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RAPID-I

Submission date 04/06/2018	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 08/06/2018	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 02/11/2022	**Condition category** Digestive System	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
Acute pancreatitis is a serious condition in which the pancreas becomes inflamed and is damaged. It causes intense abdominal pain and may lead to multiple organ failure. Those suffering from the disease may need help with breathing, heart and kidney function. One in twenty patients with acute pancreatitis dies, which is more likely to happen to those who develop organ failure. Treatment can be prolonged, often with extended stays in hospital of many weeks. To date many drugs have been tested to treat acute pancreatitis, but none cure the illness or accelerate recovery. This study tests a drug called infliximab, which is made from natural protein and is currently used to treat bowel and joint disease. Infliximab works by blocking an important process in the progression of the disease. This process leads to inflammation in both the pancreas and other parts of the body. The study also looks to see if there are any links between genes and the development of acute pancreatitis, and to see if there are any links between the genes and the way infliximab works. This may help target the right treatment to the right patients and help gain understanding of how infliximab works. If infliximab is beneficial in the treatment of acute pancreatitis, major improvements will be possible in the health of a large number of NHS patients, patient suffering and hospital waiting times will be reduced, and significant savings will be made to NHS costs.

Who can participate?
Adult patients attending A&E with acute pancreatitis

What does the study involve?
Participants are randomly allocated to receive a single, 2-hour infusion of either 5 mg/kg infliximab, 10 mg/kg infliximab, or placebo (dummy drug). Infliximab is given within half a day of a patient arriving in hospital, much earlier than with other drugs tested in acute pancreatitis. Whilst the patient is in hospital, information is recorded and blood samples are taken. Patients are followed up until Day 90 (Day 1 beginning from when the patient receives the trial infusion).

What are the possible benefits and risks of participating?
Acute pancreatitis is a common and serious disease that needs emergency admission to hospital, but there are no medicines to cure the illness or speed up recovery. By taking part in this study, participants may find their symptoms of acute pancreatitis get better. Infliximab helps in bowel and joint disease and early research shows that infliximab may help patients with acute pancreatitis. The results of this study may help others with acute pancreatitis and will be

valuable in developing new medicines to treat acute pancreatitis. Millions of patients in the world have been treated with infliximab for various diseases. Infliximab is a safe medicine and usually very well tolerated. Side effects from infliximab are uncommon. Most side effects occur with repeated doses of infliximab, unlike in this study which tests a single dose of infliximab. The two side effects that could occur with a single dose of infliximab, although unlikely, are allergic reactions (also known as infusion reactions) and infections. This study also requires exposures to ionising radiation. Depending on their clinical indications, participants will receive a chest x-ray at screening and a dual phase CT scan for the diagnosis and/or monitoring of pancreatitis. Depending upon the clinical indications, the number of CT scans as standard of care can vary but is likely to be less than three, although more may be performed if indicated. Participants will only receive one additional examination although it is noted that this examination may be performed as part of the standard of care.

Where is the study run from?
1. Royal Liverpool and Broadgreen University Hospitals NHS Trust (UK)
2. Glasgow Royal Infirmary (UK)
3. University Hospitals Birmingham NHS Foundation Trust (UK)
4. Leeds Teaching Hospital NHS Trust (UK)

When is the study starting and how long is it expected to run for?
January 2018 to April 2023

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

Who is the main contact?
Rapid.One@liverpool.ac.uk

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
2017-003840-19

IRAS number

ClinicalTrials.gov number
NCT03684278

Secondary identifying numbers
38354

Study information

Scientific Title
Phase IIb, randomised, double-blind, placebo-controlled, multi-centre trial of infliximab with transcriptomic biomarker and mechanism evaluation in patients with acute pancreatitis

