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Precipitating factors causing hyperbilirubinemia during chronic hepatitis C treatment with paritaprevir/ritonavir/ombitasvir and dasabuvir

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Abstract

Background: Hepatic decompensation is a fatal on-treatment side effect during chronic hepatitis C treatment with paritaprevir/ritonavir/ombitasvir and dasabuvir (PrOD). Prompt bilirubin testing can reveal hepatic failure in susceptible patients, and clinical parameters precipitating early elevation of bilirubin can warn clinicians to avoid PrOD prescription.

Methods: This retrospective study included 169 Hepatitis C virus (HCV)-genotype 1b patients who underwent a 12-week course of PrOD with or without ribavirin. Laboratory data underwent χ^2 analysis with Fisher's exact test to determine the precipitating factors causing hyperbilirubinemia in patients who had received 1 week of treatment.

Results: Sustained viral response was achieved in 164 patients (97.0%). Total bilirubin was ≥2 mg/dL (21.3%) in 36 patients after 1 week of treatment. Pretreatment white blood cell (WBC) <4500/μL and platelet <100,000/μL correlated with total bilirubin ≥2 mg/dL (relative risk [RR]: 21.64, 95% CI: 5.23-89.64, $p < 0.001$) after 1 week of treatment. Pretreatment platelet ≥100 000/μL and WBC <4500/μL correlated with direct bilirubin ≥0.45 mg/dL (RR: 6.56, 95% CI: 1.42-30.38, $p = 0.016$) and indirect bilirubin ≥0.6 mg/dL (RR: 4.77, 95% CI: 1.03-22.15, $p = 0.046$). Pretreatment platelet <100,000/μL with F3/F4 fibrosis correlated with first week total bilirubin ≥2 mg/dL (RR: 3.57, 95% CI: 1.35-9.09, $p = 0.010$).

Conclusion: PrOD is an effective antiviral regimen for HCV genotype 1b patients. Total bilirubin ≥2 mg/dL after 1 week of treatment serves as an early warning of irreversible progression toward hepatic decompensation, and the current study provides a guide by which to monitor chronic hepatitis C patients undergoing PrOD treatment.

Keywords: Hepatitis C virus; Hyperbilirubinemia; Platelet count

1. INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of liver cirrhosis and hepatocellular carcinoma, affecting over 200 million people worldwide.[1] The goal of chronic HCV treatment is to achieve viral RNA clearance in serum and a sustained virologic response 12 weeks following the completion of treatment (SVR_{12}) is demonstrated by undetectable HCV RNA 12 weeks following end of treatment. The standard treatment for chronic hepatitis C (CHC) was a combination of pegylated interferon (PEG-IFN) alpha and ribavirin (RBV) until 2014, when IFN-free, direct-acting antiviral agents (DAAs) revolutionized CHC treatment. Sofosbuvir, a potent NS5B polymerase nucleotide inhibitor, combined with the NS5A replication complex inhibitor ledipasvir with or without RBV for 12 weeks became the standard treatment for genotype 1 HCV infection, achieving an SVR > 90%.[2,3] Moreover, the paritaprevir/r (ritonavir-boosted NS3/4A protease inhibitor)-based regimen in combination with ombitasvir (NS5A replication complex inhibitor) and dasabuvir (NS5B polymerase non-nucleotide inhibitor), or paritaprevir/ritonavir/ombitasvir and dasabuvir (PrOD) (with or without RBV) attained a similar SVR when given for 12 weeks.[4,5]

The PrOD regimen was approved by the United States Food and Drug Administration (FDA) in December of 2014.[6] SVR_{12} of

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96.7% to 100% for noncirrhotic and 98.5% to 100% for cirrhotic genotype 1b HCV cases were achieved using PrOD with or without RBV for 12 weeks.[7–14] However, the FDA revised its guideline on the safety of PrOD in October of 2015 based on 26 global cases of worsened hepatic injury, hepatic decompensation, and liver failure.[15] These changes were made to protect patients with advanced liver disease such as Child-Pugh B or C cirrhosis, in which liver injury tended to arise within 1 to 4 weeks after starting PrOD therapy. PrOD-mediated hepatotoxicity was attributed to the NS3/4A protease inhibitor paritaprevir given that the sofosbuvir/simeprevir regimen also caused hepatic decompensation in patients with cirrhosis of Child-Pugh B or worse.[16,17]

NS3/4A protease inhibitors such as paritaprevir, simeprevir, and asunaprevir inhibit the bilirubin glucuronide (BG) transporter OATP1B1/1B3 (organic anion transporter peptide 1B1/1B3).[18,19] Additionally, simeprevir and asunaprevir are also inhibitors of OATP2B1.[20] Unconjugated bilirubin is enzymatically conjugated by UDP-glucuronosyltransferase 1A1 (UGT1A1) to form the more water-soluble BG.[21] BG is subsequently transported to the bile. Under physiological conditions, a substantial fraction of hepatic cell BG is rerouted to the blood, that is, the portal vein or hepatic venule, where it is then absorbed via hepatocyte OATP1A and 1B transporters.[22] When OATP1A- or 1B-mediated reuptake is suppressed during DAA treatment, BG can accumulate in the blood, leading to hyperbilirubinemia.

In Taiwan, the PrOD regimen has achieved SVR at a rate >98% for genotype 1b HCV.[23,24] Hsieh et al[24] previously reported pretreatment serum albumin <3.6 g/dL and advanced age as predictors of on-treatment hepatic decompensation. Since the PrOD regimen is effective in treating chronic HCV-1b infection, we made an attempt to determine the factor that trigger on-treatment bilirubin increase 1 week following drug administration. Contrary to Hsieh et al's result, we found that pretreatment serum albumin <3.6 g/dL was unable to predict hyperbilirubinemia (total bilirubin ≥2 mg/dL). Rather, white blood cell (WBC) <4500/μL and platelet <100 000/μL predicted total bilirubin ≥2 mg/dL and direct bilirubin ≥0.45 mg/dL after 1 week of PrOD. Our study provides a guide to determine the potential efficacy of PrOD in the treatment of genotype 1b CHC, particularly among cases unresponsive to other drug therapies.

