One + all | we care

Royal Cornwall Hospitals NHS Trust

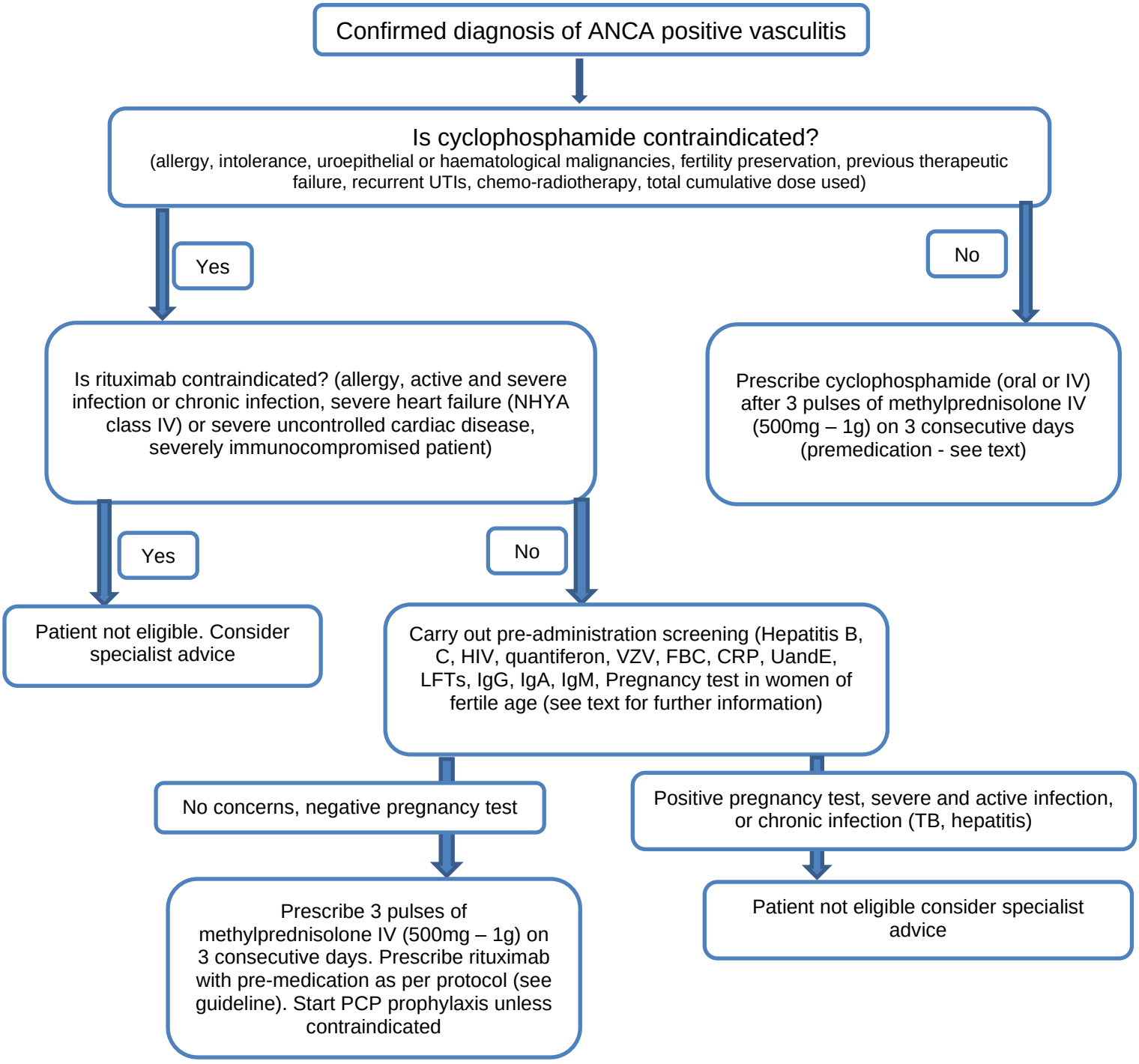
Renal Vasculitis in Adult Patients Clinical Guideline

V1.0

March 2023

Summary

Figure 1: Flow chart for consideration of immunosuppression prescribing decision



1. Aim/Purpose of this Guideline

1.1 This guideline applies to all patients who have had a diagnosis of ANCA-positive renal vasculitis and are cared for by the RCHT renal multidisciplinary team. It sets out which patients should receive rituximab treatment for the management of a new or relapsing ANCA-positive renal vasculitis. This guideline is appropriate for all staff who work within inpatient and outpatient services. Practitioners prescribing for patients are responsible for their own clinical practice including clinical competency.

1.2 This guideline provides treatment options and prescribing process which can be followed for all presentations of small vessel vasculitis with renal involvement including granulomatosis with polyagiitis (GPA), microscopic polyangiitis (MPA), Eosinophilic granulomatosis with polyangiitis (EGPA), glomerulonephritis (GN)

Data Protection Act 2018 (General Data Protection Regulation – GDPR) Legislation

The Trust has a duty under the Data Protection Act 2018 and General Data Protection Regulations 2016/679 to ensure that there is a valid legal basis to process personal and sensitive data. The legal basis for processing must be identified and documented before the processing begins. In many cases we may need consent; this must be explicit, informed, and documented. We cannot rely on opt out, it must be opt in.

Data Protection Act 2018 and General Data Protection Regulations 2016/679 is applicable to all staff; this includes those working as contractors and providers of services.

For more information about your obligations under the Data Protection Act 2018 and General Data Protection Regulations 2016/679 please see the Information Use Framework Policy or contact the Information Governance Team

Royal Cornwall Hospital Trust rch-tr.infogov@nhs.net

2. The Guidance

2.1 Introduction

2.1.1 Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis is a broad definition which includes several potentially life-threatening diseases, including granulomatosis with polyangiitis (GPA, Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, or Churg-Strauss syndrome). Without appropriate treatment, ANCA-positive vasculitides are usually fatal. In the presence of appropriate treatment, the 5-year survival rate of ANCA-positive vasculitides is 74-91% for GPA, 45-76% for MPA, and 60-97% for EGPA.

