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Ultrasound Guided Synovial Biopsy to determine treatment response to Rituxumab versus Tocilizumab

Submission date
22/08/2013

Recruitment status
No longer recruiting

Registration date
22/08/2013

Overall study status
Completed

Last Edited
25/01/2021

Condition category
Musculoskeletal Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol

Background and study aims
Rheumatoid arthritis (RA) is the most common form of inflammatory arthritis and the diagnosis can have devastating consequences for those affected both medically, with severe joint pain, fatigue and a shortened life span, and socially with a diagnosis frequently resulting in unemployment, depression and social isolation. Although new types of treatment termed biological therapies have revolutionized the outlook for patients with RA, approximately only 30% of patients respond completely to these treatments, with a further 30% responding partially and 40% having no response. At present guidance from the UK government body NIHCE (National Institute for Health and Clinical Excellence) states that all RA patients should be treated initially with a type of biologic drug called tumour necrosis factor inhibitors (TNFi) and when/if patients fail on these drugs either due to lack of effect or side effects they should be switched over to a different biologic medication called rituximab. Whether rituximab is the correct choice of drug at this stage is presently unknown, indeed there are a number of different biologic drugs, all licensed to treat RA, which could be used at this stage instead of rituximab, including a medication called tocilizumab. Again neither rituximab nor tocilizumab work for all patients who have failed treatment with TNFi and at present it is impossible to predict which patients will respond to which drug. Such a situation is very frustrating for both doctors and patients as cycling through ineffective drugs can leave patients with months or years of suffering, biologic therapies can have serious side effects and furthermore they are very expensive treatments, costing upwards of approximately £8,000 per year. The main aim of the study is to find out whether the patterns and absence/presence of B-cells within the joint can predict the response, resistance and the likelihood of reversion in people who receive Rituximab versus those who receive another drug, Tocilizumab. The ultimate aim is to provide a tailored approach to treatment decisions in patients at this stage of their disease, in order to maximise their potential to respond to therapy.

Who can participate?
Individuals who are over 18 years old, have rheumatoid arthritis and have failed other drug therapies (DMARDS or anti-TNF) can take part in this study.

What does the study involve?
Willing indiciduals will be invited for a screening visit. If they are entered into the study, they will then undergo an ultrasound-guided biopsy procedure. A needle is placed into the joints under ultrasound guidance in a germ-free environment and a number of samples are taken form the lining of the joint. These samples are then taken to the laboratory and used for the research purposes. Local anaesthetic is used to numb the skin and joint so as to minimise any discomfort. The participants are then randomly allocated (this is a process where a computer randomly allocates an individual to a treatment; the doctors do not decide) to receive Rituximab or Tocilizumab. Both of these drugs are already licensed and widely used to treat RA. Following treatment, participants are followed up monthly in order to assess response to treatment. They will have x-rays and ultrasound tests taken at certain time points during the study. At 16 weeks, participants will be invited to have a second biopsy, at which point patients will be switched to the other treatment if they have not responded to the first allocated treatment; i.e. patients who received Rituximab will receive Tocilizumab and vice-versa.

What are the possible benefits and risks of participating?
There are no specific advantages to you as the patient, however future patients may benefit from the research by allowing a more tailored approach to their treatment. Blood samples are obtained by inserting a needle into a vein and can cause discomfort and may result in bruising, clotting, or rarely, infection. Both discomfort and bruising should disappear in a few days. The synovial biopsy is a well-tolerated procedure. The majority of patients have no adverse reaction to the procedure but there are a number of possible complications such as infection of the joint or skin, bleeding, pain and rarely nerve or tendon damage (less than 1in 10,000). The drugs used in this study are the same medications that would be prescribed on the NHS for treatment of RA. However, as with any medication, there are always associated risks and patients should discuss these risks with their study doctor.

Where is the study run from?
The study is already underway at Queen Mary University of London / Barts Health Trust and will run in other sites in the UK, Belgium, Italy, Portugal, and Spain.

When is the study starting and how long is it expected to run for?
December 2012 to July 2019

Who is funding the study?
The National Institute for Health Research (NIHR), UK.