2. METHODS

2.1. Study population

In this study, we retrospectively enrolled genotype 1b HCV-infected patients who received PrOD with or without weight-based RBV for 12 weeks at Taipei Veterans General Hospital from January 2017 to September 2017. All patients were above 20 years of age, males and females were both included, and all subjects had chronic HCV infection defined by the presence of detectable anti-HCV antibody (Abbott HCV EIA 2.0; Abbott Laboratories, IL, USA) and HCV RNA (Cobas TaqMan HCV Test v2.0; Roche Diagnostics GmbH, Mannheim, Germany; lower limit of quantification [LLOQ]: 15 IU/mL) in serum for longer than 6 months. Patients were excluded if decompensated cirrhosis, stage 5 chronic kidney disease, or HCV other than genotype 1 were present. The study was approved by the Institutional Review Board of Taipei Veterans General Hospital and was conducted in accordance with the Declaration of Helsinki as well as the International Conference on Harmonization for Good Clinical Practice. All patients read and signed informed consent forms before drug prescription and study-related procedures were implemented.

2.2. Study design

Baseline demographic data were collected before the treatment. Hemogram, serum biochemical profiles (albumin, total bilirubin, direct bilirubin, aspartate aminotransferase [AST], alanine aminotransferase, creatinine, international normalized ratio [INR], estimated glomerular filtration rate [eGFR]), anti-HCV, hepatitis B virus surface antigen (Abbott Architect HBsAg qualitative assay; Abbott Laboratories), HCV RNA, and HCV genotype (Abbott RealTime HCV Genotype II; Abbott Laboratories) were collected for all included patients. Hemogram and serum biochemistry were collected at weeks 1, 2, 4, 8, and 12. Noncirrhotic patients were treated with paritaprevir/ritonavir and ombitasvir (Viekirax, 75/50/12.5 mg film-coated table; AbbVie Deutschland GmbH, Ludwigshafen, Germany) with a regimen of two tablets daily in addition to dasabuvir (Exviera, 250 mg film-coated table; AbbVie Deutschland GmbH) one tablet twice daily for 12 weeks. Compensated cirrhotic patients received PrOD with weight-based RBV (Robatrol, 200 mg capsule, Genovate Biotechnology Co., Ltd., New Taipei City, Taiwan; 1,200 mg daily if the body weight ≥75 kg; 1,000 mg daily if the body weight <75 kg) for 12 weeks.

2.3. Virologic assessment

On-treatment effectiveness was assessed by measuring serum HCV RNA at weeks 4 and 12. Efficacy at the end of treatment was measured as SVR_{12}, defined as serum HCV RNA level <LLOQ 12 weeks following the completion of treatment.

2.4. Statistical analysis

Statistical analysis was performed using STATA (12th ed., developed by StataCorp LLC, College Station, TX). Pretreatment patient characteristics are shown as medians (range) and percentages where appropriate. Treatment efficacy during and after drug therapy is shown as values and percentages. Predetermined attributes related to SVR_{12} were compared using χ^2 analysis with Fisher's exact test, producing a relative risk (RR) of total bilirubin ≥2.0 mg/dL for every pretreatment parameter. Linear regression was applied to determine correlation of drug-related hyperbilirubinemia with pretreatment parameters. All statistics were two-tailed, and the results are considered statistically significant with $p < 0.05$.

3. RESULTS

3.1. Patient attributes

One hundred sixty-nine CHC patients were included in the study. The median age was 67 years, and 75 patients (44%) were male. Seventy-three (43%) patients were treatment-naive, and six (5.1%, 52 patients did not have associated HBs data) were also infected with HBV. No patients received antiviral therapy for HBV, developed HBV reactivation, or displayed hepatitis flare during PrOD therapy. One hundred forty-three patients (85%) received PrOD without RBV, and 26 (15%) received PrOD with RBV for 12 weeks. One patient was coinfected with HIV and was on the anti-HIV drug triumeq during PrOD therapy. One patient received prior liver transplantation, and three patients received prior renal transplantation. The median $\log_{10}$ HCV RNA level was 6.32. Fifty-eight (34%) patients had a baseline viral load <800 000 IU/mL. Fifty-two patients (31%) had a Fib-4 fibrosis of stage F3 and 27 patients (16%) were of stage F4 (Table 1).

3.2. Effectiveness

Among the 169 patients included in the study, three discontinued treatment because of hyperbilirubinemia 1 week after drug administration (Table 1). Age, condition, and underlying diseases were considered before ceasing treatment. One patient discontinued treatment at week 1 due to general malaise. One patient experienced a further elevation in HCV RNA after 4 weeks of treatment (baseline 3 358 224 IU/mL compared to week 4 level of 6 029 915 IU/mL). Therefore, a total of 164

Table 1

Characteristic

	Patients (n = 169)
Male sex, n (%) (%)	75 (44)
Age, median (range)	67 (42-90)
Age <55 y, n (%)	23 (14)
Treatment-naive, n (%)	73 (43)
PrOD regimen	
PrOD for 12 wk, n (%)	143 (85)
PrOD with RBV for 12 wk, n (%)	26 (15)
HBsAg (n = 117)	
HBsAg positivity, n (%)	6 (5.1)
HBsAg negativity, n (%)	111 (94.9)
Anti-HBc positivity, n (%)	53 (45.3)
Anti-HBs positivity, n (%)	33 (28.2)
Anti-HIV positivity, n (%)	1 (0.6)
Postliver transplantation, n (%)	1 (0.6)
Postrenal transplantation, n (%)	3 (1.8)
BMI, kg/m^2, median (range)	24.8 (16.7-38.3)
BMI <30 kg/m^2, n (%)	130 (92)
Hemoglobin level, g/dL, median (range)	13.5 (9.1-17.1)
White blood cell count, 10^9 cells/L, median (range)	5.8 (2.4-12)
Platelet count, 10^9 cells/L, median (range)	159 (23-423)
INR, median (range)	1.04 (0.9-2.7)
Albumin, g/dL, median (range)	4 (2.9-4.8)
Total bilirubin, mg/dL, median (range)	0.77 (0.2-2.01)
Direct bilirubin, mg/dL, median (range)	0.33 (0.15-0.93)
AST × ULN, median (range)	1.2 (0.3-9.5)
ALT × ULN, median (range)	1.7 (0.2-13.7)
Creatinine, mg/dL, median (range)	0.81 (0.55-11.31)
eGFR, mL/min/1.73 m2, median (range)	80 (5-129)
eGFR ≥60 mL/min/1.73m2 n (%)	137 (81)
HCV RNA level, log$_{10}$ IU/mL, median (range)	6.32 (2.31-7.85)
HCV RNA level <800 000 IU/mL, n (%)	58 (34)
HCV RNA level <6 000 000 IU/mL, n (%)	122 (72)
Stage of hepatic fibrosis by FIB-4, n (%)	
Non-F3, F4	90 (53)
F3	52 (31)
F4	27 (16)

ALT = alanine aminotransferase; Anti-HBc = antibody against hepatitis B core antigen; AST = aspartate aminotransferase; BMI = body mass index; eGFR = estimated glomerular filtration rate; FIB-4 = fibrosis-4; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; PrOD = paritaprevir/ritonavir/ombitasvir and dasabuvir; RNA = ribonucleic acid; ULN = upper limit of normal.

patients (100%) completed 12 weeks of treatment and had serum HCV RNA level < LLOQ by week 12. SVR$_{12}$ rate was 97.0% (Table 2). Nine patients had a diagnosis of hepatocellular carcinoma, and all achieved SVR without the appearance of on-treatment hepatic decompensation.

