Treatment of acute hepatitis C genotypes 1 and 4 with 8 weeks of grazoprevir plus elbasvir (DAHHS2)

Boerekamps, Anne; De Weggheleire, Anja; van den Berk, Guido E.; Lauw, Fanny N.; Claassen, Mark A. A.; Posthouwer, Dirk; Bierman, Wouter F.; Hullegie, Sebastiaan J.; Popping, Stephanie; van de Vijver, David A. C. M.

Published in:
The lancet. Gastroenterology & hepatology

DOI:
10.1016/S2468-1253(18)30414-X

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

Treatment of acute hepatitis C genotypes 1 and 4 with 8 weeks of grazoprevir plus elbasvir (DAHHS2): an open-label, multicentre, single-arm, phase 3b trial

Anne Boerekamps, Anja De Weggheleire, Guido E van den Berk, Fanny N Lauw, Mark A A Claassen, Dirk Posthouwer, Wouter F Bierman, Sebastiaan J Hullegie, Stephanie Popping, David A C M van de Vijver, Anthonius S M Dofferhoff, Gert Jan Kootstra, Eliane M Leyten, Jan den Hollander, Marjo E van Kasteren, Robert Soetekouw, Heidi S M Ammerlaan, Janke Schinkel, Eric Florence, Joop E Arends, Bart J A Rijnders

Summary

Background Direct-acting antivirals effectively treat chronic hepatitis C virus (HCV) infection but there is a paucity of data on their efficacy for acute HCV, when immediate treatment could prevent onward transmission. We assessed the efficacy of grazoprevir plus elbasvir treatment in acute HCV infection and investigated whether treatment can be shortened during the acute phase of HCV infection.

Methods The Dutch Acute HCV in HIV study number 2 (DAHHS2) study was a single-arm, open-label, multicentre, phase 3b trial. Adult patients (≥18 years) with acute HCV genotype 1 or 4 infection (duration of infection 26 weeks or less, according to presumed day of infection) were recruited at 15 HIV outpatient clinics in the Netherlands and Belgium. All patients were treated with 8 weeks of grazoprevir 100 mg plus elbasvir 50 mg administered as one oral fixed drug combination tablet once daily. The primary efficacy endpoint was sustained virological response at 12 weeks after the end of treatment (SVR12; HCV RNA <15 IU/mL) in all patients who started treatment. Reinfection with a different HCV virus was not considered treatment failure in the primary analysis. This trial is registered with ClinicalTrials.gov, number NCT02600325.

Findings Between Feb 15, 2016, and March 2, 2018, we assessed 146 patients with a recently acquired HCV infection for eligibility, of whom 86 were enrolled and 80 initiated therapy, all within 6 months after infection. All patients who initiated treatment completed treatment and no patients were lost to follow-up. 79 (99%, 95% CI 93–100) of 80 patients achieved SVR12. All 14 patients who were infected with a virus carrying a clinically significant polymorphism in NS5A were cured. If reinfections were considered treatment failures, 75 (94%, 86–98) of 80 patients achieved SVR12. Two serious adverse events not considered related to the treatment were reported (traumatic rectal bleeding and low back surgery). The most common adverse event was a new sexually transmitted infection (19 [24%] of 80 patients). The most common reported possibly drug-related adverse events were fatigue (11 [14%] patients), headache (seven [9%] patients), insomnia (seven [9%] patients), mood changes (five [6%] patients), dyspepsia (five [6%] patients), concentration impairment (four [5%] patients), and dizziness (4 [5%] patients), all of which were regarded as mild by the treating physician. No adverse events led to study drug discontinuation.

Interpretation 8 weeks of grazoprevir plus elbasvir was highly effective for the treatment of acute HCV genotype 1 or 4 infection. The ability to treat acute HCV immediately after diagnosis might help physicians to reach the WHO goal of HCV elimination by 2030.

Funding Merck Sharp and Dohme and Health-Holland.

Introduction

In 2016, WHO released a global health sector strategy on viral hepatitis.[1] A goal of this strategy was combating hepatitis C virus (HCV) and working towards its elimination as a public health threat, with the aim of a 90% reduction in new HCV infections (incidence) and a 65% reduction in HCV-related deaths (mortality) by 2030.[1] With the emergence of direct-acting antivirals (DAAs), this goal could be more achievable in well defined populations with a high prevalence of HCV, such as HIV-positive men who have sex with men (MSM).[2] However, HIV-positive MSM also have a high incidence of acute HCV infections and reinfections.[3,4] Although HIV-positive MSM represent an intermediate prevalence and incidence group (1·0–1·5 cases per 100 patient-years of follow-up) compared with people who inject drugs, a subgroup of MSM have extremely risky behaviour and therefore a much higher incidence of HCV. Because of the treatment-as-prevention effect of DAAs, recent modelling and observational studies suggest that systematic and nationwide treatment of chronic HCV in HIV-infected MSM could lead to a substantial decrease in HCV prevalence and the incidence of new HCV infections.[2,5–8]

Lancet Gastroenterol Hepatol 2019; 4: 269–77

Published Online January 16, 2019 http://dx.doi.org/10.1016/S2468-1253(18)30414-X

See Comment page 256

Department of Internal Medicine and Infectious Diseases (A Boerekamps MD, S J Hullegie MD, B J A Rijnders PhD) **and Department of Viroscience** (S Popping MD, D A C M van de Vijver PhD), **Erasmus MC, Rotterdam, Netherlands; Department of Clinical Sciences, Institute of Tropical Medicine Antwerp, Antwerp, Belgium** (A De Weggheleire MD, E Florence PhD); **Department of Internal Medicine and Infectious Diseases, OLVG, Amsterdam, Netherlands** (G E van den Berk MD); **Department of Internal Medicine and Infectious Diseases, Slotervaart MC, Amsterdam, Netherlands** (F N Lauw PhD); **Department of Internal Medicine and Infectious Diseases, Rijnstate Ziekenhuis, Arnhem, Netherlands** (M A A Claassen PhD); **Department of Internal Medicine and Medical Microbiology, Maastricht UMC+, Maastricht, Netherlands** (D Posthouwer PhD); **Department of Internal Medicine and Infectious Diseases, Universitair Medisch Centrum Groningen, Groningen, Netherlands** (W F Bierman PhD); **Department of Internal Medicine and Infectious Diseases, Radboud University Medical Center, Nijmegen, Netherlands** (A S M Dofferhoff MD); **Department of Internal Medicine and Infectious Diseases, Medisch Spectrum Twente, Enschede,**

