Efficacy of the combination of simvastatin plus rifaximin in patients with decompensated cirrhosis to prevent ACLF development: a multicenter, double-blind, placebo controlled randomized clinical trial.

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The aim of this study is to assess the efficacy of oral administration of simvastatin plus rifaximin in patients with decompensated cirrhosis to halt the progression of the disease as assessed by prevention of the development of ACLF.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55488

Source
ToetsingOnline

Brief title
LIVERHOPE_EFFICACY

Condition

- Other condition
- Hepatic and hepatobiliary disorders

Synonym
Decompensated liver cirrhosis, liver damage with loss of function

Health condition

Cirrose

Research involving
Human

Sponsors and support

Primary sponsor: IDIBAPS (Institut d'Investigacions Biomediques August Pi i Sunyer)
Source(s) of monetary or material Support: Gefinancierd wordt door de Europese Commissie op grond van het Horizon 20/20-programma. het onderzoek wordt gesponsord door het Institut d'Investigacions Biomediques August Pi-Sunyer (IDIBAPS);Barcelona (Spanje).

Intervention

Keyword: Decompensated cirrhosis, LIVERHOPE_EFFICACY, Rifaximin, Simvastin

Outcome measures

Primary outcome

Efficacy of treatment in halting the progression of decompensated cirrhosis as

assessed by time to first ACLF during the treatment period, defined according

to criteria by Moreau et al., Gastroenterology 2013.

Secondary outcome

1. Time to transplant-free survival. Incidences at 1 month, 3 months, 6 months,

9 months and 12 months.

2. Severity of ACLF assessed by number and types of organ failures at baseline,

1 month, 3 months, 6 months, 9 months and 12 months.

3. Frequency of hospital admissions due to complications of cirrhosis assessed

at baseline, 1 month, 3 months, 6 months, 9 months and 12

months.

4. Development/worsening of individual complications of cirrhosis (ascites,

acute kidney injury, gastrointestinal bleeding, hepatic

encephalopathy (HE), bacterial infections) assessed at baseline, 1 month, 3

months, 6 months, 9 months and 12 months, defined as:

4.1. ASCITES:

1A. Development of new-onset ascites or worsening of preexisting ascites as

estimated by:

• Percentage of patients with new-onset ascites.

• Percentage of patients presenting worsening of ascites,

defined as:

o Increased diuretic dosage, as indicated by a double of the diuretic dose

received at entry into the study, to a dose of at least spironolactone 200

mg/day (or its equivalent dose in other aldosterone antagonists) and furosemide

20 mg/day (or its equivalent dose in other loop diuretics).

o Need for large-volume paracentesis in patients who had never been treated

with this procedure.

1B. Number of episodes of ascites per patient requiring large volume

paracentesis during the treatment period.

4.2. ACUTE KIDNEY INJURY:

• Percentage of patients developing episodes of renal function impairment

defined by AKI criteria, following criteria of the *EASL Clinical Practice

Guidelines for the management of patients with decompensated cirrhosis*.

• Percentage of patients developing episodes of renal function impairment

defined by AKI criteria as AKI IB or higher.

• Number of episodes of AKI1B or higher per patient.

• Number of patients developing severe AKI requiring RRT.

• Number of patients developing AKI-HRS syndrome (following the criteria established by the *EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis*).

4.3. GASTROINTESTINAL BLEEDING:

• Percentage of patients developing the first episode of bleeding by esophageal or gastric varices and number of bleeding episodes per patient during the treatment period.

• Percentage of patients developing recurrent variceal bleeding, defined as a second episode of variceal bleeding.

• Complications of variceal bleeding, defined as the percentage of patients requiring:

o blood transfusion during an episode of variceal bleeding.

o alternative treatment to variceal bleeding (transjugular intrahepatic portosystemic shunt).

4.4. HEPATIC ENCEPHALOPATHY

• Percentage of patients developing the first episode of HE, grade II or greater, and number of episodes of HE (grade II or greater) per patient during the follow-up period.

