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

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Summary

Background Both hepatitis C virus (HCV) mono-infected and HIV/HCV co-infected patients are in need of safe, effective, all-oral HCV regimens. In a phase 2 study we aimed to assess the efficacy and safety of grazoprevir (MK-5172; HCV NS3/4A protease inhibitor) and two doses of elbasvir (MK-8742; HCV NS5A inhibitor) in patients with HCV mono-infection and HIV/HCV co-infection.

Methods The C-WORTHY study is a phase 2, multicentre, randomised controlled trial of grazoprevir plus elbasvir with or without ribavirin in patients with HCV; here, we report findings for previously untreated (genotype 1) patients without cirrhosis who were HCV mono-infected or HIV/HCV co-infected. Eligible patients were previously untreated adults aged 18 years or older with chronic HCV genoype 1 infection and HCV RNA at least 10 000 IU/mL in peripheral blood without evidence of cirrhosis, hepatocellular carcinoma, or decompensated liver disease. In part A of the study we randomly assigned HCV-mono-infected patients to receive 12 weeks of grazoprevir (100 mg) plus elbasvir (20 mg or 50 mg) with or without ribavirin (arms A1–3); in part B we assigned HCV-mono-infected patients to 8 or 12 weeks of grazoprevir (100 mg) plus elbasvir (50 mg) with or without ribavirin (arms B1–3) and HIV/HCV co-infected patients to 12 weeks of therapy with or without ribavirin. The primary endpoint was the proportion of patients achieving HCV RNA less than 25 IU/mL 12 weeks after end of treatment (SVR12). Randomisation was by presence or absence of ribavirin, 8 or 12 weeks of treatment, and dosage of elbasvir. Patients were stratified by gentoype 1a versus 1b. The patients, investigators, and study site personnel were masked to treatment group assignements but the funder was not. Analysis was by intention to treat. This trial is registered at ClinicalTrials.gov, number NCT01717326.

Findings 218 patients with HCV mono-infection (n=159) and HIV/HCV co-infection (n=59) were enrolled. SVR12 for patients treated for 12 weeks with or without ribavirin ranged from 93–98% in mono-infected and 87–97% in co-infected patients. SVR12 rates in mono-infected and co-infected patients treated for 12 weeks without ribavirin were 98% (95% CI 88–100; 43/44) and 87% (95% CI 69–96; 26/30), respectively, and with ribavirin were 93% (95% CI 85–97; 79/85) and 97% (95% CI 82–100; 28/29), respectively. Among mono-infected patients with genotype 1a infection treated for 8 weeks, SVR12 was 80% (95% CI 61–92; 24/30). Five of six patients who discontinued early for reasons other than virological failure had HCV RNA less than 25 IU/mL at their last study visit. Virological failure among patients treated for 12 weeks occurred in seven patients (7/188, 4%) and was associated with emergence of resistance-associated variants to one or both drugs. The safety profile of grazoprevir plus elbasvir with or without ribavirin was similar in mono-infected and co-infected patients. No patient discontinued due to an adverse event or laboratory abnormality. The most common adverse events were fatigue (51 patients, 23%), headache (44, 20%), nausea (32, 15%), and diarrhoea (21, 10%).

Interpretation Once-daily grazoprevir plus elbasvir with or without ribavirin for 12 weeks in previously untreated HCV-mono-infected and HIV/HCV-co-infected patients without cirrhosis achieved SVR12 rates of 87–98%. These results support the ongoing phase 3 development of grazoprevir plus elbasvir.

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Introduction

Globally, 80–185 million people are infected with hepatitis C virus (HCV), of who an estimated 5 million are HIV/HCV co-infected.[1–3] Both mono-infected and co-infected patients are at risk for progression of HCV disease, leading to cirrhosis, end-stage liver disease, hepatocellular carcinoma, liver transplantation and death. Moreover, HIV/HCV co-infected patients have

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higher viral loads, accelerated disease progression, and few treatment options.[4] HCV has emerged as a leading cause of death among people living with HIV.

HCV antiviral treatment leading to virological cure has been associated with lower risk of HCV-related morbidity and mortality in both mono-infected and co-infected patients.[5] However, HCV treatment in mono-infected and co-infected patient populations has not been very effective and, in most regions, relatively few co-infected people with chronic HCV infection have achieved sustained virological response.[6] Although many heterogenous barriers to effective HCV treatment exist, the need for interferon alfa—the backbone of therapy since the early 1990s—has represented a major impediment.[7] Furthermore, clinically significant adverse effects and drug interactions between first-generation HCV direct-acting antivirals and antiretroviral drugs reduce the suitability of treatment for most co-infected patients with newer approved therapies, many of which include pegylated interferon (peginterferon).[8] Without a direct-acting antiviral, sustained virological response rates with a regimen of peginterferon plus ribavirin is low, particularly for patients with co-infection.[9]

Since 2011, additional oral HCV direct-acting antivirals with multiple mechanisms have emerged as the treatment of choice for chronic HCV infection. These drugs directly target HCV non-structural proteins (NS3/4A protease, NS5B polymerase, and the NS5A protein) that have crucial roles in the HCV lifecycle; regimens incorporating direct-acting antivirals minimise the negative effect of host factors (eg, race and ethnic origin, *IFNL3* (also known as *IL28B*) genotype, and HIV co-infection) on the likelihood of achievement of sustained virological response. In clinical trials, interferon-free oral combinations of direct-acting antivirals have been well tolerated and highly efficacious in mono-infected patients. Although guidelines for HCV treatment are changing rapidly, current recommendations include oral direct-acting antiviral regimens with and without interferon alfa, marking the advent of interferon-free therapy for some patients.[10,11] Grazoprevir and elbasvir (Merck & Co, Inc, Whitehouse Station, NJ, USA) are once-daily, highly potent inhibitors of the HCV NS3/4A protease and NS5A protein, respectively.[12,13] In vitro and in vivo, the combination of grazoprevir and elbasvir has a high barrier to resistance and activity against many common resistance-associated variants.[14] Additionally, this direct-acting antiviral combination can be coadministered with antiretroviral regimens that contain the integrase inhibitor raltegravir and dual nucleoside-nucleotide reverse transcriptase inhibitors (eg, tenofovir or abacavir plus emtricitabine or lamivudine) without dose adjustments. As such, the combination of grazoprevir plus elbasvir has the potential to provide an all-oral, highly efficacious, simple, and well-tolerated regimen for the treatment of HCV genotype 1 infection in patients with and without HIV co-infection.

We aimed to assess the safety, tolerability, and efficacy of the oral combination of grazoprevir plus elbasvir with or without ribavirin for the treatment of HCV genotype 1 infection in previously untreated patients with no cirrhosis, with and without HIV co-infection, in a randomised phase 2 trial.

Methods

Study design and participants

The C-WORTHY trial (protocol 035) was a randomised, parallel-group, multicentre, open-label, international phase 2 trial that assessed several diverse patient populations with HCV genotype 1 infection. In this report we describe outcomes for previously untreated patients without cirrhosis from two cohorts enrolled in parts A and B of the study: HCV mono-infected patients and HIV/HCV co-infected patients. Previously untreated

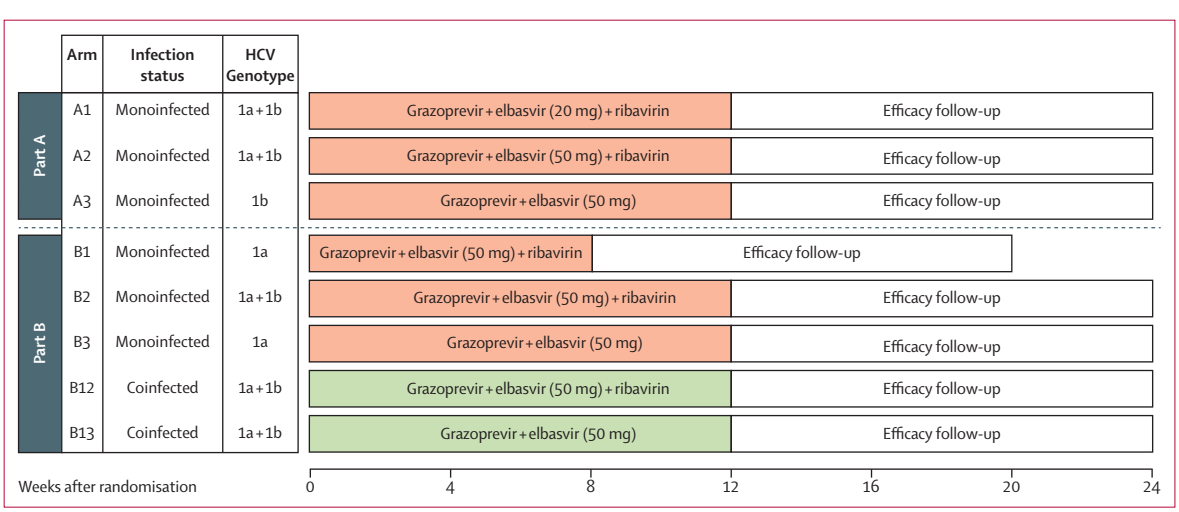


Figure 1: **Treatment groups**
HCV=hepatitis C virus. SVR12=proportion of patients achieving HCV RNA less than 25 IU/mL 12 weeks after end of treatment. The dosages of study drugs were 100 mg of grazoprevir once daily, 20 or 50 mg of elbasvir once daily, and 800–1400 mg of ribavirin per day (total daily doses based on patients' bodyweight in kg: 51–65 kg, 800 mg/day; 66–80 kg, 1000 mg/day; 81–105 kg, 1200 mg/day; >105–125 kg, 1400 mg/day) in two divided oral doses given in the morning and evening.

adults with HCV genotype 1 infection aged 18 years or older were eligible. Inclusion criteria included bodyweight of at least 50 kg and HCV RNA plasma concentration of at least 10 000 IU/mL. Exclusion criteria included evidence or history of hepatitis not caused by HCV, evidence of hepatocellular carcinoma, decompensated liver disease, and previous HCV therapy. Key HIV-related enrolment criteria included well-controlled HIV infection with raltegravir plus two nucleoside or nucleotide reverse transcriptase inhibitors for at least 8 weeks before enrolment, evidence of undetectable HIV RNA for at least 24 weeks, and CD4 count of at least 300 cells per µL.

We obtained informed consent from each patient; the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the appropriate institutional review committee in each institution.

Randomisation and masking

Randomisation occurred centrally with an interactive voice response system. The trial was divided into two parts. In part A we randomly assigned HCV-mono-infected patients with HCV genotype 1b in a 2:2:3 ratio to receive 12 weeks of treatment with grazoprevir 100 mg in combination with either ribavirin and 20 mg elbasvir (arm A1), ribavirin and 50 mg elbasvir (arm A2), or arm A3 which consisted of 12 weeks of treatment with 100 mg grazoprevir with 50 mg elbasvir and no ribavirin. Patients with HCV genotype 1a were randomly assigned in a 1:1 ratio to arm A1 or A2. The patients, investigators, and study site personnel were masked to the treatment group assignments but the funder was not.

In Part B, we randomly assigned HCV-mono-infected patients with HCV genotype 1a in a 2:1:2 ratio to receive 8 weeks (arm B1) or 12 weeks (arm B2) of treatment with grazoprevir 100 mg plus elbasvir 50 mg with ribavirin, or 12 weeks of grazoprevir 100 mg plus elbasvir 50 mg without ribavirin (arm B3). HCV-mono-infected patients with HCV genotype 1b were not randomised within this cohort and instead were all assigned to arm B2. Patients co-infected with HCV and HIV (irrespective of HCV genotype) were randomly assigned in a 1:1 ratio to 12 weeks of treatment with grazoprevir 100 mg plus elbasvir 50 mg with (arm B12) or without (arm B13) ribavirin.

Total daily doses of ribavirin were based on patients' bodyweight in kg: 51–65 kg, 800 mg/day; 66–80 kg, 1000 mg/day; 81–105 kg, 1200 mg/day; and >105 kg to 125 kg, 1400 mg/day

Procedures

A central laboratory (Pharmaceutical Product Development, Wilmington, NC, USA) assessed HCV RNA by Roche COBA Taqman HCV test, version 2.0 (lower limit of quantitation 25 IU/mL and limit of detection 15·1 IU/mL). Tests were done on blood samples drawn from each patient at screening, days 1, 3, 5, 7, weekly between treatment weeks 2 and 12, and after end of treatment at follow-up weeks 2, 4, 8, 12, and 24. Baseline results (HIV RNA, HCV RNA, haemoglobin, albumin, alanine aminotransferase, aspartate aminotransferase, bilirubin, and platelets) were determined with samples taken on day 1 after enrolment. HCV genotyping was done with the Versant HCV genotype (LiPA) 2.0 manufactured by Innogenetics (Ghent, Belgium). Plasma samples were collected at screening for *IFNL3* genotype assessment (rs12979860, CC *vs* non-CC).

We defined virological breakthrough as a confirmed HCV RNA of 25 IU/mL or higher after being less than 25 IU/mL previously. Relapse was defined as a confirmed HCV RNA at least 25 IU/mL after end of all study therapy after becoming undetectable (HCV RNA <15·1 IU/mL) at end of treatment. For both virological breakthrough and relapse, we defined confirmation as a result of HCV RNA of 25 IU/mL or higher from a separate blood draw repeated within 2 weeks. The failure time point was the time that HCV RNA was 25 IU/mL or higher after being less than 25 IU/mL or undetectable previously.

