Grazoprevir (MK-5172) + Elbasvir (MK-8742) for the treatment of ACUTE hepatitis C genotype 1/4. The Dutch Acute HCV in HIV Study (DAHHS-2)

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The goal of this study is to document the efficacy of a shortened 8-week therapy with grazoprevir and elbasvir in patients with acute HCV genotype 1 or 4 infection.

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

Summary

ID

NL-OMON43933

Source
ToetsingOnline

Brief title
DAHHS 2

Condition

- Hepatic and hepatobiliary disorders
- Viral infectious disorders

Synonym
acute hepatitis c

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Merck

Intervention

Keyword: Acute Hepatitis C, Treatment

Outcome measures

Primary outcome

Main study endpoint

SVR 12 weeks after the end of all therapy in the ITT population

Secondary outcome

Secondary study endpoints

1. SVR12 in all genotype 1 infected patients in the mITT.

2. SVR12 in genotype 4 infected patients (ITT and mITT)

3. SVR12 in all patients included (=genotype 1 and 4, ITT and mITT)

4. SVR12 in RVR2 and RVR4 (mITT)

5. SVR12 in all patients (=genotype 1+4) according to IL28 genotype (*)

6. SVR24 (mITT and ITT)(%)

7. Cost-effectivity of treatment during the acute phase of HCV in comparison with treatment 12 months later for chronic HCV or treatment only at a certain level of liver fibrosis.

8. SVR12 in genotype 1a infected patients with no NS5a polymorphisms at positions 28/30/31 or 93 versus SVR12 in patients with 1 or more of these polymorphisms

(*) The reason to include this analysis as a secondary endpoint is that despite the fact that no interferon is used, IL28 genotype may impact the SVR rates

because it determines the spontaneous cure rates of acute HCV. Therefore, a favorable IL28 genotype may work synergistically with DAA and increase SVR rates.

(%) The SVR12 endpoint was only thoroughly validated for the treatment of chronic HCV. Therefore, we prefer to include SVR24 as a secondary endpoint, to confirm that SVR12 is also a reliable predictor of SVR24 in acute HCV therapy

Study description

Background summary

A newly acquired HCV infection is mostly asymptomatic. Therefore, if liver enzymes are not measured in the context of medical care for another disease, the new HCV infection remains undiagnosed for years or decades in most patients (ref1). Since 2004, a new epidemic of sexually transmitted HCV infections among HIV positive men who have sex with men (HIV+MSM) emerged in Europe (ref2a 2b). This new epidemic was rapidly identified because regular liver enzyme testing is a standard procedure to look for liver injury induced by combination antiretroviral therapy (cART). In 2014, a prospective observational study in 18 Dutch HIV treatment centers showed that this HCV epidemic is now well established throughout the Netherlands. During the 12 months of the study, 91 acute HCV infections were diagnosed among 8723 HIV positive MSM in care in these centers. The incidence of acute HCV was therefore 11/1000 patient years, which means that 1.1% of Dutch HIV+MSM acquired a new HCV infection in 2014 alone. This is 100-1000 fold higher than what can be expected in the general Dutch population. Of these acute HCV infections, 74% were genotype 1 (n=71) and 16% genotype 4 (n=15). Other genotypes were rarely seen (genotype 2 in 2 and genotype 3 in 3 patients respectively) (ref.3).

Until recently, acute hepatitis C infections were almost exclusively seen in HIV-positive patients because only this risk was screened several times a year for hepatitis during their HIV control. London was the first increase of acute hepatitis C in HIV-negative gay men seen. In the Netherlands last year, however, was rolled out PrEP (pre exposure prophylaxis) implementation program in Amsterdam. In this program HIV negative gay men at risk for HIV take drug that protects them against HIV. In this context, they are tested for HIV several times a year but also hepatitis. As a result, it is now also possible

to detect acute HCV infections in HIV-negative patients, because it can be proved in this setting that it is a recent infection (on the basis of a preliminary negative hepatitis test).

