

Clinical Commissioning Policy Statement: Rituximab bio-similar for the treatment of myasthenia gravis (adults)

NHS England Reference: 170084P

Version 2

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1 Plain language summary

Myasthenia gravis is a rare long-term chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.

It most commonly affects the muscles that control the eyes and eyelids, facial expressions, chewing, swallowing and speaking. But it can affect most parts of the body. It can affect people of any age, typically starting in women under 40 years and men over 60 years.

Implementing the use of rituximab would require that patients had been optimally managed with standard treatments. This would require referral to and assessment by myasthenia clinics to identify those who fulfil the criteria for refractory myasthenia. It is anticipated that a proportion of patients referred to a specialised neurology unit within a neuroscience centre for consideration of rituximab would be successfully treated with standard treatment under expert guidance and withdrawn from maintenance intravenous immunoglobulin therapy without the need for rituximab.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to suspend or rescind policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

2 Background

Myasthenia gravis (MG) is an autoimmune disorder resulting in muscular weakness characterised by a wide range of symptoms, depending on which muscle groups are affected. The severity of the disorder varies from trivial to life-threatening and a variety of treatments are used depending on severity. Severely affected patients are stabilised with plasma exchange or intravenous immunoglobulin (IVIg) therapy if required, with longer term treatment consisting of steroids to induce and maintain remissions, and non-steroid immunosuppressive therapies. MG is categorised according to blood antibody studies into seropositive or seronegative for the acetylcholine receptor antibodies. Rarer patients are seropositive for the muscle specific kinase antibody (MuSK). The condition is also categorised into the less severe ocular form which affects the eyes only, and the generalised form that may affect limb, swallowing and breathing muscles.

Rituximab destroys CD20 positive B cells and has been licensed to treat a variety of autoimmune disorders. Based on its mechanism of action, it has increasingly been tried speculatively for immune-mediated disorders that fail to respond to conventional

corticosteroid and non-steroid immunosuppressant treatments with success in a wide range of conditions. A series of retrospective studies of rituximab in refractory and non-refractory seropositive MG patients have been published over the last decade, all of which show a significant response.

Treatment options for refractory MG include IVIg and plasma exchange, for which there is evidence of efficacy and ready access. Rituximab has been used when available and there is increasing evidence of its efficacy and cost-effectiveness. Implementing the use of rituximab would require that patients had been optimally managed with standard treatments. This would require referral to, and assessment by, myasthenia clinics within a specialised neuroscience centre to identify those who fulfil the criteria for refractory myasthenia.

It is anticipated that a proportion of patients referred to specialised neuroscience centre for management and consideration of rituximab would be successfully treated with standard treatment under expert guidance and withdrawn from maintenance IVIg therapy without the need for rituximab. Even with optimum treatment there remains a small group of patients who are refractory to treatment.

3 Commissioning position

3.1 Indications

NHS England has concluded that there is sufficient evidence to support the routine commissioning of this treatment for patients who fulfil the criteria listed. The MG population to be considered for rituximab treatment are the following:

1. **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.
2. **MG patients with crisis:** MG patients, with frequent hospital admissions due to MG crisis or significant MG relapses (despite adequate oral immunosuppression who require regular treatment with IVIg or plasmapheresis, as well as continuing treatment with high doses of corticosteroids and other steroid sparing immunosuppression, to achieve stabilisation of symptoms.
3. **MG patients with frequent significant relapses:** Patients in whom corticosteroids are relatively contraindicated (e.g. poorly controlled diabetes, morbid obesity, psychiatric issues), and where stabilisation from steroid sparing immunosuppression may be insufficient or delayed.