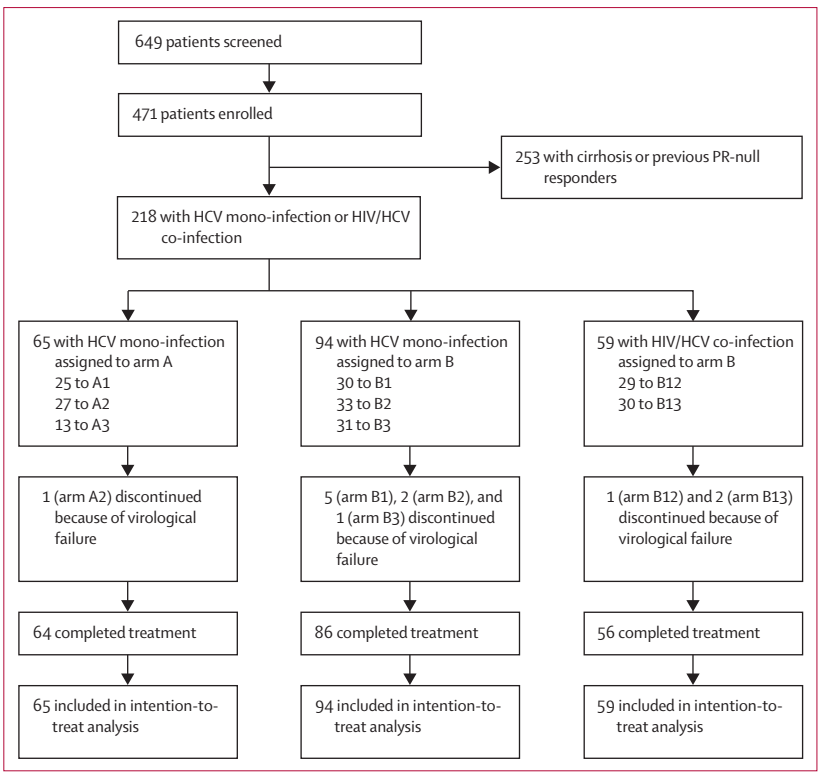


Figure 2: **Study profile**
HCV=hepatitis C virus. SVR12=proportion of patients achieving HCV RNA less than 25 IU/mL 12 weeks after end of treatment. PR-null=previous null responder to therapy with pegylated interferon and ribavirin.

Outcomes

The primary efficacy objective was to assess sustained virological response rate 12 weeks after the end of all study therapy (SVR12) for each of the treatment groups. We defined SVR12 rate as the proportion of patients with HCV RNA concentration less than 25 IU/mL at 12 weeks after the end of all study therapy.

	HCV mono-infected				HIV/HCV co-infected			All patients
	Ribavirin	Ribavirin	No ribavirin	With or without ribavirin	Ribavirin	No ribavirin	With or without ribavirin	With or without ribavirin
Duration of treatment (weeks)	8	12	12	8 or 12	12	12	12	8 or 12
Treatment arms	B1	A1, A2, B2	A3, B3	A1–3, B1–3	B12	B13	B12, B13	A1–3, B1–3, B12, B13
Number of patients	30	85	44	159	29	30	59	218
Age, years	52·0 (25–63)	51·0 (20–70)	52·0 (24–73)	51·0 (20–73)	48·0 (27–63)	44·5 (22–62)	47·0 (22–63)	50·0 (20–73)
Men	18 (60%)	40 (47%)	23 (52%)	81 (51%)	23 (79%)	24 (80%)	47 (80%)	128 (59%)
Race								
White	27 (90%)	81 (95%)	36 (82%)	144 (91%)	24 (83%)	24 (80%)	48 (81%)	192 (88%)
Non-white	3 (10%)	4 (5%)	8 (18%)	15 (9%)	5 (17%)	6 (20%)	11 (19%)	26 (11%)
Ethnic origin								
Hispanic or Latino	2 (7%)	8 (9%)	5 (11%)	15 (9%)	3 (10%)	2 (7%)	5 (8%)	20 (9%)
Non-Hispanic or Latino								
Fibrosis stage								
Metavir F0–F2	27 (90%)	81 (95%)	39 (89%)	147 (92%)	27 (93%)	27 (90%)	54 (92%)	201 (92%)
Metavir F3	3 (10%)	4 (5%)	5 (11%)	12 (8%)	2 (7%)	3 (10%)	5 (8%)	17 (8%)
Baseline HIV RNA <50 copies/mL	..	..	..	..	29 (100%)	30 (100%)	59 (100%)	59 (100%)
HCV genotype 1 subtype								
Genotype 1a	30 (100%)	52 (61%)	30 (68%)	112 (70%)	24 (83%)	22 (73%)	46 (78%)	158 (72%)
Genotype 1b	0 (0%)	31 (37%)	14 (32%)	45 (28%)	5 (17%)	8 (27%)	13 (22%)	58 (27%)
Genotype 1 other*	0 (0%)	2 (2%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)
Screening HCV RNA, IU/mL								
≤800 000	5 (17%)	22 (26%)	11 (25%)	38 (24%)	7 (24%)	5 (17%)	12 (20%)	50 (23%)
>800 000	25 (83%)	63 (74%)	33 (75%)	121 (76%)	22 (76%)	25 (83%)	47 (80%)	168 (77%)
Baseline HCV RNA, IU/mL								
Log_{10} of geometric mean (SD)	6·38 (0·73)	6·21 (0·80)	6·39 (0·56)	6·30 (0·73)	6·34 (0·85)	6·36 (0·99)	6·35 (0·92)	6·31 (0·78)
≤2 million	12 (40%)	41 (48%)	21 (48%)	74 (47%)	12 (41%)	10 (33%)	22 (37%)	96 (44%)
>2 million	18 (60%)	44 (52%)	23 (52%)	85 (53%)	17 (59%)	20 (67%)	37 (63%)	122 (56%)
≤10 million	24 (80%)	73 (86%)	36 (82%)	133 (84%)	22 (76%)	21 (70%)	43 (73%)	176 (81%)
>10 million	6 (20%)	12 (14%)	8 (18%)	26 (16%)	7 (24%)	9 (30%)	16 (27%)	42 (19%)
Body-mass index, kg/m²	25·1 (3·9)	26·8 (6·9)	26·4 (5·3)	26·4 (6·0)	23·1 (3·0)	23·0 (2·8)	23·0 (2·9)	25·5 (5·5)
<30 kg/m²	27 (90%)	67 (79%)	35 (80%)	129 (81%)	28 (97%)	30 (100%)	58 (98%)	187 (86%)
≥30 kg/m²	3 (10%)	18 (21%)	9 (21%)	30 (19%)	1 (3%)	0 (0%)	1 (2%)	31 (14%)
Baseline haemoglobin, g/dL	14·9 (1·3)	14·6 (1·5)	14·8 (1·8)	14·7 (1·5)	14·8 (1·6)	14·7 (1·1)	14·7 (1·3)	14·7 (1·5)
Baseline albumin, g/L	4·53 (0·19)	4·41 (0·30)	4·41 (0·31)	4·43 (0·28)	4·38 (0·29)	4·46 (0·21)	4·42 (0·25)	4·43 (0·28)
≥35 g/L	30 (100%)	85 (100%)	44 (100%)	159 (100%)	29 (100%)	30 (100%)	59 (100%)	218 (100%)
Baseline ALT, IU/L	67·3 (44·5)	81·2 (90·6)	69·2 (47·1)	75·3 (73·3)	60·1 (42·3)	75·5 (68·6)	67·9 (57·2)	73·3 (69·3)
Baseline AST, IU/L	47·6 (33·6)	58·8 (51·0)	51·0 (26·5)	54·5 (42·5)	48·2 (25·6)	52·1 (34·4)	50·2 (30·2)	53·3 (39·5)
Baseline total bilirubin, mg/dL	0·542 (0·258)	0·464 (0·168)	0·535 (0·245)	0·498 (0·212)	0·448 (0·184)	0·423 (0·221)	0·435 (0·202)	0·481 (0·211)
Baseline platelets × 1000/μL	229·0 (55·4)	216·2 (50·9)	206·1 (57·7)	215·8 (53·9)	204·3 (50·4)	221·8 (54·3)	213·2 (52·7)	215·1 (53·5)
IFNL3 (*IL28B*) genotype								
CC	9 (30%)	20 (24%)	8 (18%)	37 (23%)	11 (38%)	8 (27%)	19 (32%)	56 (26%)
Non-CC	20 (67%)	64 (75%)	36 (82%)	120 (75%)	18 (62%)	22 (73%)	40 (68%)	160 (73%)
Unknown	1 (3%)	1 (1%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)

Data are n (%), median (range), or mean (SD). ALT=alanine aminotransferase. AST=aspartate aminotransferase. HCV=hepatitis C virus. *Not able to subtype HCV at baseline.

