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Safety and Efficacy of Elbasvir/Grazoprevir in Patients With Hepatitis C Virus Infection and Compensated Cirrhosis: An Integrated Analysis

Ira M. Jacobson,[1] Eric Lawitz,[2] Paul Y. Kwo,[3] Christophe Hézode,[4] Cheng-Yuan Peng,[5] Anita Y. M. Howe,[6] Peggy Hwang,[6] Janice Wahl,[6] Michael Robertson,[6] Eliav Barr,[6] and Barbara A. Haber[6]

[1]Mount Sinai Beth Israel and Icahn School of Medicine at Mount Sinai, New York, New York; [2]Texas Liver Institute, University of Texas Health Science Center, San Antonio, Texas; [3]Indiana University School of Medicine, Indianapolis, Indiana; [4]Henri Mondor Hospital, Créteil, France; [5]China Medical University Hospital, Taichung City, Taiwan; and [6]Merck & Co., Inc, Kenilworth, New Jersey

CLINICAL LIVER

BACKGROUND & AIMS: Persons with hepatitis C virus (HCV) infection are at risk of progressive liver disease, cirrhosis, and decompensation. We analyzed the effects of the direct-acting antiviral agents elbasvir and grazoprevir in patients with HCV infection and compensated cirrhosis, combining data from 6 clinical trials. **METHODS:** We performed an integrated analysis of 402 patients with HCV genotype 1, 4, or 6 infection and Child-Pugh A compensated cirrhosis enrolled in 6 clinical trials. All patients received elbasvir/grazoprevir 50 mg/100 mg once daily, with or without ribavirin, for 12−18 weeks. The primary end point was sustained virologic response 12 weeks after completion of therapy (SVR12), defined as a level of HCV RNA <15 IU/mL. **RESULTS:** Among treatment-naïve and treatment-experienced patients receiving elbasvir/grazoprevir for 12 weeks, 97.8% (135 of 138) and 88.9% (48 of 54) achieved SVR12, respectively. Among patients receiving elbasvir/grazoprevir for 12 weeks, addition of ribavirin did not increase the proportion of treatment-naïve patients (90.3%, 28 of 31) or treatment-experienced patients who achieved an SVR12 (91.4%, 74 of 81). All (49 of 49) treatment-experienced patients receiving elbasvir/grazoprevir with ribavirin for 16 or 18 weeks, and 93.9% (46 of 49) of patients receiving elbasvir/grazoprevir without ribavirin for 16 or 18 weeks achieved SVR12. Virologic failure was higher among patients with HCV genotype 1a infections compared with patients with genotype 1b or 4 infections, particularly in patients who had not responded to previous interferon therapy. Baseline tests for resistance-associated substitutions (RASs) led to an individualized approach for selecting treatment duration and established a need for ribavirin for patients with HCV genotype 1a infection and RASs, regardless of treatment history. Among patients with HCV genotype 1a infection with and without baseline RASs in HCV nonstructural protein 5A who received elbasvir/grazoprevir for 12 weeks, 73% (8 of 11) and 98% (96 of 98) achieved SVR12, respectively. Both patients with HCV genotype 1a infection with baseline RASs who received 16 or 18 weeks of elbasvir/grazoprevir and ribavirin achieved SVR12. Grade 3 or 4 increases in levels of alanine aminotransferase and aspartate aminotransferase, which did not cause symptoms, were reported in 2.3% (6 of 264) of patients receiving elbasvir/grazoprevir. Serious adverse events were reported in 3% (8 of 264) patients and no patient had a decompensation-related event. **CONCLUSIONS:** In an analysis of data from 6 clinical trials, rates of SVR12 ranged from 89% to 100% in patients with HCV genotype 1, 4, or 6 infections and compensated cirrhosis treated with elbasvir/grazoprevir, with or without ribavirin. Addition of ribavirin to a 12-week regimen of elbasvir/grazoprevir had little effect on the proportion of treatment-naïve or treatment-experienced patients who achieved an SVR12. However, virologic failure did not occur in any treatment-experienced patients when the duration of elbasvir/grazoprevir and ribavirin therapy was extended to 16 or 18 weeks. Baseline analysis of RASs (or in the absence of this test, a history of nonresponse to interferon) can be used to determine treatment duration and the need for ribavirin in patients with HCV genotype 1a infection. Clinicaltrials.gov ID: NCT02092350, NCT02105662, NCT02105467, NCT02105701, NCT01717326, and NCT02105454.

Keywords: NS5A; Virus Mutation; Fibrosis; ALT.

People infected with the hepatitis C virus (HCV) are at risk of progressive liver disease, which ultimately leads to cirrhosis and sequelae such as decompensation and hepatocellular carcinoma. The estimated prevalence of cirrhosis 20 years after initial infection is 16%.[1] In patients with cirrhosis (METAVIR F4 on biopsy), the estimated risk of progression to hepatic decompensation events or hepatocellular carcinoma is 37.2% at 5 years.[2] Estimates suggest that a period of 40 years will elapse between the peak incidence of HCV infection (in the 1980s) and the peak prevalence of HCV-related cirrhosis, implying that HCV-related cirrhosis will peak during the 2020s at an estimated 1.04 million cases.[3]

Abbreviations used in this paper: **AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; EBR, elbasvir; GT, genotype; GZR, grazoprevir; HCV, hepatitis C virus; PR, peginterferon/ribavirin; RAS, resistance-associated substitution; RBV, ribavirin; SVR12, sustained virologic response at 12 weeks.**

Most current article

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EDITOR'S NOTES

BACKGROUND AND CONTEXT

Treatment of HCV-infected cirrhotic patients with all-oral regimens can require the addition of ribavirin and/or extension of therapy beyond 12 weeks, particularly in those with GT1a infection and/or interferon experience.

NEW FINDINGS

SVR12 was achieved by 98% and 89% of treatment-naïve and -experienced compensated cirrhotic patients receiving elbasvir/grazoprevir for 12 weeks. Most virologic failure were GT1a-infected with baseline RASs. All treatment-experienced patients receiving 16 weeks of elbasvir/grazoprevir with ribavirin achieved SVR12.

LIMITATIONS

This was a retrospective integrated analysis of HCV-infected patients with compensated cirrhosis encompassing significant heterogeneity in baseline demographic and clinical features.

IMPACT

Elbasvir/grazoprevir was highly effective and safe in patients with HCV GT1/4 infection with compensated cirrhosis. Most patients achieved SVR with elbasvir/grazoprevir for 12 weeks. GT1a patients with RASs require extension of therapy to 16 weeks and addition of ribavirin.

