Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial

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Summary

Background **Hepatitis C virus (HCV) infection is a leading cause of morbidity and mortality in patients with HIV-1. The C-EDGE CO-INFECTION study assessed the efficacy, safety, and tolerability of grazoprevir (MK-5172) plus elbasvir (MK-8742) in patients with HCV and HIV co-infection.**

Methods **In this uncontrolled, non-randomised, phase 3, open-label, single-arm study, treatment-naive patients with chronic HCV genotype 1, 4, or 6 infection and HIV co-infection, with or without cirrhosis, were enrolled from 37 centres in nine countries across Europe, the USA, and Australia. Patients were either naive to treatment with any antiretroviral therapy (ART) or stable on ART for at least 8 weeks. All patients received grazoprevir 100 mg plus elbasvir 50 mg in a fixed-dose combination tablet once daily for 12 weeks. The primary endpoint was sustained virological response (HCV RNA <15 IU/mL) 12 weeks after the end of therapy (SVR12). The primary population for efficacy analyses was all patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, number NCT02105662.**

Findings **Between June 11, 2014, and Aug 29, 2014, 218 patients were enrolled and received grazoprevir plus elbasvir for 12 weeks, all of whom completed follow-up at week 12. SVR12 was achieved by 210 (96%) of 218 patients (95% CI 92·9–98·4). One patient did not achieve SVR12 because of a non-virological reason, and seven patients without cirrhosis relapsed (two subsequently confirmed as reinfections). All 35 patients with cirrhosis achieved SVR12. The most common adverse events were fatigue (29; 13%), headache (27; 12%), and nausea (20; 9%). No patient discontinued treatment because of an adverse event. Two patients receiving ART had transient HIV viraemia.**

Interpretation **This HCV treatment regimen seems to be effective and well tolerated for patients co-infected with HIV with or without cirrhosis. These data are consistent with previous trials of this regimen in the monoinfected population. This regimen continues to be studied in phase 3 trials.**

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Introduction

HIV co-infection is common in patients with hepatitis C virus (HCV) infection.[1–4] HIV co-infection accelerates the progression of HCV-related liver disease, making HCV a leading cause of morbidity and mortality in patients with HIV-1.[5–7] Compared with patients with HCV monoinfection, patients with HIV and HCV co-infection have higher baseline HCV viral loads, more rapid progression of liver disease,[8] and an increased risk of cirrhosis, end-stage liver disease, and hepatocellular carcinoma.[9] Co-infected patients are also more susceptible to anaemia and more rapid progression to AIDS and AIDS-related death.[5,6,10] Direct-acting antiviral agents have revolutionised treatment of HCV infection;[11–15] however, many regimens for patients with HIV and HCV co-infection are restricted by their requirement for co-administration with peginterferon or ribavirin, particularly in patients infected with HCV genotype 1a and in those with cirrhosis.[16] Grazoprevir, an NS3/4A protease inhibitor (MK-5172), and elbasvir, an NS5A inhibitor (MK-8742; Merck & Co, Inc, Kenilworth, NJ, USA), are being assessed as a once-daily, fixed-dose combination tablet. The phase 2 C-WORTHY study showed a good safety profile and high efficacy of grazoprevir plus elbasvir with or without ribavirin for 12 weeks in monoinfected and co-infected patients with HCV genotype 1 infection, with or without cirrhosis.[13,17] The C-EDGE CO-INFECTION study assessed the efficacy, safety, and tolerability of a fixed-dose combination of grazoprevir plus elbasvir in patients with HIV and HCV co-infection.

Methods

Study design and participants

The C-EDGE CO-INFECTION study was an uncontrolled, non-randomised, open-label, single-arm, multicentre study. Treatment-naive patients older than 18 years with chronic HCV genotype 1, 4, or 6 infection and baseline HCV RNA of at least 10 000 IU/mL were

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Research in context

Evidence before this study

Management of HIV and hepatitis C virus (HCV) co-infection is a major challenge because of the increased risk of progression of hepatic disease including fibrosis and end-stage liver disease. To integrate our study in the evolving treatment landscape, we searched PubMed for articles published between Jan 1, 2000, and Feb 19, 2015, for late-stage clinical trials on the treatment of HCV infection in patients co-infected with HIV. We did not apply any language restrictions.