3.3. Stratified analysis of baseline attributes related to SVR$_{12}$

Stratified SVR$_{12}$ rates against patient attributes are shown in Table 3. SVR$_{12}$ rates were similar with respect to gender (p = 0.384), age at a cut-off value of 55 years (p = 1.000), HBsAg status (p = 1.000), RBV usage (p = 1.000), and eGFR (p = 1.000). Prior treatment with PEG-IFN+RBV produced a higher SVR rate compared with the naive group (p = 0.014), given that five patients who did not complete the treatment course were later placed in the naive group. Pretreatment HCV RNA levels did not significantly affect SVR$_{12}$ rates (p = 0.661 at cut-off value of 800 000 IU/mL; p = 1.000 at cut-off value of 6 000 000 IU/mL). F3/F4 fibrosis revealed lower SVR$_{12}$ rate than F1/F2 fibrosis (p = 0.021).

Table 2

Viral response during and after PrOD treatment

Serum HCV RNA <LLOQ	Patient (n/N)	%
During treatment		
Week 4	160/164	97.6
Week 12	164/164	100
After the end of treatment		
Week 12 (SVR$_{12}$)	164/169	97.0

Three patients discontinued treatment at week 1 attributed to treatment-induced hyperbilirubinemia; one patient discontinued treatment at week 4 attributed to drug resistance; one patient discontinued treatment at week 1 attributed to drug-related general malaise.
HCV = hepatitis C virus; LLOQ = lower limit of quantification; PrOD = paritaprevir/ritonavir/ombitasvir and dasabuvir; RNA = ribonucleic acid; SVR = sustained virologic response.

Table 3

Sustained virologic response according to subgroups

Subgroup	Patients no (n = 169)	SVR$_{12}$ (%)	p
Sex			0.384
Male	75	99	
Female	94	96	
Age, y			1.000
<55	23	100	
≥55	146	97	
Prior treatment			0.014
Naive	73	93	
Experienced	96	100	
RBV usage			1.000
No	143	97	
Yes	26	100	
HBsAg (n = 117)			1.000
Negative	111	95	
Positive	6	100	
eGFR			1.000
<60 mL/min/1.73 m2	32	97	
≥60 mL/min/1.73 m2	137	97	
HCV RNA level			0.661
<800 000 IU/mL	58	98	
≥800 000 IU/mL	111	96	
HCV RNA level			1.000
<6 000 000 IU/mL	122	97	
≥6 000 000 IU/mL	47	98	
Stage of hepatic fibrosis by FIB-4			0.021
Non-F3, F4	90	100	
F3, F4	79	94	

eGFR = estimated glomerular filtration rate; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; RBV = ribavirin; RNA = ribonucleic acid; SVR = sustained virologic response.

3.4. Precipitating factors that led to hyperbilirubinemia after 1 week of treatment

Hepatic decompensation with ensuing liver failure is a dangerous complication during DAA therapy. Thus, it is necessary to establish objective criteria by which hepatic decompensation can be avoided. In this study, we treated 169 genotype 1b CHC patients with PrOD. Pretreatment total bilirubin was <2.0 mg/dL, with the exception of one case with 2.01 mg/dL. Three patients had elevated total bilirubin 1 week after taking PrOD and thus stopped treatment (Supplementary Table 1 http://links.lww.com/JCMA/A62). Varying baseline values of albumin, WBC count, platelet count, INR, and Fib-4 score were observed among the three patients. Based on these observations, we determined the factors that precipitated direct bilirubin ≥0.45 mg/dL, indirect

bilirubin ≥0.6 mg/dL, and total bilirubin ≥2 mg/dL 1 week after drug administration. As shown in Table 4, pretreatment albumin, WBC, and platelet values inversely correlated with direct, indirect, and total bilirubin levels at week 1, and both INR and Fib-4 scores positively correlated with direct, indirect, and total bilirubin levels at week 1.

Of the five factors (albumin level, WBC count, platelet count, INR, and Fib-4 score), WBC < 4500/μL increased week 1 risk of direct bilirubin ≥0.45 mg/dL (RR: 9.97, 95% CI: 2.25-44.14, p = 0.002), indirect bilirubin ≥0.6 mg/dL (RR: 3.50, 95% CI: 1.13-10.84, p = 0.030), total bilirubin ≥1.5 mg/dL (RR: 2.52, 95% CI: 1.17-5.39, p = 0.018), and total bilirubin ≥ 2.0 mg/dL (RR: 2.67, 95% CI: 1.18-6.07, p = 0.019) (Table 5). Platelet count <100 000/μL increased week 1 risk of indirect bilirubin ≥0.6 mg/dL (RR: 5.55, 95% CI: 1.23-24.98, p = 0.026), total bilirubin ≥1.5 mg/dL (RR: 6.67, 95% CI: 2.70-16.67, p < 0.001), and total bilirubin ≥2.0 mg/dL (RR: 8.33, 95% CI: 3.57-20.00, p < 0.001). Platelet count <150 000/μL increased week 1 risk of direct bilirubin ≥0.45 mg/dL (RR: 4.46, 95% CI: 1.99-9.78, p < 0.001), indirect bilirubin ≥0.6 mg/dL (RR: 2.33, 95% CI: 1.07-5.11, p = 0.034), total bilirubin ≥1.5 mg/dL (RR: 4.13, 95% CI: 2.11-8.05, p < 0.001), and total bilirubin ≥2.0 mg/dL (RR: 3.69, 95% CI: 1.67-8.18, p = 0.001). Platelet count <200,000/μL, F3/F4 grade fibrosis, and RBV also increased week 1 risk of on-treatment hyperbilirubinemia. The above statistical results show that these precipitating factors increased week 1 risk of direct bilirubin elevation greater than the indirect bilirubin.

