m.[6] As compared to the AChR patient group, a statistically significantly greater proportion of patients achieved these results in the MuSK patient group ($P < 0.001$). Based on multivariate regression analysis, the authors reported that MG type, severity, and age at RTX treatment appear to be predictors of response to treatment, whereas age at onset of MG, duration of MG before RTX treatment, the RTX induction regimen, and the total number of infusions did not appear to be predictors of response. Among the patients with available safety data, side effects were reported in 14% of the patients; these included flushing agranulocytosis and pneumonia, bronchitis, dyspnea, myocardial infarction, altered sweet taste, chills and rigor, diabetes and hypertension, rash, hot sensation, pruritus, reactivation of oral herpes zoster, and spondylodiscitis.

The retrospective study by Asanasiev and colleagues included 28 patients with resistant MG who were treated with RTX, and found a statistically significant improvement at six months follow-up in myasthenic muscle score (MMS) ($P < 0.0001$).[8] This improvement appeared to remain stable up to 36 months; however, data for all patients were not available at time points after 6 months. Overall, 50% of the patients appeared to have responded to RTX, based on post-intervention status (PIS). Treatment with RTX resulted in reduction in prednisone dose. Side effects were reported in 39% of the patients and severe side effects were observed in 14% of patients. No patient died of MG at the end of their follow-up.

The prospective study by Beecher et al. included 22 patients with refractory MG who were treated with RTX, and reported statistically significant reductions in manual muscle testing (MMT) scores ($P < 0.0001$)[14]. In 14 patients taking prednisone, there was a statistically significant reduction in prednisone dose following RTX therapy ($P = 0.002$). Seven patients experienced relapse and required repeat cycles of RTX.

The retrospective study by Cortes-Vincente et al.,[15] included 25 patients with resistant MuSK MG and compared three different RTX regimens: Group 1 (protocol: [4+2] RTX), Group 2 (protocol: [1+1] RTX), and Group 3 (protocol [4] RTX) (details presented in Appendix 4, Table 10). It reported that all patients achieved MM or better MG Foundation of America post-treatment status (MGFA PIS). For all patients, after start of RTX, prednisone was either decreased or withdrawn. Relapse rates were 18.2%, 80%, and 33.3% in Groups

1, 2, and 3 respectively. During infusion, seven patients experienced mild symptoms with none experiencing severe adverse events.

The prospective study by Hehir et al.[16] included 55 patients with MuSK MG and compared RTX treatment with control (i.e., those not started on RTX treatment). It reported that 58% of the patients achieved the primary outcome (i.e., MG Status and Treatment Intensity (MGSTI) level 2 or better) compared with 16% of control group patients (*P* = 0.002). Also, at the final visit, 29% of the RTX-treated patients were taking prednisone compared to 74% in the control group (*P* = 0.001). There was no mention of adverse effects.

The prospective study by Jing et al.[17] included eight patients with refractory generalized MG and examined treatment with RTX. It reported that there were statistically significant improvements with respect to Quantitative MG (QMG), manual muscle testing (MMT), and MG related activities of daily living (MG-ADL) at three and six months post-RTX treatment. (*P* values ranged between 0.005 and 0.016). No statistically significant improvements were found with respect to MG quality of life (MG-QoL) (*P* values ranged between 0.07 and 0.09). Also, statistically significant B cell depletion was reported (*P* values ranged between 0.007 and 0.008) but no statistically significant change was reported for $CD4^+$ or $CD8^+$ T-cells (*P* values ranged between 0.72 and 0.92). All patients had a reduction in prednisone dose, and at 6 months follow-up, mean reduction in prednisone dose was 43% (*P* = 0.018). No allergic reactions or other serious side-effects with RTX were observed during the follow-up period.

The prospective study by Landon-Cardinal et al.[18] included 11 patients with refractory generalized acetylcholine receptor antibody positive MG (AChR MG and examined treatment with RTX. It reported some improvements in some patients with respect to myasthenic score (MMS), QMG, MGFA-PIS and forced vital capacity (FVC) but not in other patients (details are available in Appendix 4, Table 10). There were no changes with respect to SF-36 clinical and mental components. Additional treatments were needed, including immunosuppressants, IVIg or plasmapheresis. During the study period, adverse events, such as non-febrile flu-like syndromes, viral gastroenteritis, cutaneous infections, and herpes zoster infection, were reported. No serious adverse events occurred during RTX infusion.

The retrospective study by Memon et al.,[19] included patients with immune-mediated neurological disorders, of which three had MG. It evaluated the safety of RTX treatment and reported that in the MG patients, infections occurred in 75% of the patients; though, no serious adverse events were reported.

The retrospective study by Peres et al.,[20] included six patients with refractory or severe MG. It compared outcomes and costs, before and after treatment with RTX. Use of RTX resulted in a reduction in the other treatments that were usually needed, such as use of prednisone and immunosuppressive drugs. A comparison of the year before and after RTX treatment, demonstrated an improvement in QoL (difference in EQ-5D = +0.492) and decrease in health care costs (-€ 2,243). Two patients had major side effects with RTX (i.e., sustained hypogammaglobulinemia in one patient, and a macrophage activation syndrome in one patient); and two patients had minor side effects.

The retrospective study by Robeson et al.,[21] included 16 patients with refractory AChR MG, and examined treatment with RTX. It was reported that after completing the initial set of RTX cycles, 10 patients achieved complete stable remission, three patients achieved pharmacological remission (i.e. needed either prednisone or azathioprine), and three

patients achieved an MM score of -0 (i.e., minimal manifestations but no therapy for MG). After the last treatment cycle, nine patients had a relapse within a mean follow-up of 36 months, and seven patients maintained clinical benefit during a mean follow-up of 47 months. Levels of AChR antibodies decreased with RTX treatment; though, the authors did not report information describing whether these levels were at or below the threshold for clinical significance. No infusion reactions were observed. One patient developed leukopenia after the second cycle of RTX but it was resolved without intervention.

The retrospective study by Stieglbauer et al.,[24] included four patients with refractory MG, and examined RTX treatment. It showed that all patients achieved sustained clinical improvements and did not need other drugs (immunosuppressants or steroids). RTX was reported as being well tolerated. There were no side effects, with the exception of two patients who occasionally experienced headaches. The Diagnosis Related Group score of hospital admissions related to MG (DRG-MG) score following RTX treatment was lower than before RTX treatment, and the authors reported that this indicated a reduction in the costs of inpatient hospital care in the patients.

The retrospective study by Sudulagunta et al.,[25] included 42 patients with refractory MG and examined RTX treatment. Of the 42 aptients, 39 patients who were also receiving prednisone, demonstrated an average 94.6% reduction in prednisone dose after three cycles of RTX. After RTX therapy was initiated, plasma exchange sessions were needed less frequently, and there was a decrease in AChR antibody levels. Adverse reactions were reported by 15 patients. The most common adverse reactions included pruritis and flushing, flushing and shortness of breath, and chills/rigors. However RTX therapy did not have to be stopped because of adverse reactions and there were no deaths due to adverse effects.

In summary, evidence from non-randomized studies, which were mostly retrospective and non-comparative, suggests that RTX treatment offers some clinical benefit (based on various outcome measures) for adult patients with MG. The MuSK MG subgroup appeared to experience greater clinical benefit compared to the AChR MG subgroup. QoL was reported in a few studies and there was suggestion of improvement with RTX treatment. RTX treatment resulted in a reduction in prednisone use. Antibody levels were reduced after RTX treatment. Generally, the side effects with RTX were few and were not reported as being serious.

What is the clinical effectiveness of rituximab re-treatment for the treatment of myasthenia gravis?

No studies were identified that exclusively examined RTX retreatment for the treatment of MG. Rather, the studies that were identified examined RTX therapy as a continuum of treatment with RTX of varying doses and frequencies (as described previously).

What is the clinical effectiveness of rituximab maintenance therapy for the treatment of myasthenia gravis?

No relevant studies were identified that exclusively examined RTX maintenance therapy for the treatment of MG. Rather, the studies that were identified examined RTX therapy as a continuum of treatment with RTX of varying doses and frequencies, and these have been described in a previous section.

What is the cost-effectiveness of rituximab therapy versus other therapies for the treatment of myasthenia gravis?

No relevant studies were identified that evaluated the cost-effectiveness of RTX therapy versus other therapies for the treatment of MG. However, one study by Peres et al.,[20] reported on change in cost in the year before and after RTX treatment and has been presented in the previous section.

What are the evidence-based guidelines regarding rituximab for the treatment of myasthenia?

One evidence based guideline (reported in two documents[22,26]) regarding management of MG was identified. This guideline mentioned a number of treatment options including RTX therapy for patients with refractory MG, and further mentioned that available evidence describing the efficacy of RTX is currently being generated, therefore precluding a formal consensus regarding recommendations. It also mentioned early treatment with RTX in MuSK MG patients who have unsatisfactory response to immunotherapy.

Limitations

There are several limitations to this review.

Comparison across studies was difficult, as the rituximab doses and the frequencies of treatment varied. Furthermore, outcome measures used also varied making it difficult to determine if results were similar. Most of the studies were non-comparative; hence, it is unclear how rituximab compares with other treatment modalities.

Studies which reported results at different time points, the number of patients with available data decreased at the later time points, or the number of patients at the different time points was not specified. Hence, it is unclear to what extent or in which direction this missing data would impact the findings.

The systematic reviews included uncontrolled, non-randomized studies and also included case reports. No relevant randomized controlled trials were identified. The evidence described in this report comes from non-randomized studies, the majority of which were retrospective in design; hence, the risk of bias is high. Furthermore, the primary studies included a small number of patients ranging from three to 55, and the systematic reviews lacked methodological rigour.

One systematic review[6] did not provide a list of the included studies, and one systematic review[5] provided a partial list of included studies, hence it was difficult to determine the extent of overlap in the included studies in the two systematic reviews.