During the past decade there has been substantial improvement in treatment options available to patients with HIV and HCV. In 2004, three clinical trials were published describing the use of peginterferon and ribavirin in co-infected patients. In these studies, rates of sustained virological response (SVR) in patients with HCV genotype 1 infection ranged from 27% to 40%, which is substantially lower than the SVR rates reported in studies in mono-infected patients treated with the same regimen (40–50% in patients with HCV genotype 1 infection). Furthermore, in these early studies in co-infected patients, 25–39% of participants did not complete therapy, and substantially more patients needed adjustments or interruptions to their treatment regimens to help manage adverse events. In these three studies, treatment was given for 48 weeks. More recently, the introduction of direct-acting antiviral agents has altered treatment options for patients with HCV infection, with several studies showing an increase in patients achieving SVR with shorter treatment durations. Despite these advances, most studies have investigated the use of direct-acting antiviral agents in combination with peginterferon or ribavirin, or both; thus these regimens are limited by the associated adverse effects and the restricted populations in which these drugs can be used. In the PHOTON-2 study, the most recent of these studies to be published, patients with HCV genotype 1 and HIV co-infection who were treated with sofosbuvir plus ribavirin for 24 weeks achieved an SVR rate of 85%, but only 17 participants (15%) had cirrhosis. The combination regimen had a safety profile consistent with the use of ribavirin, including decreases in haemoglobin concentration and increased bilirubin concentration. Additionally, the TURQUOISE-1 study of patients with HCV genotype 1 infection who received ombitasvir-paritaprevir-ritonavir, dasabuvir, and ritonavir for 12 weeks or 24 weeks showed SVRs of 93·5% and 90·6%, respectively; however, the study was limited by the small number of patients enrolled (31 patients in the 12 week group, and 32 patients in the 24 week group). Overall, these data highlight the marked improvements in treatment options for patients with HIV and HCV co-infection during the past decade, but also underline the need for new interferon-free and ribavirin-free regimens. The phase 2, open-label, C-WORTHY study assessed an all-oral interferon-free regimen of grazoprevir plus elbasvir (with and without ribavirin), in patients with HCV genotype 1 infection, and included a cohort of 59 patients with HIV co-infection. After 12 weeks of treatment, reported SVR rates were 97% in co-infected patients assigned to grazoprevir plus elbasvir and ribavirin, and 87% in co-infected patients assigned to grazoprevir plus elbasvir alone. In the ribavirin-free group there was no decrease in haemoglobin concentrations, and there was an overall increase in CD4 cell count during the course of treatment.

Added value of this study

The C-EDGE CO-INFECTION study is the largest published study of treatment-naive patients with HIV and HCV co-infection, with a substantial proportion of patients with cirrhosis and a robust proportion of patients with HCV genotype 4 infection. SVR rates of more than 90% were recorded in patients receiving the once-daily, all-oral fixed-dose combination of grazoprevir plus elbasvir for 12 weeks, and no patient discontinued treatment because of an adverse event. Our findings suggest that similar efficacy is achievable with an interferon-free, ribavirin-free regimen across important subpopulations, such as patients with HCV genotype 4 infection, patients with cirrhosis, and patients of African descent.

Implications of all the available evidence

Data from our study represent the latest stage in the development of effective and safe treatment regimens for patients with HIV and HCV co-infection. During the past decade there has been a gradual decrease in the duration of treatment coupled with a progressive increase in the proportion of patients who achieve viral eradication. The C-EDGE CO-INFECTION study extends these advances with a 12 week treatment duration while achieving SVR in more than 90% of patients. This interferon-free and ribavirin-free regimen addresses the tolerability concerns associated with the historical use of peginterferon and ribavirin while providing broad applicability to the important population of co-infected patients with or without cirrhosis.

enrolled. All patients were co-infected with HIV-1 and either naive to antiretroviral therapy (ART) or on stable ART with tenofovir or abacavir, and either emtricitabine or lamivudine plus raltegravir, dolutegravir, or rilpivirine for at least 8 weeks before enrolment. ART-naive patients had to have CD3 or CD4 T-cell counts of more than 500 cells per µL and HIV RNA viral load of less than 50 000 copies per mL; patients on stable ART had to have CD3 or CD4 T-cell counts of more than 200 cells per µL and undetectable HIV RNA (<20 copies/mL). Patients with and without cirrhosis were eligible; managed enrolment was used to enrol roughly 20% of patients with cirrhosis (see appendix for assessment of fibrosis staging). Patients with decompensated liver disease (presence or history of ascites, oesophageal or gastric variceal bleeding, hepatic encephalopathy, or other signs of advanced liver disease), and patients with cirrhosis who were Child-Pugh class B or C, or with a

See Online for appendix

Child-Turcotte-Pugh score of more than 6 points were excluded. Patients with hepatitis B virus co-infection, history of malignant disease, or evidence of hepatocellular carcinoma were excluded. The protocol is available in the appendix.

This study was done in accordance with the Declaration of Helsinki, current guidelines on Good Clinical Practice, and local ethical and legal requirements. All patients provided voluntary written informed consent.

Procedures

All patients received open-label grazoprevir 100 mg plus elbasvir 50 mg as a fixed-dose combination tablet once daily for 12 weeks without food restriction. This was a single-arm study. All patients received grazoprevir plus elbasvir without randomisation.

Samples for HCV RNA were assessed at baseline, every 2 weeks during treatment, and at follow-up weeks 4, 8, 12, and 24. HIV RNA was assessed at treatment weeks 4, 8, and 12, and at follow-up weeks 4, 8, 12, and 24. Plasma HCV RNA viral loads were measured with the Roche COBAS AmpliPrep/COBAS TaqMan HCV test version 2.0 (Roche, Indianapolis, IN, USA) with a lower limit of quantitation of less than 15 IU/mL. HIV RNA was measured with the COBAS AmpliPrep/COBAS TaqMan HIV-1 test version 2.0 (Roche), with a lower limit of quantitation of less than 20 copies per mL.

Safety was assessed through monitoring of adverse events, vital signs, and laboratory assessments. Events of clinical interest were first instance of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 500 IU/mL, first instance of ALT or AST more than three times the upper limit of normal (ULN) and more than 100 IU/mL, and first instance of alkaline phosphatase more than three times ULN.