Bivariate analysis (Table 6) revealed that WBC < 4500/μL with platelet <100 000/μL increased week 1 risk of total bilirubin ≥1.5 mg/dL (RR: 27.33, 95% CI: 3.39-220.24, p = 0.002) and total bilirubin ≥2.0 mg/dL (RR: 21.64, 95% CI: 5.23-89.64, p < 0.001). WBC <4500/μL in combination with F3/F4 grade fibrosis and RBV also precipitated week 1 hyperbilirubinemia, which was mainly attributed to direct bilirubin. Platelet ≥100,000/μL with albumin <3.5 g/dL increased week 1 risk of total bilirubin ≥2.0 mg/dL (RR: 5.16, 95% CI: 1.06-25.19, p = 0.043). Platelet ≥100,000/μL with WBC <4500/μL increased week 1 risk of direct bilirubin ≥0.45 mg/dL (RR: 6.56, 95% CI: 1.42-30.38, p = 0.016) and indirect bilirubin ≥0.6 mg/dL (RR: 4.77, 95% CI: 1.03-22.15, p = 0.046). Platelet ≥100,000/μL with F3/F4 grade fibrosis or RBV also precipitated week 1 risk of on-treatment hyperbilirubinemia. Notably, RBV-induced hyperbilirubinemia in Table 5 was not associated with either WBC or platelet count but was weakly associated with F3/F4 grade fibrosis (Table 6).

Finally, we chose to focus on the F3/F4 grade fibrosis subgroup. Among these cases, WBC level was not a precipitating factor, but platelet <100,000/μL was correlated with increased risk of hyperbilirubinemia as shown in Table 7 (total bilirubin ≥1.5 mg/dL, RR: 3.03, 95% CI: 1.09-8.33, p = 0.034; total bilirubin ≥2 mg/dL, RR: 3.57, 95% CI: 1.35-9.09, p = 0.010). Moreover, platelet <150,000/μL was correlated with increased

Table 4

Linear regression of stratified baseline factors against bilirubin levels 1 week after PrOD administration

	Direct bilirubin		Indirect bilirubin		Total bilirubin	
Baseline factors	r^2	p	r^2	p	r^2	p
Albumin	$(-0.33)^2$	<0.001	$(-0.19)^2$	0.031	$(-0.35)^2$	<0.001
White blood cell	$(-0.26)^2$	0.002	$(-0.21)^2$	0.016	$(-0.28)^2$	<0.001
Hemoglobin	$(-0.19)^2$	0.032	$(0.03)^2$	0.754	$(-0.10)^2$	0.227
Platelet	$(-0.25)^2$	0.004	$(-0.36)^2$	<0.001	$(-0.30)^2$	<0.001
INR	$(0.17)^2$	0.047	$(0.22)^2$	0.013	$(0.20)^2$	0.011
Creatinine	$(-0.09)^2$	0.324	$(-0.12)^2$	0.185	$(-0.10)^2$	0.190
Egfr	$(-0.10)^2$	0.275	$(-0.01)^2$	0.913	$(-0.06)^2$	0.457
ALT	$(-0.01)^2$	0.978	$(-0.03)^2$	0.744	$(-0.01)^2$	0.939
AST	$(0.09)^2$	0.326	$(0.03)^2$	0.758	$(0.08)^2$	0.333
FIB-4 score	$(0.28)^2$	0.001	$(0.40)^2$	<0.001	$(0.34)^2$	<0.001
HCV RNA	$(0.03)^2$	0.715	$(0.08)^2$	0.355	$(-0.09)^2$	0.237

ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; FIB-4 = fibrosis-4; HCV = hepatitis C virus; INR = international normalized ratio; PrOD = paritaprevir/ritonavir/ombitasvir and dasabuvir; RNA = ribonucleic acid.

Table 5

Stratified factors correlated with hyperbilirubinemia 1 week after PrOD administration

	DB ≥ 0.45 mg/dL (n = 87)		InDB ≥ 0.6 mg/dL (n = 91)		TB ≥ 1.5 mg/dL (n = 64)		TB ≥ 2 mg/dL (n = 36)	
Baseline factors	**RR (95% CI)**	p	**RR (95% CI)**	p	**RR (95% CI)**	p	**RR (95% CI)**	p
Alb <3.5 vs Alb ≥3.5 g/dL	3.23 (0.37-2.70)	0.291	1.08 (0.20-5.80)	0.932	2.86 (0.81-1.03)	0.102	3.23 (0.93-11.11)	0.066
WBC <3500 vs WBC ≥3500/μL	1		2.03 (0.42-9.86)	0.380	3.04 (0.97-9.54)	0.056	2.95 (0.95-9.15)	0.061
WBC <4500 vs WBC ≥4500/μL	9.97 (2.25-44.14)	0.002	3.50 (1.13-10.84)	0.030	2.52 (1.17-5.39)	0.018	2.67 (1.18-6.07)	0.019
Plt $<10^5$ vs Plt $\geq 10^5$/μL	1		5.55 (1.23-24.98)	0.026	6.67 (2.70-16.67)	<0.001	8.33 (3.57-20.00)	<0.001
Plt $<1.5 \times 10^5$ vs Plt $\geq 1.5 \times 10^5$/μL	4.46 (1.99-9.78)	<0.001	2.33 (1.07-5.11)	0.034	4.13 (2.11-8.05)	<0.001	3.69 (1.67-8.18)	0.001
Plt $<2 \times 10^5$ vs Plt $\geq 2 \times 10^5$/μL	2.78 (1.19-6.25)	0.017	2.03 (0.87-4.71)	0.100	2.63 (1.18-5.88)	0.018	3.45 (1.14-10.00)	0.028
Plt $<2.5 \times 10^5$ vs Plt $\geq 2.5 \times 10^5$/μL	3.70 (1.11-12.50)	0.032	4.44 (1.35-14.60)	0.014	0.98 (0.33-2.86)	0.967	1.96 (0.42-9.09)	0.392
INR ≥1.2 vs INR <1.2	1		2.21 (0.25-19.56)	0.476	4.97 (0.97-25.42)	0.054	2.20 (0.50-9.69)	0.297
Hepatic fibrosis by FIB-4								
F3/F4 vs F1/F2	5.16 (2.29-11.59)	<0.001	2.28 (1.05-4.94)	0.037	5.98 (2.97-12.02)	<0.001	10.42 (3.79-28.65)	<0.001
RBV Yes vs No	12.84 (1.66-99.17)	0.014	4.88 (1.08-22.10)	0.040	11.48 (3.71-35.47)	<0.001	5.37 (2.18-13.25)	<0.001

Alb = albumin; CI = confidence interval; DB = direct bilirubin; FIB-4 = fibrosis-4; InDB = indirect bilirubin; INR = international normalized ratio; Plt = platelet; PrOD = paritaprevir/ritonavir/ombitasvir and dasabuvir; RBV = ribavirin; RR = relative risk; TB = total bilirubin; WBC = white blood cell.

