

Ombitasvir, Paritaprevir, Ritonavir, and Dasabuvir With or Without Ribavirin in Patients With Kidney Disease



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Introduction: Patients with hepatitis C virus (HCV) infection and chronic kidney disease (CKD) are a high-priority population for treatment.

Methods: We performed a *post hoc* pooled efficacy and safety analysis that included HCV genotype 1-infected patients with compensated liver disease and CKD stages 1 to 3 who received the all-oral 3-direct-acting antiviral regimen of ombitasvir, paritaprevir, ritonavir, and dasabuvir ± ribavirin (OBV/PTV/r + DSV ± RBV) in 11 phase 3 clinical trials. Sustained virologic response rates at posttreatment week 12 (SVR12) and treatment-related adverse events (AEs), serious AEs, and renal-associated AEs are reported. Mean changes from baseline in serum creatinine and estimated glomerular filtration rate (eGFR) were calculated to assess changes in renal function. Factors associated with improved eGFR were assessed by stepwise logistic regression analysis of data from 7 trials in which baseline urinalysis was collected.

Results: SVR12 rates in patients with stage 1, 2, and 3 CKD were 97% (439/453), 98% (536/547), and 97% (32/33), respectively, with OBV/PTV/r + DSV; and, 96% (1172/1221), 96% (1208/1254), and 93% (55/59), respectively, with OBV/PTV/r + DSV + RBV. Overall rates of serious AEs and renal AEs were 3% (95/3567) and 2% (56/3567), respectively. Factors associated with an eGFR increase of ≥10 ml/min per 1.73 m² were baseline proteinuria, body mass index, nonblack race, and history of diabetes.

Conclusion: OBV/PTV/r + DSV ± RBV achieved high SVR rates and was generally well tolerated irrespective of CKD stage.

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KEYWORDS: chronic hepatitis C; chronic kidney disease; direct-acting antiviral; hepatitis C virus

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Patients with HCV infection have an increased risk of developing CKD.^{1–4} Moreover, patients with CKD and HCV have a greater risk of CKD progression and end-stage renal disease (ESRD),^{3,5} and the prevalence of HCV infection is higher in patients who require hemodialysis than in the general population.^{6,7}

Furthermore, HCV infection is associated with reduced graft survival after renal transplantation.⁷ Therefore, it is critical that patients with HCV and CKD receive treatment for HCV.

Contemporary HCV treatment guidelines recommend that patients with extrahepatic manifestations of HCV infection be considered a priority for treatment owing to increased risk of disease progression.^{8,9} However, few data are available on the safety and efficacy of direct-acting antiviral (DAA) regimens in patients with CKD.

Components of the 3-DAA regimen of ombitasvir, paritaprevir with the pharmacokinetic enhancer ritonavir, and dasabuvir (OBV/PTV/r + DSV) are primarily metabolized by the liver with minimal renal elimination, with no dose adjustment required in patients with

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mild to severe renal impairment.^{8,9} However, patients with HCV genotype (GT) 1a infection require treatment with ribavirin (RBV), which is renally excreted and requires dose reduction in patients with a creatinine clearance (CrCl) ≤ 50 ml/min.¹⁰ OBV/PTV/r + DSV ± RBV is recommended in guidelines for treatment of HCV in patients with CrCl < 30 ml/min or ESRD requiring hemodialysis.^{8,9}

To better define the safety and efficacy profile of OBV/PTV/r + DSV ± RBV, we conducted a *post hoc* pooled analysis of OBV/PTV/r + DSV in HCV GT1-infected patients with CKD stages 1 to 3 across 11 phase 3 studies.

METHODS

Study Design

This is a *post hoc* pooled analysis of the efficacy and safety of the all-oral 3-DAA regimen of OBV/PTV/r + DSV ± RBV among patients with CKD, as determined by baseline eGFR using the Modification of Diet in Renal Disease equation. Patients from 11 phase 3 studies were included. Patients with a CrCl < 30 ml/min were excluded from TURQUOISE-III, TOPAZ-I, and TOPAZ-II, and patients with a CrCl < 60 ml/min were excluded from TURQUOISE-I, TURQUOISE-II, PEARL-II, PEARL-III, PEARL-VI, SAPPHIRE-I, and SAPPHIRE-II.

