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

Rituximab for the fourth-line or later treatment of refractory myasthenia gravis in adults (OW12)

December 2021

ONE WALES INTERIM DECISION

Rituximab for the fourth-line or later treatment of refractory myasthenia gravis in adults

Date of original decision: April 2019
Date of review: December 2021

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been endorsed by health board Chief Executives.

Using the agreed starting and stopping criteria, rituximab can continue to be made available within NHS Wales for the fourth-line or later treatment of refractory myasthenia gravis in adult patients where other health technology appraisal approved regimens are unsuitable.

The rituximab product with the lowest acquisition cost should be chosen for newly initiated patients.

Rituximab is not licensed to treat this indication and is therefore 'off-label'. Each provider organisation must ensure all internal governance arrangements are completed before this medicine is prescribed.

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

Providers should consult the relevant guidance 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 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 myasthenia gravis

These criteria have been adapted from the NHS England Clinical Commissioning Consultation document and with clinical expert advice from Welsh clincians[1].

Starting and stopping criteria

Starting criteria:
It is expected that a proportion of people referred for consideration of rituximab would be complex and following assessment may be successfully treated with standard treatment under expert guidance and withdrawn from maintenance intravenous immunoglobulin (IVIg) without the need for rituximab. Seropositive myasthenia gravis (MG) includes both acetylcholine receptor (AChR) positive and muscle specific kinase receptor (MuSK) positive MG.

Rituximab should be made available for the treatment of generalised MG 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, in an adequate dose. An adequate duration of treatment is a minimum of 6 months on an adequate 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. Generally, brittle patients are most likely to have frequent relapses in the first year of treatment until non-steroid immunosuppressants begin to work.
OR

- Seropositive MG patients in whom oral immunosuppression is complicated by significant side effects:

Patients in whom corticosteroids are relatively contraindicated (for example poorly controlled diabetes, morbid obesity, psychiatric complications), or where stabilisation on steroid sparing immunosuppression may be insufficient or delayed. Patients who are intolerant to various steroid-sparing immunosuppressants. Patients who experience multiple and serious infections from oral immunosuppression, and who are unable to tolerate oral immunosuppression and where their MG remains active and uncontrolled. It is likely that these patients would be receiving IVIg or plasma exchange to control their symptoms.
OR

- Seropositive patients whose disease at onset is “explosive” and are unresponsive to conventional rescue treatments:

Rescue treatments such as plasma exchange or IVIg, and whose bulbar and respiratory functions are not responding in a timely fashion to high doses of corticosteroids and

rescue treatments, 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, then rituximab can be considered a treatment option.

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.

Rituximab should always be initiated in a specialised neuroscience centre.

The 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 up to 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:
The extent of B lymphocyte depletion in peripheral blood does not predict the success of rituximab therapy. 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. The CD20 count should be measured 4 weeks following a first course of rituximab. Non-responders should be retreated.
If a patient has depleted their CD19/20 count but has not responded to rituximab after 9 months, a further course should be given. If this fails to bring symptoms under control in a further 12 months the patient should be considered to be a non-responder and rituximab should be discontinued, and alternative treatments considered.

Criteria for clinical failure to respond:
Patients response to treatment should be followed using the MG Composite score, their steroid requirement as well as the number of admissions to hospital and need for IVIg and plasma exchange. If, despite CD19/20 depletion for 12 months, there is no reduction in hospital admissions, IVIg courses or plasma exchange requirements, then a 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 reduced efficacy or rising CD19/20 counts are identified a further course of rituximab will be offered.

References

1. NHS England. Clinical Commissioning Policy Statement: Rituximab bio-similar for the treatment of myasthenia gravis (adults). Sep 2018. Available at: https://www.england.nhs.uk/wp-content/uploads/2018/10/Rituximab-biosimilar-for-the-treatment-of-myasthenia-gravis-adults-1.pdf. Accessed March 2019.

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

Background
Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction resulting in muscle weakness and is characterised by a range of symptoms depending on the muscle groups affected. MG 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 MG in adults[1]. 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.

Current One Wales Interim Decision
Using the agreed starting and stopping criteria, rituximab can be made available within NHS Wales for the fourth-line or later treatment of refractory myasthenia gravis in adults. November 2020.

Licence status
Rituximab as fourth-line or later treatment of refractory MG in adults remains off-label.

Guidelines
No new guidelines for the treatment of myasthenia gravis have been issued since the International MG/COVID-19 Working Group published guidance for the management of MG and Lambert Eaton myasthenic syndrome during the COVID-19 pandemic[2]. The guideline stressed the importance of talking with patients about the risks and benefits of taking immunosuppressant therapy during the pandemic. The Association of British Neurologists' guidance on COVID-19 for people with neurological conditions, their doctors and carers (March 2020) advise that patients with acute COVID-19 infection and MG should not suspend immunosuppression but seek advice from their medical team[3].

