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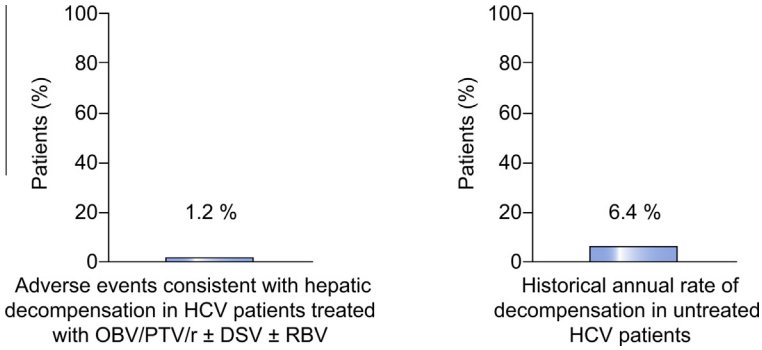
Safety of the 2D/3D direct-acting antiviral regimen in HCV-induced Child-Pugh A cirrhosis – A pooled analysis

Graphical abstract



Highlights

- OBV/PTV/r ± DSV ± RBV was well tolerated in patients with Child-Pugh A cirrhosis.
- Low rates of serious adverse events and those leading to discontinuation of study drugs.
- Events consistent with hepatic decompensation occurred in 1.2% of patients (13/1066).
- Decompensation events occurred across the treatment period and post treatment.
- Rates of decompensation events were comparable in treated and untreated patients.

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Lay summary

This pooled safety analysis in 1066 HCV-infected patients with compensated cirrhosis, receiving treatment with ombitasvir, paritaprevir, and ritonavir with or without dasabuvir, with or without ribavirin, shows that the rate of hepatic decompensation events was similar to previously reported rates in untreated patients.

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Research Article

JOURNAL OF HEPATOLOGY

Safety of the 2D/3D direct-acting antiviral regimen in HCV-induced Child-Pugh A cirrhosis – A pooled analysis

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Background & Aims: Chronic hepatitis C virus (HCV)-infected patients with cirrhosis are a high-priority population for treatment. To help inform the benefit–risk profile of the all-oral direct-acting antiviral (DAA) combination regimen of ombitasvir, paritaprevir, and ritonavir, with or without dasabuvir (OBV/PTV/r ± DSV) in patients with Child-Pugh A cirrhosis, we undertook a comprehensive review of AbbVie-sponsored clinical trials enrolling patients with Child-Pugh A cirrhosis.

Methods: Twelve phase II or III clinical trials of the 2-DAA regimen of OBV/PTV/r ± ribavirin (RBV) or the 3-DAA regimen of OBV/PTV/r + DSV ± RBV that included patients with Child-Pugh A cirrhosis were reviewed; patients who completed treatment by November 16, 2015 were included in a pooled, *post hoc* safety assessment. The number and percentage of patients with treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs consistent with hepatic decompensation were reported.

Results: In 1,066 patients with Child-Pugh A cirrhosis, rates of serious TEAEs and TEAEs leading to study drug discontinuation were 5.3% (95% confidence interval [CI]: 4.1–6.8) and 2.2% (95% CI: 1.4–3.2), respectively. Thirteen patients (1.2%; 95% CI: 0.7–2.1) had a TEAE that was consistent with hepatic decompensation. The most frequent TEAEs consistent with hepatic decompensation were ascites (n = 8), esophageal variceal hemorrhage (n = 4), and hepatic encephalopathy (n = 2).

Conclusions: This pooled analysis in 1,066 HCV-infected patients with Child-Pugh A cirrhosis confirms the safety of OBV/PTV/r ± DSV ± RBV in this population. These results support the use of OBV/PTV/r ± DSV ± RBV in this high-priority population.

Lay summary: This pooled safety analysis in 1,066 HCV-infected patients with compensated cirrhosis, receiving treatment with ombitasvir, paritaprevir, and ritonavir with or without dasabuvir, with or without ribavirin, shows that the rate of hepatic decompensation events was similar to previously reported rates in untreated patients.

Introduction

Chronic hepatitis C virus (HCV) infection is characterized by progressive liver damage and fibrosis, which can lead to liver failure or hepatocellular carcinoma.[1] In 2013, an estimated 357,800 people worldwide died from HCV-related cirrhosis, and an additional 342,500 people died from liver cancer caused by HCV.[2] The burden of HCV-associated liver disease is projected to continue to increase in many countries in the coming decades.[3]

Cirrhosis is characterized by an initial compensated phase during which clinical symptoms are frequently absent, followed by a progressive decompensated phase during which clinical findings manifest.[1] Clinical symptoms and complications of decompensated cirrhosis include jaundice, ascites, variceal hemorrhage, and hepatic encephalopathy.[4,5] Based on three published reports, including a systematic review of 118 studies, the estimated risk of progression to decompensated cirrhosis in HCV-infected patients with compensated cirrhosis is ⩽6.4% per annum.[6–8] Survival rates following diagnosis of decompensated cirrhosis are 82% at one year, decreasing to 51% at five years post diagnosis.[5] Unfortunately, there continues to be a high burden of morbidity and mortality among patients with decompensated cirrhosis who achieve a sustained virologic response (SVR) following successful treatment with direct-acting antiviral (DAA) therapy.[9]