• Percentage of patients developing recurrent HE, defined as two episodes of HE grade II or greater within a period of 6 months during the study period.

• Percentage of patients developing severe HE, defined of grade III or IV HE.

• Percentage of patients without minimal HE, as estimated by PHES questionnaire, at entry into the study, who developed minimal HE at some point

during follow-up.

4.5. BACTERIAL INFECTIONS

• Percentage of patients developing bacterial infections during the study follow up period, defined by one of the following:

o Presence of infection confirmed by positive cultures and need for antibiotic treatment.

o Clinical suspicion of infection based on clinical and analytical data requiring empirical antibiotic therapy.

• Number of infections per patient during the study period requiring hospital admission.

• Percentage of patients developing septic shock.

5. Changes from baseline in systemic inflammatory response, evaluated by measurement in a large array of plasma cytokine levels including, but not limited to TNFα, IL-6, IL8, IL-10, IL-1β, IFN-*, G-CSF, VCAM, VEGF, as well as an oxidized form of albumin, human nonmercaptalbumin-2 (HNA2), dimethylarginine (ADMA and SDMA) at 3 months, 6 months and 12 months.

6. Changes from baseline in plasma biomarkers (FABP4, sCD-163), von Willebrand factor (vWF) and urine biomarkers (NGAL, MCP-1 and albumin) at 3 months, 6 months and 12 months.

7. Changes from baseline in vasoactive hormones: plasma renin concentration, plasma norepinephrine and plasma copeptin at 3 months, 6 months and 12 months.

8. Changes from baseline in blood levels of bacterial DNA or bacterial products at 3 months, 6 months and 12 months.

9. To evaluate changes in microbiome composition by analysis of microbial genes and signature in patients included in the study at baseline, 3 months, 6 months and 12 months.

10. Changes from baseline in liver function, evaluated by MELD score, CLIF-AD score and Child Pugh Score (see Appendix 4) at 1 month, 3 months, 6 months, 9 months and 12 months.

11. Quality of life, functional assessment and in Minimal Hepatic Encephalopathy during treatment period, as assessed by CLDQ (Chronic Liver Disease Questionnaire), Liver Frailty Index and PHES (Psychometric Hepatic Encephalopathy Score) questionnaires at baseline, 1 month, 3 months, 6 months, 9 months and 12 months.

12. Changes from baseline in stigmatization in patients with decompensated cirrhosis as assessed by a previously validated specific questionnaire (see appendix 8) at 3 months, 6 months and 12 months.

13. Appearance of muscle toxicity at baseline, 1 month, 3 months, 6 months, 9 months and 12 months as defined using a specific statinassociated myopathy questionnaire.

14. Assessment of genetic polymorphisms of statins membrane transporter OATP1B1 in all the patients included in the study.

15. To evaluate liver or muscle toxicity as defined by analytical changes from baseline in liver or muscle enzymes (transaminases, alkaline phosphatase and creatine kinase) at 1 month, 3 months, 6 months, 9 months and 12 months.

16. Proportion of patients and severity of treatment-related adverse events

during the study period.

17. Annualized incidence of ACLF.

18. Time to overall and time to disease related survival.

Study description

Background summary

Chronic inflammatory diseases of the liver are very common worldwide. They may occur either as a result of chronic viral infections, due to hepatitis B or C, excessive alcohol consumption, non-alcoholic fatty liver disease (usually associated with obesity and/or diabetes), autoimmune diseases or miscellaneous conditions. The main risk of a chronic inflammatory reaction of the liver is the development of liver cirrhosis. Cirrhosis increases markedly the risk of carcinogenesis so that a significant proportion of patients develop primary liver cell cancer, also known as hepatocellular carcinoma.
Because of its high frequency and high progression rate, liver cirrhosis is one of the most common causes of death worldwide.
This indicates that cirrhosis is one of the chronic diseases with greatest impact in patients' life. In addition to high mortality and impaired quality-of-life, cirrhosis is responsible fora high number of hospitalizations which are very costly and represent a high burden tor health systems.
The standard of care for patients with cirrhosis is based on the management of each complication individually. Currently, there is no an overall therapeutic strategy based on a mechanistic approach to complications of cirrhosis.
Therefore, there is an unmet need in the management of patients with cirrhosis of a therapy that could prevent the development of complications, particularly ACLF, reduce hospital readmissions and overall cost, and improve survival.

