Prospective study on peripheral and intrahepatic immune cells derived from chronic hepatitis B patients during and after long-term treatment with direct antivirals

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To identify correlations between immune changes at the cellular or molecular level in the serial FNAB and blood samples before and after withdrawal of treatment, and * in case of relapse - to identify correlations between the degree of immune...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatic and hepatobiliary disorders
Study type	Observational invasive

Summary

ID

NL-OMON49813

Source
ToetsingOnline

Brief title
HBV-FNAB-002 study

Condition

- Hepatic and hepatobiliary disorders
- Viral infectious disorders

Synonym
chronic hepatitis B

Research involving
Human

Sponsors and support

Primary sponsor: Stichting Leveronderzoek
Source(s) of monetary or material Support: Janssen-Cilag,Stichting Leveronderzoek

Intervention

Keyword: - fine needle liver aspirate biopsy, - intrahepatic immune change, - stop long-term treatment with direct antivirals

Outcome measures

Primary outcome

The focus of the research is a comparison between all samples (cross-sectional and prospective study) of fine needle liver aspirates of patients at different chronic HBV infection phases with the aim to identify correlates between intrahepatic immune changes at the cellular or molecular level and viral control.

Secondary outcome

Multiple assessments are scheduled tor the same time point: vital signs, physical examinalion, blood collection tor safety, biochemica! and serological parameters, blood collection tor PBMC isolation, blood collection for serum and whole blood parameters and liver FNABs. Cells from blood and liver will be evaluated tor their phenotype by flow cytometry, and for their gene expression by RNA sequencing.

Study description

Background summary

Globally 257 million people are chronically infected with hepatitis B virus (HBV). In these patients the immune system is incapable of clearing the virus.

The levels of HBV DNA, ALT and hepatitis B envelope antigen (HBeAg) vary greatly between patients, and may fluctuate in the same patient. The long-term consequences of chronic HBV infection can be severe, since patients are at increased risk for developing liver fibrosis, cirrhosis and/or hepatocellular carcinoma. To better describe the disease state of the patient and to guide treatment strategies, a clinical distinction into four phases was made based on variations in serum HBV DNA, ALT and HBeAg levels. These four clinical HBV phases are known as the immune tolerant (IT), immune active (IA), inactive carrier (IC) and HBeAg-negative hepatitis (ENEG) phase. The molecular events characterizing each phase and determining the transition between clinical phases are still poorly understood.
Permanent immune control occurs only in a minority of chronic HBV patients, either spontaneously or following chronic treatment with direct antivirals. Currently, HBsAg conversion or loss in serum is seen as the most useful clinical hallmark for a transition to a state where the host immune system prevents further proliferation of the virus and avoids a reactive inflammatory state which is a major driver of fibrosis, cirrhosis and hepatocellular carcinoma. However, this situation occurs infrequent in NA(s) treated patients and therefore it is of importance to identify additional predictors for sustained response.
A complementary longitudinal study will be performed by the same investigators as the HBV-FNAB-001 study on patients with liver samples before and after stopping of chronic suppressive treatment with direct antivirals. In this approach the link between immune cell states and functional control will be made through the comparison of liver cell changes in successful controllers and in patients with different timing and extent of viral and clinical relapse.

Study objective

To identify correlations between immune changes at the cellular or molecular level in the serial FNAB and blood samples before and after withdrawal of treatment, and * in case of relapse - to identify correlations between the degree of immune control (or lack thereof) and the timing and intensity of virological and clinical relapse.

Study design

Part 2 prospective multi-center study in about 20 CHB patients on NA treatment at 3 sites (Erasmus MC Rotterdam, University Hospital Toronto and Massachusetts General Hospital, Boston).

Study burden and risks

Patients enrolled in this study will not directly benefit from this study as this is an exploratory study to identify correlates between intrahepatic immune changes at the cellular or molecular level and viral control.

Per patient 3 or 4 FNABs will be collected. This is a minimally invasive technique to obtain safe and repeated liver samples. The procedure is well tolerated by patients and has been performed for many years by our team without any complications related to the procedure. Moreover, it can be performed on any patient without anaesthesia or other preparations. Furthermore, blood collections will be performed for each patient at each visit. Depending if patient is a responder or relapser six is the maximal number of blood collections in this study and blood collection does not pose an extra risk for the patient.
If a subject is identified as clinical relapser a safety follow up of 6 months will follow. No study materials will be taken during the 6 month safety follow up.

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

- man or woman, age of ><=18 and <<= 70 years
- chronic Hepatitis B (HBsAg positive for minimum 6 months)
- > 3 years on treatment with direct antivirals for CHB
- HBV DNA undetectable or < 60 IU/mL, on NA treatment for minimal 2 years
- HBeAg negative, while on NA treatment for minimal 2 year
- ALT < 1.5 ULN (by local assay), while on NA treatment for minimal 1 year and at screening
- no evidence of cirrhosis
- HBV Genotype A, B, C, D or E
- otherwise healthy and medically stable
- written informed consent

Exclusion criteria

- positive HIV test
- hepatitis A, C, D or E co-infection
- Subject had severe hepatitis activity (ALT >= 10xULN) while on NA(s) treatment 2years before screening, or elevation ALT Level>1xULN 1 year before screening and at screening
- decompensated cirrhosis or hepatocellular carcinoma (documented medical history)
- Subject has an underlying condition which preclude the choice of direct antivirals as treatment
- participation in another translational research study
- use of any investigational drug or use of an invasive investigational medical device within 90 days before screening
- Subject has received immuno-modulating drugs (within 18 months prior to screening) for HBV
- any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject
- major surgery (e.g. requiring general anaesthesia) within 12 weeks before screening
- history of drug or alcohol abuse within 1 year before screening
- divers lab parameters (platelets, INR, bilirubin, Hb, eGFR, AFP)
- anticoagulation therapy or bleeding diathesis
- hemoglobinopathy
- pregnancy or breast-feeding

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-03-2020
Enrollment:	7
Type:	Actual

Ethics review

Approved WMO Date:	17-12-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
CCMO	NL70481.078.19