British Sjögren's Syndrome Association

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TRACTISS: A Trial of anti-B-cell Therapy in Patients with Primary Sjögren's Syndrome

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In 2009, Arthritis Research UK awarded funding of circa £950,000 for a clinical research trial of a drug called Rituximab in primary Sjögren's Syndrome. The medication itself has been provided free by the manufacturer, Roche Pharmaceuticals. Arthritis Research UK is the fourth largest medical research charity in the UK and the only charity in the UK dedicated to investigating arthritis in all its forms.

The trial will be organized by the University of Leeds Clinical Trials Research Unit and led by Professor Paul Emery (Leeds), Dr Simon Bowman (Birmingham), Professor Costantino Pitzalis (London) and many other colleagues from around the UK. We hope to start inviting patients to participate from early 2011. This article is all about this study.

What is the purpose of the study?

Although, Sjögren's Syndrome can affect different parts of the body, typically primary Sjögren's Syndrome affects the tear and salivary glands. The result of this is dry eyes and a dry mouth. Patients with dry eyes often experience irritation, burning, or the feeling of grit in their eyes. A dry mouth can make it difficult to swallow certain foods. Fatigue is another common complaint of Sjögren's Syndrome where patients may get easily exhausted and feel tired and worn out.

Studies have found that a medication called Rituximab can help people with rheumatoid arthritis (RA), and since RA and Sjögren's Syndrome have similarities, we believe that Rituximab may be able to help people who suffer from primary Sjögren's Syndrome.

What is Rituximab?

Rituximab is a new type of medication called a monoclonal antibody, which removes antibody-producing white blood cells (called B-cells). Antibodies are proteins, which are produced by the body in response to germs, viruses or any other material that the body sees as foreign or dangerous. However, in people with rheumatoid arthritis, or Sjögren's Syndrome or other conditions that affect the immune system, some B-cells produce harmful 'autoantibodies'. The purpose of Rituximab is to recognize these harmful B-cells and remove them using the body's own natural defenses. Rituximab also removes B-cells that make useful antibodies, but these return after some months.

When and how is Rituximab given?

Rituximab is given by intravenous infusion (commonly known as a 'drip') in a hospital clinic or daycase unit. A steroid infusion is usually given first. Two infusions are given 2 weeks apart. In this study this 'course' of treatment is repeated again 6 months later, so you will receive 4 infusions of Rituximab or placebo (dummy medication – see next page) in total.

What are the alternatives for treatment?

Depending on patients' symptoms the standard treatment for primary Sjögren's Syndrome includes hydroxychloroquine, non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids, and although these can be helpful they are known to be of only modest benefit.

Who are we inviting to take part?

We are hoping to find 110 patients who suffer from primary Sjögren's Syndrome who are willing to take part in this study. We are looking for patients with Sjögren's Syndrome who also have 1) anti-Ro antibodies (one of the typical autoantibodies found in about two-thirds of patients with primary Sjögren's Syndrome) 2) raised total antibody levels or some other feature of Sjögren's apart from dryness 3) substantial levels of fatigue 4) substantial levels of dry mouth. At the moment we are currently inviting patients to take part in the UK Primary Sjögren's Syndrome Registry (UKPSSR) led by Dr Fai Ng in Newcastle (see previous newsletter article and http://www.sjogrensregistry.org/for-patients) and if you are part of this registry then we may approach you about this study to see if you might be interested if your information held by the Registry suggests that you might be suitable for it. If you are not yet part of this Registry you can contact **Mrs Sheryl Mitchell** on **0191-2448943** for further information.

Do patients have to take part?

It is entirely up to each individual whether or not to take part. The doctors running the study are not paid anything if patients take part, and will not be upset if patients decide not to take part, so, take your time in deciding. If you decide to take part, you will be asked to sign a consent form. Before deciding whether to take part it is a good idea to discuss things with friends, relatives and your GP.

What does randomisation mean?

Because we do not know whether Rituximab will work or not in primary Sjögren's Syndrome we need to make a fair comparison by putting patients into two different groups. One group will receive Rituximab and the other group will receive a placebo (A placebo is a dummy treatment such as a pill, injection or infusion, which looks like the real thing but is not. It contains no active ingredient). In this way you will have a 50/50 chance of getting either Rituximab or placebo, so, for every one patient who receives Rituximab, one patient will receive the placebo, Randomised means that the groups are selected by a computer, which has no information about the individuals. Neither you, nor your doctor will be able to decide whether you receive the Rituximab or the placebo.

