AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence Status Report: rituximab for the treatment of myasthenia gravis (adults)
April 2019

KEY FINDINGS

Report background
Myasthenia gravis is an autoimmune disorder of the neuromuscular junction whereby normal communication between neurons and muscles is disrupted. This disruption results in muscle weakness and is characterised by a range of symptoms depending on the muscle groups affected. Myasthenia gravis can become refractory to standard treatments for a proportion of people and they may rely on regular intravenous immunoglobulin and plasma exchange to alleviate symptoms. In 2018 NHS England supported the commissioning of rituximab biosimilar for the treatment of refractory myasthenia gravis in adults. This use of rituximab is currently off-label. Clinicians in Wales consider there is an unmet need and have identified a cohort of people who could benefit from this treatment. This medicine was therefore considered suitable for assessment via the One Wales process.

Efficacy/Effectiveness
The evidence of clinical effectiveness of rituximab to treat myasthenia gravis (adults) comes from phase II studies, retrospective case studies, prospective case studies and systematic reviews. Despite the various dosing schedules and outcome measures used, the studies presented here mostly indicate that rituximab is efficacious in the treatment of myasthenia gravis. Specifically, two phase II studies showed improvements in terms of steroid-sparing effect and myasthenia gravis functional scores. A number of case studies, both retrospective and prospective, showed improvements in a variety of outcome measures. These include improvements in steroid-sparing effect, decreased need for treatments such as plasma exchange, duration of response to rituximab, functional scores, achieving pharmacological or complete stable remission. Across studies, people with muscle-specific kinase receptor positive myasthenia gravis appear to gain the greatest benefits from treatment. However there were some people, mostly with acetylcholine receptor-positive myasthenia gravis, who did not benefit from rituximab treatment.

Safety
No new safety concerns have been observed for rituximab to treat myasthenia gravis.

Patient factors
Rituximab is administered by intravenous infusion. Different doses and regimens have been used to treat myasthenia gravis.

Cost effectiveness
No cost-utility analyses have been published comparing rituximab with alternative therapies. A retrospective study on 10-year outcomes for four people suggested that the probability of myasthenia gravis-related hospital admissions could be substantially reduced when people received rituximab. A second retrospective study showed a gain of 0.452 quality adjusted life years following rituximab treatment.

Budget impact
Specialist clinicians consulted by AWTTC estimate that three people in Wales per year would be likely to be eligible to receive rituximab in this setting. It is assumed that people would remain on treatment for at least three years. This is associated with an annual cost of [confidential data removed], which is highly dependent upon the treatments displaced, relative efficacy of rituximab and which rituximab product is used (biosimilar or reference product). The budget impact is therefore subject to significant uncertainty.

Welsh commercial access agreements
This medicine is currently not licensed for the indication under consideration (i.e. off-label) and therefore as the Pharmaceutical Industry's code of practice prevents a company from promoting an off-label use of a medicine, a commercial agreement cannot be offered by the company.

Impact on health and social care services
The impact is expected to be minimal, considering the small numbers of people needing treatment.

Innovation and/or advantages
Rituximab represents an alternative treatment option for those people who have failed on standard oral immunosuppressants and would otherwise be eligible for more invasive and potentially more costly regimens including intravenous cyclophosphamide, intravenous immunoglobulins and plasma exchange.

BACKGROUND

Target group

The indication under consideration is fourth-line or later treatment of refractory myasthenia gravis (MG) in adults after failure of /intolerance to earlier lines of treatment which will include: anticholinesterases, corticosteroids and first-line immunosuppressive drugs (mycophenolate, azathioprine and methotrexate). There should be a lower threshold to consider rituximab in people with muscle specific kinase receptor (MuSK) positive MG who also have bulbar disease (characteristic of this form of the condition), who respond poorly to intravenous immunoglobulin or plasma exchange, or who demonstrate poor tolerability to immunosuppression[1].

Technology

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody that destroys CD20 positive B cells. Rituximab binds specifically to the transmembrane antigen CD20 on pre-B and mature B lymphocytes which mediates B-cell lysis and also induces cell death by apoptosis[2].

Marketing authorisation date

Rituximab is not licensed to treat refractory MG; its use in this indication is off-label. The European patent for rituximab (MabThera®) expired in 2013 and biosimilars are now available.

Dosing

The NHS England Clinical Commissioning Policy on the use of rituximab biosimilar for the treatment of MG (adults) outlines two dosing schedules[1]. All rituximab doses are administered by intravenous infusion. Dosing schedule A recommends 1,000 mg rituximab followed by a second 1,000 mg dose two weeks later[1]. Dosing schedule B recommends 375 mg/m^2 body surface area, administered once weekly for four weeks (four infusions in total)[1]. Rituximab requires either two or four admissions (day-case) per course (every six months) with most people responding by 36 months on average[1]. Dosing schedule B was used in the BeatMG phase II clinical trial of rituximab in MG and is frequently found within published studies[3,4]. However, there is wide variability in dosing protocols found within published literature with others using different rituximab concentrations and/or different administration schedules[5,6].

Specialist clinicians consulted by AWTTC have used the rheumatology protocol, which is equivalent to dosing schedule A[7]. Corticosteroids and antihistamines are given at the same time.

Clinical background

MG is an autoimmune disorder of the neuromuscular junction[8]. In MG, antibodies targeting components of the neuromuscular junction, such as acetylcholine receptors (AChR) and MuSK receptors located at the post-synaptic muscle membrane, are generated and disrupt normal communication between neurons and skeletal muscles[8]. Without proper neuronal-muscle communication, muscle weakness results and is characterised by a range of symptoms, depending on which muscle groups are affected[8]. MG muscle weakness is aggravated after activity and improved after rest but, after onset, symptoms do progress over time[9]. The muscle groups most commonly affected are those responsible for eye and eyelid movement (which can be affected early), facial expression, chewing, talking, swallowing, breathing control, neck and limb movements[9]. Myasthenic crisis may be experienced by approximately 15–20% of people where exacerbation of symptoms is so severe as to necessitate the use of mechanical ventilation[10].

