Monitoring the intrahepatic immune responses in chronic HBV patients after long-term treatment with tenofovir

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Study of the phenotype and function of NK cells obtained from peripheral blood and liver of patients who are successfully being treated for at least 3-4 years for their chronic HBV infection with tenofovir in a flow-up study (METC nr. 2008-271).

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

Summary

ID

NL-OMON41768

Source
ToetsingOnline

Brief title
HBV-FNAB FU

Condition

- Hepatic and hepatobiliary disorders
- Viral infectious disorders

Synonym
chronic hepatitis B

Research involving
Human

Sponsors and support

Primary sponsor: Stichting Maag-, Darm- en Leveronderzoek
Source(s) of monetary or material Support: Gilead ,Stichting Lever Onderzoek (SLO)

Intervention

Keyword: hepatitis B, Immune system, liver, NK cells

Outcome measures

Primary outcome

Frequency, phenotype and function of intrahepatic and peripheral NK cells

Secondary outcome

N.A.

Study description

Background summary

Many therapies for chronic viral infections and liver diseases are expensive, have many side effects and do not cure. To develop better treatments, knowledge of these specific diseases is necessary. At the moment it is still indistinct which factors play a role in clearing viral infections. To get a better understanding, our research group investigates pathophysiological mechanisms of chronic hepatitis C to eventually identify pathophysiological markers for disease progression. Moreover, this research could in the future lead to better therapies.
Currently it is estimated that more than 350 million people are chronically infected with HBV. These people have a 20% incidence of cirrhosis of the liver and a 100-fold increased risk of developing liver cancer. HBV causes about 1 million deaths per year worldwide. Chronic HBV infection is the result of a complex interaction between a replicating non-cytopathogenic virus, and a down-regulated antiviral immune response. Cells of the innate immune system, such as natural killer (NK) cells represent the first line of defense against viral infections. NK cells contribute to the anti-viral immune responses by direct cytotoxicity of virus-infected cells and the production of cytokines that can control viral replication.
We have shown that, in particular, the cytokine production by NK cells in blood of patients with chronic HBV infection is reduced, which may lead to perturbed antiviral responses against the virus. Because replication of HBV takes place almost exclusively in hepatocytes in the liver, it is very important to understand the intrahepatic immunity directed against the virus in detail. However, despite the fact that NK cells are one of the most frequent cells within the intrahepatic lymphocyte population their role in HBV infection is relatively unknown.

By making use of the minimally invasive technique of fine needle aspiration biopsies (FNAB) it has been possible to monitor liver material in a safe way and frequent so that the local anti-viral immune responses could be studied during the course of antiviral treatment in chronic HBV patients. In the "Tenofovir FNAB study" this reduction in HBV viral load was obtained by treatment with tenofovir, a highly specific and potent inhibitor of HBV replication.
In the *tenofovir-FNAB study*, we have shown that the effects on intrahepatic NK cells following tenofovir treatment for 48 weeks were minimal despite a normalization of ALT and viral load decline in all patients (undetectable HBV DNA). At week 48 after initiation of tenofovir treatment serum levels in these patients demonstrated the absence of HBV DNA and normalization of ALT, but relatively high HBsAg levels. Almost all patients are HBeAg-negative patients. Since it is known that HBsAg has immunomodulatory activity, a possible explanation of the lack of recovery of the activity of NK cells may lie at the persistent high levels of HBsAg. A proportion of patients (up to 10 patients of the original 20 patients) are currently, approximately 3-4 years after the end of the clinical study, still under treatment with tenofovir or tenofovir in combination with IFN-alpha.
Virological parameters obtained from standard diagnostics showed that in a proportion of patients a substantial decline in serum HBsAg levels had occurred, and in some cases HBsAg loss.
In order to get to the long-term effects of treatment in the liver, the restoration of the immune system, and a better understanding of the importance of HBsAg, and more insight in the disruption of immunity, it is desirable to evaluate another FNAB and blood sample from specific patients from the previous "tenofovir FNAB study"3-4 years after start of tenofovir treatment, and also investigates these samples for NK cell functionality. This knowledge is important because current clinical trials for treatment of HBV are desperately looking for approaches to achieve successful off-treatment responses in patients to prevent that patients have to be on lifelong antiviral medication.

Study objective

Study of the phenotype and function of NK cells obtained from peripheral blood and liver of patients who are successfully being treated for at least 3-4 years for their chronic HBV infection with tenofovir in a flow-up study (METC nr. 2008-271).

Study design

In his study, chronic HBV patients who participated in the "Tenofovir-FNAB study" (METC nr. 2008-271) will be asked to will be asked to donate eight tubes of heparin blood and one FNAB for research, like they have done multiple times in the "Tenofovir-FNAB study". In addition, there will be done a FibroScan in order to determine the degree of liver damage.

Serum and isolated blood and liver cells will partially be investigated directly and partially be stored with a study code for future investigations.

Study burden and risks

For each patient, extra blood and one fine-needle aspiration biopsy (FNAB) will be collected for the assessment of intrahepatic immune responses. Using this minimally-invasive technique of fine-needle aspiration biopsy (FNAB), it is now possible to obtain safe and frequent liver samples to monitor local antiviral immune responses in chronic HBV patients during antiviral therapy. The procedure is well tolerated by patients. A large series, in which thousands of FNABs were evaluated, describes an excellent safety profile with little discomfort reported by the patients. Furthermore, in our clinic, we are experienced with the collection of over hundreds of FNABs without any serious complications to the patient. The patients are familiar with the procedure since they have participated in the "Tenofovir FNAB-study" and did not experience any adverse events.
Venapunction and a FNAB can cause mild pain and/or a bruise.

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

* Chronic HBV patients who were included in the Tenofovir-FNAB study, and are currently still under treatment with tenofovir or became HBsAg-negative (HBsAg loss) in the meantime
* Signed informed consent

Exclusion criteria

* (Re-) infection with HIV, hepatitis B or C after the Tenofovir-FNAB study * Decompensatedcirrhosis (Child * Pugh Grade B or C) * Ultrasonic or other prove of hepatocellular
carcinoma or other carcinoma * Pregnant woman * Any other condition or prescribed medication in which in the opinion of the investigator would make the patient unsuitable for enrollment.

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):	01-06-2015
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	05-01-2015
Application type:	First submission
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	NL50758.078.14