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Stratification of biologic therapies for rheumatoid arthritis by pathobiology

Submission date
05/11/2015

Recruitment status
No longer recruiting

Registration date
05/11/2015

Overall study status
Completed

Last Edited
12/08/2022

Condition category
Musculoskeletal Diseases

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

Plain English summary of protocol

Background and study aims
Rheumatoid arthritis (RA) is a long-term disease causing pain, swelling (inflammation) and stiffness in the joints. It is part of a group of diseases called autoimmune diseases, where the immune system starts to attack healthy joints. In healthy people, the body produces different types of immune cells. One of these is the B-cell, which produces antibodies to fight infection. In people with RA, these do not behave properly and produce antibodies which attack a person's own body even if there is no infection. There are 26,000 new cases of RA each year, which costs the NHS around £560 million annually. Often the first line of treatment involves the use of disease-modifying anti-rheumatic drugs (DMARDs), which work by slowing down the progress of the disease by suppressing the immune system. In about 40% of cases however, patients do not show any real signs of improvement (DMARD failures). In recent years, drug treatments for RA have improved dramatically. So-called "biologic treatments" such as the drug tocilizumab, are made from proteins and work by blocking the activity of the chemicals or cells which trigger the inflammation of the joints. Another important treatment used in RA is a group of drugs known as anti-TNF (anti-tumour necrosis factor), such as etanercept and rituximab, which work directly on the immune system to reduce the number of B-cells, stopping them from producing antibodies which will attack the healthy cells. Currently patients are treated with tocilizumab, etanercept or rituximab on a trial and error basis. The aim of this study is to predict which treatment will work best for patients, this is known as stratified or personalised medicines.

Who can participate?
Adults with RA who have DMARD failure and are eligible for antiTNFa therapy.

What does the study involve?
Participants have a minimally invasive synovial biopsy of an inflamed joint and are then randomly allocated to one of three groups, who are each treated with a different drug. Those in the first group receive a 50mg subcutaneous injection (injection under the skin) of etanercept once a week. Those in the second group receive a 1000mg intravenous infusion (a drip into a vein) of rituximab day 1 and 15 of the study this treatment is repeated every 24 weeks. Those in the third group receive a 162mg subcutaneous injection of tocilizumab once a week. Participants

come in for monthly visits for 1 year. The main outcome of the trial is the number of participants in each treatment group who show more than a 20% improvement (ACR20) in their symptoms 16 weeks into the study.

What are the possible benefits and risks of participating?
Benefits include regular reviews and if treatment is not effective it will be switched at 4months rather than at 6 months. There is a small risk of complications associated with the biopsy and patients receiving Rituximab as part of the trial might not be guaranteed to continue to receive it. This is because treatment with Rituximab typically requires you to have been treated with another biological drug first in standard care.

Where is the study run from?
Centre for Experimental Medicine and Rheumatology, Barts and the London School of Medicine and Dentistry, Queen Mary University of London (UK)

When is the study starting and how long is it expected to run for?
June 2015 to January 2021 (updated 11/12/2020, previously: December 2020)

Who is funding the study?
1. Medical Research Council (UK)
2. Arthritis Research UK

Who is the main contact?
Jo Peel

Contact information

Type(s)
Public

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Ms Jo Peel

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Additional identifiers

Clinical Trials Information System (CTIS)
2014-003529-16

Protocol serial number
18178

Study information

Scientific Title
Stratification of Biologic Therapies for Rheumatoid Arthritis by Pathobiology (STRAP): A randomised, open-labelled biopsy driven stratification trial in DMARD inadequate responder patients randomised to etanercept, tocilizumab or rituximab

Acronym
STRAP

Study objectives
In patients failing DMARD therapy, with a B cell poor synovial pathotype, Rituximab is inferior to Tocilizumab and Etanercept therapy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Wales Research Ethics Committee, 16/12/2014, ref: 314/WA/1209

Study design
Three-arm randomised parallel trial

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions
Participants are randomly allocated to one of three groups:

Group 1: Participants receive 50mg etanercept administered subcutaneously once weekly for the study duration.
Group 2: Participants receive 1000mg rituximab by iv infusion on days 1 and 15. This cycle is repeated every 24 weeks.
Group 3: Participants receive 162 mg tocilizumab administered subcutaneously once weekly for the study duration.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
1. Etanercept 2. Rituximab 3. Tocilizumab

Primary outcome(s)
Treatment efficacy is determined by calculating the number of patients with an ACR 20 response at 16 weeks.