The study designs and primary outcomes are described elsewhere.^{11–20} The studies were conducted in accordance with the International Conference on Harmonisation guidelines, applicable regulations, and the principles of the Declaration of Helsinki; study protocols were approved by independent ethics committees at each study site; and all patients provided written informed consent.

Patient Population

Patients infected with HCV GT1 without cirrhosis or with Child–Pugh A cirrhosis who had received ≥ 1 dose of OBV/PTV/r + DSV ± RBV were included in the analysis. Data collected before January 1, 2016 were included. In this analysis, patients were grouped according to baseline eGFR and CKD stage (CKD5: ≤ 15 ml/min per 1.73 m²; CKD4: > 15 – 30 ml/min per 1.73 m²; CKD3: > 30 – 60 ml/min per 1.73 m²; CKD2: > 60 – 90 ml/min per 1.73 m²; and CKD1 > 90 ml/min per 1.73 m²). One patient with CKD5 on hemodialysis received OBV/PTV/r + DSV + RBV.

Study Medication

Patients with HCV GT1 infection without cirrhosis received OBV/PTV/r (25/150/100 mg every day) and DSV (250 mg twice a day) for 12 weeks; patients with GT1a infection also received RBV. Patients with

compensated cirrhosis received OBV/PTV/r (25/150/100 mg every day) and DSV (250 mg twice a day) with RBV for 12 or 24 weeks for GT1b and GT1a infection, respectively. In the TURQUOISE-III trial, GT1b patients with cirrhosis did not receive RBV and were treated for 12 weeks. RBV was dosed according to body weight (1000 mg: < 75 kg; 1200 mg: ≥ 75 kg) for patients with baseline CrCl ≥ 50 ml/min and was dose-adjusted for patients with CrCl < 50 ml/min.¹⁰ Patients with CKD4 to 5 who required RBV received 200 mg every day. Investigators in all studies could reduce, interrupt, or resume RBV based on hemoglobin levels.

Virologic Response

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

SVR rates at posttreatment week 12 (SVR12; HCV RNA less than lower limit of quantitation) were calculated for all patients, including those who discontinued OBV/PTV/r + DSV ± RBV prematurely.

Safety

Data on all treatment-emergent AEs, as reported by the study investigator, were collected from the start of study drug administration until 30 days after the last dose. AEs were assessed by study investigators for relation to study drug and severity. Serious AEs were collected from the time of signed consent until 30 days after the last dose of OBV/PTV/r + DSV ± RBV. Clinical laboratory chemistry and hematology tests were assessed throughout each study. Renal-associated AEs were defined by the Standardized Medical Dictionary for Regulatory Activities (MedDRA version 18.1) Queries Acute Renal Failure and Chronic Kidney Disease and the Custom MedDRA Query (version 18.1.3) Designated Medical Event Acute Renal Failure. Mean changes from baseline to end of treatment (EOT) of serum creatinine (SCr) and eGFR were calculated to assess changes in renal function.

Statistical Analyses

Efficacy and safety populations included all patients who received at least 1 dose of OBV/PTV/r + DSV ± RBV. Efficacy and safety analyses were performed for CKD stages 1 to 5. Results for patients with CKD4 to 5 are not presented in full owing to low patient numbers. Safety comparisons between treatment groups and CKD subgroups were performed using Fisher exact test.

