Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study

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Summary

Background Chronic hepatitis C virus (HCV) infection in patients with stage 4–5 chronic kidney disease increases the risk of death and renal graft failure, yet patients with hepatitis C and chronic kidney disease have few treatment options. This study assesses an all-oral, ribavirin-free regimen in patients with HCV genotype 1 infection and stage 4–5 chronic kidney disease.

Methods In this phase 3 randomised study of safety and observational study of efficacy, patients with HCV genotype 1 infection and chronic kidney disease (stage 4–5 with or without haemodialysis dependence) were randomly assigned to receive grazoprevir (100 mg, NS3/4A protease inhibitor) and elbasvir (50 mg, NS5A inhibitor; immediate treatment group) or placebo (deferred treatment group) once daily for 12 weeks. Randomisation was done centrally with an interactive voice response system. An additional cohort of patients who were not randomised received the same regimen open-label and underwent intensive pharmacokinetic sampling. The primary efficacy outcome was a non-randomised comparison of sustained virological response at 12 weeks (SVR12) after the end of therapy for the combined immediate treatment group and the pharmacokinetic population with a historical control. The primary safety outcome was a randomised comparison between the immediate treatment group and the deferred treatment group. After 4 weeks of follow-up (study week 16), unmasking occurred and patients in the deferred treatment group received grazoprevir and elbasvir. The primary efficacy hypothesis was tested at a two-sided significance level (type I error) of 0·05 using an exact test for a binomial proportion. Safety event rates were compared between immediate treatment and deferred treatment groups using the stratified Miettinen and Nurminen method with baseline dialysis status as the strata. The study is registered at ClinicalTrials.gov, number NCT02092350.

Findings 224 patients were randomly assigned to the immediate treatment group with grazoprevir and elbasvir (n=111) or the deferred treatment group (n=113), and 11 were assigned to the intensive pharmacokinetic population. Overall, 179 (76%) were haemodialysis-dependent, 122 (52%) had HCV genotype 1a infection, 189 (80%) were HCV treatment-naive, 14 (6%) were cirrhotic, and 108 (46%) were African American. Of the 122 patients receiving grazoprevir and elbasvir, six were excluded from the primary efficacy analysis for non-virological reasons (death, lost-to-follow-up [n=2], non-compliance, patient withdrawal, and withdrawal by physician for violent behaviour). No patients in the combined immediate treatment group and intensive pharmacokinetic population and five (4%) in the deferred treatment group discontinued because of an adverse event. Most common adverse events were headache, nausea, and fatigue, occurring at similar frequencies in patients receiving active and placebo drugs. SVR12 in the combined immediate treatment group and intensive pharmacokinetic population was 99% (95% CI 95·3–100·0; 115/116), with one relapse 12 weeks after end of treatment when compared with a historical control of 45%, based on meta-analyses of interferon-based regimens used in clinical trials of patients infected with HCV who are on haemodialysis.

Interpretation Once-daily grazoprevir and elbasvir for 12 weeks had a low rate of adverse events and was effective in patients infected with HCV genotype 1 and stage 4–5 chronic kidney disease.

Funding Merck Sharp & Dohme Corp.

Introduction

Hepatitis C infection accelerates the decline in kidney function in patients with chronic kidney disease and increases mortality among patients on haemodialysis[1] compared with patients not infected with hepatitis C on dialysis.[2–6] Studies among kidney transplant patients show infection with hepatitis C also has an adverse effect on patient and graft survival.[7–9] These data suggest that clearance of hepatitis C infection among patients with stage 4–5 chronic kidney disease (estimated glomerular

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Research in context

Evidence before this study

Patients with stage 4–5 chronic kidney disease and hepatitis C infection have few treatment options for hepatitis C virus (HCV). At the time this study was designed, the Kidney Disease: Improving Global Outcomes (KDIGO) recommended treatment was interferon or pegylated interferon. Some investigators also explored adding ribavirin to pegylated interferon. Unfortunately, these regimens are associated with treatment-limiting toxic effects and suboptimum efficacy. We searched PubMed for clinical trials published before Jan 31, 2015, describing the treatment of hepatitis C in patients with advanced chronic kidney disease. Although this search returned a total of 97 relevant articles, the data on this subject are summarised most concisely in a series of meta-analyses. The most recent of these meta-analyses (based on data from 28 clinical trials done between 1990 and 2006, and including 645 patients) suggests that interferon or pegylated interferon monotherapy was associated with a sustained virological response (SVR) in about one in three patients when treated for 16–48 weeks, whereas about 20–25% of patients did not complete treatment. In the past 5 years, the introduction of direct-acting antiviral therapies has dramatically improved treatment options for patients with hepatitis C. High rates of SVR, coupled with improved tolerability, are now available to many patients with HCV infection; however, in our literature review, we were unable to identify any published studies of direct-acting antiviral therapies in patients with advanced chronic kidney disease. Thus, patients with hepatitis C and stage 4–5 chronic kidney disease remain underserved by current direct-acting antiviral hepatitis C treatment regimens.

Added value of this study

This study is the first phase 3 study to assess an interferon-free, ribavirin-free, all-oral treatment regimen for patients with HCV infection and advanced (stage 4–5) chronic kidney disease. Patients receiving grazoprevir plus elbasvir for 12 weeks had a low rate of adverse events compared with a deferred treament group and achieved a 99% SVR12 compared with a historical control.

