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)

August 2019

ONE WALES INTERIM COMMISSIONING DECISION

Rituximab for the fourth-line or later treatment of refractory myasthenia gravis in adults
Date of advice: August 2019

The following Interim Pathways Commissioning Group (IPCG) recommendation has been endorsed by health board Chief Executives.

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.

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

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 General Medical Council 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 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[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would be complex and following assessment may be successfully treated with standard treatment under expert guidance and withdrawn from maintenance intravenous immunoglobulin (IVIg) without the need for rituximab.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 intravenous immunoglobulin, 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

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.

One Wales Interim Commissioning Process
Interim Pathways Commissioning Group (IPCG) summary of decision rationale

Medicine: **rituximab**
Indication: **fourth-line or later treatment of refractory myasthenia gravis (adults)**
Meeting date: **29 April 2019**

Criteria	IPCG opinion
Clinical effectiveness	IPCG notes that the clinical evidence is from phase II studies, case studies and systematic reviews. IPCG consider that there was reasonable evidence of clinical effectiveness. Rituximab has been shown to reduce relapse rates, decrease the need for rescue therapies and provide a steroid-sparing effect. Rituximab has been shown to improve myasthenia gravis functional scores and remission rates. IPCG considers that the target group will be those who have failed or are intolerant to earlier lines of therapy including first-line immunosuppressive drugs.
Cost-effectiveness	IPCG notes that no cost utility analyses have been undertaken comparing rituximab with alternative treatment options. There are limited data on quality of life and resource use.
Budget impact	IPCG considers that the clinical estimate of patient numbers reported is reasonably accurate. Alternative treatment scenarios were presented whereby the choice of rescue treatment was varied. The budget impact results are subject to uncertainty, however treatment with rituximab is associated with potentially significant cost savings by Year 3 when compared to next best treatment.
Other factors	IPCG notes that there is evidence that rituximab is likely to be most efficacious for people with muscle specific kinase receptor (MuSK) positive myasthenia gravis.
Final recommendation	IPCG recommends that rituximab is made available for the fourth-line or later treatment of refractory myasthenia gravis 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 MuSK positive myasthenia gravis 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. This recommendation is subject to the development of appropriate start/stop criteria, using an agreed dosing regimen and choosing a rituximab product with the lowest acquisition cost for newly-initiated patients.
Summary of rationale	There is reasonable evidence that rituximab is clinically efficacious in this later line setting and value for money as it is likely to be associated with significant savings due to the reduction in need for expensive rescue treatments.