Netherlands (G J Kootstra MD); Department of Internal Medicine and Infectious Diseases, MC Haaglanden, The Hague, Netherlands (E M Leyten MD); Department of Internal Medicine and Infectious Diseases, Maasstad Ziekenhuis, Rotterdam, Netherlands (J den Hollander MD); Department of Internal Medicine and Infectious Diseases, Elisabeth-TweeSteden Ziekenhuis, Tilburg, Netherlands (M E van Kasteren PhD); Department of Internal Medicine and Infectious Diseases, Spaarne Gasthuis, Haarlem, Netherlands (R Soetekouw MD); Department of Internal Medicine, Catharina Hospital, Eindhoven, Netherlands (H S M Ammerlaan PhD); Department of Medical Microbiology, Section of Clinical Virology, Academic Medical Center, Amsterdam, Netherlands (J Schinkel PhD); and Department of Internal Medicine and Infectious Diseases, Universitair Medisch Centrum Utrecht, Utrecht University, Utrecht, Netherlands (J E Arends PhD)

Correspondence to:
Dr Anne Boerekamps, Department of Internal Medicine and Infectious Diseases, Erasmus MC, 3000 CA Rotterdam, Netherlands
anneboerekamps@gmail.com

See Online for appendix

Research in context

Evidence before this study

To identify clinical trials of direct-acting antivirals (DAAs) for acute hepatitis C virus (HCV), we searched PubMed for clinical trials with the search terms "hepatitis C" and "acute" published since Jan 1, 2008, as well as ClinicalTrials.gov, the EU Clinical Trials Register, and conference abstracts of all major hepatology and HIV conferences. We considered studies publised in English only. We excluded clinical trials with interferon-based regimens. The earliest clinical trials with 6 or 12 weeks of sofosbuvir and ribavirin for acute HCV genotype 1 showed only moderate results with proportions of patients cured between 32% and 59%. More recently, trials with 6–8 weeks of combination DAA therapy for acute HCV showed proportions of patients cured between 77% and 100%. However, given the low number of patients in each of the studies (20–30 patients) and the fact that almost all patients were infected with genotype 1 only, no definitive conclusions could be drawn.

Added value of this study

To our knowledge the DAHHS2 study is the first to include a sufficient number of patients (n=80) to show that a short 8 week regimen of grazoprevir plus elbasvir is an effective therapy for acute HCV of both genotypes 1 and 4 (ie, the first study with sufficient statistical power). 99% of patients were cured, which is similar to the success observed when longer (12 week) treatment is given to patients with chronic HCV infection of the same genotypes. When reinfection was classed as treatment failure, the cure rate was 94%.

Implications of all the available evidence

In specific populations at risk of HCV transmission to others (eg, transmission to sex partners in men having sex with men or to needle sharing partners in people who inject drugs) being able to start curative HCV therapy immediately after diagnosis of an acute HCV infection will not only prevent transmission to others but will also lead to direct (shorter treatment duration) and indirect (prevention of new infections) cost savings. Our study shows that treatment of HCV infection with grazoprevir plus elbasvir is effective in the acute phase of infection, and this treatment strategy should be considered in populations with a high risk of onward HCV transmission.

However, additional interventions are also needed if HCV elimination is to be achieved.[9] While large and conclusive studies on the efficacy of DAA for treatment of acute HCV are lacking, treatment during the acute phase of infection is often not possible because of registration or reimbursement restrictions. Therefore, treatment of acute HCV has to be postponed until the chronic phase. This delayed treatment approach is unsatisfactory from an individual patient and public health perspective, since overall health-care costs are likely to increase because of ongoing HCV transmissions caused by this treatment delay. Indeed, modelling studies have shown a cost benefit for treatment initiated in the acute phase of infection in patients with a risk of transmitting HCV to others.[10] If HCV could be effectively treated in the acute phase of infection among high-risk patients such as HIV-positive MSM, this could aid microelimination of HCV from this subgroup and contribute to global elimination of HCV according to the WHO elimination goals.[11]

8 weeks of grazoprevir plus elbasvir treatment was shown to be very effective for patients with chronic HCV genotype 1b and a METAVIR score of F0–F2, with 79 (98%) of 81 patients achieving a sustained virological response 12 weeks after treatment (SVR12) in the STREAGER trial.[12] A similar study is ongoing for patients infected with HCV genotype 4.[13] However, 8 weeks of grazoprevir plus elbasvir led to less favourable results for patients with chronic HCV genotype 1a infection in a phase 2 study (SVR12 80%, 95% CI 61–92).[14]

Interferon treatment of HCV was most effective when administered during the first 6–12 months after infection, even when the treatment duration was shortened substantially.[15–17] The small number of studies[18] that have examined the efficacy of interferon-free DAA therapy during the acute phase of an HCV infection included few patients (n=20–30), most of whom had genotype 1 infection. Observed proportions of patients being cured varied between 77% and 100%, but the studies were too small to draw any definitive conclusions.[18]

In the Dutch Acute HCV in HIV study number 2 (DAHHS2), we aimed to evaluate the efficacy and safety of grazoprevir plus elbasvir for 8 weeks in people with acute HCV genotype 1 or 4 infection.