Implications of all the available evidence

Grazoprevir and elbasvir is an investigational medicine and is not approved for the treatment of HCV infection. However, data from the present study suggest that the availability of a grazoprevir and elbasvir regimen for patients with stage 4–5 chronic kidney disease could represent a marked improvement in treatment for this significantly underserved patient group.

filtration rate [eGFR] ≤29 mL/min per 1·73 m² or on dialysis), especially those who are candidates for kidney transplantation, is of great importance.

Treatment options for patients with hepatitis C infection and stage 4–5 chronic kidney disease remain suboptimum. Approved all-oral therapies are not ideal regimens because they contain drugs whose metabolites are cleared by the kidney (such as sofosbuvir) or because they need co-administration with ribavirin, which is associated with anaemia.

Grazoprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and elbasvir, an NS5A protein inhibitor, are undergoing clinical assessment as a once-daily regimen for the treatment of HCV genotype 1, 4, and 6 infections.[10–14] Phase 1 studies have shown that less than 1% of grazoprevir and elbasvir are renally excreted, and that dose adjustments of grazoprevir or elbasvir are not needed in the setting of non-dialysis-dependent stage 4–5 chronic kidney disease and dialysis-dependent stage 5 chronic kidney disease.[15] C-SURFER (Hepatitis C: Study to Understand Renal Failure's Effect on Responses) is the first phase 3 study of an all-oral HCV regimen in patients with stage 4–5 chronic kidney disease and HCV genotype 1 infection. The aims of the study were to assess the efficacy, safety, and tolerability of grazoprevir plus elbasvir in patients with HCV genotype 1 infection and with chronic kidney disease stage 4–5.

Methods

Study design and participants

C-SURFER is a multicentre, phase 3, double-blind study comprising a randomised study of safety and an observational study of efficacy. Adult patients infected with HCV genotype 1 and with chronic kidney disease (stage 4–5 with or without haemodialysis dependence) were selected for inclusion. Complete eligibility criteria are provided in the study protocol. Chronic kidney disease stages 4 and 5 were defined based on eGFR (according to the Modification of Diet in Renal Disease [MDRD]-4 equation)[16] 15–29 mL/min per 1·73 m² and less than 15 mL/min per 1·73 m² or on dialysis, respectively. Patients were either treatment-naive for HCV or had previously received an interferon regimen. Liver staging was based on biopsy within 24 months of enrolment; Fibroscan within 12 months of enrolment; or a combination of Fibrotest score greater than 0·75 and an AST to platelet ratio of greater than 2.[17–19]

The study was done at 68 centres in the USA, Argentina, Australia, Canada, Estonia, France, Israel, South Korea, Lithuania, Netherlands, Spain, and Sweden in accordance with the Declaration of Helsinki, the International Conference on Harmonization guidelines, and other regulations governing clinical study conduct. The protocol was approved by an independent ethics committee or institutional review board at each participating site. All patients provided written informed consent.

Randomisation and masking

Participants were randomly assigned (1:1) to receive grazoprevir 100 mg and elbasvir 50 mg once daily (immediate treatment group) or placebo (deferred treatment group) for 12 weeks. 4 weeks after the end of treatment (week 16), patients and site personnel were unmasked, and those randomised to the deferred

treatment group received grazoprevir 100 mg and elbasvir 50 mg once daily for 12 weeks (appendix). An additional cohort received open-label grazoprevir 100 mg and elbasvir 50 mg once daily for 12 weeks and underwent intensive pharmacokinetic sampling. Patients were recruited on a voluntary basis at study sites with expertise in conducting pharmacokinetic studies.

Randomisation for the safety study was done centrally using an interactive voice response system and stratified according to dialysis (yes/no) and presence of diabetes (yes/no) with a block size of 4. Grazoprevir, elbasvir, and placebos were manufactured to preserve masking (confirmed as visually identical) and packaged identically. All clinical supplies were provided by Merck & Co., Inc. Patients, investigators, and site personnel were masked to treatment assignment.

Procedures

Blood samples for assessment of HCV RNA were collected at baseline, at treatment weeks 1, 2, 3, 4, 6, 8, 10, and 12, and at 4, 12, and 24 weeks after end of treatment. Plasma HCV RNA concentrations were measured using Roche COBAS Ampliprep/COBAS Taqman HCV test v2.0 (Roche, Indianapolis, IN, USA) with a lower limit of quantification of less than 15 IU/mL. Blood samples for assessment of viral resistance were collected at baseline from all patients, and at virological failure for patients with HCV RNA greater than 1000 IU/mL who met criteria for virological failure. For patients on haemodialysis, laboratory sampling was done before dialysis.

See Online for appendix

Patients underwent routine laboratory testing, electrocardiograms, and symptom-directed physical examinations at baseline, and during, and after completion of treatment. Adverse events were graded according to a standardised scale (study protocol, appendix).

The deferred treatment group served as an internal control for potential safety signals in the immediate treatment group. Active therapy in the deferred treatment group is ongoing: data described herein are observations from the initial placebo treatment period plus 14 days (results of the deferred open-label treatment with grazoprevir and elbasvir will be presented elsewhere). All patients will be followed for 24 weeks after completion of therapy.

