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Targeting the rheumatoid arthritis synovial fibroblast via cyclin dependent kinase inhibition - an early phase trial

Submission date
26/09/2014

Recruitment status
No longer recruiting

Registration date
26/09/2014

Overall study status
Completed

Last Edited
24/10/2023

Condition category
Musculoskeletal Diseases

[X] Prospectively registered

[X] Protocol

[X] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Rheumatoid arthritis is a long-term condition causing pain, swelling and stiffness in the joints. The main aim of this study is to find out how much of the drug seliciclib can be given to patients with Rheumatoid Arthritis (RA) who have active RA despite treatment with anti-TNF monotherapy.

Who can participate?
Adult patients with rheumatoid arthritis

What does the study involve?
In stage 1, patients are grouped into seven groups of three patients each. They receive 200mg, 400mg, 600mg, 800mg or 1000mg seliciclib once daily for 4 consecutive days every week for 4 cycles. This determines the highest dose of seliciclib for stage 2. In stage 2, 18 participants receive seliciclib at the dose found in stage 1 for 12 cycles. Blood samples are taken during the study and in stage 2 small biopsies (samples) are taken from the lining of one of the joints (synovial biopsy) and participants may have an optional PET-CT (positron emission tomography-computerized tomography) scan.

What are the possible benefits and risks of participating?
There may be no direct benefit to participants taking part in this study although it is possible that their arthritis symptoms will improve. If seliciclib is found to be an effective treatment for rheumatoid arthritis this may result in an alternative treatment that helps people with rheumatoid arthritis who have not experienced benefit from the currently available drugs. Seliciclib has previously been successfully tested on patients with certain types of cancer, but this is the first time this drug has been used in rheumatoid arthritis. All drugs can have side effects. The most commonly occurring side-effects encountered by patients taking seliciclib in cancer studies were fatigue (tiredness) and nausea (feeling sick), in the great majority of cases the symptoms experienced were not considered severe. Possible side-effects are monitored by the study doctors and, where possible, treatment is given to relieve symptoms. It is not known whether patients with rheumatoid arthritis taking seliciclib will encounter the same side-effects

as those with cancer. Taking blood samples may cause some discomfort and minor pain, and occasionally patients feel faint during or after the procedure. Sometimes patients have some bruising where the blood has been taken. Trained members of staff perform these procedures and every effort is made to prevent these problems. A local anaesthetic is used to numb the skin and joint to minimise any discomfort during the biopsy. The doctor uses ultrasound to guide them to the part of the joint to take samples from, to minimise the chance of complications. There may be some mild bruising after the procedure. As the local anaesthetic wears off after the procedure, up to one third of patients experience mild, temporary pain or discomfort which usually disappears within 24 hours. Very rarely (with a risk of less than 1 in 500) more significant complications may occur, such as an infection of the joint or skin, bleeding into the joint, deep vein thrombosis (blood clot), neurological (nerve) damage or thrombophlebitis (inflammation of a superficial vein). The procedure may leave a small (2-3 mm or 1/8 inch) scar. PET-CT scans involve the use of x-rays and gamma rays which are forms of radiation. Exposure to radiation is associated with increasing the risk of subsequent cancer. Everyone is exposed to natural or background radiation and everyone is at risk of developing cancer at some point. The overall risk of any of us developing cancer is about 1 in 3, and the additional risk for the PET-CT scan is considered to be very small. The benefits of the increased information from the test are thought to justify the use of radiation for this purpose. The dose of radiation that a participant would be exposed to is still well within the acceptable safety limits for radiation exposure.

Where is the study run from?
The study will run at Newcastle, Birmingham, Glasgow, Middlesbrough and London (UK)

When is the study starting and how long is it expected to run for?
October 2014 to December 2023

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

Who is the main contact?
Chrissie Butcher, Chrissie.butcher@ncl.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Chrissie Butcher

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Additional identifiers

EudraCT/CTIS number
2014-001339-35

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
17409

Study information

Scientific Title
Targeting the RA synovial fibroblast via cyclin dependent kinase inhibition an early phase trial (TRAFIC): a non-randomised trial

Acronym
TRAFIC

Study objectives
Repurposing study, using an oncology drug, Seliciclib, in rheumatoid arthritis in a two-part trial to determine maximum tolerated dose and then assess clinical response at 12 weeks.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee North East Tyne and Wear South, 15/09/2014, ref: 14/NE/1075

Study design
Non-randomized; Interventional; Design type: Treatment

Primary study design
Interventional

Secondary study design
Non randomised study

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
Part 1: Participants will receive either 200mg, 400mg, 600mg, 800mg or 1000mg seliciclib once daily for 4 consecutive days every week for 4 weekly cycles*. Results from part 1 will determine the Maximum Tolerated Dose (MTD) of seliciclib for part 2.