MG is a heterogeneous condition and the variations in clinical presentation and autoantibody presence allow MG to be categorised into subtypes which both guides the therapeutic approach and informs individual prognosis[4,8]. Muscle weakness confined to the ocular muscles defines the less severe ocular form of MG (15% of people) and if this presentation remains stable for 2–3 years, it is unlikely that the disease will become more generalised[1,8]. The more generalised form of MG may also affect bulbar and proximal skeletal muscles. Antibodies to AChR are present in 85% of all people[4,11]. The remainder of people either have antibodies targeting MuSK receptors (7.5% of people), antibodies targeting other components of the neuromuscular junction (for example lipoprotein receptor-related protein [1–2%]) or are seronegative[4].

The prognosis for people with MG is generally good in relation to quality of life, muscle strength and functional abilities[8]. The goals of therapy are symptomatic improvement followed by full or nearly full pharmacological remission (the absence of MG symptoms and signs while receiving therapy)[8]. Myasthenic exacerbations or relapse can occur due to stressors such as infection, surgery and pregnancy, however myasthenic crisis can sometimes be averted with early intervention[4,10]. With advances in diagnosis and treatment, and with optimal care, mortality is rare and the majority of people lead normal lives[10].

For the small group of people with refractory MG, in contrast to the above, this group is likely to experience a decrease in quality of life, they may require hospitalisation for potentially lethal exacerbations, and the disease is associated with a considerable financial burden[9].

Incidence/prevalence

Annual incidence of MG is 0.3 to 2.8 new cases per 100,000 people with a mean of 1 new case per 100,000 people[12]. There is some variability in the literature but this is a broad approximation. Annual incidence has been rising but this can be partially attributed to improvements in diagnosis, an aging population and a longer lifespan[13,14]. In Wales this incidence rate would equate to 32 new cases of MG per year, while 3–5 of these new cases (10–15%) may have refractory MG[4]. In terms of prevalence, there are approximately 15 people in 100,000 who have MG[15]. In Wales this would equate to approximately 469 people of the total population, while 47–70 of these people (10–15%) may have refractory MG[16].

Specialist clinicians consulted by AWTTC estimated that only 2–3 people in Wales per year would be likely to be eligible to have rituximab for refractory MG indicating that the usage would be considerably lower when compared with the prevalence of people with refractory MG. These numbers fit with Individual Patient Funding Requests (IPFR) data.

Current treatment options

The Association of British Neurologists' management guidelines for MG published in 2015 recommend first-line treatment with oral pyridostigmine, followed by oral prednisolone for those people not achieving a satisfactory response[17]. For people who do not achieve remission on corticosteroids, or who have significant side effects, an oral immunosuppressant such as azathioprine is recommended. If azathioprine has failed or the patient cannot tolerate it, a second-line immunosuppressive drug such as mycophenolate mofetil, methotrexate, ciclosporin or rituximab may be used[17].

International consensus guidance for management of MG published in 2016 details treatments for MG that remains refractory after the use of standard immunosuppressive medicines[18]. These include plasma exchange or IVIg infusion, cyclophosphamide and rituximab which are listed as second-line immunosuppressant options. As the effects of plasma exchange or IVIg infusion typically last for a short time-frame they should be combined with other treatments such as other immunosuppressive drugs[18].

MG responds well to available immunosuppressive treatment options in about 80% to 85% of people with MG. Those people who have refractory MG (around 15%) are indicated by sub-optimal responses with multiple immunosuppressive therapies, intermittent requirement for IVIg infusions or plasma exchange, or inability to reduce steroid dose without relapse.

Eculizumab is a monoclonal antibody targeting the complement C5 protein and is licensed for use in refractory AChR positive MG[19]. It is the first medicine to be approved for refractory MG. However the marketing authorisation holder has not submitted to the All Wales Medicines Strategy Group (AWMSG) and the National Institute for Health and Care Excellence's appraisal for use in refractory MG has been suspended[20].

A specialist clinician consulted by AWTTC places rituximab after failure of /intolerance to a second immunosuppressant; with the alternative treatment options at this point in the treatment pathway being regular IVIg infusion, courses of cyclophosphamide or plasma exchange.

Guidance and related advice

- NHS England Clinical Commissioning Policy (2018). Rituximab biosimilar for the treatment of myasthenia gravis (adults)[1]
- British Medical Journal Best Practice Guidelines: Myasthenia gravis (2018)[10]
- Myasthenia Gravis Foundation of America. International consensus guidance for management of myasthenia gravis (2016)[18]
- Myasthenia gravis: Association of British Neurologists' management guidelines (2015)[17]

SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

A comprehensive literature search conducted by AWTTC identified two phase II studies, three retrospective case studies, one prospective case study and one systematic review of rituximab to treat myasthenia gravis published since publication of the NHS England Clinical Commissioning Policy in 2018[1]. These together with the relevant studies included in the NHS

England Clinical Commissioning Policy and additional key studies put forward by specialist clinicians consulted by AWTTC, are briefly described below. A table summarising all studies is provided in Appendix 1.

