Augmenting response to entecavir using a temporary peginterferon alpha-2a add-on strategy for the treatment of HBeAg-positive chronic hepatitis B (ARES study) - Long-term follow-up of a peginterferon alpha-2a add-on strategy in chronic hepatitis B patients treated with entecavir

Published: 23-01-2009
Last updated: 17-08-2024

To investigate the use of a temporary peginterferon alpha-2a add-on strategy during entecavir therapy in patients with HBeAg-positive chronic hepatitis B by comparing the efficacy of this regimen versus entecavir monotherapy.To evaluate the long-...

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

Summary

ID

NL-OMON39757

Source
ToetsingOnline

Brief title
ARES LTFU

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: Stichting Leveronderzoek

Intervention

Keyword: chronic hepatitis B, entecavir, peginterferon, sustained response

Outcome measures

Primary outcome

The combined presence of HBV DNA level < 200 IU/mL and HBeAg loss at week 48

According to amendment 5:

1. HBeAg loss and presence of HBV DNA level <200 IU/ml

Secondary outcome

• ALT normalization

• Undetectable HBV DNA (* 60 IU/mL)

• HBsAg and HBeAg loss from serum

• The emergence of HBV polymerase mutations associated with reduced

susceptibility to entecavir

• Sustained response defined as the combined presence of HBV DNA level < 200

IU/mL and HBeAg loss at week 96

According to amendment 5:

2. HBeAg seroconversion (HBeAg negative & anti-HBe positive)

3. Serum HBsAg levels

4. HBsAg loss and/or seroconversion

5. Reconversion to HBeAg positivity after initial HBeAg loss (sustainability of response)

6. HBV DNA negativity (<20IU/ml as measured by PCR)

7. Regression of fibrosis and inflammation in liver biopsy

8. Liver failure, Hepatocellular carcinoma, liver transplantation, death

9. IL28B and other genetic variations in relation to points 1-8.

Study description

Background summary

Entecavir is cyclopentyl guanosine analogue, and a potent and selective inhibitor of viral replication in vitro.(1) In one study of 709 HBeAg-positive chronic hepatitis B patients entecavir showed superior antiviral efficacy compared to lamivudine, demonstrating undetectable serum HBV DNA (< 300 copies/mL) in 67%, and HBeAg-seroconversion in 21% of patients after 48 weeks of treatment.(2) Although treatment with nucleoside 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.(3, 4) 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 HBeAgseroconversion can only be achieved in about 30% of PEG-IFN treated patients.(5, 6) HBV-specific T-cell response plays a crucial role in control of viral infection. Viral persistence is believed to be associated with functional tolerance of helper T (TH) cell and cytotoxic T-lymphocytes (CTL) to HBV.(7) In chronic HBV infected patients levels of HBV-specific TH and CTL are generally low and T-cell response can be antigenically restricted.(8) Treatment with a nucleoside analogue and subsequent viral decline has shown to restore helper T-cell (TH-cell) and cytotoxic T-cell (CTL) responsiveness in chronic HBV infected patients.(9-11) Add-on treatment with PEG-IFN can be expected to further stimulate adaptive

immune reactivity and may therefore result in higher rates of response. Recent pilot studies investigating the effect of lowering viral load with nucleoside analogue therapy prior to the initiation of PEG-IFN showed contradictory findings. A study by Sarin et al. showed a significantly higher rate of sustained HBeAg loss in patients who received 4 weeks of lamivudine before PEG-IFN therapy (n=36) compared to those receiving placebo for 4 weeks (n=27) (36% vs. 15%, p=0.05).(12) However, in a study by Chan et al. sustained HBeAg seroconversion occurred in only 1 of 10 patients (10%) treated with lamivudine for 8 weeks prior to PEG-IFN therapy, while HBeAg seroconversion was observed in 6 of 9 patients (67%) who started lamivudine and PEG-IFN simultaneously (p=0.04).(13) It is unknown whether a temporary peginterferon alpha-2a add-on strategy during entecavir therapy increases response rates compared to entecavir monotherapy.

The ARES study is the first study to investigate a PEG-IFN add-on strategy in patients who are treated with ETV. As such, little is known about the long-term durability of response and safety with this approach. It is important to investigate whether the patients in the add-on arm achieve more HBsAg-loss in the long-term as compared to patients treated within the ETV-monotherapy arm. Therefore, our aim is to evaluate the long-term durability of response and safety in these patients.

Study objective

To investigate the use of a temporary peginterferon alpha-2a add-on strategy during entecavir therapy in patients with HBeAg-positive chronic hepatitis B by comparing the efficacy of this regimen versus entecavir monotherapy.

To evaluate the long-term durability of response and the late response of patients treated within the Ares study.

Study design

Multicenter randomized, open-label, phase III study with two treatment arms

- long term follow up

Intervention

A temporary peginterferon alpha-2a add-on strategy during entecavir therapy for 24 weeks

Study burden and risks

Patients will be treated with peginterferon alfa-2a, which is an antiviral agent with a lot of side effects. Furthermore, patients will have to visit the

outpatient clinic more frequently (9 times in case a subject is treated with entecavir and receives a temporary peginterferon add-on strategy; only 2 times in case a subject is treated with entecavir monotherapy). During every visit blood will be drawn. A liver biopsy will be done at baseline and at week 52.
No burden of risk during the long term follow up extension.

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 hepatitis B (HBsAg positive > 6 months)
• HBeAg positive, anti-HBe negative at screening
• ALT > 1.3 x ULN within 60 days prior to screening and during screening
• Liver biopsy performed within 2 years prior to screening or during screening
• Age > 18 years

• Written informed consent
• Adequate contraception for males and females during treatment and follow up; negative pregnancy test (for
women of childbearing potential)

Exclusion criteria

• Antiviral therapy against HBV within the previous 6 months
• Treatment with any investigational drug within 30 days of screening
• Previous treatment with lamivudine or telbivudine for more than six months
• 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 *1,500/mm3) or thrombocytopenia (platelets *90,000/mm3)
• Co-infection with hepatitis C virus or human immunodeficiency virus (HIV)
• Other acquired or inherited causes of liver disease (i.e. 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 alpha-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, lactation
• 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 principal 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:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-08-2009
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Baraclude
Generic name:	Entecavir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Pegasys
Generic name:	peginterferon alpha 2A
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	23-01-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-05-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-08-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-09-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-10-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-11-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-11-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	26-04-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-05-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-12-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-02-2014
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	EUCTR2008-006239-11-NL
ClinicalTrials.gov	NCT00877760
CCMO	NL26630.078.09