4. **MG patients in whom oral immunosuppression is complicated by significant side effects:** for example, steroid-related side effects, or in whom comorbidities such as diabetes limits the use of high-dose steroids, or patients demonstrating intolerance to various steroid-sparing immunosuppressant; also MG patients who experience multiple and serious infections from oral immunosuppression, and are therefore unable to tolerate oral immunosuppression and where their MG remains active and uncontrolled.
5. **Patients whose disease at onset is "explosive", and are unresponsive to conventional rescue treatments:** Rescue treatments such as plasmapheresis 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.
6. There should be a lower threshold to consider the drug in MuSK antibody positive MG patients with bulbar disease (which characterises this form of the condition), responding poorly to IVIg or plasmapheresis, or who demonstrate poor tolerability to immunosuppression

3.2 Dose

The rituximab biologic with the lowest acquisition costs should be used. This is likely to be a rituximab biosimilar.

Dosing schedule A:

1000 mg by intravenous infusion followed by a second 1000 mg intravenous infusion two weeks later.

Dosing schedule B:

375 mg/m² body surface area, administered as an intravenous infusion once weekly for 4 weeks (four infusions in total).

Rituximab requires 2 or 4 day-case admissions per course (every 6 months) with most patients responding for by 36 months on average (see section 3.5 below).

3.3 Contra-indications

- Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients listed in the Summary of Product Characteristics (SPC)
- Active, severe infections
- Patients in a severely immunocompromised state

3.4 Exclusions

- Patients who have not been assessed and treated by a myasthenia specialist
- The Association of British Neurologists management guidelines for MG have not been followed

3.5 Starting and stopping criteria

Starting criteria:

It is anticipated that a proportion of patients referred to a specialised neuroscience centre for consideration of rituximab would be complex and that following assessment might be successfully treated with standard treatment under expert guidance and withdrawn from maintenance intravenous immunoglobulin therapy without the need for rituximab.

Sero-positive 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 MCV, depending on drug). An adequate duration of treatment is a **minimum of 6 months** on an adequate dose.

Sero-positive 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 plasmapheresis, as well as continuing treatment with high doses of corticosteroids and other steroid sparing immunosuppression to achieve stabilisation of symptoms.

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

Patients in whom corticosteroids are relatively contraindicated (e.g. 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.

Sero-positive patients whose disease at onset is "explosive", and are unresponsive to conventional rescue treatments:

Rescue treatments such as plasmapheresis 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.

Sero-positive 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 myasthenia. 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.

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 myasthenia. Having responded, just over half of 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.

4 Effective from

This policy is effective from 2018.

5 Evidence Summary

5.1. Overview of Clinical Evidence

NHS England has considered the evidence submitted as part of the preliminary policy proposal to establish the clinical commissioning policy statement, including the clinical criteria for initiating and discontinuing the intervention. This includes up to three of the most clinically impactful publications, identified using a literature search strategy defined by the clinical lead. These publications are summarised below.

5.2. Clinical Effectiveness

Publication 1 (Hehir et al 2017)

This was a multi-centre, blinded, prospective review, comparing anti-MuSK-positive patients with MG treated with rituximab to those not treated with rituximab. The primary clinical endpoint was the Myasthenia Gravis Status and Treatment Intensity (MGSTI), a novel outcome that combines the Myasthenia Gravis Foundation of America (MGFA) post-intervention status (PIS) and the number and dosages of other immunosuppressant therapies used. A priori, an MGSTI of level #2 was used to define a favourable outcome. Secondary outcomes included modified MGFA PIS of minimal manifestations or better, mean/median prednisone dose, and mean/median doses of other immunosuppressant drugs.

Seventy-seven of 119 patients with anti-MuSK MG evaluated between January 1 2005 and January 1 2015, at 10 neuromuscular centres were selected for analysis after review of limited clinical data by a blinded expert panel. An additional 22 patients were excluded due to insufficient follow-up. Baseline characteristics were similar between the rituximab-treated patients (n = 24) and the controls (n = 31). Median follow-up duration was 3.5 years. At last visit, 58% (14/24) of rituximab-treated patients reached the primary outcome compared to 16% (5/31) of controls (p = 0.002). Number needed to treat for the primary outcome is 2.4. At last visit, 29% of rituximab-treated patients were taking prednisone (mean dose 4.5 mg/day) compared to 74% of controls (mean dose 13 mg/day) (p = 0.001 and p = 0.005).