Most of the included articles included patients with refractory or resistant MG but two articles[16,19] on MG patients did not specifically mention refractory MG.

No relevant study specifically addressing the clinical effectiveness of rituximab retreatment therapy for MG was identified. No relevant study specifically describing the clinical effectiveness of rituximab maintenance therapy for the treatment of MG was identified. Finally, no relevant study on the cost-effectiveness of rituximab therapy versus other therapies for the treatment of MG was identified.

Conclusions and Implications for Decision or Policy Making

Sixteen eligible publications were identified. These comprised one health technology assessment,[23] two systematic reviews,[5,6] 11 non-randomized studies,[8,14-21,24,25] and one

guideline published in two reports.[22,26] No randomized controlled trials or cost-effectiveness studies were identified. Evidence from non-randomized studies, the majority of which were retrospective, suggested that rituximab treatment offers some clinical benefit (based on a variety of outcome measures) for adult patients with MG. The MuSK MG subgroup appeared to experience greater clinical benefit compared to the AChR MG subgroup. Quality of life was reported in three studies with improvements observed following rituximab treatment. Studies reporting on prednisone use found that rituximab treatment resulted in a reduction of prednisone use. Antibody levels were reduced after rituximab treatment. Generally, side effects with rituximab were few and were not considered serious by the study authors.

One evidence based guideline (reported in two documents[22,26]) regarding management of MG mentioned rituximab therapy as a treatment option, however they emphasized that evidence regarding the efficacy of rituximab for the management of MG is increasing and they therefore did not reach a formal consensus regarding recommendations.

Uncertainty remains with respect to the types of MG patients who are likely to benefit most from rituximab treatment, as well as the optimal treatment regimen. Afanasiev et al[8] reported that there appeared to be neither a general consensus as to when to introduce rituximab, nor criteria to justify additional rituximab doses. Robeson et al.[21] suggested that identification of markers of disease activity, responsiveness to therapy, clinical relapse, and remission are important factors to consider for administering effective treatment with rituximab for patients with MG. In a retrospective analysis of medical records describing refractory MG patients, Sudulagunta et al.[25] observed that refractory MG patients were most likely to be females, have onset of disease at an early age, MuSK MG, and thymomas. They suggested further research to identify biomarkers that may better predict response to therapy.

Rituximab therapy appears to be associated with improvement in patients with MG, however definitive conclusions are not possible and the findings need to be interpreted in the light of the limitations mentioned. Well-designed, prospective, comparative studies are needed to better understand the effects of rituximab therapy in patients with MG.

References

1. The National Institute of Neurological Disorders and Stroke. Myasthenia gravis fact sheet. 2017; https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Myasthenia-Gravis-Fact-Sheet#1 Accessed 2018 Aug 13.
2. Mantegazza R, Antozzi C. When myasthenia gravis is deemed refractory: clinical signposts and treatment strategies. *Ther Adv Neurol Disord.* 2018;11:1756285617749134.
3. Breiner A, Widdifield J, Katzberg HD, Barnett C, Bril V, Tu K. Epidemiology of myasthenia gravis in Ontario, Canada. *Neuromuscul Disord.* 2016;26(1):41-46.
4. Mayo Clinic. Myasthenia gravis. 2017; https://www.mayoclinic.org/diseases-conditions/myasthenia-gravis/symptoms-causes/syc-20352036 Accessed 2018 Aug 13.
5. Iorio R, Damato V, Alboini PE, Evoli A. Efficacy and safety of rituximab for myasthenia gravis: a systematic review and meta-analysis. *J Neurol.* 2015;262(5):1115-1119.
6. Tandan R, Hehir MK, 2nd, Waheed W, Howard DB. Rituximab treatment of myasthenia gravis: a systematic review. *Muscle Nerve.* 2017;56(2):185-196.
7. Anderson D, Phan C, Johnston WS, Siddiqi ZA. Rituximab in refractory myasthenia gravis: a prospective, open-label study with long-term follow-up. *Ann Clin Transl Neurol.* 2016;3(7):552-555.
8. Afanasiev V, Demeret S, Bolgert F, Eymard B, Laforet P, Benveniste O. Resistant myasthenia gravis and rituximab: a monocentric retrospective study of 28 patients. *Neuromuscul Disord.* 2017;27(3):251-258.
9. Rituximab for MuSK antibody-positive myasthenia gravis: a review of the clinical effectiveness, safety, and cost-effectiveness. *(CADTH Rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2014: https://www.cadth.ca/sites/default/files/pdf/htis/dec-2014/RC0595%20Ritixumab%20for%20Myasthenia%20Gravis%20Final.pdf. Accessed 2018 Aug 13.
10. MacDonald D, Crosbie T, Christofides A, Assaily W, Wiernikowski J. A Canadian perspective on the subcutaneous administration of rituximab in non-Hodgkin lymphoma. *Curr Oncol.* 2017;24(1):33-39.
11. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 2018 Aug 13.
12. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf. Accessed 2018 Aug 13.
13. Agree Next Steps Consortium. The AGREE II Instrument. Hamilton (ON): AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2018 Aug 13.
14. Beecher G, Anderson D, Siddiqi ZA. Rituximab in refractory myasthenia gravis: extended prospective study results. *Muscle Nerve.* 2018;09:09.
15. Cortés-Vicente E, Rojas-Garcia R, Diaz-Manera J, et al. The impact of rituximab infusion protocol on the long-term outcome in anti-MuSK myasthenia gravis. *Ann Clin Transl Neurol.* 2018;5(6):710-716.
16. Hehir MK, Hobson-Webb LD, Benatar M, et al. Rituximab as treatment for anti-MuSK myasthenia gravis: multicenter blinded prospective review. *Neurology.* 2017;89(10):1069-1077.
17. Jing S, Song Y, Song J, et al. Responsiveness to low-dose rituximab in refractory generalized myasthenia gravis. *J Neuroimmunol.* 2017;311:14-21.
18. Landon-Cardinal O, Friedman D, Guiguet M, et al. Efficacy of Rituximab in refractory generalized anti-AChR myasthenia gravis. *J Neuromuscul Dis.* 2018;5(2):241-249.
19. Memon AB, Javed A, Caon C, et al. Long-term safety of rituximab induced peripheral B-cell depletion in autoimmune neurological diseases. *PLoS One.* 2018;13 (1):e0190425.

20. Peres J, Martins R, Alves JD, Valverde A. Rituximab in generalized myasthenia gravis: clinical, quality of life and cost-utility analysis. *Porto Biomed J.* 2017;2(3):81-85.

21. Robeson KR, Kumar A, Keung B, et al. Durability of the Rituximab response in acetylcholine receptor autoantibody-positive myasthenia gravis. *JAMA Neurol.* 2017;74(1):60-66.

22. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I. International consensus guidance for the management of myasthenia gravis: executivce summary *Neorology.* 2016;87(4):419-425.

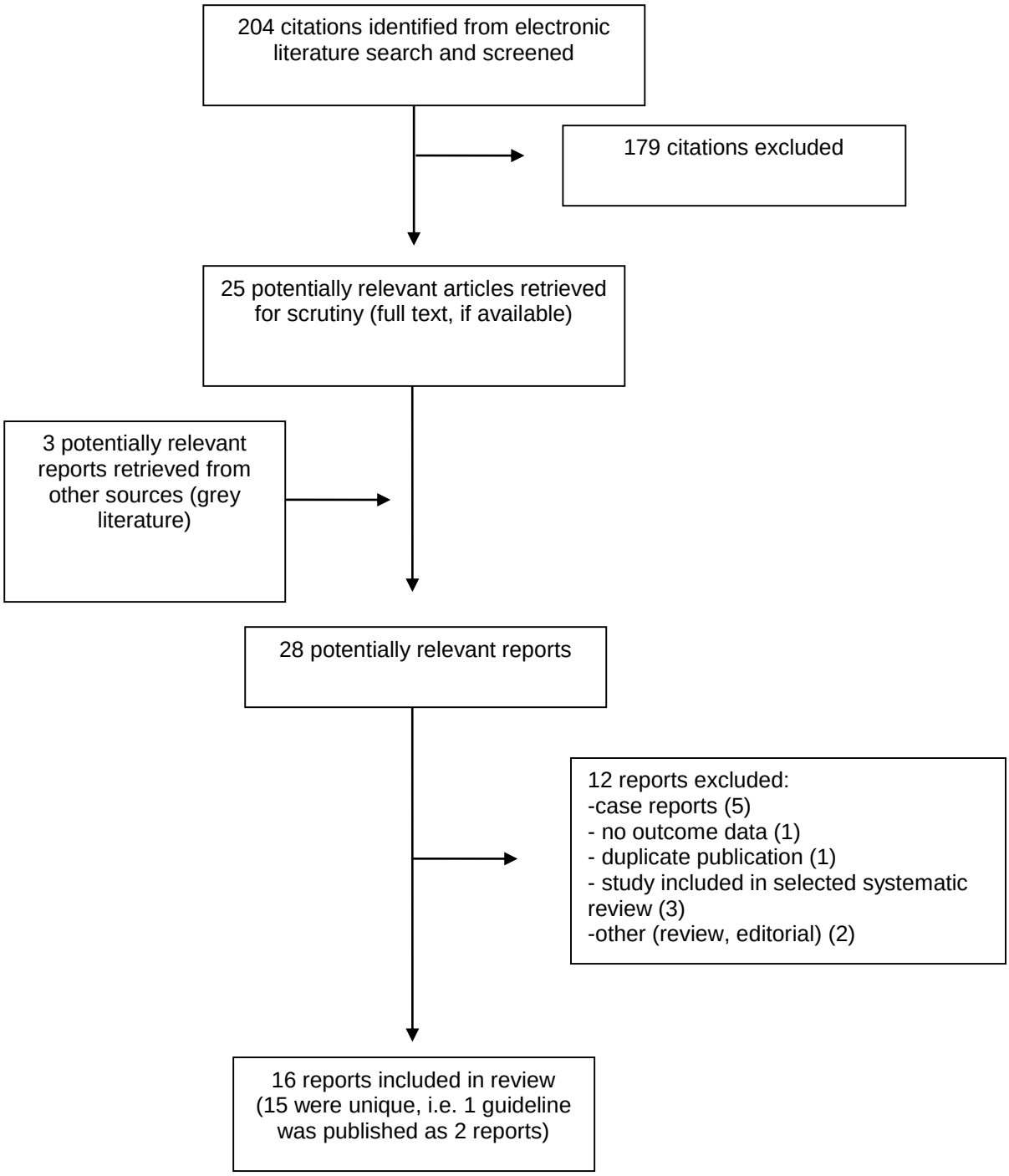
23. Sinclair A, Nicolau I, Xie X, Dendukuri N, McGregor M. The effectiveness and safety of rituximab (anti-CD20) in neurologic autoimmune diseases. Montreal (QC): Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC); 2013: https://muhc.ca/sites/default/files/micro/m-TAU/muhc_tau_2013_64_rituximab.pdf. Accessed 2018 Aug 13.

