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The Anti-Freaze-F Study - "Anti-TNF for treatment of frozen shoulder" - a feasibility study

Submission date
07/09/2021

Recruitment status
Stopped

Registration date
21/12/2021

Overall study status
Stopped

Last Edited
17/05/2024

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Current plain English summary as of 29/03/2022:

Background and study aims
Frozen shoulder is a common condition affecting approximately 9% of people aged 25-64 years. During the early phase the pain is usually unbearable and the later restriction in movement is severely limiting. It occurs when the flexible tissue (capsule) that surrounds the shoulder joint becomes inflamed, thickened and tight. The pain can be very severe and lasts 3-9 months, followed by a 4-12 month period of increasing stiffness, after which the condition usually improves. Frozen shoulder often affects a person's ability to sleep, carry out everyday activities, and work. Current treatments include rest, painkillers, anti-inflammatories, physiotherapy and steroid injections. If stiffness persists, surgery is sometimes recommended. However, there is no evidence that any of these treatments lead to significant benefit in the long term, with many being ineffective.
The aim of this study is to find out if it is possible to run a larger study to test whether an injection of adalimumab can reduce pain and prevent the disease from getting worse, if given during the early painful phase of frozen shoulder. We need to conduct this smaller study first to be sure it's possible to identify and treat people with early stage frozen shoulder, before we conduct a much larger study to find out if this treatment works.

Who can participate?
In this study the investigators will include 84 adults from 5 sites with painful early stage frozen shoulder who have not yet received treatment.

What does the study involve?
People will be randomised to receive either an injection of the drug adalimumab or a dummy injection of saline (placebo) directly into the shoulder joint, both guided by ultrasound. All participants will also receive standardized advice on how to manage their shoulder pain. The investigators will assess participants before treatment and three months later. Adalimumab has been used very successfully to treat other inflammatory diseases such as rheumatoid arthritis.

What are the possible benefits and risks of participating?
We hope the information we obtain from this study will be used to help treat people with frozen shoulder problems more effectively.
There is a possibility you will be harmed by this treatment, although this is unlikely. You may experience some soreness after your shoulder injection or after completing some of the exercises suggested by the physiotherapist. This is normal, and you will be given advice on how to manage this soreness.
People sometimes feel uncomfortable answering certain questions about their health. If the researcher, health professional, or follow-up questionnaire asks you questions that you are uncomfortable with, then you do not have to answer them.

Where is the study run from?
University of Oxford (UK)

When is the study starting and how long is it expected to run for?
June 2021 to June 2023

Who is funding the study?
National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) programme (UK)
180 Life Sciences (US)

Who is the main contact?
Alison Evans, aff@kennedy.ox.ac.uk
Prof Jagdeep Nanchahal, jagdeep.nanchahal@kennedy.ox.ac.uk

Previous plain English summary:

Background and study aims
Frozen shoulder is a common condition affecting approximately 9% of people aged 25-64 years. During the early phase the pain is usually unbearable and the later restriction in movement is severely limiting. It occurs when the flexible tissue (capsule) that surrounds the shoulder joint becomes inflamed, thickened and tight. It's not fully understood why this happens but it is more common in people with diabetes or Dupuytren's disease, which causes the fingers to curl into the palm. It can also occur following shoulder injury or surgery. The pain can be very severe and lasts 3-9 months, followed by a 4-12 month period of increasing stiffness, after which the condition usually improves. Frozen shoulder often affects a person’s ability to sleep, carry out everyday activities, and work. Current treatments include rest, painkillers, anti-inflammatories, physiotherapy and steroid injections. If stiffness persists, surgery is sometimes recommended. However, there is no evidence that any of these treatments lead to significant benefit in the long term, with many being ineffective. Steroid injections only help in the short term.
The aim of this study is to find out if it is possible to run a larger study to test whether an injection of adalimumab can reduce pain and prevent the disease from getting worse, if given during the early painful phase of frozen shoulder. We need to conduct this smaller study first to be sure it’s possible to identify and treat people with early stage frozen shoulder within the current NHS system, before we conduct a much larger study to find out if this treatment works.

Who can participate?
In this study we will include adults with painful early stage frozen shoulder who have not yet received treatment.

What does the study involve?
People will be randomised to receive either an injection of the drug adalimumab or a dummy injection of saline (placebo) directly into the shoulder joint, both guided by ultrasound. All participants will also receive standardised advice on how to manage their shoulder pain. We will assess participants before treatment and three months later. Adalimumab has been used very successfully to treat other inflammatory diseases such as rheumatoid arthritis. This drug has been chosen as the biological processes underlying frozen shoulder are similar to those in Dupuytren's disease, where we found it helps to stop the cells causing the disease.
The views of patients with frozen shoulder are important to us and have been incorporated into this study. We have worked with a group of patients who have experienced frozen shoulder. All were supportive of our study aims and design. They provided useful feedback that has been incorporated into the study. A patient representative is part of the team for this application. Patient representatives will also be part of the committee that oversees the study.

