Standard Operating Procedure for use of Rituximab in Frequently Relapsing, Steroid Dependent Nephrotic Syndrome in Childhood.

Standard Operating Procedure Development

1.1 Membership of Development Group

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The views of the Scottish Paediatric Renal and Urology Network (SPRUN) were sought throughout. There was the opportunity to comment and feedback through the Managed Knowledge Network discussion pages of SPRUN.

1.2 Patient population and target audience

This document provides information on the Standard Operating Procedures (SOP) for the investigation, treatment with Rituximab and subsequent management of frequently relapsing or steroid dependent nephrotic syndrome in children. The SOP applies to children throughout Scotland with steroid sensitive idiopathic nephrotic syndrome. The SOP may not be appropriate for children with atypical presentations and does not apply to children with congenital nephrotic syndrome, steroid resistant nephrotic syndrome and nephrotic syndrome secondary to other systemic disease or other structural glomerular disease. The SOP does not apply to the use of Rituximab in other non-renal diseases

This document is intended for use by all health professionals (for example, doctors, nurses, dieticians and pharmacists) who look after children receiving Rituximab as part of treatment of their nephrotic syndrome within Scotland.

1.3 Objectives and clinical questions

SOP objectives:

- Describe eligibility criteria for Rituximab use in steroid sensitive idiopathic nephrotic syndrome of childhood.
- Detail investigations required in preparation for administration of Rituximab in children considered eligible of steroid sensitive idiopathic nephrotic syndrome.
- Describe the SOP for the safe and effective administration of Rituximab.
- Provide dosing guidelines, accepting a lack of confirmed superiority of any given dosing regimen.
- Provide guidance on the subsequent clinical management of children with steroid sensitive idiopathic nephrotic syndrome treated with Rituximab, including immunosuppression withdrawal.
- Detail the follow up investigations of children with steroid sensitive idiopathic nephrotic syndrome treated with Rituximab through joint network clinics.
- Provide guidance on the indications for referral for specialist nephrology advice and review if further nephrotic relapse after Rituximab administration.
- Provide adequate information for children and their families on the use of Rituximab, its monitoring and planned follow up.

Clinical questions addressed in the SOP:

- What are the eligibility criteria for Rituximab use in steroid sensitive idiopathic nephrotic syndrome of childhood?
- What are the screening investigations required before administration of Rituximab?
- What is the SOP for the safe and effective administration of Rituximab?
- What is the recommended procedure for immunosuppressant withdrawal after Rituximab administration?
- What follow-up and investigations are recommended after Rituximab administration?
- What is the recommended procedure for further relapsing nephrotic syndrome after Rituximab administration?
- What information on Rituximab treatment in steroid sensitive idiopathic nephrotic syndrome of childhood do families and patients require?

1.4 Methodology

This SOP has used the best evidence currently available including literature searches of PubMed, using the terms “paediatric” / “children”, “nephrotic syndrome”, “steroid sensitive” and Rituximab. Evidence currently is predominantly from open labelled studies and expert opinion. Only articles written in English were included. The SOP has used procedural information from other professional bodies including BSPAR and the BSR. The revision has also incorporated feedback from the experience in administering Rituximab locally at RHSC, Glasgow.

The procedure has been agreed by consensus in the working group. There were no areas of disagreement.

INTRODUCTION

Rituximab is a genetically engineered chimeric mouse / human monoclonal antibody which causes lysis of B lymphocytes, depleting antibody producing B cells.
Rituximab has been licensed in the UK since 1998 for the treatment of non-Hodgkins lymphoma and in 2006 it was licensed for use in severe active RA following clinical trials (1, 2). It has been subject to NICE approval in RA (3).
It has been used as a component of the treatment of post-transplantation lymphoproliferative disease, non-Hodgkin's lymphoma, Hodgkin's lymphoma, and severe cases of resistant immune modulated disease including idiopathic thrombocytopenia purpura, haemolytic anaemia, and systemic lupus erythematosus.
It has been used to treat cases of frequently relapsing/steroid dependent nephrotic syndrome when other treatment modalities have failed (4, 5). Initial dosing was similar to that used in lymphoma treatment. More latterly, lower doses have been used in nephrotic case series (6-9), though there is no evidence of superiority of any dosing regimen.
Patients with difficult to control NS, despite use of recognised second line therapies, or with unacceptable side effects of therapy, may be considered for this treatment.

ELIGIBILITY

- Frequently relapsing or steroid dependent nephrotic syndrome refractory to conventional therapy.
- Unacceptable side effects of steroids or other second line immunosuppressants
- Ciclosporin dependent nephrotic syndrome.

Patients **must** be referred to and reviewed by a paediatric nephrologist before treatment is initiated. If patients are to receive Rituximab, a registration form (http:*link)*) should be completed and sent to DESIGNATED PERSON (?Susan)

Contraindications

- Active acute or chronic infection.
- Hypersensitivity to Rituximab or other murine proteins
- Severe immunodeficiency – Hypogammaglobulinaemia or known low CD4/CD8 counts

PRE-TREATMENT SCREENING

Detailed history - including

- chronic or recent co-morbidity
- recurrent infections
- allergies

Physical examination to exclude contraindications

SCREENING INVESTIGATIONS

Prior to first dose of Rituximab

1. FBC + diff WBC
2. Renal, bone, liver profiles
3. Immunoglobulins (IgA, IgG and IgM)
4. CNI trough drug levels (e.g. Tacrolimus/Ciclosporin)
5. Viral serology (clotted sample): CMV, EBV, varicella, Hepatitis B and C
6. Viral serology (clotted) for adenovirus or parvovirus ONLY IF recent symptomatic illness

7. Viral PCR: CMV and EBV
8. CD19/20 count (lymphocyte subsets)
9. Spot urine for protein/creatinine ratio (P:CR)

NB: If patients need inactivated vaccinations e.g. influenza, the course should be completed 1 month prior to commencing Rituximab or given at least 7 months after treatment to ensure efficacy of immunisation.
Patients who have not already had pneumococcus immunisation should ideally be immunised 3 months before commencing first course of Rituximab.

TREATMENT

Day-case admission is required, but no specific dietary requirements or lifestyle changes prior to/during the study.

TREATMENT DOSE AND CO-MEDICATION
Regimen
• I.V. Rituximab 375mg/m^2 (max 5~~10~~00mg)

Prescription
The doctor should prescribe and check with renal pharmacist:

PRE-MEDICATION DRUGS
• IV Methylprednisolone 60 minutes before Rituximab infusion

1-5years - 50mg

6 years and above - 100mg

• Paracetamol 15mg/kg (max. 1gm) orally - 60 minutes prior to infusion
• Chlorphenamine orally 60 minutes prior to infusion

1-5 years – 1mg

6 -12 years – 2mg

12 years+ - 4mg

INFUSION THERAPY*
The following prescription is based on 2mgs/ml (MabThera 10mg/ml dilution)

First infusion - DAY 1
• I.V. Rituximab (calculated dose) in normal saline (NaCl 0.9%) (2mg/ml dilution)
To be infused as follows:

- 1st 30 minutes 1**mg**/kg/hour (0.5ml/kg/hour)
- 2nd 30 minutes 2**mg**/kg/hour (1ml/kg//hour)
- Thereafter the rate can be increased by 1**mg**/kg/hour (0.5ml/kg/hour) every 30 minutes to a **maximum** rate of 8**mg**/kg/hour (4ml/kg/hour) providing no adverse reactions occur

*NB: Rituximab can be diluted to a concentration of between 1-4mgs/ml in normal saline if clinically indicated

Concentration	1mg/ml	**2mg/ml (Preferred concentration above)**	4mg/ml
Volume of fluid	1000ml	**500ml**	250ml

PRACTICAL CONSIDERATIONS

Rituximab should only be administered in an area where full resuscitation facilities and close monitoring are available. This is usually done on a day-case basis. A doctor should be present on the ward/unit while the infusion is commenced.

Consideration should be given to the length of infusion time, ensuring that the patient arrives early enough in the day to complete the infusion.

