NHS England

Clinical Commissioning Policy: Rituximab for the treatment of Steroid Resistant Nephrotic Syndrome in paediatric patients

Reference: NHS England E03/P/c

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Additional Circulation List	Regional Medical Directors; Regional Directors of Specialised Commissioning; Regional Clinical Directors of Specialised Commissioning; Regional Directors of Nursing
Description	NHS England will routinely commission this specialised treatment in accordance with the criteria described in this policy.
Cross Reference	
Superseded Docs (if applicable)	
Action Required	
Timing / Deadlines (if applicable)	
Contact Details for further information	jeremyglyde@nhs.net for policy issues

Document Status

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Contents

1 Executive summary

Policy Statement

NHS England will commission rituximab for the treatment of steroid resistant nephrotic syndrome in paediatric patients 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

Steroid resistant nephrotic syndrome is a therapy resistant form of nephrotic syndrome, a disease in which the kidney filters break down and essential blood proteins leak into the urine. The disease is now known to be caused by either a genetic mutation (in up to 20% of children), or an abnormality of the immune system.

For the latter group of patients, when steroids fail to work, second-line immunosuppression is usually attempted and can benefit some children. Often, second line immunosuppression fails, and in this case, it has been shown in small groups of patients, that rituximab can be effective. This policy aims to recommend firstly how to recognise the group of patients in which rituximab is most likely to be

beneficial using current evidence, and secondly when it should be used in the treatment pathway.

2 Introduction

Idiopathic Nephrotic syndrome (INS) is one of the most common glomerular diseases in children and adults with the central event being podocyte injury. INS is a heterogeneous disease and treatment is largely empirical and unsuccessful, with steroids as the initial mainstay of therapy. Close to 70 % of children with INS have some response to steroids and are labeled as steroid 'sensitive' (SSNS), and the rest as steroid 'resistant' (SRNS, also termed FSGS), with single gene mutations underlying a large proportion of the latter group. The burden of morbidity is enormous, both to patients with lifelong chronic disease, and the NHS, particularly managing dialysis and transplantation.

The current protocol for management of INS is treatment with high dose steroids. Of resistant patients, only 30% will respond over time to powerful 2nd and 3rd line immunosuppression, the rest suffer major long-term morbidity and renal failure requiring dialysis/transplantation. Up to 50% will develop rapid recurrence post-transplantation, with eventual graft loss despite highly intensive treatments. Identification of 'non-responders' by genetic screening has been estimated to save £68,900 per patient pre-dialysis (figure submitted in UKGTN approval) by avoidance of unnecessary investigations and treatment.

Once genetic forms of INS have been excluded, it is widely accepted that there is a 'circulating factor' underlying a proportion of patients with INS, which is produced by the immune system. This policy focuses on those patients with SRNS, who are candidates for current 2nd and 3rd line immunosuppression regimes, mostly in the form of a calcineurin inhibitor (CNI) and/or mycophenolate mofetil (MMF).

Rituximab is licensed in the UK (2008) for the treatment of non-Hodgkins Lymphoma and in 2006 licensed for use in severe active RA following clinical trials. It is currently not licensed to treat SRNS. The anti-B cell therapy has evolved into practice in

patients in whom there appears to be "circulating factor disease" but without any ability for meaningful patient selection. There is growing evidence that in a proportion of patients this can be very effective therapy, avoiding the toxicity of broader immunosuppressive drugs.

3 Definitions

ISKDC: International Study of Kidney Disease in Childhood

Nephrotic syndrome: Oedema, proteinuria >40mg/m2/h or protein:creatinine ratio >200mg/mmol, hypoalbuminaemia <25g/l

Remission: Urine protein excretion <5mg/m2/h, first morning urine protein:creatinine ratio <20mg/mol for three consecutive days or first morning urine dipstick test zero or trace for three consecutive days

Relapse: Urine protein >40mg/m2/h, first morning urine protein:creatinine ratio >200mg/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 mg/m2/day (max 80mg).

4 Aim and objectives

This policy aims to:

- Provide an overview of the current evidence for use of rituximab in SRNS

The objectives are to:

- Provide a rationale for which patients with SRNS can be treated with rituximab

5 Epidemiology and needs assessment

In children, the incidence of SRNS is 1-2/100,000. There is currently a comprehensive UK cohort of SRNS, collected via all tertiary paediatric nephrology centres, and recruiting for the past 5 years (www.renalradar.org). Current recruitment stands at 302 patients, which is estimated to be 70-80% of the prevalent population.

6 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 open label 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 SRNS group of patients was defined as remission “full, partial and no remission”.

The authors found 6 studies meeting the inclusion criteria- 3 case series (n=4-70) , one cohort study (n=33) and one open-label RCT (n=31)- all but one reported the favourable outcomes in the use of rituximab The data from studies on complete remission after rituximab therapy were available for these 6 studies (119 patients) which showed that the overall pooled results for prevalence of complete remission is 0.27 (0.2, 0.34) with the range of 0.19 to 0.6.

