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Cirrhosis and Faecal microbiota Transplantation (ChiFT) protocol: a Danish multicentre, randomised, placebo-controlled trial in patients with decompensated liver cirrhosis

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ABSTRACT

Introduction Liver cirrhosis is a progressive disease with high mortality. Gut microbiota derangement, increased gut permeability, bacterial translocation and chronic inflammation all drive disease progression. This trial aims to investigate whether faecal microbiota transplantation (FMT) may improve the disease course in patients with acute decompensation of liver cirrhosis.

Methods and analysis In this Danish, multicentre, randomised, double-blinded, placebo-controlled trial, 220 patients with acute decompensation of liver cirrhosis and a Child-Pugh score≤12 will be randomised (1:1) to oral, encapsulated FMT or placebo in addition to standard of care. Before the intervention, the patients will be examined and biological samples obtained, and this is repeated at 1 and 4 weeks and 3, 6 and 12 months after the intervention. The primary outcome is the time from randomisation to new decompensation or death. Secondary endpoints include mortality, number of decompensation events during follow-up and changes in disease severity and liver function.

Ethics and dissemination The Central Denmark Region Research Ethics Committee approved the trial protocol (no. 1-10-72-302-20). The results will be published in an international peer-reviewed journal, and all patients will receive a summary of the results.

Trial registration number ClinicalTrials.gov study identifier NCT04932577.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study is powered to assess the efficacy of faecal microbiota transplantation (FMT) on clinical outcomes.
⇒ The use of oral capsules for both the intervention and the placebo group increases the feasibility of FMT delivery and importantly enables double-blinding.
⇒ In our protocol, we chose to treat patients three times within 1 week using faeces from randomly selected healthy donors. While this does not investigate a possible benefit from rational donor selection, it allows unbiased investigation of microbial signatures that predict the clinical effect.
⇒ The comprehensive biological sampling and analysis of exploratory endpoints will enable insights into the mechanisms of action of FMT in liver cirrhosis. The drawback of extensive sampling and frequent visits is that it may burden the frail patients and reduce compliance during follow-up, leading to potentially missing data points.
⇒ The trial is nationwide, with patient recruitment and treatment at six Danish hepatology centres. Because it is not international, there is a risk that the generalisation of any findings may be limited to similar healthcare settings.

INTRODUCTION

Cirrhosis is the final common path for end-stage liver disease regardless of aetiology and is responsible for 2.4% of global deaths each year.[1] In Denmark, the predominant cause of liver cirrhosis is alcohol, and globally alcohol consumption is increasing. The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) is increasing worldwide, making liver an increasing global health threat.[2] Liver cirrhosis is progressive, and the mortality is high.[3 4] Clinically, liver cirrhosis manifests as episodes of decompensation with ascites, gastrointestinal bleeding, hepatic encephalopathy (HE) or infection. Liver transplantation remains the only curative treatment, but this is highly limited by organ availability. Other current treatment options are symptomatic and directed against the various complications without improving the underlying disease processes.[5]

Reduction in intestinal microbiota diversity, alterations in its metabolome and increased gut barrier permeability are all well-established features of liver cirrhosis and

are associated with disease severity and increased risk of decompensation.[6–10] These disease-associated changes are accompanied by increased bacterial translocation and systemic inflammation, which is thought to drive disease progression.[11–15] Faecal microbiota transplantation (FMT) is a direct way of restoring a disturbed intestinal microbiota. FMT is a therapeutic approach to transfer minimally processed donor faeces from a healthy donor to a patient. The intention is to drive engraftment of a donor-like microbiota in the recipient to re-establish eubiosis.[16–18] FMT is an established and highly efficient treatment for recurrent *Clostridioides difficile* infection (CDI) with a high safety profile.[19–22] Pilot studies with FMT for the treatment of HE,[23–25] alcohol-associated hepatitis,[26–28] acute-on-chronic liver failure[29] or MASLD[30] have shown promising results, but these studies are small and limited by short follow-up. Trials powered to assess efficacy are highly warranted.

The present trial aims to investigate the efficacy of FMT in addition to standard of care to reduce the risk of acute decompensations and death in patients with decompensated liver cirrhosis. We hypothesise that FMT will reduce complications and mortality in patients with acute decompensated liver cirrhosis compared with placebo.

