



Clinical Commissioning Policy: Rituximab for the treatment of ANCA-associated vasculitis in adults

Reference: NHS England A13/P/a

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Rituximab for the treatment of ANCA- associated vasculitis in adults

First published: January 2015

**Prepared by NHS England Specialised Services Clinical Reference
Group for Specialised Rheumatology**

Published by NHS England, in electronic format only.

NHS England INFORMATION READER BOX**Directorate**

Medical	Commissioning Operations	Patients and Information
Nursing	Trans. & Corp. Ops.	Commissioning Strategy
Finance		

Publications Gateway Reference: 02659

Document Purpose	Policy
Document Name	A13/P/a: Clinical Commissioning Policy: Rituximab for the treatment of ANCA-associated Vasculitis in Adults
Author	NHS England
Publication Date	January 2015
Target Audience	CCG Clinical Leaders, CCG Accountable Officers, CSU Managing Directors, Foundation Trust CEs, Medical Directors, Directors of PH, Directors of Nursing, NHS England Regional Directors, NHS England Area Directors, Directors of Finance, GPs, NHS Trust CEs
Additional Circulation List	
Description	This policy aims to ensure equitable and cost-effective use of rituximab as a treatment option for people with ANCA-associated vasculitis, both as a remission-induction and a maintenance agent.
Cross Reference	A13/S/a Service Specification - Specialised Rheumatology Services (Adult)
Superseded Docs (if applicable)	A13/P/a: Clinical Commissioning Policy: Rituximab for the treatment of ANCA-associated Vasculitis in Adults - April 2013
Action Required	
Timing / Deadlines (if applicable)	
Contact Details for further information	NHS England Medical Directorate Specialised Services Skipton House, 80 London Road SE1 6LH 0300 311 2233 www.england.nhs.uk/commissioning/
Document Status	This is a controlled document. Whilst this document may be printed, the electronic version posted on the intranet is the controlled copy. Any printed copies of this document are not controlled. As a controlled document, this document should not be saved onto local or network drives but should always be accessed from the intranet

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Policy Statement

NHS England will commission rituximab for patients with ANCA-associated vasculitis in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment, including NICE guidance. 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

Throughout the production of this document, due regard has been given to eliminate discrimination, harassment and victimization, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited in under the Equality Act 2010) and those who do not share it.

Plain Language Summary

ANCA Associated Vasculitis is a disease in which blood vessels become inflamed, often associated with the presence in the blood stream of ANCA auto-antibodies. Normal antibodies are produced by the immune system to fight infectious agents (such as bacteria). Auto-antibodies are abnormal antibodies that can attack one's own cells and tissues. ANCAs are a type of autoantibody that is associated with inflammation in the walls of small and medium blood vessels in different tissues and organs of the body.

Conventional drug treatments which may involve the use of chemotherapy drugs, such as cyclophosphamide, are usually effective but also have significant potential toxicity. In people whose disease has been unresponsive to conventional treatment or has relapsed despite this, further conventional treatment is likely to produce cumulative toxicity and a poorer response to treatment.

Rituximab has been shown to be an effective alternative treatment and is likely to offer particular benefit in specific situations when conventional treatment has either failed or cannot be safely used, or where future fertility may be an issue. Rituximab is therefore available as a treatment option for patients with ANCA Associated Vasculitis according to the criteria outlined in

this document. 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. Management of all three conditions is identical and involves three phases; remission induction, remission maintenance, and treatment of relapse. At regular intervals it is essential to formally assess and define disease activity and damage status using a formal instrument (e.g. BVAS, VDI), 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 that additional critical organ damage will occur, leading to an irreversible deterioration in health. Relapse is often associated with significantly increased NHS costs e.g. hospitalisation, and both the costs (drug and day case activity) and infection risk from steroids and immunosuppression of remission re-induction. Significant costs also accrue at relapse from the accumulation of further organ damage, particularly if this leads to further renal damage and risk of renal replacement therapy. Thus prevention of relapse is a key priority, as this improves long-term outcomes for people living with vasculitis and directly reduces NHS activity and costs.

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 inducing premature ovarian failure, bone marrow depression and infection, haemorrhagic cystitis, and an increased risk of future uroepithelial (bladder) cancer.

Thus new treatments that can potentially avoid the chemotherapy side effects

of Cyclophosphamide are needed.