24. Stieglbauer K, Pichler R, Topakian R. 10-year-outcomes after rituximab for myasthenia gravis: efficacy, safety, costs of inhospital care, and impact on childbearing potential. *J Neurol Sci.* 2017;375:241-244.

25. Sudulagunta SR, Sepehrar M, Sodalagunta MB, et al. Refractory myasthenia gravis - clinical profile, comorbidities and response to rituximab. *Ger Med Sci.* 2016;14:Doc 12.

26. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guiadance for the management of myasthenia gravis. 2016: http://n.neurology.org/content/neurology/suppl/2016/06/29/WNL.0000000000002790.DC1/Full_Statement.pdf. Accessed 2018 Aug 13.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Health Technology Assessment and Systematic Reviews

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcomes
Health Technology Assessment				
Sinclair,[23] 2013, Canada	HTA report. Aim: To assess the efficacy ,safety , and cost of rituximab treatment in four rare autoimmune diseases: myasthenia gravis, neuromyelitis otica, dermatomyositis, and chronic inflammatory demyelinating polyneuropathy Note: The HTA report has been described in detail in the previous CADTH report,[9] so not reiterated here.	Reported elsewhere	Reported elsewhere	MGFA clinical classification and post-intervention status, QMG, remission, relapse, change in medication use, and adverse effects
Systematic reviews				
Iorio,[5] 2015, Italy	Systematic review included 37 uncontrolled observational studies. Of these 37 studies, 15 studies were used for meta-analysis; case reports or studies with fewer than 2 patients were excluded. These 15 studies were published between 2008 and 2013. Countries for the included studies were not reported. Citations for the studies were not presented. Aim: To evaluate the efficacy and safety of rituximab for MG	Adult patients with MG (85% with refractory MG) N= 168 (subgroups: 91 are AChR-ab+, 70 are MuSK-ab+, 7 are SN) Age (mean) (years) : (subgroups: 43 in AChR, 43 in MuSK, 38 in SN) % Female: (subgroups: 51% in AChR, 83% in MuSK, 25% in SN) MG duration (mean) (years): (subgroups: 9.2 in AChR, 7 in MuSK, 12.8 in SN)	RTX (no comparators). RTX dose varied: 137 patients received 4 x 375 mg/m^2 ; 12 patients received 500 mg per week for two weeks; 8 patients received two infusions of 1 g each; and 11 patients received various regimens	MGFA –PIS. AE. Follow-up (median): 16 months for AChR-ab+, 26 months for MuSK-ab+, and 12 months for SN.
Tandan,[6] 2017, USA	Systematic review included 47 articles of which 28 articles were single case reports and 19 articles were reports	Adult patients with refractory MG N = 169	RTX (no comparators). RTX dose varied. RTX induction regimen:	PIS-m, QMG, relapse rate. Antibody titer

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcomes
	on two or more patients (range: 2 to 22). These articles were published between 2000 and 2015 Countries for the included studies were not reported. Aim: To assess the efficacy and safety of rituximab for MG	Age (mean ± SD) (years): 44.6 ± 17.1. % Female: 75% Duration of MG (median [range]) (months): 60 (0 to 531). Number of immunosuppressive medications before rituximab (mean ± SD): 3.6 ± 1.4	8% of patients received 500 mg, days 1 and 14; and 12% of patients received other doses. Rituximab follow-up regimen in 19% of patients	AE Follow-up (mean ± SD) (months): 22.5 ± 17.3

ab = antibody; ab+ = antibody positive; AChR = acetylcholine receptor; AE = adverse effects; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; MuSK = muscle specific tyrosine kinase; PIS = post-intervention status, PIS-m = post-intervention scale-modified; SD = standard deviation; SN = sero-negative

Table 3: Characteristics of Included Clinical Studies

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcomes
Non-randomized Studies				
Afanasiev,[8] 2017, France	Retrospective study (patient charts, letters, laboratory and electrophysiological results were reviewed) Setting: Single center (hospital in Paris., Data of patients who received rituximab between January, 2004 and August, 2015, were reviewed	Adult patients with resistant MG N = 28 (21 AChR MG, 3 MuSK MG, and 4 SN MG) Age (mean) (years): 50.6 % Female: 57 Duration of disease prior to RTX treatment (mean) (years): 11.4	RTX (no comparators). Mean total dose of RTX: 4.8 g ± 2.5 g RTX schedule: 54% of the patients received systematic infusion every 6 months and 46% of the patients were treated as needed	MMS, MGFA- clinical classification, PIS, chronic antimyasthenic treatment change, prednisone dose change. Side effects Follow-up (mean [range]) (months): 27(.26 to 60)
Beecher,[14] 2018, Canada	Prospective, open-label study Setting: University of Alberta Hospital, from 2012 to 2018	Adult patients with refractory MG. N = 22 (10 AChR, 9 MuSK, 3 SN) Age (mean ± SD) (years):49.4 ± 13.4 %Female: 45	RTX (no comparators). RTX induction regimen 1: 375 mg/m^2 per dose; or RTX induction regimen 2: 750 mg/m^2 per dose. (Patients received 1 or 2 doses).	MMT score, prednisone dose, relapse Follow-up (mean ± SD) (months): 49.4 ± 13.4

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcomes
		Duration of disease prior to RTX treatment (mean ± SD) (months): 51.4 ± 53.7.	Maintenance regimen: 750 mg/ m^2 per dose, max 1 g per dose (Repeat maintenance cycles were dictated by clinical worsening)	
Cortes-Vincente,[15] 2018, Spain	Retrospective study Setting: 11 hospitals in Spain; patients were treated between January 20o6 and March 2016	Adult patients with resistant MuSK MG (MGFA classes were IIB,IIIB, IVB, V) N = 25 (11 on 4+2 doses [Group1], 5 on 1+1 dose [Group 2], and 9 on 4 doses [Group 3]) Age (mean) (years): 55.4 in Group 1, 46.3 in Group 2, and 49.2 in Group 3. % Female: 100% in Group 1, 80% in Group 2, and 100% in Group 3. Duration of disease prior to RTX treatment (mean) (years): 8.7 in Group 1, 6.8 in Group 2, and 8.7 in Group 3.	RTX (no comparators). Three different RTX regimens were used Group 1: 4+2 doses (375 mg/m^2 for 4 consecutive weeks, then monthly for the next 2 months); Group 2: 1+1 doses (two 1 g doses separated by 2 weeks); and Group 3: 4 doses (375 mg/m^2 for 4 consecutive weeks).	MGFA PIS (MM or better), relapse rate, change in other drugs (especially prednisone) administered. AE Follow-up ((mean ± SD) (years): 5.0 ± 3.3
Hehir, [16] 2017, USA	Blinded prospective study of RTX Setting: Patients were treated at 10 neuromuscular centers from January 2005 to 2015. MG specialists were provided patient information such as age, severity of MG, comorbidities, number of hospitalizations, all previous and current immune-based treatments (excluding RTX) during the first year of treatment for	Adult patients with MuSK MG N = 55 (77 patients satisfied the inclusion criteria, however 22 patients were excluded due to insufficient data, leaving 55 patients for evaluation). Of the 55 patients, 24 patients in RTX group and 31 patients in control group. Age (mean ± SD) (years): 40.5 ± 14.7 in RTX, 48.1 ± 15.5 in control	RTX versus no RTX (i.e. control Rituximab dosing: The initial dose of RTX in all RTX treated patients was 375 mg/m^2 weekly for 4 weeks. Of the 15 patients who received RTX re-treatment, 13 patients received 375 mg/m^2 weekly for 4 weeks, and 2 patients received 1000 mg weekly for 2 weeks.	MGFA PIS, MGSTI (combines the MGFA PIS and immunosuppressant doses), change in doses of prednisone and other immunosuppressants. Follow-up (median [range]) (months: 45 (6 to 116) in RTX, and 54 (6 to 184) in C

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcomes
	MuSK MG. The specialists were asked if it would be reasonable to enroll the patient in a clinical trial comparing RTX with placebo. Each patient was enrolled based on positive responses from ≥ 4 or 5 specialists. Enrolled patients were assigned to RTX group or control group (method of assignment was not specified)	% Female: 88 in RTX, 81 in control Duration of disease between onset and last visit (mean) (years): 9.2 in RTX, 10.9 in control		
Jing,[17] 2017, China	Prospective study Setting: Patients were enrolled from 2015 to 2016	Adult patients with refractory generalized MG. N = 8 Age (mean ± SD) (years): 35.0 ± 12.5. % Female: 87.5 Duration of disease before starting RTX (mean ± SD) (months): 59.5± 34.6	RTX (no comparators). RTX dose = 600 mg (referred to as low dose) One patient received 3 cycles of RTX, 2 patients received 2 cycles each and the remainder received a single cycle each. Patients were allowed to receive repeat cycles of 600 mg every 6 months depending on clinical status and the patient's preference.	QMG, MMT, MG-ADL, MG-QoL Change in prednisone or other treatment. Laboratory parameters. Side effects Follow-up range: 6 to 15 months
Landon-Cardinal,[18] 2018, France	Prospective study Setting: Patients were enrolled from January 2008 to September 2010	Adult patients with severe refractory generalized AChR MG. N =12 (11 were analyzed) Age (median [range]) (years): 44 (24 to 61) % Female: 73 Disease duration at the time of entering study (median [range]) (years): 13 (3 to 32)	RTX (no comparators). Patients were given two infusions of 1 g of RTX separated by 2 weeks, followed by 1 g infusion 6 months after the day-14 (D14) injection.	MMS, QMG, MGFA-PIS, FVC, SF-36. Change in use of other drugs AChR antibody titer. Adverse events (Primary end-point : at least 20-points on MMS at 12 months). Follow-up: 18 months