Recent studies have shown that treating HCV reduces all-cause mortality, even in patients with cirrhosis[4,5]; however, patients with HCV infection and cirrhosis have long been regarded as difficult to treat, typified by low response rates and poor tolerability to interferon-based regimens.[6,7] Although treatments have improved, with all-oral regimens now the accepted standard of care, many patients with cirrhosis still require intensified treatment regimens.[8,9] Currently approved all-oral direct-acting antiviral regimens for treatment-naïve and treatment-experienced compensated cirrhotic patients with HCV genotype (GT)1 infection include 12-week regimens of sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, and elbasvir/grazoprevir (EBR/GZR; in the United States for all GT1b patients and GT1a patients without baseline NS5A resistance variants, with 16 weeks of EBR/GZR+ribavirin [RBV] for GT1a-infected patients with baseline resistance-associated substitutions [RASs]). Cirrhotic patients who are not suitable for these regimens, such as those who have failed a prior treatment regimen that included a direct-acting antiviral agent, might need alternative regimens that require treatment durations of 24 weeks or addition of RBV to attain high rates of sustained virologic response at 12 weeks (SVR12).[8,9]

The combination of EBR, an HCV NS5A inhibitor, and GZR, an NS3/4A protease inhibitor, has been shown to be a safe and highly effective treatment for chronic HCV infection in phase 2/3 clinical trials.[10–15] EBR/GZR is administered once daily, without regard to food intake, and in vitro has been shown to retain activity against many clinically relevant RASs.[16–18] Phase 3 studies of EBR/GZR in patients with HCV GT1, 4, or 6 infection have evaluated a diverse population of patients, including treatment-naïve[11] and treatment-experienced[13,19] patients, and those with human immunodeficiency virus (HIV) co-infection[10] or stage 4/5 chronic kidney disease.[12] In these populations, EBR/GZR has a generally favorable tolerability profile, with very few serious adverse events (AEs) or discontinuations due to AEs seen in phase 2/3 studies to date.[20] Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations reported with high-dose GZR (400−800 mg/d) in a phase 2 study[21] are uncommon in patients who receive lower doses of GZR (100 mg/d), occurring in <1% of patients and generally resolving with continued therapy or scheduled end of therapy.[20]

Patients with compensated, Child-Pugh A cirrhosis were allowed entry into the EBR/GZR phase 2/3 clinical trial program, and we have therefore conducted an integrated analysis of 402 patients with HCV GT1, 4, or 6 infection and compensated cirrhosis who received EBR/GZR alone or with RBV in these studies.

Methods

This is an integrated analysis of data from 6 international phase 2/3 clinical trials. All studies were carried out in accordance with the Declaration of Helsinki, current guidelines on Good Clinical Practices, and local ethical and legal requirements. All patients provided voluntary written informed consent before trial entry. The detailed methodology and primary outcomes from these studies have been published previously (Phase 3: C-SURFER[12] [Protocol PN052]; C-EDGE CO-INFECTION[10] [Protocol PN061]; C-EDGE TREATMENT-NAÏVE[11] [Protocol PN060]; C-EDGE TREATMENT EXPERIENCED [Protocol PN068][19]; Phase 2: C-WORTHY[14,15] [Protocol PN035]; and C-SALVAGE[13,22] [Protocol PN048]). All co-authors had access to the study data and reviewed and approved the final manuscript.

Patients

Patients enrolled in these studies were aged older than 18 years and had chronic HCV GT 1, 4, or 6 infection and HCV RNA at baseline >10,000 IU/mL. They were either treatment-naïve or had previously failed HCV therapy with peginterferon/RBV (PR) with or without a first-generation protease inhibitor (boceprevir, telaprevir, or simeprevir).[13] Treatment-experienced patients had prior response categorized as prior relapse (undetectable HCV RNA at end of treatment followed by detectable HCV RNA during follow-up) or prior on-treatment failure (prior partial or null response, protocol-defined as >2 log decline in HCV RNA but quantifiable or <2 log decline at treatment week 12, respectively [patients with prior virologic breakthrough on PR were not enrolled]). These studies collectively enrolled a diverse group of patients with HCV infection. Patients enrolled in the C-SURFER study had stage 4 or 5 chronic kidney disease with estimated glomerular filtration rate 15−29 mL/min per 1.73 m^2 and <15 mL/min per 1.73 m^2, respectively.[12] Patients enrolled in C-EDGE CO-INFECTION had HIV co-infection and were either naïve to antiretroviral therapy or were receiving stable antiretroviral therapy with tenofovir or abacavir, and either emtricitabine or lamivudine plus raltegravir, dolutegravir, or rilpivirine.[10] Patients enrolled

from C-SALVAGE had previously failed ≥4 weeks of therapy with PR plus boceprevir, telaprevir, or simeprevir.[13,22] In all studies, patients with decompensated liver disease (presence or history of ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy, or other signs of advanced liver disease) or evidence of hepatocellular carcinoma were excluded.

To be eligible for inclusion in the present integrated analysis, patients were required to have had Child-Pugh A compensated cirrhosis based on at least 1 of the following criteria: liver biopsy consistent with METAVIR F4 at any time before entry into the study; FibroScan >12.5 kPa within 12 months of study entry; or AST-to-platelet ratio index (APRI) >2.0 and FibroTest >0.75 within 12 months of study entry. Laboratory exclusion criteria differed between the original treatment studies due to the different patient populations enrolled; however, all patients met the inclusion criteria for their initial treatment study, were considered cirrhotic according to biopsy, FibroScan or FibroTest + APRI criteria, and all had either 6 or 7 Child-Turcotte-Pugh points.

Treatment

All patients received EBR/GZR 50 mg/100 mg once daily with or without RBV (800−1400 mg/d based on body weight), administered either as a co-formulated fixed-dose combination tablet or as separate entities. Treatment-naïve patients were treated for 12 weeks and treatment-experienced patients were treated for 12 or 16/18 weeks.

Outcomes

The primary end point of all 6 studies was SVR12, defined as HCV RNA <15 IU/mL. Plasma HCV RNA levels were measured using the COBAS AmpliPrep/COBAS TaqMan HCV test (version 2.0, Roche Molecular Diagnostics, Branchburg, NJ) with a lower limit of quantitation of 15 IU/mL. In all studies, relapse was defined as detectable HCV RNA after the end of therapy, after undetectable HCV RNA at the end of therapy. Virologic rebound was defined as HCV RNA >1 log increase from nadir while on treatment, and virologic breakthrough was defined as HCV RNA above the lower limit of quantitation after previously being below the lower limit of quantitation. Safety and tolerability were assessed through the monitoring of AEs, vital signs, and laboratory assessments.

Population sequencing was performed at baseline and at the time of virologic failure. The specific NS5A loci evaluated were any polymorphism at amino acid positions 28, 30, 31, and 93 based on data from the EBR/GZR phase 2/3 clinical program, which indicate that only polymorphisms at these 4 positions impact the efficacy of EBR/GZR.[23] HCV RNA was reverse-transcribed and amplified using reverse transcription polymerase chain reaction followed by population sequencing of the NS5A gene on an ABI Sequencer from samples with RNA levels of ≥1000 IU/mL. The limit of minority variant detection in the population was approximately 20% of the viral population.

Analyses

This is an exploratory retrospective analysis of data from phase 2/3 clinical trials. Efficacy analyses are based on the full analysis set population, which includes all randomized patients who received 1 or more doses of drug. The resistance analysis population included all patients with baseline sequencing available and a treatment outcome of either SVR12 or virologic failure.