2.1.2 A negative ANCA result does not exclude vasculitis. It is important to note that 10-20% of patients with GPA are ANCA-negative. In such patients, the diagnosis will rely on the results of the kidney biopsy (evidence of crescentic glomerulonephritis) alongside the clinical signs and symptoms.

2.1.3 Rituximab is a monoclonal antibody against the protein CD20, mainly found on the surface of the B-cells, and is used in several inflammatory conditions, including haematological cancers, rheumatoid arthritis, and ANCA-positive renal vasculitis (EULAR/ERA-EDTA 2016). In patients with ANCA-positive renal vasculitis, rituximab is as effective as cyclophosphamide for remission induction and in refractory/relapsing disease and can be associated with a more favourable safety profile (Guerry M 2012).

2.2 Selection of suitable patients and treatment options

2.2.1 Figure 1 found above should be used to support the clinician in treatment management of patients showing vasculitis with renal involvement. Treatment should always be patient specific with a personalised approach.

2.2.2 Cyclophosphamide is first line therapy for ANCA-positive vasculitis as per NICE guidance.

2.2.3 Rituximab is an alternative for patients who:

- Are of fertile age, to avoid the exposure to the gonadotoxic effects of cyclophosphamide
- Have a history of urological or haematological cancers
- Have a history of recurrent urinary tract infections
- Are on active chemo or radiotherapy
- Have an allergy or intolerance to cyclophosphamide
- Have previous therapeutic failure on cyclophosphamide.
- Have any other contraindication to cyclophosphamide as per the summary of product characteristics.

2.2.4 Rituximab is considered second line therapy to cyclophosphamide but is non-inferior and considered superior in relapsing disease.

2.3 Pre-treatment screening tests and procedures

2.3.1 ANCA and anti-GMB testing must already have been carried out to confirm diagnosis and consider dual positivity.

2.3.2 Table 1: Required prior to first treatment (and see prior to all treatments below).

Viral screening	Tuberculosis (TB) screening	Other
Hepatitis B and C screen Hep B core total	Chest X-ray Quantiferon Gold Test	Renal biopsy (optional)

Viral screening	Tuberculosis (TB) screening	Other
HIV Varicella zoster virus (VZV)		
Also see table 2 below		

- If VZV screening is negative, consider offering VZV vaccination at least 4 weeks prior to vasculitis treatment. The live VZV vaccine should not be offered if immediate treatment is required.

- Positive hepatitis B, C and HIV results should be referred to the appropriate specialist. Treatment with cyclophosphamide or rituximab should not be initiated in patients with evidence of current hepatitis B infection or HIV with inadequately controlled viral loads. Positive hepatitis C patients should be discussed with microbiology prior to treatment.

- Do not delay treatment whilst waiting for TB screening results unless the patient is considered high risk for TB. Any clinical suspicion of TB should be discussed with respiratory and microbiology prior to treatment with rituximab or cyclophosphamide. Treatment should not be initiated in patients with evidence of current TB infection.

2.3.3 Table 2: Required prior to all treatments (see table 1 for additional requirements with first treatment)

Blood tests	Clinical signs	Other
Full blood count (FBC) * C-reactive protein (CRP) Urea and electrolytes (UandE – renal to include bicarb level) Bone profile Liver function tests (LFTs) Immunoglobulins (IgA, IgG, and IgM) Hep B and C screen (for rituximab only)	Blood pressure Heart rate Respiratory rate Temperature Oxygen saturations	Pregnancy test if applicable (blood test if unable to produce urine sample)
*Senior doctor review is required prior to treatment if neutrophils <1.5 x10^9/L or platelets <75 x10^9/L. If LFTs raised ensure Hep B screens have been completed.		

- Do not proceed if patient showing active signs or markers of infection. Seek specialist advice from renal consultant.

- Blood pressure should be controlled prior to starting treatment.

- Results from a pregnancy test must be back prior to treatment. If life threatening vasculitis, discuss with gynaecology to determine risk of rituximab use over B cell depletion in the foetus.

2.3.4 **Vaccinations**

2.3.4.1. Live vaccines should be given at least 2 weeks prior to immunosuppressing treatment and ideally more than 4 weeks before rituximab treatment.

2.3.4.2. If required, inactivated vaccines should aim to have the course completed more than 2 weeks before commencing treatment. For immunosuppressive treatment the vaccine can be given as soon as possible except with rituximab when it should be delayed by at least 3 months (ideally 6 months).

2.3.4.3. For patients on maintenance treatment, the Covid 19 vaccine should be administered 4-8 weeks after any rituximab doses. The absence of a Covid 19 vaccination is not a contraindication to rituximab therapy in life and/or organ threatening disease.

2.4 Treatment – Induction

2.4.1 The induction phase of renal vasculitis management is usually considered 3-6 months from diagnosis to rapidly reduce the inflammation and prevent permanent organ damage and is required prior to cyclophosphamide or rituximab.

2.4.2 **Steroids**

- Pulsed methylprednisolone sodium succinate IV (500mg or 1g) for 3 days may be given prior to oral steroids.
- Suggested oral steroids regimes are available from the PEXIVAS and MYCYC trials (see appendices).
- Patients with existing or new diabetes should have a blood sugar monitoring device at home.
- Gastro and bone protection should be considered for patients on long term steroids.

2.4.3 **Cyclophosphamide**

- The use of cyclophosphamide is established treatment for renal vasculitis. Oral administration is daily and intravenous is pulsed therapy.
- Intravenous treatment delivers a lower total cumulative dose with reduced leucopenia, therefore is considered the recommended route.
- Intravenous cyclophosphamide requires administration as an inpatient or as an outpatient on medical day unit, therefore capacity issues may mean that oral therapy is required. IV cyclophosphamide needs to be prepared in pharmacy tech services with 24 hours' notice.