Open label RCT (Magnasco et al 2012)

The open label RCT included 31 children with idiopathic nephrotic syndrome unresponsive to the combination of calcineurin inhibitors and prednisone. All children continued prednisone and calcineurin inhibitors at the doses prescribed before enrollment, and one treatment group received two doses of rituximab (375 mg/m2 intravenously) as add-on therapy. The authors reported that rituximab did not reduce proteinuria at 3 months (change, -12% [95% confidence interval, 273% to 110%]; P=0.77 in analysis of covariance model adjusted for baseline proteinuria). In terms of adeverse effects, one patient developed a severe reaction with bronchospasm and hypotension and another had a severe acute allergic reaction to the bolus of chlorpheniramine maleate during the premedication
therapy. Other minor side effects were more frequent and consisted of abdominal pain (four cases), skin rash (three cases), and mild dyspnea (two cases).

No cost-effectiveness studies were found.

The number of studies on the use of rituximab in SRNS children is small with variable results. The results from studies on the benefit of rituximab are conflicting. Some studies do not report a positive response to rituximab in patients with SRNS (Kari et al 2011,Bagga et al 2007 and Magnasco et al 2012), while other studies have shown complete or partial response in SRNS children treated with rituximab. However, there is clinical consensus that the differences in outcomes in the studies are due to the patient's disease characteristics in the studies. Ding et al (2014) gives the best method to date of identifying those patients who are most likely to respond. These patients are those that are initially steroid sensitive, or 'delayed resistant' as stated in

the study by Magnasco et al (2013). Bagga et al. (2007) supports findings from Ding et al (2014), as all patients in the study were delayed resistant, and all showed some or complete response to Rituximab. Furthermore, none of the patients in any of the studies had genetics analysed.

Overall, there is compelling biological and supportive evidence in the literature to treat those SRNS patients who can be identified as likely circulating factor disease. Therefore it is important to maintain Rituximab as a clinical option in SRNS, as long as sufficient clinical and genetic screening criteria are applied.

7 Rationale behind the policy statement

A small proportion of NS presents within the first three months of life (congenital) or the first year of life (infantile), and most of these are found to have a genetic basis for their disease[1]. It is rare that these patients are treated with steroids, as there is very little evidence that they will respond to any immunosuppression.

There is a subset of children who eventually become resistant to all therapies. There is evidence that those who are steroid resistant from the outset are more likely to have a genetic cause[2]. Thus there is the possibility that this initially sensitive group has a different pathophysiology which confers response to steroids, the form of disease caused by a circulating plasma factor, putatively released by activated cells of the immune system. This appears an important distinction to be made and represents the subset more likely to respond to rituximab, and requires further study [2].

Children with a definite family history of NS or phenotypic anomalies consistent with a syndromic (and hence genetic) cause for their disorder. There is a high likelihood of discovering a known genetic mutation, or if not an as yet unknown mutation responsible for the NS in these patients.

8 Criteria for commissioning

NHS England will commission this therapy for:

a. Indications

Patients 1 – 18 years of age.

Patients must be referred to and reviewed by a Consultant Paediatric Nephrologist before treatment is initiated. Rituximab will be given at the specialist centre.

Patients with SRNS, after formal exclusion of other forms of glomerulonephritis, and of genetic causes using UKGTN approved Next Generation Sequencing test (www.nbt.nhs.uk/genetics)

Patients with SRNS in whom trial of CNI +/- MMF therapy has failed or unacceptable side effects.

b. Exclusions

Children 0-12 months at time of treatment

Patients with a monogenic disorder known to result in SRNS (variants that are not firmly established as pathogenic may still be considered)

Patients in stage 3-5 CKD (GFR < 60 ml/min/1,73m2) unless post-transplant

Contraindications

As per the drug company information on contraindications.

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.

Starting and stopping criteria (where appropriate)

Dosage of Rituximab will be 750mg/m^2 x 2 doses at fortnightly intervals. Depletion of B cells will be monitored by CD19/20 levels in peripheral blood.

Response to the treatment will be monitored by regular urine dipsticks for protein, as well as urine protein/creatinine ratios and plasma albumin levels. If there is a clinically useful response, then consideration of re-dosing of Rituximab should be given when CD19/20 levels recover (usually from 6-9 months from initial therapy).

Subsequent treatments following relapse

Subsequent treatments should only be given at a minimum of 6 months post last course and only if there was response to the previous course.

This policy has been agreed on the basis of NHS England's understanding of the likely price of care associated with enacting the policy for all patients for whom NHS England has funding responsibility, as at the time of the policy's adoption. Should these prices materially change, and in particular should they increase, NHS England

may need to review whether the policy remains affordable and may need to make revisions to the published policy.

9 Patient pathway

The current treatment algorithm for patients diagnosed with steroid resistant idiopathic nephrotic syndrome (INS) is:

1. Intravenous (IV) methylprednisolone (MP) 600mg/m^2 (maximum dose 1gm) daily for 3 days.

    a. After completion of pulsed iv methylprednisolone start oral prednisolone at a dose of 40mg/m^2 on alternate days for 4 weeks.