Recently 2 interferon-free single tablet HCV therapies, sofosbuvir/ledipasvir and dasabuvir/ombitasvir/ paritaprevir/ritonavir received European Medicines Agency approval for the treatment of genotype 1 and 4. In patients with chronic HCV but without cirrhosis, both regimens cure >95% of the patients. Previously, sofosbuvir, simeprevir and daclatasvir received EMA approval for the treatment of chronic HCV. The current medication costs for a 12-week treatment with e.g. sofosbuvir/ledipasvir is 94500 USD (approximately 81000 euro). This very high cost per treatment and therefore major impact on national health-care budgets has resulted in a restrictive reimbursement policy in most European countries. In the Netherlands, only patients with chronic HCV and documented severe liver fibrosis or cirrhosis get their treatment reimbursed by the health insurance.

None of these new HCV therapies have been well studied for the treatment of acute HCV and are therefore not registered for this indication. The only treatment for acute HCV that is currently reimbursed in most countries is pegylated or unpegylated interferon. Interferon based therapy for the treatment of HCV has been shown to be much more effective when given during the acute phase of the HCV infection than at a time when the infection has become chronic. Based on our own review of studies published as a full paper or a conference report, acute HCV infections can be cured with interferon-based therapy in 542 of 711 (76%) HIV negative patients with an acute HCV. In HIV+ patients the cure rates were somewhat lower at 310/467 or 66%. These responses of 66-76% are in sharp contrast with cure rates of only +- 35-45% for chronic HCV genotype 1/4 with pegylated interferon and ribavirin. A likely explanation for this difference in success for acute versus chronic HCV therapy is a substantial immune response that is present during the acute phase of HCV infection, but becomes exhausted during chronic infection (ref4). This potent immune response is broadly targeted against various HCV epitopes and eradicates approximately 20% of HCV infections within the first 12 to 18 months of infection. However, spontaneous cure of HCV becomes very rare after the first 12 to 18 months of infection due to immune exhaustion. It is likely that the synergistic effect of the host's immune response and antiviral therapy when given during the first 6 months of HCV infection makes antiviral therapy during acute HCV infection more effective.

A the end of 2013, the investigator initiated Dutch Acute HCV in HIV Study (DAHHS) started to recruit acute HCV genotype 1 infected patients in 10 Dutch HIV treatment centers. In 14 months, 65 patients were included (out of the >100 acute genotype 1 and 4 infections that were diagnosed in these 14 months). After spontaneous clearance was observed in 8 patients, the 57 remaining patients started treatment with 12 weeks of boceprevir peginterferon and ribavirin. We observed that the vigorous immune response during the acute phase of HCV, together with the addition of a single first-generation DAA to the

peginterferon ribavirin therapy, cured 85% of the patients with only 12 weeks of treatment. We were therefore able to shorten peginterferon therapy with 50% without loss of efficacy. In the subset of patients with a rapid viral response at week 4, 98% reached SVR12 (study results as of 10/JUN/2015, Bart Rijnders). It became clear that the DAHHS network is able to recruit a very significant number of acute HCV infected patients in a short time without any patients being lost-to-follow up. Another relevant observation in the DAHH-study was that, with all patients being on cART, their median CD4 count was very high at 660/mm3. This is substantially higher than the median CD4 count seen in patients with HIV and chronic HCV. Therefore, from an immunological point of view HIV+MSM diagnosed with an acute HCV are comparable to HIV negative patients.

Two recent phase II and 1 phase III clinical trial showed that chronic HCV genotype 1 can be cured with 12 weeks of combination therapy with grazoprevir (MK-5172) and elbasvir (MK-8742) in 95% of HCV mono-infected and 87% (without ribavirin) to 97% (with ribavirin) of HIV-HCV co-infected patients. Furthermore, all 18 patients with genotype 4 infection that were treated for 12 weeks in the C-EDGE study were cured. Larger clinical trials for the treatment of chronic HCV genotype 4 are ongoing but the in vitro potency of MK-8742 and MK-5172 against HCV genotype 4 is very high with an EC50 of 0.003-0.0003 nM and 0.062 nM respectively.