- Bloods need to be checked the day before or the day of IV cyclophosphamide administration and 10-14 days post administration (nadir bloods).

2.4.3.1. Table 3: Pulsed IV cyclophosphamide dosing:

Age (years)	Creatinine clearance ≥30mL/min	Creatinine clearance <30mL/min
<60	15mg/kg/pulse	12.5mg/kg/pulse
60-69	12.5mg/kg/pulse	10mg/kg/pulse
≥70	10mg/kg/pulse	7.5mg/kg/pulse
(as per KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases)		

- At weeks 0, 2, 4, 7, 10, 13 (additional weeks 16, 19, 21, 24 if required depending on clinical response).

- The maximum dose of IV cyclophosphamide per infusion is 1.2g and should be rounded to the nearest 20mg.

2.4.3.2. Mesna is required with IV cyclophosphamide to prevent haemorrhagic cystitis. It should be prescribed as 20% of IV cyclophosphamide dose and administered before the cyclophosphamide, and then two oral doses of 40% of the IV cyclophosphamide dose administered 2 hours and 6 hours post infusion (rounded to the nearest tablet – 400mg or 600mg).

2.4.3.3. Table 4: Mesna dosing table:

IV cyclophosphamide dose	<500mg	500mg	750mg	1g	1.2g
IV mesna dose	100mg	100mg	150mg	200mg	250mg
Oral mesna dose	400mg	400mg	400mg	400mg	600mg

2.4.4 **Oral cyclophosphamide**

2.4.4.1. Oral cyclophosphamide is an alternative to IV cyclophosphamide where hospital admissions are being reduced.

2.4.4.2. Table 5: Once daily oral cyclophosphamide dosing:

Age (years)	Creatinine clearance ≥30mL/min	Creatinine clearance <30mL/min
<60	2mg/kg	1.5mg/kg

Age (years)	Creatinine clearance ≥30mL/min	Creatinine clearance <30mL/min
60-69	1.5mg/kg	1mg/kg
≥70	1mg/kg	0.5mg/kg
(as per KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases)		

2.4.4.3. Oral cyclophosphamide should be prescribed on an outpatient prescription via the outpatient pharmacy with a maximum daily dose of 200mg. The usual duration is 3 months with a possible extension to 6 months under consultant agreement.

2.4.4.4. Bloods should be checked weekly for patients on oral cyclophosphamide in primary care requested on ICE for the designated renal consultant.

2.4.5 **Rituximab**

2.4.5.1. Ensure no contraindications to rituximab (allergy, active, severe or chronic infection, severe heart failure (NHYA class IV) or severe uncontrolled cardiac disease, severely immunocompromised patient.

2.4.5.2. See appendices for prescription and infusion checklists, infusion protocol, observation chart, and information leaflet.

2.4.5.3. Ensure rituximab has been diluted appropriately as per the infusion protocol (appendix 6).

2.4.5.4. Table 6: Rituximab dosing table

Rituximab dose	Administration
1g via intravenous infusion (500mg if patient <50kg*)	ASAP (day 1) then at day 15, with further infusions at 6,12,18 and 24 months for maintenance therapy (total of 6 infusions)
Pre-medication: Methylprednisolone IV 100mg (60 minutes prior to rituximab) Paracetamol 1g orally (500mg if <50kg) (30 minutes prior to rituximab) Chlorphenamine 4mg orally (30 minutes prior to rituximab)	
*a patient with a weight lower than 50 would typically have a body surface of 1.5 m^2 or lower, hence the reduced dose if patient <50 Kg	

2.4.5.5. Patients should be counselled appropriately, and patient information leaflets should be supplied.

2.4.6 **Plasma exchange**

Plasma exchange is a recognised treatment for ANCA positive vasculitis which may be considered in patients with pulmonary haemorrhage or severe renal disease. This is not routinely used at RCHT and would require consultant discussion and renal unit approval for implementation outside of this guideline.

2.4.7 **PCP prophylaxis**

Prophylaxis for *Pneumocystis jirovecii* pneumonia is required for patients treated with rituximab or cyclophosphamide. First line is co-trimoxazole 480mg once daily. If there are any contraindications to co-trimoxazole this will require discussion with the microbiology consultant.

- The course should be the length of the cyclophosphamide course plus 4 weeks.

- The course should be continued throughout the rituximab course and for a further 6 months from the last rituximab infusion.

2.4.8 **Remission maintenance therapy**

2.4.8.1. Maintenance therapy should be considered in patients on completion of cyclophosphamide. Maintenance therapy is not routinely required following completion of rituximab.

2.4.8.2. Patients with confirmed ANCA positive vasculitis should receive regular MRSA screening and eradication therapy with muprocin if Staphylococcus aureus carriage is confirmed as nasal carriage can increase the risk of relapse particularly in patients with granulomatosis with polyagiitis.

2.4.8.3. Female patients should be considered for CIN screening and HPC vaccination.

2.4.8.4. **Azathioprine**

- Azathioprine should be considered first line maintenance therapy after induction completion. TPMT enzyme levels should be checked prior to commencing to support dosing decisions. In patients with low TPMT levels a lower dose of azathioprine is required, or an alternative (mycophenolate mofetil) should be prescribed.

- Azathioprine dose is usually 1.5-2mg/kg/day, although this will be guided by the renal consultant. The maximum daily dose should not exceed 200mg, and the dose should be rounded to the nearest 25mg for ease of administration.

- Consideration of azathioprine prescribing in patients on allopurinol and/or feboxustat as the patient may require a dose reduction of azathioprine to 1/5th of the daily dose.

- Side effects include bone marrow suppression, cholestasis and disturbed liver function, pancreatitis, fever and rigors, myalgia, AKI (interstitial nephritis).