Samples were taken from all patients at baseline, and at time of failure in patients who met virological failure criteria (HCV RNA concentration greater than the lower limit of quantitation measured from two separate blood draws within 2 weeks). The *NS3* and *NS5A* genes were amplified and sequenced in patients who met virological failure criteria with HCV RNA concentration more than 1000 IU/mL to assess for known viral mutation (see appendix for HCV sequencing analysis method).

Outcomes

The primary endpoint was sustained virological response 12 weeks after the end of therapy (SVR12; defined as HCV RNA concentration less than the lower limit of quantitation at follow-up week 12). The secondary endpoint was SVR24, and exploratory endpoints were the proportion of patients with undetectable HCV RNA and HCV RNA concentration less than the lower limit of quantitation at treatment weeks 2, 4, and 12 (SVR24 data will form the basis of a future publication). Lack of efficacy was defined as non-response (detectable HCV RNA at end of treatment with HCV RNA greater than lower limit of quantitation throughout treatment); rebound (HCV RNA >1 $\log_{10}$ increase from nadir while on treatment); breakthrough (HCV RNA greater than lower limit of quantitation after previously being less than lower limit of quantitation); and relapse (HCV RNA greater than lower limit of quantitation during follow-up after having undetectable HCV RNA at end of treatment).

Statistical analysis

This study planned to allocate 200 patients to receive grazoprevir plus elbasvir. On the assumption of a true response rate of at least 85%, the study had more than 99% power to establish whether the SVR12 rate was superior to the historical reference rate of 70% (derived from the PHOTON-1 study[18]) at an overall one-sided 2·5% α level.

The full analysis set, consisting of all patients who received at least one dose of study treatment, was used as the primary population for efficacy analyses. The per-protocol population, which excluded patients who discontinued for reasons other than virological failure, and patients with deviations from the protocol that might substantially affect the results of the primary endpoints, was used in exploratory analyses. The all-patients-as-treated population, including all enrolled patients, was used for safety analyses.

An exact binomial test was undertaken to ascertain whether the true SVR12 is 70% or higher. A hypothesis of H0: p≤0·70 was tested against the alternative H1: p>0·70, where p was the proportion of patients achieving

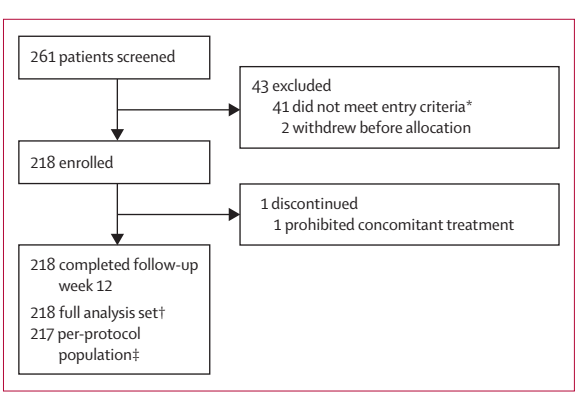

***Figure 1*: Patient flow diagram**

*The most common inclusion criteria not met were CD4 cell count more than 200 cells per μL or more than 500 cells per μL at screening (n=8, 20%); HCV RNA 10 000 IU/mL or more at the time of screening (n=7, 17%); and undetectable plasma HIV-1 RNA at screening and at least 8 weeks before screening, or less than 50 000 copies per mL in patients not on ART (n=7, 17%). The most common exclusion criterion not met was exclusionary laboratory value (n=4, 10%). †The full analysis set, consisting of all patients who received at least one dose of study treatment, was used as the primary population for efficacy analyses. ‡The per-protocol population, which excluded patients who discontinued for reasons other than virological failure, and patients with deviations from the protocol that might substantially affect the results of the primary endpoints, was used in exploratory analyses.

	All patients (n=218)
Age (years)	48·7 (8·9)
Sex (male)	183 (84%)
Race	
White	167 (77%)
Black or African-American	38 (17%)
Asian	6 (3%)
Other	7 (3%)
Ethnic origin	
Hispanic or Latino	14 (6%)
Not Hispanic or Latino	194 (89%)
Not reported	10 (5%)
Body-mass index (kg/m^2)	25·31 (4·62)
Baseline $\log_{10}$ HCV RNA (IU/mL)	6·03 (0·57)
Baseline HCV RNA concentration	
≤800 000 IU/mL	91 (42%)
>800 000 IU/mL	127 (58%)
HCV genotype	
1a	144 (66%)
1b	44 (20%)
4	28 (13%)*
6	2 (1%)
Fibrosis stage	
F0–F2	160 (73%)
F3	23 (11%)
F4	35 (16%)†
IL28B genotype	
CC	77 (35%)
Non-CC	141 (65%)
Baseline haematology values‡	
Haemoglobin (g/L)	145 (14·1)
Platelets (×10^3 per μL)	195 (60·11)
Alanine aminotransferase (U/L)	74 (60·30)
Aspartate aminotransferase (U/L)	59 (41·33)
Bilirubin (μmol/L)	45·97 (37·13)
Baseline CD3 or CD4 count (cells per μL)	
Mean (SD)	613 (0·57)
Median (IQR)	568 (424–766)
(Table 1 continues in next column)	

