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

Rituximab for the treatment of generalised myasthenia gravis in adults (OW12)

April 2023

ONE WALES INTERIM DECISION

Rituximab for the treatment of generalised myasthenia gravis in adults

Date of advice: April 2023

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been endorsed by the All Wales Medicines Strategy Group (AWMSG) and ratified by Welsh Government.

Using the agreed starting and stopping criteria, rituximab can be made available within NHS Wales:

- as a first-line add-on treatment for generalised myasthenia gravis in adults;
- as a fourth-line or later treatment option for refractory generalised myasthenia gravis in adults.

Rituximab should be prescribed on the basis of lowest acquisition cost.

The risks and benefits of the off-label use of rituximab for these indications should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment Group decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice assists consistency of access across NHS Wales.

Starting and stopping criteria for rituximab for the treatment of generalised myasthenia gravis

These criteria have been adapted from the NHS England Clinical Commissioning Consultation document (based on refractory use) and with clinical expert advice from Welsh clinicians.

First-line setting

Starting and stopping criteria

Starting criteria:
Rituximab should be made available for the treatment of newly diagnosed **generalised** seropositive MG in combination with corticosteroids. This excludes the treatment of MG confined to the ocular muscles only. Newly diagnosed is defined as generalised symptom onset within the past twelve months. Patients can have ocular symptoms longer than twelve months. Seropositive MG includes both acetylcholine receptor (AChR) positive and muscle specific kinase receptor (MuSK) positive MG. Low titres of AChR antibodies (<20 x 10^{-10} Mol/L) should be interpreted with caution and confirmed by measuring clustered AChR antibody titres.

Screening:
Prior to commencing rituximab, pre-screening should be undertaken to exclude:

- Active or latent tuberculosis
- Hepatitis virus or HIV
- Current acute infections (viral, bacterial, fungal or parasitic)
- Severe heart failure (NYHA class IV)
- Immunoglobulin (Ig) G deficiency (defined as <6 g/L)
- Pregnancy or breast feeding

It is recommended that immunoglobulin levels are determined prior to initiating treatment. The status of varicella zoster immunity should be determined. Caution should be exercised in any patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. Women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with rituximab[1].

Rituximab should always be initiated by an experienced neurologist, preferably following documented discussion with a clinician experienced in the management of MG and / or a multidisciplinary team discussion.

Patients who satisfy the eligibility criteria will be prescribed rituximab following consultation with the patient and/or carer considering potential adverse effects, cautions and contraindications. This consultation should be recorded in the patient's notes.

The recommended rituximab treatment dose regimen for adults with MG in the first line setting is a single dose of 500 mg rituximab administered by intravenous infusion. Repeat single doses of 500mg may be given at six monthly intervals.

Continuing and stopping criteria:
Stopping criteria are based on response to treatment according to predefined efficacy measures. It is important that outcomes are collected for this patient cohort and the outcomes will be reviewed by the One Wales Medicines Assessment Group after 12 months.

Outcome data to determine treatment efficacy:
The following outcome data must be collected to assess a patient's response to treatment:

- MG Composite score and/or the MG Activities of Daily Living (MG-ADL) and/or the MG Quality of Life (MG-QoL) score (at least two of the three outcomes must be recorded at baseline, week 16 and week 24 post treatment)
- steroid requirement at baseline and six months;
- number of admissions to hospital (for MG and other indications)
- need for intravenous immunoglobulin (IVIg) and /or plasma exchange.

Criteria for clinical failure to respond:
If, despite CD19/20 depletion, there is no reduction in clinical improvement (defined as a reduction in MG-ADL / MG composite of at least 2 points), hospital admissions, IVIg courses or plasma exchange requirements or meaningful reduction in steroid dose at 6 months, the patient is a non-responder and rituximab should be discontinued.

Relapse following a period of response to rituximab:
Currently there are no published data on the relapse rate of patients responding to early low dose rituximab treatment. Observational data would predict that the majority of responders to rituximab will lose benefit after a mean of 6-18 months. However, relapse can be delayed for up to 4 years. Patients who are considered responders should be monitored using the criteria detailed above and retreated when symptoms return.