- Blood monitoring is required in patients on azathioprine. FBC and ALT every 2 weeks for 1 month, then monthly for 3 months, then every clinic visit thereafter. Stop if WBC <4 x109/L if restarting wait until WBC>4 x109/L with a dose reduction of 25mg and weekly monitoring for 4 weeks following. If LFTs become deranged stop treatment and consider switching to mycophenolate mofetil.

2.4.8.5. **Mycophenolate**

- If mycophenolate mofetil is used for maintenance therapy, the dose should be guided by the renal consultant and tailored to the individual patient.

2.4.8.6. **Rituximab**

- The total 6 infusions of rituximab are considered the initiation and maintenance course for ANCA positive vasculitis.

2.4.8.7. The appropriate clinical and laboratory follow-up of all patients with ANCA-positive vasculitis will remain a responsibility of the renal consultants, who will discuss them at the complex renal diseases MDT meetings when clinically indicated. During the follow-up visits, validated disease activity scores such as BVAS could be used, at the discretion of the renal consultant. The BVAS online calculator form is available at Birmingham Vasculitis Activity Score (BVAS).

3. Monitoring compliance and effectiveness

Information Category	Detail of process and methodology for monitoring compliance
Element to be monitored	Compliance with the guideline Error reports responded to appropriately
Lead	Giorgio Gentile, Consultant Nephrologist RCHT
Tool	Audit tool Response to error reporting
Frequency	Every 12 months
Reporting arrangements	Medicines Practice Committee
Acting on recommendations and Lead(s)	Renal Governance Committee

Information Category	Detail of process and methodology for monitoring compliance
Change in practice and lessons to be shared	Renal consultant, registrar and CNS Education Pharmacist education.

4. Equality and Diversity

4.1. This document complies with the Royal Cornwall Hospitals NHS Trust service Equality and Diversity statement which can be found in the 'Equality, Inclusion and Human Rights Policy' or the Equality and Diversity website.

4.2. Equality Impact Assessment

The Initial Equality Impact Assessment Screening Form is at Appendix 2.

Appendix 1. Governance Information

Information Category	Detailed Information
Document Title:	Renal Vasculitis in Adult Patients Clinical Guideline V1.0
This document replaces (exact title of previous version):	New Document
Date Issued/Approved:	24 February 2023
Date Valid From:	March 2023
Date Valid To:	March 2026
Directorate / Department responsible (author/owner):	Giorgio Gentile Consultant Nephrologist RCHT Suzy Powell Renal Transplant and Critical Care Pharmacist
Contact details:	01872 252590
Brief summary of contents:	This guideline detailed the recommendations and monitoring requirements for the treatment and management of renal patients with ANCA positive vasculitis
Suggested Keywords:	Vasculitis, renal, rituximab, ANCA, kidney, cyclophosphamide
Target Audience:	RCHT: Yes CFT: No CIOS ICB: No
Executive Director responsible for Policy:	Chief Medical Officer
Approval route for consultation and ratification:	Renal Governance Group Medicines Practice Committee
General Manager confirming approval processes:	Iain Davidson (Chief Pharmacist)
Name of Governance Lead confirming approval by specialty and care group management meetings:	Pollyanna Bastian (Renal Governance Lead)
Links to key external standards:	NICE TA308 https://www.nice.org.uk/guidance/ta308

Information Category	Detailed Information
	NHS England Clinical Commissioning Policy: Rituximab for the treatment of ANCA-associated vasculitis in adults https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/a13-ritux-anca-vascul.pdf
Related Documents:	https://www.vasculitis.org.uk/about-vasculitis/anca-and-the-kidney https://www.uptodate.com/contents/immunizations-in-autoimmune-inflammatory-rheumatic-disease-in-adults/print https://pharmaceutical-journal.com/article/ld/managing-anca-associated-vasculitis https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/cyclophosphamide https://kdigo.org/wp-content/uploads/2017/02/KDIGO-Glomerular-Diseases-Guideline-2021-English.pdf
Training Need Identified?	No
Publication Location (refer to Policy on Policies – Approvals and Ratification):	Internet and Intranet
Document Library Folder/Sub Folder:	Renal/ Nephrology

Version Control Table

Date	Version Number	Summary of Changes	Changes Made by
17.01.2023	V1.0	Initial issue	Giorgio Gentile Consultant Nephrologist RCHT Suzy Powell Renal Pharmacist RCHT

All or part of this document can be released under the Freedom of Information Act 2000

This document is to be retained for 10 years from the date of expiry.
This document is only valid on the day of printing

Controlled Document

This document has been created following the Royal Cornwall Hospitals NHS Trust

Policy for the Development and Management of Knowledge, Procedural and Web Documents (The Policy on Policies). It should not be altered in any way without the express permission of the author or their Line Manager.

Appendix 2. Equality Impact Assessment

Section 1: Equality Impact Assessment (EIA) Form

The EIA process allows the Trust to identify where a policy or service may have a negative impact on an individual or particular group of people.

For guidance please refer to the Equality Impact Assessment Policy (available from the document library) or contact the Equality, Diversity and Inclusion Team rcht.inclusion@nhs.net

Information Category	Detailed Information
Name of the strategy / policy / proposal / service function to be assessed:	Renal Vasculitis in Adult Patients Clinical Guideline V1.0
Directorate and service area:	Renal (specialist medicine)
Is this a new or existing Policy?	New
Name of individual completing EIA (Should be completed by an individual with a good understanding of the Service/Policy):	Pollyanna Bastian, Renal Governance Lead
Contact details:	01872 252598

Information Category	Detailed Information
1. Policy Aim - Who is the Policy aimed at? (The Policy is the Strategy, Policy, Proposal or Service Change to be assessed)	To optimize the management of patients with organ and/or life threatening ANCA positive vasculitis in order to reduce the mortality rate and the risk of end stage renal disease required renal replacement therapy
2. Policy Objectives	To initiation treatment in patients with ANCA positive vasculitis with minimal complications
3. Policy Intended Outcomes	To increase the efficacy and safety of current clinical practice in the treatment of anca positive vasculitis
4. How will you measure each outcome?	By comparing the outcomes of patients with anca positive vasculitis before and after guideline publication
5. Who is intended to benefit from the policy?	Ward/ outpatient clinicians treating renal vasculitis and patient outcomes

