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Can we identify predictors of treatment responses to biologic therapies in patients with rheumatoid arthritis?

Submission date
15/05/2019

Recruitment status
No longer recruiting

Registration date
17/05/2019

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 antiTNF 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 2018 to January 2021

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Jo Peel
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Study website
http://www.matura-mrc.whri.qmul.ac.uk/

Contact information

Type(s)
Public

Contact name
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Additional identifiers

EudraCT/CTIS number

2017-004079-30

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
STRAP-EU

Study information

Scientific Title
Stratification of biologic Therapies for RA by Pathobiology: a randomised, open-labelled biopsy-driven stratification trial in DMARD inadequate responder patients randomised to Etanercept, Tocilizumab or Rituximab

Acronym
STRAP-EU

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)
1. Approved 01/02/2018, Ethics Committee Hospital-Faculty Saint-Luc (Avenue Hippocrate 55.14 -Tour Harvey, niveau O - 1200 Bruxelles; 027645514; commission.ethique-saint-luc@uclouvain. be), ref: 2017/21NOV/526.
2. Approved 06/07/2018, AOU Inter-company Ethics Committee "Major of Carita" (C.so Mazzini n. 18 - 28100 Novara; 03213733081; segreteria.scientifica@comitatoeticonovara.it), ref: CE 32/18.
3. Approved 24/08/2018, Ethics Committee for Clinical Research (CEIC) (Lisbon) (Joao Eurico Cabral da Fonseca Centro Hospitalar de Lisboa Norte, EPE - Hospital de Santa Maria Servico de Reumatologia, Avenida Prof. Egas Moniz, Piso 7, 1649-035, Lisbon), ref: LC/LC/OF/2018/9325 /20180526.
4. Approved 29/06/2018, Research Ethics Committee with medicines at the Hospital Clínic de Barcelona (Villarroel, 170 – 08036 Barcelona (España); 93 227 54 00), ref: 10/2018.
5. Approved 13/03/2019, Univ. Policlinico Foundation A. Gemelli Ethics Committee (Fondazione Policlinico Unlversitario Agostino Gemelli IRCCS Universita Cattolica del Sacro Cuore, Largo Agostino Gemelli 8, 00168 Roma; +39 06 3015 6124 -5556; comitato.etico@policlinicogemelli.it), ref: 0011631/19.
6. Approved 24/07/2018, Independent Ethics Committee University Hospital of Cagliari (Azienda Ospedallero Unlversltarla di Cagliari
P.O. San Giovanni di Dio: via Ospedale 54 - 09124 Cagliarl Segreteria Tecnlco Scientlflca; 0706092547), ref: PG/2018/9999.

Study design
Three-arm randomised parallel trial

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 below to request a patient information sheet

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

Interventions
1. Rituximab
Rituximab (MabThera® 500mg concentrate for infusion, Roche Products Ltd) is available as 50ml single-use vials containing 500mg Rituximab for infusion (10mg/ml). Patients randomised to receive rituximab therapy will be given treatment on days 1 and 15, which is one infusion cycle. A patient initially randomised to Rituximab and deemed a responder at 16 weeks will be retreated at 24 weeks. All treatment infusions will be prepared, administered and monitored according to the guidance included in the SmPC. Patients with inadequate response at week 16 to Rituximab will be switched to Etanercept at that visit or the following visit.

2. Tocilizumab
Tocilizumab (RoActemra SC® 162mg solution for injection in a pre-filled syringe, Roche Products Ltd) subcutaneous (SC) formulation is a sterile, yellowish, preservative-free liquid solution of approximately pH 6.0 for SC injection. It is supplied at a concentration of 180 mg/mL in syringe /autoinjector (AI) forms with a nominal amount of 162 mg of Tocilizumab in 0.9 mL of arginine, methionine, and histidine buffered solution. Tocilizumab will be prescribed as per license. The recommended dose of Tocilizumab for adult patients with RA is 162mg administered as a weekly subcutaneous injection and it will be self-administered by patients. Patients will be treated with tocilizumab for up to 48 weeks unless they switch treatment during the trial. Patients with inadequate response at week 16 to Tocilizumab will be switched to Etanercept at that visit or the following visit.

3. Etanercept
Etanercept (Enbrel® 50mg solution for injection in pre-filled pen, Pfizer) is available in pre-filled pens containing 50mg of Etanercept in a clear, and colourless or pale yellow solution. Etanercept will be prescribed as per license. The recommended dose of Etanercept for adult patients with RA is 50 mg (given as a subcutaneous injection) once a week and it will be self-administered by patients. Patients will be treated with etanercept for up to 48 weeks unless they switch treatment during the trial. Patients who have an inadequate response at 16 weeks to Etanercept will be switched to Rituximab at that visit or the following visit.

Secondary failures (i.e. after week 16) to first biologic:
Patients showing initial clinical response by 16 weeks will be subsequently classified as a secondary failure at subsequent study visits, if their ACR response is less than 20% at any subsequent follow up visit. Such patients should switch treatment either at that visit or the following visit.

The total treatment period is 48 weeks and a 30 day safety follow-up will be performed 30 days after the patients last trial visit.

Randomisation
Patients will be stratified according to synovial histopathology (2 strata based on B cells, or a third strata where result is unknown) and methotrexate use (yes/no), and randomised using ratio 1:1:1 to three treatments.

Intervention Type
Drug

Phase
Not Applicable

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

Primary outcome measure
Treatment response will be assessed using the ACR20 response at 16 weeks

Secondary outcome measures
1. For the B-cell rich synovial pathotypes, we aim to compare treatment effects (with 95% confidence intervals) of Rituximab to Tocilizumab and Etanercept (treated together for analysis).
2. The interaction between treatments and B-cell status (rich and poor) will be tested using the likelihood ratio test between nested logistic regression models. The model will use all the sample and will be adjusted for MTX.
3. Patients who fail to respond during the first 16 weeks and cross-over treatment will also provide evidence regarding the efficacy of the two treatments and the predictive significance of B-cells in synovial biopsies. The post cross-over results will be combined with the pre-cross-over results in a secondary analysis stratified by pre/post cross-over.

Overall study start date
01/09/2017

Completion date
09/01/2021

Eligibility

Key inclusion criteria
Patients will be recruited with active RA:
1. 2010 ACR / EULAR Rheumatoid Arthritis classification criteria for a diagnosis of RA
2. DMARD failure eligible for anti-TNF-α therapy as per UK NICE guidelines
3. 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. Capable of giving informed consent and the consent must be obtained prior to any screening procedures

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
207 patients (this recruitment target combines both STRAP-EU (EudraCT number: 2017-004079-30) and the UK STRAP trial (EudraCT number: 2014-003529-16). Target for STRAP-EU trial: maximum of 60 patients.

Total final enrolment
226

Key exclusion criteria
Patients will be excluded if they have any contraindication to Etanercept, Rituximab or Tocilizumab therapy:
1. Pregnant or breastfeeding
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 the 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 the 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 anticoagulants. Oral antiplatelet agents are permitted.
24. Currently recruited to another clinical trial.
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

Date of first enrolment
21/06/2018

Date of final enrolment
31/05/2019

Locations

Countries of recruitment
Belgium

Italy

Portugal

Spain

Study participating centre
Cliniques Universitaires Saint-Luc
10 Avenue Hippocrate
Brussels
Belgium
1200

Study participating centre
AOU Maggiore della Carita de Novara
Corso Mazzini 18

Novara
Italy
28100

Study participating centre
CENTRO HOSPITALAR LISBOA NORTE, E.P.E. – HOSPITAL DE SANTA MARIA
Avenida Prof. Egas Moniz
Lisbon
Portugal
1649-035

Study participating centre
Hospital Clinic de Barcelona
Calle Villarroel, 170
Barcelona
Spain
08036

Study participating centre
Fondazione Policlinico Universitario A. Gemelli
Largo Francesco Vito, n.1
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Study participating centre
Azienda Ospedaliero Universitaria (AOU) di Cagliari
via Ospedale, 54
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09124

Sponsor information

Organisation
Queen Mary University of London

Sponsor details

Joint Research Management Office
5 Walden Street
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England
United Kingdom
E1 2EF
020 7882 7275
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Sponsor type
University/education

Website
http://www.jrmo.org.uk/

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

Results and Publications

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

Intention to publish date
30/06/2022

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?
Basic results		16/12/2021	09/03/2022	No	No
Protocol file	version 3.0	25/03/2020	12/08/2022	No	No