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Targeted treatment with etanercept plus methotrexate for early rheumatoid arthritis patients that have not received any treatment yet. The treatment is rationalised based on the normality of the T-cell stratification.

Submission date
16/10/2023

Recruitment status
No longer recruiting

Registration date
20/02/2024

Overall study status
Completed

Last Edited
03/07/2024

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 (RA) is the most common form of inflammatory arthritis. It is a condition where your body's immune system affects the joints, resulting in symptoms of pain with joint swelling. If not adequately controlled, RA results in damage and deformity of joints.

As there is no cure for RA , the current optimal treatment strategy is to start treatment early using a disease modifying anti-rheumatic (DMARD) drug called methotrexate, following a 'Treat to Target' approach. The aim of this approach is to achieve the target of remission (absence of signs and symptoms of disease activity). If this target cannot be achieved in an individual patient (who perhaps has longstanding disease), this approach aims to achieve the best possible state of low disease activity. Treat to target initially requires frequent routine clinical assessments when the disease activity score is calculated. This score guides therapy changes, with the aim of getting the disease activity under control so that the target of remission is reached. The clinical assessments typically involve your overall assessment of disease, counting the number of tender and swollen joints and simple blood tests that measure the level of inflammation present in the blood.

These standard clinical measures can, however be influenced by different factors e.g. pain thresholds or painful joints due to previous damage rather than active disease. Also, milder swelling in the lining of the joint might be difficult to detect by the doctor. Previous studies have shown that patients may deteriorate despite achieving clinical remission, as assessed by these standard clinical measures. Therefore, there is a need for more specific markers for disease activity and to define remission.

Predicting which patients will respond to methotrexate is key to identifying those patients who may benefit from an alternative, more targeted treatment approach in the early stages after

diagnosis i.e. biologic therapy. Multiple predictors of remission have been reported but are not used in routine clinical practice. Diseases like RA are thought to be caused by abnormalities of the cells of the immune system, which are found in the blood (commonly referred to as white blood cells). Abnormalities of one type of cell, the 'naïve T-cell', is key in the development of RA.

Previous research in Leeds has demonstrated that by measuring the number of naïve T-cells in the blood via a simple blood test, we can predict which patients are likely to respond to methotrexate, in those who are newly diagnosed and have not started any form of treatment. Specifically, patients with an abnormally low level of naïve T-cells (compared to a normal reference range in healthy individuals of the same age and gender) did not respond as well to treatment in the study.

This study aims to identify whether measuring a patient's naïve T-cells via a single blood test at diagnosis and before starting any treatment can predict whether they will respond to and do well with standard treatment with methotrexate or not. For those who are predicted to have a poorer response (low naïve T-cells), an alternative and more targeted therapy can be considered without any harmful delay, therefore reducing the risk of disease progression (not current clinical practice).

The information we get might help improve the treatment of people with rheumatoid arthritis. For patients with abnormal T-cells it may be that inflammation can be controlled quicker and more fully with early biologic therapy; to prevent potential deformity and disability.

Who can participate?
Adults over 18 years with a new diagnosis of RA can participate in the study.

What does the study involve?
All participants will be screened and a set of assessments will be performed. Based on all these screening test results, an eligibility assessment will be made and the participants will be randomised to one of the 3 arms in eligibility has been confirmed and then baselined. There will be 3 follow up visits after baseline at 4 weeks, 12 weeks and 24 weeks.

What are the possible benefits and risks of participating?
Benefits: We cannot promise the study will help participants but the information we get might help improve the treatment of people with rheumatoid arthritis. For patients with abnormal T-cells it may be that we can control inflammation quicker and more fully with early biologic therapy; to prevent potential deformity and disability.
Risks/Side effects of Benepali: Benepali®: The study doctor can provide the patient with an information sheet from the manufacturer. The most commonly reported adverse reactions are injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), infections (such as upper respiratory infections, bronchitis, bladder infections and skin infections), allergic reactions, development of autoantibodies, itching, and fever.