Table 1. Baseline patient demographics and disease characteristics

Baseline characteristic	OBV/PTV/r + DSV				OBV/PTV/r + DSV + RBV				Total (N = 3567)
	CKD1 (n = 453)	CKD2 (n = 547)	CKD3 (n = 33)	Subtotal (n = 1033)	CKD1 (n = 1221)	CKD2 (n = 1254)	CKD3 (n = 59)	Subtotal (n = 2534)	
Male sex, n (%)	242 (53)	261 (48)	10 (30)	513 (50)	825 (68)	704 (56)	30 (51)	1559 (62)	2072 (58)
Race, n (%)									
White	406 (90)	497 (91)	32 (97)	935 (91)	1095 (90)	1156 (92)	52 (88)	2303 (91)	3238 (91)
Black	33 (7)	40 (7)	1 (3)	74 (7)	93 (8)	72 (6)	6 (10)	171 (7)	245 (7)
Other ^a	14 (3)	9 (2)	0	23 (2)	33 (3)	26 (2)	1 (2)	60 (2)	83 (2)
Hispanic/Latino ethnicity, n (%)	27 (6)	36 (7)	2 (6)	65 (6)	108 (9)	83 (7)	3 (5)	194 (8)	259 (7)
Age, yr, mean±SD	48.7±12.7	54.5±10.2	61.4±9.9	–	49.6±10.9	54.7±9.4	59.3±4.8	–	–
BMI, kg/m ² , mean±SD	26.5±4.7	26.3±4.3	27.9±5.2	–	26.6±4.9	26.7±4.3	27.9±4.3	–	–
HCV subtype, n (%) ^b									
GT1a	75 (17)	126 (23)	4 (12)	205 (20)	844 (69)	847 (68)	46 (78)	1737 (69)	1942 (54)
GT1b	378 (83)	421 (77)	29 (88)	828 (80)	376 (31)	405 (32)	13 (22)	794 (31)	1622 (45)
<i>IL28B</i> non-CC genotype, n (%)	367 (81)	422 (77)	28 (85)	817 (79)	970 (79)	947 (76)	39 (66)	1956 (77)	2773 (78)
HCV RNA ≥800 000 IU/ml, n (%)	327 (72)	428 (78)	26 (79)	781 (76)	964 (79)	1036 (83)	53 (90)	2053 (81)	2834 (79)
Fibrosis stage, n (%) ^c									
F0–F1	298 (66)	331 (61)	13 (39)	642 (62)	650 (53)	664 (53)	28 (47)	1342 (53)	1984 (56)
F2	72 (16)	103 (19)	8 (24)	183 (18)	140 (11)	173 (14)	7 (12)	320 (13)	503 (14)
F3	60 (13)	81 (15)	3 (9)	144 (14)	113 (9)	142 (11)	5 (8)	260 (10)	404 (11)
F4	23 (5)	30 (5)	9 (27)	62 (6)	317 (26)	275 (22)	19 (32)	611 (24)	673 (19)
Treatment naive, n (%)	287 (63)	392 (72)	19 (58)	698 (68)	736 (60)	783 (62)	38 (64)	1557 (61)	2255 (63)
History of hypertension, n (%)	99 (22)	163 (30)	18 (55)	280 (27)	284 (23)	395 (31)	27 (46)	706 (28)	986 (28)
History of diabetes mellitus, n (%)	6 (1)	11 (2)	0	17 (2)	45 (4)	34 (3)	1 (2)	80 (3)	97 (3)
Albumin (g/l), mean±SD	43.3±3.7	42.9±3.4	41.7±3.2	–	42.6±3.9	42.3±3.5	42.4±3.3	–	–
Platelet count (×10 ⁹ /l), mean±SD	217.3±60.5	220.6±65.3	205.2±55.8	–	209.8±72.7	212.3±68.0	196.8±66.4	–	–
eGFR (ml/min per 1.73 m ²), mean ± SD	105.5±14.7	79.0±7.5	53.2±6.8	–	107.0±14.0	78.8±7.7	52.7±6.9	–	–

–, not applicable; BMI, body mass index; CKD, chronic kidney disease; DSV, dasabuvir; eGFR, estimated glomerular filtration rate; GT, genotype; HCV, hepatitis C virus; *IL28B*, interleukin 28B; OBV, ombitasvir; PTV/r, paritaprevir/ritonavir; RBV, ribavirin.

