ISRCTN70800019 https://doi.org/10.1186/ISRCTN70800019

Effects on tocilizumab drug therapy on fat tissue proteins in rheumatoid arthritis

Submission date	Recruitment status	[X] Prospectively registered
30/03/2015	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
05/04/2015	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
11/05/2016	Musculoskeletal Diseases	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Rheumatoid arthritis is an autoimmune disease that affects the joints, in particular the hands, feet and wrists. The sufferers own immune system attacks the joints which, over time, can lead to damage to the joint, cartilage and nearby bone. Symptoms include pain, swelling (inflammation) and stiffness in the joints. Tocilizumab is a drug for rheumatoid arthritis which acts against an inflammatory protein called IL-6. We think that taking this drug results in improvements in the body cholesterol (lipid) profile as well as a reduction in inflammatory proteins released from fat tissue (adipokines). If treatment with tocilizimab decreases inflammatory proteins and improves cholesterol profiles, it may decrease the long term risk of heart disease and strokes in affected patients compared to drugs that are not associated with these changes.

Who can participate?
Participants of the 'ACT-NEUTS' study who were given tocilizimab.

What does the study involve?
The participants of the previous study (the 'ACT-NEUTS' study) are approached for this study. These patients all had blood samples collected at the start of this previous study and on three other occasions over the course of 12 months. We use the surplus blood samples collected as part of that original study to measure and compare blood levels of some inflammatory proteins from fat tissue ('adipokines') and cholesterol levels before and after this drug was administered. Information regarding blood pressure, smoking status, family history, rheumatoid arthritis disease severity, X-ray changes and other medications are obtained from the hospital medical records. No further blood sample collection or drug administration is performed during this study.

What are the possible benefits and risks of participating?
There are no immediate benefits to patients participating in the study, though outcomes of the study may influence treatment choices in rheumatoid arthritis in the future. We do not anticipate any risks to patients participating in the study.

Where is the study run from?
Aintree University Hospital NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
April 2014 to September 2015

Who is funding the study?
Obesity and Endocrinology Research Department, University of Liverpool

Who is the main contact?
Professor John Wilding
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
UoL001080

Study information

Scientific Title
Observational study on the effects of IL-6 inhibitor therapy on adipokines in patients with rheumatoid arthritis

Study objectives
To study whether IL-6 inhibitor therapy in rheumatoid arthritis is associated with metabolically favourable changes in adipokine and lipid profiles

Ethics approval required
Old ethics approval format

Ethics approval(s)
London City and East REC, 23/03/2015, ref: 15/LO/0544

Study design
Observational study involving analysing samples already collected from subjects with rheumatoid arthritis.

Primary study design
Observational

Secondary study design

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Rheumatoid arthritis

Interventions
Nineteen patients with rheumatoid arthritis participated in the ACT-NEUTS study in 2010-2011 (EUDRACT Number 2010-018331-18; REC Reference: 10/H0904/14), and were treated with the drug tocilizumab as part of the study.These individuals provided fasting blood samples prior to tocilizumab administration and at three timepoints thereafter (at approximately 3 months, 6 months and 12 months after tocilizumab therapy). Blood samples and clinical information as part of the study were collected, link-anonymised and securely stored within the university.

We intend to approach the participants of the ACT-NEUTS study through members of their usual healthcare team and request their consent to utilising the already collected samples as well as relevant clinical and pharmacological information for the purposes of our study. Other than the purpose of requesting informed consent, no further clinical contact with the patient is required for this study. No further blood sample collection or drug administration will be performed during this study.

For the patients who provide informed consent, plasma adipokines (leptin, adiponectin, resistin, visfatin, SPARC, TNF-alpha and IL-6), lipid profiles and other inflammatory markers will be measured in samples that were obtained for the ACT-NEUTS study Information regarding blood pressure, smoking status, family history, rheumatoid arthritis disease activity scores, radiographic changes and other medications will be obtained from the hospital medical records.

This study aims to analyse changes in anthropometric measures, disease activity score, lipid profiles and measured adipokines from baseline to twelve months of treatment with

tocilizumab. We anticipate this study will be completed within a period of three months. This will be followed by dissemination and publication of results, and application for grants for future randomised controlled trials in this field.

Intervention Type
Drug

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

Primary outcome measure
1. Changes in circulating adipokine concentration
2. Change in metabolic syndrome determinants towards a favourable cardiovascular risk profile

Secondary outcome measures
1. Changes in anthropometric measures
2. Rheumatoid arthritis disease severity scores
3. Radiographic changes

Overall study start date
01/04/2014

Completion date
01/08/2016

Eligibility

Key inclusion criteria
1. Male or non-pregnant, non-nursing female
2. ≥ 18 years of age
3. Diagnosis of moderate to severe active RA of ≥ 6 months duration
4. DAS28 ≥ 3.2 at screening and baseline
5. Receiving treatment on an outpatient basis
6. If inadequate response to a biologic DMARD, this treatment was discontinued according to approximately 5-half lives for the agent, prior to receiving TCZ. That is, prior to randomization, have discontinued etanercept for ≥ 2 weeks, infliximab or adalimumab for ≥ 8 weeks, anakinra for ≥ 1 week; rituxamab > 24 weeks (or B-cell count has returned to levels prior to treatment and pt meets active disease criteria)
7. If continuing a non-biologic DMARD, dose was stable for at least 8 weeks.
8. In patients receiving an oral corticosteroid, the dose must have been stable for at least 25 out of 28 days prior to treatment (baseline).
9. Able and willing to give written informed consent and comply with the requirements of the study protocol