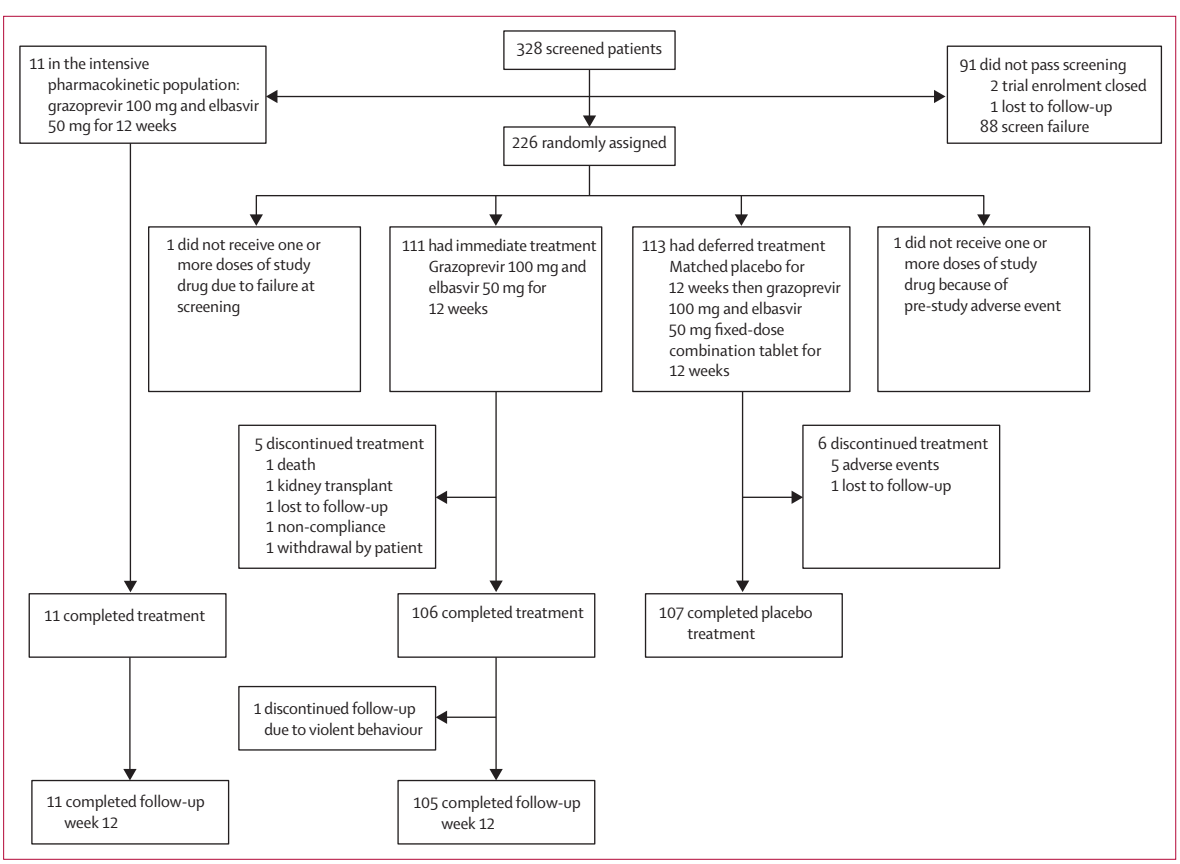

Figure 1: **Trial profile**

For the deferred treatment group, this figure does not show two deaths (pneumonia and unknown cause of death) that occurred after completion of treatment. In total, there were three deaths in the deferred treatment group (aortic aneurysm, pneumonia, and unknown cause of death): one patient discontinued due to an adverse event and then died (listed as discontinued). One patient in the immediate-treatment group discontinued study drug due to a kidney transplant at treatment week 4 but was not excluded from the modified full analysis set population because the patient continued to participate in the study, remaining in follow-up despite early discontinuation of the study drug.

	Grazoprevir and elbasvir pharmacokinetic population (n=11)	Grazoprevir and elbasvir immediate treatment group (n=111)	Grazoprevir and elbasvir deferred treatment group (n=113)	Total (n=235)
Sex				
Male	11 (100%)	81 (73·0%)	80 (70·8%)	172 (73·2%)
Female	0	30 (27·0%)	33 (29·2%)	63 (26·8%)
Age, years	58·2 (6·8)	56·5 (9·1)	55·2 (10·1)	56·0 (9·5)
Race				
White	6 (54·5%)	55 (49·5%)	48 (42·5%)	109 (46·4%)
African-American	5 (45·5%)	50 (45·0%)	53 (46·9%)	108 (46·0%)
Asian	0	5 (4·5%)	9 (8·0%)	14 (6·0%)
Other	0	1 (0·9%)	3 (2·7%)	4 (1·7%)
Ethnic origin				
Hispanic–Latino	2 (18·2%)	11 (9·9%)	14 (12·4%)	27 (11·5%)
Not Hispanic–Latino	9 (81·8%)	98 (88·3%)	99 (87·6%)	206 (87·7%)
Other	0	2 (1·8%)	0	2 (0·9%)
HCV genotype				
1a	10 (90·9%)	53 (47·7%)	59 (52·2%)	122 (51·9%)
1b	1 (9·1%)	58 (52·3%)	53 (46·9%)	112 (47·7%)
1 other	0	0	1 (0·9%)	1 (0·4%)
IL28B				
CC	2 (18·2%)	30 (27·0%)	30 (26·5%)	62 (26·4%)
Non-CC	9 (81·8%)	79 (71·2%)	83 (73·5%)	171 (72·8%)
Missing	0	2 (1·8%)	0	2 (0·9%)
Cirrhosis				
No	11 (100·0%)	104 (93·7%)	106 (93·8%)	221 (94·0%)
Yes	0	7 (6·2%)	7 (6·2%)	14 (6·0%)
Hepatitis fibrosis stage				
F0–F2	11 (100%)	76 (68·5%)	76 (67·3%)	163 (69·4%)
F3	0	13 (11·7%)	15 (13·3%)	28 (11·9%)
F4	0	7 (6·3%)	7 (6·2%)	14 (6·0%)
Other*	0	15 (13·5%)	15 (13·3%)	30 (12·8%)
Baseline HCV RNA				
≤800 000 IU/mL	3 (27·3%)	50 (45·0%)	47 (41·6%)	100 (42·6%)
>800 000 IU/mL	8 (72·7%)	61 (55·0%)	66 (58·4%)	135 (57·4%)
HCV treatment history				
Naive	10 (90·9%)	91 (82·0%)	88 (77·9%)	189 (80·4%)
Experienced	1 (9·1%)	20 (18·0%)	25 (22·1%)	46 (19·6%)
Dialysis status				
On dialysis	6 (54·5%)	86 (77·5%)	87 (77·0%)	179 (76·2%)
Not on dialysis	5 (45·5%)	25 (22·5%)	26 (23·0%)	56 (23·8%)
Diabetes status				
Diabetes	6 (54·5%)	38 (34·2%)	36 (31·9%)	80 (34·0%)
No diabetes	5 (45·5%)	73 (65·8%)	77 (68·1%)	155 (66·0%)
Chronic kidney disease stage				
4	4 (36·4%)	18 (16·2%)	22 (19·5%)	44 (18·7%)
5	7 (63·6%)	93 (83·8%)	91 (80·5%)	191 (81·3%)