The safety analysis was based on the all patients as treated population, which includes all patients who received more than 1 dose of study medication. The integrated safety population included an additional 62 treatment-naïve patients with Child-Pugh A cirrhosis who were treated for 18 weeks with EBR/GZR with or without RBV in the C-WORTHY studies[14,15] who were not included in the efficacy analyses. These studies showed that an 18-week treatment regimen with or without RBV provided no incremental benefit in terms of improved efficacy for treatment-naïve patients compared with 12 weeks of therapy. We therefore elected not to include an efficacy analysis of treatment-naïve patients treated for 18 weeks.

Results

Patient Characteristics

A total of 402 patients with Child-Pugh A compensated cirrhosis were included in the present analysis (Table 1). Most patients were white (n = 324 [81%]) with HCV GT1a (n = 219 [54%]) or 1b/other 1 (n = 157 [39%]) infection (Table 2). Overall, 42% were treatment-naïve and 58% were treatment-experienced (including 34 patients who had failed treatment on prior PR plus a first-generation protease inhibitor), and 10% of patients (n = 40) had HIV co-infection. Seven patients with stage 4/5 chronic kidney disease from the C-SURFER study were also included. Cirrhosis was diagnosed by biopsy in 29% of patients, by FibroScan in 64% of patients, and by APRI + FibroTest in 7%. Of the 258 patients diagnosed by FibroScan, 36% had FibroScan values >25.0 kPa. Albumin was <3.5 g/dL in 6% of patients and platelet count was <100,000 cells/μL in 25% of patients.

Four patients discontinued treatment early due to reasons unrelated to study medication: 2 patients died during treatment (1 treatment-naïve patient due to coronary artery disease and 1 treatment-experienced patient due to a motor vehicle accident), and 2 treatment-experienced patients discontinued treatment (1 due to noncompliance and 1 due to lymphoma). No patients were lost-to-follow-up.

Virologic Response

In this integrated population of treatment-naïve cirrhotic patients with HCV GT1 or 4 infection, SVR12 was achieved by 97.8% (135 of 138) of patients receiving EBR/GZR for 12 weeks and 90.3% (28 of 31) of those receiving EBR/GZR+RBV for 12 weeks (no treatment-naïve patients with HCV GT6 infection were included in this analysis) (Figure 1). Of the 138 patients not given RBV, 3 failed to achieve SVR12: 1 patient died after completing treatment (coronary artery disease unrelated to study drug) and there were 2 virologic failures (breakthrough, n = 1; relapse, n = 1). The lower response in the EBR/GZR+RBV arm was likely due to the small sample size; evaluable patients came from one treatment arm in the phase 2 C-WORTHY study. Three patients in the RBV-containing treatment arm experienced virologic failure (2 patients with relapse and 1 on-treatment breakthrough).

Table 1. Original Treatment Studies

Treatment group/protocol number	Study	Regimen	Patients included, n
Treatment-naïve patients			
5172-035	C-WORTHY	EBR/GZR for 12 wk	29
5172-052	C-SURFER	EBR/GZR for 12 wk	4
5172-060	C-EDGE TN	EBR/GZR for 12 wk	70
5172-061	C-EDGE HIV	EBR/GZR for 12 wk	35
5172-035	C-WORTHY	EBR/GZR+RBV for 12 wk	31
Total			169
Treatment-experienced patients			
5172-035	C-WORTHY	EBR/GZR for 12 wk	14
5172-052	C-SURFER	EBR/GZR for 12 wk	3
5172-068	C-EDGE TE	EBR/GZR for 12 wk	37
5172-035	C-WORTHY	EBR/GZR+RBV for 12 wk	12
5172-048	C-SALVAGE	EBR/GZR+RBV for 12 wk	34
5172-068	C-EDGE TE	EBR/GZR+RBV for 12 wk	35
5172-035	C-WORTHY	EBR/GZR for 16/18 wk	11
5172-068	C-EDGE TE	EBR/GZR for 16/18 wk	38
5172-035	C-WORTHY	EBR/GZR+RBV for 16/18 wk	12
5172-068	C-EDGE TE	EBR/GZR+RBV for 16/18 wk	37
Total			233

In treatment-experienced cirrhotic patients receiving EBR/GZR with or without RBV for 12 weeks, or EBR/GZR with or without RBV for 16/18 weeks, SVR rates were 91.4% (74 of 81), 88.9% (48 of 54), 100% (49 of 49), and 93.9% (46 of 49), respectively (Figure 1). In the 12-week arms, 3 treatment-experienced patients discontinued treatment for reasons unrelated to treatment (motor vehicle accident, noncompliance, lymphoma; no RBV, n = 2; RBV, n = 1). Of the 98 treatment-experienced patients included in the 16-/18-week analysis population, 49 received RBV (of which 37 were treated for 16 weeks and 12 for 18 weeks) and 49 did not (of which 38 were treated for 16 weeks and 11 for 18 weeks). All cirrhotic patients receiving EBR/GZR+RBV for 16/18 weeks achieved SVR (49 of 49, 100%, including 37 of 37 treated for 16 weeks) compared with 93.9% (46 of 49) of patients in the no RBV group treated. Complete details of all 18 patients with virologic failure included in this integrated analysis (GT1a infection, n =11; GT1b, n = 2; GT1-other, n = 1; GT4/6, n = 3) are provided in Supplementary Table 1.

Predictors of Response

Subgroup analysis showed high rates of SVR12 across all patient subgroups, regardless of treatment history or baseline demographic characteristics (Table 3). Of particular note, SVR12 was high regardless of severity of cirrhosis, as indicated by the generally high response rates in patients with albumin <3.5 g/dL, platelets $<100 \times 10^3$ cells/μL, and FibroScan values >25.0 kPa, although SVR12 tended to be slightly lower among the treatment-experienced patients in these subgroups who were treated for 12 weeks. There were no patients in this analysis with albumin <3.0 g/dL at baseline. Sixteen treatment-naïve patients and 20 treatment-experienced patients had platelets $<75 \times 10^3$ cells/μL; SVR was achieved by 15 of the treatment-naïve and 18 of the treatment-experienced patients, respectively.

In patients with GT1b infection, SVR was 100% among both treatment-naïve and -experienced patients receiving EBR/GZR without RBV for 12 weeks (56 of 56 in treatment-naïve patients and 13 of 13 in treatment-experienced patients). In patients with GT4 infection, SVR12 was 100% (6 of 6) in treatment-naïve patients receiving EBR/GZR without RBV for 12 weeks but was lower in treatment-experienced patients treated for 12 weeks (4 of 6 [67%]) or for 16 of 18 weeks without RBV (1 of 2 [50%]). All 4 treatment-experienced patients with GT4 infection who received EBR/GZR+RBV for 16 of 18 weeks achieved SVR12. Among treatment-naïve patients receiving EBR/GZR for 12 weeks (no RBV), SVR rates were 100% (33 of 33) and 97.1% (102 of 105) in those with baseline viral load ≤800,000 IU/mL and >800,000 IU/mL, respectively. Among treatment-experienced patients receiving EBR/GZR (no RBV) for 12 weeks, SVR rates were 92.9% (13 of 14) and 87.5% (35 of 40) in those with baseline viral load ≤800,000 IU/mL and >800,000 IU/mL, respectively. All 36 treatment-experienced patients receiving EBR/GZR+RBV for 16 weeks with baseline viral load >800,000 IU/mL achieved SVR (100%, 36 of 36).

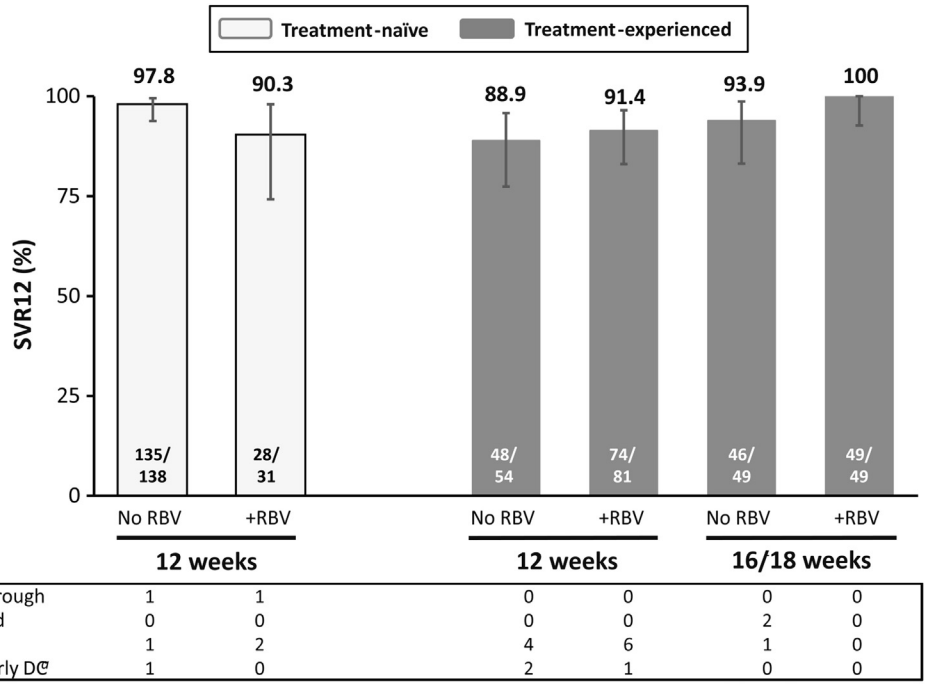
HCV GT1a-infected patients were most likely to have virologic failure. Among patients with GT1a infection receiving EBR/GZR without RBV for 12 weeks, SVR12 was 96.1% (73 of 76; 95% confidence interval [CI], 88.9%−99.2%) and 88.6% (31 of 35; 95% CI, 73.2%−96.8%) in treatment-naïve and treatment-experienced cirrhotic patients, respectively (Table 3). A total of 3 treatment-naïve and 4 treatment-experienced patients with GT1a-infection failed to attain SVR: 2 patients discontinued treatment for reasons unrelated to study medication (1 treatment-naïve patient died after completing treatment and 1 treatment-experienced patient was discontinued due to

Table 2. Patient Demographic Characteristics

Characteristic	Treatment-naïve (n = 169)	Treatment-experienced (n = 233)
Male, n (%)	113 (66.9)	151 (64.8)
Age, *y*, mean (range)	55.8 (32–82)	56.6 (19–76)
Race, n (%)		
White	131 (77.5)	193 (82.8)
Black	16 (9.5)	21 (9.0)
Asian	17 (10.1)	19 (8.2)
Other	5 (3.0)	0 (0)
Hispanic or Latino, n (%)	11 (6.5)	21 (9.0)
BMI, $\geq$*30 kg/m*^{2}, n (%)	34 (20.1)	68 (29.2)
HCV genotype, n (%)		
1a	96 (56.8)	123 (52.8)
1b or other 1	67 (40.9)	90 (38.7)
4	6 (3.6)	17 (7.3)
6	0	3 (1.3)
Baseline viral load, n (%)		
$\leq$800,000 IU/mL	37 (21.9)	49 (21.0)
>800,000 IU/mL	132 (78.1)	184 (79.0)
HIV co-infection, n (%)	35 (20.7)	5 (2.1)
Chronic kidney disease stage 4/5, n (%)	4 (2.4)	3 (1.3)
Prior treatment response, n (%)		
Prior null	NA	120 (51.5)
Prior on-treatment failure excluding null	NA	54 (23.1)
Prior relapse	NA	59 (25.3)
Direct-acting antiviral agent	NA	34 (14.6)
Platelet count, n (%)		
$<100 \times 10^3/\mu$L	40 (23.7)	61 (26.2)
$<75 \times 10^3/\mu$L	16 (9.5)	20 (8.6)
ALT, *IU/L*, mean (SD)	102.4 (69.5)	98.9 (61.3)
Albumin level, n (%)		
<3.5 g/dL	9 (5.3)	16 (6.9)
<3 g/dL	0 (0)	1 (0.4)
Cirrhosis determination method, n (%)		
Biopsy	43 (25.4)	72 (30.9)
AST-to-platelet ratio index+FibroTest	12 (7.1)	17 (7.3)
FibroScan	114 (67.5)	144 (61.8)
12.6–15.0 kPa	33 (28.9)	35 (24.3)
15.1–20.0 kPa	40 (35.1)	33 (22.9)
20.1–25.0 kPa	10 (8.8)	14 (9.7)
>25.0 kPa	31 (27.2)	62 (43.0)
IL28B genotype, n (%)		
CC	63 (37.3)	32 (13.7)
CT/TT	106 (62.7)	200 (85.8)

noncompliance; both had no NS5A RASs at baseline) and the remaining 5 patients relapsed. Among the 35 treatment-experienced GT1a patients receiving EBR/GZR for 12 weeks, there were 3 virologic failures, all of whom had prior null or partial response to PR. All 3 patients with virologic failure had treatment-emergent NS5A RASs (Supplementary Table 1: patients 151237, 680432, and 680801). A full description of the treatment outcomes in patients with HCV GT1a infection, including SVR according to baseline viral load, is presented in Supplementary Table 2.

Further analysis of patients with GT1a infection receiving EBR/GZR for 12 weeks, based on the presence of baseline NS5A RASs, was conducted in the resistance analysis population, which included patients with available baseline RAS analysis and an outcome of either SVR or virologic failure (Table 4). The 2 GT1a-infected patients receiving EBR/GZR for 12 weeks who discontinued treatment for reasons unrelated to study medication were excluded from the resistance analysis population. Among patients with GT1a infection receiving EBR/GZR for 12 weeks, NS5A RASs were detected in 10.7% (8 of 75) of treatment-naïve and 8.8% (3 of 34) of treatment-experienced patients (Table 4). In treatment-naïve GT1a patients receiving EBR/GZR for 12 weeks, SVR12 was achieved by 66 of 67 (98.5%) patients with no NS5A RASs at baseline and 7 of 8 (87.5%) patients with baseline NS5A RASs. Among treatment-experienced GT1a-infected patients receiving EBR/GZR for 12 weeks, SVR12 was achieved by 30 of 31 (96.8%) patients with no NS5A RASs at baseline and 1 of 3 (33.3%) patients with baseline NS5A RASs (34 of 35 treatment-experienced patients with GT1a infection were evaluable for resistance analysis, while 1 patient had



Breakthrough	1	1	0	0	0	0
Rebound	0	0	0	0	2	0
Relapse	1	2	4	6	1	0
LTFU/early DC[a]	1	0	2	1	0	0

Figure 1. SVR12 (full analysis set). [a]Includes all patients who received at least 1 dose of study medication). DC, discontinuation; LTFU, lost-to-follow up.

unavailable sequence data). NS5A RASs were detected in 6.9% (2 of 29) of treatment-experienced patients receiving EBR/GZR+RBV for 16/18 weeks. All 29 treatment-experienced patients receiving EBR/GZR+RBV for 16 weeks, including both those with NS5A RASs at baseline, achieved SVR12.