Methods

Study design and participants

DAHHS2 was a single-arm, open-label, multicentre phase 3b trial. Adult patients (≥18 years), irrespective of HIV status, with acute HCV genotype 1 or 4 infection were recruited at 15 hospitals with an HIV outpatient clinic (and treated in nine of these centres) in the Netherlands and Belgium. Any patient with acute HCV could enrol in the study. All HIV treatment centres in the Netherlands and in the Dutch speaking part of Belgium were informed about the trial and invited to refer patients to one of the study sites. The largest HIV treatment centre in each major Dutch city participated as a study site (appendix). Furthermore, the staff of all other Dutch HIV centres were informed about the study and received newsletters with contact information to facilitate referral to one of the study sites. Information about the study was posted on several websites. In Belgium, the HIV centre with the highest reported incidence of acute HCV was the study site (Institute of Tropical Medicine Antwerp, Antwerp, Netherlands), but all HIV centres could refer

patients to Antwerp. Patients were eligible for inclusion if they had an acute HCV genotype 1 or 4 infection for a duration of 26 weeks or less according to the presumed day of HCV infection. Acute HCV infection was defined as positive anti-HCV IgG or positive HCV RNA in the presence of a documented negative HCV antibody or HCV RNA test in the previous 12 months. If there was no documented negative test in the preceding 12 months patients were also eligible, but only if they fulfilled all of the following criteria: positive HCV RNA in association with an acute rise in alanine aminotransferase more than five times the upper limit of normal, with documented normal alanine aminotransferase in the previous 12 months; no recent introduction of any other medication that might explain the alanine aminotransferase increase; a documented negative HCV IgG antibody test at any time in the past; and no other explanation for the alanine aminotransferase increase (eg, infection with hepatitis A or E, infection with cytomegalovirus).[19] The presumed day of HCV infection was calculated as the midpoint between the most recent date without any laboratory signs of an HCV infection (negative HCV test or normal alanine aminotransferase) and the date of the first positive HCV test. Therapy was initiated no later than 26 weeks after the calculated day of HCV infection. Patients with HIV had to be on combination antiretroviral therapy (ART) with HIV RNA less than 400 copies per mL at the time of screening, unless their CD4 cell proportion was greater than 500 cells per µL without therapy. Patients with a history of liver cirrhosis of any cause, patients with untreated chronic hepatitis B virus (HBV) infection, and patients with virologically controlled HBV who had significant liver fibrosis on transient elastography (METAVIR score F2 or higher) were excluded.

The institutional review board of all participating centres and the competent authorities of Belgium and the Netherlands approved the study. The study was done in accordance with Good Clinical Practice standards. All patients gave written informed consent. The full protocol is available in the appendix.

Procedures

All patients were treated with 8 weeks of grazoprevir 100 mg plus elbasvir 50 mg administered as an oral fixed drug combination tablet (Merck & Co, Pike West Point, PA, USA) once daily. The decision to observe patients for possible spontaneous clearance of HCV infection was left to the treating physician. Patients were seen in an HIV clinic at screening and baseline, weeks 2, 4, and 8 during therapy, and weeks 4, 12, and 24 after therapy. Laboratory results of these visits were reported to the investigators by the participating study centres after each study visit. Adherence was evaluated by pill counts during week 2, week 4, and week 8 of the study.

HCV RNA was determined with the local standard of care HCV RNA test (TaqMan 2.0 assay; Roche Diagnostics; Risch-Rotkreuz, Switzerland; or Abbott Realtime M2000; Abbott Laboratories; Chicago, IL, USA). The lower limit of HCV RNA detection of the TaqMan assay is 15 IU/mL and the lower limit of HCV RNA detection of the Abbott assay is 12 IU/mL. Because the incidence of HCV reinfection is high in HIV-positive MSM,[2,20] patients with documented HCV reinfection 12 weeks after the end of therapy were not considered to have treatment failure in the primary analysis, as predefined in the study protocol. We defined reinfection as the detection of a different virus at SVR12 compared with the baseline virus, either by HCV genotype switch or by detection of a different HCV variant of the same genotype by phylogenetic analysis with a fragment of the envelope E2 gene, which includes hypervariable region 1.[21] Patients who were HCV RNA-positive at SVR12 with the same virus as baseline were considered to have treatment failure. Sequences were analysed in the context of local HCV MSM variants known to be circulating in populations of MSM.[21]

The genotype and subtype of the sequences were first assessed using the Rega HCV genotyping tool.[22] Sequences classified with a particular genotype were then aligned to a reference sequence with the same genotype and trimmed to equal length. NS5A resistance-associated substitutions were defined as all changes in amino acids at positions 28, 30, 31, 58, and 93. Additionally, at position 58 we considered only 58D resistance-associated substitution relevant.

Outcomes

The primary efficacy endpoint was SVR12 (HCV RNA <15 IU/mL) in all patients who started treatment. Secondary endpoints were safety, SVR12 in genotype 1 and genotype 4 infections separately, and SVR12 in all patients who started treatment, excluding those lost to follow-up or those who discontinued treatment for reasons other than virological failure. We did not analyse the other secondary endpoints listed in the protocol, nor will they be reported elsewhere.

Adverse event data were collected according to the Common Terminology Criteria for Adverse Events[23] version 4.0, by the participating study centres and reported to the investigators after each study visit.

Statistical analysis

With a sample size of 80 patients and a non-inferiority margin of 10%, the study would have 89% power to detect non-inferiority at the SVR rate of 93% observed in patients treated with 12 weeks of grazoprevir plus elbasvir for chronic HCV of genotypes 1a or 4 in the phase 3 C-EDGE study.[24]

For the primary and secondary endpoints, we calculated the proportion of patients with SVR12 with exact two-sided Clopper-Pearson CIs and we concluded non-inferiority if the lower 95% CI of the SVR12 was greater than 83%.