Who is the main contact?
1. Chief Investigator: Professor Costantino Pitzalis
c.pitzalis@qmul.ac.uk
+44 (0)20 7882 8191 (PA: 8192)
2. Trial Manager: Joanna Peel
emrclinicaltrials@qmul.ac.uk
+44 (0)20 7882 3497

Contact information

Type(s)
Scientific

Contact name

Ms Joanna Peel

Contact details
EMR Clinical Trials Manager
Centre for Experimental Medicine and Rheumatology
2nd Floor, John Vane Science Centre
William Harvey Research Institute
Barts and the London School of Medicine and Dentistry
Charterhouse Square
London
United Kingdom
EC1M 6BQ
+44 (0)20 7882 3497
emrclinicaltrials@qmul.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2012-002535-28

Protocol serial number
14524

Study information

Scientific Title
A randomised, open labelled study in anti-TNFa inadequate responders to investigate the mechanisms for response - Resistance to Rituximab versus Tocilizumab in RA (R4-RA)

Acronym
R4-RA

Study objectives
Despite the advent of biological agents to treat Rheumatoid Arthritis (RA), inducing and sustaining remission is still carried out on a trial and error basis. Following DMARD and anti-TNF failure, current National Institute of Clinical Excellence (NICE) guidelines recommend the B-cell depleting agent Rituximab, followed by a switch to other biologics such as IL-6 blockade through Tocilizumab. There are few head to head trials of biologic agents and therefore limited scientific rationale behind the choices made by clinicians in the treatment of the disease.

B-cells play an important role in RA both as autoantibody producing cells, antigen presenting cells and through the expression of proinflammatory cytokines. Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen expressed by B-cells, resulting in depletion in both the synovium and peripheral blood. The response, however, is varied, with only 60% reaching an ACR 20 response at 6 months. (1, 2). There is emerging evidence from the MRC funded Pathobiology of Early Arthritis Cohort initiative, led by QMUL, in which synovial biopsies have been taken from patients with early arthritis that there are at least three distinct histo-morphological subtypes. These are described as fibroblast (pauci-immune), lymphoid (B-cell rich, with or without germinal centre formation) and Myeloid (rich in monocytes but poor in B cells), which correspond to different transcriptomic signatures.

With these subsets in mind, the overarching hypothesis of this study is whether a diagnostic synovial biopsy showing a B-cell rich / B- cell poor pathotype can predict response and define certain disease responsive / resistance subsets for patients stratification and help to rationalize drug choice.
The purpose of this study is to test the hypothesis that the presence or absence of specific synovial and molecular signatures (B-cells and B-cell associated signatures), assessed through obtaining tissue from a synovial biopsy, will enrich for response / non-response to Rituximab, an B-cell depleting anti-CD20 monoclonal antibody. In addition, we will examine if clinical response is associated with inhibition of B cell-linked pathways within the synovium and dependent on local B-cell lineage depletion and whether the survival of auto-reactive B cells within protected synovial inches are responsible for re-population within the joint and subsequent disease resistance or relapse.
The primary aim of this project is to show that in patients failing anti-TNF therapy, with a B cell poor pathotype, Rituximab is inferior to Tocilizumab therapy. For the B-cell rich pathotypes we aim to show non-inferiority of Rituximab compared to Tocilizumab. The response /resistance patterns seen in germinal centre pathotypes will constitute an exploratory component to the trial.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/11/2012, Research Ethics Committee (REC) for Wales (Sixth Floor, Churchill House, 17 Churchill Way, Cardiff CF10 2TW; +44 (0)2920376829; corinne.scotte@wales.nhs.uk), ref: 12 /WA/0307

Primary study design
Interventional

Study design
Randomised; Interventional; Design type: Not specified

Study type(s)
Treatment

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

Interventions
Rituximab/Tocilizumab: Following synovial biopsy and stratification patients will be randomized to receive Rituximab or Tocilizumab within each histolomorphological subtype group (1:1). Both of these drugs are already licensed and widely used to treat RA. Participants will be followed up 4 weekly in order to assess response to treatment.; US guided synovial biopsy, Patients who are enrolled into the trial will undergo an ultrasound-guided synovial biopsy at baseline and subsequently stratified into one of three distinct histolomorphological subtype groups: 1. B-cell poor, 2. B-cell rich or 3. Germinal Centre.
Optional synovial biopsies will be undertaken at week 16, week 48 and week 96.; Follow Up Length: 24 month(s); Study Entry : Single Randomisation only