METHODS AND ANALYSIS

Objectives

The primary objective of this trial is to assess whether FMT can prevent or delay complications, progression and mortality in patients with decompensated liver cirrhosis. Therefore, the primary endpoint is the time from randomisation to the development of a new episode of intervention-requiring decompensation or death at 12 months. A new episode of decompensation is defined in the same way as the decompensation that led to inclusion and may represent either a recurrent event or a new type of decompensation. If the patient develops refractory ascites, only the first paracentesis will count as a new decompensation. Secondary endpoints include time to decompensation or death registered at 3 and 6 months, change in mortality and change in the number of decompensation events within 1 year of trial intervention. We will perform subgroup analyses to compare the efficacy based on the type of decompensation, leading to inclusion, the aetiology of liver cirrhosis, disease severity, and the use of antibiotics or proton pump inhibitors.

Secondary objectives are to improve the understanding of the mechanisms of action of FMT in liver cirrhosis and the implications of its implementation for the patients and the healthcare system. Therefore, other secondary endpoints include changes in disease severity as measured by Model for End-stage Liver Disease (MELD),[31] Child-Pugh[32] and CLIF-C acute decompensation scores,[33] metabolic liver function, liver stiffness, liver frailty score, body composition and cognitive function at 3, 6 and 12 months, as well as quality-adjusted life-years and additional healthcare-related cost after 1 year. We will use biological samples to measure the stability of the transplanted gut microbiome, its metabolites and the effects on the gut barrier, bacterial translocation, systemic inflammation and immune function in response to FMT. See online supplemental table 1 for the full list of primary and secondary endpoints.

Trial design

The study is a multicentre, nationwide, randomised, double-blinded, placebo-controlled trial initiated by the Department of Hepatology and Gastroenterology, Aarhus University Hospital, Denmark, and conducted throughout Denmark (figure 1). We will randomise 220 patients with acute decompensation of liver cirrhosis in

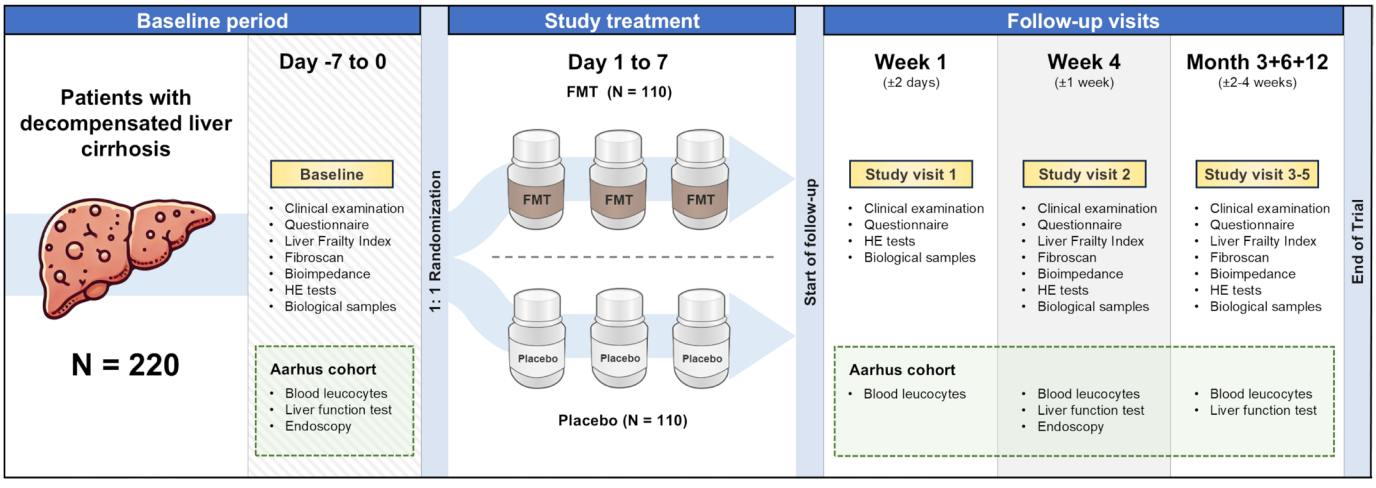

Figure 1 Patient flowchart. 220 patients admitted for acute decompensation of liver cirrhosis will be randomised to either faecal microbiota transplantation (FMT) or placebo capsules. The patients will receive FMT or placebo capsules on three separate days within 1 week following randomisation and will be followed up for 1 year. For all study participants, clinical data and biological samples will be collected before randomisation and after 1 and 4 weeks and 3, 6 and 12 months. Patients recruited in Aarhus will have additional blood samples taken to isolate blood leucocytes and will undergo a metabolic liver function test and upper endoscopy (baseline and 4 weeks) to collect duodenal mucosal biopsies. HE, hepatic encephalopathy.

