

PATIENT INFORMATION SHEET

Optimal management of Rheumatoid Arthritis patients who require Biologic Therapy (ORBIT study) – a randomized controlled trial comparing Rituximab and anti-TNF therapy.

Invitation

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Please feel free to talk to others about the study if you wish, and ask us if there is anything that is not clear.

Introduction

Patients with rheumatoid arthritis have inflammation in their joints causing pain, stiffness and difficulty in moving. Most patients need "second line drugs" like sulphasalazine or methotrexate to try and slow down the arthritis. These drugs help reduce pain and stiffness, and protect the joints against damage. Unfortunately, they do not stop or cure the arthritis and most patients continue to have some symptoms. Some patients continue to have a lot of pain and stiffness despite the use of second line drugs. In these patients, biologic drugs can be effective in controlling the arthritis. In the UK there are two main types of biologic therapy available, namely, anti-TNF therapy and rituximab therapy.

What is the purpose of this research?

At the moment, rituximab therapy is only used in patients who have already failed anti-TNF therapy. Rituximab may be more effective, less effective or equally effective as anti-TNF therapy. The purpose of this research trial is to discover whether anti-TNF therapy or rituximab therapy is more effective in controlling patients' symptoms.

Why have I been invited to take part?

Your arthritis has not been well controlled on second line therapy, and you and your doctors have suggested trying a biologic drug to try to improve your symptoms.

Do I have to take part?

No. It is up to you to decide whether you want to take part in the study. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive. Data collected up until then would be used but no further information would be collected. Your participation in the trial may not be of direct benefit to you (though all patients in the trial will be offered active treatment with the aim of achieving the best possible control of their arthritis), but may help in the development of treatment for the benefit of future patients. If you do take part in this trial, your GP will be informed of your participation and the treatment you receive.

Which treatments are being used in the study?

If you agree to take part in the study you may receive anti-TNF therapy and/or rituximab therapy:

1. Anti-TNF therapy.

TNF is produced by the body and causes inflammation, which helps to fight infection but is also the cause of the symptoms of arthritis. In arthritis patients, the levels of TNF are high and reducing TNF levels can improve pain and stiffness in the joints. On the other hand, it can increase the risk of infections. The anti-TNF drugs being used in this trial are etanercept and adalimumab. These are both given by an injection under the skin, usually at home, every 1 to 2 weeks.

2. Rituximab therapy

B cells are also involved in fighting infection and causing inflammation. The number of B cells in the blood can be greatly reduced by using rituximab. This can improve pain and stiffness in the joints, but (like anti-TNF therapy) may be associated with an increased risk of some infections. Rituximab is given by drip, and involves being in the Rheumatology Unit for several hours on the day of your treatment. A course of rituximab consists of two drips given a

fortnight apart, and the course of treatment can be repeated, if necessary, after 20 weeks. Before each rituximab treatment you will receive paracetamol, a steroid and an antihistamine by drip. These help to minimise side-effects that sometimes occur when rituximab is given. The paracetamol and steroid may temporarily improve the symptoms of your arthritis but the purpose of the study is to look at the effects of the biologic treatment over a year.

What will happen to me if I take part?

Before you start any biologic treatment (anti-TNF or rituximab therapy) we will test you to make sure that you do not have hepatitis or evidence of previous exposure to TB. This will involve an examination, chest X-ray and some blood tests.

If you decide to participate in this study, you will be allocated at random (by chance, like the toss of a coin) to receive either anti-TNF treatment or rituximab treatment. Before you agree to participate in the study, you should read the ARC (Arthritis Research Campaign) information sheets on anti-TNF and rituximab. You will also receive an information leaflet with your medicines which you should read carefully as this includes information on how to use the medicines safely. You are free to decline any drug treatment that is offered to you. You should continue all your other drug therapy unchanged, unless your doctor tells you otherwise.

We will ask you to provide some extra blood (up to 14 teaspoonfuls) at the start of the study and after three and six months for analysis of your genes and the proteins in your blood. In the future, we hope that these samples will help us predict which patients will respond best to treatment. Your blood and DNA will be stored in a Biobank at St Bartholomew's Hospital, London. We may use the samples for future research, but only after research ethics approval has been given for any such studies.

