Rituximab
PROTOCOL FOR PAEDIATRIC RHEUMATOLOGY

1. Background and indications

Rituximab is a monoclonal antibody that works by removing B-cells (a type of white blood cell that produce antibodies). The aim of the B cell depletion is to reduce auto-antibodies (such as rheumatoid factor) and thereby disease activity. These B-cells reappear after 4-12 months after therapy. CD27 + B-cells representing memory B-cells can remain suppressed for 2 years after depletion. The use of Rituximab is considered in patients with active Juvenile onset Systemic Lupus Erythematosus (JSLE), dermatomyositis, vasculitis, RF positive Polyarticular JIA and widespread scleroderma who have not responded to standard treatments, such as Azathioprine, Mycophenolate Mofetil, Methotrexate, steroids and appropriate biologics. Rituximab can be used in combination with Prednisolone, Hydroxychloroquine, Methotrexate or Cyclophosphamide. Other immunosuppressants are usually temporarily stopped during rituximab treatment, but may be recommenced afterwards.

Rituximab is not currently licensed for use in children, but has been extensively used in adult rheumatic diseases with a good safety profile.

2. Dose and frequency

- Prior to prescribing, ensure that:
  - Rationale and funding for Rituximab treatment established & Pharmacy informed paedoncpharmacists@ouh.nhs.uk
  - Patient and parents have received and understand information on Rituximab
  - Recent weight recorded on EPR

- Rituximab 750mg / m² (rounded up to the nearest 100mg, max dose 1 gram)
- 2 doses given 10-14 days apart.
- This can be repeated after 6 months if needed.

3. Procedures

3.1. Pre-treatment tests

Prior to the first infusion, all patients should have had the following (unless reason for deviation recorded by Consultant in the medical notes):

- Screen for hepatitis A, B and C
- CXR should be done within last year

The paediatric rheumatology team may advise patients stop anti-hypertensives 12 hours prior to administration (to reduce risk of hypotension)

3.2. Cannulation and bloods on the day

- Baseline – FBC, ESR, U&E’s, LFT’s, CRP, Lymphocyte subsets CD19 or CD20 & Immunoglobulins (G, A & M). Rheumatoid factor titre if requested by paediatric rheumatology team
These should all be repeated on day 7-10 after the 1st dose of Rituximab. Repeat Lymphocyte subsets (CD19 or CD20) & Immunoglobulins (G, A & M) after 2 months, then 3 monthly until B cells are normal. If patient doesn’t have an appointment to have these done, please inform paediatric rheumatology CNS.

3.3. Clerking

Rituximab SHOULD NOT BE GIVEN if:

- Patient has had a severe allergic reaction to Rituximab or any other product that was made with murine proteins.
- There is evidence of current, active infection
- The patient has had TB (tuberculosis), unless suitable antibiotics are being given to treat TB, or if there has been recent contact with someone who might have TB. A CXR must have been performed in all patients (+/- mantoux/Elispot if considered high risk).
- Patient is pregnant. Sexually active patients must use effective birth control while taking rituximab and for 12 months after treatment has ended.

In the following circumstances please discuss with the paediatric rheumatology team as it may be necessary to withhold the Rituximab.

- Recent infection or contact with an infectious disease. The infection could be an open cut or sore, a chest infection or an infection that affects the whole body (such as the flu or chicken pox).
- The patient has heart failure or other heart conditions, multiple sclerosis, or Guillain-Barré syndrome, or if the patient has experienced numbness, tingling, or had a seizure.
- Lived in or visited an area of the country where an infection called histoplasmosis or coccidioidomycosis (an infection caused by a fungus that affects the lungs) is common.

- Abnormal blood results
  - Low blood cell count (Hb less than 100, platelets less than 150), symptoms and signs of which may include bruising, bleeding, pallor, or if patient has a temperature above 37.5°C.
  - Neutrophils less than 1.5
  - Liver Function - If ALT more than 120

Vaccinations

- **Live vaccines** such as oral polio, rubella, MMR, chicken pox, BCG and yellow fever **should not be given** whilst patient is on Rituximab.
- Should non-live vaccinations be required, these should be completed at least 4 weeks prior to commencing the next course of Rituximab. Annual flu vaccines are recommended and should be given.
• It is not known whether patients may need re-immunisation of previous non-live vaccines following rituximab. Once immunoglobulins back to normal, check specific antibodies (Tetanus, Hib, Polio etc) from previous immunisations and if low, re-immunise and recheck levels.
• If patient has a contaminated wound (has received rituximab within the last 6 months) and there is any doubt about the patient’s tetanus status, then a tetanus immunoglobulin should be administered.

3.4. Pre-medication

• IV Methylprednisolone: 100mg (Dilute in 50-100mls 0.9% sodium chloride)
• IV Chlorphenamine:
  o 1–5 years = 2.5 mg
  o 6–12 Years = 5 mg
  o Over 12 years = 10mg
• PO Paracetamol: 15mg/kg (max 1g)

3.5. Drug preparation & storage

• Store vials in a refrigerator (2°C–8°C). Do not freeze.
• Keep the vial(s) in the outer carton in order to protect from light.
• Each Rituximab vial contains 10mg/ml solution in the following sizes:
  o 100mg/10ml
  o 500mg/50ml
• ANTT should be used throughout.
• Calculate dose of Rituximab and fluid volume to be withdrawn
• Dilute the required dose of Rituximab with 0.9% Sodium Chloride to make a final concentration of 2mg/ml.
• Gently invert to mix, to avoid foaming.
• Prior to administration solution should be inspected for particulate matter or discolouration. If this is present discard the solution and inform pharmacy.
• After preparation solution must be administered immediately, or within 4 hours if stored in fridge.

