DOCUMENT CONTROL PAGE

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The Walton Centre for Neurology & Neurosurgery NHS Trust

Rituximab for Neurological Disease

Contents

Protocol for use of Rituximab in Neurological Disease

Background

Rituximab is a monoclonal antibody that binds to the CD-20 positive B Lymphocytes which mature and produce antibodies. The exact mode of action is unknown.
Rituximab was approved by the United States Food and Drug Administration in 1997 for treatment of B cell non Hodgkin's lymphoma resistant to other chemotherapy regimes[1]. In the United Kingdom it is approved for use in resistant follicular non Hodgkin's lymphoma and in diffuse large B cell lymphoma in combination with a chemotherapy regime (e.g. CHOP). In rheumatology rituximab is licensed for use in combination with methotrexate for severe active rheumatoid arthritis in adults[2]. However its use in neurological disease is limited to retrospective case studies and case series. They have shown favourable outcomes following treatment in patients with multiple sclerosis, neuromyelitis optica and polyneuropathy [3 - 8].

Neuromyelitis optica is an rapidly disabling inflammatory demyelinating relapsing disease which affects the optic nerve and the spinal cord. A retrospective multicentre case series looked at 25 patients diagnosed with neuromyelitis optica who were treated with rituximab[4] showed improvement in the post treatment relapse rate and an overall improvement in functional outcome. Rituximab is not licensed for treatment in neuromyelitis optica or other neurological disease so the prescriber and the Trust take full responsibility for its use. This protocol has been compiled based on the evidence in treatment of neuromyelitis optica **and is primarily directed at treatment of patients with neuromyelitis optica.** However patients with other neurological diseases who do not respond to standard medical treatment may also be considered for treatment with rituximab where appropriate. Patients are admitted to the Walton centre for treatment.

Patient Selection

Two consultant neurologists should agree that treatment with rituximab is appropriate.

Absolute contraindications

1. Heart failure
2. Active infection
3. Hepatitis B (risk of reactivation of hepatitis B with fulminant hepatitis)

Concomitant use of other immunosuppressant

Combining rituximab with other immunosuppressants (e.g. azathioprine, mycophenolate, methotrexate) may predispose to infection and thus these are *generally* discontinued when on Rituximab. Rituximab **should not** be given in combination with ciclosporin A or other calcineurin inhibitors due to the increased risk of infection.

Prescribing Rituximab

1. Funding must be agreed with primary care before treatment is arranged, and a WCNN one-off non-formulary drug application completed.
2. The patient should be informed that this is an unlicensed use of rituximab and given written information.
3. It should be prescribed by a consultant, using the rituximab prescription sheet (at end of this document or available on intranet or from pharmacy). This may be done in advance.
4. It is prepared only in a controlled environment by the pharmacy Aseptics unit. Pharmacy should be informed when patients are admitted for treatment (or in advance if possible), and the prescription faxed to Aseptics on 5190.

5. When patients are admitted, baseline tests must be undertaken. Provided a consultant has signed the prescription, any grade of doctor may complete the pre-treatment checklist and sign to declare the patient fit for treatment that day.

Rituximab Storage and Stability

Once reconstituted, rituximab must be stored at 2 to 8 degrees Celsius and is stable for 24 hours only. Pharmacy will not usually prepare the rituximab infusion until pre-treatment checks are complete, to prevent wastage if treatment cannot proceed.

Pre treatment Investigations (usually within preceding 5 days of each infusion)

1. FBC with differentials *(risk of pancytopenia, marrow hypoplasia, late onset neutropenia,)*
2. Urea, creatinine, LFTs, electrolytes
3. Screen for hepatitis B and C done in last 4 weeks *(risk of reactivation)*
4. Pregnancy test *(risk of teratogenicity)*
5. ECG (*risk of chest pain, fatal cardiac failure, cardiac arrhythmias)*
6. CXR *(risk of reactivation of dormant TB, bronchiolitis obliterans and pneumonitis)*

CXR, hepatitis screens and pregnancy tests need not be repeated before the second dose of each course unless there is new pertinent history or findings (eg; cough with fever; jaundice, sex without contraception)

If any of these tests show abnormal results, they should be discussed with the patient's consultant who will decide whether treatment may go ahead or not.

