



**Clinical Commissioning Policy:
Rituximab for the treatment of
relapsing steroid sensitive nephrotic
syndrome**

Reference: NHS ENGLAND XXX/X/X

NHS England

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Rituximab for the treatment of relapsing steroid
sensitive nephrotic syndrome**

Prepared by NHS England Clinical Reference Group for Paediatric Medicine

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Contents

Policy Statement	4
Equality Statement	4
Plain Language Summary	4
1. Introduction	5
2. Definitions	6
3. Aim and objectives	6
4. Epidemiology and needs assessment.....	7
5. Evidence base.....	7
6. Rationale behind the policy statement.....	9
7. Criteria for commissioning.....	9
8. Patient pathway.....	11
9. Governance arrangements.....	20
10. Mechanism for funding.....	20
11. Audit requirements	20
12. Documents which have informed this policy.....	20
13. Links to other policies.....	21
14. Date of review	21
<i>References</i>	21
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Policy Statement

NHS England will commission Rituximab in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Throughout the production of this document, due regard has been given to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited in under the Equality Act 2010) and those who do not share it.

Plain Language Summary

In nephrotic syndrome, the kidneys leak too much protein into urine, leading to a drop in the levels of protein in the blood. This causes swelling in the body, especially in the face, legs and feet (oedema). Relapsing steroid sensitive nephrotic syndrome is a condition that responds to steroids but if there are multiple relapses the child may get severe side effects from steroids, including weight increase, poor growth, high blood pressure, risks of infection, cataracts, diabetes, behavioural problems and others. There are other drugs which may allow a reduction in steroid dose but if these fail rituximab offers another very successful option for treatment. Without this treatment the child may remain in relapse – this has very serious consequences including the risk of life threatening infection, strokes, high cholesterol levels and the associated risks and kidney failure.

This policy aims to address the place of rituximab in the management of relapsing steroid sensitive nephrotic syndrome.

1. Introduction

Idiopathic nephrotic syndrome is the commonest glomerular disease of childhood, with an incidence of 2 cases per 100,000 children in the UK [1]. A wide variety of glomerular lesions can be seen in INS. These include minimal change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), membranoproliferative glomerulonephritis (MPGN), C3 glomerulonephritis (C3GN), IgA nephropathy, diffuse mesangial proliferation, and others.

The presenting episode is treated with high-dose oral prednisolone to which >90% make a complete response, responders receiving the diagnostic label of steroid-sensitive nephrotic syndrome (SSNS) [2,3]. Frequently relapsing nephrotic syndrome (FRNS) is defined as steroid-sensitive nephrotic syndrome (SSNS) with 2 or more relapses within 6 months, or 4 or more relapses within a 12-month period. Steroid-dependent nephrotic syndrome (SDNS) is defined as SSNS with 2 or more consecutive relapses during tapering or within 14 days of stopping steroids. The optimum duration of prednisolone therapy at presentation remains unclear and is currently being further investigated in the NIHR-sponsored PREDNOS study (ISRCTN16645249), which is due to complete recruitment in September 2014.

Following successful initial treatment, 70% to 80% of children develop disease relapses necessitating further 4- to 8-week courses of high-dose prednisolone, and around 50% develop frequently relapsing disease [4]. Nephrotic syndrome relapses are associated with a risk of significant complications, including sepsis, thrombosis, dyslipidaemia and malnutrition [5]. The treatment of relapses is with a standard course of high-dose prednisolone (60mg/m² daily (max 80mg) until urinary remission, then 40mg/m² (max 60mg) on alternate days for 28 days (14 doses)). This therapy may be associated with major adverse effects, including hip avascular necrosis, hypertension, diabetes and behavioural problems [6]. Furthermore, children miss school during relapses, resulting in impaired academic performance and parental absence from work. It is well recognised that at least 50% of relapses are precipitated by a viral upper respiratory tract infection (URTI), possibly mediated through cytokine release [7].

Various long-term immunosuppressive strategies are employed to reduce the frequency of relapses in those with frequently relapsing disease. These include the use of long-term low-dose alternate-day prednisolone, levamisole, cyclophosphamide, ciclosporin, tacrolimus, mycophenolate mofetil and more recently rituximab.