If failure to achieve remission within 14 days of iv methylprednisolone:

2. Ciclosporin 5mg/kg/day given in 2 divided doses.

    a. Continue prednisolone 40mg/m^2/ alternate days for a total of 4 weeks then 30 mg/m^2/alternate days for 5 months then wean and stop.

        i. Consider tapering prednisolone sooner than 6 months if remission achieved during this period.

OR

3. Tacrolimus 0.25mg/kg/day given in 2 divided doses. Dose adjusted to maintain levels of 5-10.

If no response after six months consider adding:

Mycophenolate mofetil (MMF) at a starting dose of 600mg/m^2 b.d. (maximum total daily dose 2g – see medicines for children)

Amendments to this pathway will be as follows:

All children with SRNS will be tested at the start of this pathway for all known SRNS gene mutations, using the clinically approved NGS test.

Children positive for a causative gene mutation will be considered for withdrawal or reduction of immunosuppression and will not be eligible for rituximab.

Children negative for a causative gene mutation, and without a family history of SRNS will be considered for treatment with rituximab, if they have demonstrated complete resistance to a CNI +/- MMF

Children with secondary steroid resistance ('initial steroid sensitivity') who fail to respond to CNI +/- MMF should be treated with rituximab [2]

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 the following tests are recommended for consideration:

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 SRNS 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 pnueumococcal 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.

TREATMENT DOSE AND CO-MEDICATION

For patients weighing ≥ 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 4 mg orally - 60 minutes prior to infusion

INFUSION THERAPY*

The following prescription is based on 2mgs/ml (Rituximab 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 50**mg**/hour (25mls/hour)

• 2nd 30 minutes 100**mg**/hour (50mls/hour)

• Thereafter the rate can be increased by 50**mg**/hour (25mls/hour) every 30 minutes to a **maximum** rate of 400**mg**/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 100**mg**/hour (50mls/hour)
• 2nd 30 minutes 200**mg**/hour (100mls/hour)
• Thereafter the rate can be increased by 100**mg**/hour (50mls/hour) every 30 minutes to a **maximum** rate of 400**mg**/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*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/m^2 (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 - 60 minutes prior to infusion

INFUSION THERAPY*

The following prescription is based on 2mgs/ml (Rituximab 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 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

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 2**mg**/kg/hour (1ml/kg//hour)

• 2nd 30 minutes 4**mg**/kg/hour (2ml/kg//hour)

• Thereafter the rate can be increased by 2**mg**/kg/hour (1ml/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). 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 : -

• 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 ≥ 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 ≥ 50kg

Time	mg/hour	ml/hour
1st 30 minutes	50**mg**/hour	25**ml**/hour
2nd 30 minutes	100**mg**/hour	50**ml**/hour
Thereafter the rate can be increased by 50**mg**/hour (25mls/hour) every 30 minutes to a **maximum** rate of 400**mg**/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 ≥ 50kg if the patient had no reaction to the first infusion

Time	mg/hour	ml/hour
1st 30 minutes	100**mg**/hour	50**ml**/hour
2nd 30 minutes	200**mg**/hour	100**ml**/hour
Thereafter the rate can be increased by 50**mg**/hour (25mls/hour) every 30 minutes to a **maximum** rate of 400**mg**/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 ≤50kg

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 (0.5mls/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 DAY 15 INFUSION IN PATIENT ≤50kg 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 (1mls/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 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 >38.5ºC; 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)

This policy has been agreed on the basis of NHS England's understanding of the likely price of care associated with enacting the policy for all patients for whom NHS England has funding responsibility, as at the time of the policy's adoption. Should these prices materially change, and in particular should they increase, NHS England may need to review whether the policy remains affordable and may need to make revisions to the published policy.

10 Governance arrangements

All tertiary paediatric nephrology units treating patients with SRNS routinely are able to administer and monitor rituximab treatment.

For all medicines that are unlicensed or used for an unlicensed indication each provider must assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through a Trust Drugs and Therapeutics committee or similar and NHS England may ask for assurance of this process.

11 Mechanism for funding

Rituximab is no longer listed on the NHS Payment Scheme Annex A (high-cost drugs), so use of this drug is in-tariff.

12 Audit requirements

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

13 Documents which have informed this policy

Guidance for genetic testing and management is on the rarerenal.org website (http://rarerenal.org/clinician-information/nephrotic-syndrome-clinician-information/srns-clinical-genetic-testing/), the public site for the UK Renal Association Rare Disease Strategy (http://www.renal.org/docs/default-source/what-we-do/UK_Rare_Kidney_Disease_Strategy_APRIL_2010.pdff).

14 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).

15 Date of review

This policy will be reviewed in March 2017 unless information is received which indicates that the proposed review date should be brought forward or delayed.

References

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