(Table 1 continues on next page)

An external data monitoring committee met when 50% of patients had completed treatment week 4 or discontinued before treatment week 4 and again when all patients had completed treatment week 8 or discontinued before treatment week 8. After each meeting, it was recommended the study continue as planned.

Outcomes

The primary efficacy outcome was a non-randomised comparison of sustained virological response at 12 weeks after the end of therapy (SVR12) for patients in the immediate treatment group and intensive pharmacokinetic population versus historical control patients with a reference SVR12 of 45% (appendix). Relapse was defined as detectable HCV RNA following the end of therapy, after undetectable at end of treatment. The primary safety outcome was a comparison between the randomised immediate treatment and deferred treatment groups. Tier 1 safety events were defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 500 IU/L; ALT or AST greater than three times the baseline and greater than 100 IU/L; alkaline phosphatase greater than three times the upper limit of normal. Tier 2 safety events were defined as patients with one or more adverse events, a drug-related adverse event, a serious adverse event, a serious renal adverse event, a serious and drug-related adverse event, an adverse event leading to discontinuation from treatment, and changes in renal function (increasing dialysis frequency in patients on haemodialysis at baseline, initiation of maintenance haemodialysis in patients not on haemodialysis at baseline, or an increase in chronic kidney disease stage). Tier 2 safety parameters also included change from baseline in serum creatinine, blood urea nitrogen, and eGFR in patients not receiving haemodialysis at baseline. Pharmacokinetic data are not reported here. Secondary endpoints not reported here are the SVR24 for the immediate treatment group and SVR12 for the active treatment phase of the deferred group.

Statistical analysis

According to the primary hypothesis, patients receiving grazoprevir and elbasvir in the immediate treatment group and intensive pharmacokinetic population will achieve an SVR12 rate higher than the reference rate of 45% (appendix). This value is based on a meta-analysis indicating an SVR rate of 39% in patients with stages 3–5 chronic kidney disease receiving interferon monotherapy[20] and an SVR of 40% in patients with HCV genotype 1 infection without renal disease receiving peginterferon and ribavirin.[21] The primary hypothesis was tested at a two-sided significance level (type I error) of 0·05 using an exact test for a binomial proportion. A 95% CI was also constructed for the SVR12 rate using the Clopper-Pearson method on non-randomised populations.

The modified full analysis set served as the primary population for the analysis of efficacy, and included patients assigned to the immediate treatment group or assigned to the intensive pharmacokinetic group, excluding those who failed to receive one or more doses

of drug, died, or discontinued from the study early for reasons unrelated to hepatitis C treatment. A secondary analysis including all patients who received at least one dose of study drug (full analysis set) was also done.

Target enrolment was 105 patients in each of the immediate treatment group and deferred treatment group, and 10 patients in the intensive pharmacokinetic cohort. With this sample size, there is 95% or more power to show that the SVR12 rate in patients receiving grazoprevir and elbasvir is higher than the reference SVR12 rate of 45%, at an overall one-sided 0·025 α level, if the true SVR12 rate of grazoprevir and elbasvir is about 65%. A post-hoc descriptive summary of SVR4 (at week 16) in patients receiving placebo in the deferred treatment group is also reported. SVR12 cannot be reported for the deferred treatment group because these patients began active treatment at week 16.

The full analysis set population was used for the analysis of safety data. Tier 1 event rates were compared between immediate treatment and deferred treatment groups: p values and 95% CIs were calculated using the stratified Miettinen and Nurminen method with baseline dialysis status as the strata.[22] Safety events occurring up to 14 days after completion of treatment were captured to ensure the reporting of events that might be related to persistence of study drug. The study is registered at ClinicalTrials.gov, number NCT02092350.

Role of the funding source

Merck Sharp & Dohme Corp contributed to trial management, data collection, statistical analyses, writing, and review of the report. All authors had access to the 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 data and had final responsibility for the decision to submit for publication.