Efficacy

Measures of functionality

Myasthenic muscle scores (MMS) were used in one open label multicentre study (n = 11) as a primary outcome measure at 12 months where median MMS remained unchanged at this time[21]. Manual muscle testing (MMT) scores (assessing muscle strength and function) were used in two prospective open label studies (n = 36) both of which showed statistically significant improvements[6,22]. Most studies used MG Foundation of America post intervention status (MGFA-PIS) scores which include complete stable remission (CSR), pharmacologic remission (PR) and minimal manifestations (MM). One study in people with AChR positive MG (n=11) reported improved MGFA-PIS in six people and a decline in two. MGFA quantitative MG scores (13 item scale used to quantify disease severity) improved in five people [21]. A single centre retrospective case study series (n = 16) reported people with refractory AChR positive MG reaching CSR (n = 10), PR (n = 3) and MM requiring no MG treatment for at least 1 year (n = 3), after an initial rituximab regimen. A total of seven people maintained clinical benefit during a mean follow-up period of 47 months[23]. A retrospective multi-centre study reported improved or better MGFA-PIS in seven of ten people six months after rituximab, and in all of six people 12 months after treatment[24]. A second retrospective multi-centre study reported improvements in PR after three months (for 14 out of 53 people) and at median last follow-up of 20 months (for 24 out of 56 people)[5]. A retrospective study at a single centre found both those with AChR positive (62.5%) and MuSK positive (66.7%) MG had reached a symptom free state 12 months after rituximab treatment[25]. Clinical remission was reached in less time by people with MuSK positive MG compared to those with AChR positive MG[25]. One prospective multi-centre blinded study investigating MuSK positive MG used a novel unvalidated measure of MG severity, MG Status and Treatment Intensity (MGSTI)[26]. MGSTI combines modified MGFA post intervention status and immunosuppressant doses where Level 0 equates to CSR with no immunotherapy and Level 6 people are symptomatic and require hospitalisation with IVIg or PE for MG (within past three months). Authors defined a desirable clinical outcome as an MGSTI of Level 2 or better and 58% of people receiving rituximab achieved this compared with 16% of the control group ($p = 0.002$). Most people receiving rituximab achieved Level 1 (54% compared with 6.5%, $p < 0.001$). When comparing single or multiple courses of rituximab, 73% of those that received multiple courses (n = 15) reached Level 2 whereas 33% of those that received a single course (n = 9) reached it[26].

Relapse

Relapses following rituximab treatment were reported in two retrospective studies and three prospective studies[6,22,23,25,26]. Mean time to first relapse ranged from 17 to 36 months with second relapse reported 13.5 months later on average[6,23]. Following relapse, in one study, response to immunosuppressive therapies including IVIg or PE (n = 7), high dose prednisone (n = 1) or an additional rituximab cycle (n = 4) was reported, with some people receiving more than one therapy[23]. In another study of relapse, frequency was higher for people with AChR positive MG (58.8%) versus MuSK positive MG (37.5%)[25].

Decrease in concomitant and rescue therapies

A number of studies reported a decrease in the use of concomitant and rescue therapies with rituximab treatment, particularly in relation to steroid dose reduction[3,5,6,22-26]. A multicentre randomised, double-blind, placebo controlled phase II study (n = 52) found a statistically significant reduction in steroid use compared with placebo[3]. A retrospective study found that

people with AChR positive MG (13 out of 16) who were able to taper and discontinue all other immunosuppressive therapies were able to do so in a mean of 8.3 months since last rituximab treatment with a minimum of two cycles appearing to be needed (spanning a timeframe of one year)[23]. A second retrospective study (n = 14) found that mean prednisone dose lowered statistically significantly from baseline (20 mg/day) by both six (12.5 mg/day) and then 12 months (5 mg/day) following rituximab treatment[24]. A third retrospective study found that prednisone was tapered by at least 50% at last follow-up compared with baseline in 10 people and was discontinued in 23 (n = 39)[5]. A further retrospective study found that the mean prednisone dose requirement decreased for both those with MuSK positive MG or AChR positive MG. The maintenance dose required for IVIg or PE however was reduced in only those with MuSK positive MG and this group also required rescue therapy less frequently[25]. A prospective study investigating MuSK positive MG found that, at follow-up, 29% (n = 24) of people receiving rituximab were taking prednisone compared to 74% of the control group (n = 31)[26]. A second prospective study (n = 22) found there was a significant daily reduction in prednisone dose from 25.2 ± 15.1 mg/day to 7.3 ± 7.1 mg/day. Furthermore, four out of nine people with MuSK positive MG, one out of ten people with AChR positive MG and two out of three people with seronegative MG had discontinued all immunosuppressive therapies at last follow-up[6].

Quality of Life

One open label multicentre study which showed that rituximab was efficacious in refractory MG (n = 11) also reported quality of life measures using Rand Medical Outcomes Study 36-Item Short-Form Health Survey scores[21]. While median physical and mental components remained stable over a 12 month timeframe, physical functioning improved from a baseline median (range) score of 38 (0–70) to a score of 50 (25–95)[21].

MuSK positive and AChR positive MG

A number of studies presented outcome results specifically comparing MuSK positive and AChR positive MG[5,6,22,24,25]. MuSK positive MG was more responsive to rituximab treatment in three studies reporting a variation of outcomes including increased remission frequency; shorter time to clinical remission; lower relapse rates and requirement for rescue therapies; greater improvements in functional scores and more frequent tapering of concomitant therapies. Responses were seen for AChR positive MG, and were at times also significant, but were often not as great compared with MuSK positive MG[6].

Rituximab to treat refractory MG: systematic review

A systematic review identified 28 single case reports and 19 multi-case reports (n = 169) when investigating the use of rituximab in refractory MG and found it appeared to be a safe and effective therapy[27]. People were either AChR positive (n = 99), MuSK positive (n = 57), seronegative (n = 7), seropositive for multiple antibodies (n = 4) or antibody status unknown (n = 2). The dosing protocol used most was NHS England Clinical Commissioning Policy schedule B (n = 135) however non-standardised protocols were also used[1]. Clinical improvement was measured differently across the reports included and used at least one or more of MGFA PIS, an endpoint which combined CSR and PR grades (CSR-PR) and quantitative MG scores. MM or better was achieved by 44% of people and CSR-PR was achieved by 27%. A statistically significant greater proportion of people with MuSK positive MG achieved MM or better when compared with people with AChR positive MG ($p < 0.001$). This was also the case for CSR-PR ($p < 0.001$). A significant reduction in the number of people who had a MG relapse after rituximab treatment was in both serotype groups ($p < 0.001$), more relapses were seen for AChR positive people (33%) compared with MuSK positive people (14%) ($p = 0.05$). Pharmacokinetic data suggested that repeat dosing in people with either an incomplete response or relapse should be considered 4–6 months after first receiving rituximab. Authors suggest rituximab may be especially useful for MuSK positive MG[27].

