Rituximab in the Management of Immune-Related Adverse Effects (irAEs)

A guide for members on the prescribing and monitoring of rituximab when used in the management of irAEs caused by treatment with immune-checkpoint inhibitors.

It should be noted that this use is considered off-label use; relevant governance processes within each organisation should be followed to ensure the risks associated with this are mitigated.

British Oncology Pharmacy Association in Collaboration with The Immuno-oncology Clinical Network

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Contents

1. Introduction

- Rituximab is a genetically engineered monoclonal antibody (IgG1 kappa immunoglobulin) that specifically targets the CD20 antigen found on the surface of both normal and malignant B lymphocytes. CD20 is involved in cell cycle regulation, apoptosis and calcium signalling. By targeting CD20, rituximab promotes cell lysis while sparing the hematopoietic and plasma cells without this surface antigen.

- It is currently licenced for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and various autoimmune conditions such as rheumatoid arthritis.

- There is also emerging evidence for its use in the management of immune-related adverse events (irAEs), which can present as a result of immune-checkpoint inhibitor (ICI) treatment. Specifically, immunotherapy induced rheumatological and haematological adverse effects

- This document is intended to be used as a monograph to provide prescribing and monitoring advice once the decision has been made to initiate rituximab. It is not a clinical guideline, but a consensus view of current use of rituximab when used for irAEs. It should be used in conjunction with any local policies/procedures/guidelines and should be approved for use according to the trust clinical governance processes.

2. Prescribing and Monitoring Advice

2.1 Contraindications

- Hypersensitivity to rituximab or murine products.
- Hypersensitivity to any of the excipients.
- Patients in a severely immunocompromised state.
- Active, severe infection.
- Recurrent/persistent infections.
- Active TB.
- Hepatitis B/C.
- Hypogammaglobulinemia.
- History of severe, uncontrolled heart disease, angina pectoris and/or cardiac arrhythmias.
- Severe Heart Failure (NYHA Class IV) .
- Pregnant patients.

2.2 Precautions

- Avoid live immunisations. Contact specialist for advice.
- Risk of hepatitis B reactivation.
- **Omit anti-hypertensive medication at least 12 hours prior to treatment** to prevent transient hypotension.
- If the patient has a tetanus prone wound within 24 weeks of rituximab, they may need passive immunisation with tetanus immunoglobulin.
- Risk of progressive multifocal leukoencephalopathy (PML) see section 2.9 for further details.
- use effective contraceptive methods during and for 12 months following treatment.

2.3 Pre-treatment assessment

- FBC, U&Es and LFTs
- Virology Hep B/C HIV (before initiation of treatment), EBV, CMV
- History of chicken pox/varicella zoster virus
- Immunoglobulin levels
- Chest Xray
- Please note there is NO need to screen latent TB (as per other biologics) as there is no increased risk of activation.

2.4 Pharmaceutical form

- Brands of IV rituximab available: e.g. Rixathon©, Truxima©, MabThera©, Ruxience©
    - Different biosimilars may be introduced as directed by individual Integrated Care Boards (ICB).
    - Rituximab should be prescribed by brand. Use of electronic prescribing systems will ensure consistency of brand with accurate traceability.
    - Brands appear to be bioequivalent but try to ensure consistency in brand prescribed.
- Each 50ml vial contains 500mg of rituximab. It is a clear, colourless liquid. It is a ready-mix solution and does not require any reconstitution.
- Subcutaneous rituximab is only licenced for the treatment of lymphoma. **This can't be used for irAEs.**

2.5 Dosage

- Doses will vary depending on indication. **Please speak to a specialist for advice.**
- For haematological irAEs, such as, aplastic and autoimmune haemolytic anaemias (AIHAs), pancytopenia, haemophagocytic lymphohistiocytosis (HLH), early consultation with a haematologist is advised for both diagnosis and management.
- For irAEs, such as, arthritis, vasculitis, myositis and lupus, discussion with rheumatology is recommended.
- For neurological irAEs some populations may potentially benefit from rituximab and discussion with the neurology team would be of benefit
- There are NHS England clinical commissioning policies for a number of indications eg Dermatomyositis/Polymyositis: Rituximab-for-the-treatment-of-dermatomyositis-and-polymyositis-adults.pdf
- No dose adjustments are required for renal or hepatic impairment.