Publication 2 (Robeson et al 2017)

A retrospective study reported by Robeson KR et al examined the duration of rituximab response in 16 patients with refractory seropositive generalised myasthenia managed in two specialist myasthenia clinics. Refractory disease was defined as a failure to achieve remission, a failure to maintain remission on treatment reduction, or adverse effects limiting use of traditional immunosuppressive agents. All patients achieved complete stable remission (63%), pharmacological remission (19%) or minimal symptom manifestations (19%) as defined by the Myasthenia Gravis Foundation of America criteria at 18-84 months after rituximab treatment. Nine patients (56%) relapsed at a mean follow-up of 36 months. Seven (44%) did not relapse during a follow-up of 47 months. Those who relapsed responded to further rituximab treatment. Ultimately 8 patients showed an extended durable response to 2 cycles of Rituximab, 7 patients to 3 cycles and 1 patient to 4 cycles. Most patients needed 12 months of treatment before being able to taper off other treatments

Publication 3 (Robeson et al 2017)

The largest and most recent review published in 2017 by Tandan et al collected 169 cases from series and case reports. Antibodies to AChR were identified in 59% and MuSK in 34%. Minimal manifestations or better was achieved in 30% of the AChR +ve myasthenia and 72% of MuSK myasthenia. Decreased post-treatment antibody titres were seen in 26% of AChR and 82% of MuSK MG cases, confirming the relationship between successful antibody depletion and response, the absence of which may be a useful early marker of treatment failure. In addition to controlling symptoms and reducing the need for intravenous immunoglobulins and plasma exchange, rituximab reduced the need for other treatments.

5.3. Safety

Adverse events in refractory myasthenia include complications arising from under-treated myasthenia, the adverse effects of the individual treatments and the combinations of multiple immunosuppressive and immunomodulatory agents. It is therefore difficult to identify the precise causes of adverse effects, and the changes in treatments that would be required to minimise them. In the review of 161 patients, two serious and two non-serious infective complications were identified, and one patient experienced a severe allergic response to Rituximab. There were 17 non-serious adverse events identified.

6 Cost

The cost will depend on the rituximab product used, the price of which is commercial in confidence. Only the rituximab product with the lowest acquisition cost will be reimbursed under this policy (likely to be a biosimilar).

7 Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

8 Mechanism for funding

Rituximab will be commissioned and funded by NHS England Specialised Commissioning under existing arrangements for the provision of specialised neurology services. Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

9 Responsible CRG

Neurosciences Clinical Reference Group

10 Date approved

September 2018.

11 Policy review date

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

12 Links to other Policies

Not applicable.

13 List of abbreviations and acronyms

AChR - Acetylcholine receptor (AChR) antibodies are autoantibodies produced by the immune system that mistakenly target proteins.

CD20 - B-lymphocyte antigen CD20 or CD20 is an activated-glycosylated phosphoprotein. Classification determinant and often abbreviated as CD, is a protocol used for the identification and investigation of cell surface molecules providing targets for immunophenotyping of cells.

IVIg - intravenous immunoglobulin

MuSK - muscle specific kinase antibody

MCV – Mean corpuscular volume (MCV) is the average volume of red cells

MGSTI - Myasthenia Gravis Status and Treatment Intensity

MGFA - Myasthenia Gravis Foundation of America

PIS - post-intervention status

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Change form for published Specifications and Products developed by Clinical Reference Group (CRGs)

Product name: Clinical Commissioning Policy Statement: Rituximab bio-similar for the treatment of myasthenia gravis (adults)

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Description of changes required

Describe what was stated in original document	Describe new text in the document	Section/ Paragraph to which changes apply	Describe why document change required	Changes made by	Date change made
The subject was not included in the policy	Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.	8. Mechanism for funding	There is a requirement to complete a prior approval form which has been in use for the policy since publication and was included in the circular. However, queries have been raised by some regions that as it is not included in the policy then the prior approval is not required. The change is to reflect the prior approval requirement in the policy.	Head of Clinical Policy Team	25 th March 2021