Precautions

1. Anaphylactic reaction to the infusion may occur (cardiac arrest trolley should be available on ward).

2. Withhold antihypertensive medications on the morning of the infusion (as rituximab infusion may drop the blood pressure).
3. Female patients should be advised on and agree to use effective contraceptive methods during and after treatment i.e. from day 1 of treatment to 12 months after receiving treatment. (Please refer to patient information leaflet and patient consent form.)

Administration (Please refer also to the infusion table provided)

Pre-medication:

Immediately before each rituximab infusion, the following drugs should be given:

Methylprednisolone 125 mg iv

Chlorphenamine 10mg IV

Paracetamol 1 gram orally

The recommended dose is 1g in 500ml sodium chloride 0.9% or glucose 5%. Two doses are given, two weeks apart, ie on days 1 and 15. The course is usually repeated every six to twelve months (minimum 16 weeks between courses).

The infusion is started slowly and the rate gradually increased if tolerated. On day 1, start at 50mg/hour and increase every 30 minutes by 50mg/hour, up to a maximum rate of 400mg/hour. On day 15, start at 100mg/hour and increase every 30 minutes by 100mg/hour, up to a maximum of 400mg/hour. (See the prescription and administration chart.)

Observation during Infusion

- Regular clinical observation of the patient

- Blood pressure, oxygen saturation, pulse rate, respiratory rate and temperature every 15 minutes until maximum infusion rate reached then every 30 minutes until 1 hour after completion of infusion

Management of Infusion related complications

Infusion related reactions include chills, fever, mucosal swelling, breathing difficulty (bronchospasm), skin rash and hypotension (drop in blood pressure by 30mmHg).

Mild infusion related reaction

- Infusion should be reduced to half the initial infusion rate – (i.e. from 100mg/hr to 50mg/hr)
- Once reaction resolves, keep reduced rate for an additional 30 minutes
- If reduced rate is tolerated, infusion rate may be increased to next closest rate on schedule – leave IV line in situ 1 hour

Moderate to severe infusion related reaction

Infusion should be stopped immediately and appropriate symptomatic treatment administered (eg fluids support, antihistamines, paracetamol, steroids). The neurology team, on call registrar or outreach team should be called. The infusion should not be restarted until all the symptoms have disappeared and then at half the rate. If reduced rate is tolerated for 30 minutes, infusion rate may be increased to next highest rate on infusion table. Leave IV line in situ for 1 hour.

Post infusion - Follow up blood test

Check FBC (differential), urea and electrolytes and liver function tests one week following each dose of Rituximab and then monthly.

The treating consultant should be informed of any significant abnormality. These tests can be done locally but can be organised at the Walton Centre if required.

References

1. D. G. Maloney, A. J. Grillo-Lopez, D. J. Bodkin, C. A. White, T. M. Liles, I. Royston, C. Varns, J. Rosenberg, and R. Levy, "Idec-C2b8: Results of a Phase I Multiple-Dose Trial in Patients with Relapsed Non-Hodgkin's Lymphoma," *J Clin Oncol* 15, no. 10 (1997): 3266-74.

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MabThera Summary of Product Characteristics via www.medicines.org.uk last accessed 15-1-09.

Aintree University Hospitals NHS Foundation Trust Guidelines on the Use of Rituximab.

The Walton Centre for Neurology and Neurosurgery

GP Information Leaflet

To Dr

Practice:

Patient name:

D.O.B:

NHS no:

Address:

Date

Dear Dr

Re **Rituximab**

This patient has been diagnosed with _____

and has undergone treatment with rituximab. Rituximab is a monoclonal antibody that binds to CD-20+ lymphocyte B cells. Rituximab has been used in treatment of various neurological diseases, though it is not licensed for these indications. Treatment for this condition is based on small case series and there are no randomised clinical trials. Rituximab is widely used in rheumatology and haematological diseases.