Table 1: **Demographics and baseline characteristics**

Statistical analysis

For our power analysis we used two-sided 95% CIs for SVR12 rates under varying assumptions of the number of successes, assuming a rough 10% rate of protocol violation. The result of this analysis suggested a goal of 30 participants from different patient populations to be randomly assigned into each of the various treatment regimens, with the exception of arm A3 (12 weeks of

grazoprevir plus elbasvir without ribavirin in patients with genotype 1b infection).

We did intention-to-treat analyses in all patients who were randomly assigned and received at least one dose of study drug. We calculated two-sided 95% CIs using the Clopper-Pearson method for the SVR12 for each group separately. There was no formal efficacy hypothesis testing conducted in this study. To analyse outcomes we combined patients in arms A1, A2 and B2 because these patients received identical treatment schedules.

Exploratory subgroup analyses (not prespecified in the protocol) were done to assess the consistency of response across various demographic and baseline clinical characteristics for mono-infected and co-infected patients. Two-sided 95% confidence intervals for the difference in the proportion of patients who achieved SVR12 were calculated using the Miettinen and Nurminen method.[15]

Role of the funding source

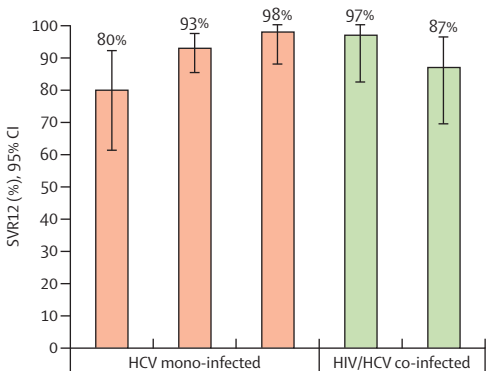
Merck contributed to trial management, data collection, statistical analyses, writing, and review of the report. All authors had access to the study data, reviewed and approved the final report, and take full responsibility for the veracity of the data and statistical analysis. The corresponding author had full access to the study data and final responsibility for the decision to submit for publication.

Results

We enrolled patients from Feb 27, 2013, and concluded data collection for SVR12 on July 2, 2014. 471 patients were enrolled in the C-WORTHY study. We describe findings for 218 patients without cirrhosis (159 mono-infected with HCV and 59 co-infected with HCV and HIV; figures 1, 2, appendix). For HCV-mono-infected patients we assigned 25 to arm A1, 27 to arm A2, 13 to arm A3, 30 to arm B1, 33 to arm B2, and 31 to arm B3; for patients co-infected with HCV and HIV we assigned 29 to arm B12 and 30 to arm B13. There were no deviations from the protocol in the conduct of the study as a whole (eg, objectives, hypothesis, or stratification).

Patients in this study were predominantly white (192, 88%) and male (128, 59%), with a median age of 50 years (range 20–73). 122 (56%) patients had baseline HCV RNA more than 2 000 000 IU/mL, 158 (72%) had HCV genotype 1a, and 160 (73%) were *IFNL3* non-CC (rs12979860). Co-infected patients had a higher percentage of males (47 [80%] *vs* 81 [51%]) and were younger (median age 47 years *vs* 51 years) with higher baseline HCV RNA (>10 million IU/mL, 16 [27%] *vs* 26 [16%]) and lower body-mass index (23·0 kg/m² *vs* 26·4 kg/m²) compared with mono-infected patients (table 1).

During the first month of treatment, the rates of HCV RNA viral decline were similar between mono-infected and co-infected patients and between patients treated with or without ribavirin (appendix). 12 weeks after the end of treatment, the SVR12 rates for mono-infected patients treated for 12 weeks were 93% (79/85; 95% CI 85–97) with ribavirin and 98% (43/44; 88–100) without ribavirin, respectively, whereas in co-infected patients, the SVR12 rate was 97% (28/29; 95% CI 82–100) with ribavirin and 87% (26/30; 69–96) without ribavirin (figure 3, appendix). In a post-hoc analysis omitting the six patients lost to follow-up or who discontinued early because of reasons other than virological failure, the SVR12 rate among those given a 12-week regimen was 97% (122/126) in mono-infected and 95% (54/57) in co-infected patients. On the basis of the 95% CIs, we noted no significant differences between the SVR12 rates for mono-infected and co-infected patients, or for regimens containing ribavirin and those without ribavirin (table 2). The SVR12 rates for patients treated with a 12-week regimen were also similar in patients with HCV genotype 1a (92%) and genotype 1b (95%) subtype infection (figure 4). The 8-week treatment arm (arm B1) included ribavirin and enrolled only mono-infected patients with HCV genotype 1a subtype, resulting in SVR12 of 80% (24/30; 95% CI 61–92). By comparison, SVR12 for the 12-week regimen with genotype 1a and ribavirin was 95% (72/76; 95% CI 87–99).



Treatment duration (weeks)	8	12	12	12	12
Ribavirin	Ribavirin (arm B1)	Ribavirin (arms A1, A2, B2)	No ribavirin (arms A3, B3)	Ribavirin (arm B12)	No ribavirin (arm B13)
SVR12 (95% CI)	24/30, 80% (61–92)	79/85, 93% (85–97)	43/44, 98% (88–100)	28/29, 97% (82–100)	26/30, 87% (69–96)
Lost to follow-up or discontinued early due to reasons other than virological failure	1	3	0	0	2
Virological breakthrough	0	1*	0	0	2
Virological relapse	5	2†	1	1	0

Figure 3: **SVR12 rates after treatment with grazoprevir plus elbasvir**
We defined SVR12 as HCV RNA less than 25 IU/mL 12 weeks after the end of all study therapy in the intention-to-treat population. The Roche COBAS Taqman test has a lower limit of quantification of 25 IU/mL and a limit of detection of 15·1 IU/mL. Five of six patients who discontinued early had HCV RNA less than 25 IU/mL at their last study visit. HCV=hepatitis C virus. SVR12=proportion of patients achieving HCV RNA less than 25 IU/mL 12 weeks after end of treatment. *Breakthrough was a new infection with HCV genotype 2b (or a minor genotype 2b variant at baseline). †One of the patients who relapsed did not receive grazoprevir and only received only elbasvir plus ribavirin for the first month of treatment.