What will happen at each visit to the hospital?

You will attend the clinic (or day ward) every month for 12 months. Every time you come to hospital we will examine your joints and take a blood sample, to assess the activity of your arthritis. We will ask you to fill in some questionnaires about how your arthritis affects your lifestyle, day-to-day activities and work. Each visit should last approximately half an hour in addition to any time required for your treatment.

What should I do if I feel unwell?

Because all biologic drugs are associated with an increased risk of infection, it is important that if you develop any signs of infection (such as fever, pain passing your urine, cough with green spit) you should contact the hospital immediately for advice. Very rarely, patients who have received rituximab have developed a serious brain infection called PML. PML stands for progressive multifocal leukoencephalopathy. It is an extremely rare but life threatening condition so it is very important that you are aware of the signs and symptoms. The vast majority of people treated with rituximab will not develop PML but some cases have been reported in patients with arthritis who have been treated with rituximab. PML is caused by the re-activation of the JC virus. JC virus does not normally cause any problems and is present in 70 – 90% of healthy adults. However, rarely, when the immune system is suppressed by rituximab the JC virus may activate and progressive damage to the brain and spinal cord can develop very rapidly. At present there are no treatments available for PML and it is not possible to predict who will develop the complication. If you experience memory loss, trouble thinking, difficulty walking or loss of vision, you should contact your doctor. If your doctor suspects you may be developing PML then he/she may suggest that you have further tests including a lumbar puncture (taking some fluid from around the spinal cord) or an MRI scan.

You will be monitored closely during the trial. Patients who do not respond well to, or develop side effects to anti-TNF therapy will be able to switch to rituximab therapy. In the same way, patients who do not respond well to, or develop side effects to rituximab will be able to switch to anti-TNF therapy.

What happens at the end of the trial?

At the end of the study, all patients will discuss their treatment with their doctor. Those who have responded to an anti-TNF drug will be able to continue on this treatment. If you are treated with rituximab first, and respond well you may or may not be able to continue on rituximab at the end of the trial. Rituximab is not yet approved in the NHS for use before anti-TNF therapy, so it will be up to your NHS Health Board or Trust and your doctor to decide if you will be able to continue on rituximab after the end of the trial. If this is not possible, then you will be offered an alternative (such as an anti-TNF drug) instead. Patients who start with an anti-TNF treatment but switch to rituximab will be able to continue with rituximab therapy after the end of the trial if they have responded to treatment.

Can I become pregnant or breast feed during the study?

You must not take part if you are breast feeding, pregnant, planning to become pregnant or are not using a reliable method of contraception. If appropriate we will advise you about contraception before you decide whether to take part in the trial, and a pregnancy test will be performed in women of child-bearing potential before starting treatment. You should not fall pregnant or breast feed during therapy or for 6 months after stopping treatment with adalimumab or etanercept. If you are treated with rituximab then you should not fall pregnant or breastfeed for 12 months after your last rituximab treatment course.

Travel expenses

You can claim back any travel expenses associated with attending the hospital for the research.

What should I do if I am not happy with my care?

In the event that something goes wrong and you are harmed during the research, and this is due to someone's negligence, then you may have grounds for a legal action for compensation but you may have to pay your legal costs. There are no special arrangements for compensation in this study, and the normal National Health Service complaints and compensation scheme will still be available to you.

Private Health Insurance

If you have private medical insurance, you should check with your insurer whether participating in this study will affect your cover.

Who has reviewed this study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the West of Scotland (1) Research Ethics Committee.

Who is funding the research?

The research is being funded by the Arthritis Research Campaign.

Can I find out the results of the research?

If you would like to know the final results of the study then a copy of the journal article will be sent to you on request.

Who can I speak to if I want further information?

If you would like to speak to another health professional who is not directly involved in the study, please phone Sister Joan Roberts (telephone number 0141 211 3057). If you have any problems, or queries, contact Dr Duncan Porter, (telephone number 0141 211 3262).