Table 6

Stratified factors correlated with hyperbilirubinemia 1 week after PrOD administration by two-variant analysis

	DB ≥ 0.45 (mg/dL)		InDB ≥ 0.6 (mg/dL)		TB ≥ 1.5 (mg/dL)		TB ≥ 2 (mg/dL)	
Subgroup baseline factors	**RR (95% CI)**	***p***	**RR (95%CI)**	***p***	**RR (95% CI)**	***p***	**RR (95% CI)**	***p***
WBC <4500/μL (n=133)								
Alb <3.5 vs Alb ≥3.5 g/dL	2.20 (0.22-21.88)	0.502	0.52 (0.07-3.89)	0.527	0.94 (0.17-5.35)	0.945	0.90 (0.10-8.09)	0.925
Plt <10^5 vs Plt ≥10^5/μL	1		1		27.33 (3.39-220.24)	0.002	21.64 (5.23-89.64)	<0.001
Plt <1.5 × 10^5 vs Plt ≥1.5 × 10^5/μL	3.31 (1.38-7.94)	0.007	2.01 (0.83-4.86)	0.120	4.14 (1.90-9.04)	<0.001	3.66 (1.44-9.35)	0.007
Plt <2 × 10^5 vs Plt ≥2 × 10^5/μL	1.79 (0.75-4.27)	0.192	1.81 (0.74-4.40)	0.190	2.32 (0.98-5.46)	0.054	2.51 (0.80-7.95)	0.116
Plt <2.5 × 10^5 vs Plt ≥2.5 × 10^5/μL	2.54 (0.77-8.41)	0.127	3.56 (1.06-11.88)	0.039	0.77 (0.26-2.32)	0.643	1.50 (0.31-7.16)	0.611
Hepatic fibrosis by FIB-4 F3/F4 vs F1/F2	3.58 (1.52-8.44)	0.004	2.12 (0.89-5.02)	0.089	6.33 (2.83-14.14)	<0.001	7.75 (2.65-22.66)	<0.001
RBV Yes vs No	11.59 (1.45-92.47)	0.021	3.74 (0.79-17.76)	0.097	7.41 (2.22-24.68)	0.001	6.40 (2.09-19.63)	0.001
WBC ≥4500/μL (n=36)								
Alb <3.5 vs Alb ≥3.5 g/dL	1		1		1		9.33 (0.91-95.57)	0.060
Plt <10^5 vs Plt ≥10^5/μL	1		0.73 (0.09-6.04)	0.773	1.83 (0.47-7.13)	0.382	2.31 (0.57-9.41)	0.242
Plt <1.5 × 10^5 vs Plt ≥1.5 × 10^5/μL	3.67 (0.20-67.65)	0.382	1.11 (0.10-12.75)	0.933	2.06 (0.38-11.04)	0.398	1.62 (0.27-9.85)	0.602
Plt <2 × 10^5 vs Plt ≥2 × 10^5/μL	27 (0.89-821.79)	0.059	1		1.36 (0.08-23.61)	0.834	1	
Plt <2.5 × 10^5 vs Plt ≥2.5 × 10^5/μL	1		1		1		1	
Hepatic fibrosis by FIB-4 F3/F4 vs F1/F2	1		0.90 (0.08-10.21)	0.935	2.83 (0.55-14.47)	0.211	1	
RBV Yes vs No	1		1		1		2.81 (0.59-13.34)	0.193
Plt <10^5/μL (n = 30)								
Alb <3.5 vs Alb ≥3.5 g/dL	NA		1		1		0.67 (0.08-5.54)	0.707
WBC <4500 vs WBC ≥4500/μL	NA		1		0.17 (0.02-1.62)	0.123	0.30 (0.06-1.49)	0.140
Hepatic fibrosis by FIB-4 F3/F4 vs F1/F2	NA		1		1		1	
RBV Yes vs No	NA		1		5 (0.51-48.75)	0.166	1.40 (0.30-6.53)	0.669
Plt ≥10^5/μL (n = 139)								
Alb <3.5 vs Alb ≥3.5 g/dL	2.15 (0.22-21.38)	0.514	0.52 (0.07-3.81)	0.516	1.67 (0.36-7.83)	0.514	5.16 (1.06-25.19)	0.043
WBC <4500 vs WBC ≥4500/μL	6.56 (1.42-30.38)	0.016	4.77 (1.03-22.15)	0.046	2.48 (0.91-6.81)	0.077	2.77 (0.86-8.97)	0.088
Hepatic fibrosis by FIB-4 F3/F4 vs F1/F2	2.91 (1.25-6.75)	0.013	1.56 (0.68-3.60)	0.295	4.11 (1.90-8.89)	<0.001	6.32 (2.11-18.91)	0.001
RBV Yes vs No	8.11 (1.00-65.90)	0.050	2.58 (0.53-12.63)	0.242	10.41 (2.72-39.78)	0.001	6.12 (1.83-20.41)	0.003
Plt <1.5 × 10^5/μL (n=75)								
Alb <3.5 vs Alb ≥3.5 g/dL	0.83 (0.08-8.27)	0.876	0.36 (0.05-2.41)	0.292	1.96 (0.35-10.84)	0.441	1.50 (0.31-7.30)	0.615
WBC <4500 vs WBC ≥4500/μL	7.33 (0.87-61.58)	0.066	2.30 (0.56-9.42)	0.247	1.24 (0.47-3.23)	0.665	1.43 (0.53-3.84)	0.475
Hepatic fibrosis by FIB-4 F3/F4 vs F1/F2	6.60 (1.62-26.92)	0.009	2.78 (0.73-10.51)	0.132	5.23 (1.47-18.53)	0.010	9.88 (1.22-80.30)	0.032
RBV Yes vs No	4.05 (0.48-34.50)	0.200	5.29 (0.63-44.48)	0.125	8.92 (1.87-42.56)	0.006	2.44 (0.82-7.26)	0.110
Plt ≥1.5 × 10^5/μL (n=94)								
Alb <3.5 vs Alb ≥3.5 g/dL	1		1		3.25 (0.43-24.57)	0.253	8.44 (1.0667.47)	0.044
WBC <4500 vs WBC ≥4500/μL	6.62 (0.75-58.32)	0.089	4.17 (0.47-36.77)	0.199	2.49 (0.51-12.10)	0.259	3.24 (0.55-19.24)	0.195
Hepatic fibrosis by FIB-4 F3/F4 vs F1/F2	2.06 (0.66-6.43)	0.212	1.18 (0.38-3.71)	0.773	3.52 (1.21-10.25)	0.021	8.75 (2.23-34.27)	0.002
RBV Yes vs No	1		2.63 (0.28-24.93)	0.399	9.56 (1.70-53.63)	0.010	14.29 (2.65-77.07)	0.002
RBV Yes (n=26)								
Alb <3.5 vs Alb ≥3.5 g/dL	1		1		1		0.42 (0.03-5.30)	0.500
WBC <4500 vs WBC ≥4500/μL	1		1		1		1.25 (0.24-6.44)	0.790
Plt <10^5 vs Plt ≥10^5/μL	1		1		2.73 (0.24-30.66)	0.416	2.33 (0.46-11.81)	0.306
Plt <1.5 × 10^5 vs Plt ≥1.5 × 10^5/μL	1		3.75 (0.19-74.06)	0.385	3.20 (0.35-28.94)	0.301	0.75 (0.13-4.36)	0.749
Plt <2 × 10^5 vs Plt ≥2 × 10^5/μL	1		1		2 (0.15-26.19)	0.597	1.10 (0.13-9.34)	0.930
Plt <2.5 × 10^5 vs Plt ≥2.5 × 10^5/μL	1		1		1		1	
Hepatic fibrosis by FIB-4 F3/F4 vs F1/F2	1		1		18 (1.37-235.69)	0.028	2.75 (0.40-18.88)	0.303
RBV No (n=143)								
Alb <3.5 vs Alb ≥3.5 g/dL	3.39 (0.38-30.04)	0.273	1.03 (0.18-5.90)	0.974	2.31 (0.55-9.70)	0.254	5.79 (1.33-25.15)	0.019
WBC <4500 vs WBC ≥4500/μL	9.36 (2.07-42.37)	0.004	2.96 (0.92-9.46)	0.068	1.81 (0.75-4.36)	0.186	2.84 (1.05-7.69)	0.039
Plt <10^5 vs Plt ≥10^5/μL	1		3.16 (0.66-15.06)	0.150	5.68 (1.96-16.42)	0.001	10.19 (3.41-30.43)	<0.001
Plt <1.5 × 10^5 vs Plt ≥1.5 × 10^5/μL	4.07 (1.73-9.58)	0.001	1.86 (0.81-4.27)	0.141	3.43 (1.62-7.27)	0.001	4.40 (1.67-11.58)	0.003
Plt <2 × 10^5 vs Plt ≥2 × 10^5/μL	2.46 (1.04-5.85)	0.041	1.90 (0.79-4.54)	0.152	2.53 (1.01-6.33)	0.047	4.85 (1.08-21.79)	0.040
Plt <2.5 × 10^5 vs Plt ≥2.5 × 10^5/μL	3.60 (1.01-12.81)	0.048	4.69 (1.31-16.81)	0.018	1.03 (0.30-3.56)	0.960	1	
Hepatic fibrosis by FIB-4 F3/F4 vs F1/F2	3.81 (1.65-8.82)	0.002	1.47 (0.65-3.30)	0.351	4.42 (2.04-9.56)	<0.001	12.82 (3.59-45.82)	<0.001