This is a double-blind study, which means neither you, nor your doctor will know if you are receiving Rituximab or placebo. Your doctor, if necessary, can find out.

What will happen to me if I take part?

The best way of finding out whether a new treatment is effective

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or not is in a randomised study, which will now be described in this section.

If you do decide to take part you will be given an information sheet to keep and asked to sign a consent form before any screening and baseline assessments are performed.

We would need to see you on up to 14 occasions each time for around an hour for most visits but the initial visit may take a bit longer and some other visits, for example where you are given the drip or if you have a lip biopsy (see below) are likely to take several hours.

Screening and baseline:
You will attend your hospital clinic within 7 days of starting the study where the study will be discussed again with you and you will be asked to sign a consent form if you wish to proceed. The following assessments will be performed: A medical history, your height and weight, vital signs, a physical examination, a pregnancy test (if you are female and of childbearing potential), an electrocardiogram (ECG), a chest X-ray, blood tests (for monitoring your health and for research) and simple tests for tear production and salivary flow. We would ask you to fill out a booklet of questionnaires.

In some centres we are also asking patients if they might be willing to have a Labial Gland Biopsy before, during (week 16) and after the treatment (week 48). This is so that we can better understand what is happening inside the salivary glands as a result of the treatment. If you agree to this an extra visit may be scheduled for each of these procedures. We would explain in more detail about this separately if you think you might be willing to take part in this part of the project.

The results of these screening examinations, amongst other things, will determine whether or not you can take part in the clinical study.

Further visits: (the exact details below may change slightly by the time the project starts)

Visit 1 (week 0):
Pregnancy test for females of childbearing potential and vital signs. Begin first infusion of study treatment (Rituximab) or placebo (Dummy treatment). Because Rituximab is a protein, it cannot be taken as a tablet but needs to be given directly into the blood stream (intravenously). This is done by inserting a needle into your arm and allowing the drug to slowly enter your body over a period of time, which normally is between 4 and 5 hours. If you agree to take part in the study intravenous infusions of either Rituximab or placebo will take place on Week 1, Week 2 and Week 24 and Week 26.

Visit 2 (week 2):
Pregnancy test for females of childbearing potential, vital signs and blood tests. Second infusion of the study treatment (Rituximab) or placebo.

Visit 3 (week 6):
Pregnancy test for females of childbearing potential, vital signs and blood tests. Measurement of tear production and salivary flow. Complete questionnaire booklet.

Visit 4 (week 16):
Similar to visit 3. If you have consented to the Labial Gland Biopsy an extra visit may be scheduled for this procedure. There is a separate information sheet and consent form for this optional biopsy.

Visit 5 (week 24):
Similar to visit 3. Physical examination.

Visit 6 (week 24 +/- 14 days):
Pregnancy test for females of childbearing potential. Vital signs. Third infusion (2nd course) of the study treatment (Rituximab) or placebo.

Visit 7 (week 26):
Similar to visit 2.

Visit 8 (week 30):
Similar to visit 3.

Visit 9 (week 36):
Similar to visit 3. Physical examination.

Visit 10 (week 48):
Pregnancy test for females of childbearing potential, ECG, chest X-ray, physical examination, vital signs, blood sampling, measurement of tear production and salivary flow. Complete questionnaire booklet.

If you have consented to the Labial Gland Biopsy an extra visit may be scheduled for this procedure. There is a separate information sheet and consent form for this optional biopsy.

What do I have to do to take part?
You must be willing to adhere to the restrictions and to attend the scheduled visits. It is also important that you take any medication during the study as directed, and tell us about any other medication you are taking before and during the study.

May I take other medicines after a course of Rituximab?
You should discuss any new medications with your study doctor before starting them. Rituximab is not a painkiller. If you are already on a non-steroidal anti-inflammatory drug (NSAID) or painkillers you may carry on taking these during the study, unless your doctor advises otherwise. It is important not take over-the-counter medications or herbal remedies without discussing this first with your doctor.