Results

In total, 237 patients were enrolled and 235 received one or more doses of study drug between March 30, 2014, and Nov 28, 2014. Of these, 224 were assigned to the immediate treatment group (n=111) or deferred treatment group (n=113), and an additional 11 patients were assigned to the intensive pharmacokinetic treatment group (figure 1).

Demographic and baseline characteristics were generally balanced between the immediate treatment group, intensive pharmacokinetic, and deferred treatment group populations (table 1). Overall, 179 (76%) of 235 patients were on haemodialysis and 191 (81%) had chronic kidney disease stage 5 at baseline. 80 (34%) patients had diabetes, 96 (41%) had cardiovascular disease, 122 (52%) had HCV genotype 1a infection, 189 (80%) were HCV treatment-naive, and 14 (6%) were cirrhotic.

Of the 122 patients in the immediate treatment and intensive pharmacokinetic population, six were excluded from the modified full analysis set population for reasons other than virological failure (death, lost to follow-up, non-compliance, patient withdrawal, and withdrawal by physician due to violent behaviour; figure 1). All six patients had HCV RNA less than 15 IU/mL at time of

	Grazoprevir and elbasvir pharmacokinetic population (n=11)	Grazoprevir and elbasvir immediate treatment group (n=111)	Grazoprevir and elbasvir deferred treatment group (n=113)	Total (n=235)
(Continued from previous page)				
Previous renal transplant				
Yes	2 (18·2%)	15 (13·5%)	28 (24·8%)	45 (19·1%)
No	9 (81·8%)	96 (86·5%)	85 (75·2%)	190 (80·9%)
Primary aetiology of renal disease				
Hypertension	4 (36·4%)	46 (41·4%)	42 (37·2%)	92 (39·1%)
Type 1 diabetes	2 (18·2%)	4 (3·6%)	7 (6·2%)	13 (5·5%)
Type 2 diabetes	2 (18·2%)	19 (17·1%)	25 (22·1%)	46 (19·6%)
Congenital cystic kidney disease	0	4 (3·6%)	1 (0·9%)	5 (2·1%)
Chronic autoimmune glomerulonephritis	0	11 (9·9%)	5 (4·4%)	16 (6·8%)
Pyelonephritis	0	2 (1·8%)	0	2 (0·9%)
Urinary tract obstruction	0	4 (3·6%)	2 (1·8%)	6 (2·6%)
Cryoglobulinaemia	2 (18·2%)	2 (1·8%)	0	4 (1·7%)
Other	1 (9·1%)	19 (17·1%)	31 (27·4%)	51 (21·7%)

Data are n (%) or mean (SD). *IL28B*=interleukin 28B gene. *Other category applies to 30 patients assessed by Fibrotest but could not be considered cirrhotic.

Table 1: **Patient demographics**

	Grazoprevir and elbasvir immediate treatment group and pharmacokinetic population	Grazoprevir and elbasvir deferred treatment group
SVR12 (HCV RNA<LLoQ)		
Modified full analysis set	115/116 (99·1% [95·3–100·0])	..
Full analysis set	115/122 (94·3% [88·5–97·7])	..
On-treatment and follow-up virological response (mFAS, TND)*		
Treatment week 2	51/122 (41·8%)	0/113
Treatment week 4	94/121 (77·7%)	1/113 (0·9%)
Treatment week 12	119/119 (100%)	1/113 (0·9%)
Follow-up week 4	117/118 (99·2%)	1/113 (0·9%)
On-treatment virological response (mFAS<LLoQ)*		
Treatment week 2	81/122 (66·4%)	0/113
Treatment week 4	109/121 (90·1%)	2/113† (1·8%)
Treatment week 12	119/119 (100%)	1/113 (0·9%)
Follow-up week 4	118/118 (100%)	1/113 (0·9%)
Relapse (mFAS)	1/116 (0·9%)	..

Data are n/N (SVR% [95% CI]) or n/N (SVR%). The 95% CI was estimated based on the Clopper-Pearson method. SVR=sustained virological response. HCV=hepatitis C virus. LLoQ=lower limit of quantification (HCV RNA is detected but <15 IU/mL). mFAS=modified full analysis set. TND=HCV RNA target not detected (no calculated HCV RNA result obtained (ie, HCV RNA undetectable). *Modified full analysis set was not defined for the deferred treatment group so data are presented for the full analysis set population (all patients who received one or more doses of study drug). †In the deferred treatment group, two patients had HCV RNA <LLoQ at treatment week 4; one patient had undetectable HCV RNA and one patient had detectable but unquantifiable HCV RNA.