Use of corticosteroids is most common in SSRN however their use is not without risks for producing serious side effects, especially when used in high doses for prolonged durations. During short-term therapy these include increased appetite, weight gain, fluid retention, gastritis, headache, mood swings, increase in blood sugar, hypertension and glaucoma. Adverse effects seen when therapy is given for longer duration include suppressed immunity, increased susceptibility to infections, increased cholesterol levels, weight gain, osteoporosis, deposition of body fat, thinning of skin, cataracts, stunting and hypothalamopituitary axis suppression. Therefore, there is a need for alternative therapies for SSNS patients (Deshmukh 2007).

Rituximab is a genetically engineered chimeric mouse / human monoclonal antibody

which causes lysis of B lymphocytes, depleting antibody producing B cells. It 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 [8, 9]. It has been subject to NICE approval in RA [10]. 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.

Rituximab has emerged as a potentially useful agent in SSNS, particularly in those with disease relapses which have become unresponsive to other conventional therapies and those with unacceptable adverse-effects of therapy. The number of publications reporting positive clinical experiences with this agent have significantly increased in recent years, though the number of prospective randomised trials is very small. The purpose of this document is to provide guidelines based on the current literature regarding the appropriate use of this agent in relapsing steroid sensitive nephrotic syndrome.

2. Definitions

ISKDC: International Study of Kidney Disease in Childhood

Nephrotic syndrome: Oedema, proteinuria $>40\text{mg}/\text{m}^2/\text{h}$ or protein:creatinine ratio $>200\text{mg}/\text{mmol}$, hypoalbuminaemia $<25\text{g}/\text{l}$

Remission: Urine protein excretion $<5\text{mg}/\text{m}^2/\text{h}$, first morning urine protein:creatinine ratio $<20\text{mg}/\text{mol}$ for three consecutive days or first morning urine dipstick test zero or trace for three consecutive days

Relapse: Urine protein $>40\text{mg}/\text{m}^2/\text{h}$, first morning urine protein:creatinine ratio $>200\text{mg}/\text{mmol}$ for three consecutive days or first morning urine dipstick of 2+ protein or more for three consecutive days, having previously been in remission.

(NB The American Academy of Paediatrics also define relapse as early morning urine dipstick of 2+ or more for 3 out of 5 consecutive days.)

Frequent relapsing nephrotic syndrome: Two or more relapses within 6 months of initial response, or more than 4 relapses in any 12 month period

Steroid dependence: Two consecutive relapses occurring during steroid treatment or within 14 days of its cessation

Steroid resistance: Failure to achieve response in spite of four weeks of Prednisolone at $60\text{mg}/\text{m}^2/\text{day}$

3. Aim and objectives

This policy aims to:

- Overview the current evidence regarding the efficacy and safety of rituximab in SSNS.

The objectives are to:

- Provide guidelines for the rational use of rituximab for the treatment of relapsing SSNS.

- 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 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.

4. Epidemiology and needs assessment

The incidence of childhood idiopathic nephrotic syndrome is reported to be around 2 cases per 100,000 child population/year. A study in Yorkshire reported an incidence of 2.3 cases per 100,000 person-years in children below 15 years of age [1]. (this is the same as per 100,000 children per annum). Of these, 2.0 cases/100,000 had SSNS and 0.3 cases/100,000 had SRNS. Although the overall incidence of childhood nephrotic syndrome has been relatively stable, the incidence of SRNS appears to be increasing in children and adults, particularly in the non-white population [referencing difficult here, as mostly from US Black and Hispanic populations].

Nephrotic syndrome is more common in boys, with a male/female ratio of 1.6:1 (1.7:1 for SSNS and 1.2:1 for SRNS).