Where is the study run from?
University of Leeds (UK)

When is the study starting and how long is it expected to run for?
February 2020 to July 2025

Who is funding the study?
Samsung Bioepis (South Korea)

Who is the main contact?
Dr Kulveer Mankia, K.S.Mankia@leeds.ac.uk

Contact information

Type(s)
Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
2016-002344-16

IRAS number
207599

ClinicalTrials.gov number
NCT03813771

Secondary identifying numbers

RR16/209, IRAS 207599, CPMS 34918

Study information

Scientific Title
Targeted treatment early with etanercept (biosimilar) plus methotrexate or methotrexate with T2T care for DMARD-naïve early RA patients. A prospective, longitudinal cohort study with an embedded pilot randomised controlled trial to assess treatment rationalisation based on naïve CD4+ T-cell stratification.

Acronym
TEEMS

Study objectives
A greater proportion of patients with normal naïve CD4+ T-cell frequencies for their age (Arm A) will achieve clinical remission after 24 weeks of first-line therapy with MTX and T2T care compared to those with abnormally low naïve CD4+ T-cell frequencies (Arm B)

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 21/02/2021, HRA and Health and Care Research Wales (HCRW) (Castlebridge 4, 15-19 Cowbridge Rd E, Cardiff, CF11 9AB, United Kingdom; +44 2920 230457; healthandcareresearch@wales.nhs.uk), ref: 17/YH/0155

Study design
Single centre Phase IV open-label prospective longitudinal cohort study with an embedded pilot randomized controlled trial

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 patient information sheet.

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

Interventions

Screening appointment to confirm eligibility, obtain written consent and to collect the necessary clinical and laboratory data as per the study schedule. Following the screening visit, patients will attend a baseline assessment within four weeks.

Patients will be stratified based on their naïve CD4+ T-cell frequency (normal or abnormal based on our pre-defined cut-off values according to age and sex-matched controls).
Patients with a normal T-cell frequency (Arm A) will commence MTX 15 mg/week PO* as per standard T2T practice. Follow-up (4, 12 and 24 weeks), dose escalation of MTX and treatment of flare will also be conducted in line with T2T care.
Patients with an abnormal T-cell frequency will be randomized 1:1 into 2 groups using randomly permuted block sizes and also followed up as per T2T care:
- The first group (Arm B) will receive MTX 15 mg/week PO*
- The second group (Arm C) will receive MTX 15 mg/week PO* in combination with 50 mg subcutaneous Benepali® administered weekly.

The total duration of the trial is 24 weeks/6 months for all study arms.

Intervention Type
Drug

Pharmaceutical study type(s)
Dose response

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Etanercept biosimilar (Benepali), methotrexate

Primary outcome measure
Number of patients in clinical remission (DAS28ESR ≤2.6) at 24 weeks measured using a combination of: Patient general health assessment on a visual analog scale (0-100 mm), IJA count of 28 joints for swelling and tenderness, and ESR value

Secondary outcome measures
1. Number of patients in clinical remission (DAS28ESR ≤2.6) after 12 weeks measured using a combination of: Patient general health assessment on a visual analog scale (0-100 mm), IJA of 28 joints for pain and tenderness, and ESR value
2. Patient-reported outcome measures after 12 weeks & 24 weeks:
2.1. Elderly Mobility Scale (EMS)
2.2. VAS scales from 0 to 100 to measure General health, global pain, disease activity
2.3. HAQ-DI, a measure of the ability to perform daily activities
3. Number of patients in imaging remission (PD=0) after 24 weeks measured using ultrasound scan
4. Number of patients with normal naïve CD4+ T-cells at 24 weeks measured using flow cytometry
5. Cumulative amount of corticosteroid use at 24 weeks usually measured in prednisolone equivalent cumulative dose

