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Randomised double blind clinical trial in acute severe colitis: The IASO Trial

Submission date	**Recruitment status**	[X] Prospectively registered
25/09/2017	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
12/10/2017	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
22/05/2023	Digestive System	[_] Record updated in last year

Plain English summary of protocol

Background and study aims

Ulcerative colitis is a condition in which the body's large intestine, known as the colon, becomes inflamed. In most patients, ulcerative colitis involves some periods without strong symptoms but also periods (called flares) where the symptoms become more severe. Sometimes, the intensity of the symptoms means that a patient needs to be admitted to hospital. If this happens, the patient will be given drugs called corticosteroids to reduce the inflammation and alleviate symptoms. If these make the patient better, the patient can then leave hospital after a few days. If the corticosteroids aren't making the condition better, other medicines can be given. This would be either a drug called infliximab or ciclosporin. Either drug can be used and both are equally effective. If these treatments still don't work, then doctors and the patient discuss surgery to remove the colon. This is called a colectomy. Currently, it is known that around half of patients given the initial treatment (corticosteroids) will get better, whilst the other half will go on to need one of the other medications, and some patients will still need to go on to surgery. The aim of this trial is to test whether giving patients another medicine, called anakinra, in addition to the initial treatment with corticosteroids will increase the number of patients who get better without needing to go on to receive additional medical treatments or surgery.

Who can participate?

Adults aged 16 to 80 years old who have ulcerative colitis.

What does the study involve?

Participants are randomly allocated to one of two equal-sized groups. Both groups receive the standard treatment for acute severe ulcerative colitis, intravenous corticosteroid injections. In addition to this, one group receives the trial drug (anakinra), and the other group receives a placebo (a dummy medication). Both the trial drug and the placebo look identical and are given as injections twice a day over five days. After this, participants' response to treatment are monitored up to approximately six months. Participants' hospitalisation records will be reviewed up to five years after they start the trial treatment, to investigate what the long term impact of the trial treatment is.

What are the possible benefits and risks of participating?

There is no guarantee that participants will benefit from taking part in this trial. They may

experience relief in their symptoms or an improvement in their disease. However, information collected as part of patients taking part in this trial may benefit patients with severe ulcerative colitis flares in the future. Participants may develop bruising or localised skin irritation at the site of skin injections. This can occur with either the drug or the placebo, but does not require any special treatment. Participants will also be required to give some additional blood (up to 15 mL, about 3 teaspoons each day) for research purposes. Donating this additional blood should not cause any problems and wherever possible research blood collection will be coordinated with standard routine care blood tests. Participants may experience the potential side effects of anakinra if they are in the active treatment group.

Where is the study run from?
1. Addenbrookes Hospital (UK)
2. Norfolk and Norwich University Hospital (UK)
3. Royal Victoria Infirmary (UK)
4. Royal Liverpool University Hospital (UK)

When is the study starting and how long is it expected to run for?
March 2017 to May 2023

Who is funding the study?
1. National Institute for Health Research (UK)
2. Wellcome Trust (UK)
3. Swedish Orphan Biovitrum AB (UK)

Who is the main contact?
Carol Davis-Wilkie
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Study website
https://www.journalslibrary.nihr.ac.uk/programmes/eme/1420102/#/

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
2017-001389-10

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
35703

Study information

Scientific Title
A phase II randomised placebo controlled double blinded trial of Interleukin 1 blockade in Acute Severe Colitis

Acronym
IASO

Study objectives
The aim of this trial is to test whether giving patients another medicine, called anakinra, in addition to the initial treatment with corticosteroids will increase the number of patients who get better without needing to go on to receive additional medical treatments or surgery.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Cambridge Central REC, 05/10/2017, ref: 17/EE/0347

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
See additional files

Health condition(s) or problem(s) studied
Acute Severe Colitis

Interventions
Initially, participants are asked some basic medical information, to confirm that they are definitely suitable for the trial.

Following this, if they are suitable for the trial, participants are asked some more medical questions and to complete 2 short questionnaires about their current symptoms. A blood sample is then taken (about 3 teaspoons or ~15 mL) in addition to a stool sample.

Participants are then be randomly allocated, by computer, to one of two, equal sized groups (randomised). Both groups receive the standard treatment with corticosteroid injections. In addition to this standard treatment, one group receives the trial drug (anakinra), and the other group receives a dummy drug (called placebo). Placebo looks exactly the same as the anakinra, but it contains no active ingredients.

The reason this has to be done is because it is not known whether anakinra will help patients or not, so it is necessary to have a group of patients who are not receiving the drug to compare all the results to. Neither the participant, nor the trial team or the participants' doctors will know which treatment they are receiving. This is called a double-blind trial. However in an emergency, doctors can find out which treatment participants are receiving.

The first dose of trial drug is usually be given on the same day as all the steps above, or sometimes as soon as possible the next day, if it is already late in the day. The first dose is given as an injection into the vein (also called an IV injection). Almost immediately after this, the participant receive a second dose as an injection given using a very fine needle just under the skin (also called an SC injection).

Participants continue to receive injections into the skin twice a day for up to 11 total doses (1 IV and 10 SC) over 5 days. Each day, the participant’s medical condition are reviewed and recorded. Participants are also have a research blood sample taken (about 2 teaspoons, ~10 mL) at least once every 72 hours and to a maximum of once a day. On Day 5, another stool sample is collected.

