

# Lowering viral load with nucleos(t)ide analogues prior to peg-interferon alfa-2b treatment to increase sustained response in HBeAg-positive chronic hepatitis B (PADD-study)

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To investigate sustained HBeAg response to peg-interferon alfa-2b in chronic HBeAg-positive hepatitis B patients who are pretreated with nucleos(t)ide analogues, thereby lowering viral loadDetermine the effect of PEG-IFNa on NK cell function and...

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

## Summary

### ID

NL-OMON35145

### Source

ToetsingOnline

### Brief title

PEG-IFN in HBV patients with an incomplete response to NA-therapy

### Condition

- Hepatic and hepatobiliary disorders
- Viral infectious disorders

### Synonym

chronic hepatitis B virus infection

### Research involving

Human

## Sponsors and support

**Primary sponsor:** Erasmus MC, Universitair Medisch Centrum Rotterdam

**Source(s) of monetary or material Support:** Afdeling Maag- Darm- en Leverziekten; Erasmus MC; Rotterdam

## Intervention

**Keyword:** chronic hepatitis B, nucleos(t)ide analogues, peginterferon alfa-2b, sustained response

## Outcome measures

### Primary outcome

Sustained response defined as HBV DNA level < 200 IU/ml and HBeAg loss at week 72

Frequency, phenotype and function of NK cells, Tregs and DCs.

Determination of HBV-specific T cell response

Determination of HBV and proteins in/on NK cells

### Secondary outcome

not applicable

## Study description

### Background summary

The introduction of nucleos(t)ide analogues heralded a new era in the treatment of chronic hepatitis B, and provided a safe, effective, and well-tolerated alternative for interferon. Although treatment with nucleos(t)ide analogues profoundly suppresses serum HBV DNA levels and response can be maintained over prolonged periods with ongoing therapy, response to treatment may not be durable in a large proportion of patients after discontinuation of therapy, indicating the necessity of long-term, and maybe indefinite, treatment. In contrast, antiviral potency of peginterferon (PEG-IFN) is inferior to nucleoside analogues, but response to PEG-IFN probably is more durable in the majority of patients due to its immunomodulatory effects. However, sustained response can only be achieved in about 30% of PEG-IFN treated patients.

HBV specific T cell responses are usually weak or absent in chronic HBV patients. Treatment with a nucleoside analogue and subsequent viral decline has shown to restore immune responsiveness in chronic HBV infected patients. Add-on treatment with PEG-IFN can be expected to further stimulate adaptive immune reactivity and may therefore result in higher rates of response.

## **Study objective**

To investigate sustained HBeAg response to peg-interferon alfa-2b in chronic HBeAg-positive hepatitis B patients who are pretreated with nucleos(t)ide analogues, thereby lowering viral load

Determine the effect of PEG-IFNa on NK cell function and induction HBV-specific immunity in patients with relatively low viral load.

Determine whether NK cell function and HBV-specific T cell response can be predictive for sustained off-treatment effective HBV-specific immunity

## **Study design**

Monocenter randomized open-label pilot study with two treatment arms

## **Intervention**

Addition of peginterferon alfa-2b therapy for 24 weeks in chronic hepatitis B patients treated with nucleos(t)ide analogues

## **Study burden and risks**

Patients will be treated with peginterferon alfa-2b, an antiviral agent with many side effects. As a consequence, blood will be drawn more frequently (every 4 weeks during peginterferon treatment vs. every twelve weeks during nucleos(t)ide analogue monotherapy) to monitor for side effects during peginterferon treatment. Normally, a venapuncture can give the patient a sensation of minor pain and cause a small swelling, bruise, and/or infection.

## **Contacts**

### **Public**

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## Scientific

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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 hepatitis B (HBsAg positive > 6 months)
- HBeAg positive, anti-HBe negative within one month prior to initiation of peg-interferon alfa-2b
- HBV DNA < 2000 IU/ml during nucleos(t)ide analogue treatment within one month prior to initiation of peg-interferon alfa-2b
- Compensated liver disease
- Age > 18 years
- Written informed consent

### Exclusion criteria

- Treatment with any investigational drug within 30 days of entry to this protocol
- Severe hepatitis activity as documented by ALT > 10 x ULN
- History of decompensated cirrhosis (defined as jaundice in the presence of cirrhosis, ascites, bleeding gastric or esophageal varices or encephalopathy)
- Pre-existent neutropenia (neutrophils < 1,800/mm<sup>3</sup>) or thrombocytopenia (platelets < 90,000/mm<sup>3</sup>)
- Co-infection with hepatitis C virus, hepatitis D virus or human immunodeficiency virus (HIV)
- Other acquired or inherited causes of liver disease: alcoholic liver disease, obesity induced liver disease, drug related liver disease, auto-immune hepatitis, hemochromatosis, Wilson's

disease or alpha-1 antitrypsin deficiency

- Alpha fetoprotein > 50 ng/ml
- Hyper- or hypothyroidism (subjects requiring medication to maintain TSH levels in the normal range are eligible if all other inclusion/exclusion criteria are met)
- Immune suppressive treatment within the previous 6 months
- Contra-indications for alfa-interferon therapy like suspected hypersensitivity to interferon or PEG-interferon or any known pre-existing medical condition that could interfere with the patient's participation in and completion of the study.
- Pregnancy, breast-feeding
- Other significant medical illness that might interfere with this study: significant pulmonary dysfunction in the previous 6 months, malignancy other than skin basocellular carcinoma in previous 5 years, immunodeficiency syndromes (e.g. HIV positivity, auto-immune diseases, organ transplants other than cornea and hair transplant)
- Any medical condition requiring, or likely to require chronic systemic administration of steroids, during the course of the study
- Substance abuse, such as alcohol (>80 g/day), I.V. drugs and inhaled drugs in the past 2 years.
- Any other condition which in the opinion of the investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in and completing the study

## Study design

### Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

**Primary purpose:** Treatment

### Recruitment

NL	
Recruitment status:	Recruitment stopped
Start date (anticipated):	22-05-2009
Enrollment:	30
Type:	Actual

## Medical products/devices used

Product type:	Medicine
Brand name:	PegIntron
Generic name:	peginterferon alfa-2b
Registration:	Yes - NL outside intended use

## Ethics review

Approved WMO	
Date:	10-02-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	
Date:	26-03-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	
Date:	06-07-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	
Date:	15-07-2010
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
EudraCT	EUCTR2008-007446-54-NL
CCMO	NL25927.078.08