International guidelines on the treatment of chronic HCV consider patients with cirrhosis as a high-priority population for treatment with approved regimens.[10] The Child-Pugh scoring system incorporates bedside findings and laboratory variables to help stratify the severity of cirrhotic liver disease.[11] Among

Keywords: Ombitasvir; Paritaprevir; Dasabuvir; Ribavirin; Child-Pugh A; Cirrhosis.
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HCV treatment-naive or treatment-experienced patients with Child-Pugh A compensated cirrhosis, the all-oral 3-DAA regimen of ombitasvir, paritaprevir (identified by AbbVie and Enanta), with the pharmacokinetic enhancer ritonavir, and dasabuvir (OBV/PTV/r + DSV), demonstrated SVR rates of 94% in genotype (GT) 1a-infected patients, on a 24-week regimen with ribavirin (RBV), and 100% in GT1b-infected patients, treated for 12 weeks without RBV.[12,13] Among treatment-naive or treatment-experienced GT4-infected patients with Child-Pugh A compensated cirrhosis, the all-oral 2-DAA regimen of OBV/PTV/r + RBV achieved SVR rates of 96–97% with 12 weeks of treatment.[14,15] The safety profiles of OBV/PTV/r + DSV and OBV/PTV/r in patients with Child-Pugh A compensated cirrhosis were generally similar to those in patients without cirrhosis.[12–21] In a separate ongoing study of GT1-infected patients with Child-Pugh B cirrhosis treated with OBV/PTV/r + DSV, all 11 patients achieved sustained virologic response at post-treatment week 12 (SVR12); however, the sample size was not sufficient to fully characterize the safety profile of this regimen in these more advanced patients.[22]

Recently, the AASLD/IDSA HCV Guidance Panel published an update to the *Hepatitis C Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C Virus* regarding the use of OBV/PTV/r + DSV and OBV/PTV/r regimens.[6] This update was prompted by a change to the US Prescribing Information for OBV/PTV/r + DSV and OBV/PTV/r, which contraindicated their use in patients with Child-Pugh B cirrhosis.[23] This change followed post-marketing reports describing cases of hepatic decompensation in patients with cirrhosis who were receiving OBV/PTV/r + DSV. However, due to the nature of the pharmacovigilance process, reported cases may lack sufficient information to accurately characterize events and determine their relationship to treatment regimens. Moreover, it is difficult to calculate the frequency at which these outcomes occur, because reporting is inconsistent and total numbers treated are not known. Analyses of pooled safety data from clinical trials, which include systematically collected information on adverse events and baseline characteristics, allow for accurate quantification of risks, albeit the patient populations are often small and homogeneous. To better characterize the benefit–risk profile of OBV/PTV/r ± DSV ± RBV in patients with Child-Pugh A cirrhosis, we undertook a comprehensive review of AbbVie-sponsored clinical trials that enrolled patients with Child-Pugh A cirrhosis. We report results from this *post hoc* pooled safety assessment of OBV/PTV/r ± DSV ± RBV in HCV-infected patients with Child-Pugh A compensated cirrhosis in 12 phase II or III trials.

Patients and methods

Study design

This was a *post hoc* pooled safety assessment of the 2-DAA regimen of OBV/PTV/r ± RBV and the 3-DAA regimen of OBV/PTV/r + DSV ± RBV across 12 phase II or III studies that included patients with compensated cirrhosis. The criteria for establishing a diagnosis of compensated cirrhosis were study specific but across studies was determined by liver biopsy, FibroScan, or serum markers including FibroTest or aspartate aminotransferase to platelet ratio index.

Study designs have been described previously.[12–15,19,24–29] All patients in the studies provided written informed consent before any study-specific procedures were carried out. The studies were conducted in accordance with the International Conference on Harmonisation guidelines, applicable regulations, and the principles of the Declaration of Helsinki. The study protocols were approved by each of the independent ethics committees or institutional review boards at each of the participating study sites. All authors had access to the study data and reviewed and provided feedback on all subsequent versions of the manuscript and made the decision to submit the manuscript for publication.

Patient population

All phase II or III clinical trials of OBV/PTV/r ± RBV or OBV/PTV/r + DSV ± RBV that included patients with Child-Pugh A cirrhosis at screening and had patients who had completed treatment by November 16, 2015 were included in the pooled *post hoc* safety assessment. HCV-infected patients with Child-Pugh A compensated cirrhosis who had completed or prematurely discontinued treatment with either OBV/PTV/r ± RBV or OBV/PTV/r + DSV ± RBV were included in the safety assessment (data cut-off date November 18, 2015). Although only patients with Child-Pugh A cirrhosis at the time of screening were enrolled in these trials, a small number of patients had an increase in Child-Pugh score between the screening visit and the baseline visit (day 1); thus, 19 patients with Child-Pugh B cirrhosis at baseline were included in this analysis. Patient eligibility criteria for each of the 12 studies have been described previously.[12–15,19,24–29]

Study medication

Patients with HCV GT1b, GT2, or GT4 infection in the PEARL-1, AGATE-I and -II, and GIFT-I and -II trials received OBV/PTV/r (25/150/100 mg once daily [QD]) for 12, 16, or 24 weeks. Patients with HCV GT1 infection in the TURQUOISE-II, -III, and -IV, TOPAZ-I, -II, and -III, and TOPAZ-VA trials received OBV/PTV/r (25/150/100 mg QD) and DSV (250 mg twice daily) for 12 or 24 weeks. Patients in some treatment arms received RBV dosed according to body weight, with a total daily dose of 1,000 mg ($<$75 kg) or 1,200 mg ($\geqslant$75 kg).

Safety

Data on all treatment-emergent adverse events (TEAEs) were collected from the start of study drug administration through to 30 days after the end of treatment. Serious adverse events (SAEs) were recorded from the time a patient signed the informed consent through to at least 30 days after the last dose of study drug or the end of study participation. Adverse events and SAEs were considered treatment-emergent if they had an onset during the period from the start of study drug administration through to 30 days after the end of treatment. This analysis assessed the number and percentage of patients with TEAEs reported by the study investigator that were consistent with hepatic decompensation, based on adjudication of hepatic disorders according to the Standardized Medical Dictionary for Regulatory Activities (MedDRA version 18.1) Query (SMQ) Hepatic Disorders (broad).[30] Preferred terms that could be adjudicated as a TEAE consistent with hepatic decompensation are presented in Table S1. Given that PTV is an inhibitor of the bilirubin transport protein OATP1B1 and can cause benign indirect hyperbilirubinemia, especially when administered with RBV, hyperbilirubinemia, in the absence of other findings suggestive of hepatic dysfunction, was considered most likely a result of this effect. Therefore, isolated events of jaundice or hyperbilirubinemia without concomitant evidence of hepatic decompensation or insufficiency (*e.g.* increased international normalized ratio [INR], decreased albumin) were not considered events consistent with hepatic decompensation in this analysis.

Virologic response

Plasma HCV RNA levels were determined by a central laboratory using the Roche COBAS TaqMan® real-time reverse transcriptase polymerase chain reaction (RT PCR) assay v2.0 (lower limit of quantification [LLOQ] = 25 IU/ml) (Roche, Nutley, NJ, USA) or Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 (LLOQ = 15 IU/ml) (Roche, Nutley, NJ, USA).

Rates of SVR12 at (HCV RNA $<$ LLOQ) were calculated for patients who experienced an event consistent with hepatic decompensation.

Statistical analyses

Baseline demographics and disease characteristics were summarized for patients with cirrhosis who were treated with OBV/PTV/r ± DSV ± RBV in the selected studies. Safety was assessed among all patients who received at least one dose of the study drug.

An exploratory stepwise logistic regression modeling assessed predictors (significance level = 0.10 to enter and stay in model) of TEAEs consistent with hepatic decompensation. Presence or absence of a TEAE consistent with hepatic

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decompensation was the dependent variable, and baseline characteristics considered as independent variables were HCV RNA (continuous, $\log_{10}$ IU/ml); platelet counts (continuous, 10^9/L); serum albumin (continuous, g/L); serum bilirubin (continuous, mg/dl); INR (continuous); calculated creatinine clearance by Cockcroft-Gault equation (continuous, ml/min); model for end-stage liver disease (MELD) score (continuous); history of esophageal varices (yes, no); history of diabetes (yes, no); prior history of non-selective beta blocker use for varices (yes, no), sex (male, female); race (black, white, Asian, other); age (continuous, years); body mass index (continuous, kg/m^2); ethnicity (Hispanic or Latino, Japanese, not Hispanic or Latino or Japanese); and prior HCV treatment status (naive, experienced).

SAS® software (SAS Institute, Inc., Cary, NC, USA), for the UNIX operating system, was used for all analyses.

For further details regarding the materials used, please refer to the Supplementary material and the CTAT table.

Results

Baseline characteristics

A total of 1,066 HCV-infected patients with cirrhosis were included in the pooled safety assessment; 332 (31.1%) were treated with OBV/PTV/r ± RBV, and 734 (68.9%) were treated with OBV/PTV/r + DSV ± RBV. Most patients (864; 81.1%) received RBV. Baseline demographics and disease characteristics are presented in Table 1. Overall, 346 (32.5%) were female, 185 (17.4%) were ⩾65 years old, and the median body mass index was 27.2 kg/m^2. The majority of patients (859; 80.6%) had a baseline HCV RNA ⩾800,000 IU/ml. Most patients (874; 82.0%) were infected with HCV GT1. Approximately half of the patients (480; 45.0%) were HCV treatment-naive. The majority of patients (891; 85.6%) had a baseline Child-Pugh score of five, 130 (12.5%) had a score of six, and 19 (1.8%) had a score of seven or eight. Baseline platelet counts <50 and <90 cells×10^9/L were recorded in nine (0.8%) and 191 (17.9%) patients, respectively. Few patients had a prior history of ascites (3; 0.3%), hepatic encephalopathy (4; 0.4%), or esophageal varices (91; 8.5%).