^aData missing for 1 patient.

^bNon-GT1a/b genotype in 3 patients.

^cData missing for 3 patients.

Analysis of covariance was used to assess changes in renal function from baseline to EOT.

Changes in post-baseline eGFR at EOT in 255 patients in the placebo arms were compared with 769 patients in the OBV/PTV/r + DSV + RBV treatment arms of the SAPPHERE-I and -II trials. Changes in post-baseline eGFR at EOT were assessed in 2663 patients from 7 trials (SAPPHERE-I, SAPPHERE-II, TURQUOISE-II, TOPAZ-II, PEARL-II, PEARL-III, PEARL-IV) in which urinalysis was conducted at baseline and baseline factors associated with a ≥10 ml/min per 1.73 m² increase in eGFR at EOT were examined by stepwise logistic regression.²¹

RESULTS

Baseline Patient Demographics and Characteristics

A total of 3567 patients were included in the pooled analysis; 29% (1033/3567) received OBV/PTV/r + DSV and 71% (2534/3567) received OBV/PTV/r + DSV + RBV. Baseline characteristics are presented in Table 1. Overall, 47% (1674/3567), 50% (1801/3567), and 3% (92/3567) of patients had stage 1, 2, or 3 CKD,

respectively. Only 1% (22/3567) of patients had an eGFR <50 ml/min per 1.73 m² (data not shown).

Efficacy Outcomes

Among patients treated with OBV/PTV/r + DSV without RBV, SVR12 rates were high irrespective of CKD stage (CKD1 97% [439/453]; CKD2 98% [536/547]; CKD3 97% [32/33]) or presence of cirrhosis (Figure 1a). In patients with cirrhosis receiving OBV/PTV/r + DSV without RBV, SVR12 was 100% (62/62), including 61 patients with GT1b infection (Figure 1; Supplementary Figure S1). High SVR12 rates were also achieved with OBV/PTV/r + DSV + RBV. The SVR12 rate was 93% (55/59) in patients with CKD3 and 96% in those with CKD1 or CKD2 (1172/1221 and 1208/1254, respectively; Figure 1b). RBV dose modification was required in 11% (273/2534) of patients with CKD1 to 3; SVR rates were not decreased among patients who had RBV dose reduction (Supplementary Figure S2). SVR12 rates in subgroups were high irrespective of CKD stage and did not differ from the overall SVR12 rates (Figure 1). There were no statistically significant differences among CKD stages 1, 2, and 3.