Part 2: 18 participants will receive seliciclib (at the MTD determined in Part 1) for 12 cycles*

* one cycle equates to a week of treatment: a daily dose of seliciclib for four consecutive days followed by 3 days with no treatment.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Seliciclib

Primary outcome measure
Part 1:
1. Dose Limiting Toxicities (DLT) at baseline (BL), week 2, 3, 4 and 5
2. Adverse Events and Adverse Reactions (AE/AR) at BL week 2, 3, 4 and 5

Part 2:
1. EULAR and ACR20 response rates at screening, BL, week 2, 3, 4, 7, 10 and within 5 days of final dose
2. Macrophage number in the sub lining layer of synovium at BL and week 12
3. MRI (Rheumatoid Arthritis MRI Scoring System (RAMRIS)) at pre BL and week 12

Secondary outcome measures
Part 1:
1. Drug PK parameters and PD biomarkers in peripheral blood at BL and week 4

Part 2:
1. Drug PK parameters and PD biomarkers in peripheral blood at BL and week 12
2. PD biomarkers in synovial tissue at BL and week 12
3. Fatigue questionnaire at screening, BL, week 2, 3, 4, 7, 10 and within 5 days of final dose
4. Urinary metabolomics at screening, BL, week 2, 3, 4, 7, 10 and within 5 days of final dose
5. Rheumatoid factor (RF) and anti-CP status at screening and within 5 days of final dose
6. Optional PET scan pre BL and within 10 days post week 12 visit

Overall study start date
01/10/2014

Completion date
31/12/2023

Eligibility

Key inclusion criteria
Current inclusion criteria as of 11/08/2017:
1. Rheumatoid arthritis fulfilling the 1987 ACR or 2010 ACR/EULAR criteria
2. Age 18 years and over
3. At least 6 months' disease duration
4. ACR Functional Class I-III
5. DAS28 ≥3.2 (for Part 1 only)
6. DAS28 ≥4.0, with clinical synovitis in at least three joints, at least one of which is a joint amenable to ultrasound-guided synovial biopsy (knee, elbow, ankle, wrist, MCP or PIP joint) (for part 2 only)
7. Currently taking anti-TNF as part of standard clinical care, and have received anti-TNF therapy for at least 3 months upon entry to the study
8. Anti-TNF may be administered as either monotherapy or with background conventional DMARDs. Permitted background DMARDs are methotrexate, sulphasalazine and hydroxychloroquine, either alone or in combination, at stable dose(s) for ≥4 weeks prior to baseline visit
9. Stable dose of non-steroidal anti-inflammatory drug (NSAID) or corticosteroid (prednisolone≤7.5mg) for ≥4 weeks
10. No intramuscular glucocorticoid administration in the 4 week period prior to baseline visit
11. Willing and able to undergo MRI scanning on two occasions. (For Part 2 only)
12. Willing to undergo ultrasound guided synovial biopsy on two occasions (under local anaesthetic). (For part 2 only)

Previous inclusion criteria:
1. Rheumatoid arthritis fulfilling the 1987 ACR or 2010 ACR/EULAR criteria
2. Age 18 years or above
3. At least 6 months disease duration
4. ACR Functional Class IIII
5. DAS28 =4.0, with clinical synovitis in at least three joints, at least one of which is a joint amenable to ultrasound-guided synovial biopsy (knee, elbow, ankle, wrist, MCP or PIP joint). (For part 2 only).
6. Currently taking anti-TNF monotherapy as part of standard clinical care and have received anti-TNF therapy for at least 6 months upon entry to the study as per NICE guidelines.
7. Willing to undergo ultrasound guided synovial biopsy on two occasions (under local anaesthetic). (For part 2 only).
8. Stable dose of non-steroidal anti-inflammatory drug (NSAID) or corticosteroid (prednisolone=7.5mg) for =4 weeks.
9. No intramuscular glucocorticoid administration in the 6 week period prior to baseline visit.
10. Willing and able to undergo MRI scanning on two occasions (Part 2 only).