Acronym
RAPID-I

Study objectives
Acute pancreatitis is a serious condition in which the pancreas becomes inflamed and is damaged. It causes intense abdominal pain and may lead to multiple organ failure. Those suffering from the disease may need help with breathing, heart and kidney function. One out of twenty patients with acute pancreatitis dies, which is more likely to happen to those who develop organ failure. Treatment can be prolonged, often with extended stays in hospital of many weeks. To date many drugs have been tested to treat acute pancreatitis, but none cure the illness or accelerate recovery. In this trial we are testing a drug called infliximab, which is made from natural protein and is currently used to treat bowel and joint disease. Infliximab works by blocking an important process in the progression of the disease. This process leads to inflammation in both the pancreas and other parts of the body. In the trial, infliximab is given once within half a day of a patient arriving in hospital, much earlier than with other drugs tested in acute pancreatitis. Whilst the patient is in hospital, information will be recorded and blood samples will be taken. Patients will be followed up for 90 days after trial treatment. The study will also look to see if there are any links between genes and the development of acute pancreatitis, and to see if there are any links between the genes and the way infliximab works. This may help target the right treatment to the right patients and help gain understanding of how infliximab works. If infliximab is beneficial in the treatment of acute pancreatitis, major improvements will be possible in the health of a large number of NHS patients, patient suffering and hospital waiting times will be reduced and significant savings will be made to NHS costs.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 04/07/2018, South Central – Oxford C Research Ethics Committee (Holiday Inn Oxford, Peartree Roundabout, Woodstock Rd, Oxford, OX2 8JD, UK; Tel: +44 (0)207 104 8290, +44 (0) 207 104 8041; Email: nrescommittee.southcentral-oxfordc@nhs.net), ref: 18/SC/0262

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 to request a patient information sheet

Health condition(s) or problem(s) studied
Acute pancreatitis

Interventions
Participants will be randomised using an online web randomisation system, by a delegated member of the research team to receive a single, 2-hour infusion of either:
Arm A: 5 mg/kg infliximab
Arm B: 10 mg/kg infliximab
Arm C: placebo (0.9% sodium chloride)

Participants will be randomised to treatment allocations in a ratio of 1:1:1, stratified by individual research sites. Patients will only receive a single, 2-hour infusion of their treatment allocation. Infliximab is given within half a day of a patient arriving in hospital, much earlier than with other drugs tested in acute pancreatitis. Whilst the patient is in hospital, information will be recorded and blood samples will be taken. Patients will be followed up until Day 90 (Day 1 beginning from when the patient receives the trial infusion).

Intervention Type
Drug

Phase
Phase II

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

Primary outcome measure
The primary efficacy outcome measure will be the difference in mean serum C-reactive protein measured on Days 2, 4, 7, 14 and 28 (summated as area under the curve) in either active arm (5 mg/kg or 10 mg/kg) versus the placebo arm; Timepoint(s): End of the study

Secondary outcome measures

1. Cumulative Pain Scores: patients will complete a numerical rating scale (between 0-10) for the first 28 days
2. Opiate requirements: recording of daily morphine equivalents for the first 28 days
3. Nutritional deficit: number of days nil by mouth +/- nutritional support for the first 28 days
4. Decline in serum albumen, measured via blood samples for the first 28 days
5. Decline in haematocrit, measured via blood samples for the first 28 days
6. Rise in neutrophils, measured via blood samples for the first 28 days
7. Presence and duration of systemic inflammatory response syndrome, present (duration of response) or absent, for the first 28 days
8. Cumulative serial organ failure assessment (SOFA score) for the first 28 days
9. Local pancreatic injury, measured using contrast enhanced CT scan assessed by a centralised panel on Day 14
10. Pancreatic sufficiency, measured by:
10.1. Faecal elastase on Day 28 and Day 90
10.2. HbA1c on Day 90
11. Severity classification, measured using the Revision of the Atlanta Classification (RAC), as and when classified
12. Infective complications, any complications reported, for the first 90 days
13. Length of hospital stay, length of time patients remain within hospital as an inpatient, up to Day 90
14. Mortality within the first 90 days
15. Patient-reported outcome: patients will complete EuroQol EQ-5D-5L, including the EQ-VAS (visual analogue scale) questionnaire on Days 4, 14, 28 and 90
16. Potential safety signals, adverse events relating to infliximab including infusion reactions and delayed serum sickness reactions, up to 90 days
17. Further safety signal, reports of significant increase in the incidence of infective complications associated with the use of infliximab over placebo, up to 90 days
18. Antibodies to infliximab assessed using blood sample analysis on Day 28
19. Absolute and/or relative expression of selected transcripts: blood samples collected for exploratory safety analyses using selected transcripts on Days 2, 4, 7, 14 and 28
20. Cytokine and leucocyte subsets profiles, assessed using blood sample analysis on Days 2, 4, 7, 14 and 28
21. Discriminant function (trial treatment versus placebo) of efficacy measures across domains: clinical, laboratory, critical care, local injury, infection, length of stay and patient reported outcome domains: selected data collected for the trial will be used for this outcome up until day 90
22. Incremental cost per quality adjusted life years (QALY) gained by trial treatment, measured using data from the EQ-5D-5L questionnaire on Days 4, 14 , 28 and 90
23. Time to recruitment of target sample size (290 patients, anticipated to be 24 months). Please note as adaptive design is used target sample size may reduce.