Information Category	Detailed Information
6a. Who did you consult with? (Please select Yes or No for each category)	• Workforce: Yes • Patients/ visitors: No • Local groups/ system partners: Yes • External organisations: Yes • Other: Yes
6b. Please list the individuals/groups who have been consulted about this policy.	**Please record specific names of individuals/ groups:** North Bristol Hospitals Trust, Teeside and Edinburgh renal unit, NHS England
6c. What was the outcome of the consultation?	Development of the guidance as “vasculitis rather than just rituximab”
6d. Have you used any of the following to assist your assessment?	**National or local statistics, audits, activity reports, process maps, complaints, staff or patient surveys:** No

7. The Impact

Following consultation with key groups, has a negative impact been identified for any protected characteristic? Please note that a rationale is required for each one.

Where a negative impact is identified without rationale, the key groups will need to be consulted again.

Protected Characteristic	(Yes or No)	Rationale
Age	Yes	Not suitable for children therefore retitled “in adults”
Sex (male or female)	No	
Gender reassignment (Transgender, non-binary, gender fluid etc.)	No	
Race	No	
Disability (e.g. physical or cognitive impairment, mental health, long term conditions etc.)	No	
Religion or belief	No	

Protected Characteristic	(Yes or No)	Rationale
Marriage and civil partnership	No	
Pregnancy and maternity	No	
Sexual orientation (e.g. gay, straight, bisexual, lesbian etc.)	No	

A robust rationale must be in place for all protected characteristics. If a negative impact has been identified, please complete section 2. If no negative impact has been identified and if this is not a major service change, you can end the assessment here.

I am confident that section 2 of this EIA does not need completing as there are no highlighted risks of negative impact occurring because of this policy.

Name of person confirming result of initial impact assessment: Pollyanna Bastian, Renal Governance Lead

If a negative impact has been identified above OR this is a major service change, you will need to complete section 2 of the EIA form available here:
Section 2. Full Equality Analysis

Appendix 3: Steroid regime options

Table 1: reducing daily prednisolone dose (in milligrams) protocol as per PEXIVAS study

Week	<50kg	50-75kg	>75kg
	Pulse	Pulse	Pulse
1	50	60	60
2	25	30	40
3-4	20	25	30
5-6	15	20	25
7-8	12.5	15	20
9-10	10	12.5	15
11-12	7.5	10	12.5
13-14	6	7.5	10
15-16	5	5	7.5
17-18	5	5	7.5
19-20	5	5	5
21-22	5	5	5
23-52	5	5	5

Table 2: reducing daily prednisolone protocol as per MYCYC study

Week	Prednisolone
	Pulse
1	1 mg/kg/day
2	0.75 mg/kg/day
3-4	0.5 mg/kg/day
5-6	0.4 mg/kg/day
7-8	0.3 mg/kg/day
9-10	0.28 mg/kg/day
11-12	0.25 mg/kg/day
13-20	12.5 mg/day
21-25	10 mg/day
25-36	7.5 mg/day
37+	5 mg/day

Doses are usually rounded to the nearest 5mg. The usual max dose is 60mg daily, but this may be changed as a senior clinician decision.

Appendix 4: Rituximab investigation schedules

Investigation	On initiation of Rituximab	Prior to each infusion
Full blood count (FBC)	y	y
Urea and electrolytes (UandEs) Including bicarbonate (renal)	y	y
Calcium and phosphate (bone profile)	y	y
Liver function tests (LFTs)	y	y
C-Reactive Protein (CRP)	y	y
Group and save	y	y
Blood glucose	y	y
Lipid profile	y	y
HIV	y	n
Hepatitis B and C (including hepatitis B core total)	y	y
Quantiferon Gold (tuberculosis TB)	y	n
ANCA (cytoplasmic, perinuclear ANCA) myeloperioxidase antibodies, proteinase 3 antibodies	y	n
GBM antibodies (anti-GBM disease)	y	n
Rheumatoid Factor	y	n
Anti-nuclear Antibody (ANA)	y	n
Compliment protein C3 and C4	y	n
Blood cultures	y	n
Varicella Zoster Virus (VZV)	y	n

Investigation	On initiation of Rituximab	Prior to each infusion
Cytomegalovirus (CMV) IgG	y	n
Epstein Barr Virus (EBV IgG)	y	n
Immunoglobulins (IgG, IgA, IgM)	y	y
Chest X-ray	y	n
Urine PCR (uPCR)	y	y
Urine dip /culture	y	y
Renal Biopsy	Optional	n

Additional tests:

Investigation	On initiation of Rituximab	Prior to each infusion
TPMT (prior to Azathioprine)	n	n
Pregnancy test	y	y
Clotting screen/ INR (if on warfarin)	n	n

Appendix 5: Rituximab prescription and infusion checklists (to be printed and stored in patient notes)

Rituximab prescription checklist	
Patient's name	
Hospital number	
NHS number	
Date	
Rituximab infusion, number (between 1 and 6)	
Rituximab dose	
Have FBC, CRP, UandEs, LFTs, immunoglobulins (IgG, IgA, IgM) been tested?	Yes/No
Has a screening for hepatitis B, C, HIV, VZV been performed?	Yes/No
Has a TB screening been performed (chest x-ray and one of the following tests: Quantiferon gold, Mantoux, Elispot)?	Yes/No
Has a pregnancy test been performed (fertile women)?	Yes/No
Has the patient received the information leaflet?	Yes/No
Has the patient provided informed consent to rituximab infusion?	Yes/No
If any "NO", rituximab CANNOT be administered	
Is the patient pregnant? (urine/blood pregnancy test)	Yes/No
Is the patient severely immunocompromised?	Yes/No
Severe heart failure (NYHA class IV) or severe uncontrolled cardiac disease?	Yes/No
Evidence of active and severe infection, or chronic infection (UTIs, chest infections, TB, hepatitis B or C, HIV, VZV, etc.)? *	Yes/No
Allergy to rituximab?	Yes/No
If any "Yes", rituximab CANNOT be administered	
*further discussion with a microbiology consultant might be necessary in some cases, see full guidance	