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 39; UK Sample Size: 39

Total final enrolment
15

Key exclusion criteria
Current exclusion criteria as of 11/08/2017:
1. If patients were previously taking leflunomide a minimum period of 20 days must have elapsed between the last dose of leflunomide and the first dose of IMP
2. Patients receiving warfarin or other anticoagulation likely to interfere with biopsy procedures (part 2 only)
3. Use of other investigational medicinal products within 30 days prior to trial entry (defined as date of recruitment into trial)
4. Serious or unstable co-morbidity deemed unsuitable by PI e.g. COPD, cardiac failure, other significant autoimmune disease
5. Patients must not drink more than 2 units of alcohol per day and no more than 10 units of alcohol per week during the trial and for a 4 week period after completion of the trial
6. Known active infection at screening visit or at baseline (except fungal nail infection)
7. Infection requiring hospitalization or IV antibiotics within 6 weeks prior to baseline
8. History of recurrent or chronic infection
9. Recent live vaccination (within 6 weeks of baseline)
10. Hb<10g/dL; neutrophils< 1.5 x109/L; platelets <100x109/L
11. Patients taking ketoconazole, voriconazole, erythromycin, clarithromycin.
12. ALT/AST/ALP>1.5x upper limit of normal
13. Glomerular filtration rate < 60ml/minute (Cockroft formula)
14. Major surgery within 8 weeks prior to baseline or planned within 3 months from baseline
15. Pregnancy, or women planning to become pregnant within the trial period, or women who are breastfeeding
16. Females or males of child bearing potential unwilling to use two forms of adequate contraception whilst taking the IMP and for one month afterwards

Previous exclusion criteria:
1. Patients currently taking, and planning to continue, methotrexate, other non-biologic DMARDs or biologic therapies other than anti-TNF therapy. For patients recently receiving non-biologic DMARD therapy at least 8 weeks must have elapsed following discontinuation of treatment prior to enrolment into the current study. If patients were previously taking leflunomide this must have been washed out with cholestyramine or activated charcoal according to leflunomides Summary of Product Characteristics
2. Patients receiving warfarin or other anticoagulation likely to interfere with biopsy procedures (part 2 only)
3. Previous participation in this trial (for Part 2 participants)
4. Use of other investigational medicinal products within 30 days prior to trial entry (defined as date of recruitment into trial)
5. Serious or unstable co-morbidity deemed unsuitable by PI e.g. COPD, cardiac failure, other

significant auto-immune disease
6. Patients must not drink more than 2 units of alcohol per day and no more than 10 units of alcohol per week during the trial and for a 4 week period after completion of the trial
7. Known active infection at screening visit or at baseline (except fungal nail infection)
8. Infection requiring hospitalization or IV antibiotics within 6 weeks prior to baseline
9. History of recurrent or chronic infection
10. Recent live vaccination (within 6 weeks of baseline)
11. Hb<10g/dL; neutrophils< 1.5 x109/L; platelets <100x109/L
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15. Major surgery within 8 weeks prior to baseline or planned within 3 months from baseline
16. Pregnancy, or women planning to become pregnant within the trial period, or women who are breastfeeding
17. Females or males of child-bearing potential unwilling to use two forms of adequate contraception whilst taking the IMP and for one month afterwards

Date of first enrolment
01/10/2014

Date of final enrolment
20/06/2022

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
High Heaton
Newcastle Upon Tyne
United Kingdom
NE7 7DN

Study participating centre
University Hospital Birmingham NHS Foundation Trust
Queen Elizabeth Medical Centre
Edgbaston

Birmingham
United Kingdom
B15 2TH

Study participating centre
NHS Greater Glasgow and Clyde
Glasgow Royal Infirmary
Castle Street
Glasgow
United Kingdom
G4 0SF

Study participating centre
Barts Health NHS Trust
Mile End Hospital
Bancroft Road
London
United Kingdom
E1 4DG

Study participating centre
South Tees Hospitals NHS Foundation Trust
The James Cook University Hospital
Marton Road
Middlesborough
United Kingdom
TS4 3BW

Sponsor information

Organisation
Newcastle Hospitals Foundation NHS Trust (UK)

Sponsor details
Newcastle Joint Research Office
Level 1 Regent Point
Regent Farm Road
Gosforth
Newcastle Upon Tyne

England
United Kingdom
NE3 3HD

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council (MRC) (UK); Grant Codes: MR/L005123/1

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
Protocol publication is in progress and is not already available online. Details of additional documents can be supplied on request. Planned publication at conferences and in peer reviewed scientific journals.

Intention to publish date
31/05/2021

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	26/06/2020	29/06/2020	Yes	No
Results article		09/03/2021	05/05/2021	Yes	No
Statistical Analysis Plan	statistical design and analysis plan	06/07/2021	08/07/2021	No	No
HRA research summary			28/06/2023	No	No