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Can IL-1ra reduce inflammation and improve clinical outcome following aneurysmal SAH?

Submission date
04/12/2017

Recruitment status
No longer recruiting

Registration date
14/12/2017

Overall study status
Completed

Last Edited
29/11/2023

Condition category
Nervous System Diseases

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

Plain English summary of protocol

Background and study aims
Subarachnoid haemorrhage (SAH) is a bleed onto the surface of the brain. It is usually caused when a weakness (aneurysm) in the wall of a blood vessel within the brain suddenly bursts. It affects up to 6,000 people every year in the UK. Up to half of all patients do not survive long enough to receive hospital treatment and those who do survive, often suffer long-term issues that impact on their daily life. In the hours and days after SAH, patients are at risk of further brain damage due to inflammation (swelling). A protein called interleukin-1 (IL-1) is the main culprit and this triggers a number of other chemicals in the circulation which may lead to physical symptoms similar to stroke but can also cause problems with language, mood, anxiety and fatigue all of which impact most on recovery and returning to work. The effect of IL-1 can be blocked, reduced or even reversed by another protein present naturally in our body; interleukin-1 receptor antagonist (IL-1Ra). A company has produced a man-made version of IL-1Ra, which has been used for many years as an anti-inflammatory treatment for rheumatoid arthritis. Inflammation occurs very early after the initial haemorrhage and can continue for up to 21 days, which means IL-1Ra should be given early and through the risk period to prevent or reduce these symptoms. Our group has successfully tested IL-1Ra in patients with subarachnoid haemorrhage and found it reduces inflammation in the circulation and brain and we now want to establish whether IL-1Ra improves recovery after subarachnoid haemorrhage. The aim of this study is to treat patients with SAD using IL-1Ra subcutaneously twice daily to see if this can improve clinical outcomes.

Who can participate?
Adults aged 18 and older who have SAH.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group receive subcutaneous injections of IL-1Ra twice daily for up to 21 days from the onset of their symptoms. Those in the second group receive a placebo (a dummy) twice daily for 21 days. All participants continue to receive the standard care for subarachnoid haemorrhage and participation in this study will not affect or delay this care. Participants provide blood samples

before the treatment, and after 3-5 days to measure levels of inflammatory markers in the blood. Participants are followed up for safety for 30 days and are followed up for six months to assess the impact of the treatment.

What are the possible benefits and risks of participating?
As this is a phase III study it will be made clear to participants that there is no evidence of benefit at this stage. Participants will also be advised that as this study is double-blind and randomised and it will not be known if they will receive study drug or placebo. Evidence from earlier phase studies showed that the study drug reduces inflammation associated with SAH and is safe to use. The results of this study will provide evidence whether reducing inflammation improves outcome and participants may be helping to provide the evidence that may change treatment for SAH in the future.

Where is the study run from?
This study is being run by the University of Manchester (UK) and takes place in hospitals in the UK.

When is the study starting and how long is it expected to run for?
July 2015 to April 2024

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Jane Pearson, SCIL@manchester.ac.uk

Study website
https://sites.manchester.ac.uk/scil/

Contact information

Type(s)
Scientific

Contact name
Ms Jane Pearson

Contact details
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Additional identifiers

EudraCT/CTIS number
2016-003725-42

IRAS number
214739

ClinicalTrials.gov number
NCT03249207

Secondary identifying numbers
CPMS 35757, IRAS 214739

Study information

Scientific Title
Does Interleukin-1 Receptor Antagonist Improve Outcome following aneurysmal Subarachnoid Haemorrhage (aSAH)? A Phase III trial

Acronym
SC IL-1Ra in SAH - phase III trial

Study objectives
Treatment with IL-1Ra subcutaneously (SC) twice daily to patients with aneurysmal subarachnoid haemorrhage will improve clinical outcome at 6 months.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 03/11/2017, North West - Haydock Research Ethics Committee (3rd Floor - Barlow House, 4 Minshull Street, Manchester, M1 3DZ, United Kingdom; +44 (0)20 7104 8137; haydock.rec@hra.nhs.uk), ref: 17/NW/0581

