Title: **RAMUS Study- R**heumatoid **A**rthritis and **Mus**cle

Summary

A clinical trial to find out whether people with rheumatoid arthritis gain muscle mass and strength when they take Tofacitinib tablets.

Tofacitinib is routinely prescribed to patients with rheumatoid arthritis when other treatments have failed. Tofacitinib controls disease activity, preventing permanent damage to the joints.

The research team, led by Prof John Isaacs, will carry out this study at The Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University.

Patients newly prescribed Tofacitinib by their rheumatologist will be offered the chance to take part in this trial.

The trial involves 5 to 8 visits to the Clinical Research Facility at the Royal Victoria Infirmary and Newcastle Magnetic Resonance Centre for tests and monitoring. The visits will be spread over 7 months.

If you are interested in taking part in this trial, please read this information sheet and discuss it with others if you wish.

Ask a member of the research team if anything is not clear or if you would like more information.

Who can give me more information?

For further information about the trial you can speak to one of the Trial Team:

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What is the purpose of the trial?

The purpose of this trial is to assess the effect of the drug Tofacitinib on the muscles of patients who have rheumatoid arthritis.

Treatments for rheumatoid arthritis have improved greatly over the past 25 years. Despite this, many patients continue to suffer from low muscle strength, low muscle mass and low physical performance.

Tofacitinib is prescribed to patients with rheumatoid arthritis when other treatments have failed. We already know that Tofacitinib is effective at controlling disease activity and preventing permanent joint damage. We think Tofacitinib may also cause muscle gain. This would lead to an improvement in strength and physical performance.

Why have I been chosen and do I have to take part?

You are invited to take part in this trial because you have rheumatoid arthritis and your rheumatologist has prescribed you Tofacitinib tablets.

It is up to you whether you decide to join the study. If you do, we will carefully describe what is involved and you will be given this Participant Information Sheet to keep. You will be given time to think this over and talk to your family and friends about it. You will then be contacted by a member from the research team. Please find and sign attached "consent to contact" at the end of the document. This will ensure that we have your contact details and that you agree to being contacted to discuss your participation in the study.

If you do decide to take part you are free to withdraw from the trial at any time and do not have to give a reason. This will not have any influence on the treatment or standard of care that you receive either now or in the future. If you do withdraw from the trial, the information already collected is still useful to us.

Am I Eligible to participate in this trial?

You are a potential candidate to take part in this trial if you are willing to undergo muscle biopsy on two occasions along with Magnetic Resonance Imaging and DEXA scan for your whole body. Certain things will exclude you from the trial as they prevent you from undergoing the aforementioned interventions. These include:

- Being on blood thinning tablets or tending to bleed more than the normal population.

- Having metal pieces in your body such as pacemakers, brain clips etc. However, metallic joint replacements, plates and pins for broken limbs will be discussed on an individual basis.

What will happen to me if I decide to take part?

Summary

You will attend 5 to 8 appointments at the Clinical Research Facility spread over 7 months. The first screening visit, will assess you **before** you start taking Tofacitinib. Later visits will monitor you once you are taking Tofacitinib as prescribed by your rheumatologist.

How long do visits last?

Appointment times may vary depending on tests or clinical requirements.Your first visit is expected to take 1- 2 hours. However, the subsequent visits will last longer as additional tests and imaging will be done. You will need to allow 4-6hours for these.

What procedures will take place in which/each visits?

The trial procedures will be conducted by the research team, which includes a research doctor specialising in rheumatology. If some of the procedures are unclear, the trial staff can explain them to you.

Informed Consent

At your first visit, a member of the research team will talk you through what is involved in this trial and answer any questions you may have. If you agree to take part, you will sign the consent form and be given a copy to keep.

Medical history, physical examination, muscle strength test and questionnaires

On your first visit you will be asked to provide a full medical history and list of medications you are taking. On follow up visits, you will usually be asked what medication you are taking, so that we can determine if anything has changed. We will also ask about any untoward events or symptoms that you have experienced since your last visit to the hospital, and request that you fill in some questionnaires about your health and your condition. You will have a physical examination including an assessment of tender and swollen joints. Your muscle strength will be tested using a dynamometer and calculating the time you need to stand up.