Two randomised clinical trials of rituximab (RAVE and RITUXVAS), and many positive case series, provide a supporting evidence base to vasculitis clinicians (predominantly nephrologists and rheumatologists) who have needed to use rituximab as an alternative to Cyclophosphamide over the last 10 years (1, 2).

NICE has published guidance on the use of rituximab for the treatment of ANCA-associated vasculitis, as an option for inducing remission in adults with severe active Granulomatosis with Polyangiitis (Wegener's) and Microscopic Polyangiitis, if specific criteria are met.

- The disease has remained active or progressed despite a course of cyclophosphamide lasting 3–6 months; OR
- Cyclophosphamide is contraindicated (as defined in the summary of product characteristics) or not tolerated; OR
- The person has not completed their family and treatment with cyclophosphamide may materially affect their fertility; OR
- Further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose; OR
- The person has had uroepithelial malignancy.

These NICE criteria also align with the recommendations in the BSR and BHPR guideline for the management of all adults with ANCA-associated vasculitis, but with one important exception (3). This relates to the definition of when *“further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose.”*

NICE has defined this dose as 25g, which is equivalent to two induction courses of IV cyclophosphamide. The current NICE guidance therefore positions the routine use of Rituximab at the time of third remission induction i.e. at second relapse. However, the evidence in the RAVE trial is that, in relapsing patients, rituximab is more effective than cyclophosphamide. Relapsing patients are also those at greatest risk of cumulative CYC toxicity, which is likely to increase even before a threshold of 25g is reached. There is therefore clinical and cost-effective justification for using rituximab at first relapse, before a threshold of 25g cyclophosphamide is reached.

NICE were restricted in their appraisal to only being able to assess the dose of rituximab that is licensed for this indication. This is the “lymphoma” regimen of four infusions at weekly intervals of 375mg/m². However, in England currently, the majority of existing centres managing patients with ANCA associated vasculitis use rituximab in routine clinical practice at the lower dose of two 1g infusions two weeks apart. This is also the dose schedule used in all other autoimmune rheumatic diseases e.g. Rheumatoid Arthritis (licensed dose) and SLE (off label use). This regimen results in a lower total dose of rituximab, delivered over a shorter period of time, and is therefore

more convenient for patients. The clinical consensus, as indicated in the BSR and BHPR guideline, is that both protocols appear equally effective. In a retrospective review of 65 patients, the two regimens were compared and were found to be of equal efficacy, with no difference in the duration of B cell depletion or the therapeutic effect.

If the lower dose schedule is employed, there is a significant NHS cost saving in terms of reduced NHS activity (50%) and reduced drug costs (40%) compared to the higher licensed dose.

Utilising the rituximab Ig x2 regimen also results in a cost saving *compared to a course of IV cyclophosphamide* for relapsing patients. This means that it is both clinically effective and cost effective to use rituximab at time of first relapse after initial cyclophosphamide induction, rather than re-treating relapsing patients with cyclophosphamide again until they had reached their maximum dose of 25g. This specific requirement has therefore been amended in this commissioning policy.

NICE also only appraised the use of Rituximab for the two most common types of ANCA associated vasculitis, namely Granulomatosis with Polyangiitis (Wegener's) and microscopic polyangiitis. These two subtypes comprise 90% of all cases of ANCA associated vasculitis. The third subtype of ANCA associated vasculitis, Eosinophilic Granulomatosis with Polyangiitis (EGPA, Churg Strauss Syndrome), is much rarer (10% of all cases), but shares similar clinical features and identical treatment strategies to the other two conditions. Although there have been no large trials of Rituximab for EGPA because of its rarity, and use in this condition is off-label, case series data report similar efficacy to that seen in the other two subtypes.

Maintenance treatment with rituximab was also outside the scope of the NICE appraisal, as this was restricted to the marketing authorisation of remission induction. However, because of the pivotal importance of preventing relapse, there is a subgroup of patients for whom maintenance rituximab is required, and this is currently commissioned by NHS England as per Commissioning Policy. This revised policy therefore continues to include specific situations where maintenance treatment is clinically and cost effective but provides greater clarity and incorporates additional criteria that must be met.

2. Definitions

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, rheumatoid arthritis, and ANCA-associated vasculitis. Rituximab is also commissioned by NHS England (off-label) in other autoimmune diseases according to specific criteria (e.g. Systemic Lupus Erythematosus Policy A13/PS/a).

3. Aim and objectives

This policy aims to ensure equitable and cost-effective use of rituximab as a treatment option for people with ANCA-associated vasculitis, both as a remission-induction and a maintenance agent.