Safety and Tolerability

Frequently observed AEs, such as fatigue, headache, nausea, and insomnia, were more common in patients receiving RBV compared with those not receiving RBV (Table 5). Drug-related AEs were also higher among patients receiving RBV (42% vs 73.1%). There was one drug-related serious AE in a 56-year-old cirrhotic white female who reported severe abdominal pain without associated symptoms on day 30 of treatment with EBR/GZR. Physical examination revealed Murphy's sign with no gallstones. Medication was continued and causality for the pain was assessed as possibly related to study medication; the symptoms resolved and did not recur while continuing study medication.

Six patients discontinued treatment due to an AE: 2 were receiving EBR/GZR (lymphoma, ALT elevation, which met protocol-defined stopping rule) and 4 were receiving EBR/GZR+RBV (uterine bleeding, tachycardia, depression, portal vein thrombosis/colitis). There were 3 deaths (lymphoma, motor vehicle accident, coronary artery disease), all unrelated to study medication. No patient showed signs of liver decompensation during treatment or follow-up, as evidenced by presence of ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy, or severe coagulopathy (international normalized ratio >2.5).

Among patients receiving EBR/GZR without RBV, there were 5 patients with grade 3 (5.1−10.0× upper limit of normal) and 1 patient with grade 4 (>10× upper limit of normal) ALT/AST elevations (Table 6 and Supplementary Table 1). None of the patients were symptomatic, and the 4 of the 5 patients with grade 3 ALT elevations had peak values occurring at treatment week 6 or later, ranging from 204 to 369 IU/L. One patient had a peak ALT of 211 IU/L at treatment week 1. All 6 patients with ALT/AST elevations achieved SVR12. The patient with a grade 4 ALT and AST elevation was a 52-year-old cirrhotic Asian female on a 12-week treatment course. This patient's eosinophils increased from 0.8% at baseline to 8.8% at treatment week 10, and her international normalized ratio increased from baseline levels of 1.1 to 1.3 at treatment week 10. This was concurrent with a grade 4 ALT/AST elevation (668/459 IU/L) which resulted in the discontinuation of study medication. Her ALT/AST returned to within normal limits (20 IU/L) at follow-up week 4 and she achieved SVR12. This was a protocol-mandated discontinuation based on a protocol-specified stopping rule, and the patient remained otherwise asymptomatic. No patient with elevated ALT/AST had concurrent increased total bilirubin, and no patient had drug-induced liver injury or met criteria for Hy's Law. Regarding other laboratory tests, a decrease in hemoglobin levels was predominantly observed in patients receiving RBV.

Discussion

This integrated analysis presents data from >400 HCV-infected patients with compensated cirrhosis treated with EBR/GZR and diverse patient characteristics, including treatment-naive, interferon-experienced, HIV co-infected, and advanced kidney disease. Consistent with a more advanced Child-Pugh A population, 36% of patients had a

Table 3. Sustained Virologic Response 12 Weeks After Completion of Therapy Subgroup Analyses (Full Analysis Set[a])

	Treatment-naïve		Treatment-experienced			
Variable	12 wk no RBV	12 wk +RBV	12 wk no RBV	12 wk +RBV	16/18 wk no RBV	16/18 wk +RBV
Overall	135/138 (97.8)	28/31 (90.3)	48/54 (88.9)	74/81 (91.4)	46/49 (93.9)	49/49 (100.0)
16 wk of treatment			—	—	35/38 (92.1)	37/37 (100.0)
18 wk of treatment			—	—	11/11 (100.0)	12/12 (100.0)
Race						
White	98/101 (97.0)	28/30 (93.3)	30/35 (85.7)	69/76 (90.8)	39/41 (95.1)	41/41 (100.0)
Black	15/15 (100.0)	0/1 (0.0)	13/14 (92.9)	3/3 (100.0)	2/2 (100.0)	2/2 (100.0)
Asian	17/17 (100.0)	—	5/5 (100.0)	2/2 (100.0)	5/6 (83.3)	6/6 (100.0)
Other	5/5 (100.0)	—	—	—	—	—
HCV genotype						
1a	73/76 (96.1)	18/20 (90.0)	31/35 (88.6)	29/33 (87.9)	24/25 (96.0)	30/30 (100.0)
1b or 1 other	56/56 (100.0)	10/11 (90.9)	13/13 (100.0)	41/43 (95.3)	20/20 (100.0)	14/14 (100.0)
4	6/6 (100.0)	—	4/6 (66.7)	4/5 (80.0)	1/2 (50.0)	4/4 (100.0)
6	—	—	—	—	1/2 (50.0)	1/1 (100.0)
Baseline viral load						
≤800,000 IU/mL	33/33 (100.0)	4/4 (100.0)	13/14 (92.9)	17/18 (94.4)	4/4 (100.0)	13/13 (100.0)
>800,000 IU/mL	102/105 (97.1)	24/27 (88.9)	35/40 (87.5)	57/63 (90.5)	42/45 (93.3)	36/36 (100.0)
Baseline albumin levels[b]						
3.0–3.5 g/dL	9/9 (100.0)	—	1/2 (50.0)	6/6 (100.0)	1/1 (100.0)	7/7 (100.0)
≥3.5 g/dL	126/129 (97.7)	28/31 (90.3)	47/52 (90.4)	68/75 (90.7)	45/48 (93.8)	42/42 (100.0)
Platelet count						
$<100 \times 10^3/\mu L$	35/36 (97.2)	2/4 (50.0)	11/15 (73.3)	20/22 (90.9)	12/13 (92.3)	11/11 (100.0)
$\geq 100 \times 10^3/\mu L$	99/101 (98.0)	26/27 (96.3)	37/39 (94.9)	53/58 (91.4)	34/36 (94.4)	38/38 (100.0)
Unknown	1/1 (100.0)	—	—	1/1 (100.0)	—	—
Age						
<65 y	117/120 (97.5)	21/24 (87.5)	42/47 (89.4)	62/69 (89.9)	37/39 (94.9)	41/41 (100.0)
≥65 y	18/18 (100.0)	7/7 (100.0)	6/7 (85.7)	12/12 (100.0)	9/10 (90.0)	8/8 (100.0)
IL28B						
CC	51/52 (98.1)	10/11 (90.9)	9/9 (100.0)	7/7 (100.0)	9/9 (100.0)	7/7 (100.0)
Non-CC	84/86 (97.7)	18/20 (90.0)	39/45 (86.7)	66/73 (90.4)	37/40 (92.5)	42/42 (100.0)
Unknown	—	—	—	1/1 (100.0)	—	—
Cirrhosis determination method						
Biopsy	38/38 (100)	4/5 (80.0)	24/26 (92.3)	17/17 (100.0)	14/14 (100.0)	15/15 (100.0)
APRI+FibroTest	8/8 (100)	3/4 (75.0)	1/1 (100.0)	7/9 (77.8)	3/3 (100.0)	4/4 (100.0)
FibroScan	89/92 (96.7)	21/22 (95.5)	23/27 (85.2)	50/55 (90.9)	29/32 (90.6)	30/30 (100)
FibroScan value, *kPa*						
12.6–15.0	25/25 (100)	7/8 (87.5)	6/7 (85.7)	12/12 (100.0)	10/10 (100.0)	6/6 (100.0)
15.1–20.0	30/31 (96.7)	9/9 (100.0)	3/3 (100.0)	14/14 (100.0)	7/8 (87.5)	8/8 (100.0)
20.1–25.0	6/6 (100)	4/4 (100.0)	3/3 (100.0)	6/8 (75.0)	2/2 (100.0)	1/1 (100.0)
>25.0	28/30 (93.3)	1/1 (100.0)	11/14 (78.6)	18/21 (85.7)	10/12 (83.3)	15/15 (100.0)
Prior treatment response						
PR/P/IFN prior null	–	–	31/34 (91.2)	23/28 (82.1)	27/29 (93.1)	29/29 (100.0)
PR/P/IFN prior partial response	–	–	5/7 (71.4)	7/7 (100.0)	8/8 (100.0)	8/8 (100.0)
PR/P/IFN prior relapse	–	–	12/13 (92.3)	12/12 (100.0)	11/12 (91.7)	12/12 (100.0)
DAA prior nonresponder	–	–	–	7/7 (100.0)	–	–
DAA prior breakthrough	–	–	–	11/13 (84.6)	–	–
DAA prior relapse	–	–	–	10/10 (100.0)	–	–
DAA experienced	–	–	–	4/4 (100.0)	–	–