Overall study start date
01/01/2018

Completion date
30/04/2023

Eligibility

Key inclusion criteria

Current participant inclusion criteria as of 14/08/2018:
1. Adult patients attending A&E at or admitted to recruiting hospitals via a general practitioner with a new diagnosis of AP established by two of:
1.1. Typical continuous upper abdominal pain;
1.2. Amylase and/or lipase three or more times the upper limit of normal;
1.3. Characteristic findings on abdominal imaging (if undertaken urgently by CT or magnetic resonance imaging, MRI);
2. Patients in whom trial treatment can be started within 12 hours of recorded admission and allowing 120 min for pharmacy to prepare trial medication
3. Patients from whom appropriate consent is obtained (consent to be given by the patient or their legal representative).

Previous participant inclusion criteria:
1. Adult patients attending A&E at recruiting centres from whom appropriate consent is obtained (consent to be given by the patient or their legal representative)
2. Patients in whom trial treatment can be started within 12 hours of admission (allowing 120 min for Pharmacy to prepare trial medication)
3. A new diagnosis of AP (all severity levels) as established by two of:
3.1. Typical continuous upper abdominal pain
3.2. Amylase and/or lipase three or more times the upper limit of normal
3.3. Characteristic findings on abdominal imaging (if undertaken urgently)
NB Please note all severity levels of AP are to be included in the trial

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 290; UK Sample Size: 290

Key exclusion criteria
1. Age < 18 or > 85
2. Body weight > 200 kg
3. Onset of abdominal pain more than 24 hours before admission to hospital
4. Known previous acute pancreatitis or chronic pancreatitis
5. Known multiple sclerosis, systemic vasculitis, Guillain-Barré syndrome or other demyelinating disorder
6. Known epilepsy
7. Moderate to severe heart failure and/or coronary heart disease (New York Heart Association (NYHA) Functional Class III/IV)
8. On home oxygen or home mechanical ventilation
9. Known advanced liver disease, on waiting list for liver transplantation or considered unsuitable for transplantation

10. Known cancer for which chemotherapy and/or radiotherapy is ongoing or was completed within less than 6 months from admission
11. Known haematological malignancy
12. Known cancer that is end-stage with ongoing palliative care or for which palliative care is appropriate
13. Known established infection prior to the onset of acute pancreatitis
14. Known history of (including that identified on chest x-ray) or household contact with individuals who have tuberculosis or opportunistic infection
15. Known history of infective hepatitis
16. Known immunosuppressive or biologic therapy within one month of admission
17. Known live vaccines or therapeutic infectious agents within one month of admission
18. Known hypersensitivity to infliximab or to inactive components of REMICADE® or to any murine proteins
19. Known pregnancy or lactation at the time of admission
20. Women of childbearing potential who do not agree to use adequate contraception up to Day 90
21. Known to be currently participating in a trial testing any investigational medicinal product or participation in a clinical study involving a medicinal product in the last three months

Date of first enrolment
30/09/2018

Date of final enrolment
30/04/2023

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Royal Liverpool and Broadgreen University Hospitals NHS Trust (Lead Site)
Royal Liverpool University Hospital
Prescot Street
Liverpool
United Kingdom
L7 8XP

Study participating centre
Glasgow Royal Infirmary
West Of Scotland Pancreatic Unit
Castle Street
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Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Trust HQ, PO Box 9551
Queen Elizabeth Medical Centre
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Study participating centre
Leeds Teaching Hospital NHS Trust
St James's University Hospital
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Sponsor information

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Sponsor type
University/education

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 15/20/01

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal as soon as possible after trial completion.

Intention to publish date
30/10/2022

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