Monitoring the intrahepatic innate immune responses in chronic HBV patients treated with tenofovir

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Our hypothesis is: HBV interferes with the function of intrahepatic innate immune cells, especially NK cells. Since NK cells play a major role in anti-viral immunity and NK cells comprise a large proportion of the intrahepatic immune cells, we would...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON33915

Source
ToetsingOnline

Brief title
IntraHepB

Condition

- Viral infectious disorders

Synonym
HBV, hepatitis B

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Foundation for Liver Research (SLO)

Intervention

Keyword: hepatitis B, immunology, treatment

Outcome measures

Primary outcome

Outcome measurements

Peripheral blood

-Frequency, phenotype and function of NK cells,Treg and DCs.

-Determination of HBV-specific T cell response

-Determination of HBV and proteins in/on NK cells

Intrahepatic

-Frequency, phenotype and function of intrahepatic NK cells and DCs

Secondary outcome

No extra secundary outcome variables

Study description

Background summary

Today more than 350 million people are chronically infected with HBV. These individuals exhibit a 20% incidence of liver cirrhosis and a 100-fold increased risk of developing hepatocellular carcinoma. HBV causes approximately 1 million deaths annually worldwide. Chronic HBV infection is the result of a complex interaction between a replicating non-cytopathic virus and a down-regulated antiviral immune response. HBV specific T cell responses are usually weak or absent in chronic HBV patients. The reason for the T cell hyporesponsiveness or tolerance is not clear.
Cells of the innate immune system, such as natural killer (NK) cells and dendritic cells (DC), represent the first line of defense against viral infections. NK cells contribute to anti-viral defenses by direct cytotoxicity of virus-infected cells and by the production of cytokines that can control

viral replication. Recent advances in the understanding of NK cell biology have highlighted the important role of NK cells in controlling adaptive responses. The requirement of NK cells in the initiation of T cell responses arises from their interaction with DCs. Defective T cell or DC activity observed in chronic HBV-infection may therefore represent a bystander effect of viral NK cell inhibition.
Despite the fact that NK cells comprise up to 50% of the intrahepatic lymphocytes, their role in HBV infection is relatively unknown. The few studies that have investigated the intrahepatic immune responses during HBV infection showed important differences between circulating and intrahepatic HBV-specific T cell responses.
Hence, these data highlight the importance of monitoring intrahepatic immune responses in addition to peripheral immune responses. Using the 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.
Reduction of the HBV viral load by treatment with the nucleotide analogue adefovir dipivoxil did partially restore the function and frequency of DC and decreased the number of Tregs. Tenofovir is a novel highly specific and potent inhibitor of HBV replication in vitro. In recent clinical trials, tenofovir demonstrated superior antiviral activity over adefovir dipivoxil and significant viral load reduction was established within 12 weeks.

Study objective

Our hypothesis is: HBV interferes with the function of intrahepatic innate immune cells, especially NK cells.

Since NK cells play a major role in anti-viral immunity and NK cells comprise a large proportion of the intrahepatic immune cells, we would like to investigate the effect of tenofovir-induced viral load reduction on the NK cell-mediated immune response in chronic HBV patients by addressing the following immunological research question:

What is the effect of tenofovir-induced viral reduction on the frequency, phenotype and function of intrahepatic and peripheral blood-derived NK cells of chronic HBV patients?

Study design

Monocenter, translational open label study with one arm of 15 chronic HBV patients.

Study burden and risks

Since extra blood is drawn at the same time as te collection blood for regular

bloodtesting, there is no additive risk involved in the retrieval of extra blood.
Normally, a venapuncture can give the patient the sensation of minor pain and cause a small swelling, bruise and/or infection. Furthermore, a FNAB can also give the patient the sensation of minor pain and cause a small swelling, bruise and/or infection. Other burdens or risks have not occured in our clinic, nor have they been described in the international literature.

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

- Male and female older than 18 years, with evidence of a chronic HBV infection
- Indication for antiviral therapy of chronic HBV accorind to current clinical guidelines
- Written informed consent

Exclusion criteria

- Other causes of liver disease/co-infections
- Other significant comorbidities
- Presence of contra-indications for antiviral therapy with tenofovir

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-02-2009
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO

Date:	19-11-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	14-12-2009
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	NL23880.078.08