ISRCTN18217497 https://doi.org/10.1186/ISRCTN18217497

A trial to compare current standard treatment of Immune Checkpoint Inhibitor-induced Inflammatory Arthritis (ICI-IA), with treatment using adalimumab without glucocorticoids

Submission date
29/08/2024

Recruitment status
Recruiting

Registration date
28/11/2024

Overall study status
Ongoing

Last Edited
16/01/2025

Condition category
Musculoskeletal Diseases

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

Plain English Summary
Background and study aims
Immune Checkpoint Inhibitors (ICI) are drugs that block 'off' signals in our immune system to help it fight cancer. A side effect of ICI treatment is that inflammation may occur in parts of the body unrelated to the cancer such as the joints (arthritis). ICI induced arthritis affects at least 5% of treated cancer patients and has a big impact upon quality of life. It may persist even after the ICI is stopped and may require treatment with drugs to suppress the immune system. The typical approach is to start with 'steroid' tablets (prednisolone) then gradually try other treatments if these fail with a 'trial and error' approach.
Aim: To compare treatment with an anti-TNF (adalimumab) drug used first-line, to current standard of care starting with prednisolone.

Who can participate?
The trial is for patients aged over 18 years who have been treated with ICI and who, based on pre-defined inclusion/exclusion criteria, are deemed eligible for the trial.
We will recruit patients with ICI-induced inflammatory arthritis (ICI-IA), for whom the treating doctors would prescribe Prednisolone.

What does the study involve?
Treatment: Patients will be either given standard of care (prednisolone), or adalimumab. Treatments will be gradually reduced once the arthritis is controlled, or further treatment given if needed. We will compare the proportion of patients in each treatment group who have no arthritis and no steroid use at 24 weeks and 48 weeks. We will also compare how fast the arthritis is controlled. We will continue to follow patients until 48 weeks to compare arthritis activity, quality of life, ability to function, total amount of immunosuppressive drugs received over time, number of ICI doses missed, new immune-related side effects, cancer outcomes and survival.

What are the possible benefits and risks of participating?
By taking part, patients will be helping us to understand if there is a difference between treatment arms in:
• the number of patients who are free of joint swelling after 24 weeks without having to use steroids such as prednisolone
• how quickly patients' arthritis gets better
If allocated to the adalimumab arm, patients may see an improvement in their arthritis without having to use prednisolone (steroid tablets).
In the long-run, we also want to also understand if early use of adalimumab may help patients to become free of arthritis and arthritis treatments. We will also collect data on the relative safety of the two treatment approaches. By taking part, you will be helping to see if Anti-TNF, in the form of adalimumab, without steroids could be used in the future as a first-line treatment for people with ICI-IA. In other words, if it should become standard of care

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

When is the study starting and how long is it expected to run for?
August 2024 to August 2028

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK).

Who is the main contact?
Prof. Benjamin Fisher, REACT@trials.bham.ac.uk

Contact information

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1009034

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
RG_23-121, IRAS 1009034, CPMS 62388

Study information

Scientific Title
REmission induction of Arthritis caused by Cancer ImmunoTherapy (REACT): a randomised, multicentre trial to guide initial therapy for immune checkpoint inhibitor-induced inflammatory arthritis

Acronym
REACT

Study hypothesis
Primary objective:
To determine the proportion of patients in glucocorticoid-free ICI-IA remission 24 weeks from initiation of anti-TNF compared to initial glucocorticoids alone.

Secondary objectives:
1. To determine the time to ICI-IA remission for first-line use of anti-TNF compared to initial Glucocorticoids alone
2. To determine the proportion of patients in drug free remission 48 weeks from initiation in each arm
3. To assess cumulative exposure of patients on each arm to immunosuppression for ICI-IA
4. To assess disease activity in each arm
5. To measure quality of life in each arm
6. To assess incidence of other IrAEs in each arm
7. To assess adverse events (AEs) attributable to the ICI-IA interventions in each arm, and serious adverse events (SAEs)
8. To assess outcomes of malignancy in each arm