Rituximab infusion checklist (to be used AFTER the prescription checklist has been satisfactorily completed)	
Patient's name	
Hospital number	
NHS number	
Date	
Rituximab infusion, number (between 1 and 6)	
Rituximab dose	
Has the patient provided informed consent to rituximab infusion?	Yes/No
If the answer is "no", rituximab CANNOT be administered	
Are baseline observations within normal parameters? BP……... HR……... SpO2…….. RR…….. Temp……..	Yes/No
If the answer is "no", please discuss with the renal consultant/renal registrar before going ahead with the infusion	
Has the patient had any previous reactions during rituximab infusion (even mild/moderate)	Yes/No
If the answer is "yes", please discuss with the renal consultant/renal registrar before going ahead with the infusion	
Has the patient received methylprednisolone 100 mg in 100 mL of standard saline 0.9%, one hour prior to rituximab infusion?	Yes/No
Has oral chlorphenamine (4 mg) been administered, 30 minutes prior to rituximab infusion?	Yes/No
Has oral paracetamol (1 g) been administered, 30 minutes prior to rituximab infusion, if not otherwise contraindicated (allergies, severe liver failure etc)?	Yes/No
If any "no", please discuss with the renal consultant/renal registrar before going ahead with the infusion	

Has rituximab been diluted according to the infusion protocol (appendix 6), i.e. 1000 mg of rituximab in 500 ml of Sodium Chloride 0.9%?	Yes/No
If the answer is "no", please discuss with the renal consultant/renal registrar/renal pharmacist before going ahead with the infusion, as the infusion rate will have to be adjusted accordingly	
Have the infusion protocol (appendix 6) and the observation chart (appendix 7) been printed and made available to staff?	Yes/No
If the answer is "no", please print appendix 4 and 5 to ensure compliance with the guideline	

Appendix 6: Rituximab infusion protocol

To be printed and stored in patient's notes at outpatient clinic appointments to monitor compliance with guideline.

Pre-medication regime (to be administered prior to rituximab infusion)

1) Methylprednisolone 100 mg, to be diluted in 100 mL of sodium chloride 0.9%. To be administered 1 hour prior to rituximab infusion. A treatment with a proton pump inhibitor IV can also be given in some selected patients, at consultant discretion.

2) Oral chlorphenamine 4 mg, 30 minutes prior to rituximab infusion.

3) Oral paracetamol 1 g, 30 minutes prior to rituximab infusion, unless otherwise contraindicated (allergies, severe liver failure, etc).

Rituximab infusion

1) Rituximab IV at the dose of 1 g (**500 mg if weight < 50 Kg**)

2) The standard infusion is made by **using 1000 mg of rituximab in 500 ml of Sodium Chloride 0.9%.**

3) For first rituximab infusions, the infusion rate of rituximab should not exceed the limits indicated in the table below, in **ml/hour**:

Time from infusion start	Maximum infusion rate (ml/hr)
0-30	25
31-60	50
61-90	75
91-120	100
121-150	125
151-180	150
181-210	175
211-240	200 (MAXIMUM RATE)
241+	200 (MAXIMUM RATE)

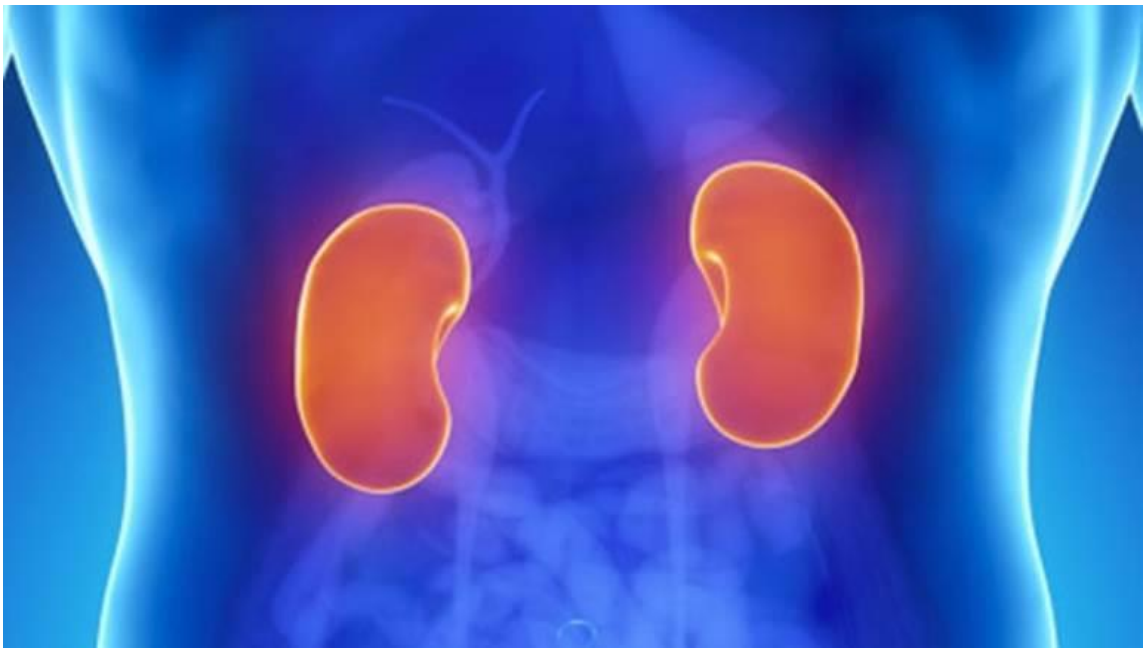
Most adverse reactions to rituximab infusion occur during the first two hours of infusion, so the patient should be carefully monitored in an appropriate environment at infusion start and throughout the infusion, particularly when the infusion rate has been increased. If any infusion-related reactions occur, the infusion should be temporarily held and the patient assessed by the Renal Consultant or Renal/Medical SpR. If the reaction is mild to moderate, the infusion can usually be restarted at a reduced rate (**no more than one half of the previous rate**), at the discretion of the supervising doctor. If the reaction is **severe**, the infusion should be permanently discontinued and the patient should receive appropriate treatment as per local policies and guidelines.