A further systematic review identified 37 uncontrolled observational studies, 15 of which were used for meta-analysis (n = 168) and reported an overall response rate of 83.9% with rituximab treatment for MG (the majority of which was refractory)[11]. People were either AChR positive (n = 91), MuSK positive (n = 70) or seronegative (n = 7), response rate was highest in MuSK positive people, although the difference between serotype groups was not significant. The dosing protocol used most was NHS England Clinical Commissioning Policy schedule B (n = 137) however non-standardised protocols were also used[1]. Authors suggest the analysis justifies the use of rituximab at the maximum tolerated dose in people with refractory MG[11].

Safety

Adverse events associated with rituximab, reported in ≥ 1 in 10 people, include bacterial and viral infections, neutropenia, leucopenia and thrombocytopenia, infusion related reactions, nausea, pruritis, fever, headache and decreased immunoglobulin G levels[2]. Cases of hepatitis B reactivation have been reported in people receiving rituximab; screening should be performed in all people prior to treatment[2]. A drug safety alert was issued in 2014 following cases of progressive multifocal leukoencephalopathy (PML), this is listed as a very rare adverse event in the Summary of Product Characteristics[28]. The risk of PML may be increased with increased use of immunosuppressive drugs[29].

In the studies evaluated in this report, and for which information was provided, adverse events were mostly infections (such as herpes zoster and upper respiratory tract infections) as well as infusion related reactions. Other adverse events reported included headaches, facial paraesthesia, fatigue and chronic pain. Across the thirteen published studies and the one as yet unpublished phase II study included in this report, serious adverse events were reported in two of these studies. Tandan et al. (2017) reported adverse events in 14% of people for whom data were available, some of these included serious adverse events specifically myocardial infarction, however it is not clear whether this was due to rituximab or an infusion related reaction[27]. Yale University (2018) reported individual instances of serious adverse events including leucopenia and septic shock in rituximab treated people (36% of this group). More serious adverse events were experienced in the control group overall (51.9% of this group)[30]. However, there was no significant difference in treatment related adverse events ($p = 0.63$) or serious adverse events ($p = 0.65$) between rituximab treated and control groups[30]. Doughty et al. (2018) who studied older people (aged > 65) had five people experience serious adverse events (unspecified) however none of the people discontinued the use of rituximab due to these effects. Across the studies evaluated for this report there were five deaths during follow up but the authors of these studies considered in each case that the death could not be attributed to rituximab[5,21,24].

An additional retrospective study investigating the long term safety of rituximab treatment over three years or longer found that rituximab was well tolerated without any serious infusion reactions and beneficial in treating people with immune mediated neurological disorders (n = 29) including MG (n = 3)[31]. A total of 32 infections were reported, two occurring in MG people. Of four infections considered to be serious adverse events (pneumonia, urinary tract infection and sinusitis) none were reported in MG people. No cases of PML or malignancy were observed. A further retrospective study evaluating pharmacoeconomic and quality of life benefits of rituximab use in MG people (n = 6) found serious adverse events in two people, one with sustained hypogammaglobulinemia and one with macrophage activation syndrome. Both people were still receiving two immunosuppressants and clear clinical causation was not established in the latter case. Minor adverse events were reported in two people; one had recurrent respiratory tract infections and the other experienced an infusion reaction during first infusion[32].

Clinical effectiveness issues

- There is currently no single recommended dose of rituximab or treatment protocol to treat myasthenia gravis. The evidence from phase II studies, retrospective case studies and prospective studies include different doses of rituximab given in different treatment protocols. One study (n = 25) found that an alternative dosing protocol (375 mg/m^2 rituximab given once weekly for four weeks then monthly for two months) provided the lowest relapse rate to people with MuSK positive MG when compared with both of the earlier described NHS England Clinical Commissioning Policy advised protocols[1,33]. Advice from clinical experts in Wales indicates that schedule A is mainly used in practice.
- The studies were varied in terms of study design, methodology (for example, relating to measurement of outcomes), and patient cohorts including medications taken prior to starting rituximab and those allowed while taking rituximab.
- The studies did not raise any new safety concerns associated with the use of rituximab in this patient group.
- Rituximab was shown in some studies to be most efficacious for people with MuSK positive MG and this is supported by clinical expert opinion[5,11,25,27].
- In addition to significant clinical improvement, rituximab also allowed for tapering and subsequent discontinuation of other immunotherapies in both AchR positive and MuSK positive MG[34]. The beneficial effect, although durable, is not permanent, given that post rituximab relapses have been observed[34].
- The durability of alternative treatments, specifically plasma exchange and IVIg infusion, is temporary. Plasma exchange provides a rapid response to treatment, within 2–3 sessions, however improvement rarely lasts longer than 4–10 weeks[10,35]. Likewise for IVIg, a response can occur within 4–5 days with effects lasting weeks[10].
- MG is heterogeneous and so the generalisability of RCTs is limited, with uncontrolled trials limited by bias[18].

SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

Cost-effectiveness evidence

No cost-utility analyses have been undertaken comparing rituximab to alternative therapies. One retrospective study has evaluated the impact of rituximab on health-related Quality of Life using the clinical notes of 6 people and applying these to the EQ-5D-3L[32]. However, this study used a before-after design without a comparator patient group. The findings of a gain of 0.492 QALYs in the post rituximab treatment commencement period are therefore associated with considerable limitations. The lack of comparator prevents identification of temporal effects and a measure of the true magnitude of effect that may be attributed to rituximab[32].

The Stieglbauer et al. (2017) paper reports on 10-year outcomes for four women receiving rituximab for MG in Austria[36]. It included a retrospective analysis of costs of hospital care associated with MG using a surrogate marker (diagnosis related groups score of hospital admissions related to MG) that looked at costs of in-hospital care for each individual in the year before and years after treatment with rituximab. People received rituximab at a dose of 375mg/m^2 every week for two consecutive weeks; monitoring of B cell counts was used to guide re-treatment. The analysis reports that the diagnosis related groups scores in the years after starting treatment with rituximab were two to ten times lower compared to the score in the year prior to commencing rituximab. The authors suggest that the probability of MG-related hospital admissions can be substantially reduced when people are treated with rituximab. However, these conclusions are limited by the small number of people and the study design (before-after, no control)[36].

