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Rheumatoid arthritis and the muscle

Submission date	Recruitment status	[X] Prospectively registered
03/10/2019	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
18/10/2019	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
03/03/2025	Musculoskeletal Diseases	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Rheumatoid arthritis is a long-term condition that causes pain, swelling and stiffness in the joints. This trial studies the role of the drug Tofacitinib in the reversal of the skeletal muscle loss, sarcopenia, that occurs in Rheumatoid Arthritis patients. It has the potential to contribute work of significant improvement in our understanding of sarcopenia, and provide targeted future therapy that's beyond the reversal of joint inflammation.

Who can participate?
Patients with active Rheumatoid Arthritis treated with tofacitinib

What does the study involve?
Participants would undergo various investigations of muscle structure and function before and during treatment. This will take place over a period of 6 months. Potential participants will be identified and recruited at routine outpatient clinics at the Freeman Hospital.

What are the possible benefits and risks of participating?
Benefits
There may be no direct benefit from taking part. However, participants 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
Risks
Having blood tests may cause minor pain and a small bruise where the needle is inserted.
Exposure to ionising radiation during DEXA scan: 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 the 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 risks: 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

Where is the study run from?
Newcastle University and the Freeman Hospital (UK)

When is the study starting and how long is it expected to run for?
October 2019 to March 2023

Who is funding the study?
Pfizer (UK)

Who is the main contact?
1. Prof John D. Isaacs, john.isaacs@ncl.ac.uk
2. Dr Josh Bennett, J.Bennett19@newcastle.ac.uk

Contact information

Type(s)
Scientific

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Type(s)
Public

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Dr Josh Bennett

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
funder ref W1238777

Study information

Scientific Title
An observational, single-arm study of skeletal muscle metabolism in patients with rheumatoid arthritis receiving Tofacitinib

Acronym
RAMUS

Study objectives
JAK inhibitors (tofacitinib) reverse sarcopenia in patients with rheumatoid arthritis

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 11/09/2019, NHS HRA South East Scotland REC 1 (NHS Lothian, Waverley Gate, 2 - 4 Waterloo Place, Edinburgh, EH1 3EG, UK; +44 (0)131 465 5473; Sandra.Wyllie@nhslothian.scot.nhs.uk), ref: 19/SS/0100

Study design
Observational single-arm study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Sarcopenia and Rheumatoid Arthritis

Interventions
Current intervention as of 05/02/2021:
Observational single-arm study of skeletal muscle metabolism in patients with rheumatoid arthritis receiving tofacitinib

Potential participants will be identified in routine out-patient rheumatology clinics by the usual care team. These are individuals with active rheumatoid arthritis for whom the decision has been made to prescribe tofacitinib. If they express interest in participating in the study, they will be approached by a member of the research team who will describe what is involved, and provide them with a Patient Information Sheet. Sufficient time will be given for them to think about the study, discuss it with family and friends, and ask questions. Once they confirm that they would like to participate, they will be asked to sign a consent form. They will be informed that they may change their mind and withdraw from the study at any point, a decision that will not affect their routine care.

They will then be asked to participate in between 6 and 9 study visits. These will take place at the Clinical Research in the Royal Victoria Infirmary and at the Newcastle Magnetic Resonance Centre. The duration of each visit will vary, with most lasting up to 2 hours. However, visits 2, 4 and 5 will last longer because of the need to carry out more complex procedures such as extra blood tests, obtaining muscle samples and radiological imaging. It is likely that the study team will decide to carry out some of the procedures for these visits on a different day to the main study visit. For this reason, the total number of study visits will be between 6 and 9.

In the above-mentioned visits, participants' medical and drug history will be noted. They will undergo a physical examination. They will be asked to provide a urine sample. Blood samples will be taken by the research nurse. They will also be asked to fill out questionnaires that address their general well being. Muscle strength will be tested by assessing their handgrip and timed-raise from chair.

Muscle samples will be obtained in visits 2 and 5 after obtaining consent. This is a day case procedure that will take place in the Clinical Research Facility in the Royal Victoria Hospital and is performed by the research doctor. The relevant area will be cleaned thoroughly, then numbed using local anaesthetics. A small cut will be made. Muscle sample will then be taken by a special type of forceps. The wound is then covered by special medical tape and doesn't require any stitches. Paracetamol and codeine will be advised to pain relief in the days following the procedure. Participants will be advised to keep the area dry and clean.

The imaging techniques that will be used in this study are: magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) and DEXA scan. These are scheduled to be done on visits 2, 3 and 5 in Newcastle Imaging Centre and CRF respectively. No dye will be used in these

studies. MRI and MRS use magnetic fields to produce images of the body. Participants will be asked to lie on their backs on a flat bed then moved into the scanner feet first. The scan will last about 45 minutes.

DEXA scans use a small and safe dose of radiation energy. Imaging is done while the participants are lying on their backs. The scanner arm then passes over the body to collect images. The scan usually takes between 10-30 minutes.