Intervention Type
Drug

Phase
Not Specified

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

Primary outcome(s)
Improvement in Clinical disease Activity using Clinical disease activity index (CDAI) at 16 weeks; Timepoint(s): Improvement in Clinical disease Activity using the Clinical disease activity index (CDAI) at 16 week

Key secondary outcome(s)
Not provided at time of registration

Completion date
10/07/2019

Eligibility

Key inclusion criteria
Inclusion criteria as of 13/01/2017:
1. Patients who have failed anti-TNF therapy (inadequate responders – ir). Note; this includes patients who have failed anti-TNF therapy because of reactions.
2. Who are eligible for Rituximab therapy according UK NICE guidelines*
3. Patients should be receiving a stable dose Methotrexate for at least 4 weeks prior to biopsy visit
4. 2010 ACR / EULAR Rheumatoid Arthritis classification criteria for a diagnosis of Rheumatoid Arthritis
5. 18 years of age or over
6. Patient must be capable of giving informed consent
7. Willingness and ability to comply with scheduled visits, treatment plans and laboratory tests and other study procedures

*Reference to NICE guidelines
1.1 Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to or intolerance of other disease-modifying anti-rheumatic drugs (DMARDs), including treatment with at least one tumour necrosis factor α (TNF-α) inhibitor therapy.

Original inclusion criteria:
Patients will be recruited with active RA:
1. Patients who have failed anti-TNF therapy (inadequate responders ir).
2. Who are eligible for Rituximab therapy according NICE guidelines
3. Patients should be receiving a stable dose Methotrexate for at least 4 weeks prior to screening.
4. 2010 ACR / EULAR Rheumatoid Arthritis classification criteria for a diagnosis of Rheumatoid Arthritis.
5. Over 18 years of age
6. Patient must be capable of giving informed consent
7. Willingness and ability to comply with scheduled visits, treatment plans and laboratory tests

and other study procedures.
Target Gender: Male & Female ; Lower Age Limit 18 years

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
164

Key exclusion criteria
Exclusion criteria as of 13/01/2017:
1. Women who are pregnant or breast-feeding
2. Women of child-bearing potential, or males whose partners are women of child-bearing potential, unwilling to use effective contraception during the study and for at least 12 months after stopping study treatment
3. History of or current primary inflammatory joint disease, or primary rheumatological autoimmune disease other than RA (if secondary to RA, then the patient is still eligible)
4. Prior exposure to Rituximab or Tocilizumab for the treatment of RA
5. Treatment with any investigational agent ≤ 4 weeks prior to baseline (or < 5 half-lives of the investigational drug, whichever is the longer).
6. Intra articular or parenteral corticosteroids ≤ 4 weeks prior to biopsy visit (Visit 2)
7. Oral prednisolone more than 10mg per day or equivalent ≤ 4 weeks prior to biopsy visit (Visit 2)
8. Active infection
9. Septic arthritis within a native joint within the last 12 months
10. Sepsis of a prosthetic joint within 12 months or indefinitely if the joint remains in situ.
11. Known HIV or active hepatitis B/C infection. Hepatitis B screening test must be performed at or in the preceding 3 months of screening visit.
12. Latent TB infection unless they have completed adequate antibiotic prophylaxis.
13. Malignancy (other than basal cell carcinoma) within the last 10 years
14. New York Heart Association (NYHA) grade 3 or 4 congestive cardiac failure.
15. Demyelinating disease
16. Latex allergy or allergy to any excipients of Rituximab or Tocilizumab
17. Any other contra-indication to the study medications as detailed in their summaries of product characteristics (SmPC), including low IgG levels at clinician’s discretion
18. Receipt of live vaccine <4 weeks prior to first infusion
19. Major surgery in 3 months prior to first infusion
20. Presence of a transplanted organ (with the exception of a corneal transplant >3 months prior to screening)

21. Known recent substance abuse (drug or alcohol)
22. Poor tolerability of venepuncture or lack of adequate venous access for required blood sampling during the study period
23. Patients unable to tolerate synovial biopsy or in whom this is contraindicated including patients on anti-coagulants (oral anti-platelet agents are permitted)
24. Patients currently recruited to other clinical trial(s) involving an investigational medicinal product (except any observational follow-up periods not involving an IMP)
25. Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that would impart, in the judgment of the investigator, excess risk associated with study participation or study drug administration, or which, in the judgment of the investigator, would make the patient inappropriate for entry into this study