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcomes
Memon,[19] 2018, USA	Retrospective study (included patients with autoimmune neurological diseases [neuromyletis optica, multiple sclerosis, and MG]; only MG patients relevant for this report are considered here) Setting: Two tertiary centers; chart review of patients who had received RTX during 2008 to 2014, for at least 36 months	Adult patients with MG N = 3 Age (mean) (years): 41 % Female: 67% Disease duration: NR	RTX (no comparators). RTX was given intravenously. Initial course of RTX was1000mg given approximately 15 days apart. Further, 1000 mg infusions were repeated every 6 to 9 months.	AE Patients were seen in the clinic every 3 months
Peres,[20] 2017, Portugal	Retrospective study (chart review). This study evaluated clinical outcomes and cost-utility of RTX treatment Setting: Neurology clinic and Autoimmune Diseases Unit of a Hospital in Amadora, Portugal. Aim: to assess the pharmacoeconomic and quality of life benefits with use of rituximab therapy for MG	Adult patients with generalized MG N = 6 (4 patients with refractory MG, and 2 patients with concurrent autoimmune disease [systemic lupus erythematosus or rheumatoid arthritis]) Age (mean ± SD) (years): 62.0 ±16.0 % Female: 83% Disease duration at start of RTX (mean): 10.8 years	RTX (no comparators). RTX course consisted of 2 infusions of 1000 mg each given 15 days apart. Retreatment was decided by a multidisciplinary team and administered with a minimum interval of 4 months between infusions	MGCS, MGFA-PIS QoL (EQ-5D,EQ-5D VAS, MG-QoL) Change in other treatments (prednisone, immunosuppressor, corticosteroids, PEX, IVIg). Side-effects Health care cost (before and after initiating RTX treatment)
Robeson,[21] 2017, USA	Retrospective study. Setting: Patients were from those referred to Yale MG clinic, Connecticut from January 2007 to December 2015	Adult patients with refractory generalized AChR MG N = 16 Age (median [range]) (years): 42 (18 to 69) % Female: 62.5 Duration of disease prior to RTX treatment (mean [range]) (months): 36 (9 to 90)	RTX (no comparator) RTX: 4 weekly infusions of 375 mg/m^2 One cycle was defined as I infusion per week for 4 consecutive weeks and the intervals between cycles were 6 months. Patients were treated initially with 2- to 4-cycles	MGFA PIS. Relapse rate. Antibody titer. Follow up (range) (months): 18 to 84

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcomes
Stieglbauer,[24] 2017, Austria	Retrospective study Setting: Austrian health care system	Adult patients with refractory MG N = 4 Age (range) (years): 22 to 50 % Female: 100 Duration of disease prior to RTX treatment (range) (years): 1 to 18	RTX (no comparators) RTX dose: infusions of 375 mg/m^2 every week for two weeks. From 2005 to 2009, decision with respect to retreatment with RTX (1 infusion of 375 mg/m^2) was guided by monitoring of B cell counts. In 2010, concerns regarding potential complications of long-term high dose, prompted rituximab infusions to be given depending on signs and symptoms of clinical deterioration. Number of RTX infusions (range): 3 to 8	QMG, DRG-MG, immunosuppressive drug use. AE Cost Follow-up after start of RTX (median [range]) (years): 10.1 (6.7 to 11.2). Includes all follow-up data until May, 2016
Sudulagunta,[25] 2016, India	Retrospective study (analysis of data from medical records) Setting: MG patients who were admitted or had presented to the outpatient department between January 2008 and January 2016; data taken from 7 hospitals of which 4 were specialized neurological centers.	Adult patients with refractory MG N = 76 (42 received RTX and for these patients findings were reported separately; however patient demographics [described below] were presented for the entire group of 76 patients) Age at onset of MG (median [range]) (years): 36 (27 to 53) % Female: 74% Duration of disease prior to RTX treatment: NR	RTX (no comparators) RTX dose: one infusion of 375 mg/m^2 every week for four consecutive weeks (this constitutes 1 cycle). Interval between cycles was 6 months. 18 patients received 2 infusions, and 24 patients received ≥ 3 infusions of RTX.	Change in prednisone use, PEX, and mycophenolate. Antibody titer Adverse reactions

AChR = acetylcholine receptor; DRG-MG = Diagnosis Related Group score of hospital admissions related to myasthenia gravis; IVIg = intravenous immunoglobulin; m = meter; mg = milligram; MG = myasthenia gravis; MG-ADL = MG-related activities of daily living; MGCS = myasthenia gravis composite scale; MGFA PIS = Myasthenia Gravis Foundation of America post-intervention status; MG-QoL = MG-specific quality of life; MGSTI = Myasthenia Gravis Status and Treatment Intensity; MM = minimal manifestation; MMT = manual muscle testing; MS = multiple sclerosis; MuSK = muscle specific tyrosine kinase; QMG = quantitative myasthenia gravis ; PEX = plasmaphoresis; RTX = rituximab; SD = standard deviation; SN = sero-negative; VAS = visual analog scale.

Table 4: Available Definitions of Refractory or Resistant MG

Author, Year, Country	Definition
Afanasiev,[8] 2017, France	Resistant MG: "Resistant (or refractory) myasthenia gravis (MG) is usually defined as a chronic condition in which patients are not relieved of severe MG symptoms despite an optimal use of prednisone and/or other second or third line drugs, such as immunosuppressants (IS) (azathioprine, mycophenolate mofetil, cyclosporin, cyclophosphamide, methotrexate, tacrolimus. . .), intravenous immunoglobulins (IVIg), or plasma exchanges (PE)." Page 251 Indication for RTX use: "patients with severe MG symptoms (Myasthenia Gravis Foundation of America – Clinical Classification (MGFACC) class IV or V) despite an optimal use of prednisone and at least of one IS during at least 6 months; or - patients with a past history of severe MG symptoms and now stabilized (MGFA-CC class I to III) at the price of a chronic treatment with IVIg and/or PE with regular programmed hospitalizations or with prednisone and IS but with side effects necessitating their withdrawal." Page 252
Beecher,[14] 2018, Canada	Refractory MG: "patients [….] were defined as having refractory MG by meeting one of the following criteria: suboptimal response (unchanged or worsening clinical status) to two or more immunosuppressive therapies, inability to tolerate side effects related to multiple immunosuppressive therapies, inability to reduce steroid dose without relapse, or requirement of maintenance IVIG infusions or PLEX." Page 4 of 14
Cortes-Vincente,[15] 2018, Spain	Resistant MG: "Patients were considered drug-resistant when no significant clinical improvement was achieved after prednisone and at least two second-line immunosuppressants."
Jing,[17] 2017, China	Refractory MG (criteria): "(1) failure to respond to multiple immunosuppressive (IS) therapies, (2) unacceptable adverse reactions to conventional treatments, (3) requirement of excessive amounts of potentially harmful agents, (4) presence of comorbidities that preclude the use of conventional treatments, (5) requirement for repeated treatment with IVIG or plasma exchange, and/or (6) frequent myasthenic crises" Page 14
Peres,[20] 2017, Portugal	Refractory MG and severe MG: "Refractory patients are defined when they cannot lower their steroid therapy without clinical relapse, are not clinically controlled on their immunotherapy regimen, or have severe side effects from immunosuppressive treatments. Severe MG was defined as a classification of MGFA ≥ IIIb." Page 82.
Robeson,[21] 2017, USA	Refractory MG: "Disease was defined as refractory when the immunotherapy dosage could not be lowered without clinical relapse, inadequate clinical control of the disease was achieved during the immunotherapy regimen, or severe adverse effects due to current immunosuppressive therapy were present." Page 61
Sudulagunta,[25] 2016, India	Refractory MG "Refractory patients were defined as those who could not lower the immunotherapy for MG without clinical relapse, with MG not clinically controlled on their immunotherapy regimen, or who had developed severe adverse effects from immunosuppressive therapy for at least a period of 12 months. There are no clearly defined criteria for refractory MG based on the duration of treatment. We considered a duration of 1 year as relevant." Page 5 of 15

IS = immunosuppressant; IVIg = intravenous immunoglobulin; MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America; MGFA-CC = Myasthenia Gravis Foundation of America – Clinical Classification ; PLEX (also PE) = plasma exchange; RTX = rituximab

Table 5: Available Explanation of Outcome Measures

Outcome Measure	Reference (first author)	Explanation
MGSTI	Hehir, [16] 2017, USA	MGSTI combines the modified MGFA PIS and immunosuppressant doses. The authors defined a desirable clinical outcome as a MGSTI of level 2 or better. This score was defined as PIS status of MM or better while taking a low dose of immunosuppressant(s).

MGFA PIS = Myasthenia Gravis Foundation of America; MGSTI = Myasthenia Gravis Status and Treatment Intensity; PIS = post intervention status

Table 6: Characteristics of Included Guidelines

First Author/ Group, Year, Country	Objective	Guideline Development Group, Target Users	Methodology
Sanders, [22,26] 2016, USA	To develop an international consensus-based guidance for the management of MG	A task force of MGFA organized a panel of 15 international experts in MG Intended users: clinicians caring for patients with MG worldwide	A formal systematic literature search was not conducted. Literature cited in recent national and regional MG treatment guidelines as well as additional literature was used for formulating guidance statements Method for evidence selection was not described. Recommendations were formulated based on voting and consensus. For formal consensus RAM was used to quantify agreement. RAM uses a multi-round modified Delphi process, by which a quantitative assessment that reflects the judgement of an expert group can be obtained. The level of appropriateness and agreement for each guidance statement using RAM Recommendations were not graded.

