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Investigating relationships between IL-17, Th17 pathway activation and therapeutic response to TNF inhibition in rheumatoid arthritis patients

Submission date
17/07/2015

Recruitment status
No longer recruiting

Registration date
03/08/2015

Overall study status
Completed

Last Edited
30/05/2019

Condition category
Musculoskeletal Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] 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. There are several treatment options for rheumatoid arthritis, such as anti-TNFα treatment, which blocks the action of the signalling protein TNFα and can reduce inflammation, but patients show different levels of response to these treatments. This study focuses on uncovering reasons for this observed difference in participants treated with anti-TNFα treatment and aims to reveal the key pathways that can be targeted to ensure the best clinical outcomes. This research may be able to identify disease characteristics that determine which future patients may be more likely to respond to anti-TNFα treatment, or those who may require a different treatment option to achieve a clinical response. IL-17 is a signalling protein in the body's immune system. The main aim of this study is to examine the relationship between the levels of IL-17 in the blood and joints and clinical response or non-response to anti-TNFα treatment.

Who can participate?
Patients aged 18 to 65 with active rheumatoid arthritis who qualify for anti-TNFα treatment.

What does the study involve?
Participants will be asked to provide blood and urine samples. Pieces of genetic information called RNA will be extracted from the blood samples (and biopsy material if you are part of the biopsy sub-study) provided by participants. This material will be analysed to reveal information about what genes are 'active' in the joint environment during the anti-TNFα treatment. This information can tell us what proteins might be involved in the inflammation of affected joints and might also be able to predict what type of response you will experience to different treatments. The analysis of research samples from this study will provide new information on the mechanisms for response/non-response.

A number of participants that have consented to the main study will be invited to take part in the optional biopsy sub-study. This will involve taking a biopsy of one of the affected joints via an ultrasound-guided procedure. The procedure is minimally invasive and has good safety and

tolerability with participants. The procedure is performed under local anaesthetic and removes tiny pieces of inflamed tissue from the lining of the joint using a needle under the guidance of an ultrasound scanner. This sub-study will collect tissue from affected joints to help answer the research questions in this study

Participants are also invited to take part in the optional DNA genetic sampling and are asked to contribute DNA samples for this study. The purpose of this optional part of the research study is to help understand how anti-TNFα treatments work and how they may cause side effects, to further understand rheumatoid arthritis, and to understand why some people respond to anti-TNFα treatments while others do not. Genetic (genotyping) testing refers to the patient sample being used for genetic research. This is the study of DNA and how it determines our traits. DNA research can also explain why some people respond well to their medications and others do not and can also provide reasons as to why some people develop some diseases and others do not. Samples from participants that have consented to the optional DNA genetic sampling will also be used for a type of genetic research called epigenetics. This is the study of chemical modifications of DNA that occur over time, without a change in DNA sequence. These modifications control the way cells produce proteins and respond to the environment. Epigenetics research is not a test to diagnose a person for a genetic disease or to determine whether a person may have a risk of developing a genetic disease. It is only used to understand prevailing disease and how drugs may work in different groups of people. In epigenetic testing, DNA samples from participants will be analysed to determine how this may influence response to anti-TNFα treatments.

What are the possible benefits and risks of participating?
The medication that is used throughout this clinical study is part of normal practice in the management of rheumatoid arthritis, and so there will be no additional advantage to taking part in this study. The findings may help make the best treatment choices for people with rheumatoid arthritis. This study poses no greater risk than would be expected in routine clinical care. The biopsies are not considered routine care and thus the main risks to participants would be associated with this procedure. Participation in this sub-study will be optional. The procedure has excellent safety and tolerability and is carried out under local anaesthetic in a sterile setting by highly experienced doctors. However, like all procedures of this kind, it does carry some small risks, including infection of the joint or skin, bleeding, pain and rarely nerve or tendon damage (less than 1:10,000 risk).

Where is the study run from?
Queen Mary University of London (UK).

When is the study starting and how long is it expected to run for?
From March 2015 to August 2016.

Who is funding the study?
Janssen Pharmaceuticals Inc. (USA) and NIHR Translational Research Partnerships (UK).

Who is the main contact?
Martha Bajwa Joseph

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
18893

Study information

Scientific Title
Investigating relationships between IL-17, Th17 pathway activation and therapeutic response to TNF inhibition in rheumatoid arthritis patients: an observational cohort study

Acronym
THERAPIST

Study objectives
Though anti-TNFa therapy has transformed the treatment of rheumatoid arthritis (RA), 30-40% patients don't respond to this treatment. Currently, there are no tests capable of predicting response and the mechanisms of non-response remain unknown. This leaves a major unmet need and a considerable health and economic burden. In the UK alone, RA drugs cost the NHS £560 million, while RA total annual economic impact is estimated £4.2 billion (NAO).

The THERAPIST study aims to address this major unmet need by exploring the capacity of disease tissue (synovium) and peripheral blood biomarkers to predict response prior to anti-TNFa therapy initiation and to understand the mechanisms of response/nonresponse. In addition THERAPIST will characterise the role of the IL17/ Th17 pathway (primary hypothesis) and, through a powerful hypothesis-free discovery investigation, potentially unveil new therapeutic targets.

More details can be found here: http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=18893

Ethics approval required
Old ethics approval format

Ethics approval(s)
First MREC approval date 05/02/2015, ref: 15/SC/0045

Study design
Non-randomised; Observational; Design type: Cohort study

Primary study design
Observational

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Topic: Musculoskeletal disorders; Subtopic: Musculoskeletal (all Subtopics); Disease: Musculoskeletal

Interventions
50 RA patients requiring anti-TNFa therapy after failure of conventional Disease Modifying Anti Rheumatic Drugs, e.g. methotrexate, according to NICE guidelines, will be recruited to the study following informed consent. Clinical responses will be assessed by standard/validated tools such as 28 tender-swollen joint count integrated into the Disease Activity Score (DAS28), as well as objective ultrasound joint imaging.