4. Epidemiology and needs assessment

The annual incidence of ANCA-associated vasculitis in England is approximately 20/million (GPA 11.3/million, MPA 5.9/million, EGPA 2.8/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 40-70 people in each senate region will need rituximab (including maintenance treatment each year).

5. Evidence base

Induction therapy

The evidence base for the effectiveness of rituximab as induction therapy has been appraised by NICE, see earlier.

Maintenance therapy

The prospective, randomized, controlled MAINRITSAN trial compared rituximab to azathioprine to maintain ANCA-associated vasculitis remission in a largely new onset GPA/MPA patient cohort (4). Once remission was obtained with a conventional cyclophosphamide and glucocorticoid regimen, patients were randomly assigned to receive two 500mg rituximab infusions at six months, then every 6 months for a total of 5 infusions (2500mg) over 18 months, or azathioprine for 22 months at an initial dose of 2mg/kg/day. The primary endpoint was the major relapse rate (EULAR/ACR criteria) at 28 months. This study demonstrated that rituximab was superior to azathioprine to maintain ANCA-associated vasculitis remission at mean duration of follow-up 34.3 months. Six out of 56 (10.7%) rituximab patients and 24/53 (45.3%) azathioprine patients had at least one major relapse. The risk of major relapse remained lower in the rituximab arm compared to the azathioprine arm (hazard ratio 0.18, 95% CI 0.09 to 0.42, $p < 0.0001$).

Several observational studies have demonstrated that maintenance rituximab is effective at preventing relapse after rituximab induction for relapsing disease, where the subsequent relapse risk is high.

Smith et al reported retrospective, standardised collection of data from sequential patients receiving rituximab for refractory or relapsing AAV at a single centre (5). Group A patients (n=28) received rituximab induction therapy (4 infusions of 375 mg/m² or two 1g infusions) and further rituximab only at the time of subsequent relapse. Group B patients (n=45) received routine rituximab re-treatment for 2 years; two 1g infusions for remission induction, followed by 1g every 6 months. Group C patients (n=19) comprised patients in group A who subsequently relapsed and began routine re-treatment for 2 years.

Response (complete/partial remission) occurred in 26 of the 28 patients (93%) in group A, 43 of the 45 patients (96%) in group B, and 18 of the 19 patients (95%) in group C. At 2 years, relapses had occurred in 19 of 26 patients (73%) in group A, 5 of 43 (12%) in group B ($P < 0.001$), and 2 of 18 (11%) in group C ($P < 0.001$). At the last follow-up (median of 44 months), relapses had occurred in 85% of those in group A (22 of 26), 26% of those in group B (11 of 43; $P < 0.001$), and 56% of those in group C (10 of 18; $P = 0.001$). Glucocorticoid dosages were decreased and immunosuppression therapy was withdrawn in the majority of patients. Routine rituximab re-treatment was well tolerated, and no new safety issues were identified.

In a retrospective study of scheduled redosing of 172 patients who were treated after remission induction or transitioned from another maintenance regimen, a very low major relapse rate of 5% was observed during a median follow-up of 2.1 years, without any unexpected safety signals and with overall survival similar to a matched general population (6).

The role of rituximab in maintenance of remission, in comparison to azathioprine, is being evaluated in a randomised controlled trial of relapsing ANCA-associated vasculitis (RITAZAREM). This worldwide study is jointly coordinated from Cambridge, and is being conducted in a number of specialised vasculitis centres (nephrology and rheumatology) in England.

6. Rationale behind the policy statement

The evidence base for the effectiveness of rituximab as induction therapy, used at its licensed dose, has been appraised by NICE. This policy is aligned with the NICE guidance apart from the removal, for clinical and cost effective reasons, of the requirement to have received up to 25g of cyclophosphamide before reaching eligibility for rituximab.

The evidence base for maintenance therapy (an off-label indication) is limited and there are currently no published formal analyses of cost effectiveness of this therapy. However, maintenance therapy significantly reduces the risk of relapse. Each relapse carries a risk that additional critical organ damage will occur, leading to an irreversible deterioration in health. Relapse is associated with significantly increased NHS costs e.g. hospitalisation, and both the costs (drug and day case activity) and infection risk from steroids and immunosuppression of remission re-induction. Significant costs also accrue at relapse from the accumulation of further organ damage, particularly if this leads to further renal damage and risk of renal replacement therapy. Thus prevention of relapse is a key priority, as this improves long-term outcomes for people living with vasculitis and directly reduces NHS activity and costs.