Table 2: **Virological response**

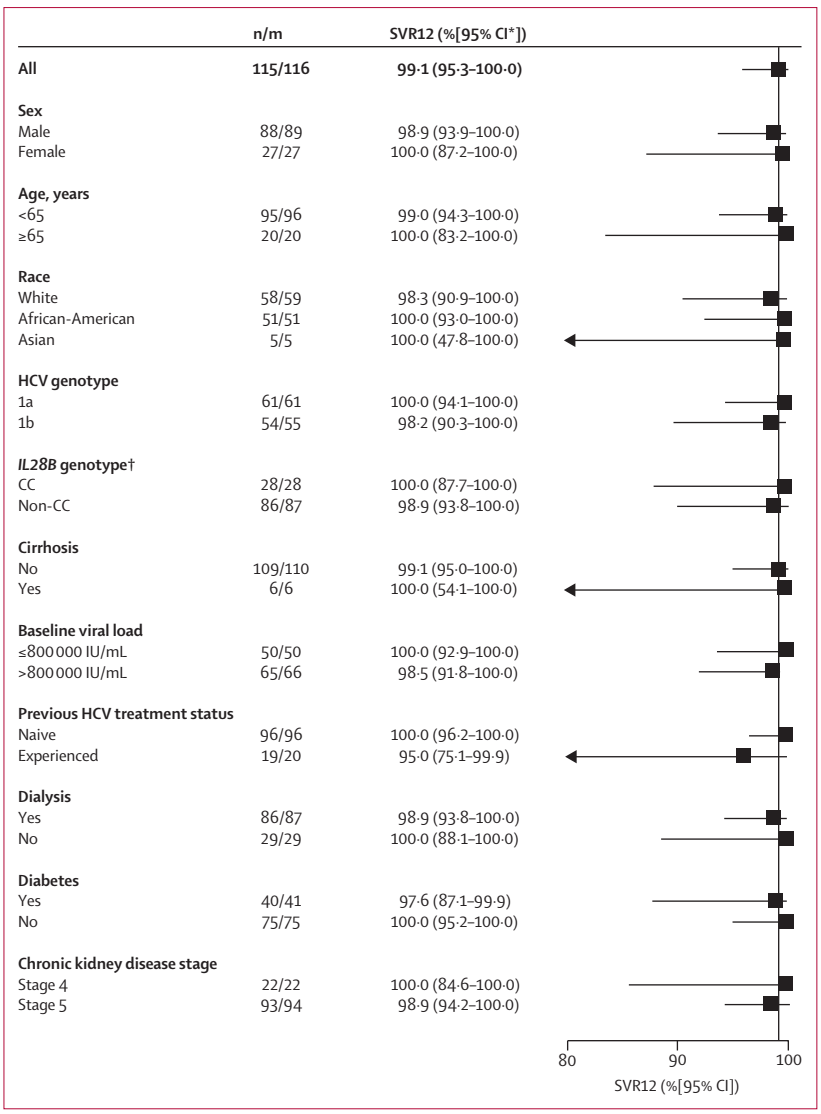

Figure 2: **SVR12 subgroup analyses (modified full analysis set)**
SVR=sustained virological response. m=number of patients included in the analysis. n=number of patients who achieved SVR12 (HCV RNA <LLoQ [<15 IU/mL]) at 12 weeks after end of treatment. *Based on the Clopper-Pearson method. †One patient was missing baseline *IL28B* genotype.

discontinuation. Of the 116 remaining patients (immediate treatment group, n=105; intensive pharmacokinetic group, n=11), 115 (99%) achieved SVR12, a rate better than the historical control rate of 45% (p<0·001). One non-cirrhotic patient with HCV genotype 1b infection and chronic kidney disease stage 5 relapsed 12 weeks after the end of treatment (table 2).

In the full analysis set population, 115 (94%) of 122 patients achieved SVR12. Of the seven patients who did not achieve SVR12, six patients discontinued the study for reasons other than virological failure and one patient relapsed.

High response rates were observed in all subgroups (figure 2), including haemodialysis and non-haemodialysis, and those with characteristics historically associated with poor response to HCV therapy. In particular, SVR12 was achieved in 51 (100%) of 51 African American patients, 86 (99%) of 87 patients with the *IL28B* non-CC genotype, 40 (98%) of 41 patients with diabetes, and all six patients with cirrhosis.

The SVR4 rate in patients receiving placebo in the deferred treatment group was one (<1%) of 113. HCV RNA was undetectable in one patient receiving placebo 4 weeks after the end of the placebo treatment period. This patient denied taking any HCV therapy outside the study, had not initiated deferred active therapy, and it was confirmed that the study drug dispensed during the treatment period was placebo.

Baseline NS3/4A or NS5A resistance-associated variants were detected in 36 (32·1%) of 112 and 17 (14·8%) of 115 patients in the immediate treatment group and intensive pharmacokinetic population with sequencing data, respectively (based on population sequencing). SVR12 was achieved in 36 (100%) of 36 and 16 (94·1%) of 17 of these patients, respectively. The patient who relapsed had an NS5A *L31M* mutation at baseline.

The frequencies of adverse events were comparable between the immediate treatment and deferred treatment groups (76% *vs* 84%; table 3), and most adverse events were of mild or moderate intensity in both treatment groups. The most common adverse events (≥10% frequency) were headache, nausea, and fatigue and were comparable in the two groups. Cardiac serious adverse events were reported in two patients in the immediate treatment group (one cardiac arrest, one myocardial infarction) and three in the deferred treatment group (two myocardial infarctions, one cardiomyopathy; appendix). Two cases of congestive heart failure occurred in the immediate treatment group within 14 days of the end of treatment; one of these, judged by the investigator to be drug-related, was reported 6 weeks after study treatment ended. A total of 16 (14%) patients in the immediate treatment group and 19 (17%) patients in the deferred treatment group reported a serious adverse event during treatment or within 14 days after the end of treatment (appendix). The serious adverse events reported were consistent with the underlying comorbidities and complications within this patient population. The only serious adverse events reported in more than one patient in the immediate treatment group were hypertension and pneumonia (n=2 each). There were no serious adverse events considered to be drug-related in the immediate treatment group.