BUDGET IMPACT

In the published studies the rituximab regimens varied. For simplicity, dosing schedule A, equivalent to the rheumatoid arthritis regimen has been used and repeated at six months[1,2]. Due to the heterogeneity of MG and the range of comparable (unlicensed) treatments, assumptions based on potential treatment pathways were made (outlined in table 2). Medicine and administration costs for rituximab regimens and comparators are shown in Table 1. Clinical experts estimate that three people will be eligible for treatment with rituximab in Year 1, with three additional people eligible in each subsequent year. It is assumed that people remain on treatment for three years.

Table 1. Estimated annual acquisition costs in Wales

Regimen/Medicine	Treatment cost	Administration cost	Total annual cost per patient	Source
Schedule A. Rituximab (MabThera®) or rituximab biosimilar (Truxima®): four 1,000 mg doses (2 cycles)*	¶¶	£1,252	¶¶	National Schedule of Reference Costs (HRG codes SB14Z and SB15Z) for administration[37]
Schedule B. Rituximab (MabThera®) or rituximab biosimilar (Truxima®): eight 375 mg per m^2 body surface area† (2 cycles)*	¶¶	£2,409	¶¶	National Schedule of Reference Costs (HRG codes SB14Z and SB15Z) for administration[37]
Plasma exchange: 28 per year (corresponding to 4 cycles per year)§	£40,225	NA	£40,225	National Schedule of Reference Costs (HRG codes SA14Z and SA16Z)[37].
IVIg (Gammaplex®): 4 cycles ¶	£26,752	£5,975	£32,727	BNF costs for immunoglobulin product (infusion). National Schedule of Reference Costs (HRG codes SB14Z and SB15Z) for administration[37].
Cyclophosphamide: 500 mg per m^2 body surface area† (monthly cycles for 6 months followed by 1 cycle every other month)	£161	£2,651	£2,812	BNF costs for cyclophosphamide. National Schedule of Reference Costs (HRG codes SB14Z and SB15Z) for administration[37].

* Summary of product characteristics[2]
† 1.79 m^2 average body surface area[38]
§ One cycle is equivalent to five plasma exchanges as per Nottingham University Hospitals NHS Trust protocol for plasma exchanges, four cycles is equivalent to max of 28 plasma exchanges[39].
¶ One cycle is given over two to five consecutive days dependent upon patient co-morbidities, four cycles is equivalent to between 8 and 20 infusions per year. These costs reflect four cycles given over five days at a total dose of 2 g/kg per cycle[40]. Assumed average patient weight is 76.9 kg[41].
¶¶ Confidential figure removed
BNF: British National Formulary; IVIg: Intravenous Immunoglobulin

Table 2 shows a range of potential treatment scenarios with comparators versus rituximab (Schedule A) and the net cost over three treatment years. Scenarios reflect a combination of clinical expert opinion and the studies used in the clinical efficacy section. In scenario 1, in the comparator arm, three people start cyclophosphamide each year and move to a rescue treatment (IVIg) in the following year, in year three this means three people would receive

cyclophosphamide while six people would be receiving IVIg. This scenario assumes that rituximab treatment is tolerable and efficacious for people and that most would remain taking it over a three year timeframe. The possibility that it is not tolerable/efficacious for all people is accounted for in year three whereby one patient discontinues rituximab and uses a rescue treatment (IVIg) instead. Scenario 2 assumes plasma exchange as the treatment option after cyclophosphamide rather than IVIg as the comparator. Scenario 3 assumes that a lower number of IVIg cycles are needed per year. Based on acquisition costs reducing the number of plasma exchanges per year would not affect the overall budget impact and therefore this has not been included as a potential scenario.

Table 2. Potential treatment scenarios (Schedule A rituximab)

	Year 1	Year 2	Year 3
Number of people eligible for treatment	**3**	**6**	**9**
Scenario 1: Rituximab treatment over three years with one person discontinuing rituximab and requiring a rescue treatment in year three (four cycles of IVIg per year) *versus* cyclophosphamide treatment in first year moving to rescue treatment (four cycles of IVIg per year) in subsequent years			
Total costs for cyclophosphamide/IVIg (Gammaplex®)	£8,437	£106,619	£204,801
Total costs for rituximab (Truxima®)*	¶¶	¶¶	¶¶
Net cost per year	¶¶	¶¶	¶¶
Scenario 2: Rituximab treatment over three years with one person discontinuing rituximab and requiring a rescue treatment in year three (four cycles of PE per year) *versus* cyclophosphamide treatment in first year moving to rescue treatment (four cycles of PE per year) in subsequent years			
Total costs for cyclophosphamide/PE	£8,437	£129,113	£249,789
Total costs for rituximab (Truxima®)*	¶¶	¶¶	¶¶
Net cost per year	¶¶	¶¶	¶¶
Scenario 3: Rituximab treatment over three years with one person discontinuing rituximab and requiring a rescue treatment in year three (four cycles of IVIg per year) *versus* cyclophosphamide treatment in first year moving to rescue treatment (two cycles of IVIg per year) in subsequent years			
Total costs for cyclophosphamide/IVIg (Gammaplex®)	£8,437	£57,528	£106,619
Total costs for rituximab (Truxima®)*	¶¶	¶¶	¶¶
Net cost per year	¶¶	¶¶	¶¶
*Including cost of rescue treatment ¶¶ Confidential figure removed IVIg: Intravenous Immunoglobulin; PE: Plasma exchange			

Budget impact issues

- Rituximab biosimilar NHS Wales contract costs have been used in the calculation. Costs will be higher for use of the reference product.
- The budget impact has not taken into account mortality rates. It is assumed that 100% of people respond to treatment with rituximab and require no rescue treatments and that no patient discontinues treatment due to adverse effects/inadequate treatment response in the first two years of treatment.
- In the comparator arm it is assumed that all people are eligible for, and tolerate, treatment with cyclophosphamide (monthly for six months then every other month for

six months). Based on potential side effects only one course of cyclophosphamide would be used in practice. It is also assumed that rituximab is being used as an alternative to cyclophosphamide but in practice some of these people may already have previously received cyclophosphamide treatment.