The first infusion may take between 6-7 hours to complete (i.e. IV cannula sited and pre-medication given 60 minutes; 1st infusion minimum 4 hours 15 minutes) or longer if the patient has any adverse reactions (see later section). Subsequent infusions can be completed more quickly (Rituximab infusion minimum of 3 hours 15 minutes) if the patient had no adverse effects during the first infusion.

PRE-INFUSION ASSESSMENT

This may be done in advance of the initial infusion. The assessment will be undertaken by a member of the renal team to assess general health and to check for any sign of infection.

Screening tests are detailed above.

The results of blood and urine tests should be reviewed and documented in the patient's notes. Abnormal results may require repetition on the day of infusion, or cancellation of the infusion. This should be discussed with the responsible consultant. Cancellations should be notified to pharmacy as soon as possible. If all investigations are normal, it is not necessary to repeat baseline investigations.

Advise the patient to omit any oral anti-hypertensives for 12 hours prior to infusion (Rituximab may cause hypotension during infusion). Patients should bring these medications with them to take in the event of hypertension during the infusion.

In hospitals where Pharmacy is preparing the infusion, the prescription should be sent to the Pharmacy Aseptics Facility at least 48 hours before the proposed infusion time. It is the responsibility of the renal team to then advise the Pharmacy to prepare the drug once all screening results are found to be satisfactory. Investigations **do not need to be repeated** on the day of attendance for treatment if these screening results are satisfactory.

Rituximab can be classified as a cytotoxic since it destroys B cells. However, it is different to the small molecules traditionally used as cytotoxic chemotherapy, which generally exert their effect by interfering with DNA replication. These effects are non-specific and can therefore result in adverse events when rapidly dividing healthy cells are also affected. By contrast Rituximab will only destroy CD20 positive B cells. Since the drug product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed during preparation of the infusion solution. **Rituximab does not require any special handling precautions beyond those described and is subject to the same considerations as any other preparation for intravenous use, including other monoclonal antibodies**

ADMINISTRATION

On the day of the Rituximab infusion:

The nurse should (see checklist Appendix 2): -

- Check pre-assessment has been performed
- Check that the patient has not received analgesics containing paracetamol within the last 4 hours and has omitted their morning dose of any anti-hypertensive medication.
- Take and record Temperature, Pulse, Blood Pressure and O2 Saturation levels as baseline
- Insert IV cannula
- Ensure infusion pump is ready and working
- Administer pre-infusion medications as per drug chart, commencing 60 minutes before Rituximab is given

The rate of the infusion will depend on the concentration of the Rituximab and whether it is the 1st or subsequent infusions. In the event of a reaction to the first infusion, the second infusion should be administered as per instructions for the first infusion (see above). Check infusion rate with doctor/pharmacist if concentration is not 2mg/ml.

INFUSION RATE FOR DAY 1 INFUSION

Time	mg/hour	ml/hour
1st 30 minutes	1**mg**/kg/hour	0.5**ml**/kg/hour
2nd 30 minutes	2**mg**/kg/hour	1**ml**/kg/hour
Thereafter the rate can be increased by 1**mg**/kg/hour (0.5ml/kg/hour) every 30 minutes to a **maximum** rate of 8**mg**/kg/hour (4mls/kg/hour) **providing no adverse reactions occur (see below)**		

The infusion should continue until completed **(providing no adverse reactions occur).**

INFUSION RATE FOR SUBSEQUENT INFUSIONS IN PATIENT if the patient had no reaction to the first infusion

Time	mg/hour	ml/hour
1st 30 minutes	2**mg**/kg/hour	1**ml**/kg/hour
2nd 30 minutes	4**mg**/kg/hour	2**ml**/kg/hour
Thereafter the rate can be increased by 2**mg**/kg/hour (1ml/hour) every 30 minutes to a **maximum** rate of 8**mg**/kg/hour (4mls/kg/hour) **providing no adverse reactions occur (see below)**		

The infusion should continue until completed (**providing no adverse reactions occur).**

Clinical observations DURING INFUSION

1st hour – Blood pressure, Pulse, Temperature and SaO_2 every 15 minutes
Thereafter, every 30 minutes prior to increasing the rate of infusion and throughout the course of the infusion once maximum rate is reached.
Most reactions have been noted during the first few minutes of the infusion, so the patient should be observed carefully during this time and following increases in infusion rates.