Biological responses are measured in the disease tissue (synovial biopsy substudy) in 20 patients consenting to an ultrasound-guided, minimally invasive, well-tolerated procedure, as we described (Kelly et al. Ann Rheum Disease 2013) and in peripheral blood of all 50 patients as comparators.

The biopsy substudy is essential to provide disease tissue for the proposed investigation, as 30 years of research looking for peripheral blood predictive biomarkers have proven unsuccessful. It is clear that direct sampling of the diseased tissue can provide fundamental evidence to inform therapeutic decision-making (e.g. Tamoxifen in ER+ve breast cancer).

Intervention Type
Other

Primary outcome(s)
To compare the level of blood and synovial Th17 activity in participants with RA being treated with anti-TNF therapy between responders and non-responders. Samples of tissue from the ultrasound guided synovial biopsy, together with study specific blood sampling will be used to evaluate the pattern of activity shown in the Th17 pathway. Clinical response will be assessed on the basis of the EULAR response criteria using DAS28 (CRP) at week 24. The components of the DAS28(CRP) are the number of tender joints (28 joint count), the number of swollen joints (28 joint count), a Patient Global Health index (VAS), and the CRP (in mg/L).

Key secondary outcome(s))
1. Predictability of clinical response based upon ultrasound assessments
2. To understand the mechanisms and effects of anti-TNF therapy on disease comparing responders and non-responders
3. To assess changes within the synovium over time, to be determined both at histomorphological and mRNA level
4. To investigate the cellular and angiogenic components in the relationship between the presence of ectopic lymphoneogenesis (ELN), ELN-associated markers, plus changes in cytokines and chemokines within the rheumatoid synovium and change in clinical disease activity
5. To assess B cell growth/modulating factors expression within the rheumatoid synovium and whether this correlates with autoantibody levels in the serum

6. To examine the dynamics of urine metabolites over time in relation to changes in clinical disease activity
7. Correlation of the change in IL-17/Th17 pathway activity and US assessment of synovitis by both grey-scale US and Power Doppler

Completion date
31/08/2016

Eligibility

Key inclusion criteria
1. Men and women ≥ 18 and ≤ 65 years of age, with RA as defined by the 2010 revised EULAR /ACR classification criteria
2. An RA diagnosis as defined by the 2010 revised EULAR/ACR classification criteria
3. Subjects who fulfill the NICE guidelines for biologic therapy as their first-line treatment following failure of standard disease modifying anti-rheumatic therapy
4. Subjects may be on cDMARDs of which one must be MTX, or on MTX monotherapy, but should be receiving it for at least 2 months, with a stable dose of 7.525 mg/week for a minimum of 4 weeks
5. Subjects may be on oral steroids (prednisone ≤10 mg/day, or equivalent corticosteroid) with a stable dose for the 4 weeks prior to Visit 0
6. Men and women of childbearing potential must use adequate birth control measures (e.g. abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, or surgical sterilization) for the duration of the study
7. Patient must be able to adhere to the study visit schedule
8. The patient must be capable of giving informed consent and the consent must be obtained prior to any screening procedures
9. Must have a chest X-ray within 3 months prior to commencement of anti-TNF therapy with no evidence of malignancy, infection or fibrosis

Target Gender: Male & Female; Upper Age Limit 65 years ; Lower Age Limit 18 years

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Women who are pregnant or breastfeeding
2. Previous use of rheumatoid arthritis anti-TNF biologics, or ANY other type of biologic therapy

or investigational medicinal product
3. Treatment with any other therapeutic agent targeted at reducing TNF within 3 months of screening
4. Serious infections (such as, HIV, HBV, pneumonia or pyelonephritis) in the previous 3 months. Less serious infections (such as acute upper respiratory tract infection [colds] or simple urinary tract infection) need not be considered exclusions at the discretion of the investigator
5. Have active TB or have evidence of latent TB (old or latent TB on chest x-ray,without adequate therapy for TB initiated prior to first dose of study drug). Also excluded are patients with evidence of an old or latent TB infection without documented adequate therapy. Patients with a current close contact with an individual with active TB and patients who have completed treatment for active TB within the previous 2 years are explicitly excluded from the trial. Patients with a household member who has a history of active pulmonary TB should have had a thorough evaluation for TB prior to study enrolment as recommended by a local infectious disease specialist or published local guidelines of TB control agencies
6. Presence of a transplanted organ (with the exception of a corneal transplant >3 months prior to screening)
7. Malignancy within the past 5 years (except for squamous or basal cell carcinoma of the skin that has been treated with no evidence of recurrence)
8. History of lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (such as nodes in the posterior triangle of the neck, infra-clavicular, epitrochlear, or periaortic areas), or splenomegaly
9. Known recent substance abuse (drug or alcohol)
10. Poor tolerability of venepuncture required blood sampling during the study period
11. Planning to have surgery for RA or other significant surgery during the period of study

Date of first enrolment
02/03/2015

Date of final enrolment
31/08/2016

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Queen Mary University of London
London
United Kingdom
EC1M 6BQ

Sponsor information

Organisation
Queen Mary University of London (UK)

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Industry

Funder Name
Janssen Pharmaceuticals Inc. (USA)

Funder Name
NIHR Translational Research Partnerships (UK)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available

Study outputs

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