SSNS presents most commonly in the 1-4 year old age group [1]. The ISKDC study found the median age at presentation of SSNS to be 3 years [11]

The incidence of SSNS in the UK South Asian population is four to six times higher than in the UK White population [12]

5. Evidence base

A literature review was undertaken to include systematic reviews or randomised controlled trials reporting clinical effectiveness and safety of rituximab to treat paediatric patients with steroid sensitive nephrotic syndrome. One systematic review was found and an RCT which met the inclusion criteria. Findings of the studies are presented below.

Systematic review (Mohammedjafari et al 2013)

The authors undertook a systematic review of the published literature efficacy of rituximab in treatment of childhood (<16 years old) steroid resistant and steroid dependent nephrotic syndrome (SDNS). They searched Medline, Embase, web of

science and Cochrane library databases using keywords to identify all studies published in English up to March 2013. In the SDNS group, response was defined as relapse rate in 6 or 12 months after therapy.

The authors found 11 studies reporting outcomes on SDNS. 9 case series (n= 9-70), 1 cohort study (n=33) and 1 open-label RCT (n=53)- all but one reported favourable outcomes in the use of rituximab. Based on the outcomes reported in the studies, in SDNS patients, the overall standard mean differences of relapses 12 months after treatment in the pooled findings of the four studies (56 cases) was 2.63 (2.03, 3.24), showing that the decrease is modest but significant ($P < 0.0001$) [$I^2 = 82$; $P < 0.001$]. In these dependent patients, the data on relapse rate after treatment pooled from 6 studies (162 cases) was 0.42 (0.15, 0.69).

In the open label RCT, the authors (Ravani et al 2011) included 54 children with idiopathic nephrotic syndrome dependant on prednisone and calcineurin inhibitors for >12 months in an open- label randomised controlled trial to show that a strategy based on rituximab and lower doses of prednisone and calcineurin inhibitors was non-inferior to standard doses of these agents in maintaining 3-month proteinuria as low as baseline or up to 1 g/d greater. Participants were stratified by the presence of toxicity to prednisone/calcineurin inhibitors and assigned to add rituximab to lower doses of standard agents or to continue with current therapy alone in the intervention group. In the control group, they administered prednisolone and calcineurin inhibitor without Rituximab. Rituximab (Mabthera) (375 mg/m^2) was given intravenously once (at randomisation in the absence of clinical signs of toxicity secondary to steroids and/or cyclosporine) or twice (at randomization and after 2 weeks in the presence of toxicity).

In the end of the study, three-month proteinuria was 70% lower in the rituximab arm (95% confidence interval 35% to 86%) as compared with standard therapy arm (intention-to-treat); relapse rates were 18.5% (intervention) and 48.1% (standard arm) ($P = 0.029$). Probabilities of being drug-free at 3 months were 62.9% and 3.7%, respectively ($P < 0.001$); 50% of rituximab cases were in stable remission without drugs after 9 months.

RCT (Iijima et al 2014)

In a multicentre, double-blind, randomised, placebo-controlled trial at nine centres 48 patients aged 2 years or older experiencing a relapse of FRNS or SDNS meeting the eligibility criteria of the study were randomised (24 were given rituximab and 24 placebo). Renal history of majority patients was minimal change disease (88% in treatment arm and 98% in placebo arm). Steroid toxicity was recorded in about 2/3 patients (71% in treatment arm and 79% in placebo arm).

All patients received ciclosporin between treatment start up to day 85 of follow up. If patients were taking any other immunosuppressive drugs, these drugs were discontinued by day 85. Patients assigned to rituximab arm received an intravenous dose of 375 mg/m^2 (maximum 500 mg) once weekly for 4 weeks. Of the 48 patients, 43 received all four doses- 20 patients given rituximab and 23 given placebo received all four doses.

Patients were followed up for 1 year. FRNS or SDNS was diagnosed between days 86 and 365, or steroid resistance was noted. The primary endpoint of the study was the relapse-free period. Patients were deemed to have treatment failure if a relapse had occurred by day 85. Safety endpoints were frequency and severity of adverse

events.

20 patients in the treatment arm and 4 in the placebo arm completed at week 53. 4 patients in the treatment arm discontinued (2 had treatment failure and 2 for other reasons) and 20 patients discontinued in the placebo arm (18 had treatment failure and 2 for other reasons) prior to 53 weeks.