- Based on the small number of people and for simplification, scenario analyses consider all people receiving subsequent treatment with either IVIg or plasma exchange; although it is possible that these two treatments may be used more interchangeably.
- Adverse event rates have not been included in the budget impact.

Welsh commercial access agreement

This medicine is currently not licensed for the indication under consideration (i.e. off-label) and therefore as the Pharmaceutical Industry's code of practice prevents a company from promoting an off-label use of a medicine, a commercial agreement cannot be offered by the company.

ADDITIONAL FACTORS

Prescribing unlicensed medicines

Rituximab is not licensed to treat this indication and is therefore 'off label'. Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

REFERENCES

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Appendix 1
Summary of study designs and key outcomes

Authors and study type	Myasthenia gravis subgroup	Duration / follow-up	Prior treatment	Intervention(s)	Concurrent treatments	Efficacy	Relapse	Other outcomes such as decreased need for other ISTs/ comments
Yale University, BeatMG authors[3] Multicentre, randomised, double-blind, placebo controlled phase II study based in USA (n = 52)	AChR+ MG	52 weeks	PDN (Other IST allowed but NR)	RTX as per NHSE CCP dosing schedule B	Prednisone (10 mg/day), calcium and vitamin D	NR	NR	Steroid sparing effect (≥ 75% reduction in mean daily dose with clinical improvement or no worsening of symptoms) was improved by RTX compared with placebo (p = 0.03).
Landon-Cardinal et al. 2018[21]. Open-label, multicentre phase II study based in France (n = 12 enrolled; n = 11 completed)	Refractory AChR+ MG	Follow-up of 18 months	• AZA (n = 12) • CHL (n = 1) • CSA (n = 6) • CYC (n = 2) • IVIg (n = 5) • MMF (n = 9) • PE (n = 3) • PDN (n = 12) • TAC (n = 1) • TYHM (n = 8)	1,000 mg RTX given twice separated by two weeks followed by 1,000 mg six months after second infusion.	ISTs, IVIg or PE	Median MMS unchanged at 12 months. MMS improved by at least 20 points for one person after 12 months (achieving primary outcome). Three people had at least 20 points improved MMS after 18 months.	NR	After 12 months, MGFA QMGS improved in five people and MGFA PIS improved in six people and worsened in two. RAND MOS SF-36 remained stable at 12 months while a score of physical functioning improved.
Robeson et al. 2017[23]. Single centre retrospective case series study based in USA (n = 16)	Refractory AChR+ MG	Follow-up of (range) 18 to 84 months	• AZA (n = 6) • IVIg (n = 2) • MMF (n = 2) • PDN (n =15) • PY (n = 1)	RTX as per NHSE CCP dosing schedule B however number of cycles used was based on reaching a symptom free-state and patient toleration of tapering or withdrawal of other ISTs.	Reported as current therapy: • AZA (n = 3) • IVIg (n = 1) • PDN (n = 3)	After initial set of cycles: • CSR (n = 10) • PR (n = 3) • MM but no therapy (n = 3) Clinical benefit maintained during mean follow-up of 47 months (n = 7).	After last cycle: Mean time to relapse 36 months (n = 9). Following relapse, MG responded to ISTs including IVIg or PE (n = 7), high dose PDN (n = 1) or an additional RTX cycle (n = 4) with some people receiving more than one IST.	People who were able to taper and discontinue all other ISTs were able to do so in a mean of 8.3 months since last RTX treatment (n = 13). Minimum of 2 cycles appear to be needed as most people required approximately 1 year to taper other therapies, however some people may need additional cycles.

Authors and study type	Myasthenia gravis subgroup	Duration / follow-up	Prior treatment	Intervention(s)	Concurrent treatments	Efficacy	Relapse	Other outcomes such as decreased need for other ISTs/ comments
Doughty et al. 2018[24]. Retrospective, multi-centre study (n = 14; > 65 years)	• 9 people with AChR+ • 3 people with MuSK+ • 2 people SN	NR	• PDN (n = 13) Other ISTs used but NR.	NR	PDN (number of people NR)	MGFA PIS improved or better in 7/10 people after six months and 6/6 people after 12 months.	NR	Mean PDN significantly lowered from baseline (20 mg/day) to 12.5 mg/day at six months (p = 0.008) and 5 mg/day at 12 months (p = 0.028). SAE reported for five people.
Topakian et al. 2019[5]. Retrospective, multi-centre study (n = 56)	• 39 people with AChR+ • 14 people with MuSK+ • 3 people with SN	Median follow-up of 20 months after RTX initiation	• AZA (n = 44) • CSA (n = 5) • CYC (n = 1) • MMF (n = 13) • MTX (n = 7) • TAC (n = 1)	RTX doses varied: • Majority received two infusions within two weeks of either 375 mg/m^2, 500 mg or 1,000 mg RTX (n = 47) • Various other regimens (n = 9) • Some received planned infusions six months later (n = 3) Median number of infusions received was 3. Repeat treatment was based on reappearance of B cells for 24 people and based on grounds of clinical deterioration for 17 people.	Reported at last follow-up: • PE, IVIg (n = 13) • PDN (number of people NR)	PR after three months in 14/53 people increasing to 16/41 after 12 months and at median last follow-up this increased to 24/56 people.	NR	At last follow up PDN tapered at least by 50% from baseline in 33/39 people; discontinued in 23/39 people. Remission at last follow-up was more frequent in MuSK+ (85.7%) than in AChR+ (64.1%) people.