MG = myasthenia gravis, MGFA = Myasthenia Gravis Foundation of America; RAM = RAND/UCLA Appropriateness Method

Appendix 3: Critical Appraisal of Included Publications

Table 7: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2

Strengths	Limitations
HTA	
Sinclair,[23] 2013, Canada	
Note: The HTA report by Sinclair et al. has been described in detail in the previous CADTH report,[9] and not reiterated here. (The current report is an update of the previous CADTH report (https://www.cadth.ca/sites/default/files/pdf/htis/dec-2014/RC0595%20Ritixumab%20for%20Myasthenia%20Gravis%20Final.pdf) and also has a broader focus.)	
Systematic Reviews	
Iorio,[5] 2015, Italy	
• The objective was clearly stated. • A single database (PubMed) was searched between January 2000 and January 2014. • Data extraction was done by one author and checked by two authors • Meta-analysis was conducted • The authors mentioned that there were no conflicts of interest	• The inclusion and exclusion criteria were not explicitly stated. • Study selection was not described • Flow chart of study selection was not provided • A partial list of included studies was not provided • List of excluded studies was not provided • Unclear if article selection was done in duplicate • Unclear if quality assessment of the included studies was undertaken • Characteristics of each individual study were not presented; instead characteristics were summarized. • Unclear if publication bias was explored
Tandan,[6] 2017, USA	
• The objective was clearly stated. • A single database (PubMed) was searched between January 2000 and August 2015. • Data extraction was done by one author and checked by two authors • Meta-analysis was conducted but Forest plots were not presented. Regression analyses were conducted • Disclosures of the authors were presented. Three of the four authors had received research funding from industries.	• The inclusion and exclusion criteria were not explicitly stated. • Study selection was not described • Flow chart of study selection was not provided • List of included studies was not provided • List of excluded studies was not provided • Unclear if article selection was done in duplicate • Unclear if formal quality assessment of the included studies was undertaken, however it was mentioned that the quality of data and depth of reporting varied between the publications and in many instances some elements of data were lacking. • Characteristics of each individual study were not presented; instead characteristics were summarized. • Unclear if publication bias was explored

Table 8: Strengths and Limitations of Non-randomized Studies using the Downs and Black checklist[12]

Strengths	Limitations
Afanasiev,[8] 2017, France	
• The objective was clearly stated • The inclusion criteria were stated • Patient characteristics, intervention and outcomes were described. Details of the assessment tools were not presented • *P* values were reported. • Conflicts of interest of the authors were not mentioned	• The exclusion criteria were not explicitly stated • Not randomized (retrospective study, no comparator) • Sample size does not appear to have been calculated
Beecher,[14] 2018, Canada	
• The objective was clearly stated • The inclusion criteria were stated • Patient characteristics, intervention and outcomes were described. Details of the assessment tools were not presented • *P* values were reported • The authors mentioned that there were no conflicts of interest	• The exclusion criteria were not explicitly stated • Not randomized (prospective study, no comparator) • Sample size does not appear to have been calculated
Cortes-Vincente,[15] 2018, Spain	
• The objective was clearly stated • The inclusion criteria were stated • Patient characteristics, intervention and outcomes were described. Details of the assessment tools were not presented • *P* values were reported • The authors mentioned that there were no conflicts of interest	• The exclusion criteria were not explicitly stated • Not randomized (retrospective study, no comparator) • Sample size does not appear to have been calculated
Hehir, [16] 2017, USA	
• The objective was clearly stated • The inclusion criteria were stated • Patient characteristics, intervention and outcomes were described. However it was not specified if the patients were refractory to previous treatment. • *P* values were reported • The authors provided disclosures. A few authors were associated with industry and potential for conflict could not be ruled out definitively.	• The exclusion criteria were not explicitly stated • Not randomized (prospective study, RTX compared to control [no RTX]) • Sample size does not appear to have been calculated
Jing,[17] 2017, China	
• The objective was clearly stated • The inclusion criteria were stated • Patient characteristics, intervention and outcomes were described. Details of the assessment tools were not presented • *P* values were reported • Conflicts of interest of the authors were not mentioned	• The exclusion criteria were not explicitly stated • Not randomized (prospective study, no comparator) • Sample size does not appear to have been calculated

Strengths	Limitations
Landon-Cardinal,[18] 2018, France	
• The objective was clearly stated • The inclusion criteria were stated • The exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. Details of the assessment tools were not presented • The authors mentioned that there were no conflicts of interest	• Not randomized (prospective study, no comparator) • Sample size does not appear to have been calculated • *P* values were not reported
Memon,[19] 2018, USA	
• The objective was clearly stated • The inclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • One author was associated with industry and potential for conflict could not be ruled out definitively. Conflicts of interest of the other authors were not mentioned	• Not randomized (retrospective study, no comparator) • The exclusion criteria were not explicitly stated • Not randomized (prospective study, no comparator) • Sample size does not appear to have been calculated • *P* values were not reported
Peres,[20] 2017, Portugal	
• The objective was clearly stated • The inclusion criteria were stated • Patient characteristics, intervention and outcomes were described. Details of the assessment tools were not presented • *P* values were reported • The authors mentioned that there were no conflicts of interest	• The exclusion criteria were not explicitly stated • Not randomized (prospective study, no comparator) • Sample size does not appear to have been calculated
Robeson,[21] 2017, USA	
• The objective was clearly stated • The inclusion criteria were stated • Patient characteristics, intervention and outcomes were described. Details of the assessment tools were not presented • *P* values were reported • Disclosure of one of the 10 authors was presented, and the author mentioned association with industry; potential for conflict of interest cannot be definitely ruled out. Disclosures from the remaining authors were not presented.	• The exclusion criteria were not explicitly stated • Not randomized (retrospective study, no comparator) • Sample size does not appear to have been calculated. The authors mentioned that the sample size in each subgroup of patients was too small to make any firm conclusions.
Stieglbauer,[24] 2017, Austria	
• The objective was clearly stated • The inclusion criteria were stated • Patient characteristics, intervention and outcomes were described. Details of the assessment tools were not presented • The authors mentioned that there were no conflicts of interest	• The exclusion criteria were not explicitly stated • Not randomized (retrospective study, no comparator) • Sample size does not appear to have been calculated. • *P* values were not reported

Strengths	Limitations
Sudulagunta,[25] 2016, India	
• The objective was clearly stated • The inclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • *P* values were reported • The authors mentioned that there were no conflicts of interest	• The exclusion criteria were not explicitly stated • Not randomized (retrospective study, no comparator) • Sample size does not appear to have been calculated. However, the authors mentioned that the small sample size was a limitation.

Table 9: Strengths and Limitations of Guidelines using AGREE II

Strengths	Limitations
Sanders,[22,26] 2016, USA	
• The scope and purpose were clearly stated. • The guideline development group had relevant expertise (international experts in myasthenia gravis) • Some evidence on rituximab was presented • The executive summary of the guidance report appears to have been externally reviewed as it was published in the journal: Neurology • Conflicts of interest were declared and authors had association with industry. The potential for bias cannot be ruled out.	• A systematic review was not conducted. Instead literature cited in national and regional myasthenia treatment guidelines and also additional literature were used • Unclear if patient preferences were considered • Resource implications were not considered as treatment costs and availability vary by country and it is not possible to make a general statement applicable for all countries • Unclear if implementation barriers were considered. • Unclear if a policy was in place for updating the guideline • Recommendation were not graded

Appendix 4: Main Study Findings and Author's Conclusions

Table 10: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Health Technology Assessment	
Sinclair,[23] 2013, Canada	
The HTA report by Sinclair et al. has been described in detail in the previous CADTH report (https://www.cadth.ca/sites/default/files/pdf/htis/dec-2014/RC0595%20Ritixumab%20for%20Myasthenia%20Gravis%20Final.pdf),[9] so not reiterated here. (The current report is an update of the previous report and also has a broader focus.)	The authors of the HTA report concluded that *"The available evidence is based on case series and case reports involving small numbers of subjects, and therefore should be interpreted with caution. However, the rarity of these disorders means that higher quality data may never be obtained. [….]* *There is a small but consistent body of evidence from uncontrolled studies that suggests that patients with severe MG that is refractory to standard treatment, or who cannot tolerate standard treatment, may respond to rituximab, with in some cases marked clinical improvement to the point of remission. […]* *There is a small but consistent body of evidence from uncontrolled studies that suggests that patients with MG who require very frequent dosing (eg, weekly) with IVIg and/or PE to avoid deterioration may be able to abolish or reduce their dependence. In such cases, use of rituximab may result in savings in cost and reduction in need for resources. […]* *Adverse events were reported for all the MG, […] and hospitalizations due to infection were reported for patients with MG[…]. The small size of the dataset means that it is difficult to assess increased risk of adverse events due to rituximab."*

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td colspan="2">Systematic Reviews</td></tr>
<tr><td colspan="2">Iorio,[5] 2015, Italy</td></tr>
<tr><td>Adult patients with MG (> 85% with refractory MG)

Efficacy of rituximab in MG patients (results from meta-analysis)
<table>
<tr><th>Subgroup</th><th>No. of studies</th><th>Response rate (95% CI)</th></tr>
<tr><td>AChR-ab+</td><td>11</td><td>0.80 (0.69 to 0.88)</td></tr>
<tr><td>MuSK-ab+</td><td>11</td><td>0.88 (0.79 to 0.95)</td></tr>
<tr><td>SN</td><td>2</td><td>0.85 (0.42 to 0.98)</td></tr>
</table>
The differences in response rates among the different subgroups were not statistically significant. The MGFA status after treatment was used as a measure of response.