	All patients (n=218)
(Continued from previous column)	
ART status	
Receiving ART with undetectable HIV RNA	211 (97%)
Naive to ART	7 (3%)
ART regimen	
Abacavir-containing regimen	47 (22%)
Tenofovir-containing regimen	164 (75%)
None	7 (3%)
ART third agent	
Raltegravir	113 (52%)
Dolutegravir	59 (27%)
Rilpivirine	38 (17%)
None	8 (4%)

Data are mean (SD) or n (%), unless otherwise stated. HCV=hepatitis C virus. ART=antiretroviral therapy. *Of the 28 patients with HCV genotype 4, 18 (64%) were genotype 4d, nine (32%) were genotype 4a, and one (4%) patient was genotype 4 non-subtypeable. †All patients were required to have liver disease staging by liver biopsy, FibroScan (Echosens, Paris, France; cirrhosis defined as >12·5 kPa), or combination of FibroTest and aspartate aminotransferase:platelet ratio index (APRI; cirrhosis defined as FibroTest score >0·75 and an APRI >2). Of the 35 (16%) patients with cirrhosis, 27 were diagnosed by FibroScan, six by biopsy, and two by combination of FibroTest and APRI. ‡Normal ranges for laboratory values were: haemoglobin 125–170 g/L (men) or 110–155 g/L (women); platelets 125–375 × 10^3 per μL; alanine aminotransferase 10–40 U/L (men) or 10–33 U/L (women); aspartate aminotransferase 10–43 U/L (men) or 10–36 U/L (women); bilirubin 8·84–97·24 μmol/L; and CD3/CD4-cell count 490–1740 cells per μL.

***Table 1*: Baseline characteristics**

SVR12. A one-sided exact test was done at an α significance level of 0·025. Rejection of the null hypothesis will lead to a conclusion that the true proportion of patients achieving SVR12 was more than 70%. Missing values were deemed treatment failures. Safety events, including adverse events of clinical interest, were summarised as proportions with corresponding 95% CIs. This study is registered with ClinicalTrials.gov, number NCT02105662.

Role of the funding source

The funder of the study was responsible for study design, study management, data collection, and data analysis, and was involved in the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Patients were enrolled between June 11, 2014, and Aug 29, 2014, at 37 centres in nine countries across Europe, the USA, and Australia. 261 patients were screened; 218 were enrolled and received grazoprevir plus elbasvir for 12 weeks (figure 1; table 1).

In the overall population, 210 (96%) achieved SVR12 (95% CI 92·9–98·4), exceeding the historical reference rate of 70% (table 2). Five patients relapsed after having undetectable HCV RNA concentrations at the end of treatment (table 3). All relapsed patients were non-cirrhotic and included four patients with HCV genotype 1 infection, and one patient with HCV genotype 4 infection. Among this small number of relapsed patients, there was no clear association between any individual patient characteristic and the propensity for relapse. Two additional patients who did not achieve SVR12 were infected with a different HCV genotype during follow-up (one with genotype 1a and one with genotype 1b at enrolment; both with HCV genotype 3 at follow-up week 12). In the per-protocol analysis, these patients were classified as relapsed, but sequencing data are consistent with reinfection after treatment. One patient did not achieve SVR12 because of a non-virological reason and was excluded from the

per-protocol analysis (figure 1). In the per-protocol analysis, 210 (97%) of 217 had SVR12 (95% CI 93·5–98·7).

SVR12 was high across all subgroups, including in those with characteristics historically associated with poor response. SVR12 was recorded in all 35 patients (100%) with cirrhosis (95% CI 90·0–100), 134 (95%) of 141 with the *IL28B* non-CC genotype (90·0–98·0), 36 (95%) of 38 African-Americans (82·3–99·4), and 121 (95%) of 127 with baseline HCV viral load of more than 800 000 IU/mL (90·0–98·2; figure 2).

Baseline NS3 resistance-associated variants were detected in 74 (41%) of 182 patients with HCV genotype 1 infection; only one patient had a baseline NS3 resistance-associated variant known to confer more than five times resistance to grazoprevir (Asp168Glu [D168E]). At baseline, 69 (50%) of 139 patients with genotype 1a infection had NS3 resistance-associated variants compared with only five (12%) of 43 with genotype 1b. The most common variants in patients with genotype 1a infection were Gln80Lys/Arg (Q80K/R; 50 patients) and Ser122Gly (S122G; seven patients). In patients with NS3 resistance-associated variants at baseline, 66 (96%; 95% CI 87·8–99·1) of those with genotype 1a and five (100%; 47·8–100) of those with genotype 1b had sustained virological response, compared with 68 (97%; 90·1–99·7) of 70 and 37 (97%; 86·2–99·9) of 38 without baseline resistance-associated variants.

Baseline NS5A resistance-associated variants were detected in 15 (8%) of 183 patients with HCV genotype 1 infection: ten (7%) of 140 with genotype 1a and five (12%) of 43 with genotype 1b. The most common variants in patients infected with HCV genotype 1a were Met28Val (M28V; six patients), Leu31Met (L31M; four patients), and Tyr93Cys/His/Ser (T93C/H/S; four patients), and in patients with genotype 1b they were Leu31Met (L31M) and Tyr93His (T93H), each occurring in two patients. In patients with genotype 1, 13 of 15 patients with baseline NS5A resistance-associated variants achieved SVR12 (87%; 95% CI 59·5–98·3) compared with 164 of 168 without (98%; 94·0–99·3). In patients with genotype 1a, three of four who had baseline NS5A resistance-associated variants conferring more than five-fold resistance to elbasvir had SVR12 (75%, 19·4–99·4) compared with 127 of 130 without resistance-associated variants (98%, 93·4–99·5).