2.6 Method of administration – *Please follow local policies for pre-medication and administration of rituximab. Rapid/ultra rapid infusions may apply depending on the indication to be treated*

Rituximab should be administered as an intravenous infusion via a dedicated line. It should NOT be administered as an IV push/ bolus. Rituximab should only be administered in an area where full resuscitation facilities and close monitoring are available. Infusion rates should be as per local guidance as this will also be dose dependent. Due to the potential for Rituximab to cause infusion related reactions it should not be infused concomitantly with other intravenous medications as it would make it difficult to establish which drug the patient was reacting to.

Pre-medication of an anti-pyretic, an antihistamine and a steroid should be given. Use local policies if available

Pre-medication suggestion:

- Methylprednisolone 100mg IV (100mg in 100mL 0.9% sodium chloride infused over 30 minutes) to be started 60 minutes before the Rituximab infusion (i.e. to be completed 30 minutes prior to Rituximab infusion).
- Paracetamol 1g orally: 30-60 minutes before Rituximab infusion.
- Chlorphenamine 4mg orally or 10mg IV: 30-60 minutes prior to Rituximab infusion.

Initial infusion rate

Appropriate for:

- Patients receiving their first rituximab infusion
- Patients receiving their first infusion of a rituximab biosimilar switch
- Patients who are contraindicated to rapid / ultra rapid infusion rate

The recommended initial rate for infusion is 50mg/hr for the first 30 minutes.

If well tolerated, increase by 50mg/hr every 30 minutes to a maximum of 400mg/hr providing no adverse reactions occur.

If hypersensitivity or an infusion related event occurs, the infusion should be temporarily slowed or interrupted. Upon improvement of symptoms the infusion can be resumed at half the previous rate.

Subsequent infusion rates

In the field of irAEs the patient may only require a one-off dose of rituximab, and therefore not receive subsequent infusions.

In other settings there is evidence and guidance for increasing the rate of subsequent infusions. In the irAE setting the evidence is lacking, although dependent on the irAE being managed it maybe be appropriate to consider increasing rate on infusion in line with other indications.

The table below gives some guidance on how to do this although this should always be used in conjunction with local policy and advice.

	Inclusion Criteria	Rate
Second infusion	No reaction to initial infusion Same brand as initial infusion	Infuse the first 20% of the total volume over 30 minutes. Repeat observations. If observations stable, infuse the remaining 80% of the infusion over 1 hour. Repeat observations. If patient becomes unwell during the above, stop infusion and call for a medic to review.
Rapid infusion – seek specialist advise from haematology	Non-rheumatoid arthritis indication No reaction to previous infusions Same brand as previous infusions No significant cardiovascular disease	Administer at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30-minute intervals, to a maximum of 400 mg/h.
Ultra rapid infusion	Second or subsequent infusions for patients with rheumatoid arthritis	Seek specialist advice from rheumatology

	No reaction to previous infusions (inc other biologics). No significant cardiovascular disease	

For infusion related reactions please refer to local policies or the UK SACT Board Publication Anaphylaxis and hypersensitivity reactions: guidance for the management of adults receiving intravenous systemic anti-cancer therapy (SACT) for the treatment of solid tumours

2.7 No therapeutic drug monitoring required for rituximab

2.8 Other monitoring

Prior to each rituximab infusion:

- FBC – there may be a transient drop in WCC initially. Speak to the relevant consultant if persistent.
- U&Es
- LFTs
- In some indications the proportion of CD19 positive lymphocytes are monitored to assess response to treatment.

Monitoring during each rituximab infusion:

Blood pressure, pulse, temperature, oxygen saturations and respiration rate:

- At baseline
- Every 15 minutes for the first hour of the Rituximab infusion
- Then every 30 minutes until completion

Once the infusion is completed, flush the line with at least 30mls of 0.9% sodium chloride.