What are the possible benefits and risks of participating?
We hope the information we obtain from this study will be used to help treat people with frozen shoulder problems more effectively.
There is a possibility you will be harmed by this treatment, although this is unlikely. You may experience some soreness after your shoulder injection or after completing some of the exercises suggested by the physiotherapist. This is normal, and you will be given advice on how to manage this soreness.
People sometimes feel uncomfortable answering certain questions about their health. If the researcher, health professional, or follow-up questionnaire asks you questions that you are uncomfortable with, then you do not have to answer them.

Where is the study run from?
University of Oxford (UK)

When is the study starting and how long is it expected to run for?
June 2021 to May 2023

Who is funding the study?
National Institute for Health Research (NIHR) (UK)
180 Life Sciences (US)

Who is the main contact?
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Prof Jagdeep Nanchahal, jagdeep.nanchahal@kennedy.ox.ac.uk

Study website
https://aff.octru.ox.ac.uk/

Contact information

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Public

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Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2021-003509-23

IRAS number
1004069

ClinicalTrials.gov number
NCT05299242

Secondary identifying numbers
IRAS 1004069, IRAS 50971

Study information

Scientific Title
Anti-TNF (adalimumab) injection for the treatment of adults with frozen shoulder during the pain-predominant phase: a multi-centre, randomised, double blind, parallel group, feasibility study

Acronym
Anti-Freaze-F

Study objectives

To assess the feasibility of conducting a large randomised controlled trial to assess whether an intra-articular injection of adalimumab can reduce pain and improve function in people with pain predominant early stage frozen shoulder

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 06/12/2021, North East - Newcastle & North Tyneside 1 Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 2071048285; newcastlenorthtyneside1.rec@hra.nhs.uk), ref: 21/NE/0214

Study design
Multi-centre randomized double blind parallel group feasibility study

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request participant information sheet.

Health condition(s) or problem(s) studied
Frozen shoulder

Interventions
Participants will be randomly allocated (using the OCTRU computer ranomisation system) to receive either: 1) intra-articular injection of anti-TNF (adalimumab 160mg) or 2) placebo injection (saline), both under ultrasound guidance.
A second injection of the allocated treatment (adalimumab 80mg) or equivalent volume of placebo will be administered at 2-3 weeks, unless participants report significant improvement from the first injection and they decline a second injection. All participants will receive a physiotherapy advice leaflet providing education and advice about frozen shoulder and pain management. The total duration of treatment and follow up will be 5 months.

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)

Adalimumab - Idacio

Primary outcome measure

Current primary outcome measure as of 29/03/2022:

1. Rate of recruitment of participants with pain predominant frozen shoulder
2. Number of participants consenting to be included in the trial.
3. Days between baseline assessment and time to first injection
4. Days Between first injection and second injection.
5. Standard deviation of the Shoulder Pain and Disability Index (SPADI) score and attrition rate at 3 months from baseline in order to estimate the sample size for a definitive trial

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Previous primary outcome measure:

Shoulder Pain and Disability will be measured at baseline and 3 months using the SPADI (Shoulder Pain and disability Index).

Secondary outcome measures

Current secondary outcome measures as of 29/03/2022:

1. Pain (Shoulder Pain And Disability Index, 5-item subscale) - These will be recorded at baseline and 3 months, core range from 0 to 100, lower scores indicate better outcome.
2. Function (Shoulder Pain And Disability Index, 8-item subscale) - These will be recorded at baseline and 3 months, score range from 0 to 100, lower scores indicate better outcome
3. Fear Avoidance Belief Questionnaire - score range from 0 to 24, higher scores indicate better outcomes -This will be measured at baseline and 3 months.
4. Pain Self Efficacy Questionnaire - This will be measured at baseline and 3 months, score range from 0 to 12, higher scores indicate better outcomes
5. Insomnia Severity Index - This will be measured at baseline and 3 months, Sleep disturbance will be measured using the Insomnia Severity Index, score range from 0 to 28, higher scores indicate worse outcomes.
6. Return to desired activities (RDA) - These will be recorded at baseline and 3 months, Return to desired activities will be measured using an adapted version of the Disabilities of the Arm, Shoulder and Hand (QUICKDASH) questionnaire.
7. Global impression of change - These will be recorded at baseline and 3 months, this will be measured using the Likert scale, score range from -5 to +5, higher scores indicate better outcomes.
8. Number of visits to Healthcare Professionals - These will be recorded at baseline and 3 months.
9. Adverse events graded 3 or above (clinician assessed) related to intra-articular injection of adalimumab in the shoulder- These will be recorded after the first injection and at 3 months.
10. Shoulder range of motion in degrees using a goniometer, These will be recorded at baseline and 3 months.