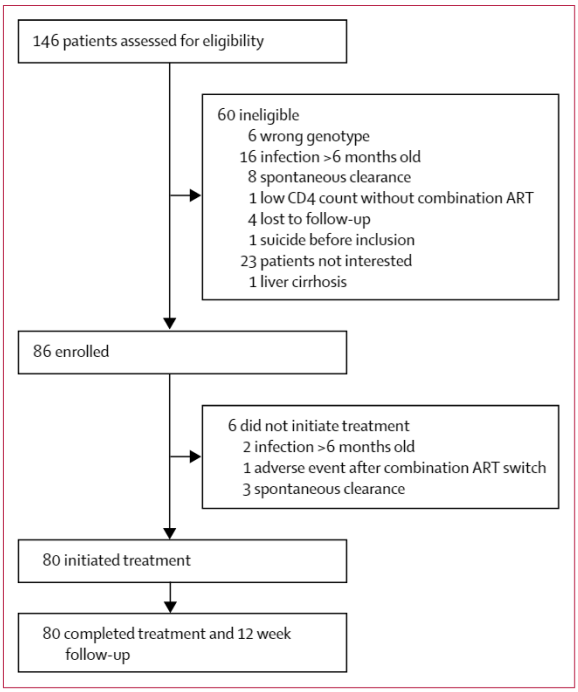

Figure: **Trial profile**
ART=antiretroviral therapy.

	All patients (n=80)	HCV genotype 1a (n=51)	HCV genotype 4 (n=29)
Age (years)	47 (10)	47 (10)	49 (8)
Male sex	80 (100%)	51 (100%)	29 (100%)
Race			
White	72 (90%)	46 (90%)	26 (90%)
HCV transmission route			
MSM	80 (100%)	51 (100%)	29 (100%)
Current episode is a reinfection	19 (24%)	12 (24%)	7 (24%)
Number of HCV episodes			
1	61 (76%)	39 (76%)	22 (76%)
2	15 (19%)	9 (18%)	6 (21%)
≥3	2 (3%)	3 (6%)	1 (3%)
Alanine aminotransferase concentration (IU/mL)	139 (74–315)	144 (76–310)	136 (70–427)
HCV RNA concentration (IU/mL)	310 000 (34 000–1 400 000)	330 000 (31 000–1 400 000)	250 000 (49 000–1 500 000)
Time between estimated infection date and HCV treatment (months)	4·4 (1·2)	4·3 (1·1)	4·6 (1·3)
Time between first positive HCV RNA test and HCV treatment (months)	2·0 (1·0)	2·0 (1·0)	2·0 (1·1)
HBV co-infection	0	0	0
HIV co-infection	73 (91%)	46 (90%)	27 (93%)
CD4 cell count (per µL)	605 (490–765)	601 (497–770)	610 (396–767)
HIV viral load <50 copies per mL	71 (97%)	45 (98%)	26 (96%)
Patient on combination ART	73 (100%)	46 (100%)	27 (100%)

Data are mean (SD), n (%), or median (IQR). HCV=hepatitis C virus. MSM=men who have sex with men. HBV=hepatitis B virus. ART=antiretroviral therapy.

Table 1: **Baseline characteristics**

Data were analysed with IBM SPSS version 21. This trial is registered with ClinicalTrials.gov, number NCT02600325.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. AB and BJAR had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 15, 2016, and March 2, 2018, we assessed 146 patients with a recently acquired HCV infection for eligibility, of whom 86 were enrolled and 80 initiated therapy (figure). All patients who initiated treatment completed the treatment period and no patients were lost to follow-up. A negative HCV RNA or antibody test on plasma that had been collected and stored at the preceding HIV outpatient visit (typically 6 months before screening for eligibility) led to acute HCV diagnosis in 72 (90%) of 80 patients, while eight patients fulfilled the alternative eligibility definition.

The mean patient age was 47 years (SD 10), all patients were MSM, and 72 (90%) patients were white (table 1). In 19 (24%) patients, the current HCV episode was a reinfection. 51 (64%) of 80 patients had acute HCV genotype 1a infection and 29 (36%) of 80 patients had acute genotype 4 infection. The median baseline alanine aminotransferase was 139 IU/mL (IQR 74–315) and the median baseline HCV RNA was 310 000 IU/mL (34 000–1 400 000). 73 (91%) patients were co-infected with HIV and all were on combination ART, with an HIV viral load less than 50 copies per mL in 71 (97%) patients and a median CD4 cell count of 605 per µL (IQR 490–765). Four (57%) of seven HIV-negative patients were receiving pre-exposure prophylaxis. Two (3%) of 80 patients had symptomatic (icteric) acute hepatitis C at screening. The mean total bilirubin concentration was 13 µmol/L (SD 6) and only 13 (16%) of 80 patients had a total bilirubin above the upper limit of normal (>17 µmol/L; maximum 39 µmol/L).

75 (94%) of 80 patients who were enrolled and started treatment achieved SVR12. No patients were lost to follow-up or had interrupted treatment. Of the five (6%) patients with positive HCV RNA 12 weeks after the end of therapy, phylogenetic analysis showed that one had treatment failure and the other four were reinfected with a different HCV strain (appendix p 1). Therefore, we observed the primary endpoint in 79 (99%, 95% CI 93–100) of 80 patients and this was non-inferior to the predefined 93% success rate. If the four HCV reinfections were considered treatment failures, the SVR rate was 94% (86–98), which was also non-inferior to the predefined 93% success rate. In the four cases of HCV reinfection, HCV RNA was below the limit of detection at the end of therapy. Therefore, reinfection is likely to have occurred

	All patients (n=80)		Genotype		HIV status	
	Reinfection not counted as treatment failure (primary endpoint)	Reinfection counted as treatment failure	Patients with genotype 1a infection (n=51)*	Patients with genotype 4 infection (n=29)*	HIV-positive patients (n=73)*	HIV-negative patients (n=7)*
Started therapy	80	80	51	29	73	7
Primary endpoint	80	80	51	29	73	7
SVR12	75	75	49	26	68	7
Reinfection	4	4	2	2	4	0
Treatment failure	1	1	0	1	1	0
Total patients cured	79 (99%; 93–100)	75 (94%; 86–98)	51 (100%; 93–100)	28 (97%; 82–100)	72 (99%; 93–100)	7 (100%; 59–100)

Data are n or n (%; 95% CI). SVR12=sustained virological response 12 weeks after the end of treatment. *Reinfections were not counted as treatment failure in these patients.

Table 2: **Treatment outcomes overall and according to genotype and HIV status**

between weeks 8 and 20 of the study. The genotypes detected at the time of reinfection were genotype 1a in two patients and genotype 4 in two patients.