NOTE. Values are presented as n (%).
APRI, AST-to-platelet ratio index; DAA, direct-acting antiviral; IFN, interferon; P, peginterferon; PR, peginterferon/RBV.
[a]Includes all patients who received at least 1 dose of study medication.
[b]There were no patients with albumin levels $<3.0 \times 10^3$ cells/μL.

FibroScan score >25 kPa, and 25% of patients had a platelet count <100,000 cells/μL at baseline.

These data demonstrate that cirrhotic patients with HCV GT1 or 4 infection can achieve high rates of SVR12 with EBR/GZR-based treatment regimens. In treatment-naïve patients, SVR12 was 98% among cirrhotic patients treated for 12 weeks, with no incremental benefit of concomitant RBV therapy, and a 16-week/18-week treatment duration with concomitant RBV in treatment-experienced patients, resulted in a SVR12 of 100%.

High efficacy was maintained across all important patient subgroups, including those with platelet counts

Table 4. Impact of NS5A Resistance-Associated Substitutions on Sustained Virologic Response 12 Weeks After Completion of Therapy in Patients with Hepatitis C Virus GT1a Infection (Resistance Analysis Population[a])

	Treatment-naïve		Treatment-experienced			
SVR12	EBR/GZR for 12 wk[b]	EBR/GZR+RBV for 12 wk	EBR/GZR for 12 wk[b]	EBR/GZR +RBV for 12 wk	EBR/GZR for 16/18 wk	EBR/GZR+RBV for 16/18 wk[c]
All patients, n (%) [95% CI]	73/75 (97.3) [90.7–99.7]	18/20 (90.0) [68.3–98.8]	31/34 (91.2) [76.3–98.1]	29/32 (90.6) [75.0–98.0]	24/25 (96.0) [79.6–99.9]	29/29 (100) [88.1–100]
With NS5A RASs,[c] n (%)	7/8 (87.5)	2/4 (50.0)	1/3 (33.3)	1/3 (33.3)	2/3 (66.7)	2/2 (100)
No NS5A RASs,[c] n (%)	66/67 (98.5)	16/16 (100.0)	30/31 (96.8)	28/29 (96.6)	22/22 (100.0)	27/27 (100)

[a]Resistance analysis population included patients with sequence data available and who either achieved SVR12 or met criteria for virologic failure. Three patients from the full analysis set were excluded from the resistance analysis population (EBR/GZR for 12 wk, n = 2; EBR/GZR+RBV for 16 wk, n = 1). Population sequencing: limit of variant detection >25% of circulating viral quasi-species (only samples >1000 IU/mL sequenced). Only substitutions at amino acids 28, 30, 31, and 93 were included.
[b]Two patients (1 treatment-naïve and 1 treatment-experienced) who discontinued treatment early due to administrative reasons were excluded from this analysis (1 patient died after completing treatment, before follow-up week 4, and the other patient was discontinued due to noncompliance; both had no NS5A RASs at baseline). Among patients with relapse, 1 of 2 treatment-naïve patients and 2 of 3 treatment-experienced patients had NS5A RASs present at baseline.
[c]Excludes 1 treatment-experienced patient with unavailable sequence data who also achieved SVR12.

<100,000 cells/μL, serum albumin <3.5g/dL, and FibroScan scores >25 kPa, suggesting no decline in efficacy with advanced compensated cirrhosis. The difference in SVR rates between GT1a-infected treatment-naïve and -experienced patients receiving EBR/GZR (no RBV) for 12 weeks (96% vs 89%) may be attributable to the limited number of patients included in this analysis, although an increased impact of RASs in treatment-experienced patients cannot be excluded. Sarrazin and colleagues[24] recently reported that among patients with GT1 infection receiving ledipasvir/sofosbuvir for 12 weeks, SVR12 was 99% and 96% in treatment-naïve patients without and with high-impact baseline NS5A RASs (RASs conferring >100-fold loss of sensitivity to ledipasvir at a frequency of at least 15%), respectively (P = .066); whereas in treatment-experienced patients, SVR rates in those without and with high-impact NS5A RASs were 97% and 65%, respectively (P < .05).

In the absence of baseline NS5A RASs, a 12-week RBV-free regimen resulted in high rates of SVR12 regardless of treatment history. In total, 11 GT1a-infected patients with baseline NS5A RASs received 12 weeks of EBR/GZR, of which 8 (73%) achieved SVR12, whereas 96 of 98 (98%) of GT1a-infected patients without RASs at baseline achieved SVR12. Although patient numbers are small in this cirrhotic population, increasing treatment duration to 16 of 18 weeks and adding concomitant RBV appeared to overcome the effect of NS5A RASs, a finding similar to that seen in the non cirrhotic population.[19] These data also suggest that if there

Table 5. Safety and Adverse Events

Variable	EBR/GZR (n = 264)	EBR/GZR+RBV (n = 193)
≥1 AEs	193 (73.1)	164 (85.0)
Fatigue	40 (15.2)	59 (30.6)
Headache	44 (16.7)	40 (20.7)
Nausea	11 (4.2)	26 (13.5)
Insomnia	8 (3.0)	25 (13.0)
Drug-related AEs	111 (42.0)	141 (73.1)
Serious AEs	8 (3.0)	6 (3.1)
Serious drug-related AEs	1 (0.4)	0 (0.0)
Deaths	1 (0.4)	1 (0.5)
Discontinued due to an AE	2 (0.8)	4 (2.1)

NOTE. Values are presented as n (%). Safety population includes 62 additional patients enrolled in C-WORTHY (treatment-naïve cirrhotic patients treated for 18 wk). Discontinuations due to AE: without RBV, lymphoma, and ALT elevation; with RBV, uterine bleeding, tachycardia, depression, and portal vein thrombosis/colitis; placebo, rash.

Table 6. Laboratory Assessments

Variable	EBR/GZR (n = 264)	EBR/GZR+RBV (n = 193)
Hemoglobin		
Grade 2: 9.0–9.9 g/dL	2 (0.8)	18 (9.3)
Grade 3: 7.0–8.9 g/dL	0 (0.0)	8 (4.1)
Grade 4: <7.0 g/dL	0 (0.0)	0 (0.0)
ALT,[a] *IU/mL*		
Grade 3: 5.1–10.0× ULN	5 (1.9)	1 (0.5)
Grade 4: >10.0× ULN	1 (0.4)	0 (0.0)
AST, *IU/mL*		
Grade 3: 5.1–10.0× ULN	2 (0.8)	0 (0.0)
Grade 4: >10.0× ULN	1 (0.4)	0 (0.0)
Elevation of total bilirubin,[a] *mg/dL*		
Grade 3: 2.6–5.0× ULN	1 (0.4)	12 (6.2)
Grade 4: >5.0× ULN	0 (0.0)	1 (0.5)
Direct bilirubin,[a] *mg/dL*		
Grade 3: 2.6–5.0× ULN	3 (1.1)	8 (4.1)
Grade 4: >5.0× ULN	0 (0.0)	1 (0.5)

NOTE. Values are presented as n (%).
ULN, upper limit of normal.
[a]No patient met the criteria for Hy's law.

is a history of interferon-based treatment and baseline RAS data are not available, efficacy may be optimized by extending treatment with EBV/GZR to 16 weeks and adding RBV.

Data from this analysis are based on population sequencing with a sensitivity threshold of 20% to 25%. Next-generation sequencing data are not available for this cohort of cirrhotic patients; however, data from the EBR/GZR clinical program indicate that population sequencing with a sensitivity threshold of 20%−25% and next-generation sequencing with a 10% threshold both identify a comparable small set of EBR RASs among which the efficacy of EBR/GZR is reduced. Increasing next-generation sequencing sensitivity to a 1% threshold identifies a broader group of EBR RASs, but those have a smaller impact on SVR compared with those identified by population sequencing.

EBR/GZR was generally well tolerated. Six patients discontinued treatment due to an AE, one of which was considered drug-related (abdominal pain). Four patients had late ALT elevations after initially normalizing on treatment and 1 patient discontinued treatment due to a grade 4 ALT elevation with increased eosinophils. There were no decompensation events in this generally healthy cirrhotic population, and no other evidence of declining liver function while on treatment.

Therapeutic treatment options for patients with cirrhosis frequently involve extended treatment durations of 24 weeks and/or the use of RBV. In an integrated analysis of 513 cirrhotic patients receiving sofosbuvir/ledipasvir±RBV, an overall SVR12 rate of 96% was achieved, although SVR12 rates were slightly lower in treatment-experienced patients treated for 12 weeks (90% vs 98% in patients treated for 24 weeks). SVR rates were also lower in treatment-experienced patients with platelet count $<$75,000 cells/μL (SVR of 82%) and those with NS5A RASs at baseline (SVR of 85% in cirrhotic patients receiving sofosbuvir/ledipasvir for 24 weeks).[25] The recommended treatment regimen for treatment-experienced patients with compensated cirrhosis is sofosbuvir/ledipasvir for 24 weeks, but a 12-week regimen with addition of RBV is also a therapeutic option for patients who are eligible for RBV therapy.[26] A French randomized, multicenter study has shown similar rates of SVR12 in patients with compensated cirrhosis receiving sofosbuvir/ledipasvir+RBV for 12 weeks compared with those receiving sofosbuvir/ledipasvir alone for 24 weeks (96% vs 97%).[27] In a randomized study of patients with Child-Pugh A cirrhosis receiving paritaprevir/ritonavir, ombitasvir, dasabuvir, and RBV for 12 or 24 weeks, SVR 12 was achieved by 91.8% and 95.9% of patients in the 12- and 24-week treatment arms, respectively.[28] Cirrhotic patients with HCV GT1a infection require ombitasvir, paritaprevir/ritonavir plus dasabuvir and RBV for 24 weeks.[29] More recently, the combination of sofosbuvir/velpatasvir has received approval as a 12-week regimen for compensated cirrhotic patients with GT1a infection, regardless of treatment history without need for treatment extension or addition of RBV (including for prior direct-acting antiviral failures).[30] Data from the present analysis suggest that SVR12 rates of 98% are achievable with a regimen of EBR/GZR for 12 weeks in the 89%−93% of cirrhotic patients with HCV GT1a infection who have no baseline NS5A RASs. In the small proportion of GT1a-infected patients with NS5A RASs at baseline (6.9%−10.6% of patients in this analysis), extending therapy to 16 weeks and the addition of concomitant RBV can overcome the negative impact of NS5A RASs.

This integrated analysis is subject to several limitations. The analysis was not prespecified nor powered for statistical comparison between treatment arms. Most patients had well-compensated cirrhosis, and thus these data cannot be extrapolated to patients with more advanced cirrhosis or decompensated disease. Indeed, the use of EBR/GZR is contraindicated in patients with Child-Pugh B or C cirrhosis. Furthermore, subgroup analyses frequently include small numbers of patients, including limited numbers of patients with HCV GT4 or 6 infection. EBR/GZR is not approved for the treatment of patients with HCV GT6 infection, whereas the EBR/GZR prescribing information indicates that patients with GT4 infection should be treated with 12 weeks if treatment-naïve or 16 weeks with the addition of RBV if treatment-experienced.[31] In addition, small numbers of patients are included in several of the patient subgroups with baseline NS5A RASs or previous treatment failure that are used to discriminate extended durations of treatment. However, the conclusions from this analysis of cirrhotic patients are supported by similar observations from larger analyses of noncirrhotic patients receiving EBR/GZR, which also endorse the use of RAS testing to define treatment duration in patients with GT1a infection.[31] Finally, the laboratory criteria used to define cirrhosis differed across the original treatment studies, and the presence of cirrhosis in this analysis population was not based on a single uniform set of diagnostic criteria.

