Clinical Commissioning Policy: Rituximab for Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

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Clinical Commissioning Policy: Rituximab for the Treatment of Anti-Neutrophil Cytoplasmic Antibody-Associated (ANCA) Vasculitis (AAV)

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Prepared by the NHS Commissioning Board Clinical Reference Group for Specialised Rheumatology

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Policy Statement

The NHS Commissioning Board (NHS CB) will commission rituximab for ANCA-associated vasculitis, in accordance with the criteria outlined in this document, for patients with relapsing disease, with primary treatment failure or with adverse reactions or contra-indications to cyclophosphamide.

In creating this policy the NHS CB has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

The NHS CB has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. The NHS CB is committed to ensuring equality of access and non-discrimination, irrespective of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex (gender) or sexual orientation. In carrying out its functions, the NHS CB will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which they are responsible, including policy development, review and implementation.

Plain Language Summary

ANCA Associated Vasculitis is a type of autoimmune inflammation caused by auto-antibodies. Normal antibodies are parts in the blood that are produced by the immune system to fight infectious agents (such as bacteria). Auto-antibodies are abnormal antibodies that attack one’s own cells and tissues. ANCAs are auto-antibodies that attack the walls of small and medium vessels in different tissues and organs of the body. ANCA-associated vasculitis is rare and characterised by necrotising inflammation of small vessel walls. Necrotising means ‘causing the death of a specific area of tissue’.

Conventional drug treatment is moderately effective but significantly toxic. In unresponsive or relapsing disease further treatment is likely to produce cumulative toxicity and a poorer response to treatment. Rituximab has been shown to offer greater efficacy with some reduction in toxicity, especially in longer term side effects.

Rituximab is funded for patients with relapsing disease, with primary treatment failure or with adverse reactions or contra-indications to standard drugs. Information on the outcome of rituximab use will be collected and will inform future treatments.
1. Introduction

ANCA-associated vasculitis comprises three conditions which share overlapping clinical and serological features and are characterised by necrotising inflammation of small vessel walls; Granulomatosis with Polyangiitis (GPA, Wegener’s), Microscopic Polyangiitis (MPA) and Eosinophilic Granulomatosis with Polyangiitis (EGPA, Churg Strauss Syndrome). Although the cause is unknown, ANCA antibodies, cytokine-primed neutrophils and B lymphocytes are recognised to have an important role in disease pathogenesis.

These are rare conditions, with incidence estimated at 20 per million and peak age of onset 60-70 years. Without treatment they are usually fatal, and not everyone responds to treatment; on average, 80% of those treated will be alive at two years, and 20% of these survivors will have significant renal disease. Increasing age and renal involvement at diagnosis are poor prognostic factors.

These diseases frequently involve multiple organ systems: most commonly the kidneys, ENT/respiratory tract, skin and nervous system are affected. However, in some cases the disease is “limited” to a single area (typically the head and neck) and, paradoxically, this type of disease can be less responsive to conventional treatment than systemic disease.

Management involves three phases; remission induction, remission maintenance, and treatment of relapse. At regular intervals it is important to formally assess and define disease activity and damage status using a formal instrument (e.g. BVAS), so that accurate ascertainment of remission, refractory disease or relapse can be documented in every patient.

The likelihood of relapse varies according to disease, but is highest in GPA; up to 50% of patients will relapse within 5 years, even with maintenance immunosuppression. Each relapse carries a risk of subsequent critical organ damage.

Cyclophosphamide is the standard remission induction agent, and is usually given for 3-6 months, adjusted for age, body weight and renal function. The majority of people treated with cyclophosphamide will attain remission. However, 15% will not, and will continue to have active or progressive disease that is refractory to conventional treatment.

Cyclophosphamide has significant side effects including gonadal toxicity, bone marrow depression, haemorrhagic cystitis and an increased risk of future development of bladder cancer. There are therefore specific situations where the avoidance of cyclophosphamide is desirable e.g.

- Females who have not completed their family and who are at risk of infertility due to a cyclophosphamide induced premature menopause
- Previous uroepithelial malignancy
- Intolerance of cyclophosphamide, either due to side effects or cytopenia

The 2 randomised clinical trials of rituximab, and the many positive case series, have provided a supporting evidence base for vasculitis clinicians (predominately nephrologists and rheumatologists) who have needed to use rituximab for various reasons as an alternative to cyclophosphamide. However, national commissioning
guidance is needed, to avoid the risk of inequality of access to treatment, which potentially occurs both due to post-code access/funding according to commissioner willingness to fund, and also according to clinician expertise in assessing and treating vasculitis.

2. Definitions

Rituximab
Rituximab is a monoclonal antibody that targets CD-20, a cell surface marker that is widely expressed on B-cells, leading to B cell depletion.
Rituximab has a license for the treatment of lymphomas and rheumatoid arthritis, but has also been used off-license in other autoimmune rheumatological diseases.

3. Aim and Objectives

To define criteria for the commissioning of the use of rituximab in ANCA-associated vasculitis, particularly in patients with relapsing disease, with primary treatment failure or with adverse reactions or contra-indications to cyclophosphamide.