By the end of 1 year of follow-up, 17 patients in the rituximab group and 23 in the placebo group had relapsed. The median relapse free period was significantly longer in the rituximab group (267 days, 95% CI 223–374) than in the placebo group (101 days, 70–155; hazard ratio: 0.27, 0.14–0.53; $p < 0.0001$). Concomitant angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers, or both, decreased the median relapse free period in the rituximab group, although the difference was marginally significant.

Treatment failure was reported in ten patients in the rituximab group and 20 in the placebo group. The time to treatment failure was significantly longer in the rituximab group than in the placebo group (HR 0.27, 95% CI 0.12, .59; $p = 0.0005$).

Mean daily steroid dose after randomisation was significantly lower in the rituximab group than in the placebo group (9.12 mg/m² per day [SD 5.88] vs 20.85 mg/m² per day [9.28]; $p < 0.0001$).

Ten patients (42%) in the rituximab group and six (25%) in the placebo group had at least one serious adverse event ($p = 0.36$). Although more patients had serious adverse events in the rituximab group than in the placebo group, the difference was not significant ($p = 0.36$). The most common grade 3-4 adverse events in the Rituximab group were hypoproteinemia, lymphocytopenia, and neutropenia.

The majority of studies show some benefits of rituximab in SSNS. The evidence suggests there is a reduction in the median relapse free period, reduction in proteinuria and a modest reduction in the number of relapses 12 months after treatment with rituximab. Most studies focused on the use of rituximab in patients with cyclosporine failure or toxicity.

From the available literature, the optimal dose for rituximab in SSNS is unclear. Studies have used weekly infusion of 375 mg/m² of rituximab for 4 weeks, which is similar to the protocol being used in patients with B-cell lymphoma or 2 weekly doses of the same, 2 doses once followed by a second after 2 weeks or even only a single dose of 375 mg/m². However, it seems that a single-dose infusion of rituximab induces short-term remission in comparison with more doses at initiation of treatment (Otukesh et al. 2013). A weekly infusion of 375 mg/m² of rituximab for 4 weeks showed positive results in an RCT (Iijima et al 2014).

6. Rationale behind the policy statement

There is sufficient evidence which demonstrates that rituximab for SSNS in children is clinically effective and safe. Therefore, this policy recommends it is routinely funded based on the eligibility criteria.

7. Criteria for commissioning

Eligibility criteria

1. Patients is 1-18 years of age
2. Patients must be referred to and reviewed by a Consultant Paediatric Nephrologist at a specialised centre before treatment is initiated.
3. Rituximab should not be considered as a first line treatment for a patient with nephrotic syndrome.
4. Patients should have been given:
 - a trial of an alkylating agent (unless particular concern re fertility eg in peripubertal boys) and at least 6 months therapy with a calcineurin inhibitor, unless there were specific contraindications to the former and unacceptable adverse effects of the latter.

AND

- at least 3 months therapy with MMF should also have been administered unless this was associated with unacceptable adverse effects

Indications

- Frequently relapsing or steroid dependent SSNS refractory to conventional therapy, with ongoing disease relapses, despite prior or ongoing treatment with alternate day prednisolone, levamisole, alkylating agents (cyclophosphamide or chlorambucil), calcineurin inhibitors (ciclosporin or tacrolimus) and mycophenolate mofetil, alone or in combination.
- Unacceptable adverse effects of corticosteroids as evidenced by severe end-organ damage such as osteoporosis, cataracts, obesity, behavioural problem.
- Ciclosporin-dependent nephrotic syndrome

Contraindications

- Active acute or chronic infection (including positive Mantoux test **in those in whom this has been performed***)
- Infants (<12 months)
- Known allergic reaction to rituximab
- Presence of anti-rituximab antibodies
- Severe immunodeficiency – Hypogammaglobulinaemia or known low CD4/CD8 counts or clinically significant Neutropenia/lymphopenia.
- Serologic evidence of current or past HIV, Hepatitis B, or Hepatitis C infection
- Serologic or clinical evidence of current or recent (IgM +ve or +ve PCR) CMV, EBV, adenovirus, parvovirus or varicella infection
- Complicating medical issues that cause increased risk
- History of malignancy other than PTLN
- Pregnancy.