Alb = albumin; CI = confidence interval; DB = direct bilirubin; InDB = indirect bilirubin; INR = international normalized ratio; NA = not available; Plt = platelet; PrOD = paritaprevir/ritonavir/ombitasvir and dasabuvir; RBV = ribavirin; RR = relative risk; TB = total bilirubin; WBC = white blood cell.

Table 7

Pretreatment platelet count <100,000/μL correlated with hyperbilirubinemia 1 week after PrOD administration in fibrosis stage F3/F4 patients (n = 79)

	DB ≥ 0.45 (mg/dL) (n=55)		InDB ≥ 0.6 (mg/dL) (n=52)		TB ≥ 1.5 (mg/dL) (n=47)		TB ≥ 2 (mg/dL) (n=31)	
Baseline factors	**RR (95% CI)**	***p***	**RR (95% CI)**	***p***	**RR (95% CI)**	***p***	**RR (95% CI)**	***p***
Alb <3.5 vs Alb ≥3.5 g/dL	1		1.09 (0.11-11.11)	0.945	5.26 (0.61-50.00)	0.130	2.86 (0.62-12.50)	0.179
WBC <3500 vs WBC ≥3500/μL	1		1.26 (0.24-6.61)	0.788	1.23 (0.37-4.10)	0.734	1.17 (0.36-3.78)	0.793
WBC <4500 vs WBC ≥4500/μL	1		2.11 (0.52-8.53)	0.294	1.19 (0.46-3.11)	0.722	1.70 (0.66-4.40)	0.272
Plt <10^5 vs Plt ≥10^5/μL	1		4.06 (0.82-20.05)	0.085	3.03 (1.09-8.33)	0.034	3.57 (1.35-9.09)	0.010
Plt <1.5 × 10^5 vs Plt ≥1.5 × 10^5/μL	4.80 (1.23-18.67)	0.024	2.50 (0.72-8.64)	0.147	2.32 (0.83-6.53)	0.110	1.31 (0.46-3.77)	0.616
Plt <2 × 10^5 vs Plt ≥2 × 10^5/μL	1		3.92 (0.23-67.01)	0.345	1		1	
INR ≥1.2 vs INR <1.2	1		1.38 (0.15-12.90)	0.776	2.12 (0.40-11.27)	0.377	0.90 (0.20-4.07)	0.891
RBV Yes vs No	1		1		18.62 (2.33-148.65)	0.006	2.68 (0.93-7.73)	0.068

Alb = albumin; CI = confidence interval; DB = direct bilirubin; InDB = indirect bilirubin; INR = international normalized ratio; Plt = platelet; PrOD = paritaprevir/ritonavir/ombitasvir and dasabuvir; RBV = ribavirin; RR = relative risk; TB = total bilirubin; WBC = white blood cell.

risk of direct bilirubin ≥0.45 mg/dL (RR: 4.8, 95% CI: 1.23-18.67, p = 0.024). In our study, albumin and INR were not good predictors of total bilirubin ≥2.0 mg/dL at 1 week after PrOD treatment (Table 7). Although the addition of RBV is suspected to increase the risk of hyperbilirubinemia, we found no statistical evidence of such risk in the F3/4 grade fibrosis group (total bilirubin ≥2 mg/dL RR: 2.68, 95% CI: 0.93-7.73, p = 0.068). In summary, platelet count <100,000/μL is a good indicator to clinicians that bilirubin level should be monitored carefully in patients with F3/F4 grade fibrosis. Alternatively, a physician may even elect to cease PrOD treatment early in case of hyperbilirubinemia to avoid possible liver decompensation.