Other considerations:

- Patients should be provided with an alert card stating that they have been treated with rituximab and advised of the symptoms of infection that should prompt urgent medical care
- Immunoglobulin levels should be checked a minimum of 6 monthly
- Treatment with rituximab precludes subsequent treatment with efgartigimod for 6 months

Fourth-line or later setting

Starting and stopping criteria

Starting criteria:
For the purposes of the discussion below, seropositive MG includes both AChR positive and MuSK positive MG. Low titres of AChR antibodies (<20 x 10-10 Mol/L) should be interpreted with caution and confirmed by measuring clustered AChR antibody titres.

Rituximab should be made available for the treatment of generalised MG as a fourth line or later treatment in patients who fulfil the following criteria:

- Seropositive MG patients, who demonstrate active disease despite treatment with maximal immunosuppression:
    - This includes maximal dose of corticosteroids as appropriate, and at least 2 trials of a steroid-sparing immunosuppressant (for example azathioprine, mycophenolate mofetil, methotrexate, ciclosporin or tacrolimus) unless otherwise contraindicated, for an adequate period of time (minimum of 6 months), in an adequate therapeutic dose.

OR

- Seropositive MG patients with crises or frequent relapses:
    - MG patients, with frequent hospital admissions due to MG crisis or significant MG relapses (despite adequate oral immunosuppression as defined above) who require regular treatment with IVIg or plasma exchange, as well as continuing treatment with high doses of corticosteroids as appropriate, and other steroid sparing immunosuppression to achieve stabilisation of symptoms.

OR

- Seropositive MG patients in whom oral immunosuppression is complicated by significant side effects. For MG patients:
    - in whom corticosteroids are relatively contraindicated (for example poorly controlled diabetes, morbid obesity, psychiatric complications).
    - where stabilisation on steroid sparing immunosuppression may be insufficient or delayed.
    - who are intolerant to various steroid-sparing immunosuppressants.
    - who experience multiple and serious infections from oral immunosuppression.

OR

- Seropositive patients whose disease at onset is “explosive”:
    - Patients whose bulbar and respiratory functions are not responding in a timely fashion to high doses of corticosteroids and rescue treatments, including IVIg and/or plasma exchange, and who are unable to wean from ventilatory support in a critical care setting.

OR

- Seropositive patients with significant bulbar weakness who are at risk of aspiration pneumonia:
    - Bulbar weakness may be slower to respond to conventional treatment than other symptoms. Bulbar weakness is a feature of MuSK positive

MG. Where weakness of swallowing muscles persists with an increased risk of chest infection (even if limb weakness has responded to conventional treatment) and IVIg or plasma exchange is required, rituximab can be considered a treatment option.

Screening:
Prior to commencing rituximab, pre-screening should be undertaken to exclude:

- Active or latent tuberculosis
- Hepatitis virus or HIV
- Current acute infections (viral, bacterial, fungal or parasitic)
- Severe heart failure (NYHA class IV)
- Immunoglobulin G deficiency (defined as <6 g/L)
- Pregnancy or breast feeding

It is recommended that immunoglobulin levels are determined prior to initiating treatment. The status of varicella zoster immunity should be determined. Caution should be exercised in any patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. Women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with rituximab[1].

Rituximab should always be initiated by an experienced neurologist, preferably following a documented discussion with a clinician experienced in the management of MG and / or a discussion by the MG multidisciplinary team discussion.

Patients who satisfy the eligibility criteria will be prescribed rituximab following consultation with the patient and/or carer considering potential adverse effects, cautions and contraindications. This consultation should be recorded in the patient's notes.

The usual recommended rituximab treatment dose regimen for adults with MG is 1,000 mg rituximab followed by a second 1,000 mg dose two weeks later administered by intravenous infusion. Repeat courses may be given at six monthly intervals.

Continuing and stopping criteria:
Stopping criteria are based on the literature which suggests that it can take up to 12 months for rituximab to become effective in the management of MG. Having responded, just over half relapse at a mean of 36 months, with efficacy persisting for up to 4 years in more than 40%. The majority of these show an extended response to 2 or 3 cycles of treatment.

