Rituximab - Full Clinical Guideline

Reference no.: CG/Rheum/2015/005

Protocol for the Administration of Intravenous Rituximab in Adults with Rheumatoid Arthritis

1. Purpose

To ensure that patients are receiving Rituximab in a safe and effective manner.

Rituximab is a monoclonal antibody directed against the CD20 antigen on B cells. This will be prescribed according to brand name Mabethera or its biosimilar Truxima. This decision will be made prior to treatment and will be prescribed by brand name. They both have the same licensed indications and are delivered the same way.

2. Guidelines

Indications for treatment

Rituximab in combination with methotrexate is indicated for the treatment of adult patients with severe active RA who have had an inadequate response or intolerance to other disease modifying drugs including one or more tumour necrosis factor (TNF) blocking agents.

Patients should be taking a stable dose of methotrexate. In patients unable to tolerate methotrexate, rituximab may be used as a monotherapy, or with an alternative DMARD.

Patients should avoid taking antihypertensive medication for 12 hours before the infusion due to risk of hypotension**.**

Prior to treatment

- Counselling of the patient regarding possible side effects of Rituximab therapy and provision of information sheet to take place before first treatment.
- Patients should have their 28 joint Disease Activity Score prior to first course of treatment. A DAS28 score > 5.1 indicates active disease eligible for treatment.

Contraindications

- Active severe infection and those in severely immunocompromised state
- Women who are breast feeding or pregnant (discontinue for 12 months in males and females before conception)
- History of hypersensitivity to the drug or any other components of the infusion or to murine proteins
- NYHA grade 4 congestive cardiac failure (CCF) or severe, uncontrolled cardiac disease

Treatment Schedule

Initiation of therapy should be by Consultant Rheumatologist only.

Rituximab is administered as two intravenous infusions of 1000mg at an interval of 2 weeks. Patients should be given 125mg IV methylprednisolone in 100mls normal saline infused over 30

minutes, 1 hour before being given Rituximab. Patients should also be pre-treated 1 hour before with paracetamol 1g orally and chlorphenamine (piriton) 4mg orally.

Rituximab should only be administered in an environment with immediately available full resuscitation facilities. A bed is required for all infusions. A doctor should be readily available in case of reaction.

Prior to initiating therapy please check the following has been done:

- DAS score using 28 joints count
- Full blood count, ESR
- Initial profile and Liver function tests
- CRP
- urinalysis
- Chest x-ray within the past 6 months and TB screening as per guidelines
- Baseline immunoglobulins
- Hepatitis screen
- Pneumovax status (need to have at least 4 weeks before treatment if not had)

Preparation

Reconstituted solution has a shelf life of 24 hours at 2-8°C and 12 hours at room temperature. The infusion may therefore be prepared in advance if the patient is able to be assessed the day before the infusion. Rituximab is normally prepared in a 250ml bag of normal saline (fluid will have been withdrawn such that the volume to be infused is 250mls).

A peripheral venous cannula needs to be inserted on the day of the infusion. A 500ml bag of normal saline should be hanging by the patient's bed in case of hypotension.

Do not give other IV fluids or drugs through the same line. A filter is not required.

Before each administration

Measure and record: weight, pulse, blood pressure, temperature, urinalysis (if urinary symptoms)

Collect*:* Full blood count, ESR, LFT and CRP

NB. If these have not been done within a week of the infusion these should be done as urgent samples and the results checked prior to prescribing treatment.

Paracetamol, chlorphenamine 10 mg IV and Adrenaline 0.5ml 1 in 1000 IM should be readily available (as per anaphylaxis protocol).

During infusion

NB This infusion must be given via a Volumetric Infusion pump (i.e. Baxter Colleague) and an infusion Pump Checklist completed.

Infusion schedule:

First infusion	50mg/hr for first 30 minutes Then increase by 50mg/hr to maximum of 200mg/hr (i.e. over 4hrs 15 minutes in total)
Second infusion	100mg/hr for first 30 minutes Then increase by 100mg/hr every 30 minutes to maximum of 200mg/hr (i.e. over 3 hrs 15 minutes in total)

If the first two cycles of treatment (4 infusions) are uneventful, subsequent courses of rituximab may be infused at a faster i.e.:

250mg/hr for first 30 minutes
Then increase to 600mg/hr to maximum of for the remainder of the infusion
(i.e. over 2 hours in total)

This faster rate should not be used in patients who have had previous serious infusions reactions to any previous biologic or in patients with clinically significant cardiovascular disease including arrhythmias.
In patients changing to a different brand of Rituximab, the rate of the first cycle should be infused at the starting rate.

A doctor should be readily available for the entire infusion.

Check BP, pulse and temperature every 30 minutes during the infusion and for 1 hour post infusion.

If **minor infusions reactions** occur slow the infusion, stop if necessary and restart at a slower rate (50%)
If **severe reactions** occur **(bronchospasm, severe breathlessness, hypoxia)** treat with Adrenaline, chlorphenamine and intravenous steroids in accordance with the current anaphylaxis guidelines (see copy in day case office)

Side Effects
Infusion reactions occur in 15% of patients following the first infusion and in 2% in the second infusion. Infusion reactions may include pruritus, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic oedema, throat irritation, cough and bronchospasm, with or without hypotension or hypertension. Premedication with IV steroids significantly reduces the incidence and severity of these events

Patients are at increased risk of infection (approx 1% per patient per year) particularly upper respiratory tract infections and urinary tract infections.

Other side effects include indigestion or abdominal pain (2-4%), arthralgia/musculoskeletal pain or muscle spasms, worsening angina, migraines, tingling or numbness.

Rare (<1/1000) side effects reported include late neutropenia (more than 4 weeks after last infusion, severe cardiac events (associated with infusion reaction and mainly with prior heart condition)
Very rare (<1/10,000) side effects reported include pancytopenia, aplastic anaemia, cranial or peripheral neuropathy, renal failure, pneumonitis, severe bullous skin reactions and cutaneous vasculitis, tumour lysis syndrome (associated with infusion reaction) and reactivation of hepatitis B.
There have also been reports of progressive multifocal leukoencephalopathy in patients treated with Rituximab.
It is unknown if there is a long term increased risk of some malignancies.

After infusion
Giving set is disconnected after a saline flush, but the cannula is left in situ until after observation period is complete.
Patient can go home 1 hour after infusion (see infusion schedule section for details) if they are well and observations have been satisfactory.
Inform patient of date of next infusion.
Monitoring of blood tests continues as for methotrexate.
It is for the physician to report severe adverse reactions to the manufacturers

Subsequent Assessment of Disease
Blood tests (FBC, ESR, U+E, LFT, immunoglobulins) should be performed before each infusion and results checked.

Health and Safety
Rituximab is not cytotoxic and in case of spillage, requires no special precautions or procedures

Withdrawal from Treatment
Failure to respond at 6 months will lead to withdrawal of treatment

Further courses of treatment
If indicated by disease activity, treatment can be repeated but no more often than at 6 monthly intervals and providing immunoglobulin levels are satisfactory.

3. References

1. Holroyd J, Seth R, Bukhari M, et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis. Rheumatology 2019;58(2):
2. Truxima summary of product characteristics August 2018
3. NICE guideline [NG 100] July 2018

4. Documentation Controls

Development of Guideline:	Dr Shazeen Ayub, Rheumatology Registrar Dr Sheila O'Reilly, Consultant Rheumatologist
Consultation with:	Rheumatology
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Key Contact:	Dr Sheila O'Reilly, Consultant Rheumatologist