a ratio of 1:1 to FMT or placebo in addition to standard of care according to the European Association for the Study of the Liver Clinical Practice Guidelines for the management of patients with decompensated cirrhosis.[5] The first patient was included in the trial in July 2021, and 40% of the patients have been included (June 2024). The planned date for completion of study, last patient's last visit, is July 2027. As a safety precaution, we will perform an interim analysis after the inclusion of either the first 40 patients in Aarhus or when 40% (88) of the patients in the trial have been included, whichever occurs first. An independent data monitoring committee will be unblinded to the treatment allocation and guide the investigators as to whether it is safe to continue the trial. For this purpose, they will, among other things, evaluate and compare the primary outcome and severe adverse events in the two treatment groups. The members of the data monitoring committee will be a hepatologist, a gastroenterologist with FMT expertise and a statistician, all with expertise in clinical trials.

Patient and public involvement

A lay reviewer at the Central Denmark Region Research Ethics Committee and at the Good Clinical Practice Unit at Aarhus University Hospital reviewed the protocol. Feedback was taken on board, and revisions were subsequently made. Patient involvement is enabled through a general patient panel related to our outpatient clinic, and a specific patient and relatives panel has been established concerning microbiome therapies. The panel consists of patients and relatives of patients who have received FMT either in routine clinical use or as a part of clinical trials. The aim of the panel is to provide feedback on patient information material and future trial designs. Study results will be presented to patient organisations in lay language. All patients who participate in the trial will be directly informed about the study results unless they decline further information.

Study population

The study will include patients aged 18–75 years with an acute decompensation of liver cirrhosis requiring intervention. The diagnosis of liver cirrhosis is based on histological, radiological and clinical parameters. Acute decompensation of liver cirrhosis is defined as the acute development of one or more of the following: ascites (not refractory), portal hypertension-related gastrointestinal bleeding, overt HE, alcoholic hepatitis or infection leading to progressive liver failure or jaundice. Alcoholic hepatitis is defined as a clinical syndrome with recent (<8 weeks) onset of jaundice (S-bilirubin>80 µmol/L) in patients with a recent history of high alcohol intake (>40/60 g alcohol per day for women/men, respectively) with less than 60 days of abstinence and where other causes of jaundice and liver disease have been ruled out.[34] The patient's Child-Pugh score at inclusion must be ≤12. Exclusion criteria are more than one organ failure as defined by the CLIF-SOFA score,[32 35] inflammatory bowel disease, coeliac disease, CDI, a diagnosis of HIV, untreated viral hepatitis or malignancy except for non-melanoma skin cancer, pregnancy and if the patient is considered unable to participate based on medical judgement (Box 1). Both inpatients and outpatients will be screened for inclusion. Inclusion in the trial does not alter the standard-of-care treatment: patients admitted with infections are not administered study treatment until they have shown a response to the antimicrobial therapy. However, it is not a requirement that the course of antimicrobials has been completed before trial intervention. All patients will receive standard-of-care treatment, including steroids in patients with alcoholic hepatitis and a Glasgow Alcoholic Hepatitis Score≥9 if evaluated eligible for treatment as well as antibiotics, lactulose, rifaximin and immunosuppressives. Active alcohol consumption is not an excluding factor.

Patients will be recruited from the Departments of Hepatology at Aarhus University Hospital, Aalborg University Hospital, Odense University Hospital, Hvidovre Hospital, Esbjerg Hospital and Sjælland University Hospital, Køge. All patients will provide written informed consent after reading the written patient information and discussing the trial with relatives and an investigator.

