The effect of peroxisome proliferator activator receptor * agonist pre-treatment on pegylated interferon-*2a and ribavirin efficacy in hepatitis C patients, previously resistant to treatment with pegylated interferon and ribavirin
- a randomized-controlled trial -

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON31787

Source
ToetsingOnline

Brief title
HEPAR Study

Condition

- Hepatic and hepatobiliary disorders
- Viral infectious disorders

Synonym
Viral liver disease; Hepatitis C

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Hoffmann-La Roche

Intervention

Keyword: Hepatitis C, Liver, PPAR-Y, Treatment

Outcome measures

Primary outcome

Outcome is presented as non-detectable hepatitis C virus, 6 months after

finishing PEG-IFN/RBV therapy.

Secondary outcome

Prior to randomisation, at 16 weeks and at 28 weeks, patients will undergo

liver biopsies to assess disease activity and histomorphology, and 1H-MRS to

non-invasively quantify liver fat accumulation. In addition, insulin resistance

will be assessed by an oral glucose tolerance test (OGTT). Finally, various

metabolic parameters and markers of inflammation and oxidative stress will be

measured

Study description

Background summary

Currently, hepatic steatosis or non-alcoholic fatty liver disease (NAFLD) is regarded as a key pathogenic factor and component of the metabolic syndrome. Hepatocellular steatosis in chronic hepatitis C (CHC) has been described in all

hepatitis C virus (HCV) genotypes. Whereas in genotype 3 hepatic steatosis seems a consequence of a direct toxic effect of HCV on hepatocytes, in genotype 1, metabolic derangements, in particular insulin resistance may contribute to liver fat accumulation. Thus, steatosis and insulin resistance may negatively impact on the liver, thereby adversely influencing treatment efficacy and enhance progression to fibrosis. A yet it is unknown whether prior delipidation of the liver and improvement of insulin sensitivity would improve the responsiveness to subsequent anti-viral therapy.
Peroxisome-proliferator-activator-receptor (PPAR)-* agonists or thiazolidinediones (TZD) are a new class of drugs for the treatment of type 2 diabetes. In addition to their insulin sensitizing effects, TZD have been shown to significantly reduce hepatic steatosis. The state-of-the-art noninvasive method for quantification of hepatic fat in vivo is proton (1H) magnetic resonance spectroscopy (MRS).

We hypothesize that (hepatic) insulin resistance and liver fat accumulation underlie the decreased/absent responsiveness to antiviral therapy in a subgroup of CHC patients. Pre-treatment with PPAR-* agonists, through amelioration of insulin resistance and decrease in hepatic steatosis, may result in an increase of sustained viral response (SVR) to subsequent standard antiviral therapy with PEG-IFN and RBV in patients with CHC previously non-responding or relapsing to PEG-IFN containing antiviral therapy.

Study objective

The primary objective is to study the effect of a 16-week treatment with a PPAR-* agonist versus placebo on effectiveness of subsequent standard treatment with PEG-IFN and RBV, measured as SVR, in previously non-responders or relapsers with CHC genotype 1.
Secondary objectives are to study associations of disease activity, liver fat content, liver function, liver histomorphology, insulin sensitivity and response to antiviral therapy.

Study design

Monocenter double-blind randomized placebo-controlled trial.

Intervention

Patients will be randomized for treatment with either PPAR-* agonist (pioglitazone; daily dose of 45 mg) or corresponding placebo during 16 weeks, prior to the start of PEG-IFN/RBV therapy.

Study burden and risks

The risk to and burden for the subject will be in proportion to the potential

value of the research. Subjects have a CHC infection, which opposes them with a serious health risk. The subjects in this study did not respond to standard previous treatment for this disease. Thus, there are no further validated established treatment options for these patients. We hypothesize that pre-treatment with pioglitazone may result in an increased and sustained response to antiviral treatment. This benefit outweighs the extra efforts and minor extra risks a subject is exposed to. Extra risk will be kept to a minimum.

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

* CHC genotype 1 infected men and women * 21 and * 65 yrs of age
* Previously non-responders or relapsers to any PEG-IFN-containing treatment

* Patients requiring a liver biopsy before treatment
* Fasting plasma glucose *7.0 mmol/l
* Hepatic steatosis
* Written informed consent

Exclusion criteria

* Exclusion criteria for MRI
* ALT levels * 150 IU/ml
* Co-infection with HIV or hepatitis B
* Present excessive alcohol use defined as > 2 units/day
* Cardiovascular co-morbidity
* Any type of diabetes mellitus
* Use of glucocorticosteroids, hormonal substitution, pagitaxel, theofyllin, myelosuppresive agents.
* A psychiatric, addictive or any other disorder that compromises the subjects ability to understand the study content and to give written informed consent for participation in the study
* Present abuse of i.v. drugs (including methadon)
* Subject no longer available for follow-up assessment
* Standard contraindication for treatment with PEG-IFN and RBV

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	01-04-2008
Enrollment:	50

Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Actos
Generic name:	Pioglitazone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-09-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-12-2008
Application type:	First submission
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	EUCTR2007-007075-16-NL
CCMO	NL18763.029.07
Other	volgt