See Online for appendix

	HCV mono-infected	HIV/HCV co-infected	Difference in SVR12 (95% CI)
Age			
≤50 years	56/59 (95%)	39/42 (93%)	2·1 (–8·1 to 14·6)
>50 years	66/70 (94%)	15/17 (88%)	6·1 (–5·8 to 29·2)
Sex			
Men	58/63 (92%)	42/47 (89%)	2·7 (–8·5 to 15·7)
Women	64/66 (97%)	12/12 (100%)	–3·0 (–10·5 to 21·6)
Race			
White	111/117 (95%)	46/48 (96%)	–1·0 (–7·5 to 9·3)
Non-white	11/12 (92%)	8/11 (73%)	18·9 (–14·6 to 51·1)
Ethnic origin*			
Hispanic or Latino	12/13 (92%)	5/5 (100%)	7·7 (–34·2 to 38·5)
Not Hispanic or Latino	108/114 (95%)	47/52 (90%)	4·4 (–3·6 to 15·8)
HCV genotype†			
1a	78/82 (95%)	42/46 (91%)	3·8 (–5·0 to 16·0)
1b	42/45 (93%)	12/13 (92%)	1·0 (–12·4 to 27·5)
Screening HCV RNA, IU/mL			
≤800 000	32/33 (97%)	12/12 (100%)	–3·0 (–15·5 to 21·9)
>800 000	90/96 (94%)	42/47 (89%)	4·4 (–4·7 to 17·0)
Baseline HCV RNA, IU/mL			
≤2 000 000	59/62 (95%)	22/22 (100%)	–4·8 (–13·4 to 10·4)
>2 000 000	63/67 (94%)	32/37 (86%)	7·5 (–3·7 to 22·8)
≤10 000 000	104/109 (95%)	42/43 (98%)	–2·3 (–8·5 to 7·8)
>10 000 000	18/20 (90%)	12/16 (75%)	15·0 (–10·5 to 41·9)
Body-mass index			
<30 kg/m²	95/102 (93%)	53/58 (91%)	1·8 (–6·6 to 12·5)
≥30 kg/m²	27/27 (100%)	1/1 (100%)	0·0 (–12·9 to 79·9)
Baseline ALT			
≤100 IU/L	99/105 (94%)	45/50 (90%)	4·3 (–4·1 to 16·2)
>100 IU/L	23/24 (96%)	9/9 (100%)	–4·2 (–20·6 to 26·8)
***IFNL3* (*IL28B*) genotype**			
CC	26/28 (93%)	19/19 (100%)	–7·1 (–22·9 to 10·5)
Non-CC	95/100 (95%)	35/40 (88%)	7·5 (1·8 to 21·6)
Unknown	1/1 (100%)	0/0 (0%)	..

Table shows data for 188 patients who received at least one dose of study drug and who received 12 weeks of treatment. HCV=hepatitis C virus. SVR12=proportion of patients achieving HCV RNA<25 IU/mL 12 weeks after end of treatment. *Ethnic origin was unknown for two mono-infected patients and for two HIV/HCV co-infected patients (all four of these patients achieved SVR12). †Two mono-infected patients had HCV genotype of 1 (other; not able to subtype) and both patients achieved SVR12.

Table 2: **Subgroup analysis for mono-infected and co-infected patients who received 12 weeks of treatment**

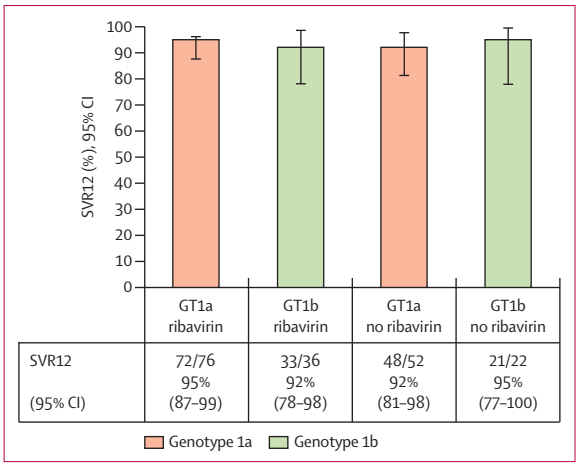


Figure 4: **SVR12 rates in the 12-week treatment arms by HCV genotype**
Figure shows SVR12 rates for genotype 1a infection vs genotype 1b infection, for 12 weeks of treatment with and without ribavirin, in both patients with HCV mono-infection and those with HIV/HCV co-infection. Figure excludes two patients who had HCV subtypes that were not genotype 1a or genotype 1b and 30 patients with HCV mono-infection who were in the 8-week treatment group arm. HCV=hepatitis C virus. SVR12=proportion of patients achieving HCV RNA less than 25 IU/mL 12 weeks after end of treatment.

Among patients treated with grazoprevir plus elbasvir with or without ribavirin for 12 weeks, the rate of virological failure was 4% (7/188; three breakthroughs plus four relapses) in mono-infected and co-infected patients. By contrast, the rate of virological failure was 17% (5/30; all relapses) for the 8-week regimen with ribavirin in mono-infected patients with HCV genotype 1a. Among these 12 patients with virological failure, ten were infected with HCV genotype 1a (appendix). The two patients with genotype 1b infection who had virological failure included one patient with genotype 2b infection at the time of breakthrough, and one patient who did not receive grazoprevir until day 28 of therapy (because of an error) and relapsed 12 weeks after the end of therapy.

Subgroup analysis (which was not prespecified) showed that with factors that are potentially positive or negative predictors of sustained virological response, CIs did not suggest significant differences for comparisons of mono-infected and co-infected patients treated for 12 weeks (table 2) for many factors including age, sex, race, ethnicity, HCV subtype, body-mass index, baseline alanine aminotransferase, or HIV status. However, the mono-infected and co-infected cohorts were not fully matched for all demographic factors. Although SVR12 rates were similar in co-infected and mono-infected patients with a high viral load (>2 million IU/mL), at the highest viral load category (HCV RNA >10 million IU/mL) mono-infected patients had an SVR12 of 90% (18/20) and co-infected patients had an SVR12 of 75% (12/16), suggestive of a possible difference but falling within the 95% CI of the SVR12 estimates. The overall importance of these findings will be assessed in large phase 3 trials in which mono-infected and co-infected patients are enrolled in the same study.

The regimens of grazoprevir plus elbasvir with or without ribavirin were generally well tolerated in mono-infected and co-infected patients. Common adverse events were mild-to-moderate fatigue, headache, nausea, and diarrhoea for both mono-infected and co-infected patients (table 3, appendix). Overall, drug-related adverse events occurred in 123 (56%) of 218 patients. Serious adverse events occurred in three patients (one case of nausea related to study drug; one case of asthenia related to study drug; and one case of staphylococcal infection not related to study drug), but no patients died

or discontinued treatment because of adverse events. The frequency of drug-related adverse events, bilirubin elevations, or haemoglobin decreases was higher in the regimens containing ribavirin than in those without ribavirin (appendix). No patient had an alanine aminotransferase increase to five times the upper limit of normal at or after 4 weeks of therapy. Persistent loss of HIV suppression or antiretroviral failure was not reported in co-infected patients.

We examined the HCV RNA sequences from patients before treatment and at the time of virological failure for potential resistance-associated variants (RAVs). To assess the effect of baseline NS3 RAVs on sustained virological response, we assessed RAVs known to confer more than five-fold resistance to grazoprevir and RAVs known to confer resistance to other protease inhibitors such as S122A/G/R and Q80K.[16,17] At baseline, 35% (75/216) of patients had a NS3 baseline RAV, of whom SVR12 was achieved in 91% (68/75); among patients with wild-type NS3 at baseline, 92% (130/141) achieved SVR12 (appendix). We detected NS5A RAVs known to confer more than five-fold resistance to elbasvir or other NS5A inhibitors in 12% (25/216) of patients at baseline, of which 68% (17/25) achieved SVR12. By comparison, for patients with wild-type NS5A at baseline, 95% (181/191) achieved SVR12 (appendix). At the time of virological failure, the most prevalent RAVs detected were NS3:Y56H, A156T and D168A/N, and NS5A:Q30R/H, L31M, and Y93H/N (appendix).