Meta-regression results:
No significant correlation was found between the mean MG severity or the mean number of reinfusions and the response rate. There appeared to be an inverse correlation trend between disease duration and response rate, however it was not statistically significant (P = 0.089)

Adverse effects:
Adverse effects were recorded in 4.2% of the patients (i.e. in 7 of the 168 patients)
Four patients had infection (herpes zoster 1, giardiasis 1, bronchitis 1, and pneumonia 1), two patients experienced prolonged B-cell depletion, and one patient after the third RTX infusion had heart failure.</td><td>The authors mentioned that "The meta-analysis here presented provides sufficient data to justify the use of RTX, administered at the maximum tolerated dose, in patients with refractory MG. [.....] The meta-analysis revealed that RTX was more effective in patients with MuSK-Ab MG than in patients with AChR-Ab MG, although the difference was not statistically significant. [.....] Furthermore the meta-regression analysis showed a trend toward an inverse correlation between the disease duration and the response rate to RTX." Page 1,118</td></tr>
<tr><td colspan="2">Tandan,[6] 2017, USA</td></tr>
<tr><td>Adult patients with MG (all had received immunosuppressive medication before rituximab)

Clinical outcomes with rituximab
<table>
<tr><th rowspan="2">Outcome</th><th colspan="2">All MG</th><th colspan="2">AChR-ab+ MG</th><th colspan="2">MuSK-ab+ MG</th></tr>
<tr><th>No. of patients</th><th>Percentage of patients with outcome</th><th>No. of patients</th><th>Percentage of patients with outcome</th><th>No. of patients</th><th>Percentage of patients with outcome</th></tr>
<tr><td>PIS-m MM or better</td><td>169</td><td>44</td><td>99</td><td>30</td><td>57</td><td>72</td></tr>
<tr><td>PIS-m CSR or PR</td><td>169</td><td>27</td><td>99</td><td>16</td><td>57</td><td>47</td></tr>
<tr><td>Relapse after RTX</td><td>101</td><td>26</td><td>63</td><td>33</td><td>29</td><td>14</td></tr>
<tr><td>Change in QMG score (mean ± SD)</td><td>18</td><td>8.2 ± 5.1</td><td>15</td><td>7.7 ± 5.4</td><td>3</td><td>10.3 ± 2.5</td></tr>
<tr><td>Mean Change in QMG score (%)</td><td>18</td><td>52.6</td><td>15</td><td>45.9</td><td>3</td><td>86.3</td></tr>
</table></td><td>The authors mentioned that "Rituximab appears to be a safe and effective therapy for patients with MG, especially those with MuSK-antibody–positive disease. MuSK-antibody– positive status, less severe disease, and younger age at time of treatment were the best predictors of response to treatment to PIS-m of MM or better. Pharmacokinetic data suggest that repeat dosing should be considered 4–6 months after an induction regimen in patients with either incomplete response or a relapse." Page 194</td></tr>
</table>

Main Study Findings	Author's Conclusion
Multivariate analysis: Factors predicting response to rituximab in myasthenia gravis patients **Response: PIS-m MM or better** • Better response is associated with MuSK MG compared to AChR MG: OR (95% CI) = 8.85 (3.68 to 21.26) • Better response is associated with age < 45 years compared with age > 45 years: OR (95% CI) = 2.44 (1.12 to 5.366) • Better response is associated with mild or moderate MG compared to severe MG: OR (95% CI) = 2.97 (1.05 to 8.41) Response: **PIS-m chronic stable remission and pharmacologic remission** • Better response is associated with MuSK MG compared to AChR MG: OR (95% CI) = 8.03 (3.18 to 20.28) • Better response is associated with age < 45 years compared with age > 45 years: OR (95% CI) = 2.58 (1.10 to 6.06) • Better response is associated with mild or moderate MG compared to severe MG: OR (95% CI) = 5.66 (1.85 to 17.38) Factors that did not appear to be predictors of response to rituximab treatment: age at onset of MG, gender, duration of MG before rituximab, the rituximab induction regimen, and the total number of infusions. **Effect of rituximab treatment on antibody titer** Pre- and post-treatment antibody titer data were available in 34% of the AChR-ab+ MG patients and 23% of the MuSK-ab+ MG patients and considering this, it was reported that reduction in antibody titer did not predict a favorable clinical response to rituximab. **Side Effects** The authors stated that "In the reports reviewed, the side effects of rituximab were not commented on for 64 patients. Side effects were reported in 15 of 105 (14%) patients for whom these data were available and included flushing in 3, and in 1 each of agranulocytosis and pneumonia, bronchitis, dyspnea, myocardial infarction, altered sweet taste, chills and rigor, diabetes and hypertension, rash, hot sensation, pruritus, reactivation of oral herpes zoster, and spondylodiscitis. No side effects were mentioned for 90 of 105 (86%) of the remaining patients." Page 192	
Non-randomized studies	
Afanasiev,[8] 2017, France	
Adult patients with resistant MG (N = 28) **Clinical efficacy of rituximab (MMS, MGFA status or PIS)**	The authors mentioned that "Our results diminish the previous positive results and demonstrate an efficacy in no more than 50% of treated patients based on the PIS. As for the previous reports, the major limit of our study is its retrospective design. We do not know if an earlier treatment and/or a longer follow-up would have modified the response rate to RTX. Prospective double-blind studies are highly needed in order to provide a

Time point (months)	MMS		MGFA therapy status		PIS	
	No. of patients	Mean MMS	No of patients	% of patients having one chronic therapy	No of patients	% of patients having improved PIS
At start of RTX	28	58.8	28	75%	28	NA
6	28	74.5	NR	NR	28	43
12	24	75.9	22	60%	24	50

Main Study Findings	Author's Conclusion

18	18	76.3	NR	NR	17	39
24	17	76.4	16	56%	18	42
30	13	76.9	NR	NR	13	38.5
36	12	72.5	12	67%	12	50
Some data were not reported in the text but were shown graphically						

At 36 months 25 % of patients received two chronic treatments, and no patient received three or more chronic treatments (additional details were presented graphically)

Clinical efficacy of rituximab (prednisone dose reduction)

Time point (months)	Prednisone use	
	No. of patients	Mean prednisone dose (mg per day)
At start of RTX	28	17.7
6	28	9.7
12	24	7.0
18	18	8.8
24	17	7.4
30	13	7.3
36	12	8.0

Other
Among the15 patients treated systematically with rituximab, 80% responded. Among the 13 patients treated with rituximab as needed, 46% responded.

Side effects
Benign side effects (such as bronchitis, flu-like syndrome, immediate hot flashes, and paresthesia) were reported in 39% of patients. Severe side effects were reported in 14% of patients.
At the end of follow-up, no patient died of MG.

precise evaluation of response rate, the auto-immune profile of responders and non-responders, and the best attitude to adopt for the maintenance regimen of RTX in resistant MG." Page258

Beecher,[14] 2018, Canada

Adult patients with refractory MG (N = 22; 10 AChR MG, 9 MuSK MG, 3 SN MG)

Clinical efficacy (MMT)

Patient group	Reduction in MMT scores (mean ± SD)	*P* value
All	10.3 ± 5.6 to 3.3 ± 3.1	< 0.0001
AChR MG	10.3 ± 5.1 to 5.5 ± 2.6	0.018
MuSK MG	10.0 ± 3.6 to 1.1 ± 2.0	< 0.0001
SN MG	13.7 ± 11.9 to 2.3 ± 2.5	0.29

Clinical efficacy (prednisone dose reduction)
For the 14 patients taking prednisone, there was a statistically significant reduction in daily prednisone dose (mean ± SD), from 25.2 ± 15.1 mg/d to 7.3 ± 7.1 mg/d (*P*=0.002).

Immunotherapy discontinuation
Four of nine MuSK MG patients, one of 10 AChR mg patients, and two of three SN MG patients discontinued all immunotherapy as of last follow-up.

Relapse
Six patients received repeat cycles due to relapse and one patient who relapsed was awaiting repeat cycle as of last follow up.

The authors mentioned that "Sustained clinical improvement was associated with rituximab after one cycle, with prolonged time to relapse and reduction in steroid dose." Page 1 of 14

