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

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

June 2024

ONE WALES INTERIM DECISION

Rituximab for the treatment of myasthenia gravis in adults

Date of original advice: April 2023
Date of review: June 2024

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been noted 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 promotes 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 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 500 mg 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 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 24/6/24
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 24/6/24

This is a summary of new evidence available and patient outcome data collected, to inform the review.

Rituximab for the treatment of myasthenia gravis (OW12)

This report was prepared by the All Wales Therapeutics and Toxicology Centre in April 2024. It summarises any new evidence available and patient outcome data collected since the One Wales reassessment in March 2023.

Background: Rituximab is available through a One Wales interim decision as either an off-label first-line treatment option, or fourth-line or later add-on treatment for generalised myasthenia gravis (MG) in adults.

Clinicians in Wales are supportive of using rituximab earlier in the treatment pathway and consider there to be an unmet need based on currently available treatment strategies. Rituximab was therefore considered suitable for reassessment though the One Wales Medicines process, and the first-line indication was added to the original fourth-line or later recommendation in April 2023.

Current One Wales Decision: Supported

Licence status: Rituximab is not licensed for treating MG; its use for this indication is off-label.

Guidelines: No new or updated guidelines reported.

Licensed alternative medicines or Health Technology Assessment advice for alternative medicines:
ID4003: the appraisal of efgartigimod alfa (VYVGART®▼) for the treatment of generalised MG is due to be published July 2024.

ID5092: the appraisal of rozanolixizumab (Rystiggo®▼) for treating antibody-positive generalised MG is currently underway, publication date TBC.

TA940: ravulizmab (Ultomiris®▼) for the treatment of generalised MG was terminated due to withdrawal of submission from the manufacturer, December 2023.

Effectiveness: A literature search undertaken by AWTTC identified two retrospective studies published since the One Wales reassessment in March 2023.

A retrospective, single-centre study evaluated the efficacy of rituximab in the management of MG for patients in Iran (n = 59, Ziaadini et al. 2022). Patients either had muscle specific kinase receptor (MuSK) positive MG (n = 23), refractory acetylcholine receptor (AChR) positive MG (n = 28) or refractory seronegative MG (n = 8). All patients received rituximab either as a 1000 mg dose at day 1 and day 15, or as four 500 mg doses repeated one week apart. Ten patients with MuSK positive MG received rituximab first-line. The Myasthenia Gravis Activities of Daily Living (MG-ADL) profile was used to assess MG symptoms and their effects on ADL at the start of treatment and at last follow-up (mean 36 months). A person's MG-ADL score can range from zero (normal) to 24 (most severe). A change of ≥ 2 points in MG-ADL is considered clinically significant. The average MG-ADL score was 4.86 ± 1.83 before treatment and 1.51 ± 2.02 in the last visit (t[55] = 11.30; 95% confidence interval [CI]: 2.79 to 3.99; p = 0.001). MG-ADL in the last visit was lower for patients

with MuSK positive MG compared with the other groups (4.38 ± 1.52 before treatment, 0.29 ± 0.85 after treatment; p = 0.001). The Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) was used to evaluate long term outcomes, and by this metric 88.1% of patients saw favourable outcomes (either complete stable remission, pharmacological remission or minimal manifestations).

An open-label study evaluated long term outcomes of patients with MG treated with rituximab (n = 30, Kefalopoulou et al. 2024). Patients either had MuSK positive MG (n = 6), generalised refractory AChR positive MG (n = 16) or refractory seronegative MG (n = 8). Four patients with MuSK positive MG received rituximab first line. Mean follow-up was 33.3 months. The primary outcome was changes in the quantitative myasthenia gravis (QMG) score, where a ≥ 2-point difference is considered clinically meaningful for mild (scores of 0-9) and moderate (score 10-16) disease. QMG showed a significant decrease over the treatment period (p < 0.001), from 11 ± 4.1 to 4.3 ± 3.8. The relapse rate reduced from 1.9 to 0.3 per year (p < 0.001) and 93.1% of patients reduced their steroid dose to ≤ 10 mg/day, from 27.3 ± 16.3 to 7.8 ± 3.3 mg/day (p < 0.001).

Safety: No relevant safety analyses identified in the repeat literature search.

Cost-effectiveness: No relevant cost-effectiveness analyses identified in the repeat literature search.

Budget impact: In the original evidence summary it was estimated that 40-50 new patients per year across Wales would be eligible for first-line treatment with rituximab for generalised MG. Since the reassessment in 2023, AWTTC have been provided with data for six patients commencing on rituximab for first-line use. This is considerably lower than the original budget impact estimates and it has been suggested that the expert-sought original numbers may have been too high. Most patients have been started on treatment in the last six months and AWTTC may also not have been made aware of all new cases started on treatment.

AWTTC will continue to monitor patient uptake as part of ongoing reviews.

Impact on health and social care services: Minimal.

Patient outcome data:
AWTTC were provided with baseline data for eight patients in total. Six of the eight patients were documented as having AChR positive MG and were receiving rituximab as first-line therapy. The majority of patients were over 60 years of age (n = 6) and six patients were taking over 10 mg of prednisolone prior to commencing therapy with rituximab. Six patients receiving rituximab as first or fourth-line treatment had been admitted to hospital in the 12 months leading up to starting rituximab, all of whom had received a course of intravenous immunoglobulin (IVIg). No patients were reported to have required plasmapheresis in the 12 months prior to commencing rituximab.

Patients are followed up at week 16, 24, month 12, 18 and 24 (timescales are approximate).
[confidential information removed]

Evaluation of evidence

The clinical evidence identified since the One Wales re-assessment in March 2023 by an AWTTC literature search and presented here supports the continued use of rituximab as a treatment option in line with the current One Wales decision. Treatment uptake, reflected by reported patient numbers, is lower than originally estimated. One of the reasons for this may be due to the majority of those patients who are receiving rituximab first-line have started treatment in the past six months. For this reason also, it is too early to assess the efficacy of rituximab first-line based on available data. [confidential information removed] AWTTC recommends continuing access to rituximab in NHS Wales via the One Wales Medicines process for the treatment of generalised MG as either a first-line option, or a fourth-line or later add-on option.

Next review date: 12 months

References: a full reference list is available on request.