INFUSION REACTIONS

• Acute infusion reactions may occur within 1-2 hrs 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

If the patient experiences an infusion reaction
Mild to moderate reactions e.g. low grade fever; hypotension <30mmHg from baseline
- Halve the infusion rate and
- Consider giving prn medication

Moderate to severe reactions e.g. fever >38.5ºC; chills; mucosal swelling; shortness of breath; hypotension by >30mmHg from baseline
- **STOP the infusion and treat the symptoms.**
- **Contact the doctor.**
- The infusion should be restarted at half the previous rate only when the symptoms have resolved.

Note: in the case of extravasation, Rituximab is not an irritant and no special action is needed

POST INFUSION
1. Remove IV cannula
2. Advise parent/patient to seek medical help if they have any symptoms that could be due to an infection e.g. fever in the hours or days after the infusion – ensure they have appropriate contact numbers for the Renal Unit or otherwise to contact GP and / or attend Emergency Department
3. Advise parent/patient to restart any anti-hypertensive drugs the day after infusion
4. Organise follow up appointment for CD19/CD20 lymphocyte subset check in 1 week.
5. Enter Rituximab prescription details in Renal database (SERPR) or send details of treatment to link nephrologist if administered in other network centre.
6. Ensure the patient has a follow up assessment at 1 month from initial Rituximab dose

ADVERSE EVENTS
• Infusion reactions
- Mild to moderate infusion reactions – 30-35% at 1st infusion; less with the 2nd
- Severe infusion reactions are uncommon – frequency is reduced by the concomitant use of IV steroids and pre-medication

• Infections
- Small increase in serious infections (not opportunistic infections e.g. TB)

Follow-up

Adequate B-cell depletion is indicated by an absence of CD19/CD20 +ve cells on flow cytometry. Most studies assume <1% is adequate depletion with a further dose recommended if there is persistence of B-cells. Up to 4 doses of 375mg/m^2 may be administered until there is B-cell depletion, but the majority of patients will require only 1 or 2.. Some patients go into permanent remission – around 1-2 in 5 - but the remainder – 3-4 in 5 – may require further courses of Rituximab once the CD20 count recovers. An alternative approach if repeat Rituximab is required is the re-introduction of MMF which may maintain remission or reduce relapse frequency.

CD20 recovery may occur between 6 and 12 + months after the initial treatment, but this appears idiosyncratic and an individual phenomenon. No predictive factors as to when this may occur have been identified. There is also insufficient data to determine whether repeated courses eventually result in permanent remission, or a continuing requirement evolves. However, the duration of remission per individual linked to CD20 count recovery does appear to follow a similar time course, so once this is established, this could be used to predict pre-treatment. The CD20 count can be monitored on a 2 monthly basis to help in this assessment.

Subsequent doses: Repeat doses can be considered for nephrotic relapse as defined by three consecutive days of 3/4+ proteinuria measured by urinary dipstick and confirmed by urine P:CR in conjunction with CD20 recovery. Remission should be achieved first with Prednisolone 60mg/m^2. For repeat treatment a single dose of Rituximab can be given as before. If 2 or greater doses of 375mg/m^2 were required initially, a single dose of 750mg/m2 should be given.

In patients who repeatedly relapse on CD20 count recovery despite other treatment measures treatment with one dose of 750mg/m^2 as the CD20 count returns to 10% of baseline can also be considered. Repeated treatments with Rituximab run the risk of inducing a prolonged hypogammaglobulinaemia. This then may need regular and long term IVIG replacement therapy.

Withdrawal of immunosuppressants and steroids after Rituximab administration

There is no standardised protocol for IS and steroid withdrawal. Suggested approaches include:

CNI – Ciclosporin/Tacrolimus

Half CNI dose after confirmation of B-cell depletion on LSS (B-cells <1%) then discontinue two weeks later.