Licensed alternative medicines/Health Technology Appraisal advice for alternative medicines
There remain no alternative licensed medicines or health technology appraisal advice for this indication.

Efficacy/Effectiveness
A repeat literature search conducted by AWTTC identified two retrospective studies.

A retrospective, single centre, observational study analysed the difference in treatment response between the anti-acetylcholine receptor-positive (AChR+) and muscle-specific kinase receptor-positive (MuSK+) MG[4]. The study included 33 patients (17 AChR+, 16 MuSK+), the mean age was 35.9 and 24 patients (72%) were female. Mean follow-up was 1,861 days and 29 patients (87.9%) were receiving prednisone before initiating rituximab therapy. The mean number of induction rituximab cycles received was 3.1. Clinical state was assigned using the Myasthenia Gravis Foundation of America (MGFA) clinical classification criteria and post-intervention status (PIS). Improved clinical status was defined as Complete Stable Remission (CSR), Minimal Manifestations (MM) and/or improved PIS change. Of the 21 patients who were

symptomatic and achieved clinical remission after rituximab treatment the median baseline was MGFA Clinical Class II MM or better PIS was attained at 12-months in 10 (58.8%) AChR+ patients and 11 (68.8%) MuSK+ patients (p = 0.72). At last follow-up MM or better PIS was attained in 11 (64.7%) AChR+ patients and 12 (75%) MuSK+ patients. Twenty-one patients achieved clinical remission (12 AChR+, 9 MuSK+) with a mean time to remission of 441.4 days for AChR+ versus 230 days for MuSK+ patients (p = 0.049). The overall relapse rate in the entire cohort was 48.5% (n = 16), occurring approximately 2.7 years after treatment. Prednisone burden was also successfully reduced in both groups[4].

A retrospective study compared efficacy and tolerability of rituximab in older and younger patients with MG[5]. The study included 40 patients who were split into two groups; < 65 years old (n = 26) and ≥ 65 years old (n = 14). Thirty-one patients (77.5%) had refractory MG across the entire cohort. The primary outcome was the proportion of patients reaching a status of "improved" or better (Pharmacologic Remission [PR], MM or CSR) on the MGFA PIS at 12 months after completion of the first cycle of rituximab, compared between patients < 65 or ≥ 65 years old[5]. Thirty patients (76.9%) achieved PIS Improved or better at 12 months post rituximab initiation, with no significant difference between those ≥ 65 years old and those < 65 years old (92.3% versus 69.2%, p = 0.11). Fifteen patients (38.5%) had reached PIS MM or better at 12 months, with no significant difference between those ≥ 65 years old and those < 65 years old (53.8% versus 30.8%, p = 0.19). Outcomes did not significantly differ by MGFA class at initiation of rituximab. For the entire cohort, the median daily dose of prednisone decreased from 20 mg at baseline to 10 mg at 12 months post-rituximab initiation (p = 0.01)[5].

Safety
No new safety issues were identified.

Cost effectiveness
A repeat literature search found no new cost-effectiveness evidence.

Budget impact
[confidential information removed] This is slightly lower than the predicted number of patients included in the original evidence summary and may be due to existing precautions when prescribing rituximab during the current pandemic.

Impact on health and social care services
The impact on the service remains minimal.

Patient outcome data
[confidential information removed]

References
1. NHS England. Clinical Commissioning Policy Statement: Rituximab bio-similar for the treatment of myasthenia gravis (adults). Sep 2018. Available at: https://www.england.nhs.uk/specialised-commissioning-document-library/policy-statements-urgent-policy-statements/. Accessed September 2021.

2. International MG/COVID-19 Working Group, Jacob S, Muppidi S et al. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. *Journal of the Neurological Sciences.* 2020;412. Available at: https://doi.org/10.1016/j.jns.2020.116803. Accessed September 2021.
3. The ABN Executive in association with subspecialist Advisory groups. Association of British Neurologists Guidance on COVID-19 for people with neurological conditions, their doctors and carers. Version 6. 2020. Available at: https://www.theabn.org/page/covid19_response Accessed September 2021.
4. Litchman T, Roy B, Kumar A et al. Differential response to rituximab in anti-AChR and anti-MuSK positive myasthenia gravis patients: a single-center retrospective study. *Journal of the Neurological Sciences.* 2020;411(116690).
5. Doughty C, Suh J, David W et al. Retrospective analysis of safety and outcomes of rituximab for myasthenia gravis in patients ≥65 years old. *Muscle and Nerve.* 2021. Available at: https://onlinelibrary.wiley.com/doi/10.1002/mus.27393. Accessed September 2021.