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

Completion date
09/01/2021

Eligibility

Key inclusion criteria
Current inclusion criteria as of 08/09/2017:
1. 2010 ACR / EULAR Rheumatoid Arthritis classification criteria for a diagnosis of RA *
2. Patient with DMARD failure eligible for anti-TNF-α therapy as per UK NICE guidelines**
3. Patients must have a minimum of 3 swollen joints – the joint selected for biopsy and a minimum of 2 from 28 joint count set, as assessed at biopsy visit
4. Selected joint for biopsy must be minimum grade 2 synovial thickening, as assessed at the biopsy visit
5. 18 years of age and over
6. Patients must be capable of giving informed consent and the consent must be obtained prior to any screening procedures
* The ACR/EULAR classification for a diagnosis of RA could have been at any time in the patient's disease history; the score does not need to be 6 or more at screening.
** Current NICE guidelines available at the following link: http://www.nice.org.uk/guidance /ta375.

Previous inclusion criteria:
1. 2010 ACR / EULAR Rheumatoid Arthritis classification criteria for a diagnosis of RA
2. Patient with DMARD failure eligible for antiTNFa therapy as per UK NICE guidelines (those who have both of the following):
2.1. Active RA as measured by DAS28>5.1
2.2. Have undergone trials of two DMARDs, including MTX (unless contraindicated). A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.
3. Over 18 years of age
4. Patients must be capable of giving informed consent and the consent must be obtained prior to any screening procedures

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group

Adult

Lower age limit
18 years

Sex
All

Total final enrolment
187

Key exclusion criteria
Current exclusion criteria as of 08/09/2017:
Patients will be excluded if they have any contraindication to Etanercept, Rituximab or Tocilizumab therapy:
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 an effective method of contraception(recommend double contraception) throughout the trial and beyond the end of trial treatment for the duration as defined in the relevant SmPC; 12 months for Rituximab, at least 3 weeks for Etanercept, and at least 3 months for Tocilizumab.
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, any anti-TNF, Tocilizumab, or any other biologic for 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 screening visit.
7. Oral prednisolone more than 10mg/d or equivalent ≤ 4 weeks prior to baseline synovial biopsy.
8. Active infection
9. Known HIV, active Hepatitis B/C infection. Hepatitis B screening test must be performed at or in the preceding 3 months of screening visit.
10. Septic arthritis of a native joint within the last 12 months
11. Septic arthritis of a prosthetic joint within 12 months or indefinitely if the joint remains in situ
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 III or IV congestive heart failure
15. Demyelinating disease
16. Known allergy to latex, Rituximab, Tocilizumab or Etanercept
17. Any other contra-indication to the study medications as detailed in the applicable SmPC including low IgG levels, at physician's discretion
18. Receipt of live vaccine <4 weeks prior to first IMP infusion or dose
19. Major surgery in 3 months prior to first IMP infusion or dose
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 trials.

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
26. For patients potentially eligible for MRI any of the following conditions: Pacemakers and/or other non-removable metal objects, diagnosis of claustrophobia or a history of anxiety or claustrophobia during previous MRI scanning, abnormal creatinine/protein ratio at screening that precludes administration of MRI contrast medium (e.g. gadolinium) in accordance with local guidelines , previous allergic reactions to MRI contrast medium (e.g. gadolinium)

The PI reserves the right to exclude patients at their centre, if they have concerns regarding compliance with the study procedures or any other aspect of the study eligibility not necessarily limited to the above exclusion criteria.

Previous exclusion criteria:
1. Women who are pregnant or breastfeeding
2. Women of childbearing potential or males whose partners are women of childbearing potential, unwilling to use effective contraception during the study (recommend double contraception) throughout the trial and beyond the end of trial treatment for the duration as defined in the relevant SmPC; 12 months for Rituximab, at least 3 weeks for Etanercept, and at least 3 months for Tocilizumab
3. History of or current inflammatory joint disease or autoimmune disease other than RA (if secondary to RA, then the patient is still eligible)
4. Prior exposure to Rituximab, any antiTNF, Tocilizumab, or any biologic for 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. Intraarticular or parenteral corticosteroids ≤ 4 weeks prior to baseline synovial biopsy
7. Oral prednisolone more than 10mg/d or equivalent ≤ 4 weeks prior to baseline synovial biopsy
8. Active infection
9. Known HIV, active Hepatitis B/C infection. Hepatitis B screening test must be performed at or in the preceding 3 months of screening visit
10. Septic arthritis of a native joint within the last 12 months
11. Septic arthritis of a prosthetic joint within 12 months or indefinitely if the joint remains in situ
12. Latent TB infection unless they have completed adequate antibiotic prophylaxis
13. Malignancy (other than basal cell carcinoma) within the last 10 years

Date of first enrolment
15/06/2015

Date of final enrolment
31/05/2019

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
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Sponsor information

Organisation
Queen Mary University of London

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Arthritis Research UK

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

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 non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		16/12/2021	10/02/2022	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol (other)		28/02/2022	12/08/2022	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes