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Are RNA signatures (biomarkers) in the tissue which surrounds the joints (synovial tissue) from patients with rheumatoid arthritis predictive of response to drug treatments?

Submission date
24/09/2022

Recruitment status
Recruiting

Registration date
20/01/2023

Overall study status
Ongoing

Last Edited
03/07/2025

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol
Background and study aims
Rheumatoid arthritis (RA) is a chronic inflammatory disease, characterised by persistent synovitis (joint inflammation), systemic inflammation and autoantibodies (particularly rheumatoid factor and citrullinated peptide, thought to play critical roles in initiating inflammatory responses in RA). In industrialised countries, RA affects 0.5-1% of adults, with 5-50 per 100,000 new cases annually.
Despite the clinical and radiological benefits of biological therapies, the vast majority of patients fail to achieve low disease activity or remission. Almost 40% of all patients treated with biologic disease-modifying anti-rheumatic drugs (b-DMARDs) do not experience minimally acceptable improvement. Thus, the treatment of RA patients according to their biomarker would provide better care (avert delay in starting a more effective drug) and prevent unnecessary exposure to potentially toxic drugs and additionally be cost-saving.
We aim to test whether RNA signatures (biomarkers), in the tissue which surrounds the joints (synovial tissue) from patients with RA are predictive of response to drug treatments such as biologic disease-modifying anti-rheumatic drugs (b-DMARDs).

Who can participate?
Adults with RA

What does the study involve?
Rheumatology patients will undergo a biopsy of their joint and then will receive either sarilumab or etanercept. Half of the patients will receive the drug randomly, and the other half will be treated according to their biomarkers. Patients will attend 4-weekly visits for up to 12 weeks, followed by a 30-day safety follow-up visit.

What are the possible benefits and risks of participating?
Participating patients may experience an improvement in the symptoms of their arthritis or may not benefit directly from this study. However, the trial will generate essential information, which

could be of benefit to others in the future. Both medications within this trial have evidence that they may be effective in patients where conventional Disease Modifying Anti-Rheumatic drugs (DMARDs) have failed. This study will find out whether specific RNA signatures enable accurate prediction of what the best treatment will be for rheumatoid patients where conventional DMARDs have failed. It has the potential to be of significant benefit to future patients.

Injection site reactions with sarilumab and etanercept may occur. The risk of such reactions as well as of infection will be discussed with the patient prior to enrolment in the study; however, patients would be at no greater risk than routine care within the NHS.

An ultrasound-guided synovial biopsy is a quick, safe and well-tolerated procedure; patients who consent to the study and therefore synovial biopsy will have a longer appointment in hospital and may experience discomfort from the local anaesthetic and biopsy procedure. However, published data on this procedure confirms that it is well tolerated and safe, and patients are agreeable to multiple biopsies.

The risks of venepuncture may include fainting, pain and/or bruising at the site of the needle puncture. Every possible effort will be taken to minimise the potential of these risks occurring.

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?
September 2022 to September 2026

Who is funding the study?
Innovative Medicines Initiative (Belgium)

Who is the main contact?
Centre for Experimental Medicine & Rheumatology (EMR) Clinical Trials team, Queen Mary University of London (UK)
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Study website
https://3tr-ra.whri.qmul.ac.uk

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Additional identifiers

EudraCT/CTIS number
2022-502021-18-00

IRAS number
1005441

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 1005441, CPMS 51079

Study information

Scientific Title
The 3TR Molecular Pathobiology-Driven Precision Therapy in RA (3TR Precis-The-RA) study

Acronym
3TR Precis-The-RA

Study objectives
This study will test the utility of synovial tissue biomarkers (=drug target signatures) to enrich for treatment response in RA patients failing csDMARD therapy and starting on a biologic (e.g. anti-TNF or IL6 inhibitor).

To this aim, we will compare ACR-50 responses at 12 weeks in biomarker positive within the treatment allocation according to biomarker group compared to biomarker negative patients in both arms.

The primary trial hypothesis is that biomarker-positive patients treated according to their highest expressed biomarker will have higher ACR-50 response at 12 weeks compared to biomarker-negative patients.

The following analysis will be done sequentially to preserve the Type I error rate:
1. Firstly, we will compare patients treated according to their biomarker in the intervention arm against the control arm as a whole (i.e. Group 1 versus 3+4), to determine the enrichment in response in the treatment allocation arm versus the standard of care response rate.
2. Secondly, to assess the efficacy of treatment allocation according to biomarker compared to random allocation, we will compare the biomarker-positive patients in the intervention arm versus the biomarker-positive patients in the control arm (i.e. Group 1 versus Group 4)
3. Finally, we aim to assess the efficacy of the strategy as a whole against the current clinical practice by comparing the control versus intervention arm (i.e. Groups 1 + 2 versus Group 3+4)

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 05/12/2022, Health and Social Care Research Ethics Committee A (HSC REC A) (Office for Research Ethics Committee Northern Ireland (ORECNI), Business Services Organisation, Lissue Industrial Estate West, 5 Rathdown Walk, Moira Road, Lisburn, BT28 2RF, United Kingdom; +44 (0)28 9536 1400; info.orecni@hscni.net), ref: 22/NI/0157