***Mandatory Mantoux testing is not required**

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.
- 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.
- 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.

Subsequent treatments following relapse

- Subsequent treatments should only be given 6-12 months post last course
- If relapses are occurring within 6 months then a review of rituximab must be made by a Consultant Paediatric Nephrologist at a specialised centre with a view to stopping the treatment

8. Patient pathway

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

(These should be completed and results reviewed prior to administration of first dose)

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, parvovirus, adenovirus, Hepatitis B and C
6. Viral PCR: CMV and EBV
7. CD19/20 count (lymphocyte subsets)
8. Spot urine for protein/creatinine ratio (PCR)

All patients with SSNS on immunosuppressive therapy are at risk of influenza and should be given seasonal inactivated influenza vaccine when available in the autumn period regardless of the timing of rituximab or the lymphocyte count. No tests of lymphocyte number or function should be done before immunisation, however clinicians should be aware that the vaccine may not be effective, or as effective, in preventing influenza as prior to the rituximab therapy.

Patients who have not already had pneumococcal immunisation should ideally be immunised 3 months before commencing first course of Rituximab with 2 doses of conjugate pneumococcal vaccine (currently Prevenar 13 in the UK). There is no evidence that a dose of pneumococcal plain polysaccharide vaccine (PPV23) confers additional benefit in these patients.

TREATMENT

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

If patients have been steroids sensitive treatment should be aimed to be given when they are protein free

TREATMENT DOSE AND CO-MEDICATION

For patients weighing \geq 50kg

Regimen

- I.V. 1000mg Rituximab on Day 1 and Day 15

Prescription

The doctor should prescribe and check with renal pharmacist:

PRE-MEDICATION DRUGS

- Methylprednisolone 100mg IV 60 minutes before Rituximab infusion
- Paracetamol 15mg/kg (max. 1gm) orally - 60 minutes prior to infusion
- Chlorphenamine 10 mg orally - 60 minutes prior to infusion

INFUSION THERAPY*

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

First infusion - DAY 1

- I.V. Rituximab 1000mg in 500mls of normal saline (NaCl 0.9%)

To be infused as follows:

- 1st 30 minutes 50mg/hour (25mls/hour)
- 2nd 30 minutes 100mg/hour (50mls/hour)
- Thereafter the rate can be increased by 50mg/hour (25mls/hour) every 30 minutes to a **maximum** rate of 400mg/hour (200mls/hour) providing no adverse reactions occur

Second infusion - DAY 15 (providing DAY 1 infusion was without adverse events)

- I.V. Rituximab 1000mg in 500mls of normal saline (NaCl 0.9%)

To be infused as follows:

- 1st 30 minutes 100mg/hour (50mls/hour)
- 2nd 30 minutes 200mg/hour (100mls/hour)
- Thereafter the rate can be increased by 100mg/hour (50mls/hour) every 30 minutes to a **maximum** rate of 400mg/hour (200mls/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	2mgs/ml (Preferred concentration above)	4mgs/ml
Volume of fluid	1000mls	500mls	250mls

TREATMENT DOSE AND CO-MEDICATION

For patients weighing < 50kg

Regimen

- I.V. Rituximab 750 mg/m² (max 1000mg) on Day 1 and Day 15

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 dose according to age orally - 60 minutes prior to infusion

INFUSION THERAPY*

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

First infusion - DAY 1

- I.V. Rituximab 1000mg in 500mls of normal saline (NaCl 0.9%)

To be infused as follows:

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

Second infusion - DAY 15 (providing DAY 1 infusion was without adverse events)

- I.V. Rituximab 1000mg in 500mls of normal saline (NaCl 0.9%)

To be infused as follows:

- 1st 30 minutes 2mg/kg/hour (1ml/kg/hour)
- 2nd 30 minutes 4mg/kg/hour (2ml/kg/hour)
- Thereafter the rate can be increased by 2mg/kg/hour (1ml/kg/hour) every 30 minutes to a **maximum** rate of 8mg/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). The second infusion 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.

