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Trial of faecal microbiota transplantation in cirrhosis

Submission date
21/02/2018

Recruitment status
No longer recruiting

Registration date
21/05/2018

Overall study status
Completed

Last Edited
29/06/2023

Condition category
Digestive System

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

Plain English summary of protocol

Background and study aims
The body contains trillions of microscopic organisms called bacteria which play an important role in keeping it healthy. These bacteria live mainly in the bowel and help the immune system fight infection. Liver disease is becoming more common in the UK and repeated liver damage causes the liver to be shrunken and scarred. This is known as cirrhosis. There are increased numbers of bowel bacteria in patients with cirrhosis with more 'unfriendly' bacteria which release substances which disrupt the immune system. These patients often develop severe infections which result in them being hospitalised and often dying. Antibiotic treatment is prescribed but sometimes this is ineffective. It could be beneficial to replace the unhealthy bowel bacteria in patients with cirrhosis with bacteria donated from a healthy person by performing a type of bowel bacteria transplant. This is safe but has only been undertaken in a handful of patients with cirrhosis. This involves flushing out 'unfriendly bacteria' and replacing them during a gastroscopy with bacteria donated from a healthy person who has been carefully screened, similar to blood donors. A gastroscopy involves passing a thin flexible camera through the mouth, down the gullet into the small bowel where the bacteria transplant is placed. This is a safe procedure and serious complications are uncommon. This study will examine whether this is a feasible treatment that is both safe and palatable to patients without any side effects. It will also examine whether treatment may improve the health of patients with cirrhosis, preventing them from developing infections.

Who can participate?
Patients aged 18–75 with advanced cirrhosis

What does the study involve?
Participants are randomly allocated to receive either a bacteria transplant or an identical transplant without bacteria known as a 'placebo'. Blood and stool samples are collected before and after the transplant (1 week, 1 month and 3 months) to assess what impact the transplant has on their bowel bacteria and their immune system.

What are the possible benefits and risks of participating?
The treatment may restore the healthy gut bacteria and reduce the complications of liver disease. All participants receive close follow up and support and have an endoscopy which will

screen for varices, which is a necessary part of the care of all patients with cirrhosis. Not everyone will receive the bacteria transplant so those who receive placebo would not be expected to benefit. There is a risk of infection (although donors are rigorously screened for known transmissible infections), the bowel preparation can cause mild dehydration and electrolyte disturbances, and the risks of endoscopy includes a small risk of bleeding and perforation, but this is true for all gastroscopy procedures and patients with cirrhosis require this as standard.

Where is the study run from?
King's College Hospital (UK)

When is the study starting and how long is it expected to run for?
May 2015 to September 2020

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

Who is the main contact?
Professor Debbie Shawcross, debbie.shawcross@kcl.ac.uk

Contact information

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Public

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Additional identifiers

EudraCT/CTIS number
2017-003629-13

IRAS number

ClinicalTrials.gov number
NCT02862249

Secondary identifying numbers
Version 2.0

Study information

Scientific Title
Prospective randomised placebo controlled feasibility trial of faecal microbiota transplantation in cirrhosis

Acronym
PROFIT

Study objectives
In patients with advanced cirrhosis FMT may reduce the progression to chronic liver failure including jaundice, ascites, bleeding, encephalopathy and the development of infection and organ dysfunction. Whether FMT is feasible in the setting of liver cirrhosis remains to be investigated. This is a feasibility trial to determine whether a FMT from a healthy donor will alleviate gut dysbiosis and immune dysfunction.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London South East Research Ethics Committee, 31/1/2018, ref: 17/LO/2081

Study design
Single-blind prospective randomised controlled trial

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
Cirrhosis

Interventions
Patients will be randomised to either FMT or placebo in a 3:1 ratio using block randomisation. This is a single treatment (FMT or placebo-saline and glycerol) administered at endoscopy via an NJ tube. Follow up is at 7, 30 and 90 days.

Intervention Type
Other

Primary outcome measure
1. Assessment of the feasibility and tolerability of FMT:
1.1. >25% consent rate (of all patients screened ~250)
1.2. >50% fulfil inclusion/exclusion criteria (of all patients consented ~64)
1.3. >80% randomised patients treated successfully and completing study up to day 90 (out of those randomised ~22)
1.4. Availability of obtaining sufficient stool donors for the study
1.5. Reflux rates of transplanted material <20% (e.g. foul taste, smell, nausea and vomiting, indigestion) assessed by direct questioning for vomiting, diarrhoea etc after endoscopy and at days 7, 30 and 90
1.6. Significant gastrointestinal side effects (including diarrhoea, constipation, abdominal pain, flatulence and bloating) of <20%, assessed by direct questioning after endoscopy and at days 7, 30 and 90
2. Assessment of the safety of FMT:
2.1. Incidence of any transmissable bacterial or viral infection that is deemed to have been acquired from the donor including Clostrium difficile infection, based on signs/symptoms of infection and culture results at days 7, 30 and 90
2.2. The development of any Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR) that is not pre-specified or is a known consequence of disease progression or complication of cirrhosis as outlined in section 7.2.5.1 that:
2.2.1. Results in death
2.2.2. Is life-threatening
2.2.3. Required hospitalisation or prolongation of existing hospitalisation
2.2.4. Results in persistent or significant disability or incapacity
2.2.5. Consists of a congenital anomaly or birth defect
Assessed via AE recording/monitoring throughout trial, after endoscopy and at trial at days 7, 30 and 90