Box 1 Inclusion and exclusion criteria

Inclusion criteria
- ⇒ Age 18–75 years
- ⇒ Liver cirrhosis, any aetiology (histology or radiology and clinical characteristics)
- ⇒ Acute decompensation requiring intervention:
  - Portal hypertension-related gastrointestinal bleeding
  - Ascites
  - HE
  - Alcohol-associated hepatitis
  - Infection
- ⇒ Child-Pugh score≤12

Exclusion criteria
- ⇒ More than one organ failure (defined by the CLIF-SOFA score)
- ⇒ Inflammatory bowel disease, coeliac disease, *Clostridioides difficile* infection
- ⇒ Untreated malignancy except non-melanoma skin cancer
- ⇒ Untreated viral hepatitis
- ⇒ HIV diagnosis
- ⇒ Pregnancy
- ⇒ Unable to participate based on medical judgement

Intervention

The patients will receive a total of three trial applications either encapsulated FMT or placebo with the first application given within 1 week of inclusion into the trial. All patients will receive two sequential trial applications within 1 week often on three consecutive days. The trial intervention will be given as oral capsules as the most feasible route of administration.[36] One FMT application is derived from approximately 50 g of donor faeces, such that each FMT recipient receives treatment derived from approximately 150 g of donor faeces in total. The faecal

Figure 2 The placebo and faecal microbiota transplantation (FMT) capsules.

donation undergoes minimal processing according to published protocols and is then dispersed into double-coated, acid-resistant enterocapsules.[37–39] In brief, the processing involves homogenising of the faeces in sterile saline, mixing with 85% glycerol and conducting a series of centrifugations to create a dense concentrate capable of encapsulation. The number of capsules varies from 12 to 30 for each application. Placebo capsules are produced from a suspension of glycerol, sterile saline and food colouring, making them indistinguishable from the FMT capsules (figure 2). All capsules are stored at −80°C and allowed to thaw for at least 30 min and a maximum of 4 hours before administration.

The processing and handling of the donor stool adhere to the standards set in the European Tissues and Cells directive[40 41] and the technical guide issued by the Council of Europe[42] and are managed by the Blood Centre, Aarhus University Hospital, which is an accredited tissue centre. Capsules for all sites are produced in the routine laboratory at the Centre for Faecal Microbiota Transplantation (CEFTA), Aarhus University Hospital, Denmark. The selected donors are healthy individuals randomly chosen among the Blood Centre's established cohort of blood donors. All FMT donors undergo a thorough screening programme according to international standards and as previously published.[37 38] In short, the screening encompasses a medical interview and questionnaire, and screening of blood and stool samples for potentially harmful microbes. If the screening is passed, this marks the start of a 30-day donation round in which the donor may produce five donations. This donation round is ended with a similar screening. The FMT components are only removed from quarantine and used if this final screening is passed. The patients receive all three FMT applications from one donor, and we plan for 20 donors to be used in the trial.

Investigations

Following written informed consent (online supplemental file 1), the patients will undergo baseline examinations. Their medical history and current and recent medication are recorded, along with standard biochemistry. Furthermore, a quality-of-life questionnaire (EQ-5D-5L) is filled in, and a clinical examination is performed. The clinical examination includes Liver Frailty Index,[43] liver elastography (FibroScan), bioimpedance analysis and an evaluation of cognitive function using continuous reaction time measurement[44] and the portosystemic encephalopathy syndrome test.[45] Baseline biological samples of blood, saliva, faeces and urine will be collected. In blood, we will measure biomarkers of bacterial translocation, liver injury and fibrosis, and study changes in the phenotype and function of circulating immune cells. We will measure pro- and anti-inflammatory cytokines in blood and stool. The microbiome composition and function will be characterised in saliva and faecal samples using shotgun metagenomic sequencing, and metabolites will be measured in blood, stool, saliva and urine. Investigations will be repeated at 1 week (± 2 days), 4 weeks (± 1 week), 3 months (± 2 weeks), 6 and 12 months (± 4

weeks) after the administration of the trial application. In the patients included in Aarhus, we will examine the liver metabolic function by aminopyrine breath test[46] and obtain duodenal biopsies at baseline and 4 weeks after intervention in addition to the above. The biopsies are taken as part of the trial and will be used to investigate the mucosa-associated microbiome, gut-barrier integrity and mucosal immune function. Throughout the trial period, patients will be proactively asked about adverse events at each trial visit. Moreover, the medical records will be reviewed at each study visit for potential contacts to the healthcare system since the last visit. The patients will also be followed up in the clinic regularly as part of standard of care and in addition to trial visits, and will be asked to contact the clinic in case of new events occurring between visits. All adverse events will be recorded in the Case Report Form (CRF), and severe adverse reactions will be reported to the relevant authorities.