Study design
Randomised; Interventional; Design type: Treatment, Drug

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 below to request a patient information sheet

Health condition(s) or problem(s) studied
Stroke

Interventions
This is a double-blind, placebo-controlled trial. Patients with aneurysmal subarachnoid haemorrhage receive subcutaneous injections of IL-1Ra or placebo twice daily for up to 21 days from the onset of their symptoms. Blood samples are taken before the start of the intervention and after 3-5 days to measure levels of inflammatory markers in the blood. Participants are followed up for safety until day 30 after the start of the intervention and are followed up after six months to assess the impact of the intervention on clinical outcome.

Intervention Type
Other

Phase
Phase III

Primary outcome measure
Clinical outcome is measured using the modified Rankin Scale (mRS) questionnaire at 6 months.

Secondary outcome measures
1. Mood is measured using the Hospital Anxiety and Depression Scale questionnaire at 6 months
2. Fatigue is measured using the GM-SAT Fatigue question and Fatigue Severity Score questionnaire at 6 months
3. Quality of life is measured using the EQ-5D-5L questionnaire at 6 months

Overall study start date
15/07/2015

Completion date
30/04/2024

Eligibility

Key inclusion criteria
1. Patients with CT positive spontaneous SAH admitted to a participating neurosurgical centre where written informed consent can be obtained and study drug can be administered within 72 hours of ictus
2. No concomitant health problems that, in the opinion of the PI or designee, would interfere with participation, administration of study drug or assessment of outcomes including safety
3. Willing and able to give informed consent or consent available from a patient representative for trial inclusion including agreement in principle to receive study drug and undergo all study assessments
4. Male or female aged 18 years or above

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 1000; UK Sample Size: 1000

Total final enrolment
612

Key exclusion criteria
Current participant exclusion criteria as of 14/08/2023:
1. Unconfirmed or uncertain diagnosis of spontaneous SAH
2. Known active tuberculosis or active hepatitis
3. Known active malignancy
4. Known Still's Disease
5. Neutropenia (ANC <1.5 x 109/L)
6. Abnormal renal function (creatinine clearance or estimated Glomerular Filtration Rate (eGFR) < 30 ml/minute) documented in the last 3 months prior to this SAH
7. Live vaccinations within the last 10 days of this SAH
8. Previous or concurrent treatment with IL-1Ra known at the time of trial entry or previous participation in this trial
9. Current treatment with TNF antagonists
10. Known to have participated in a clinical trial of an investigational agent or device in the 30 days prior to ictus
11. Known to have participated in a clinical trial of an investigational agent or device within 5 half-lives (of the previous agent or device) prior to ictus
12. Known to be pregnant or breastfeeding or inability to reliably confirm that the patient is not pregnant
13. Clinically significant serious concurrent medical condition, pre-morbid illnesses, or concurrent serious infection (including confirmed or suspected COVID-19 infection), at the PI's (or designee's) discretion, which could affect the safety or tolerability of the intervention
14. Known allergy to IL-1Ra or any of the excipients listed in the drug SmPC
15. Known allergy to other products that are produced by DNA technology using the microorganism E. coli (e.g. E.coli derived protein)
16. Current treatment with IL-6 or IL-1 inhibitors or drugs affecting the IL-1 axis
17. History of DRESS syndrome

Previous participant exclusion criteria:
1. Unconfirmed or uncertain diagnosis of spontaneous SAH
2. Known active tuberculosis or active hepatitis
3. Known active malignancy
4. Neutropenia (ANC <1.5 x 109/L)
5. Abnormal renal function (creatinine clearance or estimated Glomerular Filtration Rate (eGFR) < 30 ml/minute) documented in the last 3 months prior to this SAH
6. Live vaccinations within the last 10 days of this SAH

