An open, non-randomized, parallel-group pharmokinetic and -dynamic, investigator-initiated study on effects of obeticholic acid (OCA) in bile of patients with primary biliary cholangitis (PBC) and non-alcoholic steatohepatitis (NASH) in comparison to healthy controls

Published: 27-02-2017
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To explore the exact working mechnism of OCA in PBC / NASH patients in comparison with healthy volunteers

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON47216

Source
ToetsingOnline

Brief title
OCABILE

Condition

- Hepatic and hepatobiliary disorders

Synonym
fatty liver disease, non-alcoholic steatohepatitis, Primary biliary cholangitis, small bile duct injury

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Via Intercept

Intervention

Keyword: Bile, NASH, Obeticholic acid, PBC

Outcome measures

Primary outcome

Assess the effect of obeticholic acid (OCA) in patients with PBC [in combination with long-term UDCA treatment (15 mg/kg/d)], patients with NASH and healthy volunteers on the bile acid and lipid composition of bile and serum,

Secondary outcome

Assess the effect of obeticholic acid (OCA) in patients with PBC [in combination with long-term UDCA treatment (15 mg/kg/d)], patients with NASH and healthy volunteers on the biliary and serum levels of cytokines (e.g., IL-6, IL-8, TNF*), chemokines and enterohepatic hormones (e.g., FGF-19)

Assess the effect of obeticholic acid (OCA) in patients with PBC [in combination with long-term UDCA treatment (15 mg/kg/d)], patients with NASH and healthy volunteers on the bile acid composition and microbiome in faeces

Assess the effect of obeticholic acid (OCA) in patients with PBC [in combination with long-term UDCA treatment (15 mg/kg/d)], patients with NASH and healthy volunteers on the expression of duodenal transport proteins and enzymes

contributing to the biliary and intestinal detoxification machinery

Study description

Background summary

Obeticholic acid (OCA) is a semi-synthetic bile acid analogue, being 100 times more potent than the endogenous bile acid chenodeoxycholic acid (CDCA) as a farnesoid X receptor (FXR) activator. (7) OCA has shown anti-cholestatic, anti-inflammatory and anti-fibrotic effects in pre-clinical and clinical studies. (8) OCA is being developed in the United States and Europe for the treatment of primary biliary cholangitis (PBC), nonalcoholic fatty liver disease (NAFLD) associated with type 2 diabetes, non-alcoholic steatohepatitis (NASH), primary sclerosing cholangitis (PSC), and biliary atresia. The exact working mechanism of OCA is still unclear.

Study objective

To explore the exact working mechnism of OCA in PBC / NASH patients in comparison with healthy volunteers

Study design

11 patients suffering from PBC (treated with ursodeoxycholic acid 15mg/kg daily), 11 patients with NASH and 11 healthy volunteers matched at best in term of demographic characteristics will take obeticholic acid at a dosage of 10 mg/day during a treatment period of 28 days. Prior to intake of the study medication and 24 hours after intake of the last dose of study medication, an endoscopy of the upper gastrointestinal tract will be performed. During both endoscopies, cystic bile samples and biopsies of the duodenum will be taken. In addition, blood samples for pharmacokinetic analyses of bile acids and bile acid metabolites in serum will be drawn during 24 hours after intake of the last dose of study medication.

Intervention

Obeticholic acid 10mg once daily

Study burden and risks

- Study medicine:

In randomized controlled trials, obeticholic acid has shown to be safe and

effective in PBC and NASH patients.

- Other interventions:

At the baseline visit and at day 30 a gastroscopy will be performed. The gastroscopy will be performed under conscious sedation (with midazolam).

In this short investigation the esophagus, stomach and proximal duodenum are visualized with an endoscope. Duodenal biopsies are taken during this endoscopy. A rare but potentially severe risk of a biopsy is a perforation. In some cases perforation can be treated conservatively or endoscopically. In a minority of cases, surgery has to be performed to close the perforation (extremely rare, high burden).

Another very rare risk of an duodenal biopsy is bleeding, which can be treated endoscopically. (rare, intermediate burden)

Sedation carries the risk of aspiration (rare, intermediate burden).

Sampling of peripheral venous blood will be performed and carries the risk of hematoma (common, low burden) and phlebitis (rare, low intermediate burden).

During 4 weeks patients are asked to fill in a diary, the burden is low and the risk is zero.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef
Amsterdam Zuid-Oost 1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef
Amsterdam Zuid-Oost 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male or female patients / volunteers of 18 to 75 years of age.
- Body mass index within 18 to 40 kg/m2
- Positive AMA (anti-mitochondrial antibody) testing (for PBC patients).
- Proven non-cirrhotic liver disease compatible with PBC stage I, II, III or NASH, no reliable signs of portal hypertension such as esophageal varices or ascites and/or pylephlebectasia > 15 mm, and a fibroscan < 15 kPa.
- The diagnosis of NASH must be confirmed by a liver biopsy (e.g. according Brunt criteria) in the last 24 months

Exclusion criteria

- Existing cardiac / hematological / renal / gastrointestinal diseases which might interfere with the drugs' safety, tolerability, absorption, pharmacokinetics and / or endoscopy.
- Other acute or chronic diseases which might affect absorption or metabolism of OCA
- Existing disorders of the coagulation system or treatment with anticoagulants or agents inhibiting thrombocyte aggregation
- Positive anti-HIV-test, HBsAg-test or anti-HCV-test.
- Acute inflammation of the gallbladder.
- Cholecystectomy
- Histologically proven cirrhotic liver disease or total bilirubin > 2 mg/dl or reliable signs of portal hypertension such as esophageal varices or ascites and/or pylephlebectasia > 15 mm and / or fibroscan > 15 kPa.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-07-2017
Enrollment:	33
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Obeticholic acid
Generic name:	6a-ethyl chenodeoxycholic acid (6-ECDCA)

Ethics review

Approved WMO Date:	27-02-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-07-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2019
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	EUCTR2016-002965-67-NL
CCMO	NL57877.018.16