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
19

Key exclusion criteria
Disease:
1. Major surgery (including joint surgery) within 8 weeks prior to screening or not recovered from prior surgery
2. Rheumatic autoimmune disease other than RA, including systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), scleroderma, polymyositis, or significant systemic involvement secondary to RA (e.g. vasculitis, pulmonary fibrosis or Felty's syndrome). Patients with interstitial pulmonary disease and still able to tolerate MTX therapy are permitted, as is Sjögren's Syndrome with RA
3. Functional class IV as defined by the ACR Classification of Functional Status in RA (largely or wholly incapacitated with patient bedridden or confined to wheel chair, permitting little or no self-care)
4. Prior history of or current inflammatory joint disease other than RA (e.g. gout, reactive arthritis, psoriasic arthritis, seronegative spondyloarthropathy, Lyme disease)

Drug-specific:
5. Treatment with any investigational agent within 4 weeks (or 5 half-lives of investigational agent, whichever is longer) before screening.
6. Previous treatment with any cell-depleting therapies, including investigational agents (e.g. CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19).
7. Treatment with leflunomide in combination with MTX (washout at least 12 weeks, 8 weeks with cholestyramine)
8. Treatment with IV gamma globulin, plasmapheresis or Prosorba® column within 6 months before baseline
9. Intraarticular or parenteral corticosteroids within 4 weeks prior to baseline
10. Immunization with a live/attenuated vaccine within 4 weeks prior to baseline
11. Previous treatment with TCZ
12. Any previous treatment with alkylating agents, such as cyclophosphamide or chlorambucil, or with total lymphoid irradiation

Laboratory analyses (at screening):
13. Serum creatinine > 142 µmol/L (1.6 mg/dL) in female patients and > 168 µmol/L (1.9 mg/dL) in male patients and no active renal disease.
14. ALT (SGPT) or AST (SGOT) > 1.5 ULN (If initial sample yields ALT [SGPT] or AST [SGOT] > 1.5 ULN, a second sample may be taken and tested during the screening period)
15. Platelet count < 100 x 109/L (100,000/mm3)
16. Hemoglobin < 85 g/L (8.5 g/dL; 5.3 mmol/L)
17. WBC count < 2.0 x 109/L (2000/mm3), ANC < 1.0 x 109/L (1000/mm3)
18. ALC < 0.5 x 109/L (500/mm3)
19. Positive hepatitis B surface antigen (HBsAg) or hepatitis C antibody
20. Total bilirubin > ULN (If initial sample yields bilirubin > ULN, a second sample may be taken and tested during the screening period) – unless diagnosis of Gilbert's syndrome

21. Triglycerides > 10 mmol/L (> 900 mg/dL) at screening (non-fasted)
General medical:
22. Pregnant women or nursing (breastfeeding) mothers
23. Females of child-bearing potential who were not using a reliable means of contraception, e. g. physical barrier (patient and partner), contraceptive pill or patch, spermicide and barrier, or IUD
24. History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies
25. CXR evidence of any clinically significant abnormality, per investigator evaluation
26. Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus) or GI disease
27. In patients with a history of diverticulitis or diverticulosis requiring antibiotic treatment, the treating physician considered the benefit-risk ratio
28. A history of chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis or other symptomatic lower GI conditions that might predispose to perforation.
29. Uncontrolled disease states, such as asthma, psoriasis or inflammatory bowel disease where flares are commonly treated with oral or parenteral corticosteroids.
30. Current liver disease as determined by principal investigator. Patients with prior history of ALT /AST (SGPT/SGOT) elevation were not excluded
31. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (including but not limited to tuberculosis and atypical mycobacterial disease, clinically significant abnormalities on CXR as determined by the investigator, hepatitis B and C, and herpes zoster, but excluding fungal infections of nail beds), or any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of screening, or oral antibiotics within 2 weeks prior to screening
32. History of or active primary or secondary immunodeficiency
33. Evidence of active malignant disease, malignancies diagnosed within the previous 5 years (including hematological malignancies and solid tumors, except non-melanoma skin cancer that has been excised and cured), or breast cancer diagnosed within the previous 5 years
34. Active tuberculosis (TB) requiring treatment within the previous 3 years; patients with no recurrence in 3 yrs are eligible.
35. Patient were screened for latent TB, prior to biologics use, as per local guidelines. If screened positive, patients with latent tuberculosis should be treated with standard antimycobacterial therapy (at least 4 weeks) before initiating TCZ and have a negative CXR for active TB at screening.
36. HIV positive patient
37. History of alcohol, drug or chemical abuse within the 6 months prior to screening
38. Neuropathies or other painful conditions that might interfere with pain evaluation
39. Patients with lack of peripheral venous access
40. Body weight of > 130 kg

Date of first enrolment
01/05/2015

Date of final enrolment
01/08/2015

Locations

Countries of recruitment

England

United Kingdom

Study participating centre
Aintree University Hospital NHS Foundation Trust
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Sponsor information

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Sponsor type
University/education

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
University/education

Funder Name
Obesity and Endocrinology Research Department, University of Liverpool

Results and Publications

Publication and dissemination plan

We intend to publish Sep 2015 onwards the study results-mainly what we find n terms of longitudinal associations of circulating adipokine concentrations following IL-6 inhibitor therapy. We will also publish associations with lipid profiles as well as disease activity scores if available in clinical records.

Intention to publish date

01/09/2015

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No