Statistical analysis

Sample size estimation

We will use a statistical significance level of 0.05 and aim for a power of 80%. In patients with decompensated liver cirrhosis, the 1-year risk of new decompensation or death is predicted to be 60%.[33 47] Previous studies found a strong effect of rifaximin on the recurrence of HE (HR 0.42),[48] and an effect of beta-blockers on decompensation (HR 0.51)[49] in patients with compensated liver cirrhosis. To be able to detect an effect of FMT with an HR of at least 0.60 (a conservative presumption of a weaker treatment response than reported in the other studies), we need to randomise 220 patients with 110 in each arm.

Statistical methods

We will use Cox proportional hazards regression to examine the efficacy of FMT versus placebo on the hazard rate of the primary outcome. Although randomisation theoretically eliminates confounding, we will minimise possible residual confounding by including the following variables in the adjusted regression model: gender, age, aetiology of liver cirrhosis, type of decompensation leading to inclusion and MELD score at randomisation. We will use Schoenfeld residuals to assess the assumption of proportional hazards. For the secondary clinical outcomes, we will study the composite endpoint of new decompensation or death also at 3 and 6 months and look solely at mortality using the methods described above. Additionally, an incidence rate of new decompensations will be compared between each treatment group. The analyses will be performed as intention-to-treat and per-protocol. In the per-protocol analysis, follow-up begins at randomisation, and patients who have received two or three FMT applications will count as treated, while patients who have received zero or one will count as untreated. Thus, treatment will be considered a time-dependent variable that for the individual patient is coded as 'untreated' from the time of randomisation, and then it changes to 'treated' when the second FMT treatment has been received. For the mechanistic secondary endpoints, we will use mixed-effect models to compare changes during follow-up in blood biomarkers between the two treatment groups. For the metagenomic data, we will describe and compare changes in the alpha- and beta-diversities and the relative abundances of specific species and enterotypes between the treatment groups. We will look at correlations between the mechanistic biomarkers and clinical characteristics by calculating Spearman's correlation coefficients.

ETHICS AND DISSEMINATION

The study will be performed in accordance with the Helsinki Declaration. Data are stored in a REDCap database under Aarhus University (www.redcap.au.dk) compliant with current data protection legislation. The protocol has received approval from the Central Denmark Region Research Ethics Committees (j.no. 1-10-72-302-20). The trial follows the guidelines of the International Conference of Harmonization—GCP (ICH-GCP), and the study will be monitored according to the principles for good clinical practice (GCP) by the GCP Unit at Aarhus and Aalborg University Hospitals and site-specific monitors. The definition and handling of adverse events will follow the ICH-GCP guidelines. The Trial Master File will serve as a source for Standard Operating Procedures, data agreements, contracts, study guides and communication between sites. The study is registered at www.clinicaltrials.gov (study identifier NCT04932577). FMT will be handled as a tissue according to the EU Tissues and Cells Directive (2204/23/ec)[41] and National Legislation[40] in a continuous dialogue with the Danish Patient Safety Authority. FMT is still an investigational treatment with potential and yet unknown long-term effects. This necessitates a close monitoring and long-term follow-up of all patients and all donors, ensured through GCP and a close dialogue with the regulatory authorities. This dialogue is established through CEFTA, Aarhus University Hospital.

The results, positive as well as negative, will be presented at national and international scientific meetings. All results will be disseminated in international, peer-reviewed journals. Authorship will be determined according to the Vancouver Declaration.

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Contributors Conceptualisation: SS, HV, CH, KLT. Writing—original draft: LLE, JSL, SD. Writing—review and editing: SS, SMDB, CE, HV, PJ, CH, KLT. Statistical analysis plan: PJ. Visualisation: SD, SMDB. Funding acquisition: SS, HV, KLT. All authors edited and approved the manuscript before submission. KLT is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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