Prevention of hepatic Encephalopathy by Administration of Rifaximin and Lactulose in patients with liver cirrhosis undergoing placement of a transjugular intrahepatic portosystemic shunt: a multi-centre randomized, double blind, placebo controlled trial. The PEARL trial

Published: 07-01-2019
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This study has been transitioned to CTIS with ID 2024-512040-28-01 check the CTIS register for the current data. To assess the incidence of post-TIPS OHE within the first three months after prophylactic administration of lactulose and rifaximin...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55418

Source
ToetsingOnline

Brief title
The PEARL trial

Condition

- Other condition

Synonym
hepatic encephalopathy, neurocognitive impairment

Health condition

hepatische encefalopathie

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Subsidie ZonMw programma Goed Gebruik Geneesmiddelen.,Norgine

Intervention

Keyword: hepatic encephalopathy, prevention, rifaximin, transjugular intrahepatic portosystemic shunt

Outcome measures

Primary outcome

Primary endpoint is the development of OHE within three months after TIPS

placement determined by the West Haven criteria.

substudy 1:

Primary objective of this ancillary study is to assess the effect of TIPS

placement on microbiota-host interaction based on the following assessments at

screening, day of TIPS placement, month 3 (end of study medication treatment)

and month 12:

- 16s rRNA based analysis of microbiota in stool

- 16s rRNA based analysis of microbiota in saliva

- Circulating biomarkers for inflammatory, circulatory and endothelial function.

substudy 2:

- To compare the activation status, immunological and metabolic function of circulating monocytes/macrophages obtained from patients with alcoholic liver cirrhosis (ALD).

Secondary outcome

Secondary endpoints are 90 day mortality;

development of a second episode of OHE within the first three months;

development of OHE in the period between three and twelve months after TIPS placement;

development of MHE between TIPS placement and twelve months after placement;

time to development of OHE or MHE episode(s)

the increase of the PHES and simplified one minute animal naming test (S-ANT1) at week 4, week 12 and week 52, compared to baseline.

the change in Liver Frailty Index score at week 12 and week 52, compared to baseline

Differences in molecular composition of peripheral / portal blood samples at TIPS placement.

Differences in molecular composition of peripheral blood samples at baseline, week 12 and week 52.

Furthermore, quality of life will be assessed by the Liver Disease Symptom Index 2.0 (LDSI 2.0) and EQ-5D-5L questionnaires at baseline, week 12 and week 52.

Economic evaluation.

substudy 1:

- to assess the relationship between post-TIPS hepatic encephalopathy and microbiota composition.

- to assess the relationship between post-TIPS hepatic encephalopathy and inflammatory, circulatory and endothelial function respectively.

- to assess the relationship between post-TIPS acute decompensation/ACLF or mortality at short (3 months) and long term (< 12 months) and microbiota composition.

- to assess the relationship between post-TIPS acute decompensation/ACLF or mortality at short (3 months) and long term (< 12 months) and inflammatory, circulatory and endothelial function respectively.

substudy 2:

* Identify the levels of bacterial products, in the portal and systemic blood from patients with ALD.

* Identify the nature and levels of inflammatory cytokines reaching the liver from the gut in patients with decompensated liver disease undergoing TIPS for intractable ascites

* To determine the pre and post TIPS immunological factors that may be predictive of encephalopathy following TIPS placement.

* To determine the activation status, cytokines responses, immunological- and metabolic function by circulating monocytes present in the peripheral blood of patients admitted with acute alcoholic hepatitis and acute- on- chronic liver failure and how these individual responses may correlate with survival.

* To follow up patients longitudinally and identify a set of parameters and

read-outs that can predict patient outcome.

Study description

Background summary

Hepatic encephalopathy (HE) is a major and common complication in patients with liver cirrhosis. HE can be classified in the extensive range of neurocognitive deterioration as minimal HE (MHE), covert HE (grade I), or overt HE (OHE, grade II-IV). Liver cirrhosis is the most common cause of portal hypertension (PH). Patients who develop complications of PH, like variceal bleeding or refractory ascites, can benefit from a Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement. Unfortunately, post-TIPS HE is a common and often severe complication. Incidence of new onset or worsening of HE after TIPS is approximately 20-45%. Currently there is no strategy to prevent post-TIPS HE.

Study objective

This study has been transitioned to CTIS with ID 2024-512040-28-01 check the CTIS register for the current data.

To assess the incidence of post-TIPS OHE within the first three months after prophylactic administration of lactulose and rifaximin versus placebo in patients who undergo Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement.

Study design

A multicentre, randomized, placebo-controlled, double blind study.

Intervention

Rifaximin 550mg b.i.d. will be prescribed, in combination with a starting dose of 25mL lactulose b.i.d. (or a previous prescribed dose) and further dependent on the amount of daily bowel movements, with the objective not to exceed more than two soft stools per day.

Intervention will start 72 hours before TIPS placement, and will last till three months after TIPS placement.

The control group will receive placebo in combination with lactulose (as

described above).

Study burden and risks

Since study visits are combined with regular visits, participants have a minimal extra burden of this study. Blood withdrawl will be in combination with regular sampling. Psycomotoric tests are all non-invasive.

Study medication is safe and adverse effects of lactulose are highly dosage dependent and can be adjusted properly.

Contacts

Public
Academisch Medisch Centrum

Amsterdam 1105AZ
NL
Scientific
Academisch Medisch Centrum

Amsterdam 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Elective TIPS placement for refractory ascites or recurrent variceal

bleeding:
* Recurrent tense ascites and one or more of the following criteria:
i. Not responding to the maximal dose of diuretics (400mg spironolactone and 160mg furosemide).
ii. Kidney insufficiency (Creatinine > 135 umol/L) induced by diuretics.
iii. Electrolyte disturbances (Sodium < 125 mmol/L, Potassium > 5.5 mmol/L) induced by diuretics.
iv. Not tolerating higher dose of diuretics. (e.g. because of subjective side effects like muscle cramps).
* (Recurrent) variceal bleeding, not responsive to treatment with endoscopic band ligation and/or beta-blockers, with a high risk of failure of endoscopic treatment:
i. Patients with a variceal bleeding and Child-Pugh C (10-13 points) cirrhosis
ii. Patients with a variceal bleeding, Child-Pugh B and an active bleeding during endoscopy
2. Age * 18 years
3. Confirmed liver cirrhosis as documented by liver biopsy, elastography (e.g. Fibroscan) or combination of usual radiological and biochemical criteria.
4. Signed informed consent

Exclusion criteria

1. Any absolute contraindications for TIPS placement:
a. History of hepatic encephalopathy grade II-IV without precipitating factor
b. Heart failure NYHA * grade 3
c. Hepatocellular carcinoma (multifocal or large or centrally located)
d. Systemic infection / sepsis
e. Severe pulmonary hypertension
f. Unrelieved bile duct obstruction
g. Technically not feasible
h. Poor liver function (MELD score > 20)
2. Use of ciclosporin
3. Life-threating variceal bleeding with emergency TIPS placement
4. Age > 80 years
5. Non-cirrhotic portal hypertension
6. Portal vein thrombosis (main trunk)
7. Current or recent (<3 months) use of rifaximin
8. Overt neurologic diseases such as Alzheimer*s disease, Parkinson*s disease
9. Pregnant or breastfeeding women
10. Patients refusing or unable to sign informed consent

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-01-2020
Enrollment:	185
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Lactulose
Generic name:	Lactulose
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	TARGAXAN
Generic name:	rifaximin
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	07-01-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	06-06-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO	
Date:	08-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	
Date:	05-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	
Date:	14-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	
Date:	21-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	
Date:	22-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	
Date:	31-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	
Date:	18-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	
Date:	06-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	08-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2024
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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
EU-CTR	CTIS2024-512040-28-01
EudraCT	EUCTR2018-004323-37-NL
ClinicalTrials.gov	NCT04073290
CCMO	NL68205.018.18