Acute infusion reactions may occur within 1-2 hours of the first rituximab infusion. These consist of fever, headache, rigors, flushing, nausea, rash and URTI symptoms. Transient hypotension and bronchospasm are usually related to the infusion rate.

Carefully monitor patients with a history of cardiac arrhythmias or heart failure. Should clinically significant arrhythmias develop during the infusion then cardiac monitoring should be in place during and after subsequent infusions. In the event of a serious arrhythmia developing the infusion should be discontinued

2.9 Adverse effects

Progressive multifocal leukoencephalopathy is a very rare side effect of rituximab, but it can be fatal (risk <1:10,000) Patients treated with rituximab must be given a **patient alert card**. The alert card contains important safety information for patients regarding potential increased risk of infections, including progressive multifocal leukoencephalopathy (PML). The alert cards can be found on the summary of product characteristics (SmPC) if hard copies aren't available.

- The table below outlines the broad range of adverse events that patients can experience with rituximab.
- This is not an exhaustive list. See SmPC for further details.

Nature of adverse effect	Very Common	Common
Infections and infestations	General risk of infection. Conjunctivitis, upper respiratory tract infection, urinary tract infections	Bronchitis, sinusitis, gastroenteritis, tinea pedis
Blood and lymphatic system disorders		Neutropenia
Immune system disorders	Infusion-related reaction: hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension, rhinitis, rigors, tachycardia, fatigue, oropharyngeal pain, oedema peripheral, erythema	
General disorders and administration site conditions		
Metabolism and nutrition disorders		Hypercholesterolemia
Psychiatric disorders		Depression, Anxiety
Nervous system disorders	Headache	Paraesthesia, migraine, dizziness, sciatica Rare cases, posterior reversible encephalopathy syndrome (PRES) or progressive multifocal leukoencephalopathy (PML)
Cardiac disorders		
Gastrointestinal disorders		Constipation, dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, upper abdominal pain
Skin and subcutaneous tissue disorders	pruritus, rash, alopecia	urticaria, sweating, night sweats, +skin disorder
Musculoskeletal disorders and connective tissue disorders		Arthralgia / musculoskeletal pain, osteoarthritis, bursitis
Investigations	Decreased IgM levels	Decreased IgG levels

2.10 Drug interactions

- There is limited data on possible drug interactions with rituximab.
- The table below shows some potential interactions as per Stockley's Drug Interactions.

Drug	Interaction
Vedolizumab	The UK manufacturer of vedolizumab advises caution in patients who have previously received rituximab. If both drugs are given, monitor closely for adverse effects. There is a lack of clinical study data for the concurrent use of vedolizumab with rituximab.
Filgotinib	Rituximab is predicted to increase the risk of immunosuppression when given with filgotinib. Avoid concurrent use
Live vaccines	Live vaccines should not be given to patients receiving monoclonal antibodies because of the risk of generalised infection. Avoid concurrent use during treatment and for up to 12 months after stopping rituximab (as per Public Health England)
Clozapine	Both clozapine and rituximab might cause blood dyscrasias. Clozapine-induced neutropenia is not dose-related or predictable; it is unclear if concurrent use with other drugs known to cause neutropenia will increase the risk and/or the severity. If concurrent use is necessary, increase the frequency of full blood count (including the absolute neutrophil count) monitoring.
Imlifidase	Imlifidase is predicted to decrease the efficacy of rituximab. Give rituximab 4 days after imlifidase.
Cyclophosphamide	Cyclophosphamide appears to have no effect on the pharmacokinetics of rituximab; however, concurrent use might increase the risk of haematological toxicity. Monitor full blood count more frequently.

3. Appendix 1 Example Patient Information Leaflet

What is Rituximab?

Rituximab belongs to a group of targeted therapy drugs called monoclonal antibodies.

Monoclonal antibodies target specific proteins (receptors) on the surface of cells. Rituximab targets a protein called CD20 found on the surface of white blood cells called B-lymphocytes (B-cells).