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.

Administering the infusion IN PATIENT \geq 50kg:

Rituximab is infused through a peripheral IV cannula using an IV pump with a primed line.

NB: The following regime is based on a concentration of 2mgs/ml i.e. 1000mgs in 500mls.

The rate of the infusion will depend on the concentration of the Rituximab and whether it is the 1st or 2nd infusion. 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 IN PATIENT ≥ 50 kg

Time	mg/hour	ml/hour
1st 30 minutes	50mg/hour	25ml/hour
2nd 30 minutes	100mg/hour	50ml/hour
Thereafter the rate can be increased by 50mg/hour (25mls/hour) every 30 minutes to a maximum rate of 400mg/hour (200mls/hour) providing no adverse reactions occur (see below)		

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

INFUSION RATE FOR DAY 15 INFUSION IN PATIENT ≥ 50 kg if the patient had no reaction to the first infusion

Time	mg/hour	ml/hour
1st 30 minutes	100mg/hour	50ml/hour
2nd 30 minutes	200mg/hour	100ml/hour
Thereafter the rate can be increased by 50mg/hour (25mls/hour) every 30 minutes to a maximum rate of 400mg/hour (200mls/hour) providing no adverse reactions occur (see below)		

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

INFUSION RATE FOR DAY 1 INFUSION IN PATIENT ≤ 50 kg

Time	mg/hour	ml/hour
1st 30 minutes	1mg/kg/hour	0.5ml/kg/hour

2nd 30 minutes	2mg/kg/hour	1 ml/kg/hour
Thereafter the rate can be increased by 1mg/kg/hour (0.5mls/kg/hour) every 30 minutes to a maximum rate of 8mg/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 DAY 15 INFUSION IN PATIENT \leq 50kg if the patient had no reaction to the first infusion

Time	mg/hour	ml/hour
1st 30 minutes	2mg/kg/hour	1 ml/kg/hour
2nd 30 minutes	4mg/kg/hour	2ml/kg/hour
Thereafter the rate can be increased by 2mg/kg/hour (1mls/hour) every 30 minutes to a maximum rate of 8mg/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 on DAY 1 and DAY 15

1st hour – Blood pressure, Pulse, Temperature and SaO2 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

- o Halve the infusion rate and

- o Consider giving prn medication

Moderate to severe reactions e.g. fever >38.5°C; chills; mucosal swelling; shortness of breath; hypotension by >30mmHg from baseline.

STOP the infusion and treat the symptoms.

- o **Contact the doctor.**

- o 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 infusion 2 or follow up appointment as required
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
 - o Mild to moderate infusion reactions – 30-35% at 1st infusion; less with the 2nd
 - o Severe infusion reactions are uncommon – frequency is reduced by the concomitant use of IV steroids and pre-medication
- Infections
 - o Small increase in serious infections (not opportunistic infections e.g. TB)

Follow-up

Some patients go into permanent remission – around 1 in 4 - but the remainder – 3 in 4 – 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 PCR in conjunction with CD20 recovery. Remission should be achieved first with Prednisolone 60mg/m². For repeat treatment a single dose of 750mg/m² Rituximab can be given as before. **This should not be administered earlier than six months after the last dose.**

In patients who repeatedly relapse on CD20 count recovery despite other treatment measures treatment with one dose of 750mg/m² 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 first Rituximab infusion and discontinue after second infusion.

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)
2. Immunoglobulins (IgA, IgG and IgM)
3. FBC + diff WBC
4. Renal, bone, liver profiles

Urine tests

Spot urine for protein/creatinine ratio (uPCR)

All tests to be repeated at time of 2nd dose of Rituximab and at 1 month after first dose.

CD19 counts: at time 0; with second dose and 1 month after initial dose. Two monthly thereafter (months 3, 5, 7 etc), with rise in count predictive of potential relapse.