Mycophenolate Mofetil

If part of combined IS therapy with CNI, reduction may follow withdrawal of CNI. Dose can be reduced in 2 or more steps over a suggested timescale of 2 – 4 months.

If MMF has been used as monotherapy the dose can be reduced as for CNI.

Steroids

Steroids can be weaned in a schedule similar to that used in tapering regimens following successful induction of remission of nephrotic relapse.

Laboratory Tests (at follow up – see table)

1. CD19/20 count (lymphocyte subsets – LSS)
2. Immunoglobulins (IgA, IgG and IgM)
3. FBC + diff WBC
4. Renal, bone, liver profiles

Urine tests

Spot urine for protein/creatinine ratio (uP:CR)

1st course of Rituximab

All above tests to be repeated one week following the 1st dose of Rituximab. If B cells >1% on LSS, a further dose should be repeated as soon as practically possible. LSS should be repeated one week following each infusion to confirm B-cell depletion (to a maximum of 4 infusions of 375mg/m2 or cumulative dose of 2 grams). Once B-cell depletion has occurred, LSS and bloods above should be checked one month later, then two monthly thereafter (months 3,5,7 etc), with rise in count predictive of potential relapse, until B-cells have reconstituted (>1%, or absolute number >1.0).

2nd + subsequent courses

For subsequent doses, LSS should be checked one week following dose administration, one month later, then guided by the time to B-cell recovery from previous administration (e.g. if 1st recovery occurred in 7 months, checking LSS at 1 week, 1 month, and then 6 months). Once reconstituted, further checks are no longer necessary.

Months after first Rituximab	1	2	3	4	5	6	7	8	9	10	11	12
Clinical Evaluation	X		X		X		X		X		X	
Immunoglobulins	X		X		X		X		X		X	
CD20 count	X		X		X		X		X		X	
Urine P:CR	X		X		X		X		X		X	
Plasma Albumin	X		X		X		X		X		X	
Re-treatment	X											

If >2 courses of rituximab are proposed, discussion should occur with the paediatric nephrology team re ongoing management, monitoring, and immunosuppression.

*Note: B cells express CD19 and CD20. Rarely (normally in the context of malignancy) B cells may not express CD20 and will not therefore be eliminated by Rituximab. If there is concern that B cells are not eradicated after 7-10 days, routine B cell measurement should be repeated and can be discussed with the immunology laboratory whether direct measurement of CD20 would be helpful. This will rarely be required.

Treatment contra-indications.

1. Active infection/ positive Mantoux
2. Immunodeficiency or clinically significant Neutropenia/lymphopenia.
3. Serologic evidence of current or past HIV, Hepatitis B, or Hepatitis C infection
4. Serologic or clinical evidence of current or recent viral infection (IgM +ve or +ve PCR): CMV, EBV, varicella infection. Serology/PCR for adenovirus infection or parvovirus infection only if clinically indicated.
5. Complicating medical issues that cause increased risk
6. History of malignancy other than PTLD
7. Cardiovascular disease
8. Pregnancy.

Cautions:

- Rituximab should be used with caution in patients with a history of cardiovascular disease or renal impairment (may require dose reduction).
- The safety of vaccination, especially with live vaccines following treatment with Rituximab is not known. Live vaccines are currently contraindicated post Rituximab whilst B cells are depleted, and/or patients are on additional immunosuppressive therapy.
- It is not known whether patients may need re-immunisation of previous killed vaccines following Rituximab. Some studies have shown that Rituximab did not affect anti-tetanus antibody titres.
- A decline in immunoglobulins may make children more susceptible to infections, especially varicella. However, overall, total immunoglobulin levels are well preserved, and preliminary studies suggest that patients do not appear to be at risk of major infection or opportunistic infection due to Rituximab treatment.

The optimal therapeutic dose and schedule for re-treatment with Rituximab, based on return of signs and symptoms of illness, has not been determined, though there is evidence that low dose has slightly less good clinical outcomes compared to higher doses on long-term follow-up.~~d.~~

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