I would be happy to provide further information on this drug and the treatment experience so far if you so require. Could you kindly perform Full blood count with differentials, liver function tests and urea and electrolytes 1 week after the first and second infusions and monthly thereafter. Please notify us of any significant abnormality identified. Please note rituximab may cause blood disorders such as neutropenia, which can predispose to infection. The patient has been provided with written information on rituximab.

Yours sincerely,

Print name and grade:

On behalf of consultant:

Fax a copy of this letter to the GP, and give the patient a copy to pass on to the GP .

Rituximab Patient Information Leaflet

At The Walton Centre, rituximab is usually prescribed to treat neuromyelitis optica, so this information sheet is based on its use in this condition. Occasionally it may be used for other neurological conditions..

What is Rituximab?

Rituximab is a type of medicine known as a monoclonal antibody. It works by damaging white blood cells called B cells. These cells are thought to be attack nerve cells causing neurological symptoms.

Small studies have shown that when rituximab was given to people with neuromyelitis optica, they had a reduction in the number of attacks and symptoms and an improved ability to carry out day to day activities.

Rituximab has been approved licenced in the UK for use in rheumatoid arthritis and for certain types of cancer. It has ***not been formally approved*** for use in any neurological conditions, and studies on its safety and efficacy have only been done with small numbers of patients with these diseases. In the largest study with 25 patients of neuromyelitis optica, 2 patients died. It is not certain if the deaths were due to the illness or related the drugs. But this possibility has to be borne in mind. The remaining patients disease stabilised.

How is it given?

Rituximab is given as a drip (infusion) through a fine tube (cannula) inserted into the vein. Some people can have an allergic reaction to rituximab (detailed below). In order to reduce the risk of this, the first dose will be given slowly over a number of hours. You will be prescribed medicines such as antihistamines and steroids before treatment to help prevent any reaction.

If you develop a reaction, the infusion will be stopped and you will be assessed by the doctor. We will consider whether it is appropriate to restart the treatment when the symptoms have settled. You may need to stay in hospital overnight for the first treatment so that you can be monitored.

After that, rituximab may be given in the outpatients department and over a shorter period of time. One course of treatment consists of two doses, given two weeks apart (that is, on day 1 and day 15). The course may be repeated at intervals of six to twelve months.

What do you need to tell your doctor before the infusion?

Please inform your doctor if you have had hepatitis B infection or heart problems. There is a risk of reactivation of hepatitis infection. This may cause serious liver damage. Rituximab can rarely worsen heart disease and cause irregular heart beats. Since the effect of the drug on pregnancy and unborn babies is not known, the drug cannot be used in those who are pregnant or breastfeeding. You should not receive rituximab if you have had a very bad reaction to it in the past.

Possible immediate side effects

The reaction to the drug is variable with each person reacting differently. The most common side effects are mentioned below. There may be an immediate or late reaction to the infusion. During the infusion you may develop flu-like symptoms, fever, chills, weakness, muscle aches, tiredness, dizziness and headaches. Rituximab may cause the blood pressure to drop during infusion. Patients who take medication for high blood pressure should not take that medication for at least 12 hours before rituximab is given.

The treatment may cause you to feel sick and occasionally can cause vomiting. We can prescribe anti-sickness drugs to prevent this. You may develop allergic reactions which can manifest as skin rashes, itching, a feeling of swelling in the tongue or throat, irritation of the nasal passages, wheezing, breathlessness. You will be monitored closely during your treatment, but let your nurse or doctor know if you have any of these symptoms or feel unwell in any way. To help reduce the risk of developing an allergic reaction, antihistamines are given before the infusion. The infusion can also be slowed down or stopped until the reaction is over. Occasionally severe skin reactions can occur, such as painful sores on your skin, in your mouth, ulcers, blisters or peeling of skin.