The patient with treatment failure was a 50-year-old man with a well controlled HIV co-infection and a genotype 4d HCV infection with a baseline viral load of 14 700 000 IU/mL. Although the patient's HCV RNA load declined rapidly during therapy, HCV RNA remained detectable at the last day of therapy (17 IU/mL). No NS3 or NS5A resistance-associated variants were detected in the hepatitis C viruses sequenced at baseline or 12 weeks after the end of therapy in this patient. According to the patient, and confirmed by drug accountability records, treatment adherence was perfect. The proportion of patients achieving SVR12 was similar in patients with genotype 1 versus genotype 4 infection (100% [93–10] *vs* 97% [82–100]; p=0·4) or HIV-positive versus HIV-negative patients (99% [93–100] *vs* 100% [59–100]; p=1·0; table 2, appendix). Furthermore, we investigated the effect of baseline HCV viral load on SVR12 and found that 22 (96%) of 23 patients with a baseline viral load greater than 1 million IU/mL achieved SVR12 (appendix p 3).

12 (24%) of 51 patients infected with HCV genotype 1a had a Met28Val substitution, and one of these patients also had a Tyr39His substitution. Additionally, one patient had a single Gln30Arg substitution and another had a single Tyr93His substitution (appendix p 3). These 14 patients achieved SVR12. The baseline viral load in patients with an NS5A mutation was 366 500 IU/mL (IQR 70 925–1 039 250), similar to the viral load in those without an NS5A mutation (308 944 IU/mL, 45 200–1 380 000). Furthermore, the mean time from diagnosis to treatment initiation was similar (4·4 months [SD 1·0] in patients with HCV genotype 1a, and 4·4 months [1·2] in patients with HCV genotype 4). In the 29 patients infected with HCV genotype 4, we found no NS5A resistance-associated substitutions.

At screening, 27 (96%) of 28 patients on an HIV treatment regimen susceptible to drug–drug interactions with grazoprevir plus elbasvir were successfully switched to a compatible combination ART regimen. This patient group consisted of eight patients on elvitegravir and cobicistat, eight on efavirenz, six on nevirapine, and five on darunavir and ritonavir.

On the basis of pill count, adherence during the 8 weeks of treatment was 95%. The few patients who had not finished the 56 pills at the end of week 8 took the remaining pills in week 9. The study regimen was generally well tolerated. 59 (74%, 95% CI 63–82) of 80 patients reported at least one adverse event (table 3); 138 (66%) of 172 adverse events were considered mild by the investigator. No drug-related serious adverse events were reported and none of the adverse events led to study drug discontinuation (table 3). The most common adverse event was a new sexually transmitted infection (STI)—20 different STIs were observed in 19 (24%) patients. One patient was newly diagnosed with both *Chlamydia trachomatis* and syphilis during the study, six patients were newly diagnosed with syphilis, four with *C trachomatis*, three with gonorrhoea, two with lymphogranuloma venereum, one with scabies, one with *Shigella dysenteriae*, and one with sexually transmitted hepatitis A. The most common reported possibly drug-related adverse events were fatigue (11 [14%] patients), headache (seven [9%] patients), insomnia (seven [9%] patients), mood changes (five [6%] patients), dyspepsia (five [6%] patients), concentration impairment (four [5%] patients), and dizziness (four [5%] patients). One patient did not initiate study medication because of a (non-serious) adverse event (mood changes) after a switch in combination ART regimen, as the previous combination ART regimen was incompatible with grazoprevir plus elbasvir.

Discussion

In this single-arm, open-label, phase 3b trial, an 8 week course of grazoprevir plus elbasvir successfully treated 79 (99%) of 80 patients with acute HCV genotype 1a or 4 infection. This is, to our knowledge, the largest study to date on the treatment of acute HCV with DAAs. We also found non-inferiority to the 93% SVR reported for patients chronically infected with HCV treated with 12 weeks of grazoprevir plus elbasvir in the phase 3

	All patients (n=80)
Death	0
Serious adverse events	
Traumatic rectal bleeding	1 (1%)
Low back surgery	1 (1%)
Any adverse event	59 (74%)
Most common adverse events	
Sexually transmitted infection	19* (24%)
Upper respiratory infection	15 (19%)
Fatigue	14 (18%)
Infections	11 (14%)
Diarrhoea	9 (11%)
Insomnia	9 (11%)
Mood changes	8 (10%)
Dyspepsia	8 (10%)
Skin disorder	8 (10%)
Headache	7 (9%)
Dizziness	5 (6%)
Injury	4 (5%)
Concentration impairment	4 (5%)
Back pain	4 (5%)

Data are n (%). The most commonly reported possibly drug-related adverse events were fatigue (11 [14%] patients), headache (seven [9%] patients), insomnia (seven [9%] patients), mood changes (five [6%] patients), dyspepsia (five [6%] patients), concentration impairment (four [5%] patients), and dizziness (four [5%] patients). *20 sexually transmitted diseases in 19 patients.

Table 3: **Adverse events**

C-EDGE trial,[24] demonstrating that this regimen is also effective during the acute phase of an HCV infection. Furthermore, we achieved this high proportion of SVR12 using a shorter treatment duration. The treatment was well tolerated and overall patient compliance was excellent. In contrast to previous studies on DAA therapy for acute HCV,[25–29] our sample size was sufficiently large to draw statistical conclusions about non-inferiority and our study also included a substantial number of HCV genotype 4 infections. Although a large proportion of acute HCV infections among MSM in Europe are of genotype 4, previous studies on DAAs for acute HCV infection have been almost entirely limited to patients with genotype 1a.[18]

The grazoprevir plus elbasvir label in the USA indicates that testing for NS5A polymorphisms should be done and treatment should be extended from 12 to 16 weeks in patients with chronic HCV genotype 1a infection with certain NS5A polymorphisms. Since the relevance of NS5A polymorphisms in patients treated for acute HCV has not been determined, we used a fixed 8 week treatment duration for all patients and did not test for NS5A polymorphisms before treatment initiation. All 14 patients infected with a genotype 1a HCV with an NS5A polymorphism achieved SVR12 after 8 weeks of therapy. This result is in sharp contrast with the 39 (70%) of 56 patients with a chronic HCV genotype 1a infection treated for 12 weeks achieving SVR (p=0·02) if the virus carried baseline NS5A polymorphisms that led to a change in the amino acids at positions 28, 30, 31, and 93.[30] Furthermore, we did not observe any difference in HCV RNA kinetics during treatment of the patients with and without NS5A polymorphisms (data not shown). Therefore, our data suggest that extending the treatment duration for patients with an acute HCV genotype 1a infection in the presence of baseline NS5A polymorphisms is unnecessary.