Failure to respond to rituximab:
Some patients with a higher clearance of rituximab may not deplete their CD19/20 count and will not respond to a first course of rituximab. Non-responders should have CD19/CD20 counts measured at 4 weeks and where there is no reduction in cell count could be retreated. If a patient has depleted their CD19/20 count but has not

responded to rituximab after 9 months, they should be considered non-responders and no further rituximab treatments given.

Outcome data to determine treatment efficacy:
The following outcome data must be collected to assess a patient's response to treatment:

- MG Composite score and/or the MG Activities of Daily Living (MG-ADL) and/or the MG Quality of Life (MG-QoL) score (at least two of the three outcomes must be recorded at baseline, week 16 and week 24 post treatment)
- steroid requirement at baseline and six months;
- number of admissions to hospital (for MG and other indications)
- need for IVIg and /or plasma exchange

Criteria for clinical failure to respond:
If, despite CD19/20 depletion there is no reduction in hospital admissions, IVIg courses or plasma exchange requirements or meaningful reduction in steroid dose, the patient is a non-responder and rituximab should be discontinued.

Relapse following a period of response to rituximab:
It is expected that the majority of responders to rituximab will lose benefit after a mean of 18 months, but up to 4 years. Patients will be monitored and when symptoms recur, or rising CD19/20 counts are identified, a further course of rituximab could be offered.

Other considerations:

- Patients should be provided with an alert card stating that they have been treated with rituximab and advised of the symptoms of infection that should prompt urgent medical care
- Immunoglobulin levels should be checked a minimum of 6 monthly
- Treatment with rituximab precludes subsequent treatment with efgartigimod for 6 months

References

1. Roche Products Limited. MabThera 100 mg Concentrate for Solution for Infusion. Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/3801/smpc. Accessed 26/4/23
2. NHSE Clinical Commissioning Policy Statement: Rituximab bio-similar for the treatment of myasthenia gravis (adults). Available at: https://www.england.nhs.uk/wp-content/uploads/2021/04/Rituximab-biosimilar-for-the-treatment-of-myasthenia-gravis-adults-v2.pdf. Accessed 26/4/23

One Wales Medicine Assessment Group summary of decision rationale

Medicine: **rituximab**
Indication: **For the treatment of myasthenia gravis in adults including first-line use**
Meeting date: **20 March 2023**

Criteria	OWMAG opinion
Clinical effectiveness	OWMAG notes that the main clinical effectiveness evidence for add-on low-dose (500 mg infusion) rituximab as a first-line treatment for generalised myasthenia gravis in adults is from the double-blind, randomised, placebo-controlled RINOMAX clinical trial. This study demonstrated that use of rituximab earlier in the treatment pathway for new-onset MG reduced MG manifestations and the need for rescue treatments. However, there were imbalances in patient baseline characteristics between the rituximab and placebo arms and that the effect of these on outcomes is unclear. OWMAG also notes that a retrospective study comparing the efficacy of rituximab in new-onset vs refractory disease demonstrated that remission was achieved quicker and fewer rescue therapies were required in the new-onset group. Taken together, these studies show that using rituximab as an add-on first-line treatment may improve time to symptom control, reduce the use of long-term steroids and reduce the need for rescue treatments. However, patient numbers were small and there is a lack of longer term follow up. Additionally, the RINOMAX clinical trial included mainly patients with AChR+ MG, there is a lack of clinical evidence for using low dose rituximab first-line for patients with MuSK+ MG although there is evidence in the refractory setting that MuSK+ MG responds favourably to rituximab treatment and patients often do better than those with AChR+ disease. OWMAG considers that the evidence provided demonstrates clinical effectiveness for using low-dose add-on off-label rituximab as a first-line treatment. Rituximab is currently available through a One Wales interim decision as an off-label fourth-line or later treatment of refractory myasthenia gravis (MG) in adults (at a higher