4. DISCUSSION

The PrOD regimen was considered an effective treatment for genotype 1 CHC[7–9] before reports of hepatic decompensation in 2015. Moreover, multiple clinical trials failed to produce warning signs of liver failure among patients with preexisting cirrhosis.[7–14] Based on postmarket reports, the FDA has added warnings making severe hepatic disease a contraindication to treatment with PrOD.[15] Despite a high success rate, sporadic drug-induced hepatic injury has discouraged the use of PrOD within the field of hepatic medicine. American Association for the Study of Liver Diseases-Infectious Diseases Society of America HCV guidelines recommend extreme caution be exercised when using NS3/4A protease inhibitors to treat patients who have current or past decompensated liver disease (CTP score over 7).[25] However, Butt et al[26] compared PrOD (NS3/4A protease inhibitor + NS5A inhibitor + NS5B polymerase inhibitor), sofosbuvir + simeprevir (NS5B polymerase inhibitor + NS3/4A protease inhibitor), and sofosbuvir + ledipasvir (NS5B polymerase inhibitor + NS5A inhibitor) treatment regimens, finding the incidence of hepatic decompensation in patients who completed 12 weeks of PrOD treatment to be similar to those treated with sofosbuvir/ledipasvir regimen. Moreover, incidence of hepatic decompensation was lower with PrOD than with sofosbuvir/simeprevir. This evidence suggests that NS3/4A inhibitors may not be the primary cause of hepatic decompensation during DAA treatment. Rather, pretreatment cirrhosis is a statistical precipitating factor independent of regimen.

In this study, we retrospectively examined 169 genotype 1b CHC cases treated with PrOD. The SVR_{12} rate was 97%, similar to previous reports.[23,24] Thirty-six patients (21.3%) had on-treatment hyperbilirubinemia (total bilirubin ≥ 2 mg/dL), among whom three discontinued treatment and 33 achieved SVR. Further excluding one case of PrOD discontinuation on account of drug resistance and one case of discontinuation due to intolerable side effects, no hepatic decompensation was seen among the remaining 164 cases to achieve SVR_{12}. Hsieh et al report a 0% to 3.3% rate of on-treatment liver decompensation across eight PrOD studies, with concurrent liver cirrhosis occurring at a rate of 31.1% to 100%.[16] Hepatic fibrosis grade alone is not a reliable predictor of on-treatment hyperbilirubinemia.

Isolated hyperbilirubinemia during PrOD therapy without accompanied elevation of serum aminotransferase is a unique phenomenon that arises before hepatic decompensation[27] and is consistent with the known mechanism by which paritaprevir inhibits reuptake of BG via transporter OATP1B1/1B3.[22] This is quite different from other protease inhibitors such as asunaprevir, in which serum aminotransferase elevation is associated with increased total bilirubin.[28] Previously, low platelet count, increased total bilirubin, prolonged INR, and low albumin have been reported as risk factors of on-treatment liver decompensation among genotype 1b cases.[29,30] Low baseline HCV viral load is also associated with increased risk of PrOD-induced hepatic decompensation.[30] Since paritaprevir induces elevated bilirubin without direct hepatocyte toxicity, a predictive model for on-treatment hyperbilirubinemia at week 1 can enhance PrOD safety among CHC cases resistant to other treatments.

Three female patients experienced on-treatment hyperbilirubinemia (Supplementary Table 1 http://links.lww.com/JCMA/A62) and subsequently ceased treatment. Stratified gender analysis as shown in Supplementary Table 2 (http://links.lww.com/JCMA/A62) suggests that females are prone to develop hyperbilirubinemia 1 week following drug administration. Pretreatment laboratory data in Table 4 raise the possibility that albumin, WBC count, platelet count, INR, and Fib-4 score may also relate to on-treatment hyperbilirubinemia. As a result, pretreatment WBC <4500/μL or platelet count <200,000/μL correlated with total bilirubin ≥2 mg/dL at 1 week following treatment accounted for pretreatment platelet count in three on-treatment hyperbilirubinemia patients. Pretreatment platelet count was then narrowed down to 100 000/μL, which strongly correlated with on-treatment hyperbilirubinemia (Table 5). In noncirrhotic patients, pretreatment WBC <4500/μL with platelet <100,000/μL increased week 1 risk of hyperbilirubinemia (Table 6). Within the F3/F4 fibrosis group, pretreatment platelet count <100,000/μL correlated well with total bilirubin ≥2 mg/dL at week 1 after PrOD treatment (Table 7). Therefore, we propose that patients with platelet count <100,000/μL undergo additional blood tests at the third and seventh day following PrOD treatment to monitor hyperbilirubinemia and avoid irreversible hepatic failure. Since PrOD gives rise to hepatic decompensation at a similar rate to other regimens,[26] pretreatment platelet count may be used as an index for other DAA regimens.

One limitation of this study was that trivariant analysis such as WBC + platelet + Fib-4 score could not be performed given

low patient number. However, our clinical experience suggests that PrOD is an effective treatment for HCV genotype 1b patients. Hyperbilirubinemia attributed to elevation of direct bilirubin is an early feature of on-treatment hepatic decompensation and is avoidable through the immediate cessation of drug treatment given that PrOD regimen does not directly induce hepatocyte injury. Serious adverse events are not common, but caution should still be exercised when this regimen is used for patients with F3/F4 fibrosis and platelet count <100,000/μL. Closely monitoring serum total bilirubin level in patients with platelet count <100,000/μL may also be applied to other DAA regimens to detect hyperbilirubinemia early.

The clinical implication to identify the factors associated with elevated serum bilirubin levels 1 week after PrOD therapy is to obtain a trend that endangers the patients who may go to irreversible liver decompensation. Currently the major concern in prescribing PrOD is on-treatment hyperbilirubinemia leading to liver decompensation. Most gastroenterologists hesitate prescribing this regimen. However, it is possible to cut drug price of PrOD to save people afflicted with chronic HCV in underdeveloped countries. Total bilirubin ≥2 mg/dL 1 week following drug treatment is the cutoff for whether ceasing administration or performing additional tests. One week following PrOD administration as the ideal time point at which to administer further testing. Interestingly, failure to develop hyperbilirubinemia 1 week following PrOD avoided later total bilirubin ≥2.0 mg/dL during treatment. In summary, pretreatment platelet and WBC counts may predict total bilirubin ≥2 mg/dL 1 week following drug administration, aiding the decision-making process of clinicians.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://doi.org/10.1097/JCMA.0000000000000264.