In the deferred treatment group, serious adverse events reported in more than one patient were upper gastrointestinal haemorrhage (n=2), myocardial infarction (n=2), and aortic aneurysm (n=2). Increased lipase was the only serious drug-related adverse event in the deferred treatment group.

There were no discontinuations due to an adverse event in the immediate treatment group versus five patients in the deferred treatment group (one each

of abdominal pain, elevated ALT and AST, atrial fibrillation with myocardial infarction, increased lipase, and acute myocardial infarction). There were four deaths, none considered related to study drug, during the initial treatment plus 14 day period. One (1%) patient in the immediate treatment group died from cardiac arrest and three (3%) in the deferred treatment group died from aortic aneurysm, pneumonia, and unknown cause of death.

The frequencies and severities of liver function measures were comparable between the immediate treatment and deferred treatment groups (table 3). Rises in ALT and AST were more common among patients receiving placebo than grazoprevir and elbasvir. Rises in bilirubin and alkaline phosphatase and change in blood urea nitrogen from baseline were comparable in both treatment groups (appendix). A higher frequency of low haemoglobin (8·5–<10·0 g/dL) was noted in the immediate treatment group (n=27, 24·3%) than in the deferred treatment group (n=19, 16·8%). Erythropoietin stimulating agents were used during the treatment period by 27 (24%) patients in the immediate treatment group and 34 (30%) patients in the deferred treatment group. No adverse events suggestive of liver decompensation were reported.

The frequencies of renal system adverse events were generally comparable between treatment groups (appendix). Two patients in the immediate treatment group initiated maintenance dialysis during the study and six patients (immediate treatment group, n=4; deferred treatment group, n=2) not on dialysis at baseline had a change in chronic kidney disease stage, based on a decrease in eGFR from 15–29 mL/min per 1·73m² at baseline to less than 15 mL/min per 1·73m². Worsening of proteinuria was reported in four patients in the immediate treatment group (dialysis, n=1; no dialysis, n=3) and eight patients in the deferred treatment group (dialysis, n=4; no dialysis, n=4). There was no consistent change in mean eGFR or creatinine in either treatment group (appendix).

	Grazoprevir and elbasvir immediate treatment group (n=111)	Grazoprevir and elbasvir deferred treatment group (n=113)
Any adverse event*†	84 (75·7%)	95 (84·1%)
Headache	19 (17·1%)	19 (16·8%)
Nausea	17 (15·3%)	18 (15·9%)
Fatigue	11 (9·9%)	17 (15·0%)
Insomnia	7 (6·3%)	12 (10·6%)
Dizziness	6 (5·4%)	18 (15·9%)
Diarrhoea	6 (5·4%)	15 (13·3%)
Drug-related adverse event†	38 (34·2%)	39 (34·5%)
Serious adverse event†	16 (14·4%)	19 (16·8%)
Drug-related serious adverse event†	0	1 (0·9%)
Discontinuation due to an adverse event	0	5‡ (4·4%)
Deaths	1 (0·8%)	3 (2·7%)
Lowest haemoglobin on treatment§		
8·5–10·0 g/dL	27 (24·3%)	19 (16·8%)
<8·5 g/dL	5 (4·5%)	5 (4·4%)
Alanine aminotransferase§		
1·1–2·5 × baseline	2 (1·8%)	36 (31·9%)
>2·5 × baseline	1 (0·8%)	6 (5·3%)
>5·0 × baseline	0	1 (0·9%)
Aspartate aminotransferase§		
1·1–2·5 × baseline	4 (3·6%)	38 (33·6%)
>2·5 × baseline	0	4 (4·6%)
>5·0 × baseline	0	0
Bilirubin§		
>2·5–5·0 × baseline	1 (0·9%)	3 (2·7%)
>5·0–10·0 × baseline	0	0
>10·0 × baseline	0	0
Alkaline phosphatase§		
1·1–2·5 × baseline	42 (37·8%)	36 (31·9%)
>2·5 × baseline	0	0
>5·0 × baseline	0	0
Creatinine§ >2·5 × baseline	1 (1·2%)	0
Change in blood urea nitrogen (mg/L) from baseline at treatment week 12§¶	−1·5 (3·6)	0·9 (2·6)

Data are n (%) or mean (SE). *Incidence 10% or more in one or more treatment groups during the initial treatment period and for 14 days after the completion of treatment (all patients as treated). †Number of patients with the specific adverse event. ‡Abdominal pain, elevated alanine transaminase and aspartate transaminase, acute myocardial infarction, atrial fibrillation with myocardial infarction, and increased lipase. §Data presented for patients with more than 1·0 change from baseline. ¶Patients not on dialysis at baseline (immediate treatment group, n=25; deferred treatment group, n=24).

Table 3: **Safety and adverse events (initial treatment period and first 14 days after completion of treatment)**

Discussion

This study shows that the combination of grazoprevir and elbasvir for 12 weeks is an effective treatment regimen for patients with HCV genotype 1 infection and advanced stage 4–5 chronic kidney disease, including patients on haemodialysis and those considered difficult to treat with interferon-based antiviral therapy. Only one (<1%) of 116 patients who completed treatment with grazoprevir and elbasvir did not achieve SVR12. This non-cirrhotic patient with a NS5A *L31M* mutation at baseline relapsed after having undetectable HCV RNA at the end of treatment and at the 4-week post-treatment visit. No patient had on-treatment virological breakthrough. The short, 12-week duration of treatment with grazoprevir and elbasvir might allow waitlisting of patients for kidney transplant while on treatment for HCV infection, a practice that was previously difficult due to the 24–48 weeks of treatment needed with peginterferon and ribavirin regimens.

