ISRCTN16371380 https://doi.org/10.1186/ISRCTN16371380

BIO-FLARE: to improve understanding of why some people with rheumatoid arthritis experience flares, and what is happening to the joint when they occur

Submission date 08/04/2019	**Recruitment status** No longer recruiting	✓ Retrospectively registered ? Protocol not yet added ? SAP not yet added ? Results not yet added and study completed for more than 2 years ? Raw data not yet added ✓ Study completed
Registration date 27/06/2019	**Overall study status** Completed	
Last Edited 20/12/2023	**Condition category** Musculoskeletal Diseases	

Plain English Summary

Background and study aims
Rheumatoid arthritis (RA) is a relapsing and remitting autoimmune disease. Whilst a considerable amount is understood about factors which may contribute to the development of RA and about disease mechanisms, nothing is known of the factors that trigger disease relapses (flares), converting the disease from an inactive to an active state. The underpinning mechanism (s) of flare has been difficult to study because they occur unpredictably. The researchers will study patients who flare to capture signals that may determine which patients are most likely to flare, as well as understand the biology behind the phenomenon of flare itself. This may eventually lead to future work on treatable targets in disease management.

Who can participate?
Patients in remission from RA on traditional disease-modifying therapies (DMARDs), namely methotrexate, sulfasalazine, and/or hydroxychloroquine

What does the study involve?
The patients stop taking their DMARDs and are closely followed-up by the research team. Previous research suggests 50% will experience flare, while the remainder will remain in remission. They have regular assessment of their disease activity (physical examination and questionnaires), along with clinical and research blood samples taken. Urine samples are taken at each visit. If a patient in the study experiences a flare, they have an ultrasound-guided synovial biopsy taken under local anaesthetic. Samples of blood, urine and synovium (joint lining) are analysed for gene expression, synovial cell subtypes, molecular pathways, immune cell profiles, and antibody status. After 6 months, if a patient does not experience a flare, they are referred back to their usual rheumatologist and may be able to remain off of DMARDs. If a patient experiences flare at any time, they receive steroid treatment and be referred back to their usual rheumatologist to restart their DMARDs.

What are the possible benefits and risks of participating?
Based on previous research performed at other centres and our own, it is expect that up to half of the patients with RA in remission may be able to stop their DMARD medication without an increase in their arthritis activity. DMARD medications have an associated small risk of serious side effects. By participating in this study patients will be helping to provide important data that may help to identify markers that can predict when, how and which people with RA will flare. While it may not necessarily be of direct benefit to the participant, it is hoped that this study will help us to understand more about rheumatoid arthritis, how it develops and what treatments will be effective. There is a risk that when patients stop taking their DMARD medication their arthritis may become more active, causing joint pain and swelling. It is difficult to predict the exact chance of this happening, but previous studies suggest that this may occur in around half of the patients. Patients who experience disease activity will be seen at short notice to confirm, before being referred rapidly back to their rheumatology team who would be able to restart DMARD medications. A steroid injection/course of steroid tablets may also be offered to help settle the arthritis

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

When is the study starting and how long is it expected to run for?
July 2018 to June 2021

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

Who is the main contact?
Katie Gray, Katie.Gray@newcastle.ac.uk

Contact information

Type(s)
Public

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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Protocol/serial number
CPMS 36953, MR/N026977/1

Study information

Scientific Title
BIOlogical Factors that Limit sustAined Remission in rhEumatoid arthritis (the BIO-FLARE study)

Acronym
BIO-FLARE

Study hypothesis
The aim of this study is to measure the immune dysfunction that patients with RA undergo immediately prior to experiencing a flare. The researchers will do this by analysing immune cell expression, autoantibody levels and subtypes, synovial (joint lining) tissue composition, metabolic and genetic factors.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 06/02/2018, North East - Newcastle & North Tyneside 1 Research Ethics Committee (HRA Jarrow, Jarrow Business Centre, Room 001, Rolling Mill Road, Jarrow, NE32 3DT; Tel: +44 (0)207 1048 084; Email: nrescommittee.northeast-newcastleandnorthtyneside1@nhs.net), ref: 17 /NE/0386

Study design
Non-randomised; Both; Design type: Treatment, Drug, Management of Care, Cohort study

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

Condition
Rheumatoid arthritis

Interventions
In this study, the researchers will recruit patients in remission from RA on traditional disease-modifying therapies (DMARDs), namely methotrexate, sulfasalazine, and/or hydroxychloroquine. These patients will then discontinue their DMARDs and be closely followed-up by the research team. Previous research suggests 50% will experience flare, while the remainder will remain in remission. They will have regular assessment of their disease activity (physical examination and questionnaires), along with clinical and research blood samples taken. Urine samples will be taken at each visit. If a patient in the study experiences a flare, they will have an ultrasound-guided synovial biopsy taken under local anaesthetic. Samples of blood, urine and synovium (joint lining) will be analysed for gene expression, synovial cell subtypes, molecular pathways, immune cell profiles, and antibody status.

After 6 months, if a patient does not experience a flare, they will be referred back to their usual rheumatologist and may be able to remain off of DMARDs. If a patient experiences flare at any time, they will receive steroid treatment and be referred back to their usual rheumatologist to restart their DMARDs.