Appendix 7: Observation chart for rituximab infusion

Patient's name	
Hospital number	
NHS number	
Date	
Rituximab infusion, number (between 1 and 6)	
Rituximab dose	

Time (e.g. 16:00)	Time from infusion start, minutes	BP	HR	RR	SpO2	Temp	Infusion rate (ml/hr)	Adverse reaction	Signature
	0-30								
	31-60								
	61-90								
	91-120								
	121-150								
	151-180								
	181-210								
	211-240								
	241-270								
	271-300								
	301-330								
	331-360								

Appendix 8. Rituximab for ANCA-positive renal vasculitis in adults Information for patients



This leaflet has been created to give you information about rituximab. Rituximab has been recommended by your doctor because you do have a problem with your kidneys, called “renal vasculitis”.

What is a renal vasculitis?

A renal vasculitis is an inflammation in your kidneys. Normally, our own immune system protects us from infections (bacterial, viral and fungal) and detects and destroys abnormal cells that could otherwise cause a cancer. The immune system is very complex but the main white blood cells which defend you against infections and cancer are called lymphocytes. A group of those cells, the “B cells”, can make proteins, called antibodies, which help us to fight bacteria, viruses and cancer cells. Although those antibodies are usually beneficial, sometimes the immune system does not work properly and starts attacking our own healthy cells by mistake, causing what we call an “auto-immune disease”. You have been diagnosed with one of those autoimmune diseases, called “renal vasculitis”, where the antibodies attack the glomeruli, the tiny blood vessels which filter blood in your kidneys. A renal vasculitis can also involve several other parts of your body and can cause severe and life-threatening complications if it is not rapidly diagnosed and treated.

Why do I need a prescription of rituximab?

Rituximab is a type of drug known as a biological therapy. Rituximab is used to reduce the number of B cells in our body, as you suffer from an autoimmune condition called renal vasculitis. Rituximab is also widely used to treat several other conditions, including rheumatic diseases and even some types of blood cancer, especially when the B-cells are involved. Your kidney doctor believes that rituximab is an appropriate treatment for you. Rituximab should improve your health condition and renal outcomes and reduce the risk that you can develop severe complications from your renal vasculitis.

How will I receive rituximab?

Rituximab needs multiple infusions to be effective, including two initial infusions in a period of two weeks and a subsequent infusion at 6, 12, 18 and 24 months, for a total of six infusions (or more, if clinically needed). In order to receive the infusion, you will need a cannula inserted in your hand or your arm, so that we can use an infusion pump to give you the medication slowly through one of your veins. The rituximab infusion will reduce the number of B-cells that you have and will help to reduce the severity of your autoimmune condition. After a number of months, the number of B-cells tends to go up again, so you will need a total of six infusions in 24 months. Alongside the rituximab infusions, you will also need additional medications to keep your renal vasculitis under control, called “immunosuppressants”, as they suppress the activity of your immune system. Your renal doctor will give you all the information you need on the additional medications that you will require.

Do I need to receive any tests before the rituximab infusion?

You will need a number of blood tests before you can safely receive rituximab. We will need to check your full blood count and your liver and kidney function, and you will also need additional tests to make sure you do not have any severe active infection (chest, urinary tract, etc.) and that you do not have an active hepatitis B or C, active or advanced HIV infection, chicken pox, or tuberculosis. If you are a woman of fertile age, you will need a urinary or blood pregnancy test to ensure you are not pregnant.

Can I have my Covid-19 jab prior to the rituximab infusion? What if I already had my first infusion and I need to be vaccinated against Covid-19?

Where clinically possible, you will receive your Covid-19 vaccine 4 weeks or more before rituximab treatment. However, if your kidney doctor thinks that your renal vasculitis can put your kidney or your own life at high and immediate risk, you might need to receive rituximab before the Covid jab has been administered.

If you have already received a rituximab infusion, you may have your Covid-19 jab 4-8 weeks after the most recent rituximab infusion. However, this might depend on the local prevalence of Covid-19 in your community and if you are concerned about this delay you should speak with your kidney doctor or your general practitioner.

Do I need any particular vaccines before starting rituximab?

Before starting rituximab, you might be offered a vaccination against hepatitis B. If you haven't had chickenpox, you might be offered a vaccination against it at least 4 weeks before starting rituximab. If this is not possible (for instance, because you need immediate treatment with rituximab), you should avoid being in contact with any people with chicken pox or suspected chicken pox.

In all those cases (hepatitis B and chicken pox), vaccination might not be possible if your renal doctor thinks that you need to start rituximab treatment straight away, or if you are taking other drugs that affect your immune system, including steroids.

Can I have a live vaccine while I am on rituximab?

Live vaccines including yellow fever, rubella, chicken pox, BCG, etc. should not be given while you are on rituximab treatment. **If you are offered one of those live vaccines (for example, by your GP), you should inform the doctor that you cannot receive it.**

Can I receive a vaccination for flu or pneumococcus while I am on rituximab?

Vaccines for flu or pneumococcus can be given while you are on rituximab treatment, but they should be given at least 4 weeks before your next infusion of rituximab.

What happens on the day of my rituximab infusion?