All four relapsed patients with HCV genotype 1a infection were assessed for treatment-emergent mutations: two patients had Asp168Ala (D168A) in the NS3 region and three had Glu30Arg/Lys (Q30R/K) in the NS5A region. For the one relapsed patient with HCV genotype 4 infection, no treatment-emergent NS3 resistance-associated variant was detected and one NS5A Leu28Ser (L28S) variant was detected (table 3; see appendix for listings of virological failures).

Combination treatment with grazoprevir plus elbasvir was generally well tolerated (table 4); 161 patients (74%, 95% CI 67·5–79·6) reported at least one adverse event, 99 (62%) of which were graded as mild. The most common adverse events were fatigue (29 [13%] of 218), headache (27 [12%]), and nausea (20 [9%]). 75 patients (34%) reported drug-related adverse events, the most common of which were also fatigue (16 [7%]), headache (15 [7%]), and nausea (10 [5%]). No patient discontinued treatment because of an adverse event.

	All patients	HCV genotype 1a	HCV genotype 1b	HCV genotype 4
SVR12 (95% CI)	210/218* (96·3%, 92·9–98·4)	136/144 (94·4%, 84·5–99·4)	42/44 (95·5%, 84·5–99·4)	27/28 (96·4%, 81·7–99·9)
Lost to follow-up or other non-virological failure	1†	0	1	0
Virological breakthrough	0	0	0	0
Virological relapse	5	4	0	1
Reinfection	2	1	1	0

Data are n/N (%, 95% CI) or number of patients. Sustained virological response (SVR) defined as hepatitis C virus (HCV) RNA less than lower limit of quantitation (<15 IU/mL) at follow-up week 12. *Two patients with HCV genotype 6 infection were also included; both patients achieved SVR12. †Prohibited concomitant medication.

***Table 2*: Rates of sustained virological response after 12 weeks of follow-up (full analysis set)**

Six patients experienced serious adverse events, of which four occurred after dosing was complete. None of the serious adverse events required discontinuation of study drug; none were thought to be related to treatment. Serious adverse events of pneumonia and generalised seizure were reported during treatment, and erysipelas, acute psychosis, ulnar fracture, and spontaneous bacterial peritonitis occurred during follow-up.

Four patients had increased concentrations of hepatic enzymes during treatment. Two patients had late increase in ALT/AST (>5×ULN after treatment week 4 with an ALT/AST ≤ULN between treatment weeks 2 and 4). One increase occurred at treatment week 6 and one at treatment week 10; both normalised without discontinuation of treatment. One patient had ALT concentration more than 500 IU/L related to blockage of a biliary stent; treatment was interrupted for 3 days, and raised transaminase resolved with endoscopic intervention. One patient had raised concentrations of AST and creatine phosphokinase at treatment week 6, which were temporally associated with strenuous activity; both normalised after the patient abstained from exercise. None of these patients discontinued study medication and all achieved SVR12.

Two patients on ART had transient HIV viraemia during the treatment period. Both patients subsequently achieved undetectable HIV RNA with additional compliance education and without a change in antiretroviral regimen. See appendix for narratives for the patients with serious adverse events, increases in hepatic enzyme concentrations, or transient HIV anaemia.

Throughout the trial, there was no notable change in CD3 or CD4 T-cell count or percentage at treatment week 12 or follow-up week 12 (appendix).

	HCV subtype	ART	Baseline HCV RNA (IU/mL)	Follow-up day of virological relapse	Baseline RAVs		Post-baseline RAVs	
					NS3	NS5A	NS3	NS5A
56-year-old black/African-American man	1a	Tenofovir, emtricitabine, rilpivirine	1 117 604	28	V36M/L, Q80K	L31M/L	Q80K, D168A	Q30K, L31M
63-year-old black/African-American man	1a	None	2 059 766	28	Q80K	Y93S	Q80K, D168A	Q30R, Y93S
53-year-old white man	4	Tenofovir, emtricitabine, raltegravir	4 472 508	56	WT	WT	WT	L28S
37-year-old white man	1a	Tenofovir, emtricitabine, raltegravir	4 958 526	83	WT	WT	WT	Q30R/Q
43-year-old white man	1a	Abacavir, lamivudine raltegravir	1 830 996	102	WT	WT	WT	WT
43-year-old white man	1a	Tenofovir, emtricitabine, rilpivirine	436 155	92	V55A/V	WT	NA†	NA†
35-year-old white man	1b	Abacavir, lamivudine raltegravir	412 609	84	WT	WT	NA‡	NA‡

HCV=hepatitis C virus. ART=antiretroviral therapy. RAVs=resistance-associated variants. *All patients who met criteria for virological failure were non-cirrhotic, and all were temporally categorised as relapse. †The patient did not achieve sustained virological response at follow-up week 12 (SVR12), and testing at follow-up week 12 showed infection with a different genotype. For the 43-year-old white man, the genotype was 1a at baseline, and genotype 3 at virological failure. ‡The patient did not achieve SVR12, and testing at follow-up week 12 showed infection with a different genotype. For the 35-year-old white man, the genotype was 1b at baseline, and genotype 3 at virological failure.

