Efficacy of 12 week boceprevir in addition to standard of care therapy consisting of peginterferon-alpha-2b and ribavirin for the treatment of acute HCV genotype 1 in HIV co-infected patients. A proof of concept feasibility clinical trial.

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Document the efficacy and tolerability of 12 weeks of Boceprevir (Victrelis®) therapy in addition to standard of care (SOC) therapy consisting of weekly weight based peginterferon alfa-2b (Pegintron®) SC and ribavirin PO BID, for the treatment of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immunodeficiency syndromes
Study type	Interventional

Summary

ID

NL-OMON40134

Source
ToetsingOnline

Brief title
Dutch Acute Hepatitis C in HIV Study (DAHHS study)

Condition

- Immunodeficiency syndromes
- Viral infectious disorders

Synonym
Hepatitis C HIV

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,farmaceutische industrie,Merck Sharp & Dohme (MSD)

Intervention

Keyword: Acute Hepatitis C, HIV, Therapy, Treatment

Outcome measures

Primary outcome

Sustained viral response (SVR) 12 weeks after the end of therapy in the RVR

week 4 population (RVR4).

SVR at week 12 and RVR at week 4 is defined as HCV RNA below the limit of

detection with the TaqMan 2.0 assay (Roche Diagnostics).

Secondary outcome

1. SVR 12 weeks after the end of all therapy in the entire study population

(with or without RVR at week 4).

2. SVR 12 weeks after end of therapy in patients with already a RVR at week 1.

3. SVR 12 weeks after end of therapy in patients starting therapy <=12weeks

after the presumed HCV infection date versus others

4. Alterations of biomarkers by therapy induced viral eradication: Viral

sequencing, mutation analysis, gene expression analysis, RNA analysis and for

Erasmus MC patients only: functional assays at the cell level.

Study description

Background summary

Since 2000 outbreaks of acute HCV among HIV-positive men who have sex with men (MSM), who denied intravenous drug use, have been reported from Europe, the United States and Australia (1). Remarkably, the majority of HCV infections were related to permucosal rather than parenteral risk factors. This route of transmission contrasts with the very low incidence of HCV transmission among HCV serodiscordant heterosexual couples. In the Swiss HIV cohort the incidence of newly acquired HCV among MSM increased 18-fold from 0.3 per 100 person years in 2008 to 4.1 in 2011 (6). In 2011, for the first time, the incidence of acute HCV was even higher among MSM than among IV drug users. The majority of acute HCV infections among MSM are genotype 1. Most acute HCV genotype 1 infections in HIV positive patients can be cured with 6 months of P+R with SVR seen in 75% (4). This contrasts with the much lower (29-46%) SVR rate of chronic genotype 1 HCV in HIV positive patients when P+R treatment is given for 12 months (2).

Recently, the treatment of chronic HCV genotype 1 infection improved substantially when P+R therapy was combined with the HCV protease inhibitors boceprevir (Victrelis®) or telaprevir. Phase III trials of both drugs in HCV mono-infected patients showed an increased SVR of 67-75%.

The SVR rate of P+R therapy of acute HCV infections in HIV positive patients can be reliably predicted when HCV RNA becomes undetectable at week 4 (rapid viral response, RVR) with positive predictive values above 90% (4,5). In patients treated with peginterferon and ribavirin for chronic HCV, the RVR rate increased substantially when a HCV protease inhibitor was added. In the phase III study of telaprevir for treatment naive chronically HCV genotype 1 infected patients, the RVR rate at 4 weeks increased from 9 to 66% when telaprevir was given on top of peginterferon and ribavirin. Because boceprevir (Victrelis®) was started after a 4-week lead in phase of peginterferon ribavirin duo-therapy, comparable 4-week RVR data cannot be given. However, the HCV RNA decline is again much steeper when boceprevir (Victrelis®) is added to peginterferon and ribavirin at week 4 and therefore an increased RVR can be expected when triple therapy would be given from day 1.

None of the HCV protease inhibitors have been well studied for the treatment of acute HCV infection. As mentioned above, the addition of a HCV protease inhibitor to peginterferon ribavirin increased the RVR rate in chronic HCV genotype 1 infections. In this subset of patients with a RVR it has become possible to decrease the duration of therapy from 48 to 24 weeks. As RVR is a reliable predictor of SVR in acute HCV infection, we hypothesize that the use of boceprevir (Victrelis®) in combination with P + R will increase the RVR rate in patients treated for acute HCV and thus will allow for a shorter 12 week

treatment of acute HCV genotype 1 infection in HIV co-infected patients. Very recently, this hypothesis was confirmed for the first time in a small study (n=17) on the use of 12 weeks of telaprevir + P + R study for acute HCV genotype 1, presented at CROI March 2013 (10). Unfortunately an unexpectedly high percentage of the patients had a favorable IL28 polymorphism which is associated with a higher chance of spontaneous cure. Together with the small sample size this makes it hard to draw meaningful conclusions. However, the results are clearly encouraging.