3.6. Administration rate and monitoring

A PHYSICIAN MUST BE CLOSE BY FOR ALL INFUSIONS

• Monitor for cytokine release syndrome with fevers and rigors. Premedication and slow infusion rates might help to avoid this.
• Give Pre Medications
  o First give the IV Chlorphenamine and PO Paracetamol
  o Give IV Methylprednisolone over 30mins. Put up flush over 30mins
  o (This should ensure a 30min gap between the Methylprednisolone and the Rituximab.)
• **Observations**
  - Baseline TPR and BP prior to infusion
  - TRP and BP every 15 mins for 1 hour
  - Continue TPR and BP every 30 minutes throughout infusion and until 1 hour post infusion

**Infusing Rituximab**

- For the *initial infusion (Day 0)* start at 25mg/hour, which can be **increased by** increments of 25mg/hour every 30mins to a **maximum of 200mg/hour** as tolerated.

- For the *2nd (Day 14) infusion* start at 100 mg/hour, if tolerated the rate can be **increased by 100 mg/hour every 30 minutes**, to a **maximum rate of 400 mg/hour**.

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Infusion rate (mg/hour)</th>
<th>Infusion rate (mL/hour)</th>
<th>Set volume to be infused (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30</td>
<td>25</td>
<td>12.5</td>
<td>6.25</td>
</tr>
<tr>
<td>30-60</td>
<td>50</td>
<td>25</td>
<td>12.5</td>
</tr>
<tr>
<td>60-90</td>
<td>75</td>
<td>37.5</td>
<td>18.75</td>
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<tr>
<td>90-120</td>
<td>100</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>120-150</td>
<td>125</td>
<td>62.5</td>
<td>31.25</td>
</tr>
<tr>
<td>150-180</td>
<td>150</td>
<td>75</td>
<td>37.5</td>
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<tr>
<td>180-210</td>
<td>175</td>
<td>87.5</td>
<td>43.75</td>
</tr>
<tr>
<td>210 +</td>
<td>200</td>
<td>100</td>
<td>To complete infusion</td>
</tr>
</tbody>
</table>

- Total time to complete this infusion is approximately 5 hours

- Upon completion flush with 20ml 0.9% sodium chloride at same infusion rate. Keep cannula insitu for this hour, then it can be removed.

- In the event of an infusion related reaction the infusion rate should be reduced to half the current rate and continue to monitor closely.

- In the event of a moderate to severe reaction the infusion should be interrupted immediately, symptomatic treatment administered and the infusion rate restarted at half the previous rate when symptoms have resolved. Please discuss with rheumatology team if concerned.

- Incidence of infusion-related adverse effects decreases with subsequent infusions.

### 4. Side effects and infusion reactions

Most patients do not experience side effects and pre medication is given to reduce this. Possible side effects include:

1) **Infusion Reactions**: Can occur in 10% of patients treated with rituximab, including hypotension, bronchospasm. These are usually reversible by stopping the infusion, administering anti-pyretics & antihistamines. The infusion can normally be recommenced at a slower rate. Occasionally oxygen, IV bronchodilators & glucocorticoids are required. The patient should be encouraged to report any adverse feelings.
2) **Skin rashes**: Itchy skin rashes have occurred in a few people usually around 24 - 48 hours after the second or third infusion and can last for several days. Anti-histamine can be prescribed to reduce this. No-one has stopped the drug due to itching, the rashes usually go away after a few more doses.

3) **Increased risk of infection**: As with all arthritis treatment there is an increased risk of infection. Blood test should be monitored regularly to check for immune suppression.

4) Other side effects can include conjunctivitis, abdominal pain and more non-specific symptoms such as headaches or temporary changes to blood results including WCC and ALT.

If these symptoms or any other unusual symptoms occur please contact the on-call paediatric rheumatology consultant via switchboard

**Allergic Reaction**

If the following should occur STOP THE INFUSION AND INFORM A DOCTOR on the ward and the paediatric rheumatology team (see contact details at end of protocol):

- Swelling of the lips
- Hives (red, raised, itchy patches of skin)
- Difficulty breathing
- Chest pain
- The presence of high or low blood pressure (change by more than 20mmHg). Symptoms of lightheadedness, dizziness or headache may alert to the presence of a marked change in blood pressure.

**Contacts for Paediatric Rheumatology Team**

1. Paediatric Rheumatology Nurse Specialists 01865 (7)37341 cnspaedrheum@ouh.nhs.uk
2. Paediatric Rheumatology consultant on-call via switchboard
3. Out of hours – contact can be made with the on-call Paediatric Rheumatology consultant via switchboard

**References**

- SPC for Rituximab found at [www.medicines.org.uk](http://www.medicines.org.uk)
- BSPAR Guidelines on Rituximab use in Paediatric Rheumatology.
- BSR BHPR guidelines on the use of Rituximab in RA, Dec 2011

Modified from GOSH Infusion Guideline for Rituximab (2013)