Late onset side effects

Following treatment with rituximab you may become ***anaemic***. This may make you feel tired and breathless. Rituximab can reduce the production of white blood cells by the bone marrow, making you more prone to ***infection***. Your blood cells will be monitored by means of monthly blood tests after you have received rituximab. Please contact your doctor if your temperature goes above 38ºC (100.5ºF) or even if you feel unwell with a normal temperature, for example, sore throat, runny nose, cough or a burning pain when passing urine. Rituximab can reduce the production of ***platelets*** (which help the blood to clot) which can lead to bruising or bleeding.

Progressive Multifocal Leukoencephalopathy (PML)

A very rare but fatal side effect of rituximab is PML which is a rare brain infection caused by the activation of a virus called JC virus. It occurs during or after treatment with rituximab. The symptoms of PML may be similar to an neuromyelitis optica relapse.

- Therefore, if you believe your symptoms are getting worse or if you notice any new symptoms, it is important that you speak to your doctor..
- Discuss your treatment with your partner or caregivers. They might see new symptoms that you might not notice.

Other medications with rituximab

Please inform your doctor if you are prescribed any new treatment. Rituximab may interfere with the blood thinning drug warfarin and please ensure your INRs are monitored regularly.

Immunisations while on rituximab

Live vaccines should be avoided.

Information for female patients of child bearing age

Women of child-bearing age ***must*** use contraception while on rituximab. You must not receive rituximab if you are planning to get pregnant in the near future or if you are not using contraception.

The safety of rituximab for an unborn baby is not known, and it is also unknown whether it is safe to try for a baby shortly after having rituximab treatment. It is generally recommended to allow a gap of 12 months between having rituximab and *trying* to conceive.

Do not breastfeed while on rituximab. It is not yet known whether rituximab passes into the breast milk and the risk to the baby is not known.

Rituximab Treatment – Consent Form

Name _____

Date of Birth _____

Hospital Number _____

I understand that I have been diagnosed with a neurological condition that might possibly benefit from use of the drug Rituximab. I confirm that I have read and understood the information sheet provided on Rituximab. I have been informed about the side effects associated with Rituximab including but not limited to, Progressive multifocal lekoencephalopathy (PML) a fatal but rare viral infection, flu-like symptoms, weakness, muscle aches, tiredness, dizziness, headaches, allergic reactions, breathlessness, painful mouth sores, ulcers, blisters on skin, abnormal blood counts causing anaemia, bleeding , risk of serious infections and death. I will have regular bloods done and should any of the above symptoms occur, I have to contact my doctor.

I understand that by signing this document I am consenting to receive Rituximab treatment.

Patient Signature _____

Date _____

Consultant Signature _____

Date _____

This form should be filed in the case notes, and copies retained by the patient and consultant.

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		Yes/No	Comments
1.	**Does the policy/guidance affect one group less or more favourably than another on the basis of:**		
	• Race or ethnicity (including gypsies or travellers)	No	
	• Age	No	
	• Nationality	No	
	• Gender (Male, Female, Transsexual)	No	
	• Culture	No	
	• Religion or belief	No	
	• Sexual orientation including lesbian, gay and bisexual people	No	
	• Physical Disability	No	
	• Cognitive Impairment	No	
	• Learning Difficulties / Disability	No	
	• Sensory Impairment	No	
	• Mental Health Problems	No	
2.	**Is there any evidence that some groups are affected differently?**	No	
3.	**If you have identified potential discrimination, are any exceptions valid, legal and/or justifiable?**	N/A	
4.	**Is the impact of the policy/guidance likely to be negative?**	No	
5.	**If so can the impact be avoided?**	N/A	
6.	**What alternatives are there to achieving the policy/guidance without the impact?**	N/A	
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For advice in respect of answering the above questions, please contact:
Mr. Andrew Maloney,
Head of Human Resources,
2nd Floor,
The Walton Centre

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Signature List

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