Moreover, the cost of each year of maintenance therapy with rituximab is identical to the cost of treating a relapse with rituximab re-induction therapy, but avoids the additional cost of managing the relapse (e.g. adjunctive steroid, hospitalisation, and the costs of managing any resultant organ damage). The cost is also considerably cheaper than treating a relapse with a course of IV

cyclophosphamide.

The dose of maintenance therapy is 1g every 6 months for 2 years.

7. Criteria for commissioning

NHS England will routinely fund the use of rituximab for the treatment of ANCA-associated vasculitis as an option for inducing remission in adults, only if:

- The disease has remained active or progressed, or has relapsed, despite a course of cyclophosphamide lasting 3–6 months; OR
- Cyclophosphamide is contraindicated (as defined in the summary of product characteristics) or not tolerated; OR
- The person has not completed their family and treatment with cyclophosphamide may materially affect their fertility; OR
- The person has had uroepithelial malignancy.

Dosing regimens are either the licensed dose of four infusions at weekly intervals of 375mg/m² or at two infusions of 1g, two weeks apart.

Maintenance therapy with rituximab is not covered by the existing product marketing authorisation and use is not routinely commissioned.

NHS England will commission the use of rituximab as maintenance therapy only when one of the following three **clinical** criteria, and all three additional **centre** criteria, is met.

1. The person is enrolled in a randomised trial that includes B cell suppression as maintenance therapy (e.g. RITAZAREM); OR.
2. Relapse requiring re-induction therapy has occurred after a previous rituximab induced remission; OR
3. Rituximab has been required to induce remission in Cyclophosphamide-refractory disease and future relapse would have a high risk of organ damage.

In addition

- The decision regarding rituximab maintenance has been made at, or in conjunction with, a specialised centre AND
- The person has been provided with the opportunity to be considered for any suitable clinical trials AND
- The person is registered on the UKIVAS database, to enable identification of use and outcome of treatment.

Maintenance therapy will be stopped after 2 years, or earlier if either treatment intolerance, a contraindication, or a major relapse occurs.

Contraindications;

- 1) Hypersensitivity to rituximab or murine proteins or excipients

- 2) Active, severe infections or chronic infections (e.g. tuberculosis, sepsis, viral hepatitis)
- 3) Severe heart failure (NYHA Class IV) or severe, uncontrolled cardiac disease
- 4) Patients in a severely immunocompromised state

8. Patient pathway

The British Society for Rheumatology has published updated guidance on the management of adults with ANCA-associated vasculitis. These describe the process for assessment of people presenting with ANCA-associated vasculitis and their stratification in terms of range and severity of organ involvement. This, together with existing comorbidities and other patient specific factors is used to outline the existing patient pathway, and any proposed amendments to this pathway following approval of the policy.

The patient pathway is referral from local Consultant Rheumatologists or Nephrologists or relevant specialist for an opinion from a Specialised Centre with expertise in the management of ANCA-associated vasculitis. If, after assessment (including remote or 'virtual' assessment) by the Specialised Centre team, the agreed commissioning criteria are met, Rituximab can be prescribed either by the Specialised Centre or by the local team via networked care arrangements.

9. Governance arrangements

The service specification A13/S/a for Specialised Rheumatology describes the care pathways and key aspects of specialised services being commissioned at specialised centres for people with ANCA-associated vasculitis and should be referred to in conjunction with this policy.

10. Mechanism for funding

Funding is transacted from NHS England through local contract agreements and terms.

11. Audit requirements

All centres will be expected to provide information on activities and outcomes including compliance with this Policy, on request. People receiving rituximab should be recruited to the UKIVAS study and data collected on a central platform. The specified outcomes will include BVAS (disease activity) and VDI (disease damage), with assessment undertaken by clinicians who have certification of proficiency in using these outcome tools.

These will be measured at baseline, 6, and 12 months and annually thereafter (with the schedule modified if maintenance therapy is given so that assessment can be done at 6 and 12 months after each subsequent dose until a decision is made to discontinue rituximab therapy).

12. Documents which have informed this policy

This policy has been informed by the references listed at the end of this

document.

13. Links to other policies

This policy links to other rituximab policies e.g. Systemic Lupus Erythematosus (A13/PS/a) and to the service specification for Specialised Rheumatology Services (A13/S/a) and Renal Dialysis (A06/S/e).

14. Date of review

This policy will be reviewed in April 2016 or if information is received which indicates that the proposed review date should be brought forward or delayed.

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