Safety

Overall rates of serious TEAEs and TEAEs leading to study drug discontinuation were 5.3% (95% confidence interval [CI]: 4.1–6.8) and 2.2% (95% CI: 1.4–3.2), respectively. There were no obvious differences in these rates among the different treatment groups, except that both serious TEAEs and TEAEs leading to study drug discontinuation were less frequent in the 62 patients who received OBV/PTV/r + DSV without RBV (Table 2). In total, 13 patients (1.2%; 95% CI: 0.7–2.1) had a TEAE reported by the study investigator that was consistent with hepatic decompensation; 11 of the 13 patients (85%) received RBV. Rates of individual events were low (<1%) (Table 2). Two TEAEs consistent with hepatic decompensation (liver failure and hepatorenal syndrome), which occurred in the same patient, were considered to potentially relate to the study drug by the study investigator. Two isolated cases of hyperbilirubinemia and one case of jaundice were potentially related to the study drug. Five of the 13 patients experienced serious TEAEs consistent with hepatic decompensation, including four patients with esophageal variceal hemorrhage and one patient who developed liver failure and hepatorenal syndrome. A 59-year-old female patient who developed liver failure and hepatorenal syndrome discontinued the study drug after 56 days of treatment and was hospitalized two days later. No information is available on the clinical outcome or virologic response for this patient because she was subsequently lost to follow-up. An additional patient experienced a non-serious event of ascites after eight days of treatment, but died eight days later due to multiple organ failure as a result of community-acquired pneumonia. Five patients (38.5%) with a TEAE consistent with hepatic decompensation discontinued treatment prematurely.

Day of onset of TEAEs consistent with hepatic decompensation is presented in Fig. 1. The onset of these events was spread across the treatment period and 30 days post-treatment. Clinical outcomes for patients with TEAEs consistent with hepatic decompensation are given in Table 3. These events resolved in nine patients (69.2%), including six patients who continued treatment with the study drug. Clinical summaries for the 13 patients with TEAEs consistent with hepatic decompensation are presented in Table S2.

Change in Child-Pugh score based on changes in total bilirubin values

Among the 1,021 patients with a Child-Pugh score of five or six at baseline, 7.3% of patients (65/891) with a baseline Child-Pugh score of five and 36.2% of patients (47/130) with a baseline Child-Pugh score of six experienced an increase in their Child-Pugh score to seven or greater due to increased total bilirubin alone during treatment with OBV/PTV/r ± DSV ± RBV.

Baseline factors associated with TEAEs consistent with hepatic decompensation

Compared with patients who did not experience a TEAE consistent with hepatic decompensation, those patients who did experience such an event had a higher frequency of baseline Child-Pugh score of six or greater, platelet count <90×10^9 cells/L, and serum albumin <3.5 g/dl, all characteristics consistent with more advanced liver disease (Table 4).

The exploratory stepwise logistic regression analysis demonstrated that lower baseline albumin, prior history of non-selective beta blocker use for varices and lower baseline HCV RNA were independently associated with TEAEs consistent with hepatic decompensation (p <0.05; Table 5).

Virologic response

There were no confirmed virologic relapses or breakthroughs among the 13 patients who experienced a TEAE consistent with hepatic decompensation. Ten of these 13 patients (77%) achieved SVR; this number includes one patient who achieved SVR four weeks after the end of treatment but who had not reached post-treatment week 12 at the time of analysis. Among the patients who did not achieve SVR, one discontinued treatment prematurely, one was lost to follow-up, and one died prior to post-treatment week 12 (due to multiple organ failure as a result of community-acquired pneumonia).

Discussion

In this pooled analysis of 1,066 HCV-infected patients with Child-Pugh A cirrhosis, treatment with OBV/PTV/r ± DSV ± RBV was well-tolerated, demonstrated by low rates of SAEs (5.3%) and TEAEs leading to study drug discontinuation (2.2%). In total, 13 out of 1,066 patients (1.2%) experienced an event that was consistent with hepatic decompensation. Our observations are

Table 1. Baseline demographics and patient characteristics.