You might receive your rituximab infusion on the renal ward (Grenville) or, if you are an outpatient, in our Medical Day Unit (MDU) at the Royal Cornwall Hospital. You can have breakfast in the morning. Please bring all of your usual medications with you.

One of the renal doctors will explain the risks and benefits of the procedure to you and will ask you to give your written consent to the infusion. This conversation will happen prior to the day of the infusion (for example, during a renal clinic) or directly on the ward if you are an inpatient.

When you arrive to MDU, you will be seen by one of our nurses who will check your vital signs to see if it is safe to administer the infusion. A nurse or a doctor will then position a cannula on your hand so we can give you the rituximab infusion. Prior to start the infusion, you will be given some additional medications to minimise the risk that you can have a reaction to the medication. You will be given a drug called methylprednisolone, a steroid, through your cannula, and two drugs called chlorphenamine (an anti-histamine) and paracetamol (a painkiller) orally, unless otherwise contraindicated (allergies, severe liver disease etc.). Half an hour after those drugs have been administered, you will be given the rituximab infusion. The speed of the infusion will be established by the nurse according to a local infusion protocol and any potential reactions during the infusion. On some rare occasions, the rituximab infusion might need to be stopped because of the onset of severe reaction, or might need to be slowed down because of mild or moderate reactions. A typical rituximab infusion might need three or more hours. The first infusion might take longer than the subsequent ones, as the infusion will be slower to minimise the risk of side effects. You can bring a friend or a relative with you if you wish.

Do I need to take any additional medications because of the rituximab infusion?

You will need to start an antibiotic called co-trimoxazole, which is used to prevent a severe lung infection from a fungus called Pneumocystis jirovecii. You will need to take this antibiotic every other day until the end of your cycle of treatment with rituximab.

What side effects could I experience after rituximab?

During or after rituximab infusion you might experience some of the following side effects:

- An allergic reaction (1 in 100 people), including fever, skin rash, wheeze or fall in blood pressure; if you start to feel unwell while you are having the infusion, please let the staff know so they can slow it down. If your symptoms are bad, in some cases the staff will be forced to stop the infusion and/or administer emergency treatment, but this is a rare occurrence
- An increased risk of infections. Please tell your renal doctor or your GP if you develop any new symptoms that concern you. This could be a sore throat, a cough with phlegm, a burning pain when passing urine or an increased urinary frequency, a fever or other signs of infection.
- Very rarely (less than 1 in 10,000 people), a disease named “Progressive Multifocal Leucoencephalopathy”, a viral infection which targets the white matter of the brain and might be fatal. You should look for medical attention immediately if you develop any of the following symptoms: weakness, shaky movements, unsteadiness or difficulty moving your arms, legs or face, pins and needles, sight loss, difficulties with your speech, or changes in your behaviour or mood.

Do I need to tell anything to my kidney doctor before I receive rituximab?

Please tell your kidney doctor if:

- You have an active infection or you have had a recent infection (within the last 2-4 weeks)
- You did have a previous reaction to rituximab, or any other allergies
- You are pregnant or you are trying to become pregnant
- You have been in contact with a person with tuberculosis or have been treated/are being treated for tuberculosis
- You are aware of the fact that you suffer or have suffered from viral hepatitis (B or C)
- You are aware that you are HIV positive
- You do have a severe heart condition, including heart failure or a severe uncontrolled cardiac disease
- You are severely immunocompromised

Do I need to take any particular precautions after the infusion of rituximab?

As you have received a drug that suppresses your immune system, you have a higher risk of developing an infection and should look for medical attention if you develop a fever or any unexpected symptoms (cough with phlegm, burning pain when passing urine or increased urinary frequency etc.). You should also try to avoid contact with people with chicken pox, infections, colds, or flu. Please contact your doctor immediately if you have never had chicken pox and you are in contact with a person with chicken pox. Please also contact your doctor if you develop any skin rash within 4 months from receiving rituximab. Please inform any dentists, pharmacists and any other doctors that you have been treated with rituximab.

I am a woman of fertile age. Do I need to take any precautions after receiving rituximab?

You must use contraception for up to 12 months after your last infusion of rituximab. If you do become pregnant within the first 12 months from receiving rituximab, you should immediately inform your doctor, as it is not known whether this medication can cause any harm to an unborn baby.

I am breastfeeding. Can I carry on after receiving rituximab?

You should not continue to breastfeed after rituximab. Breastfeeding is not recommended for up to 12 months after your last infusion of rituximab, as this medication can pass into the breast milk and consequently to your baby.

How will I know if rituximab is working as expected against my renal vasculitis?

Your kidney condition might take several months to improve and the degree of improvement might be quite different in each individual patient. Your kidney doctor will regularly follow you up in clinic and will monitor your general well-being, the level of your kidney function and the levels of the antibodies which have caused your renal vasculitis.

Can I drink any alcohol while I am on rituximab?

You can drink alcohol while you are on rituximab, within the recommended limits for adults (up to 14 units per week). It is better to spread your alcohol intake across a few days. You should try to have at least two alcohol-free days every week.

Can I have an operation while I am on rituximab?

If you need an operation, make sure your surgeon knows you are on rituximab. Whenever possible (for instance, because your operation is not urgent), your operation will be scheduled after at least three months from your last infusion.

How can I have additional information on my disease and rituximab?

You might find relevant information on your disease and your rituximab treatment on a number of websites, as indicated below.

Vasculitis UK information and support group

https://www.vasculitis.org.uk/

https://www.vasculitis.org.uk/about-vasculitis/anca-and-the-kidney

Rituximab. Patient information leaflet for non-oncology indications (MHRA approval: June 2020)

https://www.medicines.org.uk/emc/rmm/894/Document

If you do have a specific requirement, including large print, Braille or audio version, or you need an interpreter etc., please email

rch-tr.PalsService@nhs.net

Author: Dr Giorgio Gentile, Renal Consultant

Version 1.0, January 2023

Royal Cornwall Hospitals NHS Trust, Truro, Cornwall