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Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12 weeks☆

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Background & Aims: Patients with chronic hepatitis C virus (HCV) infection and cirrhosis have a higher risk for liver-related complications and have historically been more difficult to cure than patients without cirrhosis. We evaluated the safety and efficacy of ombitasvir/paritaprevir/ritonavir and dasabuvir, without ribavirin, for 12 weeks in patients with HCV genotype 1b infection and compensated cirrhosis.

Methods: Treatment-naïve and peginterferon/ribavirin treatment-experienced patients received 12 weeks of ombitasvir/paritaprevir/ritonavir (25/150/100 mg once daily) and dasabuvir (250 mg twice daily). Key inclusion criteria were hemoglobin $\geqslant$10 g/dl, albumin $\geqslant$2.8 g/dl, platelet count $\geqslant 25 \times 10^9$/L, creatinine clearance $\geqslant$30 ml/min, and Child-Pugh score $\leqslant$6. Efficacy was assessed by the percentage of patients achieving SVR (HCV RNA <25 IU/ml) 12 weeks post-treatment (SVR12). Efficacy and safety were assessed in all patients receiving study drug.

Results: Sixty patients with HCV genotype 1b infection and cirrhosis received treatment. The study population comprised 62% male, 55% treatment-experienced, 83% with *IL28B* non-CC genotype, 22% with platelet count $<90 \times 10^9$/L, and 17% with albumin <3.5 g/dl. All 60 patients completed treatment, and SVR12 was achieved in 100% (95% CI, 94.0–100%) of patients. The most common adverse events were fatigue (22%), diarrhea (20%), and headache (18%). Only one patient (1.7%) experienced a serious adverse event. Laboratory abnormalities were infrequently observed and not clinically significant.

Conclusions: The HCV regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir without ribavirin for 12 weeks achieved 100% SVR12 and was well tolerated in HCV genotype 1b-infected patients with cirrhosis, suggesting that this 12-week ribavirin-free regimen is sufficient in this population.

Keywords: Cirrhosis; Direct-acting antivirals; 3D; TURQUOISE-III.
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Abbreviations: HCV, hepatitis C virus; GT, genotype; SVR, sustained virologic response; SVR12, sustained virologic response 12 weeks post-treatment; PegIFN, pegylated interferon; RBV, ribavirin; DAA, direct-acting antiviral; OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; DSV, dasabuvir; INR, international normalized ratio; LLOQ, lower limit of quantification; CI, confidence interval; AEs, adverse events.

Introduction

Among seven recognized genotypes (GTs) of hepatitis C virus (HCV), GT1 is the most common HCV infection, accounting for 46–60% of cases worldwide [1,2]. Subgenotype 1b encompasses approximately 68% of all GT1 infections and is the most prevalent subgenotype in Europe, Central America, Middle East, and Asia. Patients with chronic HCV infection and cirrhosis are at greatest risk for progression to decompensation, end-stage liver disease and disease-related death, hepatocellular carcinoma, and liver transplantation [3]. As a result, the recommendations from the American Association for the Study of Liver Diseases (AASLD), Infectious Disease Society of America (IDSA), and the European Association for the Study of the Liver (EASL) prioritize these patients for treatment [4,5]; however, achieving a sustained virologic response (SVR) has been more challenging in patients with cirrhosis. First-generation protease inhibitors in combination with pegylated interferon (PegIFN) and ribavirin (RBV) achieved low rates of response in these patients (33–77%), in part due to significant toxicities leading to drug discontinuation [6–8]. New IFN-free direct-acting antiviral (DAA) therapies have greatly improved SVR rates in patients with cirrhosis, nonetheless, rates are still lower than in patients without cirrhosis [9–13].

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Furthermore, longer treatment and/or the addition of RBV has been required with most regimens to maximize SVR rates in patients with cirrhosis [9,11,12,14,15]. As the prevalence and burden of HCV cirrhosis is projected to increase significantly in the coming years [16,17], treatments that optimize SVR in patients with cirrhosis are greatly needed.