Characteristic	OBV/PTV/r n = 140	OBV/PTV/r + RBV n = 192	OBV/PTV/r + DSV n = 62	OBV/PTV/r + DSV + RBV n = 672	Total N = 1,066
Women, n (%)	65 (46.4)	49 (25.5)	23 (37.1)	209 (31.1)	346 (32.5)
Age (years), median (range)	59.0 (38.0–76.0)	56.0 (32.0–81.0)	61.0 (26.0–78.0)	57.0 (21.0–79.0)	58.0 (21.0–81.0)
BMI (kg/m^2), median (range)	25.8 (15.0–38.4)	27.8 (18.9–47.8)	27.0 (18.0–42.3)	27.4 (17.0–51.7)	27.2 (15.0–51.7)
Race, n (%)					
White	96 (68.6)	154 (80.2)	54 (87.1)	628 (93.5)	932 (87.4)
Black or African American	0	23 (12.0)	7 (11.3)	31 (4.6)	61 (5.7)
Asian	42 (30.0)	14 (7.3)	0	11 (1.6)	67 (6.3)
Other	2 (1.4)	1 (0.5)	1 (1.6)	2 (0.3)	6 (0.6)
Ethnicity					
Hispanic or Latino	3 (2.1)	3 (1.6)	3 (4.8)	84 (12.5)	93 (8.7)
Japanese	41 (29.3)	10 (5.2)	0	0	51 (4.8)
No ethnicity	96 (68.6)	179 (93.2)	59 (95.2)	588 (87.5)	922 (86.5)
HCV RNA, n (%)					
⩾800,000 IU/ml	116 (82.9)	135 (70.3)	56 (90.3)	522 (82.1)	859 (80.6)
Viral load (log_{10} IU/ml, median (range)	6.5 (4.5–7.7)	6.2 (2.3–7.2)	6.7 (3.8–7.5)	6.4 (2.9–7.7)	6.4 (2.3–7.7)
HCV genotype, n (%)					
1	140 (100)	0	62 (100)	672 (100)	874 (82.0)
2	0	10 (5.2)	0	0	10 (0.9)
4	0	182 (94.8)	0	0	182 (17.1)
IL28B genotype, n (%)*					
CC	39 (27.9)	25 (19.1)	10 (16.1)	128 (19.1)	202 (20.1)
CT	81 (57.9)	71 (54.2)	37 (59.7)	404 (60.2)	593 (59.1)
TT	20 (14.3)	35 (26.7)	15 (24.2)	139 (20.7)	209 (20.8)
Missing	0	61	0	1	62
Prior therapy (IFN-based), n (%)					
Treatment-naive	55 (39.3)	93 (48.4)	28 (45.2)	304 (45.2)	480 (45.0)
Child-Pugh score, n (%)*					
5	119 (85.0)	168 (87.5)	48 (77.4)	556 (85.9)	891 (85.6)
6	17 (12.1)	19 (9.9)	12 (19.4)	82 (12.7)	130 (12.5)
>6†	4 (2.9)	4 (2.1)	2 (3.2)	9 (1.4)	19 (1.8)
Other‡	0	1 (0.5)	0	0	1 (0.1)
Missing	0	0	0	25	25
Platelet count, n (%)*					
<50×10^9 cells/L	0	2 (1.0)	0	7 (1.0)	9 (0.8)
<90×10^9 cells/L	31 (22.1)	34 (17.7)	13 (21.0)	113 (16.8)	191 (17.9)
Missing	0	0	0	1	1
Albumin, n (%)					
<3.5 g/dl	14 (10.0)	11 (5.7)	10 (16.1)	53 (7.9)	88 (8.3)
Total bilirubin (mg/dl), median (range)	0.76 (0.23–3.33)	0.70 (0.18–2.57)	0.80 (0.29–2.51)	0.76 (0.18–3.40)	0.76 (0.18–3.40)
INR (ratio), median (range)	1.10 (0.90–1.50)	1.08 (0.90–2.60)	1.10 (0.90–1.30)	1.07 (0.85–3.42)	1.09 (0.85–3.42)
MELD score, median (range)	7.50 (6.43–15.52)	7.50 (6.43–17.49)	7.88 (6.43–12.57)	7.50 (6.43–20.20)	7.50 (6.43–20.20)
Creatinine clearance, n (%)					
<60 ml/min	9 (6.4)	3 (1.6)	8 (12.9)	11 (1.6)	31 (2.9)
History of diabetes, n (%)	32 (22.9)	52 (27.1)	12 (19.4)	121 (18.0)	217 (20.4)
History of ascites, n (%)	1 (0.7)	0	1 (1.6)	1 (0.1)	3 (0.3)
History of hepatic encephalopathy, n (%)	0	0	0	4 (0.6)	4 (0.4)
History of esophageal varices, n (%)	15 (10.7)	11 (5.7)	8 (12.9)	57 (8.5)	91 (8.5)

OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; RBV, ribavirin; DSV, dasabuvir; BMI, body mass index; HCV, hepatitis C virus; RNA, ribonucleic acid; *IL28B*, interleukin-28B; IFN, interferon; INR, international normalized ratio; MELD, model for end-stage liver disease.

* Percentages are based on the number of patients with available data (ie, patients with missing data are not included in the calculation).

† Child-Pugh scores of 7 or 8.

‡ Child-Pugh score of 3.

further supported by a recent real-world meta-analysis among 5,158 patients receiving treatment with OBV/PTV/r ± DSV ± RBV, 63% of whom (n = 3,240) had cirrhosis, showing that in the five studies with reported data (n = 3,440), a total of 33 patients reported hepatic decompensation (0.96%; 95% CI 0.68–1.34); in the seven studies with reported data (n = 2,370), 74 patients (3.12%) reported SAEs; and in the 12 studies with reported data (n = 5,170), 129 patients (2.5%) discontinued drug for any reason.[31]

TEAEs consistent with hepatic decompensation have been reported in patients with advanced liver disease, treated with a number of DAA regimens. These events tend to occur at various times during treatment and even post treatment, as seen in the present analysis, making it difficult to establish a causal relationship with specific DAA treatments.[32–37] Given that hepatic decompensation events have been reported in association with multiple classes of DAAs, it is unclear whether direct toxicity of DAAs, including protease inhibitors, is responsible for these

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Table 2. Treatment-emergent adverse events reported by the study investigator.

