ISRCTN14174793 https://doi.org/10.1186/ISRCTN14174793

A trial to investigate whether giving albumin to patients with advanced liver cirrhosis will reverse immune suppression and improve outcome for infection

Submission date
18/03/2015

Recruitment status
No longer recruiting

Registration date
20/03/2015

Overall study status
Completed

Last Edited
25/11/2021

Condition category
Digestive System

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Liver disease is the fifth most common cause of death in the UK and is caused largely by alcohol, viruses and fatty liver disease resulting in liver damage and loss of function. People can survive with large amounts of liver damage but often have severe health complications leading to frequent hospital admissions. In particular, patents have weak immune systems and are highly prone to bacterial infection with over a third developing an infection in hospital. Infection is the major cause of death in these patients and therefore represents a huge challenge to the NHS. Currently infection in liver patients is treated with antibiotics, however the rates of death in these patients have shown little improvement over 20 years. Antibiotics may also cause harmful side-effects (e.g. diarrhoea) and overuse has led to antibiotic resistant bacteria which makes these drugs useless and will be one of medicines' greatest challenges over the next decade. Albumin is a protein found naturally in blood and is made in the liver. As liver function reduces so does albumin production and blood levels fall. Albumin is safe and currently used in patients with liver failure; however, prescription is varied and although considered beneficial the effects haven't been tested in clinical trials. Our study aims to see if giving liver patients Human Albumin Solution (HAS) restores their immune response and helps both prevent and improve treatment of infections.

Who can participate?
Aults (aged over 18) admitted to hospital with acute or worsening complications of cirrhosis of the liver.

What does the study involve?
This study includes a feasibility study, to verify whether it is possible to restore albumin levels to near normal. This is followed by a randomised control trial to confirm whether restoring albumin levels improves survival from infection compared to standard treatment. For the feasibility study, all participants are given 20% HAS during their hospital stay up to a maximum of 14 days. The dose given is dependent on how much albumin is found in the participants blood. For the

randomized controlled trial, participants are randomly allocated into one of two groups. Those in group 1 are given the immune restorative albumin protocol 20% HAS (dose dependent on blood albumin levels) during their hospital stay up to a maximum of 14 days. Those in group 2 are given standard medical care.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
The study will take place at up to 44 NHS sites in England, Wales and Scotland.

When is the study starting and how long is it expected to run for?
April 2015 to October 2017

Who is funding the study?
The National Institute for Health Research (NIHR) and the Wellcome Trust (both UK)

Who is the main contact?
James Blackstone, j.blackstone@ucl.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2014-002300-24

Protocol serial number
18450

Study information

Scientific Title
Albumin To prevenT Infection in chronic liveR failurE

Acronym
ATTIRE

Study objectives
1. Increased circulating concentrations of Cyclooxygenase (COX)-derived eicosanoid prostaglandin E2 (PGE2) drives cirrhosis-associated leukocyte dysfunction and hence the propensity to infection observed in these patients.
2. Infection triggers an acute clinical deterioration with progression of liver failure, development of liver-related complications, organ failure and mortality in patients with cirrhosis.
3. Albumin reduces PGE2 bioavailability and plays a key role in modulating PGE2-mediated immune dysfunction. As it is synthesised in the liver, circulating albumin levels are approximately 50% lower than in patients without advanced liver disease.
4. Therefore in vivo administration of 20% HAS to these patients will improve their leukocyte function thus enhancing their ability to combat infection, reducing the incidence of second /nosocomial infection. This will lead to fewer cases of organ failure and improved mortality.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee London-Brent, 26/01/15/LO/0104; First MREC approval date 26/01/2015

Primary study design
Interventional

Study design
Both; Interventional; Design type: Prevention, Treatment

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Liver cirrhosis

Interventions
Feasibility Study:
In stage 1, a Phase II feasibility study, all patients will receive a daily intravenous infusion of 20% Human Albumin Solution (HAS) during of their admission (maximum of 14 days from randomisation). The dose will be administered to target a daily serum albumin of 35 g/l. T he following suggested protocol will be provided for clinicians:
1. If serum albumin 30-34 g/l give 100 ml 20% HAS
2. If serum albumin 26-29 g/l, give 200 ml 20% HAS
3. If serum albumin 20-25 g/l, give 300 ml 20% HAS
4. If serum albumin <20 g/l, give 400 ml 20% HAS

Randomised Control Trial (RCT):
In stage 2, a phase III RCT, patients will receive a daily intravenous infusion of either the immune

restorative albumin protocol 20% HAS (dose based on the same suggested protocol as the feasibility study) or standard medical care for the duration of their admission (maximum of 14 days from trial randomisation).