Main Study Findings	Author's Conclusion
Cortes-Vincente,[15] 2018, Spain	
Adult patients with resistant MuSK MG (N = 25) **Clinical Efficacy** All patients achieved MM or better MGFA PIS. For all patients, after start of rituximab, prednisone was either decreased or withdrawn. Relapse rates were 18.2%, 80%, and 33.3% in Group 1 (protocol: [4+2] RTX), Group 2 (protocol: [1+1] RTX), and Group 3 (protocol [4] RTX) The authors stated that "The Cox proportional-hazards regression model showed that patients treated with protocol 1 + 1 had a higher risk of relapse and a greater need for reinfusion with rituximab than patients treated with protocol 4 + 2 (hazard ratio [HR] 112.8, 95% confidence interval [CI], 5.7–2250.4, *P* = 0.002). Patients treated with protocol 4 also showed a trend to a higher risk of relapse than patients treated with protocol 4 + 2 (HR 9.2, 95% CI 0.9–91.8, *P* = 0.059) (likelihood ratio test = 15.1, *P* = 0.0005)." Page 714 **Adverse effects** During infusion seven patients had mild symptoms (facial paresthesias [1]; fever [1]; skin and mucous itching [1]; mild gastrointestinal symptoms [1]; skin rash [2]; and fatigue [1]) No patients experienced serious adverse effects	The authors mentioned that "In summary, our findings add to the evidence that rituximab is effective and safe in the treatment of MuSK MG. We recommend treating patients with a sole induction regimen of rituximab following the protocol 4 + 2 (375 mg/m2 every week for 4 consecutive weeks and then monthly for the next 2 months), since this protocol ensures a minimal rate of clinical relapse and a long-lasting response to rituximab. To minimize potential adverse events, we recommend re-treating patients with rituximab in cases of clinical relapse only." Page 715
Hehir, [16] 2017, USA	
Adult patients with MuSK MG (N = 55) **Efficacy based on MGSTI** (n = 24 in RTX; n= 31 in C) Percentage of patients with Level 2 or better at end of period: 58% in RTX, 16% in control, (*P* = 0.002). Percentage of patients with Level 1 or better at end of period: 54% in RTX, 6.5% in control, (*P* < 0.001). **Efficacy based on MGFA modified PIS** at final visit (n = 24 in RTX; n= 31 in control) Percentage of patients with MGFA modified PIS MM or better: 67% in RTX, 26% in control (*P* = 0.003); Percentage of patients who are symptomatic: 8% in RTX, 22% in control; Percentage of patients with pharmacologic remission: 3% in RTX, 1% in control; Percentage of patients with complete stable remission: 7% in RTX, 0% in control. **Other outcomes** Percentage of patients wo were hospitalized for MG at any time after time 0: 25% in RTX, 6% in control, (*P* = 0.07). Percentage of patients on prednisone at final visit: 29% in RTX, 74% in control, (*P* = 0.001). Final prednisone dose (mg/d): 4.5 ± 8.1 (median 0) in RTX, 12.7 ± 11.8 (median 10) in control (*P* = 0.005). Percentage of patients on prednisone plus other at final visit: 8% in RTX, 58% in control,(*P* < 0.001). **Comparison between patients receiving multiple courses or single course of RTX** Of the 15 patients on multiple courses of RTX, 73% achieved the primary outcome, whereas of the 9 patients who received a single course, 33% achieved the primary outcome	The authors mentioned that "This study provides Class IV evidence that for patients with anti-MuSK MG, rituximab increased the probability of a favorable outcome." Page 1,076

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td colspan="2">Jing,[17] 2017, China</td></tr>
<tr><td>

Adult patients with refractory generalized MG (N =8)

Efficacy using various outcome measures

Outcome	Time point (month)	Change (mean ± SD)	*P* value
QMG	1	−0.25 ± 1.83	0.711
	3	−3.75 ± 2.87	0.011
	6	−4.63 ± 3.20	0.005
MMT	1	−9.88 ± 10.37	0.031
	3	−19.13 ± 18.11	0.012
	6	−22.00 ± 17.87	0.010
MG-ADL	1	−1.63 ± 2.67	0.129
	3	−4.25 ± 3.81	0.005
	6	−5.00 ± 3.55	0.016
MGQoL-15	1	−4.63 ± 6.63	0.089
	3	−8.63 ± 11.55	0.073
	6	−9.50 ± 12.59	0.070

Laboratory parameters

Parameter	Time point (month)	Change (mean ± SD)	*P* value
$CD19^+$ B cell	1	−9.69 ± 7.28	0.012
	3	−9.64 ± 7.29	0.007
	6	−9.50 ± 7.39	0.008

There were no statistically significant changes in $CD3^+$ T cells, $CD4^+$ T cells, and $CD8^+$ T cells at 1, 3, or 6 months post RTX treatment.
After a 6-month follow-up, serum AChR antibody levels decreased by approximately 50% in 2 patients and did not change notably in the remaining 6 patients

Prednisone and other treatment requirement
All patients had reduction in prednisone doses. At 6 months follow-up, mean reduction in prednisone dose was by 43% (*P* =0.018). No patient required rescue treatment with IVIg, or PEX

Side effects
No allergic reactions or other serious side-effects with RTX were observed during the follow-up period. RTX appeared to be well tolerated by all the patients

</td><td>

The authors mentioned that "[….] 600 mg RTX may be sufficient in depleting B cells, maintaining low B-cell counts and improving the clinical symptoms of refractory generalized MG in 6 months after a single infusion. However, a larger, randomized controlled study is needed to validate our results." Page 19

</td></tr>
<tr><td colspan="2">Landon-Cardinal,[18] 2018, France</td></tr>
<tr><td>

Adult patients with severe refractory generalized AChR MG (N =11); prospective study

Outcomes with RTX

Outcome measure	Results
MMS	The median MMS remained unchanged overtime. MMS (median [range]): 67 (27 to 87) at baseline (M0), and 66 (27 to 95) at M12. Only one patient achieved the primary end-point (≥ 20 points increase in MMS between M0 and M12). Two patients had an increase in MMS of 18.5 and 19, respectively.

</td><td>

The authors mentioned that "In conclusion, this pilot, prospective, phase II study provides data on the effect of RTX in patients with severe, refractory anti-AChR Abs generalized MG. Less spectacular effects of RTX than previously reported were seen in our cohort of MG patients that may be related to our patients' characteristics and reporting bias. Nevertheless, a

</td></tr>
</table>

Main Study Findings	Author's Conclusion
<table><tr><td></td><td>At 18M, the patient who achieved the primary end-point maintained this improvement, and 3 other patients achieved a 20-point increase in MMS</td></tr><tr><td>QMG</td><td>Five patients achieved a ≥ 3 points decrease in QMG score between M0 and M12 Between M12 and M18, 5 patients achieved ≥ 3 points decrease in QMG score</td></tr><tr><td>MGFA-PIS</td><td>MGFA-PIS improved in 6 patients, and worsened in 2 patients, between inclusion and M12. Between M12 and M18, MGFA-PIS, improved in 4 patients and worsened in 2 patients.</td></tr><tr><td>FVC</td><td>At M12, % change in FVC (mean [range]) was -3 (-12 to +8).</td></tr><tr><td>SF-36</td><td>At M12, the SF-36 physical and mental component summary scores (median) remained stable at 40 (range: 25 to 55) and 32 (range: 24 to 51), respectively. The physical functioning norm based score improved (median [range]: 50 [25 to 95])</td></tr></table> **Changes in other treatments** Following RTX treatment, 45% of the patients needed other treatments such as increase or initiation of immunosuppressants, IVIg, or plasmapheresis. The patient, who achieved the primary end-point at M12, had no change in prednisone and immunomodulatory treatments. Of the 3 patients who achieved MMS ≥ 20 points at M18, 2 patients had no change in their treatments, and one patient needed intermittent IVIg treatment. **Antibody titer** There was some improvement in AChR antibody titer (nmol/L), expressed as median (range): 49.15 (0.64 to 100 at baseline, and 30.85 (0.51 to 100) at M12. **Adverse events** One patient withdrew from the study after the second RTX infusion, and later at 15 months died of severe cardiac failure. No other patients withdrew from the study. During the study period, 6 infectious adverse events occurred: 2 non-febrile flu-like syndromes, 1 viral gastroenteritis, 2 cutaneous infections and 1 herpes zoster infection. No serious adverse event occurred during RTX infusion. (***Note:*** M0, M12, M18 indicate time points, baseline, 12 months, and 18 months respectively.)	beneficial effect of RTX on muscle function was seen at M18 in a third of patients with long-standing disease duration." Page 248
Memon,[19] 2018, USA	
Adult patients with MG (N =3); retrospective study **Adverse events** Infections occurred in 75% of the patients. No serious adverse events occurred. No malignancy occurred.	The authors mentioned that "In summary, we report long-term safety of rituximab in PIMND. Rituximab was well tolerated over time. AE and SAEs remained low throughout the observation period. Patients remained clinically stable while receiving continuous rituximab infusions. Although this is small study, nevertheless, it makes

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td></td><td>important contributions to a number of growing data documenting the long-term tolerability and efficacy of rituximab as a viable option for the treatment of PIMND. Larger, prospective, multicenter studies are still needed to further corroborate long-term safety and tolerability of rituximab and other B-cell depleting agents in treating PIMND." Page 7 and 8 of 9.

(Note: PIMND = patients with immune-mediated neurological disorders [such as neuromyletis, optica, multiple sclerosis, and MG].)</td></tr>
<tr><td colspan="2">Peres,[20] 2017, Portugal</td></tr>
<tr><td>Adult patients with refractory or severe MG (N = 6); retrospective study

Outcomes with RTX<table><tr><th>Outcome measure</th><th>Findings</th></tr><tr><td>MGCS</td><td>Decrease in MGCS score after first cycle of RTX, and even greater decrease at the final evaluation; 36% and 53% respectively, P = 0.028.</td></tr><tr><td>MGFA-PIS</td><td>After RTX treatment, all patients were classified as "improved". This level was based on clinical improvement and/or reduction of MG medications.</td></tr><tr><td colspan="2">QoL</td></tr><tr><td>EQ-5D</td><td>After RTX treatment, change in EQ-5D score was +0.492, suggesting improvement in QoL</td></tr><tr><td>VAS</td><td>After RTX treatment, change in VAS score was +48.3, suggesting improvement in QoL</td></tr><tr><td>MG-QoL15</td><td>After RTX treatment, change in MG-QoL15 score was -20, suggesting improvement in QoL</td></tr></table>Changes in other treatments
After RTX treatment there was a decrease in the number of immunosuppressors needed. On average, the number of drugs needed per patient was 2.2/ patient before RTX, 1.5/patient after the first RTX cycle, and 1.2/patient at the final evaluation (P = 0.012).

Five of the 6 patients were on prednisone. After RTX treatment there was a 53% reduction in dose from on average of 23.5 mg/day to 13 mg/day (P = 0.047).

On average, after RTX treatment there was an 83% decrease in the number of treatments with PEX or IVIg (P = 0.027).