Rituximab locks on to CD20. It then triggers the body's immune system to attack the cells and destroy them. Rituximab destroys both abnormal and normal B-cells and therefore reduces inflammation.

How do I take Rituximab?

Rituximab will be given to you by a healthcare professional

Drug level monitoring (if relevant)

No drug levels are needed.

How long will I need to take Rituximab for?

As long as it is clinically relevant to do so

Does Rituximab have any side-effects?

Allergic reaction during or after the infusion.

Some people have an allergic reaction while having this treatment. The first infusion is the most likely to cause a reaction, so it is usually given more slowly than later treatments. Before treatment, you will have medicines to help prevent or reduce any reaction.

Signs of a reaction can include:

- feeling hot or flushed
- shivering
- itching
- a skin rash
- feeling dizzy
- feeling sick
- headache
- feeling breathless or wheezy
- swelling of your face or mouth
- pain in your back, tummy or chest.

Your nurse will check you for signs of a reaction during your infusion. If you feel unwell or have any of these signs, tell them straight away. If you do have a reaction, they can treat it quickly.

Sometimes a reaction happens a few hours after treatment. If you develop any of these signs or feel unwell after you get home, contact the hospital straight away on the 24-hour number.

Always call 999 if swelling happens suddenly or you are struggling to breathe.

Blood pressure

Your blood pressure may fall when you are having rituximab. If you usually take medicine to lower your blood pressure, your doctor, nurse or pharmacist may ask you not to take it for 12 hours before having rituximab. Sometimes, rituximab can make your blood pressure go up. Your nurse will check your blood pressure regularly.

Problems at the injection site

If you have rituximab as an injection, you may have some redness and swelling where it is given (injection site). Your nurse can give you advice on coping with this.

Other side effects

There are several possible side effects that you may notice, although not everyone will experience these. They include:

- Risk of infection
- Anaemia
- Bruising/bleeding
- Feeling sick
- Constipation
- Diarrhoea
- Hair loss
- Joint pain
- Skin changes
- Effects on the lungs

It is important to tell your doctor of any side effects or unusual symptoms that you are experiencing.

If you suspect that you have an infection, this can be very serious when the number of white blood cells is low. It is important to get treated as soon as possible. If you have any of the following symptoms, **contact the hospital straight away via the 24-hour number:**

- a temperature above 37.5°C
- a temperature below 36°C
- you feel unwell, even with a normal temperature
- you have symptoms of an infection.
    - feeling shivery and shaking
    - a sore throat
    - a cough
    - breathlessness
    - diarrhoea
    - needing to pass urine (pee) often, or discomfort when you pass urine.

Can I still be vaccinated?

It is important to avoid live preparations of vaccines. The flu jab can be given either 4 weeks before rituximab or 3 months after your last infusion. Pneumovax vaccination can be given 4-6 weeks before an infusion or 6 months after your last rituximab infusion.

Is it safe to become pregnant while I am taking Rituximab?

You may have already had these conversations with your oncology team before starting immunotherapy. It is important that you do not plan a pregnancy if you are on rituximab and should use effective contraception if you are sexually active.

Can I take other medicines whilst I am taking Rituximab?

You should always check with your oncology team or pharmacist if you are started on any new medicines, including anything you may buy over the counter or any herbal medications.

Supply of Rituximab

You will not need to take anything away with you after your rituximab infusion.

Who can I contact for further information?

If you have any queries about your Rituximab the best people to speak to are the oncology team who you are under, an oncology pharmacist, or the team of specialists who have prescribed the rituximab for you.

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6. Document control

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Authors / Editors version 1.0	Sarah Freeburn, Lead Immunotherapy Pharmacist. University Hospitals Bristol and Weston Jessica Pealing, Advanced Haematology Pharmacist, The Christie NHS Foundation Trust Stuart Evans, Lead Cancer Pharmacist, Swansea Bay University Health Board Alice Tew, Consultant Pharmacist, University Hospital NHS Foundation Trust. Anna Olsson-Brown, CEO Immuno-oncology Clinical Network
Owner	BOPA.

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