Study objective

The aim of this study is to assess the efficacy of oral administration of simvastatin plus rifaximin in patients with decompensated cirrhosis to halt the progression of the disease as assessed by prevention of the development of ACLF.

Study design

This is a phase 3, multicentre, double-blind, placebo-controlled trial to evaluate the efficacy of oral administration of simvastatin plus rifaximin in patients with decompensated cirrhosis for prevention of disease progression and

ACLF development.
European tertiary care centres will participate into the clinical trial.

Two cohorts of 120 patients with decompensated cirrhosis will be randomized to receive:
1) Oral Simvastatin 20mg/day and oral Rifaximin 400 mg/8h.
2) Placebo of simvastatin and placebo of rifaximin.

Patients will receive treatment during 12 months.

Intervention

Oral Simvastatin 20mg/day and oral Rifaximin 400 mg/8h OR placebo of simvastatin and placebo of rifaximin.

Study burden and risks

Statins are one of the most prescribed drugs in patients with hyperlipidemia and for prevention of cardiovascular events, and they are in general well tolerated. The relationship between statins and hepatotoxicity has been widely studied in the general population. Safety of statins in patients with decompensated cirrhosis has been assessed in two randomized, placebo-controlled trials that evaluated the effect of statins on portal pressure and incidence of gastrointestinal bleeding. These studies included patients from all Child-Pugh classes (A, B and C), but excluded patients with severe liver failure defined as prothrombin time <40%, serum bilirubin >5mg/dL, hepatic encephalopathy grades Il-IV, Child-Pugh score >12 or serum creatinine >1.5mg/dL. These studies did not show significant elevations in serum transaminases levels in patients treated with statins compared to the
placebo group
Rifaximin is an antibiotic with braad-spectrum antimicrobial activity with minimal (<0.4-1 %) intestinal absorption, that eliminates intestinal flora non-selectively lt is a well-tolerated drug with no interactions with ether drugs, in healthy an also in cirrhotic subjects.
There are two studies that have investigated the eflicacy of rifaximin for prevention of recurrent hepatic encephalopathy in patients with cirrhosis and have demonstrated that long treatment with rifaximin (6 and 24 months respectively) is safe and well tolerated. Treatment with rifaximin did not increase the frequency of adverse events or the risk of infections caused by resistant bacteria compared to patients from the placebo group. Current guidelines of the European Association for the Study of the Liver recommend the use of rifaximin as a chronic treatrnent in the specific population of patients with cirrhosis and hepatic encephalopathy.
Therefore, statins are safe drugs with a very low incidence of severe hepatotoxicity in the general population and they appear to be safe also in patients with chronic liver diseases. Rifaximin is also a safe antibiotic with

no evidence of an increase of infections caused by resistant-bacteria after long-term use and a well- tolerated drug. Results from the present study will bring us more detailed information on the safety of the combination of statins plus rifaximin in patients with decompensated cirrhosis in order to have enough safety information prior to the development of the eflicacy study.