Table 3*: Characteristics of the seven patients who met criteria for virological failure or relapse

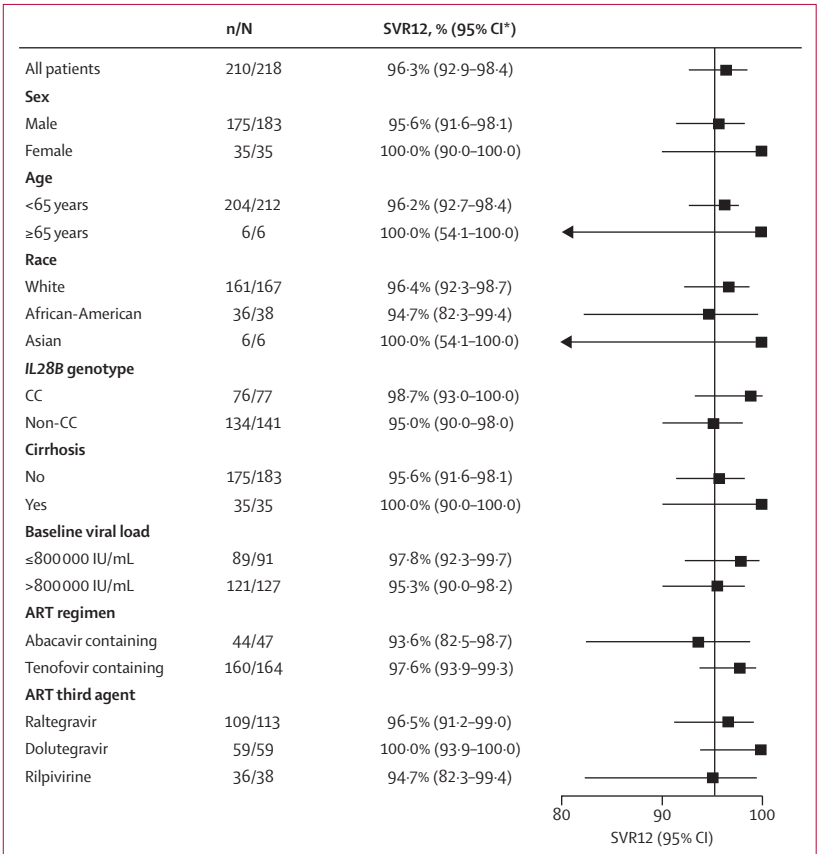

***Figure 2*: Subgroup analyses of SVR rates 12 weeks after treatment (full analysis set)**
Sustained virological response (SVR) defined as HCV RNA less than lower limit of quantitation (<15 IU/mL) at follow-up week 12. ART=antiretroviral therapy. *Based on Clopper-Pearson method.

Discussion

This single-arm, open-label trial showed the efficacy of 12 weeks of treatment with a fixed-dose combination of grazoprevir plus elbasvir in patients with HIV infection and HCV genotype 1, 4, or 6 co-infection. The overall SVR12 rate was 95% in the primary analysis and 97% in the per-protocol analysis. In the C-EDGE Treatment-Naive trial[19] in patients with HCV monoinfection, SVR12 was achieved in 95% of patients, thus supporting the growing body of data suggesting that patients with HCV and HIV co-infection have similar responses to patients with monoinfection when treated with interferon-free regimens containing only direct-acting antiviral agents for at least 12 weeks. As a consequence of these similar SVR rates, some HCV treatment guidelines no longer distinguish between HCV monoinfection and co-infection with HIV with regard to treatment indication or regimen selection.[20] Importantly, safety observations in our study were broadly similar to those in the C-EDGE Treatment-Naive study, suggesting that the quality and rate of adverse events are similar in monoinfected and co-infected patients receiving grazoprevir plus elbasvir. Earlier phase 2 studies showed high potency against HCV genotypes 1, 2, and 4–6, although with less potency against genotype 3 (4·61 $\log_{10}$ IU/mL drop compared with 2·5 $\log_{10}$ IU/mL drop after 7 days of grazoprevir 100 mg).[21] On the basis of these data, genotype 3 was excluded from our study.

Our results are also consistent with studies in patients with HCV and HIV co-infection. In the phase 2 C-WORTHY study,[13] patients with HCV genotype 1 and HIV co-infection who received grazoprevir plus elbasvir for 12 weeks achieved an SVR of 87%, which increased to 97% in patients who received concomitant ribavirin. In the

ribavirin-free group, five patients did not achieve SVR (breakthrough, n=2; relapse, n=1; lost to follow-up or discontinued because of administrative reasons, n=2). In studies of other direct-acting antiviral agents, the PHOTON-2 study[15] reported an SVR12 of 85% in patients with HCV genotype 1 and HIV co-infection who received sofosbuvir and ribavirin for 24 weeks, with most patients with virological failure relapsing after the end of treatment. In the TURQUOISE-1 study,[14] 12 weeks of treatment with ombitasvir, ritonavir-boosted paritaprevir, and dasabuvir plus ribavirin resulted in SVR in 29 (94%) of 31 patients with HCV and HIV co-infection. More recently, in the ALLY-2 study,[22] SVR12 was achieved by 96–98% of patients with co-infection who received sofosbuvir plus daclatasvir for 12 weeks, and in the ION-4 study,[23] 96% of patients with co-infection achieved SVR12 after 12 weeks of treatment with sofosbuvir plus ledipasvir. As in the present study, data from ION-4 and ALLY-2 show similar high rates of SVR in patients with and without cirrhosis. Taken together, these studies suggest that high rates of SVR are achievable in patients with HCV and HIV co-infection.