Study design
Randomized controlled open-label parallel-group study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)

Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

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

Interventions
Patients will be randomised using the online database 1:1 to a control or treatment allocation by a biomarker-driven group. If randomised to the intervention arm (treatment by biomarker), the patient's biopsy tissue will be analysed within 2 weeks. If the patient has a drug target biomarker they will be given the concordant treatment (Top Module signature). In the absence of a target biomarker, the patient will be randomised 1:1 to either etanercept or sarilumab. If the patient is randomised to the control arm, they will be randomised again 1:1 to either etanercept or sarilumab. Patients assigned to etanercept will have weekly subcutaneous injections (50 mg solution for injection in a pre-filled pen). Patients assigned to sarilumab will take fortnightly subcutaneous injections (200 mg solution for injection in a pre-filled pen (reduced dose: 150 mg solution for injection in a pre-filled pen). Patients will continue trial treatment until 12 weeks when the treatment response will be assessed as the primary endpoint. There will be a post-treatment visit/call scheduled 30+ days after week 12 (Visit 6).

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Sarilumab, etanercept

Primary outcome measure
The primary endpoint of the study will be a binary outcome of treatment responder/non-responder classified using American College of Rheumatology 50 (ACR-50) measure at 12 weeks

Secondary outcome measures
1. Treatment response measured using the percentage of patients with DAS28(ESR)<3.2 (LDA) at 12 weeks
2. Treatment response measured using the percentage of patients with CDAI ≤10 (LDA) at 12 weeks
3. Treatment response measured using the percentage of patients with CDAI remission at 12 weeks
4. Functional ability and improvement in other aspects of the patient's life measured using the change in HAQ-DI at 12 weeks from baseline
5. Functional ability and improvement in other aspects of the patient's life measured using the change in SF-36 at 12 weeks from baseline

Overall study start date
20/09/2022

Completion date
01/09/2026

Eligibility

Key inclusion criteria
Patients will be recruited with active rheumatoid arthritis:
1. 2010 ACR / EULAR classification criteria for a diagnosis of rheumatoid arthritis *
2. Patients with csDMARD failure and eligible for anti-TNF therapy according to EULAR recommendations: treatment for ≥ 3 months with ≥ 1 csDMARDs **
3. Patients must have a DAS>5.1 and a minimum of 3 swollen joints – where the patient is undergoing a biopsy at visit 2, these should include the joint selected for biopsy and 2 other joints, 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 or over
6. Patients must be capable of giving informed consent and the consent must be obtained prior to any screening procedures
7. Willingness and ability to comply with scheduled visits, treatment plans and laboratory tests and other study 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 EULAR recommendations are available at the following link: https://ard.bmj.com /content/79/6/685
***this inclusion criterion is only applicable to patients in the 3TR Precis-The-RA main study

The above inclusion criteria apply to patients in the main study. All inclusion criteria apply to the sub-study except inclusion criteria 4. There are 2 additional inclusion criteria for the 3TR Precis-The-RA sub-study, only listed below:
3TR-Precis-The-RA sub-study additional inclusion criteria:
1. Patients must have previously received a synovial biopsy prior to commencing any treatment for their RA, as part of the 3TR Early RA study, and are not eligible or willing to undergo a further biopsy.
2. The patient's previous synovial biopsy tissue must have sufficient RNA for Nanostring analysis

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
240

Key exclusion criteria
The following exclusion criteria apply to the 3TR Precis-The-RA main study. All exclusion criteria but exclusion criteria number 23 apply to the Sub study:
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.
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 any biologic/targeted DMARDs for 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, or known hypersensitivity to the IMP active substance or to any of the excipients of the IMP
17. Any other contra-indication to the study medications as detailed in the applicable SmPC
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. Patients with severe hepatic impairment (Child Pugh C classification).
27. Patients that are immunocompromised

Date of first enrolment
20/02/2023

Date of final enrolment
29/03/2026

Locations

Countries of recruitment
Belgium

England

Italy

Netherlands

Portugal

Spain

United Kingdom

Study participating centre
Mile End Hospital
Bancroft Rd
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Study participating centre
Manchester Royal Infirmary
Oxford Road
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Study participating centre
Università degli Studi del Piemonte Orientale
via Solaroli, 17
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Study participating centre
Policlinico Duilio Casula AOU Cagliari
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Sponsor type
University/education

Website
http://www.qmul.ac.uk/

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Research organisation

Funder Name
Innovative Medicines Initiative 2 Joint Undertaking IMI2 JU

Alternative Name(s)
The Innovative Medicines Initiative, Europe's Innovative Medicines Initiative, EU Innovative Medicines Initiative, IMI

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
Belgium

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Conference presentation
3. Publication on a website
4. Submission to regulatory authorities
5. Data that is shared will be anonymised and patients are asked to explicitly consent for their anonymous data to be shared with other researchers in the consent form.

Intention to publish date
01/09/2027

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

Fully anonymised data may be uploaded, where appropriate, to a public location.

IPD sharing plan summary
Data sharing statement to be made available at a later date