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 31/10/2024, East Midlands - Leicester South Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8193 ; leicestersouth.rec@hra.nhs.uk), ref: 24/EM/0202

Study design
Interventional randomized parallel group controlled trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Condition
Immune Checkpoint Inhibitor-induced Inflammatory Arthritis (ICI-IA)

Interventions
Patients will be randomised using an online tool to either:

Arm A: Standard of care. Reducing course of prednisolone with a starting dose of 20mg/day or 40mg/day decided prior to randomisation (by the treating rheumatologist). Guidance on prednisolone tapering, management in case of non-response or relapse on prednisolone withdrawal is provided in the Protocol. If arthritis fails to remit, further therapy may be provided according to clinical practice and ASCO recommendations. This may include further oral prednisolone +/- oral csDMARDs such as methotrexate, leflunomide or hydroxychloroquine, titrating up to a biologic (anti-TNF or anti-IL6R) if required. With disease control, therapy will be titrated down to the minimum amount required to control synovitis if drug cessation not possible.

Arm B: Adalimumab without glucocorticoids. 40mg every other week by subcutaneous injection. Investigators may stop adalimumab at week 24 or after, provided there has been evidence of sustained remission defined as the absence of synovitis on clinical examination on at least 2 consecutive occasions 4 weeks apart. If synovitis recurs following this, then adalimumab can be restarted. With inadequate response at week 12 or after, the dose of adalimumab can be increased to 80mg every other week. If arthritis fails to remit, then further therapy may be required in addition to adalimumab, or in place of adalimumab if the participant does not respond. Further therapy may include oral prednisolone, oral csDMARD such as methotrexate, leflunomide or hydroxychloroquine, or an alternative biologic such as anti-IL6R. With disease

control, therapy will be titrated down to the minimum amount required to control synovitis if drug cessation not possible although adalimumab will not be stopped before week 24 except in the event of non-response or toxicity.

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacogenetic, Therapy

Phase
Phase III

Drug/device/biological/vaccine name(s)
Prednisolone, adalimumab

Primary outcome measure
Glucocorticoid-free arthritis remission rate at 24 weeks where a patient is classed as being in glucocorticoid-free arthritis remission if: (i) No use of systemic or intra-articular glucocorticoids (except when used for adrenal insufficiency) within 4 weeks prior to assessment at 24 weeks and (ii) Absence of synovitis on clinical examination

Secondary outcome measures
1. Time to remission defined as time from randomisation to first absence of synovitis on clinical examination at Weeks 0, 4, 8, 12, 16, 20, 24, 32, 40, 48
2. Arthritis remission measured as absence of synovitis at 24 and 48 weeks
3. Drug-free arthritis remission measured as absence of synovitis with no ICI-IA treatment in the previous 4 weeks at 48 weeks
4. 66/68 swollen and tender joint counts at Screening, Weeks 0, 4, 8, 12, 16, 20, 24, 32, 40, 48
5. Patient arthritis disease activity global VAS (0-100) at Weeks 0, 4, 8, 12, 16, 20, 24, 32, 40, 48
6. Physician arthritis disease activity global VAS (0-100) at Weeks 0, 4, 8, 12, 16, 20, 24, 32, 40, 48
7. Fatigue VAS (0-100) at Weeks 0, 4, 8, 12, 16, 20, 24, 32, 40, 48
8. Pain VAS (0-100) at Weeks 0, 4, 8, 12, 16, 20, 24, 32, 40, 48
9. Cumulative exposure to glucocorticoids over 24 and 48 weeks
10. Cumulative exposure to anti-TNF (or other biological DMARD or targeted synthetic DMARD) over 24 and 48 weeks
11. Cumulative exposure to other conventional synthetic DMARD over 24 and 48 weeks
12. Cumulative exposure to ICI over 24 and 48 weeks
13. Adverse events related to arthritis interventions (Adverse reactions) using CTCAE version 5 at Weeks 0, 4, 8, 12, 16, 20, 24, 32, 40, 48
14. Serious adverse events using CTCAE version 5 at Weeks 0, 4, 8, 12, 16, 20, 24, 32, 40, 48
15. Other IrAEs (number of organs and toxicity level) using CTCAE version 5 at Weeks 0, 4, 8, 12, 16, 20, 24, 32, 40, 48
16. Functional status as assessed by HAQ-DI at Weeks 0, 12, 24, 48
17. Health-related quality of life as assessed by EQ-5D-5L at Weeks 0, 12, 24, 48
18. Well-being as assessed by ICECAP-A questionnaire at Weeks 0, 12, 24, 48
19. Investigator Assessed Cancer Status as complete response, partial response, stable disease, or disease progression at Weeks 0, 4, 8, 12, 16, 20, 24, 32, 40, 48
20. Cancer response at weeks 24 and 48 as defined by RECIST 1.1
21. Overall survival as time to death at Weeks 0, 4, 8, 12, 16, 20, 24, 32, 40, 48
22. Progression free survival of cancer as time to progression (defined as first occurrence of