Intervention Type
Other

Primary outcome measure
The proportion of patients who experience a confirmed flare as described in Section 5.9 of the Protocol (DAS28-CRP ≥ 3.2 or DAS28-CRP ≥ 2.4 on two occasions 7-14 days apart) at any time up

to/including 24 weeks after cessation of treatment:
1. Disease flare occurrence (proportion at 24 weeks)
2. Time to disease flare (also used to estimate proportion at 24 weeks)

Secondary outcome measures
1. Individual components of the primary outcome of 'flare' (DAS28-CRP ≥ 3.2 or DAS28-CRP ≥ 2.4 on two occasions 7-14 days apart) at any time up to/including 24 weeks after cessation of treatment. The individual components are:
1.1. Tender joint count
1.2. Swollen joint count
1.3. Visual analogue scale (patient)
1.4. CRP
2. Immune cell subsets and their activation status. The researchers will be using conventional fluorescence-based flow cytometry and also mass cytometry (CyTOF) to measure the immune cell subsets, specifically the T cells, B cells, dendritic cells and monocytes. This will be done in batches to reduce batch effect and cytometer drift. All of the samples from one patient will be analysed at a single timepoint (following stabilisation and freezing of the samples)
3. Autoantibody profiles. The researchers will transfer serum samples to their industrial partner Orgentec for assessment of antibody specificity. Antigen affinity of key autoantibodies will be measured using BIACORE surface plasmon resonance or similar techniques. Circulating cytokines will be measured in serum and/or plasma using immunoassays or ELISAs
4. Epigenetic profiles: high-order chromatin structures in immune cells, such as PBMC, CD4+ T cells and CD14+ monocytes, will be evaluated on the EpiSwitchTM PCR platform (in partnership with Oxford Biodynamics). Differentiating signatures will be refined using binary EpiswitchTM scores and logistical regression modelling, and the accuracy and robustness of the predictive model determined by ROC analysis.
5. T-cell receptor excision circles as a marker of thymic activity
6. Synovial cell lineages present, including stromal cell subtypes, as well as their associated cytokines and chemokines. Stromal and leukocyte subpopulations will be sorted from synovial biopsy samples by flow cytometry and DNA/RNA/miRNA will be extracted for further downstream transcriptomic analysis. Where possible, key findings will be validated by histology in matched tissue sections, alongside appropriate in vitro functional assays
Samples are collected September 2018 – October 2020

Overall study start date
01/04/2017

Overall study end date
30/06/2021

Eligibility

Participant inclusion criteria
1. Diagnosis of rheumatoid arthritis according to the 1987 ACR or 2010 ACR/EULAR classification criteria (applied at any time since diagnosis)
2. Current single or combination use of methotrexate, sulfasalazine and/or hydroxychloroquine. No escalations in dose are permitted in the six months prior to enrolment, although dose reductions in this time are permitted
3. Arthritis currently in remission, as judged clinically by referring healthcare professional
4. Patient and referring clinician willing to consider DMARD withdrawal
5. Age > 16 at time of first diagnosis with RA, and > 18 at time of recruitment

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 181; UK Sample Size: 181

Total final enrolment
137

Participant exclusion criteria
1. Inability to provide informed consent
2. Current participation or follow-up within another ongoing clinical interventional trial
3. Current pregnancy, or pregnancy planned within next 6 months
4. Major surgery planned within next 6 months (definition of major surgery at discretion of screening clinician)
5. Immunisation within the past 4 weeks
6. Received steroids within past 3 months (oral, parenteral or intra-articular)
7. Use of any DMARD other than methotrexate, sulfasalazine or hydroxychloroquine within the past 6 months (or past 12 months for leflunomide)
8. Increase in the dose of any DMARD in the 6 months prior to screening.
9. Use of biologic therapy within the past 6 months
10. Prior use of cell-depleting biologic therapies
11. Haemoglobin < 9g/L at baseline
12. Contraindication to synovial biopsy – e.g. bleeding diathesis or prolonged use of anticoagulant therapy (warfarin or other direct oral anticoagulants e.g. rivaroxaban)
13. Active crystal arthropathy
*Topical, inhaled and intra-nasal steroids are permitted

Recruitment start date
02/07/2018

Recruitment end date
14/12/2020

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
NHS Greater Glasgow and Clyde Health Board
NHS Greater Glasgow and Clyde
Clinical Research Facility, Glasgow Royal Infirmary
New Lister Building, 10 Alexandra Parade
Glasgow
United Kingdom
G31 2ER

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Trust HQ, PO Box 9551
Queen Elizabeth Medical Centre
Edgbaston
Birmingham
United Kingdom
B15 2TH

Study participating centre
Sandwell and West Birmingham Hospitals NHS Trust
City Hospital
Dudley Road
Birmingham
United Kingdom
B18 7QH

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
Northumbria Healthcare NHS Foundation Trust
Rake Lane
North Shields

United Kingdom
NE29 8NH

Study participating centre
Gateshead Health NHS Foundation Trust
Queen Elizabeth Hospital
Gateshead
United Kingdom
NE9 6SX

Study participating centre
City Hospitals Sunderland NHS Foundation Trust
Sunderland Royal Hospital
Kayll Road
Sunderland
United Kingdom
SR4 7TP

Sponsor information

Organisation
The Newcastle Upon Tyne Hospitals NHS Foundation Trust

Sponsor details
Freeman Hospital
Freeman Road
High Heaton
Newcastle-Upon-Tyne
England
United Kingdom
NE7 7DN

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05p40t847

Funder(s)

Funder type

Research council

Funder Name
Medical Research Council

Alternative Name(s)
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
1. Peer-reviewed scientific journals
2. Internal report
3. Conference presentation
4. Anonymous RNA sequence data will be made freely available online via the publicly-accessible National Institutes of Health (NIH) Gene Expression Omnibus (GEO)

Intention to publish date
30/12/2024

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?
HRA research summary			28/06/2023	No	No