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Previous secondary outcome measures:

1. Psychological factors will be measured at baseline and 3 months using the Fear Avoidance Belief Questionnaire

2. Pain Self Efficacy Questionnaire - will be measured at baseline and 3 months
3. Sleep disturbance will be measured at baseline and 3 months using the Insomnia Severity Index
4. Return to desired activities will be Patient-reported and reported at baseline and 3 months.
5. Global impression of change will be measured at baseline and 3 months using the Likert scale
6. Healthcare resource use will be recorded at baseline and 3 months using patient records

Overall study start date
01/06/2021

Completion date
30/06/2023

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
1. Men and women aged 18 years and above.
2. With a new episode of shoulder pain attributable to pain-predominant stage of frozen shoulder (i.e. within approximately 3 months of onset of symptoms) diagnosed using criteria set out in the BESS guidelines
3. Who are not being considered for surgery;
4. Able to understand spoken and written English;
5. Willing and able to give informed consent for trial participation and comply with all study requirements and time line;
6. Willing to allow his or her General Practitioner be notified of participation in the trial.
7. If female and of child-bearing potential OR if male and their partner is of child-bearing potential – willing to use effective contraception throughout the treatment period and for 5 months after the last injection.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
84

Total final enrolment
9

Key exclusion criteria
1. Those with frozen shoulder secondary to significant shoulder trauma (e.g., dislocation, fracture or full thickness tear requiring surgery) or other causes (e.g. recent breast cancer surgery or radiotherapy);
2. Those with a neurological disease affecting the shoulder;
3. Those with bilateral concurrent frozen shoulder;
4. Those with other shoulder disorders (e.g., inflammatory arthritis, rotator cuff disorders, glenohumeral joint instability) or with red flags consistent with the criteria set out in the BESS guidelines (33);
5. Those who have received corticosteroid injection for shoulder pain in the last 12 weeks to either shoulder;
6. Those currently taking any anti-TNF drug;
7. Those being treated with coumarin anticoagulants, such as warfarin;
8. Those who have participated in another research study involving an investigational medicinal product in the past 12 weeks;
9. Those with significant renal or hepatic impairment;
10. Those with contra-indications to anti-TNF injection:
10.1 Known allergy to any anti-TNF agent or any of the excipients;
10.2 Known Active tuberculosis (TB) or history of TB.
10.3 Known Active infection (chronic or localised) or known history of recurring infections or condition which may predispose patients to infection, including the use of concomitant immunosuppressive medications;
10.4 Known Moderate to severe heart failure (NYHA class III/IV);
10.5 Those known to have HIV, Hepatitis B or C;
10.6 Those at risk of Hepatitis B infection;
10.7 Those diagnosed with Multiple Sclerosis (MS) or other central or peripheral nervous system demyelinating disorders;
10.8 Those who have ever been diagnosed with cancer, except basal cell carcinoma (BCC);
10.9 Those requiring live vaccination prior towithin 12 weeks after of the last trial injection or within the 4 weeks prior to randomisation;
10.10 Those taking biologic DMARDS;
10.11 Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study

Date of first enrolment
31/05/2022

Date of final enrolment
07/02/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre

Good Hope Hospital Treatment Centre
Good Hope Hospital
Rectory Road
Sutton Coldfield
United Kingdom
B75 7RR

Study participating centre
Sandwell and West Birmingham Hospitals NHS Trust
City Hospital
Dudley Road
Birmingham
United Kingdom
B18 7QH

Study participating centre
United Lincolnshire Hospitals NHS Trust
Lincoln County Hospital
Greetwell Road
Lincoln
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LN2 5QY

Study participating centre
University Hospital Birmingham
Queen Elizabeth Hospital
Edgbaston
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Sponsor information

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University of Oxford

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Sponsor type
University/education

Website
https://researchsupport.admin.ox.ac.uk/ctrg

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
Research for Patient Benefit Programme

Alternative Name(s)
NIHR Research for Patient Benefit Programme, RfPB

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
180 Life Sciences

Results and Publications

Publication and dissemination plan
Planned publication in a high impact peer reviewed journal.

Intention to publish date
20/12/2023

Individual participant data (IPD) sharing plan
Summary results data will be available on the trial registration database within 12 months of the end of the trial. Requests for data (anonymised participant data) will only be provided at the end of the trial to external researchers who provide a methodologically sound proposal to the trial team aff@kennedy.ox.ac.uk (will be required to sign a data sharing access agreement with the Sponsor) and in accordance with the NIHR guidance. Participant consent for this is included in the informed consent form for the study.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol (preprint)		12/04/2022	08/06/2022	No	No
Protocol article		24/04/2023	09/06/2023	Yes	No
HRA research summary			28/06/2023	No	No
Results article		01/05/2024	17/05/2024	Yes	No