Ombitasvir (OBV) is an NS5A inhibitor co-formulated with the NS3/4A protease inhibitor paritaprevir (PTV) and the pharmacokinetic enhancer ritonavir (r), which increases peak and trough drug exposures allowing for once daily PTV dosing [18]. Administered with the non-nucleoside NS5B polymerase inhibitor dasabuvir (DSV), this multi-targeted 3-DAA regimen with or without RBV is approved in many countries to treat HCV GT1 infection. Approval for the treatment of HCV GT1 patients with compensated cirrhosis was based on the evidence of a phase III trial of 380 patients with compensated cirrhosis in which OBV/PTV/r and DSV plus RBV achieved SVR rates at post-treatment week 12 (SVR12) of 91.8% and 95.9% after 12 or 24 weeks of therapy, respectively [9]. SVR12 rates were 98.5% (67/68) in those infected with GT1b receiving 12 weeks of treatment, and 100% (51/51) following 24 weeks of treatment. In that study, all patients received RBV, leading to the treatment recommendation of OBV/PTV/r and DSV plus RBV for 12 weeks in patients with GT1b infection and cirrhosis [4,5,19]. However, RBV is not required in GT1b-infected patients without cirrhosis in whom 100% SVR12 was achieved in 301 patients who received OBV/PTV/r and DSV without RBV for 12 weeks [20–22] and the high rates of SVR achieved in those with compensated cirrhosis raises the question of whether RBV is necessary for GT1b-infected patients with cirrhosis. Eliminating RBV in this population with cirrhosis without sacrificing efficacy is expected to improve the safety profile, particularly with respect to anemia and hyperbilirubinemia.

We report the results of the TURQUOISE-III phase IIIb, open-label study designed to assess the safety and efficacy of OBV/PTV/r and DSV without RBV for 12 weeks in adults with chronic HCV GT1b infection and compensated cirrhosis, both with or without prior treatment experience with PegIFN/RBV.

Patients and methods

Study patients

Patients 18 years or older were eligible for enrollment if they had HCV genotype 1b infection for at least 6 months prior to screening, or an HCV RNA of >1000 IU/ml at the time of screening with a liver biopsy consistent with chronic HCV infection. Eligible patients had documented cirrhosis by means of liver biopsy (METAVIR score >3 or Ishak score of >4) or transient elastography (FibroScan score $\geqslant$12.5 kPa within 6 months of screening or during screening), and a Child-Pugh score of 5 or 6 with no evidence of decompensation or hepatocellular carcinoma. Those with a positive test result for hepatitis B or human immunodeficiency virus were excluded. Laboratory eligibility criteria were a serum albumin $\geqslant$2.8 g/dl, calculated creatinine clearance $\geqslant$30 ml/min, hemoglobin $\geqslant$10 g/dl, platelet count $\geqslant 25 \times 10^9$/L, total bilirubin $\leqslant$3.0 mg/dl, and an international normalized ratio $\leqslant$1.8. Treatment-experienced patients were allowed with documented treatment failure with PegIFN/RBV at least 2 months prior to screening; prior treatment experience with any DAA or investigational agent was not permitted. More detailed eligibility criteria are provided in the Supplementary data.

Study design

All patients in this phase IIIb, open-label study were assigned to receive 12 weeks of OBV/PTV/r and DSV without RBV. Co-formulated OBV/PTV/r was administered once daily (25/150/100 mg) and DSV 250 mg twice daily. Patients were followed up to 24 weeks post-treatment. Written informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institutional review board of each study site.

Efficacy, safety, and pharmacokinetic assessments

Plasma samples collected at screening and each study visit were processed by a central laboratory for HCV RNA levels using the Roche TaqMan real-time reverse transcriptase-PCR assay version 2.0. Efficacy was assessed by the percentage of patients with SVR12, defined as a HCV RNA below the lower limit of quantification (LLOQ = 25 IU/ml) 12 weeks after last dose of study drug. The first primary endpoint was non-inferiority of the SVR12 rates achieved with OBV/PTV/r and DSV for 12 weeks to the historical SVR12 rate achieved by sofosbuvir plus PegIFN/RBV in HCV GT1b-infected patients with cirrhosis (73.2%, 95% confidence interval [CI] 59.8–83.2%). Non-inferiority of the 3-DAA regimen could be claimed if the SVR12 95% CI lower limit was greater than the upper limit of the CI for the historical rate minus a 10.5% non-inferiority margin (72.7%). The second primary endpoint was superiority of the 3-DAA SVR12 rate to the historical SVR12 rate for sofosbuvir plus PegIFN/RBV in this patient population (83.2%). Secondary assessments included the percentage of patients with on-treatment virologic failure, and post-treatment relapse. Further details of historical non-inferiority calculations are provided in the Supplementary data.

Treatment-emergent adverse events (AEs) were collected from the start of study drug administration until 30 days after the last dose and were assessed by the investigators for relation to study drug and severity. Serious AEs were collected from the time of signed consent until 30 days after last study drug dose. Clinical laboratory chemistry and hematology tests were assessed throughout the study.

Blood samples were collected at baseline for *IL28B* (IFNL4-rs12979860) genotyping [23]. Blood samples for the pharmacokinetic assessment of the study drugs were collected at treatment weeks 2, 4, 8, and 12. Plasma concentrations of OBV, PTV, r, DSV, and DSV M1 metabolite were determined using a validated liquid chromatography method with tandem mass spectrometric detection with LLOQ of 0.462, 0.601, 4.93, 4.58, and 4.77 ng/ml, respectively. Drug concentrations summarized as trough levels (C_{trough}) were binned based on sample collection time within the 22–26 h or 10–14 h bins for once or twice daily drugs, respectively.

Statistical analyses

Efficacy and safety analyses were performed using all patients receiving at least one dose of study drug. The 2-sided 95% CIs for binomial proportions were calculated using the Wilson score method. With a sample size of 60 patients, an observed SVR12 rate of 90% (95% CI 79.9–95.3%) would provide >90% power to demonstrate non-inferiority to the historical sofosbuvir plus PegIFN/RBV rate. An interim analysis was planned after all patients reached post-treatment week 12 or prematurely discontinued the study. SAS (SAS Institute) for the UNIX operating system was used for all analyses.

Results

Baseline patient demographics and characteristics

Screening of patients occurred from September 19, 2014 through to November 28, 2014 at 19 sites in the United States, Canada, and Belgium. Of 72 patients screened, 12 did not meet inclusion/exclusion criteria; 60 were enrolled and received study drug. Demographics and disease characteristics are presented in Table 1. The majority of patients had prior treatment experience with PegIFN/RBV, and had *IL28B* (IFNL4-rs12979860) [23] non-CC genotype. At baseline, 19 (31.7%) patients had surrogate markers for portal hypertension and/or hepatic synthetic dysfunction: 13 had baseline thrombocytopenia (platelet count $<90 \times 10^9$/L), 10 had baseline hypoalbuminemia (serum albumin <3.5 g/dl), and 4 had both surrogate markers. Of 41 patients enrolled with a cirrhosis determination by FibroScan, 20 had baseline scores of >20 kPa.

Table 1. Baseline patient demographics and disease characteristics.

Characteristic	OBV/PTV/r + DSV N = 60
Male	37 (61.7)
White race	52 (86.7)
Hispanic/Latino ethnicity	3 (5.0)
Age, median years (range)	60.5 (26.0-78.0)
BMI, median kg/m^2 (range)	27.0 (18.0-42.3)
IL28B non-CC genotype	50 (83.3)
PegIFN/RBV experienced[a]	33 (55.0)
Non-responder[b]	18 (30.0)
Relapser/breakthrough[c]	5 (8.3)
Other[d]	10 (16.7)
HCV RNA, median $\log_{10}$ IU/ml (range)	6.8 (3.8-7.5)
Former injection drug use	20 (33.3)
Cirrhosis determination	
Biopsy	19 (31.7)
FibroScan	41 (68.3)
FibroScan, kPa	
Median (range)	19.0 (12.5-67.8)
>20 KPa	20 (48.8)[e]
FibroTest, median (range)	0.89 (0.27-0.99)
Albumin, g/dl	
Median (range)	4.0 (2.8-4.5)
<3.5	10 (16.7)
Platelet count, 10^9/L	
Median (range)	132 (54-514)
<90	13 (21.7)
Alpha fetoprotein, ng/ml	
Median (range)	11.9 (2.7-247.0)
≥20	20 (33.3)
Total bilirubin, mg/dl	
Median (range)	0.8 (0.3-2.5)
>1.5	9 (15.0)
INR, median (range)	1.1 (0.9-1.3)
Esophageal varices	7 (11.7)