Some antiretroviral drugs cannot be combined with grazoprevir plus elbasvir (eg, efavirenz or protease inhibitors), which might limit the use of this regimen in patients coinfected with HIV. However, 27 (96%) of 28 patients on an HIV regimen susceptible to drug–drug interactions with grazoprevir plus elbasvir at the time of screening for this study were successfully switched to a compatible combination ART regimen. These interactions are mainly caused by the HCV protease inhibitor grazoprevir. The same interactions are observed with the two DAA regimens most recently approved by the US Food and Drug Administration and European Medicines Agency because they also both include an HCV protease inhibitor (glecaprevir in glecaprevir–pibrentasvir [AbbVie; North Chicago, IL, USA] and voxilaprevir in sofosbuvir–velpatasvir–voxilaprevir [Gilead Sciences; Foster City, CA, USA]). Furthermore, 8 weeks of grazoprevir plus elbasvir is by far the least expensive of all DAA regimens currently available.

Although pegylated interferon was registered for the treatment of acute HCV when this study was designed in 2016, it is no longer used for this indication because of its numerous side-effects and because DAAs are now available. Additionally, the SVR observed in a large phase 3 study of 12 weeks of grazoprevir plus elbasvir for the treatment of chronic HCV was available as a comparator for our study.[24] Therefore, we used the SVR of 93% observed in this previous study[24] for patients infected with genotypes 1a and 4 combined as a comparator. Given the short 2 month interval between HCV diagnosis and initiation of therapy in our study, it could be argued that a compulsory wait period of 2–3 months for spontaneous cure might have been preferable because this might avoid unnecessary DAA therapy. However, since DAA therapy is well tolerated and the chances of spontaneous cure of HCV in patients with HIV are small,[31] we considered the DAA treatment-as-prevention effect of immediate therapy more important than avoiding unnecessary DAA therapy. Therefore, the decision to wait for spontaneous HCV clearance was left to the treating physician. Generally, HIV physicians in the Netherlands repeat HCV RNA measurement 4 weeks after acute HCV diagnosis to evaluate HCV clearance before treatment is initiated. However, this was not defined in our protocol and 14 patients started therapy within 4 weeks after diagnosis. A recent modelling study that accounted for the continued risk of onward HCV

transmission showed that treatment of patients in the acute phase of HCV with a shorter regimen is likely to be cost saving compared with a wait for spontaneous cure approach.[10] Given that spontaneous clearance of HCV infection is observed less frequently in patients with HIV than in patients without HIV, this is even more relevant for such patients.[21,32] A comprehensive review[9] of strategies and obstacles for HCV elimination is available elsewhere.

The presence of possible predictors for spontaneous HCV clearance was low in our study population: only two (3%) of 80 patients had symptomatic (icteric) acute HCV at screening and 13 (16%) of 80 patients had a total bilirubin above the upper limit of normal. Combined with the relatively low alanine aminotransferase at baseline, these results show that spontaneous clearance was unlikely in our study population. We did not investigate *IL28B* genotypes in our cohort because of resource restrictions. However, in an earlier clinical trial in HIV-positive MSM in the Netherlands in 2013–14, 25 (45%) of 55 patients had the more favourable CC genotype.[15] Whether a previous HCV infection—particularly a spontaneously cleared previous infection—is an indicator of partial protective immune memory or a predictor for spontaneous clearance of a new HCV infection remains debated.[33] In our study population, only two (11%) of 19 patients with a previous HCV infection in their medical history were cured without HCV therapy, which shows the rarity of spontaneous HCV clearance in HIV-positive patients.

Our study has several limitations. We included a uniform study population that mostly consisted of white MSM with HCV genotype 1a or 4 infection and used strict acute HCV diagnostic criteria. This acute HCV population truly represents the patient population in which acute HCV infections are diagnosed in many European countries, particularly in the Netherlands and Belgium.[2,5] However, these results might not extrapolate to other regions of the world. HCV transmission via injecting drug use has become rare in both Belgium and the Netherlands because of harm reduction interventions such as needle exchange programmes and opioid substitution.[34] Although the baseline HCV load of our population was lower than that observed in patients with chronic HCV, this viral load truly represents the distribution observed in patients with acute HCV infection. The non-pangenotypic nature of grazoprevir plus elbasvir might be a limitation in settings in which genotyping is not possible. However, this was not a limitation in the setting in which our study was done because only six (4%) of 146 patients evaluated for eligibility had HCV of a genotype other than 1 or 4. Therefore, HCV treatment with grazoprevir plus elbasvir was appropriate for 96% of patients assessed for eligibility. Many other DAA regimens have the potential to treat patients with acute HCV. However, like grazoprevir plus elbasvir, these also have limitations, including the unavailability of—or inconclusive—efficacy data in patients with acute HCV, particularly regarding shortened treatment durations and for non-genotype-1 viruses, genotype restrictions, and drug–drug interactions for the most recent pangenotypic regimens that include an HCV protease inhibitor (eg, with efavirenz for glecaprevir and voxilaprevir and with darunavir for glecaprevir). Finally, we did not collect data on risk behaviour, and the absence of a randomised control group in our study could be seen as a limitation. We used a historical comparator comprised of chronically infected, rather than acutely infected, patients. However, the 99% proportion of cures in our trial does not leave room for doubt about the efficacy of grazoprevir plus elbasvir for the treatment of acute HCV.