Figure 1 Dynamometer

The table below summarises what will happen at each visit. Visits 2, 4 and 5 may need to be split into 2 appointments on different days depending on when the scan appointments can be arranged.

Events	Visit 1 Screening	Visit 2	Visit 3 Baseline	Visit 4	Visit 5
			within 1 month of visit 1	1 month after visit 3	5 months after visit 4
Informed consent	X				
Medical history (since last appointment)	X		X	X	X
Physical examination	X		X	X	X
Urine test	X		X	X	X
Blood tests	X		X	X	X
Questionnaires			X	X	X
Muscle strength tests			X	X	X
Magnetic Resonance Imaging (MRI) scan		X		X	X
Bone density (DEXA) scan		X		X	X
Muscle biopsy		X			X
Instruction to begin taking Tofacitinib tablets			X		
Duration of visit	1-2 hours	3-4 hours	1-2 hours	3-5 hours	4-6 hours

Trial Events/ Procedures

Blood tests and urine test

At each visit,4 -5 vials of blood (about 2 tablespoons of blood) and urine samples will be taken. If you are a woman of child bearing potential, you will be asked to take a pregnancy test on the first visit.

Magnetic Resonance Imaging (MRI) & Magnetic Resonance Spectroscopy (MRS) scan of legs (visits 2, 4 and 5)

Figure 2 MRI/ MRS scanner

This scan is a routine hospital procedure which we will use to measure the change in muscle mass before and after your course of Tofacitinib. MRI scanners use strong magnetic fields and radio waves to produce detailed images of the body. There are no known risks with an MRI scan itself and they are not painful.

On the day of the scan, you may eat and drink normally and take any medication prescribed by your doctor. For your own comfort and safety wear clothes without any zip fasteners or metal clips. If this is a problem do not worry, as you will be given a hospital gown to change into on arrival at the MRI suite.

The MRI scanner is a large well-lit tunnel, which is open at both ends. The tunnel remains **OPEN** and you are **NEVER** totally enclosed. You will lie flat on your back and be moved into the tunnel on a sliding bed, feet first. This ensure that your head remains outside the tunnel. The hospital staff will help to position you as comfortably as possible. You will be offered earplugs and headphones with music to help reduce the loud noises from the scanner.

The MRI scanner is operated by a trained radiographer who will control the scanner using a computer in a different room. You will be given a small air filled rubber bulb to hold which when squeezed alerts the radiographer that you need to speak to her/him using an intercom during the procedure and they will be able to see you throughout the scan.

The MRI scan will last about 45 minutes. When the scan begins you will hear some peculiar noises such as a rapid repetitive knocking noise. This is quite normal. The knocking noise will last for several minutes, then there will be a pause whilst the next set of scans are set up and the noise will begin again. The noise tells you that the information is being collected. It is very important that you keep as still during this time. If you feel uncomfortable during the procedure, you can speak to the radiographer via the intercom and request that the scan be stopped.

The scan does not involve exposure to any ionizing radiation, and is very safe. **However, it is very important that we know about any possible pieces of metal, such as metal fragments or surgical clips, or any medical devices such as pacemakers that you may have because the MRI is magnetic and this could cause problems.** The research team will check this during the screening process.

Dual-energy X-ray absorptiometry (DEXA) scan (visits 2, 4 and 5)

The scan itself will usually take between 10 and 30 minutes.

You will be asked to lie on your back on a padded table during the scan. Unlike some other types of scan, you will not be enclosed in any way (in a tunnel, for example). You will need to keep very still during the scan so the images are not blurred. During the scan, a large scanning arm will be passed over your body to measure bone density in the center of the skeleton.

Bone density scans are very safe. They use a much lower level of radiation than standard X-rays, which means that the radiographer (the technical specialist carrying out the scan) can stay in the scanning room with you during the scan.

Muscle biopsy (visits 2 and 5)

This test involves taking a small tissue sample from one of your thigh muscles. It is a procedure with a low risk of complications. You will meet with an experienced doctor who will explain the muscle biopsy and check that you are willing to have this procedure performed. **Throughout the study you are free to change your mind about taking part in any part of the study without having to give a reason why.**

If you are willing to go ahead, the doctor will ask you questions about what medication you are currently taking, your general health and examine you. This is because if, for example, you had varicose veins over the site of where we would take the biopsy, or were taking medications that can cause bleeding, then it would not be safe to perform this and therefore you would not be eligible for this study.