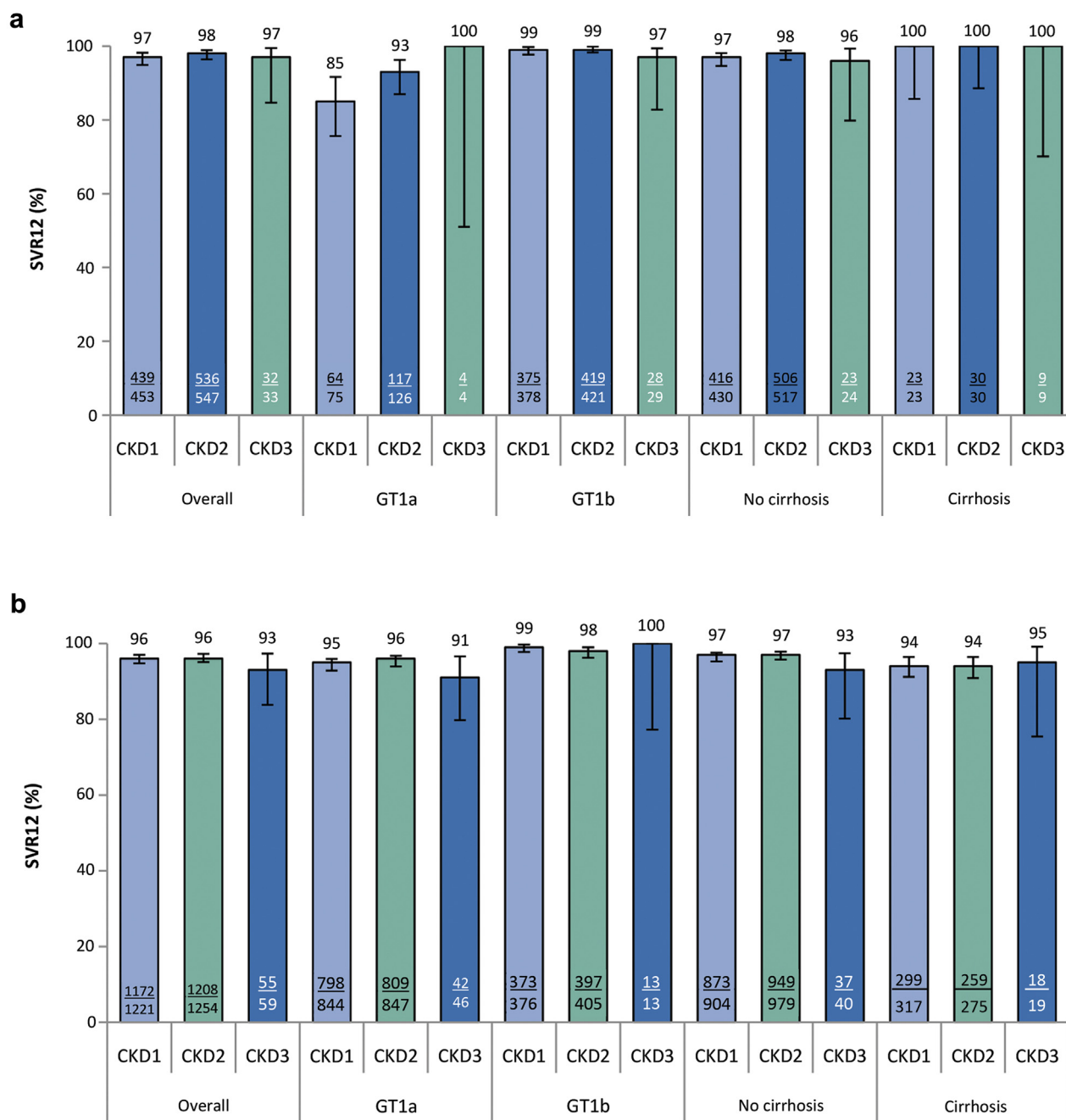


Figure 1. Sustained virologic response rates at posttreatment week 12 in patients treated with OBV/PTV/r + DSV without RBV (a) or with RBV (b) by CKD stage (CKD1: >90 ml/min per 1.73 m²; CKD2: >60–90 ml/min per 1.73 m²; CKD3: >30–60 ml/min per 1.73 m²). The percentage of patients who achieved SVR12 is plotted with 95% confidence intervals. CKD, chronic kidney disease; DSV, dasabuvir; GT, genotype; OBV, ombitasvir; PTV/r; paritaprevir/ritonavir; RBV, ribavirin; SVR12, sustained virologic response rates at posttreatment week 12.

Safety Outcomes
AEs and Serious AEs

Patients with less severe renal dysfunction tended overall to have fewer AEs, and patients treated with RBV tended to have more AEs than those treated without RBV. Of 3567 patients in this analysis, 2870 patients experienced at least 1 AE (80%; Table 2). AEs were significantly associated with CKD stage (CKD1 77% [1285/1674], CKD2 84% [1505/1801], CKD3 87% [80/92]; *P* < 0.001). The most common AEs were

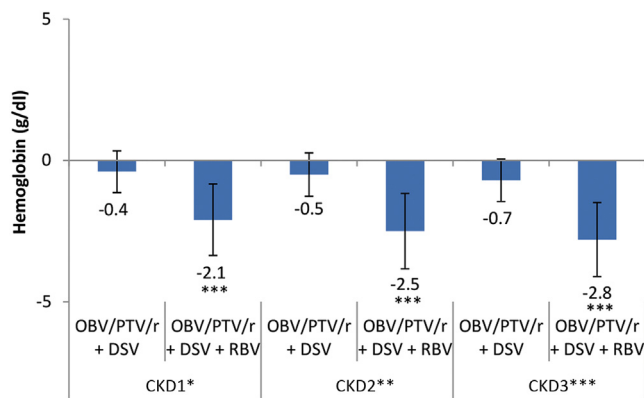
fatigue, headache, and anemia (Table 2 [see Supplementary Table S1 for AEs in ≥10% of patients]). In patients treated with RBV, the frequency of anemia reported as an AE was greater in patients with CKD3 than in those with CKD2 or CKD1 (25% [15/59] vs. 8% [103/1254], and 4% [43/1221], respectively; *P* < 0.001). Anemia was uncommon among patients who did not receive RBV (CKD3 0% [0/33], CKD2 0.4% [2/547], CKD1 0.2% [1/453]; *P* = not significant). AEs leading to treatment discontinuation were infrequent and did not

Table 2. Treatment-emergent adverse events and renal-associated adverse events by CKD stage^a

AE, n (%)	OBV/PTV/r + DSV						OBV/PTV/r + DSV + RBV						Overall (N = 3567)
	No cirrhosis			Cirrhosis			No cirrhosis			Cirrhosis			
	CKD1 (n = 430)	CKD2 (n = 517)	CKD3 (n = 24)	CKD1 (n = 23)	CKD2 (n = 30)	CKD3 (n = 9)	CKD1 (n = 904)	CKD2 (n = 979)	CKD3 (n = 40)	CKD1 (n = 317)	CKD2 (n = 275)	CKD3 (n = 19)	
Any AE	274 (64)	367 (71)	17 (71)	18 (78)	20 (67)	9 (100)	722 (80)	871 (89)	37 (93)	271 (85)	247 (90)	17 (90)	2870 (80)
Serious AE	5 (1)	7 (1)	1 (4)	–	–	1 (11)	19 (2)	23 (2)	4 (10)	19 (6)	14 (5)	2 (11)	95 (3)
AEs leading to discontinuation of study drug	2 (<1)	1 (<1)	–	–	–	–	3 (<1)	8 (<1)	–	4 (1)	8 (3)	1 (5)	27 (1)
AEs leading to RBV dose reduction	–	1 (<1)	–	–	–	–	56 (6)	96 (10)	17 (43)	34 (11)	43 (16)	6 (32)	253 (7)
Fatal AE	–	–	–	–	–	–	–	1 (<1)	–	1 (<1)	–	–	2 (<1)
Renal-associated AEs (SMQ/CMQ)	4 (1)	10 (2)	–	–	–	1 (11)	9 (1)	15 (2)	3 (8)	4 (1)	9 (3)	1 (5)	56 (2)
AEs occurring in ≥15% of patients in any subgroup													
Fatigue	88 (20)	121 (23)	5 (21)	6 (26)	6 (20)	1 (11)	269 (30)	351 (36)	14 (35)	98 (31)	112 (41)	13 (68)	1084 (30)
Headache	88 (20)	109 (21)	5 (21)	2 (9)	6 (20)	3 (33)	203 (22)	284 (29)	7 (18)	71 (22)	71 (26)	6 (32)	855 (24)
Nausea	–	–	–	–	4 (13)	–	150 (17)	201 (21)	7 (18)	54 (17)	61 (22)	5 (26)	482 (14)
Pruritus	27 (6)	40 (8)	3 (13)	1 (4)	4 (13)	1 (11)	113 (13)	140 (14)	7 (18)	49 (15)	55 (20)	3 (16)	443 (12)
Insomnia	–	–	–	3 (13)	3 (10)	1 (11)	117 (13)	160 (16)	8 (20)	45 (14)	45 (16)	5 (26)	387 (11)
Diarrhea	–	–	–	4 (17)	7 (23)	1 (11)	75 (8)	107 (11)	7 (18)	41 (13)	39 (14)	5 (26)	286 (8)
Cough	–	–	–	–	–	–	63 (7)	69 (7)	7 (18)	29 (9)	27 (10)	1 (5)	196 (5)
Dizziness	–	–	–	1 (4)	5 (17)	–	48 (5)	80 (8)	4 (10)	18 (6)	22 (8)	2 (11)	180 (5)
Anemia	1 (<1)	2 (<1)	–	–	–	–	25 (3)	70 (7)	12 (30)	18 (6)	33 (12)	3 (16)	161 (5)
Decreased appetite	–	–	–	–	–	–	50 (6)	48 (5)	6 (15)	–	–	–	104 (3)
Hemoglobin decrease	–	–	–	–	–	–	23 (3)	32 (3)	6 (15)	15 (5)	18 (7)	2 (11)	96 (3)
Rash	–	–	–	–	–	–	–	–	–	28 (9)	36 (13)	5 (26)	69 (2)
UTI	–	–	–	–	–	–	18 (2)	25 (3)	6 (15)	–	–	–	49 (1)
Abdominal pain, upper	–	–	–	1 (4)	1 (3)	1 (11)	–	–	–	21 (7)	12 (4)	4 (21)	40 (1)
Depression	–	–	–	–	–	–	–	–	–	10 (3)	11 (4)	4 (21)	25 (<1)
Blood bilirubin increase	–	–	–	–	–	–	–	–	–	8 (3)	13 (5)	3 (16)	24 (<1)
Abdominal pain	–	–	–	–	–	–	–	–	–	10 (3)	4 (2)	3 (16)	17 (<1)
Myalgia	–	–	–	4 (17)	–	–	–	–	–	–	–	–	4 (<1)