	OBV/PTV/r n = 140	OBV/PTV/r + RBV n = 192	OBV/PTV/r + DSV n = 62	OBV/PTV/r + DSV + RBV n = 672	Total N = 1,066
Serious TEAE, n (%)	7 (5.0)	10 (5.2)	1 (1.6)	38 (5.7)	56 (5.3)
Discontinuation of study drug due to a TEAE, n (%)	4 (2.9)	0	0	19 (2.8)	23 (2.2)
TEAE of interest,* n (%)					
Any event†	2 (1.4)	4 (2.1)	0	7 (1.0)	13 (1.2)
Ascites	2 (1.4)	2 (1.0)	0	4 (0.6)	8 (0.8)
Esophageal varices hemorrhage	1 (0.7)	2 (1.0)	0	1 (0.1)	4 (0.4)
Hepatic failure	0	0	0	1 (0.1)	1 (<0.1)
Hepatorenal syndrome	0	0	0	1 (0.1)	1 (<0.1)
Hypoalbuminemia	0	1 (0.5)	0	0	1 (<0.1)
Hepatic encephalopathy	0	1 (0.5)	0	1 (0.1)	2 (0.2)
Jaundice‡	0	1 (0.5)	0	2 (0.3)	3 (0.3)
Increased bilirubin‡	0	1 (0.5)	0	0	1 (0.1)

OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; RBV, ribavirin; DSV, dasabuvir; TEAE, treatment-emergent adverse event.
* TEAE consistent with hepatic decompensation from adjudication of hepatic disorders according to the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) Hepatic Disorders (broad).
† A total of 18 adverse events consistent with hepatic decompensation occurred in 13 patients; one patient had two episodes of ascites.
‡ Events of jaundice (n = 3) and increased bilirubin (n = 1) were reported in three subjects with hepatic decompensation events.

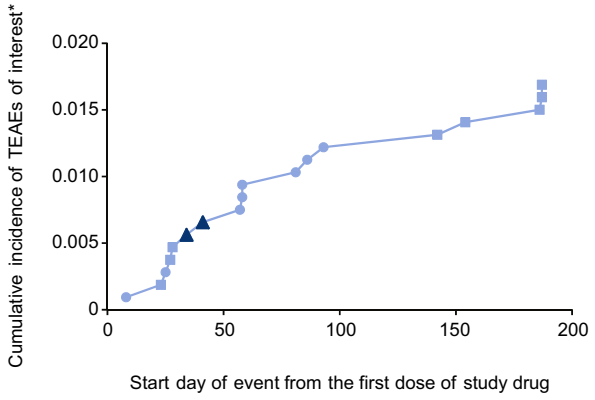

Fig. 1. Cumulative onset of treatment-emergent adverse events consistent with hepatic decompensation by planned treatment duration. Circles represent treatment-emergent adverse events (TEAEs) of interest among patients receiving 12 weeks of treatment, triangles represent TEAEs of interest among patients receiving 16 weeks of treatment, and squares represent TEAEs of interest among patients receiving 24 weeks of treatment. One patient had two episodes of ascites, one at day 142 and one at day 186. *TEAE consistent with hepatic decompensation from adjudication of hepatic disorders according to the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) Hepatic Disorders (broad).

Table 3. Clinical outcomes in patients with treatment-emergent adverse events consistent with hepatic decompensation.

TEAE of interest,* n (%)	OBV/PTV/r ± DSV ± RBV N = 13
TEAE(s) resolved†	9 (69.2)
TEAE(s) ongoing‡	2 (15.4)
Death§	1 (7.7)
Information not available	1 (7.7)

TEAE, treatment-emergent adverse event; OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; DSV, dasabuvir; RBV, ribavirin.
* TEAE consistent with hepatic decompensation from adjudication of hepatic disorders according to the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) Hepatic Disorders (broad).
† TEAEs resolved in six patients while continuing treatment and in three patients post discontinuation.
‡ At least one event was ongoing at the end of the follow-up or data cut-off date.
§ One patient died as a result of community-acquired pneumonia, leading to multiple organ failure.

events.[38] Another possibility is that hepatic decompensation events reported with DAAs are unrelated to therapy and are instead simply part of the natural history of advanced liver disease caused by HCV infection.[38] This theory is consistent with the findings of the present analysis, in which the rate of TEAEs consistent with hepatic decompensation is within the range for the previously reported annual risk of up to 6.4% for hepatic decompensation in HCV-infected patients with compensated cirrhosis.[6–8] However, prescribing information for currently available regimens containing an HCV NS3-4A protease inhibitor typically contraindicate or recommend against their use in patients with Child-Pugh B or C cirrhosis. More data are needed to establish whether there is a causal relationship between this and other classes of DAA and events of hepatic decompensation.