Overall, after RTX treatment there was a 90% decrease in short term treatments (P = 0.003)</td><td>The authors mentioned that "Rituximab is a clinical effective treatment for B cell-related diseases like MG and seems to be a cost–saving intervention. Its use is associated with a decrease in the need for other immunosuppressive treatments whilst improving quality of life and reducing health costs." Page 1 of 5

Furthermore, the authors mentioned that "Although our results in terms of clinical response, quality of life and cost–utility, favour the use of rituximab, they would need further investigation in a prospective, controlled manner." Page 4 of 5</td></tr>
</table>

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td>

Side effects
Two patients had major secondary effects associated with RTX (sustained hypogammaglobulinemia in one patient, and a macrophage activation syndrome in one patient). Two patients had minor side effects (one patient had recurrent respiratory tract infections but did not require hospitalization, and one patient had infusion reaction during the first infusion which later subsided)

Cost utility analysis (using data from the 6 patients in the study)

<table>
<tr><th rowspan="2">Parameter</th><th colspan="2">Parameter value for</th><th rowspan="2">Change in parameter</th><th rowspan="2">Findings</th></tr>
<tr><th>year before RTX treatment</th><th>year after RTX treatment</th></tr>
<tr><td>Average EQ-5D score</td><td>-0.047</td><td>0.444</td><td>0.492</td><td>Increase in QoL</td></tr>
<tr><td>Average cost per patient (€)</td><td>20,211</td><td>17,968</td><td>2,243</td><td>Decrease in cost</td></tr>
<tr><td colspan="5">Note: Health care costs were estimated based on the average of each treatment and daily charge of hospitalization</td></tr>
<tr><td colspan="5">Conclusion: Treatment with RTX appeared to be a cost-saving intervention in these patients, at least during the first year</td></tr>
</table>

</td><td></td></tr>
<tr><td colspan="2">Robeson,[21] 2017, USA</td></tr>
<tr><td>

Adult patients with refractory generalized AChR MG (N = 16); retrospective study

Clinical outcomes
Remission
In all patients, improvement in clinical status was observed in parallel with complete withdrawal or reduction of other immunotherapies.
After completing the initial RTX cycles, based on MGFA PIS criteria 10 (63%) patients achieved complete stable remission, 3 (19%) achieved pharmacologic remission, and 3 (19%) achieved MM-0 (minimal manifestation but no therapy for MG).

Relapse

<table>
<tr><th>Parameter</th><th>Patient subgroups</th><th>No of patients</th><th>Outcome</th></tr>
<tr><td rowspan="2">Time to relapse (months)</td><td>Follow-up > 48 m</td><td>12</td><td>8 patient experienced relapse at mean FU 37 (range: 29 to 47); and
4 patients had no relapse up to mean FU 66 (range: 51 to 81)</td></tr>
<tr><td>Follow-up < 48 m</td><td>4</td><td>1 patient had a relapse at 24 months; and
3 patients had no relapse up to mean FU 22 (range: 18 to 24)</td></tr>
<tr><td rowspan="2">Relapse rate</td><td>Thymectomy > 12 months before starting RTX</td><td>NR</td><td>67%</td></tr>
<tr><td>Thymectomy < 12 months before starting RTX</td><td>NR</td><td>57%</td></tr>
</table>

</td><td>The authors mentioned that "Rituximab therapy appears to be an effective option in patients with refractory AChR+ MG, who were observed to have a durable response after treatment. Identification of markers of disease relapse and sustained remission are critical next steps in the development of pathophysiology-relevant, evidence-based practice parameters for rituximab in the treatment of MG." Page 60</td></tr>
</table>

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td>

AChR antibody levels

Time period	Antibody levels (calculated considering antibody level as 100% before RTX treatment)	*P* value
After cycle 1 of RTX	67%	0.004 (pre RTX vs post cycle 1
After cycle 2 of RTX	47%	0.008 (post cycle 1 vs post cycle 2)
After cycle 3 of RTX	30%	0.02 (post cycle 2 vs post cycle 3)

Other
Levels of cytokines (IL-4, IL-5, IL-6, IL-10, IL-17A, IL-17F, tumor necrosis factor, and interferon gamma) measured were below the level of detection, indicating that their levels in serum were not elevated due to treatment.

Adverse effects.
No infusion reactions were observed. One patient developed leukopenia after the second cycle of RTX but it was resolved without intervention. Treatment was stopped in one patient due to unplanned pregnancy during the second rituximab cycle. However the patient had an uncomplicated pregnancy and delivery.

</td><td></td></tr>
<tr><td colspan="2">Stieglbauer,[24] 2017, Austria</td></tr>
<tr><td>

Adult patients with refractory MG (N = 4); retrospective study

Efficacy
In all patients, the QMG score improved after RTX treatment. QMG score before RTX was in the range 7 to 20, and since RTX treatment the most recent QMG score was in the range 0 to 5. Three patients had sustained clinical improvement after RTX and did not need other immunosuppressive drugs. The fourth patient had complete remission and within a few months of RTX treatment, steroids could be stopped.

Pregnancy
Two patients who had not received RTX > 12 months before becoming pregnant, had uncomplicated pregnancies and each delivered a healthy baby.

Hospital admission
The DRG-MG score following rituximab treatment was lower than the score before rituximab treatment, indicating a reduction in costs of in-patient hospital care in the patients. DRG-MG score ranges before and after rituximab treatment were respectively 2,132 to 7,118, and 625 to1,003.

Adverse effects
Rituximab was reported to be well tolerated. There were no side effects except two patients occasionally experienced headaches.

</td><td>The author's mentioned that "In conclusion, the 10-year outcomes of our MG patients following RTX initiation are encouraging. [….]. Multicentre trials and prospective registries may further elucidate long-term safety and efficacy of RTX, and in particular its potential future role in early treatment of MG." Page 243</td></tr>
<tr><td colspan="2">Sudulagunta,[25] 2016, India</td></tr>
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Adult patients with refractory MG (N = 42); retrospective study

Prednisone use
Of the 42 patients, 39 patients were on prednisone. All 39 patients showed a reduction in prednisone dose after 3 cycles of RTX, with 3 patients completely tapered off. The dose of

</td><td>The author's mentioned that "Rituximab is very efficient in treatment of refractory MG with adverse effects being low." Page 13 of 15</td></tr>
</table>

Main Study Findings	Author's Conclusion
prednisone administered was decreased by mean values of 59.7%, 87.9%, and 94.6% after the first, second, and third cycles of RTX, respectively. **Plasma exchange** Of the 42 patients, 36 patients received plasma exchange. For these patients there were a statistically significant reductions in plasma exchange sessions after the first, second, third, and fourth cycles of RTX; the respective *P* values being 0.0029, 0.0008, 0.0021, and 0.0023. Of these 36 patients, plasma exchange was no longer required in 20 patients after first cycle of RTX, in 10 patients after second cycle of RTX, in 4 patients after the third of RTX; and two patients continued to require plasma exchange. **Other drug use** In 7 patients there was reduction and eventually stoppage of mycophenolate mofetil from a maintenance dose of 1.5 g/day In 3 patients, azathioprine was stopped following 3 cycles of RTX, but 5 patients continued to use azathioprin. **Antibody titer** For 10 patients antibody titers were available and it was found that there was a statistically significant reduction in antibody levels after each RTX cycle, the respective *P* values for each of the RTX cycles being 0.05, 0.049, 0.039, and 0.048. **Adverse effects** Adverse reactions were reported by 15 patients. The most common adverse reactions being pruritis and flushing, flushing and shortness of breath, and chills/rigors. Less frequent adverse effects were chest pain (1 patient), leucopenia (4 patients), and deranged liver function test results (5 patients). However, all patients continued to use RTX either with slow infusion, or restarting at a later time. There were no deaths due to adverse effects	

ab = antibody; ab+ = antibody positive; AChR = acetylcholine receptor; AE = adverse event; C = control; CI = confidence interval; CSR = chronic stable remission; DRG-MG = Diagnosis Related Group score of hospital admissions related to MG; FVC = forced vital capacity; g = gram; FU = follow-up; IL = interleukin; IVIg = intravenous immunoglobulin; mg = milligrams; MG = myasthenia gravis; MG-ADL = MG-related activities of daily living;; MGFA = Myasthenia gravis Foundation of America ; MGFA PIS = Myasthenia gravis Foundation of America post-intervention status; MG-QoL = MG –specific quality of life ; MM = minimal manifestation; MMS = myasthenic muscle score; MMT = manual muscle testing; MuSK = muscle specific tyrosine kinase; NR = not reported; OR = odds ratio; PIS-m = post-intervention scale – modified; PE, PEX or PLEX = plasma exchange; PR = pharmacologic remission; QMG = quantitative myasthenia gravis; QoL = quality of life; RTX = rituximab; SAE = serious adverse event; SD = standard deviation; SF-36 = short form 36; SN = seronegative; VAS = visual analog scale; vs = versus

Appendix 5: Guideline Recommendations

Table 11: Recommendations in Guideline

Evidence	Recommendations
Sanders,[22,26] 2016, USA	
Case reports and small case series studies suggest that patients with MG, especially those with MuSK MG improve after rituximab treatment. It was reported in the literature that of 70 patients with MuSK MG (majority refractory), only 3 (i.e., 4.3%) patients failed to improve after rituximab treatment. There were no reports of severe side effects. Several reports have suggested that rituximab appeared to produce a more sustained response in MuSK MG patients than in AChR MG patients	1. Consensus guidance t statement as presented by the authors: "Patients with refractory MG should be referred to a physician or a center with expertise in management of MG. In addition to the previously mentioned IS agents, the following therapies may also be used in refractory MG: a. Chronic IVIg and chronic PLEX (see IVIg and PLEX, no. 6); b. Cyclophosphamide; c. Rituximab, for which evidence of efficacy is building, but for which formal consensus could not be reached." Page 21 in Sanders et al. 2016. (Panel votes for this guidance statement: Median = 9, range = 7 to 9) 2. Consensus guidance statement as presented by the authors: "Rituximab should be considered as an early therapeutic option in patients with MuSK-MG who have an unsatisfactory response to initial immunotherapy." Page 24 in Sanders et al. 2016. (Panel votes for this guidance statement: Median = 9, range = 4 to 9)

IS = immunosuppressive; IVIg = intravenous immunoglobulin; MG = myasthenia gravis; MuSK = muscle-specific tyrosine kinase; PLEX = plasma exchange