Patients with cirrhosis are an important subpopulation with substantial unmet need. Studies of patients with HCV and HIV co-infection have typically enrolled small numbers of patients with cirrhosis (TURQUOISE-1, six patients in the 12 week group;[14] PHOTON-1, five patients with HCV genotype 1 infection and cirrhosis[18]), with the exception of the ION-4 study, in which 67 (20%) patients with cirrhosis were enrolled, with an SVR of 94% in this subgroup.[23] In our study, all 35 patients with cirrhosis achieved SVR, and the safety profiles in patients with and without cirrhosis were similar.

Five virological failures in this study were relapses. Baseline NS3 resistance-associated variants did not seem to affect SVR12. Specifically, there was no apparent association between the Glu80Lys (E80K) polymorphism and SVR12 in patients with HCV genotype 1a infection. The presence of baseline NS5A resistance-associated variants might affect efficacy: in patients with genotype 1 infection, SVR12 was achieved by 87% of patients with baseline NS5A resistance-associated variants compared with 98% of patients without. Although the numbers are small, treatment-emergent NS5A resistance-associated variants might have affected SVR12 in patients with genotype 1a infection, because three of the four patients with relapse developed the Glu30Arg/Lys (E30R/K) mutation.

One of the main considerations in selecting an effective treatment for HCV in co-infected patients is the risk for serious drug interactions. Previous studies in healthy volunteers suggested that there were no interactions between grazoprevir plus elbasvir and either raltegravir or tenofovir.[24,25] In our study, dolutegravir, rilpivirine, or raltegravir in combination with a nucleoside or nucleotide reverse transcriptase inhibitor were allowed as ongoing ART. We saw no association between relapse and ART regimen, suggesting that plasma concentrations of grazoprevir and elbasvir were not adversely affected by ART. Furthermore, only two patients had transient HIV viraemia, and in both cases HIV suppression was restored with compliance education, and without a change in antiretroviral regimen.

Our study has several limitations. It was designed in an era when open-label single-arm studies with a historical control were acceptable for the assessment of direct-acting antiviral agents. This study design is consistent with other recent non-randomised phase 3 studies.[14,23] Although the absence of a comparator is a limitation to our study, it is important to note the findings from the C-EDGE Treatment-Naive study,[19] in which the frequency of adverse events was similar with grazoprevir plus elbasvir and placebo. Furthermore, the sample size, although sufficient to support the primary efficacy

	All patients (n=218)	95% CI
At least one adverse event	161 (74%)	67·5–79·6
Serious adverse event*	2 (1%)	0·1–3·3
Serious drug-related adverse event	0	..
Discontinuations due to adverse events	0	..
Deaths	0	..
Any adverse event occurring in >5% of patients		
Fatigue	29 (13%)	..
Headache	27 (12%)	..
Nausea	20 (9%)	..
Upper respiratory tract infection	17 (8%)	..
Diarrhoea	16 (7%)	..
Insomnia	15 (7%)	..
Drug-related adverse events occurring in >5% of patients†	75 (34%)	28·1–41·1
Fatigue	16 (7%)	..
Headache	15 (7%)	..
Adverse event of clinical interest	3 (1%)	0·3–4·0
ALT		
Grade 3: 5·1–10·0 × ULN	3 (1%)	..
Grade 4: >10·0 × ULN	2 (1%)	..
AST		
Grade 3: 5·1–10·0 × ULN	0	..
Grade 4: >10·0 × ULN	1 (<1%)	..
Late elevation of ALT or AST‡	2 (1%)	..
Elevation of total bilirubin		..
Grade 3: 2·6–5·0 × ULN	1 (<1%)	..
Grade 4: >5·0 × ULN	0	..
Lowest haemoglobin on treatment		
Grade 3: 70–89 g/L	0	..
Grade 4: <70 g/L	0	..

Data are n (%). The all-patients-as-treated population, including all enrolled patients, was used for safety analyses. ALT=alanine aminotransferase. AST=aspartate aminotransferase. ULN=upper limit of normal. *Serious adverse events were reported from the time the consent was signed until the end of the 24 week follow-up period. Two serious adverse events were reported during the treatment period (convulsion and pneumonia), and four additional serious adverse events were reported during follow-up (erysipelas; acute psychosis and urinary retention; ulnar fracture; and spontaneous bacterial peritonitis). †Reported during treatment period or first 14 days of follow-up in more than 5% of patients. ‡Defined as ALT/AST more than five times ULN occurring after treatment week 4 with an occurrence of ALT/AST less than or equal to ULN between treatment week 2 and treatment week 4.