May I drink alcohol after a course of Rituximab?
You may drink alcohol while taking Rituximab. However, if you are also taking other medication, you should only drink alcohol after discussing this with your study doctor, as alcohol can interact with some medication and damage your liver.

What are the possible disadvantages and risks of taking part?

Rituximab:
There are potential risks associated with the taking of Rituximab. These can be divided into:

Infusion related reactions:
A small proportion of patients have reactions to the Rituximab infusion, usually involving a fever and chills. Other side effects include difficulty in breathing, shortness of breath, nausea, vomiting, headache, fatigue, cold-like symptoms, swelling for the tongue or throat, rash or fall in blood pressure.

If you develop any symptoms during the infusion you should tell the person giving you the infusion straight away, because it may be necessary to slow down the infusion. Very rarely, reactions are severe enough to need to stop the treatment. Your study doctor may also give you some medication to treat these symptoms.

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Infections:
Infections may be more common after treatment with Rituximab, and so if you develop a fever or any other symptom of infection you should seek advice from your study doctor, GP or rheumatology nurse about taking antibiotics.

There are occasional reports that Rituximab may cause worsening of hepatitis B infection and we will test you for this as part of the study.

Rare but serious side effects:
Rare side effects that have been seen with the use of Rituximab are death, anaemia, abnormal heart beat, and reduced number of a type of cells (called neutrophils) that help to fight infections as well as other cells that help your blood to clot.

There is one serious but very rare condition that may be a side effect of Rituximab as it has been reported in rare occasions in patients with rheumatoid arthritis and systemic lupus erythematosus. **Progressive multifocal leukoencephalopathy** (PML) is a poorly understood condition, which affects the brain and central nervous system which can lead to deterioration and death. Because it is so rare and because it affects the brain (an organ that is difficult to study), its diagnosis and treatment are not very well understood.

For your safety, the study doctor will monitor you for these events. For example, you will have your blood pressure, pulse rate, and temperature taken every 15 minutes for the first hour and then each hour while you are receiving Rituximab. If you experience a reaction that could be related to Rituximab, your study doctor may stop the infusion and you may be withdrawn from the study.

The Rituximab medication contains a small amount of protein-based mouse DNA. There is a small chance that your immune system might develop antibodies against this. If you develop these special antibodies, it may affect your body's ability to respond to antibody medications like Rituximab in the future. This may cause your body to have an abnormal response to it. If your doctor considers any side effects you are experiencing to be serious, they will stop the infusion. In addition, your doctor may not let you continue with any further infusions of Rituximab for your own safety.

Harm to an unborn baby:
It is not known whether Rituximab can harm an unborn baby if given to a pregnant woman or can affect fertility. In order to prevent any damage to an unborn baby you should not become pregnant or father any children whilst you are on this study or for 12 months after your last Rituximab infusion.

If you are a woman of childbearing potential, you must agree to use a reliable form of contraception, and you will be asked to have a pregnancy test before entering the study and at every visit after you start your treatment.

If you are a male with a partner of childbearing potential, you will also be asked to use contraception for the duration of the study and until the number of your immune B-cells have returned to normal.

If you or your partner does become pregnant during the study, you must tell the study doctor at once who will advise you on the risks to your unborn child and the options available to you.

Once you have completed the study or if you withdraw from the study and you become pregnant during the 12 months after you last receive Rituximab, you should still tell your study doctor as soon as possible.

If you withdraw from the study, you should also not become pregnant until the numbers of your immune B cells have returned to normal or for a period of 12 months after you last receive Rituximab, whichever is longer.

What about breastfeeding?
Rituximab is an artificially produced antibody, which will pass into breast milk. You should not enter the study if you are breastfeeding, and should not breastfeed for 12 months following a course of Rituximab, because the baby's B-cells might be affected.

Since Rituximab is a relatively new drug, other side effects, discomforts, and risks may occur which are yet unknown. We will monitor you for any side effects at every visit. If you have any problems you should let the doctor know at once. The regular study visits and study blood tests are there for your safety. If your doctor is concerned at any time about the effects and experiences you are having while in this study, they may decide to stop the medication.

Corticosteroids:
A corticosteroid is a drug you may be taking or may have taken in the past. Corticosteroids have many side effects such as increased blood pressure, mood changes, and reduction in your resistance to infections. Long-term use of high doses corticosteroids may also have side effects such as diabetes (high levels of sugar in your blood) or changes in your bones that can weaken them and increase the risk of a broken bone.