Importantly, many of the events consistent with hepatic decompensation were self-limiting and improved without treatment interruption, or occurred at time points not typically associated with drug toxicity. Ascites (n = 8), variceal hemorrhage (n = 4), and encephalopathy (n = 2) were the most frequently reported events; there was one case of hepatic failure with hepatorenal syndrome. Five of the 13 patients with TEAEs consistent with hepatic decompensation discontinued study drug and 10 achieved an SVR. There was one reported death due to multiple organ failure as a result of community-acquired pneumonia. Overall, 11% of patients in this cohort experienced an increase in Child-Pugh score to seven or greater during treatment with OBV/PTV/r ± DSV ± RBV, owing to increased total bilirubin alone.

Most TEAEs consistent with hepatic decompensation were considered by the investigator causally unrelated to study drug administration. Two cases, an event of hypoalbuminemia and a case of ascites, occurred in patients with associated bacterial infections, while a second case of ascites occurred in a patient who was later diagnosed with hepatocellular carcinoma.

In the present analysis, baseline characteristics consistent with advanced liver disease were enriched in the group of patients who experienced a TEAE consistent with hepatic decom-

Table 4. Baseline demographics of patients with or without a treatment-emergent adverse event consistent with hepatic decompensation.

Characteristic	TEAE of interest*	
	No n = 1,053	Yes n = 13
Female sex, n (%)	341 (32.4)	5 (38.5)
Age (years), median (range)	57 (21–81)	60 (28–72)
BMI (kg/m^2), median (range)	27.2 (15.0–51.7)	26.7 (23.9–37.2)
Race, n (%)		
White	920 (87.4)	12 (92.3)
Black or African American	60 (5.7)	1 (7.7)
Asian	67 (6.4)	0
Other	6 (0.6)	0
Ethnicity		
Hispanic or Latino	93 (8.8)	0
Japanese	51 (4.8)	0
No ethnicity	909 (86.3)	13 (100)
HCV RNA, n (%)		
⩾800,000 IU/ml	851 (80.8)	8 (61.5)
HCV genotype, n (%)		
1	865 (82.1)	9 (69.2)
2	10 (0.9)	0
4	178 (16.9)	4 (30.8)
IL28B genotype, n (%)		
CC	198 (20.0)	4 (33.3)
CT	585 (59.0)	8 (66.7)
TT	209 (21.1)	0
Missing	61	1
Prior therapy (IFN-based), n %		
Treatment-naive	471 (44.7)	9 (69.2)
Child-Pugh score, n (%)		
5	886 (86.2)	5 (38.5)
6	122 (11.9)	8 (61.5)†
>6	19 (1.8)	0
Missing or other	25	0
Platelet count, n (%)		
<50 cells×10^9/L	9 (0.9)	0
<90 cells×10^9/L	185 (17.6)	6 (46.2)‡
Missing	1	0
Albumin, n (%)		
<3.5 g/dl	83 (7.9)	5 (38.5)§
Total bilirubin (mg/dl), median (range)	0.76 (0.18–3.40)	1.05 (0.40–1.75)
INR (ratio), median (range)	1.09 (0.85–3.42)	1.10 (0.90–1.32)
MELD score, median (range)	7.50 (6.43–20.20)	9.08 (6.43–11.66)
Creatinine clearance, n (%)		
<60 ml/min	31 (2.9)	0
History of diabetes, n (%)	214 (20.3)	3 (23.1)
History of ascites, n (%)	3 (0.3)	0
History of hepatic encephalopathy, n (%)	4 (0.4)	0
History of esophageal varices, n (%)	88 (8.4)	3 (23.1)

TEAE, treatment-emergent adverse event; BMI, body mass index; HCV, hepatitis C virus; RNA, ribonucleic acid; *IL28B*, interleukin-28B; IFN, interferon; INR, international normalized ratio; MELD, model for end-stage liver disease.

* TEAE consistent with hepatic decompensation from adjudication of hepatic disorders according to the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) Hepatic Disorders (broad).

† Child-Pugh score ⩾6 *vs.* 5 or missing/other; p <0.0003.

‡ Platelet count <90 cells × 10^9/L *vs.* ⩾90 cells × 10^9/L or missing; p = 0.0173.

§ Albumin <35 g/L *vs.* ⩾35 g/L; p = 0.0026.

pensation, compared with those who did not. Low baseline albumin (⩽3.6 g/dl), HCV RNA (⩽6.4 $\log_{10}$ IU/ml), and prior history of non-selective beta blocker use for varices were identified as predictive factors associated with TEAEs consistent with hepatic decompensation. The association between low baseline HCV RNA levels and TEAEs consistent with hepatic decompensation is consistent with previous observations that low serum HCV RNA levels may be a surrogate marker for advanced cirrhosis.[39,40]

A limitation of this analysis is that only 13 patients with TEAEs consistent with hepatic decompensation were identified, and the analysis therefore had low power to identify predictors of hepatic decompensation. Results of the stepwise logistic regression analysis should therefore be interpreted with caution.