Table 4: **Safety and adverse events (treatment period plus first 14 days of follow-up)**

analysis, might not be sufficient to detect uncommon or rare adverse events, and thus further clinical experience with this combination is needed to confirm the safety profile reported in this study.

An additional limitation is that few patients had HCV genotype 4 or 6 infection; however, this study contains the largest number of patients with HCV genotype 4 and HIV co-infection so far reported. The PHOTON-1 and TURQUOISE-1 studies did not enrol patients with genotype 4 infection,[14,18] and the ION-4 and ALLY-2 studies enrolled only seven and three patients with genotype 4 infection, respectively.[22,23] Because our study enrolled only one patient infected with genotype 6 and excluded treatment-experienced patients, conclusions regarding the efficacy and safety of grazoprevir plus elbasvir in these patient groups are limited. With regard to treatment-experienced patients, other studies have shown the combination of grazoprevir and elbasvir to be highly effective with a favourable tolerability profile in patients who have previously failed interferon-based therapy,[19] and in those who have failed previous treatment with a regimen containing direct-acting antiviral agents.[26] However, these studies did not enrol treatment-experienced patients with HCV and HIV co-infection, and thus further clinical experience with grazoprevir plus elbasvir in this patient group is warranted. Additionally, because our study enrolled patients from the USA, Europe, and Australia, data cannot be extrapolated to patients from other geographical regions, such as Africa. HCV genotype 1 and genotype 4 infections are endemic in African countries;[27] data regarding treatment in this region are scarce because regimens containing direct-acting antiviral agents are only beginning to expand into new geographical regions.[28]

As previously noted, our findings are restricted to patients receiving ART with tenofovir or abacavir, and either emtricitabine or lamivudine plus raltegravir, dolutegravir, or rilpivirine; because of the potential for drug–drug interactions, boosted HIV-1 protease inhibitors or efavirenz will not be recommended for use in combination with grazoprevir plus elbasvir. Because only seven patients naive to ART were included in the study, the use of grazoprevir and elbasvir in this population remains largely unexplored. Additionally, our study does not establish the clinical profile of grazoprevir plus elbasvir in co-infected patients with less effective control of HIV infection or viraemia. Finally, the population sequencing method used in our study also has some limitations: it can only be used in samples from patients with a viral load of more than 1000 IU/mL and is capable of only detecting variants that represent a minimum of 25% of the total viral population.

Thus, in this non-randomised study, high rates of SVR were achieved in patients with HCV and HIV co-infection who received an oral fixed-dose combination of grazoprevir and elbasvir, including the important subpopulation of patients with cirrhosis.

Contributors

HLP, MNR, JW, EB, JG, SK, and MSh participated in conception and design of the study. JKR, MN, CK, JL, JM, MB, GVM, MSS, PJZ, CO, and MSu participated in acquisition of data. JKR, HLP, B-YTN, EB, and MSu contributed to initial drafting of the report. JG and SK undertook the statistical analysis. All authors participated in data analysis and interpretation, critically revised the report, and reviewed and approved the final version for publication.

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Declaration of interests

JKR has received grant support from Gilead; has served as a consultant/adviser for AbbVie, Bionor, Bristol-Myers Squibb, Gilead, Janssen, Merck, and ViiV; and as a speaker for AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Merck, and ViiV. MN has received grant support from MSD, Bristol-Myers Squibb, ViiV, Boehringer Ingelheim, AbbVie, Gilead, and Janssen. CK has received grant support from Bristol-Myers Squibb, and Janssen; and has served as consultant for MSD, Bristol-Myers Squibb, and Gilead. JL has received research support from Merck. JM has received grant support from Merck, Bristol-Myers Squibb, Gilead, ViiV, and AbbVie; has served on advisory boards for Merck, Bristol-Myers Squibb, Gilead, ViiV, and Roche; and received support for conference travel from Gilead, Bristol-Myers Squibb, Merck, ViiV, and AbbVie. MB has received grant support from Merck, Bristol-Myers Squibb, Gilead, ViiV, and AbbVie; has served on advisory boards for Merck, Bristol-Myers Squibb, Gilead, and ViiV; and received support for conference travel from Gilead, Bristol-Myers Squibb, Merck, ViiV, and AbbVie. GVM has received grant support from Gilead, MSD, AbbVie, and Janssen; has served as a consultant for AbbVie, Gilead, and MSD; and has received travel support from Bristol-Myers Squibb, Gilead, and Roche. MSS has received grant support from Merck, Bristol-Myers Squibb, Gilead, ViiV, Janssen, and AbbVie. PJZ has received grant support from Bristol-Myers Squibb, Gilead, AbbVie, and Merck; has served as a consultant/adviser for Janssen, and as a speaker for Janssen and AbbVie. CO has received grant support from Merck, Bristol-Myers Squibb, Gilead, ViiV, and AbbVie; has served on advisory boards for MSD, Gilead, and ViiV; and has received support for conference travel from Gilead, Bristol-Myers Squibb, Merck, ViiV, and AbbVie. JG, SK, MSh, JW, B-YTN, EB, HLP, and MNR are employees/shareholders of Merck. MSu has received research grant to Johns Hopkins University from AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and Merck; has served as a consultant/adviser for Achillion, AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and Merck; and served as a member of a data and safety monitoring board to Johns Hopkins University for Gilead.

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