Original exclusion criteria:
1. Patients will be excluded if they have any contraindication to Rituximab or Tocilizumab therapy.
2. Women who are pregnant or breast-feeding
3. Women of child-bearing potential, or males whose partners are women of child-bearing potential, unwilling to use effective contraception during the study and for at least 12 months after stopping study treatment.
4. History of or current inflammatory joint disease or autoimmune disease other than RA
5. Treatment with any investigational agent = 4 weeks prior to baseline or <5 half lives of the investigational drug
6. Intra articular or parenteral corticosteroids = 4 weeks prior to baseline
7. Active infection
8. Septic arthritis within a native joint within the last 12 months
9. Sepsis of a prosthetic joint within 12 months or indefinitely if the joint remains in situ
10. Known HIV or hepatitis B/C infection
11. Latent TB infection unless they have completed adequate antibiotic prophylaxis
12. Malignancy (other than basal cell carcinoma) within the last 10 years
13. New York Heart Association (NYHA) grade 3 or 4 congestive cardiac failure
14. Demyelinating disease
15. Latex allergy or allergy to any excipients of Rituximab
16. Any other contra-indication to the study medications as detailed in their summaries of product characteristics
17. Receipt of live vaccine <4 weeks prior to first infusion
18. Surgery in 3 months prior to first infusion
19. Presence of a transplanted organ (with the exception of a corneal transplant >3 months prior to screening)
20. Known recent substance abuse (drug or alcohol)
21. Poor tolerability of venepuncture or lack of adequate venous access for required blood sampling during the study period.
22. Patients unable to tolerate synovial biopsy or in whom this is contraindicated (e.g. patients on anticoagulants such as warfarin or heparin).
23. Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that would impart, in the judgment of the investigator, excess risk associated with study participation or study drug administration, or which, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

Date of first enrolment
28/02/2013

Date of final enrolment

Locations

Countries of recruitment
United Kingdom

England

Belgium

Italy

Portugal

Spain

Study participating centre
Queen Mary University of London
Experimental Medicine and Rheumatology
2nd Floor, John Vane Science Centre
Charterhouse Square
London
United Kingdom
EC1M 6BQ

Study participating centre
Cliniques Universitaires Saint Luc
UCL 10 avenue hipocratte
Brussels
Belgium
1200

Study participating centre
Centro Hospitalar Lisboa Norte, E.P.E.
Hospital de Santa Maria
Técnicas de Reumatología
Avenida Prof Egas Moniz
Lisbon
Spain
1649-035

Study participating centre

UZ/KU Leuven
Department of Rheumatology
Division of Internal Medicine
UZ Gasthuisberg
Skeletal Biology and Engineering Research Center Herestraat 49
Leuven
Belgium
3000

Study participating centre
AOU Maggiore della Carità, Novara
Corso Mazzini 18
Novara
Italy
28100

Study participating centre
Hospital Clínic Provincial de Barcelona
Arthritis Unit
Rheumatology Dpt.
Hospital Clinic
Carrer de Villarroel, 170
Barcelona
Spain
08036

Study participating centre
Azienda Ospedaliero Universitaria (AOU) di Cagliari
Dipartimento di Scienze Mediche “M. Aresu”
Università di Cagliari
ss 554 Monserrato
Cagliari
Italy
09042

Study participating centre
Scuola di Specializzazione in Reumatologia Università di Pavia
Fondazione I.R.C.C.S Policlinico S. Matteo-Segreteria di Reumatologia
Reparti Speciali 4 piano
V.le Golgi 19
Pavia
Italy
27100

Sponsor information

Organisation
Queen Mary University of London (UK)

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Government

Funder Name
NIHR Efficacy and Mechanism Evaluation; Grant Codes: 11/100/76

Results and Publications

Individual participant data (IPD) sharing plan
The anonymised raw data will be stored in a non-publically available repository called TranSMART (once the paper has been published). More information can be found here: http://www.matura.whri.qmul.ac.uk/TranSMART.php.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	23/01/2021	25/01/2021	Yes	No
HRA research summary			28/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes