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CLINICAL—LIVER

Efficacy of Glecaprevir and Pibrentasvir in Patients With Genotype 1 Hepatitis C Virus Infection With Treatment Failure After NS5A Inhibitor Plus Sofosbuvir Therapy

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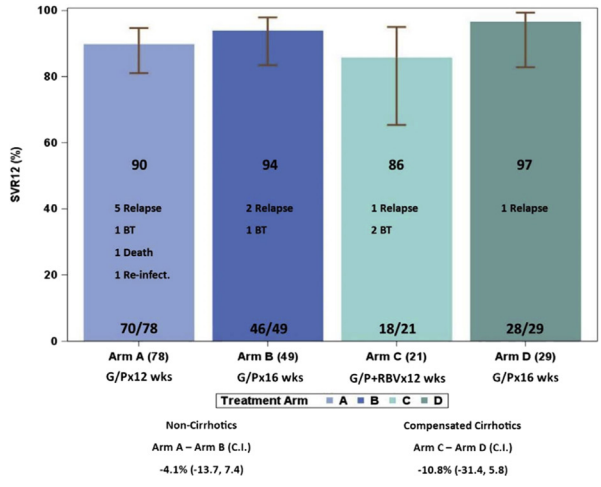

Gastroenterology

See Covering the Cover synopsis on page 1446; see editorial on page 1473.

BACKGROUND & AIMS: Treatment options are limited for patients with hepatitis C (HCV) infection with treatment failure after sofosbuvir plus an NS5A inhibitor. There are some data for the efficacy of glecaprevir/pibrentasvir (G/P) in these patients. We performed a randomized trial of the safety and efficacy of 12 and 16 weeks of G/P, with or without ribavirin, in patients with HCV genotype 1 infection with treatment failure after sofosbuvir and an NS5A inhibitor. **METHODS:** We performed a phase 3b, open-label study of patients with chronic HCV genotype 1 infection who received previous treatment with sofosbuvir plus an NS5A inhibitor. Patients without cirrhosis were randomly assigned to groups that received G/P for 12 weeks (n = 78, group A) or 16 weeks (n = 49, group B). Patients with compensated cirrhosis were randomly assigned to groups that received G/P and ribavirin for 12 weeks (n = 21, group C) or G/P for 16 weeks (n = 29, group D). The primary end point was a sustained virologic response 12 weeks after treatment. Samples collected at baseline and at time of treatment failure were sequenced for resistance-associated substitutions in NS3 and NS5A. **RESULTS:** Of the 177 patients in the 4 groups, 81% were men, 79% had HCV genotype 1a infection, and 44% were black. Proportions of patients with sustained virologic response 12 weeks after treatment in groups A, B, C, and D were 90%, 94%, 86%, and 97%, respectively. The treatment failed in 13 (7.3%)

patients with HCV genotype 1a infection, 6 (7.9%) in group A, 3 (6.1%) in group B, 3 (6.1%) in group C (6.1%), and 1 (3.4%) in group D. Most patients had baseline resistance-associated substitutions in NS5A. Treatment-emergent resistance-associated substitutions in NS3 and NS5A were observed in 9 and 10 patients with treatment failure, respectively. G/P was well tolerated. Ribavirin increased adverse events but did not increase efficacy. **CONCLUSIONS:** In a randomized study of patients with chronic HCV genotype 1 infection who received previous treatment with sofosbuvir plus an NS5A inhibitor, 16 weeks treatment with G/P produced sustained virologic response 12 weeks after treatment in >90% of patients, including those with compensated cirrhosis. ClinicalTrials.gov, Number: NCT03092375.

Keywords: Drug Resistance Variant; DAA Experienced; Protease Inhibitor; Compensated Cirrhosis.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Patients with hepatitis C virus (HCV) infection with treatment failure after sofosbuvir and NS5A inhibitor therapy have limited treatment options. Preliminary data indicate the efficacy of glecaprevir and pibrentasvir in this population, but the optimal duration of therapy for patients with compensated cirrhosis is uncertain.

NEW FINDINGS

Sixteen weeks of treatment with glecaprevir and pibrentasvir was safe and effective for patients with HCV genotype 1 infection with treatment failure after previous treatment with sofosbuvir plus an NS5A inhibitor, including those with compensated cirrhosis.

LIMITATIONS

This study did not include a group that received 16 weeks of glecaprevir and pibrentasvir with ribavirin.

IMPACT

These findings support the use of 16 weeks treatment with glecaprevir and pibrentasvir for patients with HCV genotype 1 infection, including those with compensated cirrhosis, with treatment failure after previous treatment with sofosbuvir and an NS5A inhibitor, with or without ribavirin.

The development of direct-acting antivirals (DAAs) has revolutionized hepatitis C treatment. Three classes of DAAs targeting different nonstructural (NS) proteins of hepatitis C virus (HCV)—NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors—have been approved by the US Food and Drug Administration (FDA). While several protease inhibitors and NS5A inhibitors have been approved, sofosbuvir is the only approved nucleoside polymerase inhibitor. Sofosbuvir is most often used in combination with an NS5A inhibitor, such as ledipasvir, velpatasvir, or daclatasvir, for treatment of chronic genotype (GT) 1 HCV. A combination of sofosbuvir and 1 of these NS5A inhibitors routinely achieves sustained virologic response 12 weeks after completion of treatment (SVR12) in ≥95% of DAA-naïve patients, including those with compensated cirrhosis, liver transplantation, or human immunodeficiency virus (HIV) co-infection.[1–7]

Despite the low failure rate, the absolute number of GT1 HCV patients who failed to achieve SVR after treatment with sofosbuvir plus NS5A inhibitor regimens worldwide is increasing as the result of widespread adoption of DAA treatment. Effective salvage therapy is needed for these patients, particularly those with cirrhosis in whom the failure rate is higher and the need for virologic cure more urgent. Options for salvage therapy are limited because resistance-associated substitutions (RASs) to NS5A inhibitors are selected in most if not all patients who fail to achieve SVR after treatment with regimens that included an NS5A inhibitor. Furthermore, RASs in the NS5A region tend to persist for a long time, months to years, after discontinuation of treatment, and for ledipasvir, velpatasvir, and daclatasvir, common single RASs may cause high-level resistance in vitro, as can the presence of multiple NS5A RASs.[8] RASs to sofosbuvir are rare, likely because of the reduced replication capacity.

Salvage therapy may include retreatment with sofosbuvir, an NS5A inhibitor that may be the same as that used previously, and the addition of a third DAA directed against a different target, that is, a protease inhibitor, and/or ribavirin (RBV). Indeed, clinical trials of the triple combination: sofosbuvir + velpatasvir + voxilaprevir (a second-generation protease inhibitor) for 12 weeks have shown SVR12 rates of 96%–100% in patients with chronic HCV GT1 infection who previously failed treatment with regimens containing an NS5A inhibitor with or without sofosbuvir.[9] Alternately, retreatment may include a combination of a second-generation NS5A inhibitor with more potent antiviral activity and/or different resistance profile and a second-generation protease inhibitor. One such combination—G/P, composed of glecaprevir (pangenotypic protease inhibitor) and pibrentasvir (pangenotypic NS5A inhibitor)—was approved by the FDA for GT1 HCV-infected patients who failed treatment that included an NS5A inhibitor but had no prior treatment with protease inhibitors. The approval was based on MAGELLAN-1 clinical study that included patients who failed prior NS5A inhibitor-containing regimens with documented presence of baseline NS5A RASs.[10,11] The approval of G/P without RBV for a treatment duration of 16 weeks in patients with GT1 HCV infection, who had received an NS5A inhibitor without a protease inhibitor, was based on results of the MAGELLAN-1 (part 2) study in which 17 of 18 (94%) patients who

Abbreviations used in this paper: **AE, adverse event; CI, confidence interval; DAA, direct-acting antiviral; FDA, Food and Drug Administration; G/P, glecaprevir/pibrentasvir; GT, genotype; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LLOQ, lower limit of quantification; NS, nonstructural; RAS, resistance-associated substitution; RBV, ribavirin; SAE, serious adverse event; SVR, sustained virologic response.**

Most current article

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received G/P for 16 weeks (3 of 4 with compensated cirrhosis) and 14 of 16 (88%) who received G/P for 12 weeks achieved SVR12.[11] The American Association for the Study of Liver Diseases/Infectious Diseases Society of America HCV guidelines panel recommended G/P for 16 weeks as an alternative treatment option for GT1 NS5A inhibitor experienced patients who had no prior treatment with protease inhibitors.[12] However, the European Medicines Agency did not approve G/P for patients who had prior treatment with protease inhibitor only or NS5A inhibitor only based on the paucity of data.

The objective of this study was to provide additional data to guide the use of G/P in HCV GT1, NS5A inhibitor experienced patients. We conducted an open-label, randomized, pragmatic study that included 12 and 16 weeks of G/P with or without RBV to treat chronic HCV GT1 patients who had virologic failure after treatment with a regimen containing an NS5A inhibitor and sofosbuvir with or without RBV.

Materials and Methods

This was a phase 3b, open-label, randomized, pragmatic, study conducted in 30 centers in the United States. The study was conducted in collaboration with AbbVie and within the infrastructure established by the HCV-TARGET Network, which was established in 2011 as a cohort study following real-world patients prescribed HCV therapy. The HCV-TARGET infrastructure and real-world data collection methods have been leveraged to implement a unique approach to conduct investigative new drug clinical trials using combinations of approved drugs and to fulfill post-marketing commitment studies, as well as to execute investigative new drug protocols for Large Population Expanded Access Programs and late-phase 3b trials related to HCV therapy.[13] Study management was provided by the University of Florida (led by Dr David Nelson), data analyses by the University of North Carolina (led by Dr Michael Fried), with study medications and funding support provided by AbbVie to HCV-TARGET. The study protocol was approved by the Institutional Review Boards of all participating centers and all patients provided written informed consent before enrollment. All authors had access to the study data and reviewed and approved the final manuscript.

Study Design

Eligible patients were randomized to 1 of 4 treatment arms: A: G/P12, B: G/P16-NC, C: G/P-RBV12 or D: G/P16-Cirr, stratified by HCV genotype 1 subtype (1b or non-1b) (Figure 1) to include up to 150 noncirrhotic patients and up to 75 cirrhotic patients. Patients with no cirrhosis were randomized in a 2:1 ratio to A: G/P12 and B: G/P16-NC, and patients with cirrhosis randomized in a 1:1 ratio to C: G/P-RBV12 and D: G/P16-Cirr. G/P was dosed as 3 pills once a day with food for a total daily dose of 300 mg/120 mg and RBV was dosed twice a day with food for a total daily dose of 1000 mg for body weight <75 kg or 1200 mg for body weight ≥75 kg. RBV dose was decreased or discontinued per site investigator's discretion if there were adverse events (AEs) attributed to RBV. No dose adjustment was allowed for G/P.

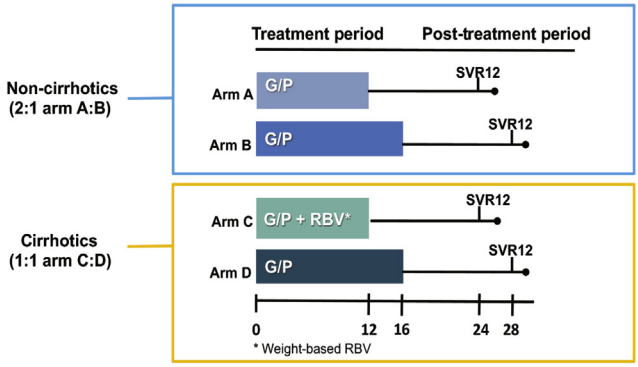

Figure 1. Clinical trial design.

Protocol Amendments

Enrollment into this study began in May 2017 before FDA approval of G/P in August 2017. In October 2017, two cirrhosis patients with HCV genotype 1a infection (of 22 who had been assigned to C: G/P-RBV12) experienced virologic breakthrough. These results prompted a Study Steering Committee review and, after discussion with the FDA, led to the temporary suspension of enrollment of patients with cirrhosis into arms C: G/P-RBV12 and D: G/P16-Cirr. In February 2018, when a third patient in arm C: G/P-RBV12 experienced rapid virologic relapse after completing therapy (day 11 post), enrollment in C: G/P-RBV12 was permanently discontinued and enrollment of cirrhosis patients into arm D: G/P16-Cirr was resumed.

Additionally, during this time, FDA's approved label for G/P and results of MAGELLAN-1 (Part 2) were reviewed by the Steering Committee. In response to the MAGELLAN-1 study showing lower SVR12 (13 of 16 [81%]) in patients who had prior treatment with the combination of an NS5A inhibitor and a protease inhibitor, the protocol was revised on October 25, 2017 to exclude patients who had prior treatment with protease inhibitors at any time. At the time of this protocol amendment, 8 patients who had failed prior treatment with an HCV protease inhibitor before re-treatment with a regimen containing an NS5A inhibitor plus sofosbuvir had been enrolled, 5 were initially randomized to arm A: G/P12 and 1 to arm C: G/P-RBV12. These patients were still receiving treatment and had their treatment extended from 12 to 16 weeks and results were analyzed along with patients in arms B: G/P16-NC and D: G/P16-Cirr, respectively. The other 2 patients with protease inhibitor experience were initially randomized to arm D: G/P16-Cirr and remained in that arm.

A second protocol amendment was executed on October 20, 2018 to include secondary efficacy analyses that compare 12 (A: G/P12 and C: G/P-RBV12 combined) and 16 weeks of G/P (B: G/P16-NC and D: G/P16-Cirr combined) and to offer retreatment with 16 weeks of G/P in combination with sofosbuvir ± RBV to patients who experienced virologic failure in this study.