Values are n (%) unless denoted otherwise.
[a]Definitions for prior treatment experience are provided in Supplementary data.
[b]Patients with documented null or partial response to prior PegIFN/RBV treatment, or non-responders with insufficient documentation of unquantifiable HCV RNA to distinguish between partial and null response.
[c]Patients with documented relapse to prior PegIFN/RBV treatment, or less well-characterized breakthrough/relapse.
[d]Patients with IFN-intolerance, or inadequate documentation of response to prior PegIFN/RBV.
[e]N = 41.
OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; DSV, dasabuvir; SD, standard deviation; BMI, body mass index; INR; international normalized ratio; IFN, interferon; RBV, ribavirin.

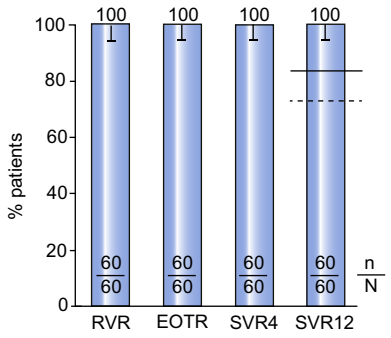

Fig. 1. Virologic response during and after treatment with OBV/PTV/r + DSV for 12 weeks. The percentage of patients achieving HCV RNA <25 IU/ml response at different time points is plotted with 95% CI using the Wilson score method. The horizontal dashed line indicates the non-inferiority margin for the historical rate achieved with sofosbuvir plus PegIFN/RBV (72.7%), and the horizontal solid line indicates the superiority threshold (83.2%). RVR, rapid virologic response at treatment week 4; EOTR, end of treatment response at week 12; SVR4, sustained virologic response at post-treatment week 4; SVR12, sustained virologic response at post-treatment week 12.

Efficacy outcomes

All 60 patients completed 12 weeks of treatment with OBV/PTV/r and DSV. Rapid serum HCV RNA decline was observed with 61.7% of patients (37/60) below LLOQ at treatment week 2, and 100% (60/60) below LLOQ by week 4 through to the end of treatment. After 12 weeks of treatment, 100% (95% CI, 94.0–100%) of patients achieved SVR12 (Fig. 1). Thus, the SVR12 rate of OBV/PTV/r and DSV was both non-inferior and superior to the historical rate achieved with sofosbuvir plus PegIFN/RBV in GT1b-infected patients with cirrhosis.

All baseline patient characteristics that have historically been predictive of poor response to treatment, including those identified in HCV GT1 patients with cirrhosis treated with OBV/PTV/r and DSV plus RBV (prior null response to PegIFN/RBV and former injection drug use [9]), had no impact on SVR12 rates. Similarly, baseline laboratory abnormalities or measures of liver disease severity associated with reduced SVR12 rates with IFN and/or DAA-containing regimens, including serum albumin, platelet count, alpha fetoprotein, interferon-γ inducible protein 10, and FibroScan score did not influence the 100% SVR12 rate achieved.

Improvement in laboratory assessments

Liver enzyme mean values rapidly declined by week 2 of treatment. Aminotransferases were normalized at the end of treatment in 45/53 (84.9%) patients with elevated baseline alanine aminotransferase (ALT), and 41/55 (74.5%) patients with elevated aspartate aminotransferase (AST). Mean improvements in laboratory values at post-treatment week 12 were also observed for albumin (+0.31 g/dl), alpha fetoprotein (−24.0 ng/ml), total bilirubin (−0.3 mg/dl), and FibroTest (−0.16).