	dose) and OWMAG continued to support this decision after their review of new evidence in December 2022. Therefore, OWMAG considers that there is sufficient clinical effectiveness evidence to support the use of off-label rituximab as a first-line add-on treatment for generalised MG. Rituximab will continue to be made available as a fourth-line or later treatment for refractory MG.
Cost-effectiveness	There is no cost-effectiveness evidence available for rituximab for this indication. A cost consequence assessment was undertaken in the meeting. The reduction in need for rescue treatments and hospitalisation rates for rituximab plus prednisolone versus prednisolone alone based on the RINOMAX study may indicate that this treatment is likely to be both cost saving and more effective that steroid treatment alone. Therefore, this treatment may fall in the bottom right quadrant of the cost effectiveness plane. These assumptions are based on data up to 48 weeks and the long-term benefit of treatment is unknown and therefore the cost effectiveness of this treatment is subject to significant uncertainty. Factors such as the high dropout rates and higher use of rescue treatments in the placebo group may have impacted on the quality of life measures used in the RINOMAX study resulting in the lack of statistical difference between the two treatment arms.
Budget impact	OWMAG considers the clinical estimate of patient numbers reported to be reasonable but may be on the high side. The group acknowledges that budget impact estimates are subject to uncertainty due to possible variation in the number of patients requiring repeated 6-monthly dosing throughout the 3-year timeframe. The group note that additional screening and monitoring and adverse event costs have not been included in the budget impact. It is important to consider that there will be an impact on the service to deliver this treatment and there may be capacity issues. OWMAG acknowledges that any cost benefits from the reduction in adverse events associated with a decrease in steroid use due to rituximab treatment has not been considered. OWMAG considers that the base case ranges provided in the report are reasonable estimates of the associated cost

	to NHS Wales. OWMAG notes that the majority of the cost is due to infusion administration costs. Based on the results from the RINOMAX study, OWMAG acknowledges that the use of rituximab as a first-line treatment option may reduce the number of patients requiring rescue therapy. OWMAG considers using the results from this study to conduct a scenario analysis modelling offset costs of rescue treatments in a population receiving add-on rituximab compared with steroid alone as appropriate. OWMAG notes that the use of first-line rituximab may be associated with a significant cost saving in Year 1. However, OWMAG acknowledges that there is limited evidence to support this assumed benefit and the lack of longer-term clinical data does not allow modelling after Year 1.
Other factors	OWMAG acknowledges that there is an unmet need based on currently available treatment strategies and that traditional non-steroidal immunosuppressant therapies (all of which are unlicensed for MG) may be slow to achieve maximum effect, are not always effective and may be associated with significant side-effects. Using rituximab earlier in the clinical pathway for early-onset MG may offer an effective treatment option for patients and reduce the use of long-term steroids and may also negate or delay the need for other immunosuppressant therapies. Additionally, a single infusion of rituximab (possibly repeated every 6-12 months) in contrast to a daily oral tablet potentially taken over a number of years, may be a preferable option for some patients. Thymectomy would still be the preferred intervention for patients who meet the criteria for surgery. Early rituximab followed by thymectomy may be the most likely treatment route for these patients. Licensed treatments for MG are either due to be appraised or are not currently recommended by NICE or AWMSG. Their place in the treatment pathway is yet to be determined but may be most likely used in the refractory setting. None of them are licensed for MuSK+ disease.
Final recommendation	OWMAG recommends the use of rituximab as an off-label first-line add-on treatment for generalised myasthenia gravis in adults. This recommendation is subject to the development of appropriate start/stop criteria.

	OWMAG also recommends that rituximab should continue to be made available as an off-label fourth-line or later treatment of refractory myasthenia gravis (MG)
Summary of rationale	There is some limited clinical evidence to support the use of rituximab earlier in the treatment pathway for generalised MG in adults. OWMAG are of the opinion that, the use of off-label low-dose rituximab as an add-on first-line treatment may improve time to symptom control, reduce the use of long-term steroids and reduce the need for rescue treatments. Real world data will be captured to assess the benefit of this treatment for this cohort of patients.

The information in this document is intended to help healthcare providers make an informed decision. This document should not be used as a substitute for professional medical advice. Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content. An Equality and Health Impact Assessment (EHIA) has been completed in relation to the One Wales policy and this found there to be a positive impact. Key actions have been identified and these can be found in the One Wales Policy EHIA document.

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