Discussion

In this study, 12 weeks of treatment with the interferon-free oral combination of two direct-acting antivirals (grazoprevir and elbasvir) with or without ribavirin was well tolerated and led to high rates of sustained virological response (87–98%) in previously untreated patients without cirrhosis with HCV genotype 1 mono-infection or HIV/HCV co-infection. The addition of ribavirin was not associated with increased rates of sustained virological response, suggesting that the once-daily, ribavirin-free regimen of grazoprevir plus elbasvir might be an effective treatment for patients with HCV genotype 1a or genotype 1b infection. The SVR12 rate reported in patients with HIV/HCV co-infection and favourable clinical and HCV disease characteristics was similar to that in patients with mono-infection alone. Findings for the efficacy, safety, and tolerability of this regimen in patients with less favorable disease paramenters (compensated cirrhosis and previous null response to peginterferon and ribavirin therapy) are reported in *The Lancet* by Lawitz and colleagues.[31]

The parallel enrolment of mono-infected and co-infected patients in this study is novel and provided a unique opportunity to directly assess the effect of HIV infection on HCV treatment outcomes. Historically, patients infected with HIV have been studied in separate clinical trials, necessitating cross-study comparisons to

	HCV mono-infected			HIV/HCV co-infected		All patients
	Ribavirin	Ribavirin	No ribavirin	Ribavirin	No ribavirin	With or without ribavirin
Treatment arm	B1	A1, A2, B2	A3, B3	B12	B13	A1–3, B1–3, B12, B13
Duration of treatment (weeks)	8	12	12	12	12	8 or 12
Number of patients	30	86*	43*	29	30	218
Serious adverse events	0 (0%)	1 (1%)	0 (0%)	1 (3%)	1 (3%)	3 (1%)
Nausea	..	1 (1%)†	..	0 (0%)	0 (0%)	1 (<1%)
Asthenia	..	0 (0%)	..	1 (3%)†	0 (0%)	1 (<1%)
Staphylococcal infection	..	0 (0%)	..	0 (0%)	1 (3%)	1 (<1%)
Drug-related adverse events	22 (73%)	56 (65%)	24 (56%)	12 (41%)	9 (30%)	123 (56%)
Change in CD4 count from baseline at week 12, cells/mm³	..	..	..	−46·7 (176)	51·7 (178)	..
HIV breakthrough	..	..	..	0 (0%)	0 (0%)	..
Common adverse events (≥10% in all patients)‡						
≥1 adverse event	26 (87%)	65 (76%)	38 (88%)	19 (66%)	15 (50%)	163 (75%)
Fatigue	14 (47%)	23 (27%)	10 (23%)	2 (7%)	2 (7%)	51 (23%)
Headache	7 (23%)	17 (20%)	15 (35%)	4 (14%)	1 (3%)	44 (20%)
Nausea	8 (27%)	16 (19%)	7 (16%)	0 (0%)	1 (3%)	32 (15%)
Diarrhoea	5 (17%)	10 (12%)	5 (12%)	1 (3%)	0 (0%)	21 (10%)
Lowest haemoglobin on treatment						
≥8·5 to <10 g/dL	1 (3%)	8 (10%)§	0 (0%)	1 (3%)	0 (0%)	10 (5%)
<8·5 g/dL	0 (0%)	1 (1%)§	0 (0%)	0 (0%)	0 (0%)	1 (0%)
ALT, IU/L						
1·1–2·5 × baseline	1 (3%)	11 (13%)	2 (5%)	0 (0%)	2 (7%)	16 (7%)
>2·5 × baseline	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AST, IU/L						
1·1–2·5 × baseline	0 (0%)	9 (11%)	1 (2%)	0 (0%)	3 (10%)	13 (6%)
>2·5 × baseline	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Late elevation of ALT or AST¶						
>2·0 to ≤5·0 × ULN	0 (0%)	1 (1%)	1 (2%)	0 (0%)	1 (3%)	3 (1%)
>5·0 × ULN	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Elevation of total bilirubin, mg/dL						
>2·5–5·0 × baseline	7 (23%)	24 (28%)	0 (0%)	7 (24%)	2 (7%)	40 (18%)
>5·0 × baseline	1 (3%)	2 (2%)	0 (0%)	2 (7%)	0 (0%)	5 (2%)
>10·0 × baseline	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Data are n (%) or mean (SD). There were no deaths or discontinuations due to adverse events. All adverse events, serious adverse events, and lowest laboratory values were recorded from the time the consent form was signed through 14 days after cessation of treatment. The relatedness (probable or possible) of the adverse event to the regimen was determined by the investigator; patients could have had more than one adverse event. HCV=hepatitis C virus. ALT=alanine aminotransferase. AST=aspartate aminotransferase. ULN=upper limit of normal. *One HCV-mono-infected patient was randomly assigned to the 12-week ribavirin-free arm but received ribavirin. For the analysis of safety, this patient is included in the HCV mono-infected 12-week ribavirin-containing group. †Related to study drug. ‡Common adverse events (incidence ≥10% in total group of patients) were determined during the treatment period and first 14 days of follow-up. Common adverse events are ordered in decreasing frequency in all patients. §Haemoglobin values missing from one patient in the HCV mono-infected ribavirin-containing group. ¶Late ALT/AST elevations were defined as elevations in ALT/AST occurring at or after treatment week 4 among patients who had ALT/AST within normal limits before treatment week 4.

Table 3: **Safety of grazoprevir plus elbasvir with or without ribavirin**

evaluate the effect of co-infection on HCV eradication.[9,18–20] The results of such comparisons have supported the notion that HIV co-infection is associated with poor response to interferon-based HCV treatment. For example, in large trials of peginterferon alfa-2a (APRICOT[9]) and alfa-2b (RIBAVIC[19]) plus ribavirin, sustained virological response in co-infected patients with HCV genotype 1 co-infection was 29% and 20%, respectively—about half that reported in mono-infected patients.[20,21] The effect of HIV co-infection on treatment efficacy observed in these studies was most evident among patients with high baseline HCV RNA (>2 million copies per mL; about 400 000 IU/mL), for whom the sustained virological response rate was only 18%.[21]

By targeting HCV directly instead of the patient's innate immune pathways through cellular receptors for type 1 interferon, oral interferon-free regimens could overcome the negative effect of HIV co-infection.[22] In our study, the rates of decline of HCV RNA on-treatment were similar between mono-infected and co-infected patients. SVR12 was achieved in 95% (122/129) and 92% (54/59) of mono-infected and co-infected patients treated with 12 weeks of grazoprevir plus elbasvir with or without ribavirin; similar results were reported in patients with high baseline HCV viral loads (>2 million IU/mL). Among a relatively small group of mono-infected and co-infected patients with HCV RNA >10^7 IU/mL, we noted a potential trend towards a higher SVR12 rate in mono-infected patients compared with co-infected patients; confirmation in a larger patient sample is needed. Sustained virological response was also similar in patients with other baseline factors predictive of poor response to interferon, including *IFNL3* CT or TT genotype (rs 12979860), age older than 50 years, and non-white race. Although there was a mixture of factors potentially positive and negative for efficacy (eg, high percentage of young, male patients and those with high baseline HCV RNA concentrations and low body-mass index) in co-infected patients compared with mono-infected patients, the SVR12 results were much the same in both groups of patients. There was no formal hypothesis testing done in this study, but these data provide evidence to support that co-infection in patients without cirrhosis is not associated with impaired virological response to interferon-free, HCV treatments, and will help inform the design of future phase 3 trials.