For the treatment of chronic HCV in HIV infected patients, P+R+boceprevir (Victrelis®) combination therapy is given for 48 weeks but is associated with non-trivial side effects (anemia, dysgeusia, rash, fatigue, depression) that increase with increased duration of therapy and often lead to premature treatment discontinuation. A shorter duration of therapy would be a major step forwards as it will be better tolerated and therefore more patients will be able to complete therapy.

This study will examine the rate of SVR after a 12-week Boceprevir (Victrelis®) +P+R combination therapy for acute HCV genotype 1 infection in HIV positive patients with a RVR at 4 weeks.

Study objective

Document the efficacy and tolerability of 12 weeks of Boceprevir (Victrelis®) therapy in addition to standard of care (SOC) therapy consisting of weekly weight based peginterferon alfa-2b (Pegintron®) SC and ribavirin PO BID, for the treatment of acute HCV genotype 1 infection in HIV positive patients with a rapid viral response (RVR) at 4 weeks.

Study design

Prospective open label proof of concept feasibility interventional clinical trial in which 60 acute HCV genotype 1 patients co-infected with HIV will receive 12 weeks of boceprevir (Victrelis®) in addition to a SOC P+R therapy. Therapy will be initiated no later than 26 weeks after the presumed day of HCV infection.

The information on a possible RVR after a 4-week P+R lead-in phase before the start of Boceprevir can be very useful in patients treated for chronic HCV. However this is not the case for acute HCV therapy because already 85% of them will have a RVR after 4 weeks of P+R therapy. Therefore, a lead-in phase, which is standard for treatment of chronic HCV infected patients, was excluded deliberately in the current protocol as it aims to show the efficacy of a shorter treatment (12 weeks as opposed to 24 weeks with the current SOC for acute HCV) by adding Boceprevir (Victrelis®) to the current SOC. Also, the risk of viral breakthrough or resistance to Boceprevir (Victrelis®) when given in

combination with SOC without a lead-in was not higher than when it was given with a lead-in (sprint-1 study) (8).

Patients with a complete RVR (HCV RNA undetectable) after 28 days of therapy will be allowed to continue Boceprevir (Victrelis®) from day 29 to 84 and will discontinue Boceprevir (Victrelis®) as well as SOC therapy at day 84.

Patients without a RVR but at least a 2log drop in HCV RNA will also continue boceprevir + P+R and will discontinue at day 84 if they have an undetectable HCV RNA at day 42 or 56. If a patient has a detectable HCV RNA at day 56 boceprevir + P+R treatement has to be continued until week 24.

Patients without a 2 log drop at day 28 will discontinue therapy at day 28. Patients with a rise in HCV RNA during the study will discontinue therapy directly.

Intervention

Treatment with boceprevir, P + R

Study burden and risks

Burden: 3 extra visits the the hospital, extra blood drawing for Erasmus MC patients only(in total 120 mL)

Risk: Risk associated with boceprevir, peginterferon and ribavirin therapy

Benefit: Possibly (but as yet unproven) a shorter treatment for acute hepatitis C (3 instead of 6 months) and therefore possibly less side-effects.
New insights in Acute HCV pathophysiology.

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

1. Documented recent HCV genotype 1 infection (<=26 weeks old at the time of the baseline visit).
2. Plan to start a SOC therapy for acute HCV consisting of 24 weeks of P + R.
3. HCV RNA plasma viral load at screening >1000 IU/ml.
4. On HAART at the time of baseline visit

Exclusion criteria

1. Disallowed co-medication that cannot be stopped or replaced: Several potentially life-threatening drug-drug interactions (DDI) are possible when boceprevir is combined with other drugs. Therefore ALL co-medication, including over-the-counter drugs should be checked for potential DDI with DDI table in the Dutch summary of product characteristics (SPC, appendix A). If the comedication is not mentioned in the SPC DDI table, www.HCV-druginteractions.org should be used. ;2. Contraindications for the use of full dose of peginterferon alfa-2b or ribavirin: neutrophils <0.50×10*9/l or trombocytes <25×10*9/l or a Hb <6.2mmol/L, creatinine clearance <50ml/min).;3. History of liver cirrhosis or >F1 fibrosis on fibroscan. Inclusion of patients with a chronic well-controlled HBV (HBV-DNA below the limit of detection) with tenofovir, lamivudine or emtricitabine therapy is allowed if fibroscan excludes >F1 fibrosis. Fibroscan reports <2 years old can be used for screening. Fibroscan is not required for other patients at screening.;4. HAART was started <4 weeks before baseline visit.;5. Inability to switch to a HAART regimen consisting of 2 nucleoside/tide reverse transcriptase inhibitors + Raltegravir (Isentress®) 400mg BID or atazanavir (Reyataz®) 300mg QD + ritonavir (Norvir®) 100mg QD.;6. Patient that virologically failed HAART in the past

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-08-2013
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Victrelis
Generic name:	boceprevir
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-06-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-07-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	01-11-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-11-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-06-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-01-2015
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	EUCTR2013-002004-14-NL
ClinicalTrials.gov	NCT01912495
CCMO	NL44825.078.13