Safety and tolerability of the combination of simvastatin plus rifaximin in patients with decompensated cirrhosis: a multicenter, double-blind, placebo controlled randomized clinical trial.

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The aim of this study is to assess the safety and tolerability of oral administration of simvastatin plus rifaximin in patients with decompensated cirrhosis.

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

Summary

ID

NL-OMON45574

Source
ToetsingOnline

Brief title
LIVERHOPE_SAFETY

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, Rifaximin, Simvastin

Outcome measures

Primary outcome

Change from baseline in transaminases, alkaline phosphatase and creatine kinase

during the treatment period, to evaluate treatment-related toxicity.

Secondary outcome

- Appearance of muscle toxicity at weeks 2, 4, 6, 8, 10 and 12 as defined using

a specific statin-associated myopathy questionnaire (see appendix 2).

- Changes from baseline in plasma renin concentration, serum aldosterone,

plasma norepinephrine, and plasma copeptin levels at weeks 2, 4, 8 and 12.

- Changes from baseline in a large array of plasma cytokine levels including,

but not limited to, VCAM-1, VEGF-A, Fractalkine, MIP-1α, Eotaxin, IP-10,

RANTES, GM-CSF, IL-1β, IL-2, ICAM-1, MCP-1, L-6, and IL-8, as well as an

oxidized form of albumin, human nonmercaptalbumin-2 (HNA2) at weeks 2, 4, 8 and

12.

- Changes from baseline in plasma biomarkers FABP4 and CD-163 and urine

biomarkers NGAL, IL-18, MCP-1, osteopontin, and albumin at weeks 2, 4, 8 and 12.

- Changes in blood levels of bacterial DNA or bacterial products at weeks 2, 4,

8 and 12.

- Assessment of genetic polymorphisms of statins membrane transporter OATPB1 in

patients developing treatment-related toxicity (defined as the primary endpoint

of the study).

- Proportion of patients with treatment-related serious adverse events during

the study period.

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 for a high number of hospitalizations which are very costly and represent a high burden for health systems.
The standard of care for patients with cirrhosis is based on the management of each complication individually (18,19). 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 safety and tolerability of oral administration of simvastatin plus rifaximin in patients with decompensated

cirrhosis.

Study design

This is a phase 2, multicenter, double-blind, placebo-controlled trial to evaluate the safety and tolerability of oral administration of simvastatin plus rifaximin in patients with decompensated cirrhosis.
Nine European tertiary care centers will participate into the clinical trial.
Three cohorts of 15 patients with descompensated cirrhosis will be randomized to receive:
1) Oral simvastatin 20 mg/day and oral rifaximin 400 mg/8h
2) Oral simvastatin 40 mg/day and oral rifaximin 400 mg/8h
3) Placebo of simvastatin and placebo of rifaximin
Patients will receive treatment during 12 weeks.

Intervention

Simvastatin 20mg or 40mg tablets and placebo of simvastatin + Rifaximin 400mg tablets 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 II-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 (39,41).
Rifaximin is an antibiotic with broad-spectrum antimicrobial activity with minimal (<0.4-1%) intestinal absorption, that eliminates intestinal flora non-selectively (39). It is a well-tolerated drug with no interactions with other drugs, in healthy an also in cirrhotic subjects.
There are two studies that have investigated the efficacy 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 treatment in the specific population of patients

with cirrhosis and hepatic encephalopathy (54).
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 efficacy study.

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

1. Age >= 18 years old.

2. Cirrhosis defined by standard clinical criteria and ultrasonographic findings and/or histology. Cirrhosis of any etiology may be included. Patients with cirrhosis of autoimmune etiology on treatment with corticosteroids must be on stable corticosteroid dose for >=3-month period before study inclusion.
3. Child Pugh B/C patients (from 7 to 12 points).
4. Women of child-bearing potential must have a negative pregnancy test in urine before the inclusion of the study and agree to use highly effective contraceptive methods (combined oral pill, injectable or implanted contraceptive, intrauterine device / intrauterine hormone-releasing system) during the study.

Exclusion criteria

1. Patients on treatment with statins or rifaximin one month before study inclusion.
2. Patients on the waiting list for liver transplantation.
3. Patients with acute-on-chronic liver failure according to the criteria published by Moreau et al. (see appendix 1)
4. Serum creatinine >=2 mg/dL.
5. Serum bilirubin>5 mg/dL.
6. INR >=2.5.
7. Patients with CK elevation of 50% or more above the upper limit of normal at study inclusion.
8. Bacterial infection within 15 days before study inclusion.
9. Gastrointestinal bleeding within 15 days before study inclusion.
10. Current overt hepatic encephalopathy, defined as grade II-IV hepatic encephalopathy.
11. HIV infection.
12. Hepatocellular carcinoma outside Milan criteria, defined as a single nodule <=5 cm or a maximum of 3 nodules with none >3 cm.
13. Patients on antiviral therapy for HCV or those who have received it within the last 6 months.
14. Patients with previous history of myopathy.
15. Patients on treatment with potent inhibitors of CYP3A4 enzyme (See section 5.2: Concomitant, nonpermitted and permitted medication)
16. Patients on treatment with drugs with potential interactions with simvastatin (see section 5.2: Concomitant, nonpermitted and permitted medication)
17. Patients with a history of significant extrahepatic 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.
18. Patients with current extrahepatic malignancies including solid tumours and hematologic disorders.
19. Patients with previous history or increased risk of intestinal obstruction.
20. Pregnancy or breastfeeding.
21. Patients included in other clinical trials in the previous month.
22. Patients with active alcohol consumption of more than 3 units per day.
23. 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.
24. Severe alcoholic hepatitis requiring corticosteroid therapy (Maddrey*s Discriminant function >= 32 and/or ABIC score > 6.7).
25. Refusal to give informed consent.
26. Patients with contraindications for statins or rifaximin.
27. Known hypersensitivity to rifaxamin (or rifamycin derivatives) or to simvastatin.

Study design

Design

Study phase:	2
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):	11-10-2017
Enrollment:	5
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:	Simvastatin

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	11-04-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-05-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-08-2017
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	EUCTR2016-004499-23-NL
CCMO	NL61020.018.17

Study results

Date completed: 20-02-2018

Actual enrolment: 3

Summary results

Trial is onging in other countries