The doctor and the nurse helping with the muscle biopsy will take you to a treatment room, set up to take a small tissue sample (biopsy) from your thigh muscle.

The procedure takes no longer than 30 minutes. Whilst lying down, you will be given a local anaesthetic injection to numb the skin and surrounding area. When the area is numb, a small cut is made in the skin to allow the biopsy to be taken. The muscle biopsy will be done with a special type of forceps. The local anaesthetic may cause a stinging sensation for a few seconds and you may feel a pulling sensation when the biopsy is taken.

The wound is so small that it will not require stitching but is closed using medical tape called “Steri-strips”. A plaster will then be applied to the area, and a tight bandage wrapped around your leg for 2 hours whilst you rest on a bed. This is done to reduce the chance of bruising and bleeding.

The biopsy site may be uncomfortable for a few days, if so, paracetamol or co-codamol is recommended for pain relief. Anti-inflammatory drugs such as aspirin or ibuprofen should be avoided in the first 48 hours. You should also avoid getting the area wet in the first 48 hours. The steri-strips can be removed after 7 days.

You will be advised to avoid strenuous activities like running or weightlifting for the first 5 days after your biopsy as this may delay the healing process and result in bleeding. However, the biopsy should not limit routine household tasks.

A member of the study team will telephone you 1 or 2 days after your muscle biopsy to ensure that you are well.

My Responsibilities

It is important that you attend for all your trial visits. If for whatever reason you need to reschedule, we may be able to move a visit by up to 3 days.

You must let the trial team know if for any reason you are admitted to hospital for any treatments not related to the trial.

If you are a woman of childbearing potential, your rheumatologist will have advised you to use contraception (oral contraception, intra-uterine device (IUD), contraceptive injection, implant or patch) while you are taking Tofacitinib. If you do become pregnant, you must inform a member of the trial team as soon as possible.

Travel Expenses and Incentives

A taxi will be arranged to bring you to your appointment and take you back home. We will reimburse all your travel expenses for each visit should you prefer to drive or come on public transport. Note that when you come for the muscle biopsy it is recommended you do not drive afterwards.

As a thank you gesture, you will additionally receive a £30 intu Eldon Square voucher.

What are the possible risks and benefits of taking part?

Risks

Blood tests

Having blood tests may cause you minor pain and a small bruise where the needle is inserted. Occasionally you may feel faint during or after the procedure.

MRI/ MRS Scan

When having a scan, there is always a small possibility that an abnormality could be observed on the images of which you and your doctors were unaware. The MRI scans we collect will be reviewed by a radiologist in the Newcastle upon Tyne Hospitals NHS Foundation Trust to look for any such findings.

It is important to recognise that the MRI scans are not being taken for diagnostic purposes and so there is no guarantee that the scans would be of the right kind to detect any abnormality which may be present.

Should the radiologist suspect anything abnormal on your scans they will inform the study Principal Investigator who will contact your clinical care team or GP in order to make recommendations about any further investigations which it may be appropriate for them to arrange.

DEXA Scan

If you take part in this study you will have 3 DEXA scans. These will be extra to those that you would have if you did not take part. These procedures use ionising

radiation to form images of your body and/or provide treatment and/or provide your doctor with other clinical information. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous.

We are all at risk of developing cancer during our lifetime. About 40 out of every 100 people will develop cancer at some point in their life. Taking part in this study will increase your risk of developing cancer by a tiny amount: 0.00015%. Put in another way, of 100,000 people, about 40,000 would normally be expected to develop a cancer during their lifetime. If they all took part in our study, 1 or 2 additional people may develop cancer. The risk is the same as six days' worth of background radiation (the radiation that you are exposed to during your normal daily activities)

Muscle biopsy

As the local anaesthetic wears off after the muscle biopsy, up to one third of patients experience mild-moderate, pain or discomfort. You may use normal painkillers (e.g. paracetamol) to treat this and it usually settles within several weeks. There are also other less common complications. Significant bruising or bleeding happens to about 1 person in 100. Damage to local nerves, which may cause a patch of numbness, happens to about 1 person in 1000.