Intervention Type
Biological/Vaccine

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
20% Human Albumin Solution

Primary outcome(s)
Current primary outcome measures as of 14/09/2020:
Feasibility Study:
1. Daily serum albumin level for the duration of trial treatment period (maximum 14 days or discharge/death (if less than 14 days)
Patients will not be followed up after trial treatment.

RCT:
Composite outcome of incidences of
1. Nosocomial infection
2. Renal dysfunction
3. Mortality
As measured during the trial treatment period (maximum 14 days or discharge/death (if less than 14 days)
Patients in the RCT will be followed up for up to 6 months following discharge from hospital.

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Previous primary outcome measures:
Feasibility Study:
1. Daily serum albumin level for the duration of trial treatment period (maximum 14 days or discharge/death (if less than 14 days)
Patients will not be followed up after trial treatment.

RCT:
Composite outcome of incidences of
1. Nosocomial infection
2. Extra hepatic organ dysfunction
3. Mortality
As measured during the trial treatment period (maximum 14 days or discharge/death (if less than 14 days)
Patients in the RCT will be followed up for up to 6 months following discharge from hospital.

Key secondary outcome(s)
Feasibility Study:
1. Daily leukocyte function assessed by laboratory based leukocyte bioassay

RCT:
2. Mortality at 28 days post randomisation and 3 & 6 months post discharge
3. Time to outcome (first event of infection/organ dysfunction/death)
4. Transplant within six months of treatment
5. Total amount of HAS administered during treatment period
6. Duration of hospital stay
7. Prognostic score (assessed by UKELD, MELD, Child's Pugh scores) at baseline and end of treatment
8. Worst daily NEWS score during the treatment period
9. Incidence of SIRS during treatment period
10. Incidence of Septic Shock during treatment period
11. Days in ICU during treatment period
12. Incremental cost and cost-effectiveness up to 6 months post discharge
13. Impact on quality of life (QOL) up to 6 months post discharge
14. Safety and tolerability of HAS as indicated by Serious Adverse Events (SAEs)
15. Requirement for nutritional support (nasogastric feed, nutritional supplements or total parenteral nutrition) during treatment period

Completion date
31/12/2019

Eligibility

Key inclusion criteria
1. All patients admitted to hospital with acute onset or worsening of complications of cirrhosis e. g. alcoholic hepatitis, hepatic encephalopathy, ascites, hepatic hydrothorax, hyperbilirubinaemia, oesophageal variceal bleed, any infection precipitating acute decompensation or any other presentation of acute decompensation / acute onset chronic liver failure
2. Over 18 years of age
3. Predicted hospital admission > 5 days at trial enrolment, which must be within 72 hours of admission
4. Serum albumin <30g/l at screening
5. Documented informed consent to participate (or consent given by a legal representative)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment

777

Key exclusion criteria
1. Advanced hepatocellular carcinoma with life expectancy of less than 8 weeks
2. Patients who will receive palliative treatment only during their hospital admission
3. Pregnancy
4. Known or suspected severe cardiac dysfunction
5. Any clinical condition which the investigator considers would make the patient unsuitable for the trial
6. The patient has been involved in a clinical trial of Investigational Medicinal Products (IMPs) within the previous 30 days (including re-randomisation into the RCT)
7. Trial investigator unable to identify the patient (by NHS number)

Date of first enrolment
30/04/2015

Date of final enrolment
30/06/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University College London
Gower Street
London
United Kingdom
WC1E 6BT

Sponsor information

Organisation
University College London (UK)

ROR
https://ror.org/02jx3x895

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

Results and Publications

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	feasibility study results	01/05/2018	15/11/2019	Yes	No
Results article	feasibility study results	01/05/2018	15/11/2019	Yes	No

Results article	results	04/03/2021	05/03/2021	Yes	No
Results article		01/11/2021	25/11/2021	Yes	No
Protocol article	protocol	25/01/2016		Yes	No
Protocol article	protocol	21/10/2018		Yes	No
HRA research summary			28/06/2023	No	No