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Table 5. Patient characteristics associated with increased risk of treatment-emergent adverse events consistent with hepatic decompensation.*

	Odds ratio [95% CI]	*p* value
Baseline albumin level (continuous, g/L)	0.85 [0.76, 0.96]	0.008
Baseline HCV RNA (continuous, $\log_{10}$ IU/ml)	0.39 [0.22, 0.72]	0.003
Prior history of non-selective beta blockers for varices (yes, no)	4.86 [1.19, 19.83]	0.028

CI, confidence interval; HCV, hepatitis C virus; RNA, ribonucleic acid; INR, international normalized ratio; MELD, model for end-stage liver disease; BMI, body mass index.
* Independent baseline variables that were considered in stepwise logisitic regression modeling (significance level = 0.10 to enter and stay in model): HCV RNA (continuous, $\log_{10}$ IU/ml); platelet counts (continuous, 10^9/L); albumin (continuous, g/L); bilirubin (continuous, mg/dl); INR (ratio); creatinine clearance (continuous, ml/min); MELD score (continuous); history of esophageal varices (yes, no); history of diabetes (yes, no); prior medical history of non-selective beta blocker for varices (yes, no), sex (male, female); race (black, white, Asian, other); age (continuous, years); BMI (continuous, kg/m^2); ethnicity (Hispanic or Latino, Japanese, not Hispanic or Latino); and prior treatment status (naive, experienced).

Despite these limitations and the fact that these events occurred at a low rate in this analysis, our results suggest caution should be exercised when considering the use of OBV/PTV/r with or without DSV in patients with signs of advanced cirrhosis.

Conclusion

In summary, this pooled analysis in 1,066 HCV-infected patients demonstrates that among patients with Child-Pugh A cirrhosis treated with OBV/PTV/r ± DSV ± RBV, the rate of TEAEs consistent with hepatic decompensation was 1.2%, which is lower than the rate of hepatic decompensation previously reported in the untreated cirrhotic population. Patients with prior evidence of advanced cirrhosis were more likely to experience such TEAEs. These data support the use of OBV/PTV/r ± DSV ± RBV in patients with cirrhosis, but these regimens should be avoided in patients with a history of hepatic decompensation.

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Conflict of interest

F. Poordad; Grant/Research Support: AbbVie, Achillion Pharmaceuticals, Anadys Pharmaceuticals, Biolex Therapeutics, Boehringer Ingelheim, BMS, Genentech, Gilead, GlaxoSmithKline, GlobeImmune, Idenix Pharmaceuticals, Idera Pharmaceuticals, Intercept Pharmaceuticals, Janssen, Medarex, Medtronic, Merck, Novartis, Santaris Pharmaceuticals, Scynexis Pharmaceuticals, Vertex Pharmaceuticals, ZymoGenetics; Speaker: Gilead, Kadmon, Merck, Onyx/Bayer, Genentech, GlaxoSmithKline, Salix, Vertex; Consultant/Advisor: AbbVie, Achillion Pharmaceuticals, Anadys Pharmaceuticals, Biolex Therapeutics, Boehringer Ingelheim, BMS, Gilead, GlaxoSmithKline, GlobeImmune, Idenix, Merck, Novartis, Tibotec/Janssen, Theravance, Vertex. D.R. Nelson; Advisory Committees or Review Panels: Merck; Grant/Research Support: Abbott, BMS, Boehringer Ingelheim, Gilead, Genentech, Merck, Bayer, Idenix, Vertex, Janssen. J.J. Feld; Grant/Research Support: AbbVie, Boehringer Ingelheim, Gilead, Janssen, Merck; Scientific Consulting/Advisory Board: AbbVie, BMS, Gilead, Janssen, Merck, Theravance. M.W. Fried; Research Grants: AbbVie, BMS, Gilead, Merck; Consulting: AbbVie, BMS, Gilead, Merck. H. Wedemeyer; Honoraria for Consulting/Speaking: Abbott, AbbVie, Achillion, BMS, Boehringer Ingelheim, Gilead, GSK, ITS, Janssen, Merck, Novartis, Roche, Roche Diagnostics, Siemens, Transgene; Grant Support: Abbott, BMS, Merck, Novartis, Roche. L. Larsen; AbbVie employee and may hold AbbVie stock or options. D.E. Cohen; AbbVie employee and may hold AbbVie stock or options. E. Cohen; AbbVie employee and may hold AbbVie stock or options. N. Mobashery; AbbVie employee and may hold AbbVie stock or options. F. Tatsch; AbbVie employee and may hold AbbVie stock or options. G.R. Foster; Grant/Research Support: AbbVie, BMS, Merck, Roche/Genentech, Gilead, Novartis, Janssen; Consultant/Advisor: AbbVie, Vertex, BMS, Merck, Roche/Genentech, Gilead, GSK, Janssen, Virco, Novartis.

Authors' contributions

All authors had access to the study data and reviewed and provided feedback on all subsequent versions of the manuscript and made the decision to submit the manuscript for publication.

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Supplementary data

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