Treatment-emergent, clinically significant adverse events were infrequent; no patients died and no patient discontinued treatment because of an adverse event. Treatment-related adverse events were more common among patients randomly assigned to receive ribavirin. Among patients treated with 12 weeks of grazoprevir plus elbasvir without ribavirin, mild-to-moderate drug-related adverse events were reported in 27% of HIV/HCV co-infected patients and 53% of HCV mono-infected patients, suggesting that the HIV disease and its treatment with selected antiretrovirals did not negatively affect the tolerability of this HCV direct-acting antiviral regimen. Additionally, HIV suppression was maintained. Although the addition of ribavirin was safe and well-tolerated, the frequency of anaemia (haemoglobin <10 g/dL) was higher among ribavirin recipients (8%; 11/145) than among patients who did not receive ribavirin (0%; 0/73). Of note, in patients with co-infection, the absolute CD4 cell counts decreased by roughly 47 cells/mm³ with ribavirin and increased by roughly 52 cells/mm³ without ribavirin; the clinical significance of this magnitude of CD4 cell count change in co-infected patients is unknown. Similar decreases in CD4 cell counts have been reported in other studies of ribavirin treatment with and without interferon, and probably result from an effect of ribavirin on lymphocytes.[9,23] Even in the absence of a placebo comparator group, the low incidence of adverse events suggests that the combination of grazoprevir plus elbasvir could compare favourably with other interferon-containing and interferon-free HCV treatments.

In phase 3 clinical trials, two interferon-free, oral, direct-acting antiviral regimens have shown high rates of sustained virological response and good tolerability in previously treated mono-infected patients with HCV genotype 1 and without cirrhosis. These studies tested the combination of sofosbuvir plus ledipasvir with or without ribavirin, and another the combination of paritaprevir plus ritonavir plus ombitasvir plus dasabuvir with or without ribavirin.[24–26] In two of the studies, the sustained virological response rates reported among mono-infected patients after 12 weeks of these regimens (sofosbuvir plus ledipasvir, 95% [95% CI 92–98]; paritaprevir plus ritonavir, ombitasvir, dasabuvir, and ribavirin 96% [94 to 98]) were similar to what we noted after 12 weeks of grazoprevir plus elbasvir (98% [88–100]).[25,26] A shorter treatment duration of 8 weeks was assessed for HCV genotype 1a in our study, similar to studies of sofosbuvir plus ledipasvir with or without ribavirin and ABT-450 plus ritonavir, ombitasvir, dasabuvir, and ribavirin.[25,27] Although relatively high rates of sustained virological response for patients with HCV genotype 1a were reported for each of these regimens (92–93% for sofosbuvir plus ledipasvir with or without ribavirin; 84% for paritaprevir plus ritonavir, ombitasvir, dasabuvir, and ribavirin), the rates of virological relapse after treatment discontinuation was higher after 8 weeks (4–12%) than after 12 weeks of therapy (1%). Additionally, the finding of similar efficacy in patients infected with genotype 1a and genotype 1b in this study of grazoprevir plus elbasvir differs from findings from the other studies of combination therapies with inhibitors of HCV NS3/4A proteases and NS5A, in which efficacy was substantially lower in patients with genotype 1a than in those with genotype 1b infection.[28]

In our study and others, virological relapse was associated with emergence of resistance-associated variants to one or both of the drugs in the regimen (panel). The presence of NS3 RAVs at baseline did not

significantly affect the efficacy of grazoprevir plus elbasvir with or without ribavirin, although NS5A baseline RAVs had some effect on SVR12 (appendix). Because strategies for the retreatment of patients with virological failure are uncertain, 12 weeks of treatment with the fixed-dose combination of grazoprevir plus elbasvir was selected for phase 3 trials in patients with HCV genotype 1 and no cirrhosis. Short treatment durations (8 weeks or less) with additional direct-acting antivirals, including the combination of sofosbuvir plus grazoprevir and elbasvir, are under investigation. Phase 3 studies have assessed interferon-free regimens (the single direct-acting antiviral combination of sofosbuvir plus ribavirin) in HIV/HCV co-infected patients. In these studies, 76–85% of patients with HCV genotype 1 infection achieved SVR12 after a lengthy treatment duration (24 weeks).[23,29] Preliminary data have also been presented for the ritonavir-boosted combination of paritaprevir plus ombitasvir, dasabuvir, and ribavirin in HIV-positive patients co-infected with HCV genotype 1; this regimen led to SVR12 in 94% (29/31) of patients after 12 weeks of treatment.[30]

The main limitations of this study are the exclusion of patients with cirrhosis, the restriction of permissible antiretroviral regimens, the fairly small number of HIV/HCV co-infected patients in this trial, and the absence of a placebo group. The similar efficacy results with the small number of co-infected patients in this trial compared to mono-infected patients will require confirmation in larger phase 3 trials with formal hypothesis testing. The patients described in this report were fairly easy-to-cure patients; our study included few F3 patients, few obese patients, and few non-white patients. Patients with cirrhosis or previous null responders or therapy with peginterferon and ribavirin were assessed in parallel arms of the C-WORTHY study for treatment durations of 12 and 18 weeks; the study findings are reported by Lawitz and colleagues in this issue of *The Lancet*.[31] The main unique consideration for HCV treatment in patients with co-infection is the potential for clinically significant drug interactions between the HIV and HCV treatment regimens.[8] Findings from studies of grazoprevir and elbasvir in healthy volunteers showed no clinically significant interactions with raltegravir and tenofovir, leading to the permissible antiretroviral therapy in our study.[32,33] Antiretroviral drugs such as boosted HIV-1 protease inhibitors and the HIV-1 non-nucleoside reverse transcriptase inhibitor efavirenz will not be recommended for use with grazoprevir and elbasvir because of the potential for clinically significant drug–drug interactions. However, in ongoing phase 3 studies, acceptable antiretroviral regimens to use with grazoprevir and elbasvir have been expanded to include dolutegravir and rilpiverine in combination with HIV-1 nucleoside or nucleotide reverse transcriptase inhibitors. Another possible limitation is that factors in the subgroup analysis that were not statistically significant in this study could become significant with larger numbers of patients or with multifactorial analysis of a larger cohort. The findings related to the subgroup analysis and to the SVR12 in patients with and without HIV co-infection will require confirmation in larger phase 3 clinical trials.

The results of this trial suggest that the combination of grazoprevir plus elbasvir provides an interferon-free oral treatment option that is likely to be effective in mono-infected and co-infected patients. The use of ribavirin was associated with anaemia and increased adverse effects, but did not seem to improve efficacy. Larger phase 3 trials are underway to assess these findings in a larger population (NCT02092350, NCT02105467, NCT02105662, NCT02105688, NCT02252016, and NCT02105701). Several of these studies will enroll mono-infected and co-infected patients together, including studies in patients who are receiving opioid substitution therapy, patients with inherited blood disorders, and treatment experienced patients. These studies are in addition to a large single

***Panel:* Research in context**

Systematic review

We searched PubMed and meeting abstracts (European Association for the Study of the Liver, American Association for the Study of Liver Diseases, Conference on Retroviruses and Opportunistic Infections, and International AIDS Conference) up to Sept 5, 2014, for clinical trials done in patients infected with hepatitis C virus (HCV) genotype 1 with or without HIV co-infection, with the terms "HCV", "hepatitis C", and "HCV and HIV". Available options for the treatment of HCV infection are expanding rapidly with direct-acting antiviral agents targeting HCV non-structural proteins including NS3/4A protease, NS5B polymerase, and NS5A. Combinations of these drugs offer the potential for interferon-sparing treatment regimens. In some patients, particularly those co-infected with HIV, the necessity of interferon has been a major barrier to HCV eradication because of lack of efficacy and frequent adverse effects. We investigated the safety, tolerability, and efficacy of the combination of a protease inhibitor, grazoprevir, and the NS5A inhibitor, elbasvir, with and without ribavirin, in patients with chronic HCV genotype 1 infection, including those with HIV co-infection.