The long-term goal of policy makers, healthcare providers and the pharmaceutical industry should be to reduce the number of new HCV infections in a substantial way. Ultimately, the eradication of HCV may be possible in certain countries and patient populations. The first patient population for which HCV eradication may become a realistic future perspective is the easy to reach population of HIV+MSM. To make this happen, health care providers should be able to treat newly diagnosed acute HCV infections as soon as they are diagnosed to prevent ongoing sexual HCV transmission. If patiens are only treated years later, at a time when fibrosis has been documented they will remain a significant source of new sexually tranmitted HCV infections for years. Treatment as prevention as soon as an acute HCV infection is diagnoses could therefore be an important measure to halt the spread of HCV among HIV+MSM just as treatment as prevention works to prevent HIV transmission.

HCV treatment as prevention, is currently not possible because DAA are not registered for the treatment of acute HCV because their effectivity in the context of acute HCV has not been shown.

Study objective

The goal of this study is to document the efficacy of a shortened 8-week therapy with grazoprevir and elbasvir in patients with acute HCV genotype 1 or 4 infection.

Study design

Single arm open label multicenter study
Treatment duration of 8 weeks
Treatment: grazoprevir (MK-5172) 100mg QD + elbasvir (MK-8742) 50mg QD given as a fixed drug combination tablet

Sample size: n=80 patients, genotype 1 or 4
At least 55 but not more than 65 patients will be infected with genotype 1
At least 15 but not more than 25 of the 80 patients will be genotype 4
Therefore, the inclusion of genotype 1 will end when 65 patients with genotype 1 are included and the inclusion of genotype 4 will end after 21 genotype 4 patients have been included. The study inclusion will end when in total 80 patients are included.

Intervention

Day 1-56: All patients will receive grazoprevir/elbasvir fixed dose combination oral tablet consisting of 100/50mg per tablet.

Study burden and risks

Burden en risks associated with treatment are estimations based on phase 1/2 trials in hiv positive patients and mainly associated with Headache, nausea, sleeplesness and diarrea. However this burden is anticipated to be much less than standard treatment with peginterferon. As there are limited phase 3 data en none phase 4 data, rare adverse events could not have been occured yet. Thus, patients have to be informed about this level of knowledge of the treatment regimen. The burden of blood, taken by venapuncture for the research is considered to be very low for non-Erasmus MC patients (additional 14 ml per study visit), for Erasmus MC patients this is considered moderate, maximum additional 54 mL per visit.
All blood drawal will be together with regular venous puncture, so there is no additional risk for hematomas.

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. Acute HCV genotype 1 or 4 infection (<=26 weeks old at the baseline visit) according to definition mentioned in the protocol

Exclusion criteria

Exclusion criteria:;1. If HIV+: Not on cART and a CD4 <500 at the time of screening
2. If HIV+: Patients on cART for >6 months with a HIV viral load >400 copies
3.Disallowed co-medication that cannot be stopped or replaced: Therefore ALL co-medication, including over-the-counter drugs should be checked for potential drug-drug interactions using the investigators brochure (appendix A). In particular, care should be taken for patients that are taking >10mg atorvastatin or >5mg rosuvastatin per day and the dose should be reduced to the lowest dose available (10mg for atorvastatin and 5 for rosuvastatin). Alternatively a switch to pravastatin may be preferred. When in doubt about drug-drug interactions, contact the coordinating investigator.
4.History of liver cirrhosis of any etiology. Inclusion of patients with a chronic well-controlled HBV (HBV-DNA F1 fibrosis. Fibroscan reports <5 years old can be used for screening.
5.If HIV+: Protease inhibitor based and NNRTI based cART regimens are not allowed. Therefore, the inability to switch to a HAART regimen consisting of 2 nucleoside/tide reverse transcriptase inhibitors and an allowed third agent which can be raltegravir (Isentress®) 400mg BID, dolutegravir (Tivicay) 50mg QD or rilpivirine 25mg QD.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-02-2016
Enrollment:	71
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Elbasvir
Generic name:	Elbasvir
Product type:	Medicine
Brand name:	Grazoprevir
Generic name:	Grazoprevir

Ethics review

Approved WMO Date:	20-10-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-11-2015
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-09-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-04-2017
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	EUCTR2015-003210-24-NL
CCMO	NL53806.078.15