Trial Follow-Ups
1. 10 days after the first injection with the trial drug
-To confirm whether any additional treatment (“rescue therapy”) was needed and to check for side effects up to this point
2. 3 months after randomisation
-To check if any surgery was needed up to this point
-To ask the participant to complete 2 short symptom questionnaires
3. 6 months after randomisation
-To ask the participant to again complete 2 short symptom questionnaires

The trial additionally looks to understand the longer-term impact of anakinra on the health of trial participants. To do this, participants hospital admissions and health data (e.g. if surgery is needed at a later time) will be tracked for up to 5 years after time of randomisation.

IASO also includes 40 patients in an optional sub-study during the hospital treatment phase. The sub-study will look to gain additional information to determine if/how anakinra is working by visually examining and taking samples from the large bowel of participants using a technique known as endoscopy.

Intervention Type
Other

Phase
Phase II

Primary outcome measure
Incidence of medical or surgical rescue therapy within 10 days following the commencement of intravenous corticosteroid therapy, as determined by patient interview or reviewing patient notes.

Secondary outcome measures
1. Incidence of colectomy by 98 days following commencement of IV corticosteroid therapy, measured by patient interview or reviewing patient notes
2. Burden of disease activity, measured using daily modified Truelove and Witts severity index (MTWSI) scores over Days 1-5 after initial trial treatment administration
3. Time to clinical response, measured at the point of the 2nd consecutive day with MTWSI <10
4. Time to medical or surgical rescue therapy, measured according to the time after the first dose of IV corticosteroids until the time that rescue therapy occurs
5. Incidence of SAEs, measured by patient interview or reviewing patient notes up to Day 10 (+3 days

Overall study start date
01/03/2017

Completion date
31/05/2023

Eligibility

Key inclusion criteria
1. Be aged 16–80 years inclusive
2. Have given written informed consent to participate
3. Be hospitalised with clinically confirmed or suspected diagnosis of acute severe ulcerative colitis and a MTWSI score ≥11
4. Have a requirement for treatment with IV corticosteroids in the judgement of the treating clinician, with the possibility to receive a first dose of trial drug within 36 hours of commencement of IV corticosteroids

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Planned Sample Size: 214; UK Sample Size: 214

Total final enrolment
113

Key exclusion criteria
Current exclusion criteria as of 21/02/2018:
1. Pregnant or breast-feeding women
2. Oral corticosteroid dosing for a duration of 8 weeks or more immediately prior to commencement of IV corticosteroid dosing
3. History of severe hepatic impairment (e.g. Child-Pugh = Grade C)
4. Moderate or Severe renal impairment (estimated glomerular filtration rate [eGFR] <60ml/min /1.73m2)
5. Neutropenia (neutrophil count < 1.5x109/l)
6. Previous treatment with anakinra for any indication
7. Evidence (from blood cultures etc) or clinical suspicion of systemic infection
8. Current or previous cytomegalovirus (CMV) infection requiring treatment with anti-viral agents
9. Current treatment with anti-TNF-α therapy or anti-TNF-α discontinuation within previous 16 weeks
10. A history of pulmonary TB infection
11. History of malignancy (with the exception of non-melanoma skin cancer) or colonic dysplasia
12. Receipt of another IMP as part of a CTIMP within the previous 16 weeks

Previous exclusion criteria:
1. Pregnant or breast-feeding women
2. Oral corticosteroid dosing for a duration of 8 weeks or more immediately prior to commencement of IV corticosteroid dosing
3. History of severe hepatic impairment (e.g. Child-Pugh = Grade C)
4. Moderate or severe renal impairment (eGFR < 50ml/minute)
5. Neutropenia (neutrophil count < 1.5x109/l)
6. Previous treatment with anakinra for any indication
7. Evidence (from blood cultures etc) or clinical suspicion of systemic infection
8. Current or previous cytomegalovirus (CMV) infection requiring treatment with anti-viral agents
9. Current treatment with anti-TNF-α therapy or anti-TNF-α discontinuation within previous 16 weeks
10. A history of pulmonary TB infection
11. History of malignancy (with the exception of non-melanoma skin cancer) or colonic dysplasia
12. Receipt of another IMP as part of a CTIMP within the previous 16 weeks

Date of first enrolment
14/02/2018

Date of final enrolment
17/03/2021

Locations

Countries of recruitment
England

United Kingdom

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

Study participating centre
Norfolk and Norwich University Hospital
Colney Lane
Norwich
United Kingdom
NR4 7UY

Study participating centre
Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Royal Liverpool University Hospital
Prescot Street
Liverpool
United Kingdom
L7 8XP

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust

Sponsor details

Addenbrookes Hospital
Hills Road
Cambridge
England
United Kingdom
CB2 0QQ

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/04v54gj93

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

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Funder Name
Swedish Orphan Biovitrum AB

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal around one year after the overall trial end date. Presentation of primary and secondary analyses at major international congresses.

Intention to publish date
31/05/2024

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publically available repository. Following completion of the study and the analysis, it is anticipated that deidentified research data including sequencing data will be made available for other researchers. This will include use of database repositories such as Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/), as well as sharing of individual deidentified participant data that underlies results reported in published articles. Any clinical data will be shared with researchers who provide a methodologically sound proposal in order to achieve aims in the approved proposal.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V1	03/08/2017	12/10/2017	No	Yes
Participant information sheet	version V1.1	22/09/2017	12/10/2017	No	Yes
Protocol article	protocol	15/02/2019	04/03/2020	Yes	No
HRA research summary			28/06/2023	No	No