–, no AE; AE, adverse event; CKD, chronic kidney disease; CMQ, Custom MedDRA Query; DSV, dasabuvir; OBV, ombitasvir; PTV/r, paritaprevir/ritonavir; RBV, ribavirin; SMQ, Standardized MedDRA Query; UTI, urinary tract infection.

^aCKD1: >90 ml/min per 1.73 m²; CKD2: >60–90 ml/min per 1.73 m²; CKD3: >30–60 ml/min per 1.73 m².



A >2–<10 reduction in Hgb by EOT:
 CKD1 49% of patients +RBV 2% without RBV
 CKD2 61% of patients +RBV 2% without RBV
 CKD3 77% of patients +RBV 3% without RBV

Figure 2. Mean change in hemoglobin from baseline to EOT by CKD stage (CKD1: >90 ml/min per 1.73 m²; CKD2: >60–90 ml/min per 1.73 m²; CKD3: >30–60 ml/min per 1.73 m²). Mean change from baseline in hemoglobin is plotted with SD. CKD, chronic kidney disease; DAA, direct-acting antiviral; DSV, dasabuvir; EOT, end of treatment; Hgb, hemoglobin; OBV, ombitasvir; PTV/r, paritaprevir/ritonavir; RBV, ribavirin. *P* values represent a comparison of the 3-DAA with the 3-DAA + RBV regimen. ***, **, and * denote *P* values statistically significant to 0.001, 0.001, and 0.05 levels, respectively.

differ significantly by CKD stage. Few patients (*n* = 20) with severe renal impairment (CKD4) or ESRD (CKD5) were included in this analysis, and none of these patients treated with OBV/PTV/r + DSV ± RBV discontinued study drug owing to an AE.