REFERENCES

1. Liang TJ, Rehermann B, Seeff LB, Hoofnagle JH. Pathogenesis, natural history, treatment, and prevention of hepatitis C. *Ann Intern Med* 2000;**132**:296–305.
2. Feeney ER, Chung RT. Antiviral treatment of hepatitis C. *BMJ* 2014;**348**:g3308.
3. Lam BP, Jeffers T, Younoszai Z, Fazel Y, Younossi ZM. The changing landscape of hepatitis C virus therapy: focus on interferon-free treatment. *Therap Adv Gastroenterol* 2015;**8**:298–312.
4. Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourlière M, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014;**370**:1604–14.
5. Andreone P, Colombo MG, Enejosa JV, Koksal I, Ferenci P, Maieron A, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. *Gastroenterology* 2014;**147**:359–65.e1.
6. Raedler LA. Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets): all-oral fixed combination approved for genotype 1 chronic hepatitis C infection. *Am Health Drug Benefits* 2015;**8**(Spec Feature):142–7.
7. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014;**370**:1973–82.
8. Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, et al; PEARL-III Study; PEARL-IV Study. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med* 2014;**370**:1983–92.
9. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014;**370**:1594–603.
10. Wedemeyer H, Craxí A, Zuckerman E, Dieterich D, Flisiak R, Roberts SK, et al. Real-world effectiveness of ombitasvir/paritaprevir/ritonavir±dasabuvir±ribavirin in patients with hepatitis C virus genotype 1 or 4 infection: a meta-analysis. *J Viral Hepat* 2017;**24**:936–43.
11. Lawitz E, Makara M, Akarca US, Thuluvath PJ, Preotescu LL, Varunok P, et al. Efficacy and safety of ombitasvir, paritaprevir, and ritonavir in an open-label study of patients with genotype 1b chronic hepatitis C virus infection with and without cirrhosis. *Gastroenterology* 2015;**149**:971–80.e1.
12. Kumada H, Chayama K, Rodrigues L Jr, Suzuki F, Ikeda K, Toyoda H, et al. Randomized phase 3 trial of ombitasvir/paritaprevir/ritonavir for hepatitis C virus genotype 1b-infected Japanese patients with or without cirrhosis. *Hepatology* 2015;**62**:1037–46.
13. Asselah T, Boyer N, Saadoun D, Martinot-Peignoux M, Marcellin P. Direct-acting antivirals for the treatment of hepatitis C virus infection: optimizing current IFN-free treatment and future perspectives. *Liver Int* 2016;**36**(Suppl 1):47–57.
14. Feld JJ, Moreno C, Trinh R, Tam E, Bourgeois S, Horsmans Y, et al. Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12weeks. *J Hepatol* 2016;**64**:301–7.
15. Food and Drug Administration. FDA Drug Safety Communication: FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie. Available at http://www.fda.gov/Drugs/DrugSafety/ucm468634.htm. Accessed May 22, 2019.
16. Stine JG, Intagliata N, Shah NL, Argo CK, Caldwell SH, Lewis JH, et al. Hepatic decompensation likely attributable to simeprevir in patients with advanced cirrhosis. *Dig Dis Sci* 2015;**60**:1031–5.
17. Soriano V, Barreiro P, de Mendoza C, Peña JM. Hepatic decompensation with sofosbuvir plus simeprevir in a patient with Child-Pugh B compensated cirrhosis. *Antivir Ther* 2016;**21**:91–2.
18. Okubo H, Ando H, Sorin Y, Nakadera E, Fukada H, Morishige J, et al. Gadoxetic acid-enhanced magnetic resonance imaging to predict paritaprevir-induced hyperbilirubinemia during treatment of hepatitis C. *PLoS One* 2018;**13**:e0196747.
19. Furihata T, Matsumoto S, Fu Z, Tsubota A, Sun Y, Matsumoto S, et al. Different interaction profiles of direct-acting anti-hepatitis C virus agents with human organic anion transporting polypeptides. *Antimicrob Agents Chemother* 2014;**58**:4555–64.
20. Furihata T, Fu Z, Suzuki Y, Matsumoto S, Morio H, Tsubota A, et al. Differential inhibition features of direct-acting anti-hepatitis C virus agents against human organic anion transporting polypeptide 2B1. *Int J Antimicrob Agents* 2015;**46**:381–8.
21. Peters WH, te Morsche RH, Roelofs HM. Combined polymorphisms in UDP-glucuronosyltransferases 1A1 and 1A6: implications for patients with Gilbert's syndrome. *J Hepatol* 2003;**38**:3–8.
22. Iusuf D, van de Steeg E, Schinkel AH. Functions of OATP1A and 1B transporters in vivo: insights from mouse models. *Trends Pharmacol Sci* 2012;**33**:100–8.
23. Liu CH, Liu CJ, Su TH, Yang HC, Hong CM, Tseng TC, et al. Real-world effectiveness and safety of paritaprevir/ritonavir, ombitasvir, and dasabuvir with or without ribavirin for patients with chronic hepatitis C virus genotype 1b infection in Taiwan. *J Gastroenterol Hepatol* 2018;**33**:710–7.
24. Hsieh YC, Jeng WJ, Huang CH, Teng W, Chen WT, Chen YC, et al. Hepatic decompensation during paritaprevir/ritonavir/ombitasvir/dasabuvir treatment for genotype 1b chronic hepatitis C patients with advanced fibrosis and compensated cirrhosis. *PLoS One* 2018;**13**:e0202777.
25. AASLD-IDSA HCV Guidance Panel. Hepatitis C guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. *Clin Infect Dis* 2018;**67**:1477–92.
26. Butt AA, Ren Y, Marks K, Shaikh OS, Sherman KE. Do directly acting antiviral agents for HCV increase the risk of hepatic decompensation and decline in renal function? Results from ERCHIVES. *Aliment Pharmacol Ther* 2017;**45**:150–9.
27. Hoofnagle JH. Hepatic decompensation during direct-acting antiviral therapy of chronic hepatitis C. *J Hepatol* 2016;**64**:763–5.

28. Sezaki H, Suzuki F, Hosaka T, Akuta N, Fujiyama S, Kawamura Y, et al. The efficacy and safety of dual oral therapy with daclatasvir and asunaprevir for genotype 1b in Japanese real-life settings. *Liver Int* 2017;**37**:1325–33.
29. Preda CM, Popescu CP, Baicus C, Voiosu TA, Manuc M, Pop CS, et al. Real-world efficacy and safety of ombitasvir, paritaprevir/r+dasabuvir+ribavirin in genotype 1b patients with hepatitis C virus cirrhosis. *Liver Int* 2018;**38**:602–10.
30. Poordad F, Nelson DR, Feld JJ, Fried MW, Wedemeyer H, Larsen L, et al. Safety of the 2D/3D direct-acting antiviral regimen in HCV-induced Child-Pugh A cirrhosis - a pooled analysis. *J Hepatol* 2017;**67**:700–7.