Patient Population

Key inclusion criteria were adults aged ≥18 years, with chronic HCV GT1 and documented treatment failure to a regimen comprising an NS5A inhibitor (ledipasvir, velpatasvir, or daclatasvir) + sofosbuvir ± RBV taken for at least 4 weeks with no documented noncompliance. Median duration of prior treatment completed by patients with and without cirrhosis was 85 and 84 days, respectively. Key exclusion criteria

included prior concurrent treatment with protease inhibitor and NS5A inhibitor, history of hepatic decompensation (Child B/C cirrhosis), active hepatitis B virus infection (hepatitis B surface antigen or hepatitis B virus DNA–positive), clinically significant abnormalities or comorbidities or recent (within 6 months) history of drug or alcohol abuse that may make the patient unsuitable for participation per site investigator, and pregnancy or plans to become pregnant during the study. Patients with prior liver transplantation and those with HIV co-infection on stable qualifying antiretroviral therapy could be enrolled. Patients with cirrhosis were required to have imaging within 6 months of screening to rule out hepatocellular carcinoma (HCC). Patients with a history of treated HCC were not excluded from participation.

Patients were determined by the study sites to have cirrhosis if they have: (1) metavir stage 4 fibrosis on liver biopsy; (2) metavir stage 3 fibrosis on liver biopsy with any 1 of the following: platelet count $<140 \times 10^9$/L, esophageal varices on endoscopy, cirrhosis or evidence of portal hypertension on imaging, Fibrotest >0.75, vibration-controlled transient elastography >12.5 kPa, or magnetic resonance elastography compatible with stage 4 fibrosis; or (3) in the absence of liver biopsy, any 2 of the following: platelet count $<140 \times 10^9$/L, esophageal varices on endoscopy, cirrhosis or evidence of portal hypertension on imaging, Fibrotest >0.75, aspartate aminotransferase to platelet ratio index >2, vibration-controlled transient elastography >12.5 kPa, or magnetic resonance elastography compatible with stage 4 fibrosis. Patients who did not meet any of these definitions of cirrhosis were considered not to have cirrhosis.

Randomization was stratified by HCV sub-genotype (GT1b vs non-1b) and performed centrally after verification of eligibility by the Clinical Coordination Center at the University of Florida.

Assessment of Efficacy, Safety, and Virologic Resistance

The primary efficacy end point was SVR12 with preplanned comparisons between arms A: G/P12 and B: G/P16-NC (non-cirrhotics), and arms C: G/P-RBV12 and D: G/P16-Cirr (compensated cirrhotics). The secondary efficacy end points were the difference in SVR12 rates between G/P given for 12 weeks (A: G/P12 and C: G/P-RBV12 combined) and G/P given for 16 weeks (B: G/P16-NC and D: G/P16-Cirr combined) and the difference in on-treatment virologic failure and relapse between arms A: G/P12 and B: G/P16-NC, and arms C: G/P-RBV12 and D: G/P16-Cirr. Other key endpoints included the safety and tolerability of G/P, and treatment-emergent substitutions in NS3 and NS5A in patients who had virologic failure.

As a pragmatic phase 3b study, patients in this study received G/P ± RBV according to randomization and were managed per standard of care. However, protocol-required laboratory safety and efficacy monitoring was conducted, along with required drug dispensing/reconciliation. Source data were the original medical record collected as part of standard of care HCV treatment, with additional required documentation of protocol inclusion/exclusion criteria, blood sample collection for central laboratory testing, drug dispensing/reconciliation, and serious AE (SAE) reporting. Data from source documents were extracted by trained personnel at the Clinical Coordinating Center as described previously.[13]

SVR12 was defined as plasma HCV RNA below the lower limit of quantification (LLOQ) 12 weeks post treatment. Virologic failure was categorized as on-treatment failure (breakthrough) or relapse. Blood samples were collected at screening, day 1, week 4, 8, 12, or end of treatment for A: G/P12 and C: G/P-RBV12, and 16 (end of treatment for B: G/P16-NC and D: G/P16-Cirr), post-treatment weeks 4 and 12, and at the time treatment was discontinued in patients who had premature discontinuation. Safety laboratory and HCV RNA tests were performed at a central laboratory—Cenetron Diagnostics in Austin, TX. HCV RNA levels were determined using the Ampli-Prep/COBAS TaqMan HCV Quantitative Test, version 2.0 (Roche Molecular Systems Inc, Branchburg, NJ); both lower limit of detection and LLOQ were 15 IU/mL. HCV genotype and subtype were determined using Versant HCV genotype Inno LiPA assay, version 2.0 or higher (LiPA, Siemens Healthcare Diagnostics, Tarrytown, NY) and when results were indeterminate, historical GT results at local site were used.

Breakthrough was defined as confirmed HCV RNA ≥100 IU/mL after HCV RNA <LLOQ during treatment or confirmed increase in HCV RNA >1 log IU/mL from nadir at any time point during treatment. Patients with these test results were required to have the tests repeated as soon as possible and if the results were confirmed, treatment was to be stopped and patients were to be followed until 12 weeks post treatment. Relapse was defined as confirmed HCV RNA greater than or equal to LLOQ between end of treatment and post-treatment week 12 among patients who completed treatment with HCV RNA less than LLOQ at the end of treatment.

Safety was assessed by direct inquiries, clinical data abstracted from submitted medical records, and laboratory tests, and analyzed on all patients who received at least 1 dose of G/P. Treatment-emergent AEs were collected from start of G/P until 30 days after it was discontinued, while SAEs were collected through end of study. Each AE was classified using the MedDRA, version 15.1, and relation to study drug (G/P ± RBV) was determined by site investigators. Adherence to study drug was assessed by pill count in the returned bottles.

Next-generation sequencing was performed using a Primer ID approach to tag individual HCV RNA[14] at Dr Gary Wang's laboratory (University of Florida Division of Infectious Diseases and Global Medicine, Gainesville, FL). A 15% detection threshold was used to identify the presence of baseline substitutions in NS3 and NS5A regions relative to subtype-specific reference sequences. Treatment-emergent substitutions in NS3 and NS5A regions were determined by comparing sequences in samples collected at the time of virologic failure and those at baseline.

Data Collection

Redacted medical records, including standard demographic, clinical, and virologic data, were prospectively collected by a Centralized Chart Data Abstraction Team of trained coders at the Clinical Coordinating Center at the University of Florida using a novel, standardized source data abstraction that had been described previously.[13] The collected data were managed using secure, web-based Research Electronic Data Capture (REDCap) tools hosted at the University of North Carolina, Chapel Hill, and reviewed for completeness and accuracy.

Statistical Methods

Demographics, medical history, baseline and treatment-emergent laboratory values, and virologic outcomes were collected and summarized by cirrhosis status for a study population consisting of all patients who started treatment and according to the arm in which they were actually treated. Analyses of the primary and secondary end points of SVR12, on-treatment virologic failure, and relapse, were performed on the "as treated" population (modified intention-to-treat population). Differences in SVR12 rates were summarized along with 2-sided 95% Wilson's score method confidence intervals (CIs). Baseline resistance data were summarized by viral genotype subtype and treatment arm; listings of RAS at treatment failure were compiled by patient demographics and virologic outcomes. Proportions of patients achieving SVR12 among subjects with and without baseline substitutions in NS3 and NS5A regions were compared using Fisher's exact tests. Frequencies of treatment-emergent and post-treatment AEs were compiled for all patients who started treatment. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc, Cary, NC).

Results

A total of 217 patients were screened between May 1, 2017 and April 24, 2018, thirty-seven were found to be ineligible. Of the 180 eligible patients, 50 had cirrhosis and 130 did not. Figure 2 (flow diagram) displays the flow of the patients. Among the 130 patients with no cirrhosis, 44 were randomized to B: G/P16-NC and 86 to A: G/P12; 3 withdrew before dosing and 5 with protease inhibitor experience had treatment extended to 16 weeks and were analyzed with B: G/P16-NC. Of the 50 patients with cirrhosis, 28 were randomized to D: G/P16-Cirr and 22 to C: G/P-RBV12, of which 1 with protease inhibitor experience had treatment extended to 16 weeks and analyzed with D: G/P16-Cirr. Thus, the results of arms A, B, C, and D were based on 78, 49, 21, and 29 patients, respectively.

Baseline Characteristics of Patients Included in the Analyses

Baseline characteristics of the 177 patients who started treatment are shown in Table 1. A majority of the patients were men (76%–82%), median age was 62 years, and >40% were black (38%–51%). Median HCV RNA was 6.4 $\log_{10}$ IU/mL and 80% had GT1a. Nine patients had HIV co-infection, 17 had a history of HCC, and 15 had liver transplantation (none had cirrhosis post transplantation). A majority of the patients failed treatment with sofosbuvir + ledipasvir, 10 failed sofosbuvir + velpatasvir, and 1 failed sofosbuvir + daclatasvir. Median interval since NS5A inhibitor exposure was more than 1 year.

SVR12 and Treatment Failures

SVR12 was achieved in 162 of 177 (91.5%) patients overall, 70 of 78 (90%; 95% CI, 81%–95%) in A: G/P12, 46 of 49 (94%; 95% CI, 83%–98%) in B: G/P16-NC, 18 of 21 (86%; 95% CI, 65%–95%) in C: G/P-RBV12, and 28 of 29 (97%; 95% CI, 83%–99%) in D: G/P16-Cirr (Figure 3*A*). All 8 patients with additional protease inhibitor experience achieved SVR12. SVR12 was achieved in 88 of 99 (89%) patients who received 12 weeks G/P and in 74 of 78 (95%) who received G/P for 16 weeks. All 34 GT1b patients who could be assessed achieved SVR12; 1 died before SVR12 assessment. Both patients with other GT1 subtypes (non-1a, non-1b) achieved SVR12. SVR12 was achieved in a numerically lower proportion of GT1a patients, 65 of 75 (87%; 95% CI, 77%–93%) who received G/P for 12 weeks and 61 of 65 (94%; 95% CI, 85%–98%) who received G/P for 16 weeks (Figure 3*B*).

Of the 14 patients with GT1a who failed to achieve SVR12, 9 (64%) relapsed (5 in A: G/P12, 2 in B: G/P16-NC and 1 each in C: G/P-RBV12 and D: G/P16-Cirr) and 4 (36%) had breakthrough (1 in A: G/P12, 1 in B: G/P16-NC and 2 in C: G/P-RBV12). One patient in A: G/P12 died from HCC before assessment of SVR12. This patient did not have evidence of HCC at enrollment, was noted to have advanced HCC near the end of treatment, and died between the end of treatment and post-treatment week 4 visit. The last available HCV RNA result showed undetected HCV RNA. One patient, also in A: G/P12, had end-of-treatment response, but HCV RNA was detected at post-treatment week 12. This patient was initially considered to have relapsed but HCV RNA sequences post treatment did not reveal any NS3 or NS5A RAS and phylogenetic analysis indicated that baseline and post-treatment samples were in different clusters supporting our contention of re-infection. Thus, only 13 (7.3%) patients experienced treatment failures, 6 of 78 (7.7%), 3 of 49 (6.1%), 3 of 21 (14.3%), and 1 of 29 (3.4%) in A: G/P12, B: G/P16-NC, C: G/P-RBV12, and D: G/P16-Cirr, respectively.

NS3 and NS5A RASs at Baseline and at Time of Virologic Failure

Baseline polymorphisms in the NS3 protein were detected in roughly half of the patients, but only 2 had substitutions at position 155, while 69 had Q80K, which is common in GT1a (Table 2). None of the patients had substitutions at positions 156 or 168. Baseline polymorphisms in NS5A protein involving positions 24, 28, 30, 31, 58, 92, or 93, which are associated with resistance to NS5A inhibitors, were present in 76% of patients. Among GT1a-infected patients with baseline polymorphisms in these positions, 91 of 103 (88%) achieved SVR12, and among GT1a subjects who did not have baseline polymorphisms at these positions, 36 of 37 (97%) achieved SVR12. This difference was not statistically significant ($P = .18$). In addition, there was no significant difference in the SVR12 rates in any arm between GT1a-infected patients with and without those baseline polymorphisms in NS5A, nor was any individual baseline NS5A polymorphism statistically significantly associated with a reduced SVR12 rate.

Of the 4 patients with breakthrough, none had NS3 RASs (except for Q80K), but all had dual or triple-linked NS5A RASs at baseline (Table 3). At the time of virologic failure, all had NS3 RASs at positions 156 ± 155 or 168, two had acquired additional treatment-emergent NS5A RASs that were linked.

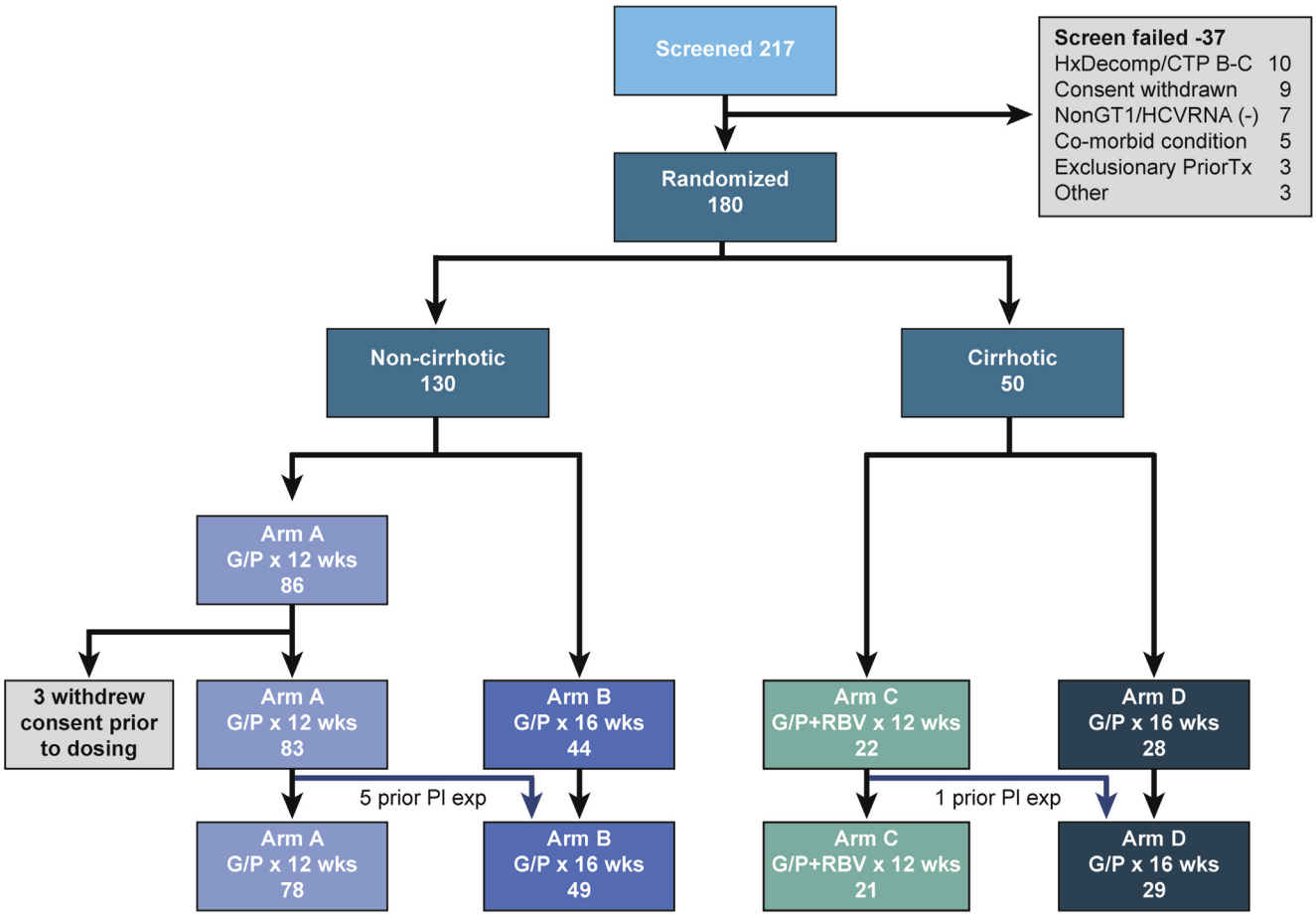

Figure 2. Flow chart showing disposition of patients.

Among the 9 patients with relapse, 1 had a R155K NS3 RAS and 8 had NS5A RASs at baseline, of which 4 had dual- or triple-linked NS5A RASs. At the time of relapse, 5 had NS3 RAS, including 1 with persistent baseline R155K, 3 had emerging RASs at position 156, and 1 at position 122 (Table 3). All 8 with baseline NS5A RASs had emerging NS5A RASs. One did not have NS5A RAS at baseline or at the time of virologic failure, but had emerging NS3 S122G at the time of virologic failure (patient 9).

Factors Associated With Virologic Failure

Virologic failure occurred in 13 of 140 (9.3%) patients with GT1a infection, 0 of 35 with GT1b, and 0 of 2 with GT non-1a, non-1b; in 4 of 50 (8%) cirrhosis and 9 of 127 (7.1%) non-cirrhosis patients; and in 9 of 99 (9.1%) patients who received 12 weeks of G/P and 4 of 78 (5.1%) who received 16 weeks of G/P. Virologic failure (all relapses) occurred in 1 of 9 (11.1%) patients who had HIV co-infection, 3 of 15 (20%) who had liver transplantation, and 3 of 17 (17.7%) who had a history of HCC (Supplementary Table 1).

Adverse Events, Serious Adverse Events, and Laboratory Abnormalities

Overall, G/P was well tolerated and none of the patients discontinued G/P because of AEs or laboratory abnormalities. Roughly two-thirds of the patients experienced at least 1 AE, the most common were fatigue, nausea, and headache. Eight patients experienced 12 SAEs, including sepsis (n = 3), myocardial infarction (n = 2), exacerbation of chronic obstructive pulmonary disease (n = 1), exacerbation of chronic renal failure (n = 1), pyelonephritis (n = 1), opioid-induced constipation (n = 1), HCC resulting in death (n = 1), acute renal injury (n = 1), and small intestinal obstruction (n = 1) (Table 4). None of the SAEs led to treatment discontinuation, but 3 patients had interruption of G/P treatment (2 days in 2 patients and 4 days in 1 patient). Two of these patients achieved SVR12 and the third, who had a 2-day interruption, relapsed. Eight of 21 patients in C: G/P-RBV12 treated with G/P plus RBV had AEs that led to RBV dose reduction (n = 7) or discontinuation (n = 1). SVR12 was achieved in 5 of 8 (62.5%) of those with (4 in arm C and 1 rolled over from arm C to arm D), and in 14 of 14 (100%) of those without RBV dose changes.

None of the patients experienced hepatic decompensation during treatment or post-treatment follow-up. One patient had new diagnosis of HCC during the study, which was advanced at the time of diagnosis, and died shortly after completion of treatment. None of the 9 patients with HIV co-infection experienced any changes in HIV control and none of the 15 liver transplant recipients experienced graft rejection.

Table 1. Baseline Characteristics of Patients

Characteristic	Noncirrhotic		Cirrhotic	
	Arm A: G/P × 12 wk (n = 78)	Arm B: G/P × 16 wk (n = 49)	Arm C: G/P = RBV × 12 wk (n = 21)	Arm D: G/P × 16 wk (n = 29)
Sex, male, n (%)	64 (82)	40 (82)	16 (76)	23 (79)
Race, black, n (%)	32 (41)	25 (51)	8 (38)	12 (41)
Age, *y*, median (range)	62 (40–77)	62 (45–75)	60 (38–70)	64 (42–81)
Body mass index, kg/m^2, median (range)	28 (19–45)	30 (19–50)	30 (19–53)	27 (23–38)
HCV genotype, n (%)				
Non-1b[a]	60 (77)	39 (80)	17 (81)	26 (90)
1b	18 (23)	10 (20)	4 (19)	3 (10)
HCV RNA, *log$_{10}$ IU/mL*, median (range)	6.4 (1.9–7.7)	6.4 (4.0–7.7)	6.3 (5.1–7.0)	6.4 (3.7–7.1)
Platelet, *K/μL*, median (range)	205 (30.0–370)	193 (100–343)	125 (46–270)	134 (63–253)
ALT, *U/L*, median (range)	41 (11–611)	38 (13–208)	59 (33–171)	70 (23–166)
Albumin, *g/dL*, median (range)	4.1 (3.2–4.7)	4.1 (2.9–4.6)	4.1 (3.2–4.5)	3.9 (3.2–4.5)
Total bilirubin, *mg/dL*, median (range)	0.6 (0.3–1.7)	0.5 (0.3–1.3)	0.8 (0.3–1.7)	0.7 (0.4–1.6)
MELD, median (range)	6.0 (6.0–11.0)	6.0 (6.0–6.0)	8.5 (7.0–11.0)	7.0 (6.0–11.0)
HIV+, n (%)	5 (6.4)	2 (4.1)	1 (4.8)	1 (3.4)
Post-liver transplantation, n (%)	5 (6.4)	10 (20.4)	0 (0)	0 (0)
History of HCC,[b] n (%)	4 (5.1)	9 (18.4)	1 (4.8)	3 (10.3)
Most recent HCV DAA treatment, n (%)				
SOF+LDV	74 (94.9)	45 (91.8)	21 (100.0)	26 (89.7)
SOF+VEL	4 (5.1)	3 (6.1)	0 (0)	3 (10.3)
SOF+DCV	0 (0)	1 (2.0)	0 (0)	0 (0)
Days since NS5Ai exposure, median (range)	505 (63–1035)	355 (39–1498)	499 (92–947)	482 (133–924)
Prior PI exposure, n (%)	0 (0)	5 (10.2)	0 (0)	3 (10.3)

ALT, alanine transaminase; DCV, daclatasvir; LDV, ledipasvir; MELD, Model for End-Stage Liver Disease; NS5Ai, NS5A inhibitor; PI, protease inhibitor; SOF, sofosbuvir; VEL, velpatasvir.
[a]Includes 2 genotype 1, non-1a, non-1b subtypes.
[b]12 of 13 noncirrhotic patients had HCC before liver transplantation and did not have cirrhosis in the allograft liver at the time of enrollment into this study.

Laboratory abnormalities grade 3 or higher were uncommon (Supplementary Table 2), the most common were glucose abnormalities in patients with known diabetes. One patient had grade 3 or higher abnormalities of aspartate aminotransferase and alkaline phosphatase secondary to new diagnosis of advanced HCC. None of the patients in C: G/P-RBV12 had grade 3 or higher abnormalities in hemoglobin.

Discussion

In this large, open-label, randomized, pragmatic phase 3b study for GT1 patients who failed prior treatment with NS5A inhibitor plus sofosbuvir, we observed high SVR12 rates with G/P when given for 16 weeks. SVR12 rates for 16-week G/P treatment were 94% among non-cirrhosis patients and 97% among cirrhosis patients. These results are consistent with the relatively small MAGELLAN-1 Part 2 data set and support FDA approval of 16-week G/P as a retreatment option for GT1 sofosbuvir plus NS5A inhibitor treatment failures.

Treatment failure rates of 8% vs 6% and relapse rates of 6% vs 4% (excluding reinfection and death before SVR12 assessment) were numerically higher among non-cirrhosis patients who received 12 vs 16 weeks G/P, but these differences were small and our study was not powered to compare the efficacy of G/P for 12 weeks vs 16 weeks. Only 4 (2%) patients had virologic breakthrough and breakthrough did not appear to be related to adherence, as adherence by pill count was 98%–100% in these 4 patients.

We found that all 36 (34 1b and 2 non-1a, non-1b) patients with GT1 non-1a infection who could be assessed achieved SVR12, while GT1a patients had lower SVR12 rates, 87% vs 94% in those who received G/P for 12 vs 16 weeks, respectively. This observation suggests that the barrier to develop NS3 and NS5A resistance with G/P is higher in GT1 non-1a infection compared to GT1a. All 13 patients with virologic failures had GT1a infection. Of these, none had baseline NS3 RAS that would decrease susceptibility to glecaprevir, and 7 developed an A156V/T/G NS3 RAS at the time of treatment failure. While the single A156T RAS in GT1a has been shown in vitro to significantly reduce the susceptibility to glecaprevir, A156V did not,[15] and A156T was the only resistance-conferring NS3 substitution that emerged in 1 of 35 patients enrolled in the glecaprevir monotherapy study.[8] Of the 13 patients with virologic failure, 12 had baseline NS5A RASs and 10 patients had additional linked NS5A RASs at the time of treatment failure. Of the 3 patients with no treatment-emergent NS5A RASs, 2 (nos. 2 and 3) presented with triple-linked NS5A RAS at

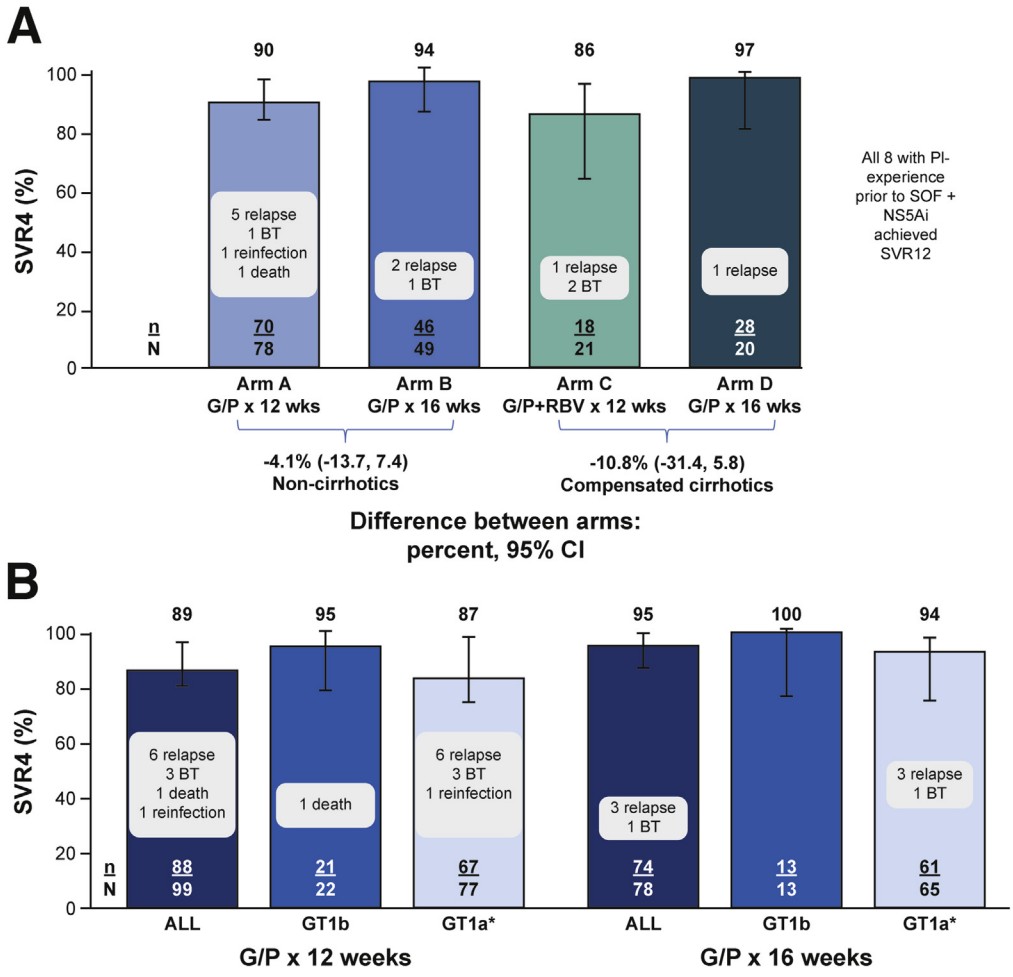

Figure 3. Efficacy of G/P by treatment arm (*A*) and by G/P duration and GT1 subtype (*B*).

Table 2. Baseline Polymorphisms in NS3 and NS5A Regions at 15% Threshold

Variable	Noncirrhotic		Cirrhotic	
	Arm A: G/P × 12 wk	Arm B: G/P × 16 wk	Arm C: G/P + RBV × 12 wk	Arm D: G/P × 16 wk
HCV genotype 1a, n	60	39	17	26
NS3,[a] n (%)				
Location: 155	1 (1.7)	0 (0.0)	0 (0.0)	1 (3.8)
Location: 80	29 (48.3)	15 (38.5)	10 (58.8)	14 (53.8)
NS5A,[b] n (%)				
Locations: 24, 28, 58, or 92	13 (21.7)	9 (23.1)	5 (29.4)	6 (23.1)
Locations: 30, 31, or 93	38 (63.3)	26 (66.7)	13 (76.5)	19 (73.1)
HCV genotype 1b, n	18	10	4	3
NS3,[a] n (%)				
Location: 155	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Location: 80	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
NS5A,[b] n (%)				
Locations: 24, 28, 58, or 92	4 (22.2)	0 (0.0)	0 (0.0)	1 (33.3)
Locations: 30, 31, or 93	16 (88.9)	9 (90.0)	3 (75.0)	2 (66.7)

[a]No substitutions observed at locations 156 and 168.
[b]Amino acid positions at which a single substitution confers resistance to at least 1 inhibitor in the NS5A class; individual patients may have had 1 or more than one substitution in NS5A.

Table 3. Resistance-Associated Substitutions at Time of Virologic Failures[a]

Patient no.	Treatment arm[b]	Age, *y*	Sex	Race	Virologic outcome	NS5A RAS baseline[c]	NS5A RAS at failure[c]	NS3 RAS baseline	NS3 RAS at failure[c]
1	A	44	M	White	Breakthrough	Q30N + Y93H	M28T + Q30N + Y93H	None	R155W + A156G
2	B	57	M	Black	Breakthrough	Q30R + L31M + H58D	Q30R + L31M + H58D	None	A156V; A156V + D168E[d]
3	C	69	M	White	Breakthrough	Q30H + L31M + Y93H	Q30H + L31M + Y93H	None	R155W + A156G
4	C	56	F	White	Breakthrough	Q30R; M28T + Q30R	M28T + Q30R + H58D	None	A156V
5	A	55	M	Black	Relapse	Q30R + L31M	Q30R + L31M + H58D	None	A156V
6	A	69	M	White	Relapse	Y93N	L31M + Y93N	None	None
7	A	53	M	White	Relapse	Q30H + Y93H	Q30N + Y93H; Q30H + L31V + Y93H	None	None
8	A	59	M	White	Relapse	Q30E	Q30E + H58D	R155K	R155K
9	A	50	M	White	Relapse	None	None	None	S122G
10	B	61	M	Black	Relapse	M28V + Q30R + L31V	M28A + Q30R + L31V	None	A156T[d]
11	B	60	M	Black	Relapse	M28T + Q30R	M28S + Q30R	None	None
12	C	54	F	Black	Relapse	L31M	L31M + P32-del	None	None
13	D	63	M	Black	Relapse	Y93N	H58D + Y93N	None	A156V[d]
14	A	48	M	Not reported	Re-infection	None	None	None	None

F, female; M, male.
[a]All had genotype 1a infection.
[b]Arms A and B: no cirrhosis, arms C and D: compensated cirrhosis.
[c]+ denotes linked variants.
[d]RAS detected at <15%.

Table 4. Summary of Adverse Events

Events	Noncirrhotic		Cirrhotic	
	Arm A: G/P × 12 wk (n = 78)	Arm B: G/P × 16 wk (n = 49)	Arm C: G/P + RBV × 12 wk (n = 21)	Arm D: G/P × 16 wk (n = 29)
Patients with any AE	56 (72)	33 (67)	17 (81)	16 (55)
Patients with any SAE[a]	5 (6)	2 (4)	1 (5)	0 (0)
DAA-related SAE	0 (0)	0 (0)	0 (0)	0 (0)
Patients with AE leading to G/P discontinuation	0 (0)	0 (0)	0 (0)	0 (0)
Patients with AE leading to RBV dose reduction/discontinuation	NA	NA	7 (33)/1 (5)	NA
Death	1 (0)	0 (0)	0 (0)	0 (0)
Common AEs (in ≥10% of patients)				
Fatigue	13 (17)	10 (20)	10 (48)	8 (28)
Headache	15 (19)	9 (18)	7 (33)	6 (21)
Nausea	7 (9)	7 (14)	2 (10)	2 (7)

NOTE. Values are n (%).
NA, Not applicable.
[a]SAEs were sepsis (n = 3), myocardial infarction (n = 2), HCC with death (n = 1), exacerbation of chronic obstructive pulmonary disease (n = 1), exacerbation of chronic renal failure (n = 1), pyelonephritis (n = 1), opioid-induced constipation (n = 1), acute renal injury (n = 1), and small intestinal obstruction (n = 1).

baseline and had treatment-emergent NS3 RAS at time of failure. The third patient (no. 9) had a treatment-emergent S122G NS3 RAS only and no NS5A RAS. Glecaprevir did not select for the NS3 S122G RAS in vitro, nor did the S122G RAS emerge in any of the patients who received 3 days of glecaprevir monotherapy.[15,16] Patient 14 had neither NS3 nor NS5A RASs at baseline and at the time of treatment failure, and phylogenetic analysis of HCV sequences suggest that he had re-infection and not treatment failure.

Despite concerns about the efficacy of G/P in patients with prior exposure to both protease inhibitors and NS5A inhibitors, all 8 patients with protease inhibitor experience before NS5A experience achieved SVR12. It should be noted that none of these patients had previously received concurrent protease inhibitor and NS5A inhibitor and all 8 received G/P for 16 weeks. Furthermore, none had baseline NS3 RAS that would reduce susceptibility to glecaprevir.

At the time this trial was designed, G/P had not yet been approved by the FDA and the optimal duration of G/P, as well as the role of RBV in patients with NS5A inhibitor experience, were unknown. Arm C: G/P-RBV12 was designed to determine whether 12 weeks of G/P plus RBV would suffice in patients with compensated cirrhosis. We found that RBV was associated with more AEs, requiring dose reduction or early discontinuation in 38% (8 of 21) patients, but not higher efficacy. While it would have been desirable to include an arm with 16 weeks of G/P plus RBV, it is doubtful that addition of RBV would further improve the SVR rates compared to what was accomplished with 16 weeks of G/P (94% in arm B and 97% in arm D).

Overall, G/P was well tolerated with no treatment-related SAEs and none of the patients discontinued G/P due to AEs or laboratory abnormalities. None of the patients, including 50 who met criteria for cirrhosis at enrollment, experienced hepatic decompensation during treatment or post-treatment follow-up. It should be noted that all patients with cirrhosis were compensated with low Model For End-Stage Liver Disease score, median score of 8 and maximum score 11. In this trial, and unlike the MAGELLAN-1 registration study, we included patients post liver transplantation, with HIV co-infection, or history of HCC, and G/P was well tolerated in these patients. Furthermore, a high proportion of patients in this study were black with similar treatment failure rates in black (6 of 77 [7.8%]) and non-black (7 of 100 [7%]) patients.

This phase 3b trial provides more robust data to support the use of G/P without RBV for 16 weeks in HCV GT1 patients who failed prior treatment of sofosbuvir and NS5A inhibitor. The number of patients with cirrhosis (n = 50) in this study was larger than in the registration study (n = 11).[10] Additionally, the 97% SVR12 rate for the 16-week G/P regimen in GT1 patients with compensated cirrhosis, who failed previous treatment with NS5A inhibitor plus sofosbuvir, is similar to the SVR12 rates obtained with 12-week treatment of the triple combination of sofosbuvir, velpatasvir, and voxilaprevir in the POLARIS-1 trial. POLARIS-1 trial enrolled patients who failed previous treatment with NS5A inhibitor with or without sofosbuvir, roughly one-third were also protease inhibitor–experienced. Of the 263 patients randomized to the initial treatment arm in POLARIS-1, overall SVR12 rate was 96%, 96% among those with GT1a and 100% for those with GT1b, 93% in patients with and 99% in those without cirrhosis.[9,17] Of the 147 patients in the deferred treatment arm who later completed treatment, SVR12 rate was 97%, and all treatment failures occurred in patients with GT1a.

This study is unique in its pragmatic design and collaboration between investigators and an industry partner, demonstrating the feasibility of efficient post-marketing

data collection in specific patient populations. There are, however, limitations to this study. Notably, the numbers of patients with sequential exposure to protease inhibitor-regimens and NS5A inhibitor regimens, post-liver transplantation, HIV co-infection, prior sofosbuvir/velpatasvir, and prior sofosbuvir/daclatasvir failures were too small to verify G/P efficacy in these subsets and to determine whether efficacy of G/P for 12 vs 16 weeks is comparable in non-cirrhosis patients. G/P drug levels were not measured and thus the impact of drug adherence on treatment failure could not be analyzed other than by pill count.

Despite the overall high SVR12 rate, 13 patients experienced treatment failure. These patients have very limited options for rescue therapy. One study found that 29 of 32 (94%) patients with G/P virologic failure achieved SVR12 with sofosbuvir/velpatasvir/voxilaprevir retreatment.[18] The MAGELLAN-3 study showed that 22 of 23 (96%) patients with G/P virologic failure achieved SVR12 with G/P plus sofosbuvir plus RBV retreatment.[19] Based on these data, patients who experienced virologic failure in this study were offered re-treatment with 16 weeks of G/P in combination with sofosbuvir ± RBV.

In summary, our study provided additional safety and efficacy data in support of the use of 16-week G/P in HCV GT1 patients (with or without compensated cirrhosis) who failed prior treatment with sofosbuvir and NS5A inhibitor. We found that baseline NS5A RASs were present in 76% of patients, yet only 7% experienced treatment failure. Further, we did not find an association between individual NS5A RAS and reduced SVR12, or a statistically significant difference in SVR12 rates between patients with and those without baseline NS5A RASs, indicating that testing for RAS before re-treatment is not helpful. The overall SVR12 rate of 95% was high and treatment failure was observed only in patients with GT1a infection and not those with GT1 non-1a infection. Our results do not apply to patients with decompensated cirrhosis in whom G/P is contraindicated.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2019.08.008.

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Conflicts of interest
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Supplementary Table 1. Baseline and Treatment Characteristics of 14 Patients With Virologic Failure

Patient no.	Sex/age, *y*	Race	Cirrhosis	HIV+	Prior liver transplantation	HCC	Actual treatment arm	Duration of treatment received, *d*	Virologic outcome
1	M/44	White	N	N	N	N	G/P × 12 wk	91	Breakthrough
2	M/57	Black	N	N	N	N	G/P × 16 wk	90	Breakthrough
3	M/69	White	Y	N	N	N	G/P+RBV x 12 wk	85	Breakthrough
4	F/54	Black	Y	N	N	N	G/P+RBV × 12 wk	67	Breakthrough
5	M/55	Black	N	N	N	N	G/P × 12 wk	84	Relapse
6	M/69	White	N	N	N	N	G/P × 12 wk	84	Relapse
7	M/53	White	N	N	N	N	G/P × 12 wk	84	Relapse
8	M/59	White	N	N	Y	Y	G/P × 12 wk	85	Relapse
9	M/50	White	N	Y	N	N	G/P × 12 wk	85	Relapse
10	M/61	Black	N	N	Y	Y	G/P × 16 wk	113	Relapse
11	M/60	Black	N	N	Y	Y	G/P × 16 wk	113	Relapse
12	F/56	White	Y	N	N	N	G/P+RBV × 12 wk	90	Relapse
13	M/63	Black	Y	N	N	N	G/P × 16 wk	118	Relapse
14	M/48	Not reported	N	N	N	N	G/P × 12 wk	113	Reinfection

NOTE. All patients had genotype 1A infection, none had prior protease inhibitor exposure.
F, female; M, male; N, no; Y, yes.

Supplementary Table 2. Laboratory Abnormalities Grade 3 or Higher[a]

Treatment-emergent laboratory abnormality	Arm A: G/P × 12 wk (n = 78)	Arm B: G/P × 16 wk (n = 49)	Arm C: G/P + RBV × 12 wk (n = 21)	Arm D: G/P × 16 wk (n = 29)
AST (>5× ULN)	1 (1)	0 (0)	0 (0)	0 (0)
Glucose (>250 mg/dL)	2 (3)	2 (4)	0 (0)	1 (4)
Alkaline phosphatase (>5× ULN)	1 (1)	0 (0)	0 (0)	0 (0)
Neutrophils (<1.0 × 10^9/L)	1 (1)	2 (4)	0 (0)	0 (0)
Lymphocytes (<0.2 × 10^3/L)	0 (0)	0 (0)	2 (10)	0 (0)
Potassium (<LLN to 3.0 mmol/L)	0 (0)	1 (2)	0 (0)	0 (0)
Phosphorous (<1 mmol/L)	0 (0)	0 (0)	0 (0)	1 (4)

NOTE. Values are n (%).
AST, aspartate aminotransferase; LLN, lower limit of normal; ULN, upper limit of normal.
[a]No patient had grade 3 or higher abnormalities in hemoglobin, alanine aminotransferase, or total bilirubin. Grade 3 or higher changes in glucose occurred in diabetic patients, hyperkalemia in a patient with renal impairment, alkaline phosphatase and AST in a patient with new diagnosis of HCC.