Trained staff carry out all of these procedures and every effort will be made to prevent these problems.

Benefits

There may be no direct benefit to you from taking part. However, you will be contributing to improving our understanding of muscle loss and developing future therapy that's beyond joint inflammation, which will benefit other sufferers of RA or other similar diseases.

How will my information and samples be stored and used?

Information

If you take part in this trial, a Research Nurse will collect some personal information about you, by means of a paper record. Non-identifiable information will be entered onto a secure database, held by Newcastle Clinical Trials Unit, Newcastle University. Access to this database will be password-protected and available only to your doctors and research staff, for the purpose of the trial. All information stored on the computer will be coded and your name will not appear. You will be given a unique trial number, under which all information and test results will be entered.

Your medical records may be looked at by representatives of regulatory authorities and by authorised people from the Newcastle upon Tyne Hospitals NHS Foundation Trust, to monitor the trial and ensure that it is being carried out correctly. Everyone who sees information has a duty to ensure that nothing that could reveal your identity is disclosed outside the research site.

All the information about your participation in this trial will be kept confidential. All data will be stored for at least 15 years and then disposed of securely.

Informing your General Practitioner

We will notify your GP that you are taking part in the trial. Participation in the trial will also be noted in your hospital records so that anyone who treats you will know that you are taking part in the trial.

Sometimes new medical conditions may arise during your trial visits that need further attention. In this instance the doctor who examines you will take appropriate action. This will usually mean writing to your GP who can assess matters further.

Samples

Throughout your participation in the trial, you will have a number of blood samples taken. Some of these blood samples are to check your general health and some are to measure the levels and effects of the trial medication. The blood samples to check your general health will be processed at your local hospital laboratory, and the results recorded in your hospital notes with any other results obtained prior to the trial. Your research team will keep you informed of any results obtained. Samples to measure the levels and effects of the trial medication will be sent to a central accredited laboratory for analysis. These samples will be anonymised (they will only be identified by your unique trial number which only the research team will know belongs to you).

You will also have a number of urine samples taken during the trial. These will be tested at site using a simple dipstick.

If, at the end of the project, any of your muscle biopsy samples are left over, we would not wish to waste them. At that stage, rather than being thrown away, your donated samples may be stored in a registered tissue bank for use in future research projects. The precise nature of any further tests that will be performed on them will depend on the projects we have running in the future but your samples will only be used in studies that are directly relevant to the trial of arthritis or related diseases. It is possible that such studies may involve collaboration with a commercial partner, such as a drug company, but your samples would never be sold.

Results of the trial

Your information and test results, along with the information and test results from all the patients taking part in this trial, will be analysed to see whether Tofacitinib was beneficial.

We will publish the results of the trial in scientific journals. We will also present the findings at international meetings and to patient groups who have been involved in the design of this trial and who have taken part in it. None of this material will include specific details of individual participants.

If you would like to know more about the results of the trial at any point, you can contact a member of the research team who will be able to discuss these results with you in further detail.

What if something goes wrong?

If you have a concern about any aspect of this trial, you should ask to speak to the researchers who will do their best to answer your questions (contact details on Page 2). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details of how to complain can be obtained by contacting the Patient Relations Department on 0191 223 1382.

In the event that something does go wrong and you are harmed during the research, and this is due to someone's negligence, you may have grounds for a legal action for compensation, but you may need to meet your own legal costs. The normal National Health Service complaints mechanisms will still be available to you, should you feel you have any cause for complaint. NHS Indemnity does not offer no-fault compensation (i.e. for harm that is not anyone's fault).

Who organises, funds and reviews this research?

The research is being organised by Prof John Isaacs and his research team which is based at Newcastle University and The Newcastle upon Tyne Hospitals NHS Foundation Trust. The work is supported by a Project Grant award from Pfizer Inc.

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee. This trial has been reviewed and approved by the South East Scotland Research Ethics Committee 01.

This trial has also been reviewed by the Health Research Authority (HRA) who are responsible for regulating all medicines and medical devices in the UK by ensuring they work and are acceptably safe.

Thank you for taking the time to read this information sheet