Authors and study type	Myasthenia gravis subgroup	Duration / follow-up	Prior treatment	Intervention(s)	Concurrent treatments	Efficacy	Relapse	Other outcomes such as decreased need for other ISTs/ comments
Litchman et al. 2018[25]. Retrospective in a single centre (n = 33)	Refractory MG • 17 people with AChR+ • 16 people with MuSK+	Mean follow-up of 1861 (± 953.4) days.	NR	RTX dose NR	PDN (number of people NR)	Change in MGFA from baseline. Symptom free state at 12 months attained by 62.5% of people with AChR+ MG and 66.7% of people with MuSK+ MG. Clinical remission attained by people with AChR+ (n = 12) in 441.4 ± 336.6 days and by those with MuSK+ (n = 9) in 230 ± 180.8 days.	Relapse rate was 58.8% for people with AChR+ MG and 37.5% for MuSK+ MG.	Maintenance IVIg or PE was reduced in people with MuSK+ MG but not in AChR+ MG. People with MuSK+ MG also required rescue therapy less frequently. Mean PDN dose requirement decreased for both AChR+ and MuSK+ MG.
Anderson et al. 2016[22]. Prospective, open-label study based in Canada (n = 14)	Refractory MG • 6 people with MuSK+ • 5 people with AChR+ • 3 people were SN	Follow-up period of 22.6 ± 2.4 months	• AZA (n = 10) • CSA (n = 3) • IVIg (n = 11) • MMF (n = 6) • PE (n = 10) • PDN (n = 14) • PY (n = 8) • TAC (n = 1) • THYM (n = 2)	RTX dose varied: • Initial dose of 375 mg/m^2 weekly four times then monthly twice • 750 mg/m^2 every two weeks for one month	Current medications at follow-up: • AZA (n = 2) • MMF (n = 2) • PDN (n = 6) • PY (n = 1) • TAC (n = 1)	MMT significantly improved for 11 people who received one RTX cycle.	One person with AChR+ MG and two with MuSK+ MG relapsed during the study but, with repeat RTX cycles, demonstrated a marked clinical response by end of follow-up (measured by MMT).	For those people receiving either PDN (n = 8), IVIg (n = 7) and/or PE (n = 4) at the start of the study, PDN dose and IVIg/PE frequency all significantly decreased by end of follow-up.

Authors and study type	Myasthenia gravis subgroup	Duration / follow-up	Prior treatment	Intervention(s)	Concurrent treatments	Efficacy	Relapse	Other outcomes such as decreased need for other ISTs/ comments
Hehir et al. 2017[26]. Prospective, multi-centre, blinded study (n = 55)	MuSK+ MG	Median follow-up of 45 months for RTX and 54 months for control	RTX group • AZA (n = 20) • CSA (n = 3) • IVIg/PE (n = 21) • MMF (n = 6) • PDN (n = 20)	RTX = 24, control = 31 RTX dose varied: • Initial dose of 375 mg/m^2 weekly four times • Followed by either 375 mg/m^2 weekly four times (n = 13) or 1000 mg weekly twice (n = 2)	RTX group measured at follow-up: • AZA (n = 2) • CSA (n =0) • IVIg/PE (n = 6) • MMF (n = 1) • PDN (n = 7)	Novel, unvalidated measure of MG severity, MGSTI, was significantly improved with 58% of people taking RTX achieving primary outcome compared with 16% of control group (p = 0.002).	Four people achieved favourable clinical responses but then relapsed. They all returned to favourable clinical responses with second RTX cycle.	Using MGFA PIS, MM achieved for 67% of people taking RTX and 26% of control people at final visit. PR for three people, CSR for seven people taking RTX with PR for one patient in control group (based on MGFA PIS). At follow-up, 29% of people taking RTX were taking PDN while 74% of control group were taking PDN.
Beecher et al. 2018[6]. Prospective, open-label study based in Canada (n = 22)	Refractory MG • 10 people with AChR+ • 9 people with MuSK+ • 3 people SN	Mean follow-up of 28.8 ± 19.0 months	• AZA (n = 11) • CSA (n = 3) • IVIg (n =10) • MMF (n = 4) • PDN (n = 8) • PE (n = 11) • PY (n = 19) • THYM (n = 6) • SCIg (n = 2)	RTX dose varied: • Induction regimen of either 375 mg/m^2 per dose or 750 mg/m^2 per dose (people receiving either one or two doses) Maintenance regimen of 750 mg/m^2 per dose with max 1,000 mg per dose (repeat cycles dictated by clinical worsening)	• AZA (n = 3) • CSA (n = 1) • IVIg (n = 4) • MMF (n = 6) • PDN (n = 14) • PE (n = 4) • PY (n = 1) • SCIg (n = 0) • TAC (n = 1)	Statistically significant reduction in MMT at average follow-up of 28.8 ± 19 months, from 10.3 ± 5.6 to 3.3 ± 3.1 (p < 0.0001). AChR+ people demonstrated a reduction from 10.3 ± 5.1 to 5.5 ± 2.6 (p = 0.018). MuSK+ people a reduction from 10 ± 3.6 to 1.1 ± 2 (p < 0.0001).	Average time to first relapse (n = 7) was 17.1 ± 5.5 months. Average time to second relapse (n = 2) was 13.5 ± 0.7 months.	Significant daily reduction in PDN dose from 25.2 ± 15.1 mg/d to 7.3 ± 7.1 mg/d (p = 0.002). Four MuSK+ (n = 9), 1 of AChR+ (n = 10) and 2 of SN (n = 3) had discontinued all ISTs at last follow up.