As a preliminary result of the Liverhope Safety Trial, it was concluded that the dose of Simvastatin 40mg per day in patients with decompensated cirrhosis was associated with an increased risk of liver and muscle toxicity. On the other hand, Simvastatin 20mg per day plus Rifaximin is not associated to a higher risk of liver or muscle toxicity in patients with decompensated cirrhosis.
These results suggested that Simvastatin 20mg/day should be preferred to 40 mg/day in studies investigating the effects of statins in patients with decompensated cirrhosis. As a result of this first safety trial, the dose of Simvastatin 20mg per day was established for
the Liverhope Efficacy Trial.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients included into the study must meet all the following criteria:
1. Age >= 18 years old.
2. Cirrhosis defined by standard clinical criteria, ultrasonographic findings and/or histology. Cirrhosis of any aetiology may be included. However, patients with cirrhosis due to autoimmune hepatitis must be on stable corticosteroid dose for >=3-month period before study inclusion.
3. Child-Pugh B patients or Child-Pugh C patients (up to 12 points).
4. Women of child-bearing potential must have a negative pregnancy test in serum before the inclusion in the study and agree to use highly effective contraceptive methods during the study. Highly effective contraceptive methods will include: intrauterine device, bilateral tubal occlusion, vasectomized partner and sexual abstinence. (only if refraining from heterosexual intercourse during the period of twelve months of duration of the study and extended to 30 days after the end of the study treatment) Hormonal contraceptive methods will be avoided due to the risk of adverse events and impairment of liver function.

Exclusion criteria

1. Patients on treatment with statins or rifaximin up to one month before study inclusion.
2. Patients with contraindications for statins or rifaximin therapy.
3. Known hypersensitivity to simvastatin or rifaximin (or rifamycin derivatives).
4. Patients with CK elevation of 50% or more above the upper limit of normal at study inclusion.
5. Patients on treatment with potent inhibitors of CYP3A4 enzyme (see section 5.2: Concomitant, nonpermitted and permitted medication).
6. Patients on treatment with drugs with potential interactions with simvastatin (see section 5.2: Concomitant, nonpermitted and permitted medication).
7. Patients with previous history of myopathy.
8. Patients with previous history of intestinal obstruction or those who are at increased risk of this complication.
9. Patients with ACLF according to the criteria published by Moreau et al. (see appendix 2).

10. Serum creatinine >=2 mg/dL (176.8 µmol/L).
11. Serum bilirubin>5 mg/dL (85.5 µmol/L).
12. INR >=2.5. Patients under anticoagulant therapy will be excluded if the INR values are >= 3.5
13. Bacterial infection within 10 days before study inclusion.
14. Gastrointestinal bleeding within 10 days before study inclusion.
15. Current overt hepatic encephalopathy, defined as grade II-IV hepatic encephalopathy according to the New-Haven classification.
16. Patients with active hepatocellular carcinoma or history of hepatocellular carcinoma that is in remission for less than six months for uninodular HCC or for less than 12 months for multinodular HCC within Milan criteria.
17. Patients on antiviral therapy for HCV or those who have received it within the last 6 months.
18. Severe alcoholic hepatitis requiring corticosteroid therapy (Maddrey*s Discriminant function >= 32 and/or ABIC score > 6.7).
19. Patients with active alcohol consumption of more than 21 units per week.
20. HIV infection.
21. Patients with a history of significant extra hepatic disease with impaired short-term prognosis, including congestive heart failure New York Heart Association Grade III/IV, COPD GOLD >2, chronic kidney disease with serum creatinine >2mg/dL or under renal replacement therapy.
22. Patients with current extra hepatic malignancies including solid tumours and hematologic disorders.
23. Pregnancy or breastfeeding.
24. Patients included in other clinical trials in the month before inclusion.
25. Patients with mental incapacity, language barrier, bad social support or any other reason considered by the investigator precluding adequate understanding, cooperation or compliance in the study.
26. Refusal to give informed consent.
27. Creatinine clearance < 30 ml/min
28. Patients with cirrhosis due to cholestatic liver disease can only be included in the study if they present clinical decompensation of cirrhosis (i.e. ascites).
29. Patients with previous organ transplantation.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-01-2019
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Rifaximin
Generic name:	Rifaximin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Simvastatin
Generic name:	Simvastin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-08-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-02-2021
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-001698-25-NL
ClinicalTrials.gov	NCT03780673
CCMO	NL66707.018.18