7. Previous or concurrent treatment with IL-1Ra known at the time of trial entry or previous participation in this trial
8. Previous or current treatment with medication suspected of interacting with IL-1Ra, listed in the drug SmPC
9. Known to have participated in a clinical trial of an investigational agent or device in the previous 30 days or 5 half-lives of enrolment (whichever is longer) of ictus, or for the period determined by the protocol of the trial / study the patient has taken part in
10. Known to be pregnant or breast feeding or inability to reliably confirm that the patient is not pregnant
11. Clinically significant serious concurrent medical condition, pre morbid illnesses, or concurrent serious infection, at the PI's (or designee's) discretion, which could affect the safety or tolerability of the intervention
12. Known allergy to IL-1Ra or any of the excipients listed in the drug SmPC
13. Known allergy to other products that are produced by DNA technology using the micro-organism E. coli (e.g. E.coli derived protein)

Date of first enrolment
31/05/2018

Date of final enrolment
30/09/2023

Locations

Countries of recruitment
England

Scotland

United Kingdom

Wales

Study participating centre
Royal Stoke University Hospital
Newcastle Road
Stoke-on-Trent
United Kingdom
ST4 6QG

Study participating centre
Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Study participating centre
University Hospital of Wales
Heath Park
Cardiff
United Kingdom
CF14 4XW

Study participating centre
Northern Care Alliance NHS Foundation Trust
Salford Royal
Stott Lane
Salford
United Kingdom
M6 8HD

Study participating centre
National Hospital for Neurology & Neurosurgery
Queen Square
London
United Kingdom
WC1N 3BG

Study participating centre
Plymouth Hospital
Derriford Hospital
Derriford Road
Plymouth
United Kingdom
PL6 8DH

Study participating centre
University Hospital Southampton NHS Foundation Trust
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre

Leeds General Infirmary
Great George Street
Leeds
United Kingdom
LS1 3EX

Study participating centre
St George's Hospital
Blackshaw Road
London
United Kingdom
SW17 0QT

Study participating centre
The Walton Centre NHS Foundation Trust
Lower Lane
Fazakerley
Liverpool
United Kingdom
L9 7LJ

Study participating centre
Brighton and Sussex University Hospitals NHS Trust
Royal Sussex County Hospital
Eastern Road
Brighton
United Kingdom
BN2 5BE

Study participating centre
Nottingham University Hospitals NHS Trust
Trust Headquarters
Queens Medical Centre
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Charing Cross Hospital
Fulham Palace Road

London
United Kingdom
W6 8RF

Study participating centre
Barts Health NHS Trust
The Royal London Hospital
80 Newark Street
London
United Kingdom
E1 2ES

Study participating centre
Southmead Hospital
Southmead Road
Westbury-on-trym
Bristol
United Kingdom
BS10 5NB

Study participating centre
Lancashire Teaching Hospitals NHS Foundation Trust
Royal Preston Hospital
Sharoe Green Lane
Fulwood
Preston
United Kingdom
PR2 9HT

Study participating centre
Addenbrookes
Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Sponsor information

Organisation

The University of Manchester

Sponsor details
Oxford Road
Manchester
England
United Kingdom
M13 9PL

Sponsor type
University/education

ROR
https://ror.org/027m9bs27

Funder(s)

Funder type
Government

Funder Name
National Institute for Health 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
Current publication and dissemination plan as of 14/08/2023:
Publication in a high-impact peer reviewed journal is planned and is likely to be in the second half of 2024.

Previous publication and dissemination plan:
Publication in a high-impact peer reviewed journal is planned and is likely to be in the second half of 2023.

The study protocol is available at https://www.journalslibrary.nihr.ac.uk/programmes/eme/1420907/#/ (added 04/06/2021)

Intention to publish date
30/08/2025

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
Protocol file	version 8.0	04/06/2020	14/08/2023	No	No
Protocol file	version 9.0	13/03/2023	13/10/2023	No	No