Safety outcomes

The majority of patients had AEs (76.7%; Table 2), though no patient discontinued the study. The most common AEs were fatigue in 13 (21.7%) patients, diarrhea in 12 (20.0%) patients, and headache in 11 (18.3%) patients. Of these patients, 8 with fatigue, 6 with diarrhea, and 6 with headache had events assessed as possibly related to study drug. Most AEs were mild or moderate, and only one patient experienced a severe event (Table 2). This patient experienced serious events of acute hypotension and syncope secondary to hypotension requiring hospitalization on day 2. At study start, this patient was taking metoprolol, lisinopril, and nisoldipine to treat hypertension. Due to CYP3A4 inhibition by ritonavir possibly leading to increased nisoldipine exposures, a 50% dosage adjustment to nisoldipine was recommended prior to study start, but was not initiated. Following the serious events, nisoldipine was discontinued with concurrent lisinopril dose increase, which stabilized the patient's blood pressure. Study drug was interrupted from day 3 to 8, whereupon treatment was re-initiated and this patient achieved SVR12.

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Table 2. Proportion of patients with treatment-emergent AEs and laboratory abnormalities.

Event	OBV/PTV/r + DSV N = 60
Any AE	46 (76.7)
Severe AE	1 (1.7)
Serious AE	1 (1.7)
AE leading to study discontinuation	0
Common AEs (≥10% of patients)	
Fatigue	13 (21.7)
Diarrhea	12 (20.0)
Headache	11 (18.3)
Arthralgia	6 (10.0)
Dizziness	6 (10.0)
Insomnia	6 (10.0)
Pruritus	6 (10.0)
Hemoglobin	
Grade 2 (<10-8 g/dl)	1 (1.7)*
Grade 3 (<8-6.5 g/dl)	0
Total bilirubin	
Grade 2 (>1.5-3 x ULN)	12 (20.0)
Grade 3 (>3-10 x ULN)	0
Alanine aminotransferase	
Grade 3 (>5-20 x ULN)	1 (1.7)
Aspartate aminotransferase	
Grade 3 (>5-20 x ULN)	0

Values are n (%).
*Grade 2 hemoglobin abnormality (9.9 g/dl) occurred at a single visit.
OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; DSV, dasabuvir; ULN, upper limit of normal.

Post-baseline laboratory abnormalities were infrequent, not clinically significant, and no grade 4 abnormalities were observed (Table 2). Total bilirubin elevations were the most common laboratory abnormalities observed occurring in 12 (20.0%) patients. Hyperbilirubinemia was primarily attributed to increases in indirect bilirubin, consistent with the inhibition of the organic anion-transporting protein 1B1 and 1B3 by paritaprevir, and were not accompanied by concurrent aminotransferase elevations. Seven of the 12 patients experiencing post-baseline grade 2 elevations in total bilirubin had abnormalities at baseline, including four with grade 2 total bilirubin elevations. The highest total bilirubin value observed during treatment in any patient was 3.0 mg/dl (1.6 mg/dl indirect bilirubin). One patient experienced a grade 2 hemoglobin decline (9.9 g/dl) at week 12; this male patient had a baseline hemoglobin level of 11.3 g/dl, below the lower limit of normal. Aminotransferase elevations were observed in one patient. This 77-year old woman had asymptomatic coincident grade 3 ALT and grade 2 AST elevations at day 16 that decreased at the next study visit and normalized during the post-treatment period.

Pharmacokinetic results

Trough plasma concentrations of OBV, PTV, r, DSV, and DSV M1 metabolite were generally comparable to the C_{trough} levels observed in GT1-infected population receiving 12 or 24 weeks of OBV/PTV/r and DSV plus RBV in the phase III TURQUOISE-II trial (Table 3) [9]. C_{trough} values of OBV, PTV, r, DSV, and DSV M1 metabolite observed in TURQUOISE-III were 16%, 61%, 8%, 16%, and 14% higher, respectively, than those from TURQUOISE-II.

Table 3. Comparison of trough plasma concentrations from TURQUOISE-III and TURQUOISE-II.

Study drug	TURQUOISE-III N	TURQUOISE-III Geometric mean (arithmetic mean, %CV)	TURQUOISE-II N	TURQUOISE-II Geometric mean (arithmetic mean, %CV)
Ombitasvir[a]	38	28.3 (32.2, 53)	242	24.5 (28.7, 68)
Paritaprevir[a]	38	108 (382.4, 204)	242	66.9 (227, 257)
Ritonavir[a]	38	67.6 (123.0, 146)	242	62.6 (132, 185)
Dasabuvir[b]	35	290 (391, 88)	231	250 (324, 96)
Dasabuvir M1[b]	35	82.0 (119, 111)	231	72.2 (93.9, 84)

The units for geometric and arithmetic means are ng/ml.
[a]Binned time interval of >22–26 h.
[b]Binned time interval of >10–14 h.
CV, coefficient of variation.

Discussion

Patients with HCV infection and cirrhosis are at the highest risk for progression to hepatic decompensation, transplantation, liver-related and all-cause mortality. Studies have shown that HCV eradication in patients with cirrhosis can reduce the risk of liver decompensation, hepatocellular carcinoma, morbidity, and improve hepatic synthetic function [24–26]. In this study, treatment with OBV/PTV/r and DSV without RBV resulted in a SVR12 rate of 100% in HCV GT1b-infected patients with compensated cirrhosis, meeting the primary endpoints of non-inferiority and superiority to the SVR12 rate of sofosbuvir plus PegIFN/RBV. These results are consistent with the SVR12 rates achieved in patients from phase III trials including 68 patients with GT1b-infection and cirrhosis who received OBV/PTV/r and DSV with RBV for 12 weeks (98.5%) and 301 patients without cirrhosis who received the 3-DAAs alone for 12 weeks (100%) [9,20–22]. These data suggest that RBV does not provide incremental efficacy benefit in patients with cirrhosis with GT1b infection when treated with OBV/PTV/r and DSV.

The results of this trial can be compared to data available for other IFN-free DAA regimens either under investigation or already approved. Although guidelines recommend 24 weeks of ledipasvir/sofosbuvir alone or ledipasvir/sofosbuvir with RBV for 12 weeks in patients with cirrhosis who have failed prior therapy [5], the 12-week RBV-free combination of ledipasvir and sofosbuvir led to SVR12 rates of 96% in 57 GT1b patients with cirrhosis [27]. In the OPTMIST II trial evaluating simeprevir plus sofosbuvir without RBV for 12 weeks in patients with cirrhosis, 26 of 31 (84%) GT1b-infected patients achieved SVR [28]. Treatment with grazoprevir and elbasvir for 12 weeks in treatment-naïve GT1b-infected patients without cirrhosis resulted in an SVR12 rate of 93%, and no additional benefit was gained with co-administration of RBV [29]. In another study of this combination, all 15 GT1b-infected, PegIFN/RBV prior null responders with cirrhosis achieved SVR, however the numbers of patients who received treatment without RBV and for 12 or 18 weeks was not reported [10]. Daclatasvir with sofosbuvir has only been evaluated with RBV in patients with cirrhosis, in whom all 11 genotype 1b patients achieved SVR12 [30]. Finally,

the triple combination of daclatasvir, asunaprevir, and beclabuvir led to a 96% response rate in 27 GT1b-infected patients with cirrhosis [15]. While difficult to compare across studies, these data clearly show that OBV/PTV/r and DSV is a highly effective interferon and RBV-free regimen for GT1b-infected patients with cirrhosis.

The disease characteristics of the patients enrolled in this study were comparable to the GT1b-infected population receiving 12 weeks of OBV/PTV/r and DSV plus RBV in the phase III TURQUOISE-II trial (Supplementary Table 1) [9]. Patients with less well documented experiences of prior treatment were permitted in this study, making comparisons to prior types of virologic failure across the two studies difficult. The two study populations were similar in terms of baseline indices of liver disease severity including platelet count, albumin, total bilirubin, alpha fetoprotein, and FibroTest. Although the FibroScan cut-off for inclusion in this study was 12.5 kPa compared to 14.6 kPa in the TURQUOISE-II trial, all but five patients in this study with FibroScan measurements had values above 14.6 kPa, and the median value was 19 kPa with 20 patients (48%) above 20 kPa. Nonetheless, efficacy in both studies was exceedingly high, with the only GT1b failure being a prior partial responder in TURQUOISE-II with elevated alpha fetoprotein and thrombocytopenia at baseline. Similarly, 100% of 301 GT1b-infected patients without cirrhosis administered OBV/PTV/r and DSV without RBV achieved SVR12, including 91 with prior treatment experience and 32 prior null responders [22]. Baseline factors suggestive of portal hypertension or more advanced liver disease including thrombocytopenia, hypoalbuminemia, and FibroScan score >20 kPa, which have been shown to predict lower rates of response with some DAA regimens [27,28], did not impact SVR rates, consistent with observations in this population receiving OBV/PTV/r and DSV plus RBV [31]. These findings suggest that RBV is not required with OBV/PTV/r and DSV in the treatment of HCV GT1b patients with cirrhosis, regardless of prior PegIFN/RBV treatment response or surrogate markers of portal hypertension.