Secondary outcome measures

The secondary objectives of the study are to provide preliminary evidence of efficacy for a larger randomised trial, with the purpose of:
1. Choosing the optimal primary outcome, and
2. Estimating the parameters for sample size calculation

1. Global liver synthetic function assessed by the MELD score (a composite score of serum bilirubin, creatinine and INR) at 90 days
2. Development of overt hepatic encephalopathy (grade 1 or more as measured by the Westhaven Criteria) at days 7, 30 and 90
3. The development of organ failure (hypotension requiring inotropic support, respiratory failure requiring ventilator support or the development of acute kidney injury requiring renal replacement therapy) and infection, assessed with AE monitoring at days 7, 30 and 90
4. The development of any infection during the 90 day follow up including chest, urinary, stool, ascites and blood infection, assessed with AE monitoring/signs of infection/culture results at days 7, 30 and 90
5. Stability of the transplanted gut microbiome by comparing the % composition of the stool microbiota with the donor microbiome, assessed with 16S rRNA/metagenomic analysis on day 7, 30 and 90
6. Comparison of the composition of the salivary microbiome with the stool microbiome as a surrogate marker of gut dysbiosis, assessed using 16S/metagenomics at baseline, day 7, day 30 and day 90

Mechanistic outcome(s):
1. Plasma endotoxin and bacterial DNA quantification at 7, 30 and 90 days
2. Faecal biomarkers (calprotectin, lactoferrin and M2-Pyruvate Kinase) at 7, 30 and 90 days
3. Leucocyte function including measurement by lipopolysaccharide-induced macrophage tumour necrosis alpha production and immunological markers using flow cytometry (HLA-DR and TLR-4 expression) at 7, 30 and 90 days

Overall study start date
19/05/2015

Completion date
02/09/2020

Eligibility

Key inclusion criteria
1. Aged 18–75 years
2. Confirmed advanced cirrhosis of any aetiology with a MELD score between 10 and 16. The diagnosis of liver cirrhosis will be based on clinical, radiological, or histological criteria
3. Patients with alcohol-related liver disease must have been abstinent from alcohol for a minimum of 6 weeks
4. Patients must be deemed to have capacity to consent to study (if patients lose capacity during the trial a legal representative will be appointed to act on their behalf)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
75 Years

Sex
Both

Target number of participants
32

Total final enrolment
23

Key exclusion criteria
1. Severe or life-threatening food allergy
2. Pregnancy or breastfeeding
3. Patients treated for active variceal bleeding, infection, overt hepatic encephalopathy, bacterial peritonitis or acute-on-chronic liver failure within the past 14 days
4. Patients who have received antibiotics in the past 14 days
5. Active alcohol consumption of >20 grams/day
6. Has had a previous liver transplant
7. Hepatocellular carcinoma outside of the Milan Criteria
8. Inflammatory bowel disease
9. Coeliac disease
10. A history of prior gastrointestinal resection such as gastric bypass
11. Patient is not expected to survive the duration of the study (90 days)
12. Severe renal impairment (creatinine >150 µmol/L)
13. HIV positive
14. Immunosuppression e.g. more than two weeks treatment with corticosteroids within 8 weeks of intervention, active treatment with tacrolimus, mycophenylate, azathioprine

Date of first enrolment
01/03/2018

Date of final enrolment
02/03/2020

Locations

Countries of recruitment
England

United Kingdom

Study participating centre

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Sponsor information

Organisation
King's College London and King's College Hospital

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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/0220mzb33

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
The trialists plan to submit the protocol for publication shortly

Intention to publish date
30/06/2022

Individual participant data (IPD) sharing plan
A copy of the final study report has been submitted to the NIHR and is available on written request to the Chief Investigator, Professor Debbie Shawcross (Debbie.shawcross@kcl.ac.uk). Fully anonymised data will be available for the purposes of inclusion in meta-analysis or for freedom of information requests on request to the Chief Investigator. Sequencing and metabonomic data will be available to be accessed from a public repository following publication of the study manuscripts.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		15/02/2019	13/09/2021	Yes	No
Basic results		15/10/2020	16/06/2022	No	No
HRA research summary			28/06/2023	No	No
Abstract results	Presented at EASL	01/08/2020	29/06/2023	No	No