Although, to our knowledge, this is the first study to report non-inferiority for the treatment of acute HCV infection with 8 weeks of grazoprevir plus elbasvir treatment compared with 12 weeks of grazoprevir plus elbasvir treatment for chronic HCV infection, other clinical trials of DAAs for acute HCV infection are ongoing. However, to our knowledge, only the REACT study (ClinicalTrials.gov, number NCT02625909) will be an adequately powered non-inferiority study of a shorter treatment duration (6 weeks) compared with the standard treatment duration (12 weeks). Nevertheless, off-label use of early DAA therapy for acute HCV in patients who might transmit HCV to others is already advocated by the 2017 European AIDS Clinical Society guideline to prevent onward transmission.[35] The four HCV reinfections and 20 (other) STIs diagnosed during the 20 weeks of follow-up in our study clearly show the continued risk behaviour and therefore risk for ongoing transmission after HCV diagnosis. Together with the observation that 19 (24%) of 80 patients in our study already had a history of HCV infection, this result shows that microelimination of HCV in MSM will also need research on behavioural interventions.

In conclusion, a short 8 week grazoprevir plus elbasvir regimen was highly effective for treatment of acute HCV genotype 1 or 4 infection.

Contributors

AB, SJH, JEA, and BJAR conceived or designed the study. AB, ADW, GEvdB, FNL, MAAC, DP, WFB, ASMD, GJK, EML, JdH, MEvK, RS, HSMA, EF, and JEA collected the data. AB, SP, DACMvdV, JS, and BJAR analysed and interpreted the data. AB, EF, JEA, and BJAR drafted the Article. ADW, GEvdB, FNL, MAAC, DP, WFB, SJH, SP, DACMvdV, ASMD, GJK, EML, JdH, MEvK, RS, HSMA, JS, EF, JEA, and BJAR did critical revision of the Article. AB, ADW, FNL, MAAC, DP, WFB, SJH, SP, DACMvdV, ASMD, GJK, EML, JdH, MEvK, RS, HSMA, JS, EF, JEA, and BJAR approved the final version of the Article for publication.

Declaration of interests

WFB reports grants and non-financial support from Janssen, outside the submitted work. SJH reports grants from Merck during the conduct of the study, and non-financial support from Gilead Sciences and Merck Sharp and Dohme outside the submitted work. SP reports grants from Gilead Sciences, ViiV Healthcare, Janssen, and Merck Sharp and Dohme during the conduct of the study. DACMvdV reports grants and travel support from ViiV Healthcare, and grants from Merck Sharp and Dohme, Janssen, and Gilead Sciences outside the submitted work.

JdH reports advisory board fees from AbbVie, Gilead Sciences, and ViiV Healthcare outside the submitted work. JS reports grants from Gilead Sciences, AbbVie, Merck Sharp and Dohme, and Janssen Pharmaceuticals outside the submitted work. EF reports grants from Janssen, Gilead Sciences, and ViiV Healthcare, and acted on advisory boards for Janssen and ViiV Healthcare, outside the submitted work. JEA reports acting on advisory boards, with renumeration being paid to their institution, for Gilead Sciences, Janssen, AbbVie, Merck Sharp and Dohme, ViiV Healthcare, and Bristol-Myers Squibb, and grants from ViiV Healthcare, Merck Sharp and Dohme, Bristol-Myers Squibb, and AbbVie, outside the submitted work. BJAR reports grants from Merck Sharp and Dohme, during the conduct of the study; and grants from Gilead Sciences, and participation in advisory boards and travel support from Merck Sharp and Dohme, Janssen-Cilag, Bristol-Myers Squibb, Gilead Sciences, Pfizer, and ViiV Healthcare, outside the submitted work. All other authors declare no competing interests.

Data sharing

Deidentified participant data can be made available upon request for non-commercial purposes and after approval of a study proposal through a signed data access agreement. The full study protocol is available online.

Acknowledgments

The study was investigator-initiated (by BJAR) and was supported by a research grant to BJAR from Merck Sharp and Dohme and Health-Holland. Merck Sharp and Dohme provided the study drugs free of charge. We thank Andre Boonstra and Gertine van Oord for logistical support in the lab. We thank Lida van Petersen, Imke Hooijenga, Inge de Kroon, Danielle van Elst, Nienke Langebeek, Gerjanne ter Beest, Robin Ackens, Karin Grintjes, Lida Beneken Kolmer, Corine Delsing, Sieds Wildenbeest, Lia Meerkerk, Jannigje Smit, and Marien Kuipers for local study coordination. We thank Sjoerd Rebers and Jelle Koopsen for phylogenetic analysis. We thank all patients that made the study a success.

References

1 WHO. Combating hepatitis B and C to reach elimination by 2030. Geneva: World Health Organization, 2016.

2 Boerekamps A, Van den Berk G, Lauw FN, et al. Declining hepatitis C virus (HCV) incidence in Dutch human immunodeficiency virus-positive men who have sex with men after unrestricted access to HCV therapy. *Clin Infect Dis* 2018; **66**: 1360–65.

3 Visser M, van Aar F, van Oeffelen AAM, et al. Sexually transmitted infections including HIV, in the Netherlands in 2016. Rijksinstituut voor Volksgezondheid en Milieu RIVM. June 23, 2017. https://www.rivm.nl/publicaties/sexually-transmitted-infections-including-hiv-in-netherlands-in-2016 (accessed Dec 12, 2018).

4 Yaphe S, Bozinoff N, Kyle R, Shivkumar S, Pai NP, Klein M. Incidence of acute hepatitis C virus infection among men who have sex with men with and without HIV infection: a systematic review. *Sex Transm Infect* 2012; **88**: 558–64.

5 Boerekamps A, Newsum AM, Smit C, et al. High treatment uptake in human immunodeficiency virus/hepatits C virus-coinfected patients after unrestricted access to direct-acting antivirals in the Netherlands. *Clin Infect Dis* 2018; **66**: 1360–65.