Authors and study type	Myasthenia gravis subgroup	Duration / follow-up	Prior treatment	Intervention(s)	Concurrent treatments	Efficacy	Relapse	Other outcomes such as decreased need for other ISTs/ comments
Tandan et al. 2017[27]. Systematic review of 47 articles, 28 of which were single case reports, published between 2000 and 2015 (n = 169)	Refractory MG • 99 people with AChR+ • 57 people with MuSK+	Mean follow-up of 22.5 ± 17.3 (SD) months available for 157 people, median follow-up of 17 months	Various: • Thymectomy (53%) • Mean of 3.6 ± 1.4 ISTs used prior to starting RTX • Mean of 1.7 ± 0.8 other ISTs used immediately prior to starting RTX	RTX dose varied: • 375 mg/m^2 given weekly four times (n = 135) • 500 mg per week for two weeks (n = 14) • Various other regimens (n = 19)	NR	Overall response rate of 44% using PIS-modified MM or better and 27% using PIS-modified CSR or PR. AChR+ response of 30% and MuSK+ of 72% using PIS-modified MM or better. AChR+ response of 16% and MuSK+ response of 47% using PIS-m CSR or PR.	Overall relapse rate of 26% after RTX. AChR+ relapse rate of 33% after RTX. MuSK+ relapse rate of 14% after RTX.	Efficacy was greater for those people with MuSK+ MG (opposed to AChR+ MG)
Memon et al. 2018[31]. Retrospective, multicentre study investigating long term safety over three years or longer (no efficacy) (n = 3)	NR	Up to 7 years	NR	RTX given every six months or on a six-nine-month cycle depending on circulating CD19 blood count • Initial dose of 1,000 mg given twice spaced by 15 days. • Followed by 1,000 mg repeated every six to nine months	NR	NR	NR	For all people with PIMND (n = 29), 32 infections were reported, two occurring in people with MG. Four infections considered SAE occurred but none in people with MG.

Authors and study type	Myasthenia gravis subgroup	Duration / follow-up	Prior treatment	Intervention(s)	Concurrent treatments	Efficacy	Relapse	Other outcomes such as decreased need for other ISTs/ comments
Peres et al. 2017[32]. Retrospective, single centre study (n = 6)	• 4 people with AChR+ MG • 2 people SN	Mean follow up of 39 months (range,11 to 67 months).	• AZA (n = 3) • CSA (n = 1) • IVIg (n = 3) • MMF (n = 1) • PDN (n = 5)	Initial dose of 1,000 mg given twice spaced by 15 days.	• AZA (n = 3) • CSA (n = 1) • IVIg (n = 1) • PDN (n = 4)	Significant decrease in MGCS seen after one RTX cycle (36%) and at final follow-up (53%).	NR	Two people experienced SAE and two people experienced minor AE, one of which was an infusion reaction. Number of ISTs being taken reduced after one RTX cycle from an average of 2.2 to 1.5 drugs per person. This decreased further to an average of 1.2 drugs at last follow-up.
Cortes Vincente et al. 2018[33]. Retrospective, multicentre study based in Spain (n = 25)	Refractory MuSK+ MG	Mean follow-up of 5 ± 3.3 years (SD)	• AZA (n = 16) • CSA (n = 8) • DFZ (n = 1) • IVIg (n =15) • MMF (n = 8) • PDN (n = 24) • PE (n = 10) • PY (n = 12) • THYM (n = 7)	RTX dose varied: • 375 mg/m^2 given weekly four times followed by monthly twice (n = 11) • NHSE CCP schedule A (n = 5) • NHSE CCP schedule B (n = 9)	• DFZ (n = 1) • CSA (n = 1) • MMF (n = 1) • PY (n = 3) • PDN (n = 11)	All people reached MGFA PIS MM.	Relapse occurred 18.2%, 80% and 33.3% when novel dose, schedule A or schedule B used respectively. Time to relapse was 3.5 ± 1.5, 1.1 ± 0.4 and 2.5 ± 1.4 years (± SD) respectively for each treatment regimen.	All people either decreased or no longer took PDN by last follow-up.

Authors and study type	Myasthenia gravis subgroup	Duration / follow-up	Prior treatment	Intervention(s)	Concurrent treatments	Efficacy	Relapse	Other outcomes such as decreased need for other ISTs/ comments
Iorio et al. 2015[11]. Systematic review of 37 uncontrolled observational studies published between 2008 and 2013. Meta-analysis performed on 15 of these studies (n = 168)	• 91 people with AChR+ MG (81 refractory) • 70 people with MuSK+ MG (68 refractory) • 7 people SN (6 refractory)	Median follow-up of 16 months, 26 months and 12 months for AChR+, MuSK+ and SN respectively	NR	RTX dose varied: • 375 mg/m^2 given four times (n = 137) • 500 mg per week for two weeks (n = 12) • 1000 mg given twice (n = 8) • Various other regimens (n = 11)	NR	Overall response rate of 83.9%	Not included in study design	No correlation found between mean MG severity or mean reinfusion number and the response rate following meta-regression analysis.

AChR+: acetylcholine receptor positive; AE: adverse events; AZA: azathioprine; CHL: chlorambucil; CI: confidence interval; CSA: cyclosporine A; CSR: chronic stable remission; CYC: cyclophosphamide; IST: immunosuppressive treatments; IQR: Interquartile range; IVIg: Intravenous immunoglobulin; MG: myasthenia gravis; MGFA: myasthenia gravis foundation of America; MGCS: MG composite scale; MGSTI: Myasthenia Gravis Status and Treatment Intensity; MM: minimal manifestations; MMF: mycophenolate mofetil; MMT: manual muscle testing scores; MMS: myasthenic muscle scores; MOS: medical outcomes study; MTX: methotrexate; MuSK+: muscle-specific tyrosine-kinase positive; NHSE CCP: NHS England Clinical Commissioning Policy; NR: not reported; PDN: prednisone; PE: plasma exchange; PIMND: people with immune mediated neurological disorders; PIS: post-intervention scale; PR: pharmacologic remission; PY: pyridostigmine; QMGS: quantitative myasthenia gravis score; RTX: rituximab; SAE: serious adverse events; SCIg: subcutaneous immunoglobulin; SD: standard deviation; SEM: standard error of the mean; SF-36: 36-item short form health survey; SN: seronegative; TAC: tacrolimus; THYM: thymectomy