Although these results show that RBV is not required for GT1b patients with cirrhosis, all 3 DAAs are likely required for optimal efficacy with 12 weeks of treatment. In the PEARL-I study, patients were treated with OBV/PTV/r without DSV for 24 weeks [32]. SVR rates of 97.9 and 96.2% were reported for treatment-naïve and treatment-experienced GT1b patients with cirrhosis, respectively. The results from both TURQUOISE-II and now TURQUOISE-III demonstrate the additional value of DSV, which has a better side effect profile than RBV and allows for shorter treatment duration.

In the absence of RBV, trough plasma concentrations of OBV, PTV, r, DSV, and DSV M1 metabolite were comparable to this regimen administered with RBV in TURQUOISE-II. However, the 61% higher PTV C_{trough} values observed in TURQUOISE-III compared to TURQUOISE-II could be due to the smaller number of samples analyzed coupled with high variability observed with PTV in both studies (Table 3). The results are consistent with the renal elimination of RBV that would not interfere with the hepatic metabolism of OBV, PTV, r, and DSV [19,33,34].

A limitation of this study includes the open-label, single-arm, non-comparator design; however, safety comparisons for the 3-DAA regimen with RBV to placebo, or to 3-DAA without RBV, were performed in phase III studies. Rates of AEs, serious AEs, and some laboratory abnormalities for OBV/PTV/r and DSV in this study were numerically lower than that of OBV/PTV/r and DSV plus RBV in the TURQUOISE-II study, presumably due to the lack of RBV in this study (Supplementary Table 2). No new safety signals were identified compared to the reported safety profile of this RBV-free regimen in HCV GT1-infected patients without cirrhosis [20,21]. The majority of laboratory abnormalities, particularly events of hyperbilirubinemia, were influenced by pre-existing liver disease due to the permissive inclusion/exclusion criteria of this study. One patient experienced AEs which were considered severe (and serious), attributable to concomitant medication and DAAs. This regimen was well tolerated and no patient prematurely discontinued study drug.

In conclusion, the 12-week 3-DAA regimen of OBV/PTV/r and DSV achieved an SVR12 rate of 100% in previously PegIFN/RBV treated and untreated patients with HCV GT1b infection and compensated cirrhosis. Treatment was well tolerated with a low rate of serious AEs and no premature treatment discontinuations. Based on a cross-study comparison in a similar patient population, the rates of common AEs, anemia, and hyperbilirubinemia were lower in this study without RBV than was observed in TURQUOISE-II where RBV was given. These results suggest that OBV/PTV/r and DSV for 12 weeks is a highly efficacious treatment for GT1b patients with compensated cirrhosis, and RBV is not required to maximize SVR rates.

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Conflict of interest

JJ Feld: Grant/Research Support: AbbVie, Boehringer Ingelheim, Gilead, Janssen, Merck; Scientific consulting/Advisory Board: AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Merck, Theravance.
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Authors' contributions

JJF, RT, LL, BF, KH, ARP, and NSS contributed to the conception and design of the study. JFF, CM, RT, ET, SB, YH, ME, DEB, ZY, RWR, LL, BF, KH, ARP, AP, NSS, and FP contributed to the generation, collection, assembly, analysis and/or interpretation of data. JFF, CM, RT, ET, SB, YH, ME, DEB, ZY, RWR, LL, BF, KH, ARP, AP, NSS, and FP contributed to critical revision of the manuscript for important intellectual content, and approved the final version of the manuscript.

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Supplementary data

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