Month post dose	1	3	5	7	9	11
Clinical evaluation	X	X	x	X	x	X
Immunoglobulins	X	X	X	X	x	x
CD20 count	X	X	x	X	x	X
Urine PCR	X	X	X	X	x	x
Plasma albumin	X	X	x	X	x	x

*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.

9. Governance arrangements

Rituximab should only be administered to children with SSNS following review by a Consultant Paediatric Nephrologist

It is recommended that rituximab is only administered in tertiary paediatric nephrology centres, though there may be other institutions with experience of the use of this agent for other indications (e.g. rheumatology, oncology), where administration may be deemed appropriate.

10. Mechanism for funding

From April 2013 the NHS England will be responsible for commissioning in line with this policy on behalf of the population of England.

11. Audit requirements

All patients who receive rituximab for the treatment of SSNS must be entered onto a renal registry to allow the collection of long term pharmacovigilance data. This is a condition of funding.

12. Documents which have informed this policy

Standard Operating Procedure for the use of rituximab in frequently relapsing steroid dependent nephrotic syndrome in childhood. Renal Unit, Royal Hospital for Sick Children, Glasgow.

13. Links to other policies

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

14. Date of review

This policy will be reviewed in April 2016 unless information is received which indicates that the proposed review date should be brought forward or delayed.

References

1. McKinney PA, Feltblower RG, Brocklebank JT, Fitzpatrick MM: Time trends and ethnic patterns of childhood nephrotic syndrome in Yorkshire, UK. *Pediatr Nephrol* 2001, 15:1040–1044.
2. Trompeter RS, Lloyd BW, Hicks J, White RH, Cameron JS: Long-term outcome for children with minimal change nephrotic syndrome. *Lancet* 1985, 1:368–370.
3. Shenoy M, Plant ND, Lewis MA, Bradbury MG, Lennon R, Webb NJ: Intravenous methylprednisolone in idiopathic childhood nephrotic syndrome. *Pediatr Nephrol* 2010, 25(5):899–903.
4. International Study of Kidney Disease in Children: Nephrotic syndrome in children: a randomised controlled trial comparing two prednisone regimens in steroid-responsive patients who relapse early. *J Pediatr* 1982, 95:239–243.
5. Webb NJA: Epidemiology and general management of childhood idiopathic nephrotic syndrome. In *Evidence-based Nephrology*. Edited by Molony D, Craig J. Wiley-Blackwell, Oxford, UK; 2008.
6. Hall AS, Thorley G, Houtman PN: The effects of corticosteroids on behaviour in children with nephrotic syndrome. *Pediatr Nephrol* 2003, 18(12):1220–1223.
7. MacDonald N, Wolfish N, McLaine P, Phipps P, Rossier E: Role of respiratory viruses in exacerbations of primary nephrotic syndrome. *J Paediatr* 1986, 108:378–382.
8. Edwards CWE, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, Stevens RM, Shaw T. Efficacy of B-Cell-targeted therapy with Rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;350: 2572-81
9. Edwards JC, Leandro MJ, Cambridge G. Repeated B Lymphocyte depletion therapy in rheumatoid arthritis: 5 year follow-up 2005 *Arthritis and Rheumatism* Volume 52:9(Supplement)

10. Rituximab for the treatment of rheumatoid arthritis (refractory). National Institute of Health and Clinical Excellence. August 2007.
<http://www.nice.org.uk/Guidance/TA126>
11. International Study of Kidney Disease in Children. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. *Kidney Int* 1978; 13: 159-165]
12. Feehally J, Kendall NP, Swift PGF, Walls J. High incidence of minimal change nephrotic syndrome in Asians. *Arch Dis Child* 1985; 60: 1018-1020
13. Otukesh et al. Rituximab in the Treatment of Nephrotic Syndrome A Systematic Review. *Iranian Journal of Kidney Diseases*, Volume 7, Number 4, July 2013.
- 14 Deshmukh C T. Minimizing side effects of systemic corticosteroids in children. *Indian J Dermatol Venereol Leprol* [serial online] 2007 [cited 2014 Oct 17];73:218-21. Available from: <http://www.ijdvl.com/text.asp?2007/73/4/218/33633>

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