6 Salazar-Vizcaya L, Kouyos RD, Zahnd C, et al. Hepatitis C virus transmission among human immunodeficiency virus-infected men who have sex with men: modeling the effect of behavioral and treatment interventions. *Hepatology* 2016; **64**: 1856–69.

7 Martin NK, Thornton A, Hickman M, et al. Can hepatitis C virus (HCV) direct-acting antiviral treatment as prevention reverse the HCV epidemic among men who have sex with men in the United Kingdom? Epidemiological and modeling insights. *Clin Infect Dis* 2016; **62**: 1072–80.

8 Braun DL, Hampel BH, Nguyen H, et al. A treatment as prevention trial to eliminate HCV in HIV+ MSM: the Swiss HCVREE trial. Conference on Retroviruses and Opportunistic Infections; Boston, MA, USA; March 4–7, 2018. Abstract 81LB.

9 Martin NK, Boerekamps A, Hill AM, Rijnders BJA. Is hepatitis C virus elimination possible among people living with HIV and what will it take to achieve it? *J Int AIDS Soc* 2018; **21** (suppl 2): e25062.

10 Bethea ED, Chen Q, Hur C, Chung RT, Chhatwal J. Should we treat acute hepatitis C? A decision and cost-effectiveness analysis. *Hepatology* 2018; **67**: 837–46.

11 Lazarus JV, Wiktor S, Colombo M, Thursz M. Micro-elimination—a path to global elimination of hepatitis C. *J Hepatol* 2017; **67**: 665–66.

12 Abergel A, Hezode C, Asselah T, et al. High efficacy and safety of grazoprevir and elbasvir for 8 weeks in treatment-naive, non-severe fibrosis HCV GT1b-infected patients: interim results of the STREAGER study. *J Hepatol* 2018; **68** (suppl 1): S110.

13 Asselah T, Pol S, Hezode C, et al. Efficacy and safety of 8 weeks of elbasvir/grazoprevir in HCV GT4-infected treatment-naive participants. International Liver Congress; Paris, France; 11–15 April, 2018.

14 Sulkowski M, Hezode C, Gerstoft J, et al. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet* 2015; **385**: 1087–97.

15 Hullegie SJ, Claassen MA, van den Berk GE, et al. Boceprevir, peginterferon and ribavirin for acute hepatitis C in HIV infected patients. *J Hepatol* 2016; **64**: 807–12.

16 Jaeckel E, Cornberg M, Wedemeyer H, et al. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001; **345**: 1452–57.

17 Zhang B, Nguyen NH, Yee BE, et al. Treatment of acute hepatitis C infection with pegylated interferon and ribavirin in patients coinfected with human immunodeficiency virus: a systematic review and meta-analysis. *Intervirology* 2015; **58**: 242–49.

18 Martinello M, Hajarizadeh B, Grebely J, Dore GJ, Matthews GV. Management of acute HCV infection in the era of direct-acting antiviral therapy. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 412–24.

19 European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel. Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference. *AIDS* 2011; **25**: 399–409.

20 Ingiliz P, Martin TC, Rodger A, et al. HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. *J Hepatol* 2017; **66**: 282–87.

21 Thomas XV, Grady BP, Van Der Meer JT, et al. Genetic characterization of multiple hepatitis C virus infections following acute infection in HIV-infected men who have sex with men. *AIDS* 2015; **29**: 2287–95.

22 de Oliveira T, Deforche K, Cassol S, et al. An automated genotyping system for analysis of HIV-1 and other microbial sequences. *Bioinformatics* 2005; **21**: 3797–800.

23 US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (accesed Oct 14, 2018).

24 Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and non-cirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial. *Ann Intern Med* 2015; **163**: 1–13.

25 Deterding K, Spinner CD, Schott E, et al. Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. *Lancet Infect Dis* 2017; **17**: 215–22.

26 Rockstroh JK, Bhagani S, Hyland RH, et al. Ledipasvir-sofosbuvir for 6 weeks to treat acute hepatitis C virus genotype 1 or 4 infection in patients with HIV coinfection: an open-label, single-arm trial. *Lancet Gastroenterol Hepatol* 2017; **2**: 347–53.

27 Naggie S, Fierer DS, Hughes M, et al. 100% SVR with 8 weeks of ledipasvir/sofosbuvir in HIV-infected men with acute HCV infection: results from the SWIFT-C trial. *Hepatology* 2017; **66**: 113A.

28 Fierer DS, El Sayed A, Palaniswami P. THU-250—Treatment of "acute" hepatitis C virus in human immunodeficiency virus-infected men with short-course sofosbuvir/ledipasvir. *J Hepatol* 2017; **66** (suppl 1): S300.

29 Martinello M, Bhagani S, Gane E, et al. Shortened therapy of eight weeks with paritaprevir/ritonavir/ombitasvir and dasabuvir is highly effective in people with recent HCV genotype 1 infection. *J Viral Hepat* 2018; **25**: 1180–88.

30 US Food and Drug Administration. Elbasvir-grazoprevir (Zepatier) prescribing information (reference ID 4055857). https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208261s002lbl.pdf (accessed Sept 18, 2018).

31 Newsum AM, Schinkel J, van de Laar TJW, van der Meer JTM, Prins M. Spontaneous clearance of hepatitis C virus infection among HIV-infected men who have sex with men. *Open Forum Infect Dis* 2017; **4:** ofx090.

32 Smith DJ, Jordan AE, Frank M, Hagan H. Spontaneous viral clearance of hepatitis C virus (HCV) infection among people who inject drugs (PWID) and HIV-positive men who have sex with men (HIV+MSM): a systematic review and meta-analysis. *BMC Infect Dis* 2016; **16:** 471.

33 Grebely J, Prins M, Hellard M, et al. Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: towards a vaccine. *Lancet Infect Dis* 2012; **12:** 408–14.

34 van den Berg CH, Smit C, Bakker M, et al. Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users. *Eur J Epidemiol* 2007; **22:** 183–93.

35 European AIDS Clinical Society. European guidelines for treatment of HIV-positive adults in Europe.Version 9.0. October, 2017. htd. eacsociety.org/files/2018_guidelines-9.1-english.pdf (accessed June 16, 2018).