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Previous intervention:
Observational single-arm study of skeletal muscle metabolism in patients with rheumatoid arthritis receiving Tofacitinib

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Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Tofacitinib

Primary outcome measure
Change in muscle bulk measured by accelerated MRI of lower limbs

Secondary outcome measures
Current secondary outcome measures as of 05/02/2021:
1. Muscle function/strength at baseline, and 1 and 6 months after commencing tofacitinib assessed by hand grip and timed raise from chair
2. Muscle biochemistry assessed by magnetic resonance spectroscopy of skeletal muscle: content of ATP, phosphocreatine and inorganic phosphate at baseline, 1 month and 6 months, assessed by magnetic resonance spectroscopy.
3. Serum biochemistry: Serum creatinine, serum creatine phosphokinase, serum aspartate transaminase, serum aldolase, serum myoglobin and serum cystatin C at baseline, 1 month and 6 months.
4. Relationship between changes in serum biochemistry (serum creatinine, serum creatine phosphokinase) to biochemical, structural, functional and histological/molecular changes in muscle
5. Relationship between changes noted in muscle and reduction in systemic inflammation
6. Body composition using DEXA at baseline, 1 month and 6 months

Previous secondary outcome measures
1. Muscle function/strength at baseline, and 1 and 6 months after commencing Tofacitinib assessed by hand grip and timed- raised from chair
2. Muscle biochemistry assessed by magnetic resonance spectroscopy of skeletal muscle: content of ATP, phosphocreatine and inorganic phosphate at baseline, 1 month and 6 months, assessed by magnetic resonance spectroscopy.
3. Serum biochemistry: Serum creatinine, serum creatine phosphokinase, serum aspartate transaminase, serum Aldolase, serum Myoglobin and serum Cystatin C at baseline, 1 month and 6 months.
4. Relationship between changes in serum biochemistry (serum creatinine, serum creatine phosphokinase) to biochemical, structural, functional and histological/molecular changes in muscle
5. Relationship between changes noted in muscle and reduction in systemic inflammation

Overall study start date
01/04/2019

Completion date

31/03/2023

Eligibility

Key inclusion criteria
1. 2010 ACR/ EULAR classification criteria for a diagnosis of rheumatoid arthritis
2. At least 6 months disease duration
3. Inadequate response to intensive therapy with synthetic disease-modifying anti-rheumatic drugs (DMARDs) alone, or inadequate response to at least one biologic DMARD, thereby qualifying for treatment with tofacitinib according to local guidelines.
4. Aged >18 years
5. Willing and able to provide written informed consent.
6. ACR Functional Class I-III
7. Willing to undergo muscle biopsy on 2 occasions.
8. Willing to undergo MRI and MRS and Dexa scan on 3 occasions
9. Active systemic disease, as exemplified by a C-reactive protein of at least 10 mg/l

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
15

Total final enrolment
15

Key exclusion criteria
1. Serum creatinine that is above the upper limit of normal at baseline.
2. Patients receiving glucocorticoids
3. Patients will be excluded if they have any contraindications to tofacitinib which include:
3.1 Pregnancy and lactation
3.2 Women of childbearing potential (WOCP) who are not prepared to use effective contraception during treatment with tofacitinib and for at least 4 weeks after the last dose.
3.3 Severe hepatic impairment (Child Pugh C)
3.4 Active TB, serious infections such as sepsis or opportunistic infections as detailed in the SmPC
3.5 Chronic infections (HIV, hepatitis B, hepatitis C)
4. Participants will be excluded if they have any contraindications to muscle biopsies. These include:
4.1 Participants on anticoagulant therapy. These include vitamin K antagonists, thrombin inhibitors, and heparin and low molecular weight heparin preparations.
4.2 Participants on antiplatelet therapy. *Participants on aspirin for primary prevention will be

included in this study. However, aspirin will be held for 7 days prior to the muscle biopsies and recommenced 48 hours after.
4.3 Participants who are known to have bleeding disorders. These include, but are not limited to, haemophilia, Factor II, V, VII, X, or XII deficiencies and Von Willebrand's disease
4.4 Previous reactions to local anesthetics
4.5 Platelets count < 100 x 109/l
5. Participants will be excluded if they have any contraindications to MRI. These include:
5.1 Limb metal pins, plates, rods of screws that were placed less than 6 weeks from scanning day
5.2 Heart pacemaker or replacement valves
5.3 Neuro-stimulator or programmable intra-cerebral shunt, cerebral aneurysm clips
5.4 Metallic foreign body in their eye
5.5 Internal hearing devices, ocular prosthesis
5.6 Weight >190 kg
5.7 Claustrophobia

Date of first enrolment
08/02/2021

Date of final enrolment
10/08/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Newcastle University
Kings Gate
Newcastle upon Tyne
United Kingdom
NE1 7RU

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

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Newcastle Joint Research Office
Level 1 Regent Point
Regent Farm Road
Gosforth
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NE3 3HD
+44 (0)19128225789
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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Industry

Funder Name
Pfizer UK

Alternative Name(s)
Pfizer Ltd, Pfizer Limited

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Results will be published in peer-reviewed scientific journals, internal reports and conference presentations. No patient identifiable details will be linked to publications.

Intention to publish date
31/07/2025

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V1.1	25/09/2019	08/11/2019	No	Yes
Protocol file	version V1.0	12/07/2019	08/11/2019	No	No
Participant information sheet	version 1.5	10/05/2021	18/08/2021	No	Yes
Protocol file	version 1.5	22/07/2021	18/08/2021	No	No
Protocol article		01/03/2023	07/03/2023	Yes	No
HRA research summary			26/07/2023	No	No