4. Criteria for commissioning

Rituximab will be routinely funded for the treatment of ANCA-associated vasculitis in the following four situations:

As an initial remission induction agent in newly diagnosed patients where avoiding the use of cyclophosphamide is desirable.

Rituximab has not replaced cyclophosphamide as the routine first agent of choice for initial remission induction, as no clear benefit over cyclophosphamide in terms of safety or efficacy has been established and the long term optimal treatment strategy i.e. timing and duration of rituximab re-treatment has yet to be determined.

However, rituximab is appropriate in situations where there is a (relative) contraindication to the use of cyclophosphamide. These would include previous uroepithelial malignancy, pre-menopausal females who have not completed their family, and previous cyclophosphamide use. Rituximab would also be appropriate where there is inability to complete planned treatment with cyclophosphamide due to allergy/intolerance or side effects.
As a remission induction agent when cyclophosphamide has not been effective
This can be defined as disease which has remained active despite an adequate trial of cyclophosphamide (3-6 months), or where new items of disease activity have occurred despite ongoing cyclophosphamide treatment. This clinical situation comprises many of the individual published case series where rituximab has been used.

As a remission induction agent at time of first relapse.
There is evidence from the RAVE trial that rituximab is more effective than cyclophosphamide in this situation, and also avoids the cumulative risk of further cyclophosphamide exposure.

As a remission maintenance agent.
It would be appropriate to use rituximab as a remission maintenance agent when:

Rituximab has been needed to induce remission, particularly when the disease has been characterised by previous relapses despite several alternative maintenance agents, and where the risk of relapse also includes (known from previous relapses) a risk of vital organ damage.

Alternative remission maintenance agents (e.g. Azathioprine, Methotrexate, Mycophenolate) have not been tolerated due to toxicity or have been ineffective.

5. Patient pathway

The British Society for Rheumatology (BSR) and the European Vasculitis Study Group (EUVAS) has produced guidelines for the management of adults with ANCA-associated vasculitis.4, 5 These are based around the use of cyclophosphamide in severe disease. These guidelines describe the process for assessment of patients presenting with ANCA-associated vasculitis and their stratification in terms of range and severity of organ involvement. This process, together with existing comorbidities and other patient specific factors describes the existing patient pathway. The BSR and EUVAS guidelines were developed before the emergence of recent data on the use of rituximab, but the treatment schedules with rituximab described in this document can be considered as developments of these earlier guidelines.

6. Governance arrangements

Accurate assessment of disease activity and damage, according to standard metrics (e.g. BVAS)3 is essential to determine both the eligibility for rituximab and assessing efficacy of treatment. This will require a multidisciplinary assessment of disease by
7. Epidemiology and needs assessment

The annual incidence of ANCA-associated vasculitis in the UK is approximately 20/million (GPA 11.3/million, MPA 5.9/million) with a prevalence of approximately 250/million. The peak age at diagnosis is 65–74 years, with more cases in men than women. Cases are managed in a stratified manner. It is estimated that approximately 20-25 patients in each region may need rituximab (including re-treatment each year).

8. Evidence Base

A recently published systematic literature review of 43 studies (including two randomized controlled trials and a predominance of small, uncontrolled series) made evidence based recommendations in five areas for the use of rituximab in ANCA-associated vasculitis.

8.1 Recommendation 1

8.1.1 In newly diagnosed ANCA-associated vasculitis

*Rituximab is as effective as cyclophosphamide for remission induction of previously untreated patients. Rituximab may be preferred, especially when cyclophosphamide avoidance is desirable. (Level of evidence 1b.)*

8.1.2 In refractory and/or relapsing disease

*Rituximab is an effective treatment of refractory and/or relapsing forms of ANCA-associated vasculitis and can be recommended (Level of evidence 1b.)*

8.1.3 According to patient subgroups

8.1.3.1 WG with head and neck manifestations

*Rituximab is an effective treatment of refractory head and neck manifestations of WG and can be recommended when conventional therapy has failed. (Level of evidence 2b/4.)*

8.1.3.2 Paediatric ANCA-associated vasculitis

*Rituximab should be considered for the treatment of children with ANCA-associated vasculitis that fails to respond to conventional*
induction therapy with glucocorticoids and cyclophosphamide; or for patients with relapsing disease where there is particular concern regarding cumulative glucocorticoid and/or cyclophosphamide toxicity. (Level of evidence 4.)

8.1.3.3 Churg–Strauss syndrome
Response rates in refractory and/or relapsing Churg–Strauss syndrome appear similar to other vasculitides and rituximab may be considered when conventional therapy has failed. (Level of evidence 4.) (Level of evidence 1b.)

8.2 Recommendation 2. What is the optimal induction dosage regimen?
Both commonly used rituximab protocols (375 mg/m²/week for 4 weeks; 1000 mg repeated after 2 weeks) appear equally effective for induction of remission, but have not been formally compared; therefore, both can be recommended. (Level of evidence 4.)