In conclusion, EBR/GZR was highly efficacious in compensated cirrhotic patients. Most patients in our analysis had HCV GT1a or 1b infection. Patients with GT1b infection achieved high rates of SVR12 with all regimens evaluated, including EBR/GZR for 12 weeks, regardless of the presence or absence of RASs; whereas the presence of NS5A RASs can be used to define the optimum treatment regimen in patients with GT1a infection. If RAS testing is unavailable, an alternative approach is to use history of prior treatment failure to define an optimal regimen. Only 1 patient discontinued treatment due to a protocol-mandated stopping rule and no patient experienced a decompensation-related event. These data suggest that EBR/GZR for 12 weeks is a safe and effective treatment option for the majority of compensated cirrhotic patients with HCV GT1 infection. An intensified regimen with RBV for 16 weeks is required for GT1a-infected patients with baseline NS5A RASs.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2017.01.050.

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Author names in bold designate shared co-first authors.

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Reprint requests
Address requests for reprints to: Ira Jacobson, MD, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029. e-mail: ijacobson@chpnet.org.

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Supplementary Table 1. Cirrhotic Patients With Virologic Failure During Phase 2/3 studies With Elbasvir/Grazoprevir±Ribavirin

Patient ID	Race	TN or TE	Genotype	Regimen	VF	Study	Prior response	*IL28B*	Baseline viral load, *IU/mL*	Fibrosis stage or FibroScan score	NS3 RASs		NS5A RASs	
											At baseline	At failure	At baseline	At failure
Genotype 1a														
150439	White	TN	1a	EBR/GZR 12 wk	Relapse	C-WORTHY	NA	CT	9868198	15.1 kPa	WT	A156A/T	WT	L31M, Q30R
435643	White	TN	1a	EBR/GZR 12 wk	BT	C-EDGE TN	NA	CC	1238923	METAVIR F4	Q80K, S122G	V36M, (Q80K, S122G), D168A	L31L/M	Q30R, (L31M)
151237	White	TE	1a	EBR/GZR 12 wk	Relapse	C-WORTHY	Null	CT	16181385	13.8 kPa	WT	A156T	WT	H58D, Q30R
680432	White	TE	1a	EBR/GZR 12 wk	Relapse	C-EDGE TE	PR partial responder	CT	4305256	METAVIR F4	WT	A156T	Q30H	(Q30H), H58D
680801	White	TE	1a	EBR/GZR 12 wk	Relapse	C-EDGE TE	PR null responder	TT	1297238	25.7 kPa	Q80K	(Q80K), A156T, D168A	L31M	Q30R, (L31M)
150402	White	TN	1a	EBR/GZR+RBV 12 wk	Relapse	C-WORTHY	NA	TC	7310263	0.88 FibroTest	Q80K, S122G	(Q80K), (S122G), D168Y	Q30L/Q, Y93H/Y	(Q30L), (Y93H), L31M
150442	White	TN	1a	EBR/GZR+RBV 12 wk	Relapse	C-WORTHY	NA	CC	5808604	Stage 4 cirrhosis (Ludwig Score)	I132V, Q80K	(I132V), (Q80K), A156G	L31V, Y93N	(L31V), (Y93N)
480048	White	TE	1a	EBR/GZR+ RBV 12 wk	Relapse	C-SALVAGE	DAA failure	CT	1756431	21.3 kPa	V36L R155K	V36L, R155K, A156T, V158V/A, D168N	WT	Q30R
680811	White	TE	1a	EBR/GZR+RBV 12 wk	Relapse	C-EDGE TE	PR null responder	TT	2913905	22.0 kPa	Q80K	Y56H (Q80K), R155I, D168V	Y93N	(Y93N)
680817	White	TE	1a	EBR/GZR+RBV 12 wk	Relapse	C-EDGE TE	PR null responder	CT	5066351	0.88 FibroTest	WT	WT	L31M	Q30R, (L31M)
680819	White	TE	1a	EBR/GZR 16/18 wk	Relapse	C-EDGE TE	PR null responder	TT	2695122	30.8 kPa	I170V	R155K	L31M	Q30R, (L31M)
Genotype 1b														
480043	White	TE	1b	EBR/GZR+RBV 12 wk	Relapse	C-SALVAGE	DAA failure	TT	1793936	0.88 FibroTest	T54S	T54S Y56F, Q80L, A156T/A, V170I	L31M	L31M Y93H
680835	White	TE	1b	EBR/GZR+RBV 12 wk	Relapse	C-EDGE TE	PR null responder	CT	673361	41 kPa	WT	WT	L31M	(L31M), Y93H
Genotype 1-other														
150427	Black/AA	TN	1-Other	EBR/GZR+RBV 12 wk	BT	C-WORTHY	NA	CT	12539741	14.6 kPa	PCR failure	PCR failure	PCR failure	PCR failure
Genotype 4/6														
680853	White	TE	4d	EBR/GZR 12 wk	Relapse	C-EDGE TE	PR null responder	CT	2646439	28.0 kPa	WT	WT	WT	L28S, M31I
680841	White	TE	4d	EBR/GZR+RBV 12 wk	Relapse	C-EDGE TE	PR null responder	CT	5122681	35.3 kPa	WT	WT	P58T	M31V, (P58T), Y93H
680836	White	TE	4a	EBR/GZR 16/18 wk	Rebound	C-EDGE TE	PR null responder	TT	1948530	32.5 kPa	WT	A156M/T/V, D168A/G, V170I	L28M, P58Y	(L28M), P58D
680007	Asian	TE	6a	EBR/GZR 16/18 wk	Rebound	C-EDGE TE	PR relapse	CT	2020413	15.3 kPa	[a]	[a]	[a]	[a]

AA, African American; DAA, direct-acting antiviral; NA, not available; TE, treatment-experienced; TN, treatment-naïve; WT, wild-type.
[a]Unable to generate sequence data for this patient.

Supplementary Table 2. Outcomes Among Patients With Hepatitis C Virus GT1a Infection

Variable	Treatment-naïve		Treatment-experienced			
	12 wk no RBV (n = 76)	12 wk +RBV (n = 20)	12 wk no RBV (n = 35)	12 wk+RBV (n = 33)	16/18 wk no RBV (n = 25)	16/18 wk+RBV (n = 30)
SVR, n (%)	73 (96.1)	18 (90.0)	31 (88.6)	29 (87.9)	24 (96.0)	30 (100)
Virologic failure, n (%)	2 (2.6)	2 (10.0)	3 (8.6)	3 (9.1)	1 (4.0)	0 (0)
Nonvirologic failure, n (%)	1[a] (1.3)	0 (0)	1[b] (2.8)	1[c] (3.0)	0 (0)	0 (0)
SVR according to baseline viral load, n/N (%)						
≤800,000 IU/mL	13/13 (100)	3/3 (100)	6/6 (100)	6/6 (100)	3/3 (100)	6/6 (100)
>800,000 IU/mL	60/63 (95.2)	15/17 (88.2)	25/29 (86.2)	23/27(85.2)	21/22 (95.5)	24/24 (100)

[a]Death due to coronary artery disease.
[b]Discontinued due to noncompliance.
[c]Death due to a motor vehicle accident.