The deferred treatment group was used to provide a comparator for safety data collected in the immediate treatment group, given the substantial comorbidities seen in patients with stage 4–5 chronic kidney disease. The safety profiles of patients who received grazoprevir and elbasvir and placebo treatment were comparable, with similar frequencies of adverse events, serious adverse events, and renal and hepatic laboratory

abnormalities. No patient discontinued due to an adverse event in the immediate treatment group. Previous studies of first-generation HCV protease inhibitors have shown a reversible decline in eGFR during treatment;[23] however, no such changes were noted in the present study, and no differences in renal function were noted between treatment groups. The five patients with cardiac serious adverse events reflect the known high prevalence of hypertension, diabetes, and cardiovascular disease in patients with chronic kidney disease, especially those on haemodialysis.

SVR12 response rates in the present study are consistent with those reported in studies of patients with HCV genotype 1 infection and normal renal function. In the C-WORTHY study, a 12-week regimen of grazoprevir and elbasvir resulted in SVR12 in 98% of non-cirrhotic and 97% of cirrhotic patients.[11,12] High response rates with grazoprevir and elbasvir have also recently been reported in patients with HCV infection and normal renal function with previous non-response to first-generation direct-acting antiviral agents and in treatment-naive patients.[13,14] Efficacy in the present study was also generally comparable with that of a 12-week regimen of sofosbuvir plus ledipasvir that achieved an SVR12 rate of 96–99% in non-cirrhotic and 94% in cirrhotic treatment-naive patients with HCV genotype 1 infection and without chronic kidney disease stage 4–5.[24,25]

There are limitations to the present study. Patient numbers in some subgroups were small. Only 14 (6%) cirrhotic patients were included. Also, patients with decompensated liver disease and those receiving peritoneal dialysis were excluded. The results of the C-SURFER study therefore cannot be generalised to all patient subgroups. A recent study including 205 Taiwanese haemodialysis patients with genotype 1b HCV infection reported an SVR rate of 64%.[26] These data suggest that an SVR rate higher than our historical control rate of 45% is achievable in Taiwanese patients with HCV genotype 1b infection on haemodialysis and receiving peginterferon plus ribavirin for 48 weeks. Their result could be an overestimate of the treatment response since their study population was all Asian and thus a high percentage carried the *IL28B* CC genotype which is strongly predictive of SVR. Finally, the present study did not have an active comparator because of the restricted treatment options available for HCV infection in patients with advanced chronic kidney disease.

In conclusion, the results from the C-SURFER study suggest that a once-daily oral regimen of grazoprevir and elbasvir for 12 weeks has an acceptable safety profile and can achieve high rates of SVR in patients with HCV genotype 1 infection and advanced chronic kidney disease. The results of this study show that the efficacy and safety profile of this combination is consistent across many patient subgroups, including those receiving haemodialysis.

Contributors

WG, MR, JW, EB, and SW were responsible for study concept and design. BJ, DR, DRN, AB, AML, MS, HM, PM, SP, M-CL, TH, PJZ, and EZ were responsible for acquisition of data. All authors had responsibility for analysis and interpretation of data. WG, DR, B-YN, and EB did the initial drafting of the manuscript. All authors critically revised the manuscript for important intellectual content. SW did the statistical analysis. All authors did a final review and approved the manuscript.

Declaration of interests

DR has served on advisory boards for Bristol-Myers Squibb and Merck. DRN has received research support from Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, and Merck. AB has served on advisory committees for Merck and Chemocentryx. AML has served on advisory boards for Gilead and Janssen. MS has served on speakers bureau or received grants from Bristol-Myers Squibb, MSD, Gilead, AbbVie, Janssen, and Boehringer. HM has served on speakers bureau and advisory boards for Merck. PM has served on advisory boards for Merck. SP has served as a speaker for GlaxoSmithKline, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Gilead, Roche, MSD, Sanofi, Novartis, Vertex, and Abbvie; has received grants from Bristol-Myers Squibb, Gilead, Roche, and MSD; and has served as a board member for GlaxoSmithKline, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Gilead, Roche, MSD, Sanofi, Novartis, Vertex, and Abbvie. M-CL has served as a speaker for Janssen, MSD, Gilead, and Bristol-Myers Squibb, and as a consultant for Janssen and Bristol-Myers Squibb. TH has received research grants from Abbvie, Boehringer-Ingelheim, Bristol-Myers Squibb, Eisai, Gilead Sciences, Idenix, Ikaria, Janssen, La Jolla Pharmaceuticals, Merck, Mochida, NGM BioPharmaceuticals, Roche, Ocera, Sundise, Salix, Taigen, Takeda, Tobria, Vertex, and Vital Therapies; served as a speaker for Baxter, Bristol-Myers Squibb, Gilead, Janssen, and Salix; and served on advisory boards for Abbvie and Bristol-Myers Squibb. PJZ has received research grants from Merck, Abbvie, and Bristol-Myers Squibb; and served on advisory boards for Abbvie and Janssen. EZ has served on advisory boards for BMS, Abbvie, Merck, Janssen, and Gilead, and as a speaker for Bristol-Myers Squibb, Abbvie, Merck, Janssen, Roche, Novartis, and Gilead. SW, B-YN, MR, EB, JW, and WG are employees and shareholders at Merck.

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