disease progression via cancer response using RECIST 1.1 or investigator assessed cancer status), or death at Weeks 0, 4, 8, 12, 16, 20, 24, 32, 40, 48

Overall study start date
23/08/2024

Overall study end date
31/08/2028

Eligibility

Participant inclusion criteria
1. Informed consent must be obtained prior to any trial related procedures being performed
2. Able to understand and comply with the requirements of the trial
3. Inflammatory arthritis with at least one clinically swollen joint at screening
4. Male and female participants aged ≥18 years
5. Patient treated with ICI (concurrent with or last dose within 12 weeks prior to onset of inflammatory arthritis)
6. Decision of two treating physicians, one of whom must have expertise in the management of inflammatory arthritis, that treatment with systemic glucocorticoids would be appropriate management for their inflammatory arthritis. Details of the physicians who have decided this will be documented in the source data.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
70

Participant exclusion criteria
1. If currently using oral glucocorticoids, use must not exceed 2 weeks prior to baseline (except hydrocortisone for adrenal replacement where longer term use is allowed).
2. Pre-existing (prior to first use of ICI) inflammatory arthritis due to rheumatic autoimmune disease
3. The arthritis not considered, by the treating physician, to be ICI-IA
4. Active or latent TB (unless having fulfilled chemoprophylaxis management according to local guidelines), or other chronic infection considered a contraindication to anti-TNF
5. Positive test for HIV, HCV (evidenced by both positive anti-HCV antibody and HCV-RNA in serum), Hepatitis B Virus (HBV) as evidenced by positive hepatitis B surface antigen (HBsAg) or anti-hepatitis B core antibodies (HBcAb) (further information on hepatitis B eligibility in Section X) within last 6 months

6. History of demyelinating disorder
7. Hypersensitivity to the active substance or to any of the excipients in the Adalimumab preparation
8. Any medical, surgical or psychiatric condition that the investigator believes may jeopardise the participant, or the validity of the trial results, were they to participate in the trial
9. Moderate to severe heart failure (New York Heart Association III/IV)
10. Concurrent use of other biological immunosuppressive drugs or Janus kinase inhibitors.
11. Live vaccine received less than 4 weeks before first dose of trial drug
12. Any current severe infection
13. Known ocular herpes simplex

Recruitment start date
31/08/2024

Recruitment end date
01/09/2026

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Queen Elizabeth Hospital
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Sponsor information

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University of Birmingham

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ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Internal report
Conference presentation
Publication on website
Other publication
Submission to regulatory authorities

Intention to publish date
31/08/2029

Individual participant data (IPD) sharing plan

Access to study data will be in accordance with the University of Birmingham and the Cancer Research UK Clinical Trial Unit (CRCTU) data sharing policy: https://www.birmingham.ac.uk /research/crctu/data-sharing-policy.aspx. The CRCTU has a defined procedure in place for data sharing which ensures that the necessary legal and ethical requirements are followed, this policy which is based on guidelines published by the Information Commissioners Office and the Medical Research Council (MRC). Please email the trial mailbox REACT@trials.bham.ac.uk in the first instance and this can then be passed on to the relevant person.

IPD sharing plan summary

Available on request