Interpretation

Our study combined an NS3/4A protease inhibitor and an NS5A inhibitor. In patients with HCV genotype 1a and 1b infection, the rates of sustained virological response were high and those of virological failure were low. Patients with HCV mono-infection and HIV/HCV co-infection had similar rates of sustained virological response and adverse events. Ribavirin was associated with higher rates of anaemia and adverse events but did not seem to affect sustained virological response. These results were similar to those in studies of other interferon-sparing, direct-acting antiviral combinations including the combination of sofosbuvir (a nucleotide analogue NS5B polymerase inhibitor) and ledipasvir (an NS5A inhibitor) and the multiple drug combination of ritonavir-boosted paritaprevir (an NS3/4A protease inhibitor), ombitasvir (an NS5A inhibitor), dasabuvir (a non-nucleoside NS5B polymerase inhibitor), and ribavirin. This regimen with grazoprevir and elbasvir offers the potential for a nucleoside-sparing (both sofosbuvir and ribavirin are nucleosides or nucleotides) regimen for patients with HCV genotype 1a. By contrast, other combinations of NS3/4A protease inhibitors plus NS5A inhibitors, such as asunaprevir plus daclatasvir, were not effective for the treatment of HCV genotype 1a infection because of high rates of HCV breakthrough during treatment and HCV relapse following treatment. The two-drug combination of grazoprevir and elbasvir has been coformulated as a single tablet given once daily and is under further investigation in phase 3 clinical trials enrolling diverse patient populations, including those with HIV co-infection and those taking opioid substitution therapy.

study of HIV/HCV co-infected patients. Together these studies will assess grazoprevir and elbasvir in diverse populations of mono-infected and co-infected patients.

Contributors

MS was the principal investigator of the trial, was involved in study design, was responsible for the clinical supervision of patients and performance of the study, and contributed to the preparation and writing of the report. CH, JG, JMV, JM, SP, MK, AM, NW, RN, OS, LS, MB, ED, and EZ were the study investigators and were responsible for patient recruitment, clinical supervision, and treatment of patients, involved in the acquisition, analysis, and interpretation of the data, and critically reviewed the report. MS and PH participated in the study design and execution, the interpretation of the data, and critically reviewed the report. AYMH performed the analysis of resistance-associated variants, and critically reviewed the report. JW, MR, and EB provided scientific input to the clinical study and contributed to the writing of the report. FD was involved in the analysis and interpretation of the data, and contributed to the writing of the report. BH was responsible for the conduct and overview of the trial, involved in the acquisition, analysis, and interpretation of the data, and contributed to the writing of the report.

Declaration of interests

MS reports funds for research grants paid directly to Johns Hopkins University and personal fees from Merck during the conduct of the study; funds for research grants paid directly to Johns Hopkins University from AbbVie, Boehringer Ingelheim, Bristol-Meyers Squibb, and Gilead; and personal fees from AbbVie, Bristol-Meyers Squibb, Gilead, Janssen, and Tobira outside the submitted work. CH reports personal fees for advising and speaking from Merck Sharp & Dohme during the conduct of the study and personal fees for advising and speaking from AbbVie, Bristol-Meyers Squibb, Gilead, Janssen, and Roche outside the submitted work. JG reports financial compensation for the clinical trial from Merck during the conduct of the study; grant and personal fees from Gilead; and personal fees from Bristol-Meyers Squibb, Medivir, AbbVie, Glaxo, Merck, and Janssen outside the submitted work. JMV has received research grants, and personal fees for Speaker's Bureau and Scientific Advisory Board from Merck for the current study; expert testimony for the Food and Drug Administration and the Centers for Disease Control and Prevention; has grants or grants pending from Abbott (AbbVie), Bristol-Meyers Squibb, Conatus, Excalenz, Genentech, Genfit, Gilead, Globeimmune, Hyperion, Idenix-Novartis, Ikaria, Intercept, Merck (formerly Schering), Mochida, Novartis, Ocera, Pfizer, Pharmasset (now Gilead), Roche, Sundise, Tranzyme, Vertex, and Zymogenetics (now Bristol-Meyers Squibb); has received payment for continuing medical education lectures including service on speakers bureaus from the American Liver Foundation, Chronic Liver Diseases Foundation, and GI and Liver Association of the Americas (GALA); has received travel, accommodations, or meeting expenses from the National Institutes of Health and the National Institute for Diabetes and Digestive and Kidney Diseases; is a past Secretary-Treasurer for Digestive Diseases Week; and is a principal for the Clinical Research Centers of America and the Liver Drug Safety Alliance. JM reports personal fees from Merck Sharp & Dohme during the conduct of this study and personal fees for lectures or advisory boards from Merck Sharp & Dohme, Janssen, Boehringer Ingelheim, ViiV, Bristol-Meyers Squibb, Gilead, and Roche outside the submitted work. SP reports personal fees from Merck Sharp & Dohme during the conduct of the study; grants and personal fees from Merck Sharp & Dohme, and Roche; and personal fees from Bristol-Meyers Squibb, Gilead, Novartis, GlaxoSmithKline, Boehringer Ingelheim, Janssen, Sanofi, Vertex, and AbbVie outside the submitted work. MK reports grants and personal fees (consulting) from Merck during the conduct of the study and grants and personal fees (consulting) from Merck outside the submitted work. AM reports personal fees during the conduct of the clinical study. NW reports personal fees from Merck Sharp & Dohme during the conduct of the study and to be investigator, consultant, or speaker for Merck Sharp & Dohme, Abbvie, Bristol-Myers Squibb, Roche, Janssen, and Gilead outside the submitted work. RN reports grants and personal fees from Merck during the conduct of the study; grants and personal fees from Bristol-Myers Squibb; and grants from Abbvie, and Gilead outside the submitted work. OS reports financial support from Merck during the conduct of the study and personal fees from Abbvie, Gilead, and Bristol-Myers Squibb outside the submitted work. LS reports financial support for the clinical trial from Merck during the conduct of the study and personal fees from Janssen, Bristol-Myers Squibb, Gilead, Abbvie, Merck, and Roche outside the submitted work. MB reports grants and personal fees from Merck during the conduct of the study; personal fees from Bristol-Myers Squibb, AbbVie, Gilead, Roche, and GlaxoSmithKline; and grants and personal fees from Janssen outside the submitted work. ED reports financial support for the clinical trial from Merck during the conduct of the study and personal fees from Gilead Sciences, Janssen, and Vertex outside the submitted work. EZ reports financial support for the clinical trial from Merck during the conduct of the study. FD, MS, PH, AYMH, JW, MR, EB, and BH are current employees of Merck & Co, Inc (Whitehouse Station, NJ, USA) and hold stock or stock options.

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