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)

November 2020

ONE WALES INTERIM COMMISSIONING DECISION

Rituximab for the treatment of refractory myasthenia gravis in adults

Date of original advice: August 2019
Date of review: November 2020

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 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 Interim Commissioning decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Interim Commissioning 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 myasthenia gravis

These criteria have been adapted from the NHS England Clinical Commissioning Consultation document[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would be complex and following assessment may be successfully treated with standard treatment under expert guidance and withdrawn from maintenance intravenous immunoglobulin (IVIg) without the need for rituximab.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 and at least 2 trials of a steroid-sparing immunosuppressant (for example azathioprine, mycophenolate mofetil, methotrexate, ciclosporin or tacrolimus) for an adequate period of time, in an adequate dose. An adequate dose is that which produces a haematological response (reduced lymphocyte count and/or elevated mean corpuscular volume (MCV), depending on drug). 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 and other steroid sparing immunosuppression to achieve stabilisation of symptoms.
  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 taking into account 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

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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 Commissioning 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. August 2019.

Licence status

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

Guidelines

In March 2020, 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 group recommends that MG patients already on immunosuppressive medications (such as rituximab) should practice extra-vigilant social distancing, using alternatives to face-to-face consultations (such as telemedicine) where clinically appropriate. Before starting a therapy such as rituximab, healthcare professionals should consider the risk/benefit of worsening myasthenia or crisis and the risk of contracting the viral infection and discuss this with the patient[2].

The Association of British Neurologists' guidance on COVID-19 for people with neurological conditions, their doctors and carers (March 2020) advised that people with MG (acetylcholine receptor (AChR)- and muscle specific kinase receptor (MuSK)-positive and negative) on immunosuppression and/or with respiratory involvement are considered to be at a greater or high risk from COVID-19[3]. However, 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 one rapid response report, one systematic review and one prospective study. An additional retrospective study was identified by the marketing authorisation holder.

The Canadian Agency for Drugs and Technologies in Health published a rapid response report in 2018, Rituximab for the Treatment of Myasthenia Gravis: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines[4]. The gathered evidence suggested that rituximab treatment offered some clinical benefit to adult patients with refractory MG. People with MuSK positive MG appeared to experience greater clinical benefit compared with those who had AChR positive MG. Quality of life was suggested to improve with rituximab treatment and it resulted in reduced prednisone use. Generally, side effects with rituximab were few and not serious. There were limitations to the evidence gathered in relation to the low quality of studies and small sample sizes[4].

Di Stefano (2020) performed a systematic review on the clinical efficacy and safety of rituximab in AChR positive MG[5]. The review contained 13 studies, six were included in last year's evidence status report[6-11], five pre-dated last year's evidence status report[12-16] and two were published within the last year[17,18]. The review was descriptive; the authors state that the quality of data and outcome

measures were heterogeneous and considered the majority of studies to have poor internal validity and low patient numbers. The authors conclude that rituximab led to a sustained clinical improvement with prolonged time to relapse, in parallel to a reduction or discontinuation of other immunosuppressive therapies. Rituximab appears to be effective in some, but not all, patients with AChR positive MG[5].

A retrospective, multi-centre, real-life study evaluated the effectiveness and safety of rituximab in MG (n = 29)[19]. Mean age of patients was 49.6 years and 58.6% were female. Most patients had AChR positive MG (n = 20) with five MuSK positive and four seronegative patients. There was variability in the dosing protocols used as the study involved multiple centres. Rituximab (1 g) intravenous infusion followed by a second dose two weeks later and every six months thereafter was most widely used (n = 22). All immunosuppressants (except steroids) were stopped when either starting rituximab (n = 10) or within three months of starting rituximab (n = 6). Myasthenic muscle scores (MMS) were determined at each infusion and both MG foundation of America (MGFA) scores and MGFA-post-intervention status (PIS) were determined at six months for all patients, and up to 12 months when possible. Compared with baseline, at 6 and 12 months respectively, 86.2% ($p > 0.0001$) and 90.5% ($p > 0.0001$) of patients demonstrated an 'improved' response or better[1] for MGFA-PIS, a statistically significant improvement. At 6 months 14.3% of patients had achieved pharmacological remission (PR) and at 12 months 38.1% had achieved either complete stable remission (CSR) or PR. Compared with baseline, MMS had increased statistically significantly at both 6 ($p < 0.0001$) and 12 months ($p = 0.006$). Alongside improvements in outcomes measures, in the 21 patients receiving steroids at baseline, steroid dose decreased statistically significantly at 6 months ($p = 0.0005$). Side effects were experienced by 42.8% of patients (n = 12) and included infections (n = 6), infusion reactions (n = 2), haematological disorders (n = 2), bradycardia (n = 1) and psychiatric (n = 1)[19]. Two deaths occurred, the authors considered that one was probably not related to treatment (suicide, the patient had received one dose of rituximab). Although depression is a known side effect of treatment, there are no specific monitoring requirements in the SPC[20]. The second (septic arthritis leading to myasthenic crisis) could not exclude the possibility of latent infection[19]. Caution is recommended on using rituximab in any patients that may have a history of chronic or recurring infection. Rituximab use is contraindicated in anyone with active severe infection[20].

A prospective, open-label study evaluated the effectiveness of low-dose rituximab every six months in treating refractory generalised MG (n = 12)[21]. Mean age of patients was 30.6 years and 83.4% were female. All patients had AChR positive MG. Rituximab (600 mg) was administered intravenously at 0, 6 and 12 months; other immunosuppressants (excluding prednisolone) were stopped when starting rituximab. Clinical status and outcomes were measured at baseline and at 3, 6, 12 and 18 months post-initial rituximab treatment. Compared with baseline, statistically significant improvements were seen at all four time points for MGFA quantitative MG scores (QMGS), manual muscle testing (MMT) scores and MG-related activities of daily living (ADL) scores ($p \leq 0.01$ for all 16 measures). Compared with baseline, the 15-item MG-specific quality of life (MGQOL-15) scores were statistically significantly improved at the latter two time points post-initial rituximab treatment ($p \leq 0.01$ at 12- and 18-months). Alongside improvements in outcomes measures, prednisolone dosage declined significantly from 6-months post-initial rituximab treatment onwards. Rituximab significantly decreased $CD19^+$ B cells and $CD27^+$ memory B cells compared with baseline. Rituximab treatment was well tolerated with no allergic reactions or other side effects reported[21].

Safety
No new safety issues were identified.

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

[1]MGFA-PIS better response includes complete stable remission, pharmacological remission or minimal manifestations.

Budget impact
In Swansea Bay University Health Board in the last 12 months, no patients received rituximab for the fourth-line or later treatment of refractory MG. A responding clinician states that rituximab should remain an option for very brittle patients or where all other treatments have failed and that there will be very few patients where this would be a consideration. No other data have been provided although the number of patients receiving rituximab for this indication may be lower over the last year as, in accordance with guidelines, healthcare professionals should have considered the risk/benefit of worsening myasthenia crisis and the risk of contracting COVID-19 and discussed this with the patient[2,3].

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

Patient outcome data
In Swansea Bay University Health Board in the last 12 months, no patients received rituximab for the fourth-line or later treatment of refractory MG. No other data have been provided.

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