8.3 Recommendation 3. What are the longer term outcomes of treatment with rituximab?

8.3.1 Relapse rate
The overall response to rituximab in refractory disease may be superior to that seen with alternative therapies in similar cohorts of patients. There is insufficient evidence on long-term outcomes with rituximab when compared with conventional therapy in newly diagnosed patients.
Relapse after rituximab is common and patients should be monitored accordingly. (Level of evidence 4.)

8.3.2 Potential predictors of relapse
No biomarker reliably predicts relapse. (Level of evidence 3.)

8.3.3 Re-treatment with rituximab
Repeat rituximab is recommended for a relapse following rituximab-induced remission. (Level of evidence 4.)
Pre-emptive re-treatment may be considered in order to reduce relapse rates. (Level of evidence 4.)

8.4 Recommendation 4. How should other immunosuppressive therapies be prescribed in patients treated with rituximab?

8.4.1 Should cyclophosphamide be administered concomitantly with rituximab?
We do not recommend the routine use of cyclophosphamide with rituximab.
Cyclophosphamide may be considered in severe, life or organ-threatening
presentations such as rapidly progressive GN in order to achieve rapid disease control. (Level of evidence 4.)

8.4.2 Should other immunosuppressant treatment be continued following rituximab?

No conclusion can be drawn from current data regarding the prescription of other immunosuppressing drugs with rituximab.

8.4.3 What glucocorticoid regimen should be adopted in patients treated with rituximab and can glucocorticoids be stopped?

High-dose intravenous or oral glucocorticoids may be administered with the initial rituximab course in order to obtain rapid control of disease. (Level of evidence 4.)

There is no clear evidence to guide steroid tapering.

8.5 Recommendation 5. How safe is rituximab in ANCA-associated vasculitis?

There is no convincing evidence that rituximab increases the frequency of severe infections when used in the treatment of vasculitis. Other drug-related adverse events occur with similar frequency to that seen in other indications. (Level of evidence 4.)

We recommend that patients receive vaccinations at least 1 month before their first dose of rituximab. (Level of evidence 3.)

The efficacy of rituximab in remission induction in ANCA-associated vasculitis, has been evaluated in two randomized controlled trials: RAVE and RITUXVAS. 1,2

RAVE enrolled 197 ANCA positive ANCA-associated vasculitis patients (newly diagnosed or relapsing), who were randomised to either rituximab 375mg/m2 intravenously (IV) once weekly for 4 weeks plus daily cyclophosphamide-placebo, or rituximab-placebo IV plus daily cyclophosphamide 2mg/kg. Those with severe renal disease or severe alveolar haemorrhage were excluded. The primary endpoint was remission, defined as BVAS/GPA of 0 and successful oral steroid withdrawal at month 6. Groups were matched for disease severity, subtype, organ involvement and ANCA type and approximately 50% in each group had relapsing disease. Remission rates were comparable in the two treatment arms, with 64% of rituximab and 53% of control group reached the primary endpoint (p=0.09). However, in a planned subgroup analysis, the rituximab-based regime (67%) was more efficacious than the cyclophosphamide-based regimen (42%) for inducing remission of relapsing disease (P=0.01).

RITUXVAS enrolled 44 patients with new onset ANCA-associated vasculitis with renal involvement; 33 were randomised to rituximab 375mg/m2 IV once weekly for 4 weeks plus 2 doses of cyclophosphamide 15mg/kg IV with the 1st and 3rd rituximab infusions; or cyclophosphamide 15mg/kg IV for 3-6 months (a standard BSR/EULAR regime) followed by azathioprine maintenance at 2mg/kg daily. The primary endpoint was remission defined as a BVAS = 0 at 6 months, sustained for a further 6 months.
Remission rates were 76% in the rituximab arm and 82% in the cyclophosphamide arm. At 2 years the primary composite outcome of relapse, death, or end stage renal failure occurred in 42% in the rituximab group compared with 36% in the cyclophosphamide group; i.e. rituximab was comparable, but not superior to, cyclophosphamide. Adverse events were comparable in the two treatment regimens at 2 years.

9. Rationale behind the policy statement

Conventional first line treatment of AAV with cyclophosphamide and corticosteroids according to BSR/EUVAS is moderately effective but significantly toxic. In refractory or relapsing disease further cyclophosphamide treatment is likely to produce further cumulative toxicity with a lower likelihood of response to treatment. Use of rituximab offers greater efficacy with some reduction in toxicity, particularly with regard to longer term side effects. There are also some patients in whom first line treatment with cyclophosphamide is unacceptably toxic for whom rituximab may be appropriate first line treatment.

10. Mechanism for funding

Through the responsible Area Team.

11. Audit Requirements

It is proposed that all patients treated with rituximab for AAV are entered into a centrally held database which would include baseline pre-treatment data of disease severity, comorbidity and treatment history. The UKVAS (UK Vasculitis Group) Registry would be a suitable vehicle to host this. Outcomes of treatment would include mortality, renal function and other major organ damage.

12. Documents which have informed this policy

See reference list below
13. Links to other policies

This policy follows the principles set out in the ethical framework that governing the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

14. Date of Review

This policy will be reviewed in April 2014 unless data received indicates that the proposed review date should be brought forward or delayed.

References