Labial gland biopsies:
We have produced a separate information sheet and consent form for this optional part of the study and will discuss this further with you if you are considering this. There is no benefit to you from this procedure which would be only be to help us understand primary Sjögren's Syndrome better. It is voluntary and will not affect you taking part in the rest of the study.

Time and inconvenience
Being involved in this research study involves commitment such as regular hospital visits and additional tests, as described above. It is not expected that you will need to stay in hospital overnight but occasionally this may be necessary to treat any side effects.

What are the possible benefits of taking part?
As mentioned previously, you will have a 50/50 chance of receiving either Rituximab or placebo. Even if you receive Rituximab we cannot guarantee that the treatment will benefit you directly (although you may see an improvement in your condition). However, the results from the study may help people like you with primary Sjögren's Syndrome in the future by helping to develop new treatments.

What happens when the research study stops?
At the end of the study your doctor will discuss available ongoing treatment options with you.

Will my taking part be kept confidential?
If you decide to take part the information collected about you will be handled in accordance with the consent that you have given and the 1998 Data Protection Act. Your full name will be included on your consent form that will be posted to the CTRU. However, every effort will be made to ensure that any further information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it.

Your data will be entered onto a secure electronic database held at the CTRU in accordance with the 1998 Data Protection Act. Your healthcare records may be looked at by the research staff,

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or the regulatory authorities to check that the study is being carried out correctly.

Your details (which will include your name, date of birth, NHS number and address) will be entered onto the National Health Service Central Register (NHSCR) at the Information Centre (IC) for Health and Social Care or traced via the NHS Strategic Tracing Service (NSTS) or relevant patient registries so that information about your health may be obtained by the CTRU if necessary.

The information collected about you may be shared with other research teams to answer new research questions in the future. Wherever possible, all names will be removed from this information.

Involvement of the General Practitioner/Family Doctor (GP):

We will tell your GP that you are taking part in TRACTISS, but otherwise all information about you and your treatment will remain confidential.

What will happen to the results of the study?

When the study is complete the results will usually be published in a medical or clinical journal, but no individual patients will be identified. If you would like to obtain a copy of the published results, please ask your study doctor.

What will happen if I don't want to carry on with the study?

If you withdraw consent from the study, your information from the study will remain on file and will be included in the study report. After the study, your data will be securely archived for a minimum of 15 years. Arrangements for confidential destruction will then be made.

Under certain circumstances it is possible that your study doctor will decide that you should be withdrawn from the study without your consent.

If you have private medical insurance, you should tell them you are taking part. They will let you know if it affects your policy.

What if something goes wrong?

If you are harmed by taking part in this study, there are no special arrangements for compensation. But if you are harmed because someone else has been negligent, then you can take legal action in the usual way. Regardless of this, if you wish to complain, or have concerns about the way you have been approached or treated during the study; the normal National Health Service complaints mechanisms should be available to you. Your study doctor will give you further information, if necessary.

Where can I obtain further information?

If you have any further questions about primary Sjögren's Syndrome or clinical studies in general, please discuss them with your GP and your rheumatologist.

If you would like any further information about Rituximab, or if you have any concerns about your treatment, you should discuss this with your GP, rheumatologist, rheumatology nurse or pharmacist. You will also find a lot of information on the internet. This may include information about Rituximab treatment for cancer. Please do not be concerned about this – although Rituximab is used for certain types of cancer, this is not the reason for using Rituximab in this study.

If you would like further information about clinical research, the UK Clinical Research Collaboration has published a booklet entitled 'Understanding Clinical Trials'. Contact UKCRC: **Tel: 0207 670 5452**; **website www.ukcrc.org**

What should I do if I think I might be interested in taking part in this study?

If you are already taking part in the UK Primary Sjögren's Syndrome Registry you will have been recruited to the Registry through a hospital rheumatology department and you can ask your rheumatologist if you might be suitable for this study.
If you are not part of the Registry you can ask your GP or rheumatologist if you might be suitable for this study and, if need be, they can refer you on to a centre at a hospital rheumatology department that is recruiting patients to this study. With regards to the Registry you can contact **Mrs Sheryl Mitchell** on **0191-2448943** for further information.