Overall study start date
28/02/2020

Completion date
31/07/2025

Eligibility

Key inclusion criteria
1. Subject has a diagnosis of RA as defined by the new ACR/EULAR 2010 classification criteria
2. Newly diagnosed (within 12 weeks)
3. Active disease at screening (DAS28ESR ≥3.2 or clinical evidence of synovitis i.e. at least one swollen joint)
4. Anti-citrullinated protein antibody (ACPA) positive
5. Male & female subjects ≥18 years old
6. DMARD (disease modifying anti-rheumatic drug) naïve
7. No use of intra-muscular, intra-articular or oral corticosteroids 4 weeks prior to screening
8. All male and female subjects biologically capable of having children must agree to use a reliable method of contraception for the duration of the study and 24 weeks after the end of the study period. Acceptable methods of contraception are surgical sterilisation, oral, implantable or injectable hormonal methods, intrauterine devices or barrier contraceptives.
9. Patients must have the capacity and be willing to provide written informed consent and comply with the requirements of the protocol
10. Subjects should be deemed to be in good health with respect to clinical examination and screening blood tests, including full blood count (FBC), urea and electrolytes (U&E), and liver functions tests (LFT) – see exclusion criteria for further details.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
90 Years

Sex
Both

Target number of participants
106

Total final enrolment
106

Key exclusion criteria
1. Use of any additional investigational medications or products within 4 weeks of screening (including prior to screening)
2. Use of intra-muscular/intra-articular or oral corticosteroids within 4 weeks prior to screening
3. Use of more than one NSAID, or increase in dose of NSAIDs within 24 hours before the

screening visit.
4. Live vaccine within <4 weeks prior to screening
5. Pregnant/lactating women or planning pregnancy within 24 weeks of last protocol treatment
6. Planned surgery within the study period (requiring omission of study medication > 4 weeks
7. The presence of other comorbidities, which the physician deems as significant to interfere with evaluation (musculoskeletal condition such as osteoarthritis & fibromyalgia)
8. Diagnosis of another inflammatory arthritis or connective tissue disease (e.g. psoriatic arthritis or Ankylosing spondylitis, primary Sjögren's syndrome, systemic sclerosis, systemic lupus erythematosus, polymyositis)
9. Concomitant severe infection requiring intravenous 4 weeks prior to screening
10. Any contraindication to conventional DMARD's/anti-TNF therapy
11. Patients with abnormal liver function at the time of screening or abnormal blood tests as shown by:
11.1. Aminotransferase (AST) / alanine aminotransferase (ALT) > 3x upper limit of normal (ULN) OR Bilirubin 50µmol/L
11.2. Serum Creatinine > 175 umol/L
11.3. eGFR below 30ml/L/min/1.73m²
11.4. neutrophils < 2000 x 10^6/L
11.5. Platelets < 125 x 10^9/L
11.6. Haemoglobin < 90 g/L for males and < 85 g/L for females

Date of first enrolment
05/03/2020

Date of final enrolment
08/04/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Leeds Institute of Cardiovascular and Metabolic Medicine
2nd Floor, Chapel Allerton Hospital Chapeltown Road
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Sponsor information

Organisation
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Sponsor type
University/education

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

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Industry

Funder Name
Samsung

Alternative Name(s)
Samsung Electronics, Samsung Electronics Co., Ltd., Samsung Group,

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Korea, South

Results and Publications

Publication and dissemination plan
The success of the trial depends upon the collaboration of all patients. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributor ship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be

based only on substantial contribution to: Conception and design, or acquisition of data, or analysis and interpretation of data, page drafting the article or revising it critically for important intellectual content, and final approval of the version to be published, and that all these conditions must be met (www.icmje.org).
In light of this, the Chief Investigator, and relevant staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.
To maintain the scientific integrity of the trial, data will not be released prior to the end of the trial, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee or the Chief Investigator. In addition, individual collaborators must not publish data directly relevant to the questions posed in the trial until the main results of the trial have been published and following written consent from the Sponsor.

Intention to publish date
31/07/2026

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.

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