Few patients (3% [95/3567]) had serious AEs, which were numerically more frequent in patients treated

with (3% [81/2534]) than without RBV (1% [14/1033]; Table 2). More patients with CKD3 who were treated with RBV had serious AEs (10% [6/59]) when compared with those with CKD1 (3%, 38/1221) or CKD2 (3% [37/1254]; *P* = 0.008), irrespective of cirrhosis status. Only 0.2% of patients (2/1040) treated with OBV/PTV/r + DSV had a serious AE that was considered possibly related to DAA study drug; both had CKD3. In patients treated with RBV, 0.5% of patients (13/2547) had serious AEs possibly related to DAA study drug (CKD2, 8; CKD1, 5). The serious AEs included anemia, acute kidney injury, and acute prerenal failure (each in 1 patient). Serious AEs are provided in Supplementary Table S2.

AEs leading to RBV dose reduction occurred in 10% of patients with CKD1 to 3 (252/2534) with a higher proportion in patients with cirrhosis than without cirrhosis (14% [83/611] vs. 9% [169/1923]; *P* < 0.001). AEs leading to RBV dose reduction were more frequent in patients with CKD3 than either CKD1 or 2 (CKD1: 7% [90/1221]; CKD2: 11% [139/1254]; CKD3: 39% [23/59]; *P* < 0.001). RBV dose reductions were not associated with reduced SVR rates (Supplementary Figure S2). Of 13 patients with CKD4 or 5, 9 (64%) had AEs leading to RBV dose reductions; none had cirrhosis.

None of the 20 patients with CKD4 or 5 discontinued study drug owing to an AE. Four (19%) had serious AEs (none of which were considered possibly related to the study drug).

Three fatal AEs occurred in patients treated with RBV. Two patients died of cancer (metastatic pancreatic

Table 3. Renal-associated adverse events by CKD stage^{a,b}

AE, <i>n</i>	OBV/PTV/r + DSV			OBV/PTV/r + DSV + RBV		
	CKD1 (<i>n</i> = 453)	CKD2 (<i>n</i> = 547)	CKD3 (<i>n</i> = 33)	CKD1 (<i>n</i> = 1221)	CKD2 (<i>n</i> = 1254)	CKD3 (<i>n</i> = 59)
Decreased CrCl	–	5	1	5	9	2
Proteinuria	1	–	–	6	3	–
Hyponatremia	1	3	–	1	4	–
Hypocalcemia	–	1	–	–	3	–
Leukocyturia	1	–	–	2	1	–
AKI	–	–	–	–	3	–
Renal failure	–	–	–	–	1	2
Blood sodium decrease	–	1	–	–	1	–
Encephalopathy	–	–	–	–	2	–
Blood potassium increase	–	–	–	–	1	–
Blood urea increase	–	–	–	1	–	–
Hyperphosphatemia	–	–	–	–	1	–
Hypoalbuminemia	–	–	–	1	–	–
Metabolic acidosis	–	–	–	–	1	–
Pericarditis	–	1	–	–	–	–
RBC urine positive	1	–	–	–	–	–

–, no AE; AE, adverse event; AKI, acute kidney injury; CKD, chronic kidney disease; CrCl, creatinine clearance; DSV, dasabuvir; OBV, ombitasvir; PTV/r, paritaprevir/ritonavir; RBC, red blood cell; RBV, ribavirin.

^aData in the table represent all reported AEs; 1 patient may have had >1 AE.

^bCKD1: >90 ml/min per 1.73 m²; CKD2: >60–90 ml/min per 1.73 m²; CKD3: >30–60 ml/min per 1.73 m².

cancer in a patient with CKD1; non-small-cell lung cancer in a CKD2 patient), and 1 patient with CKD5 died of left ventricular dysfunction.

Among patients who received RBV, hemoglobin decreases to <10 g/dl or ≥ 2 g/dl from baseline to EOT occurred in 49% (593/1220), 61% (764/1250), and 78% (45/58) of patients with CKD1, CKD2, and CKD3, respectively. Fewer patients (2% [22/1032]) who did not receive RBV had comparable hemoglobin reductions. Recipients of RBV had significantly greater hemoglobin reductions ($P < 0.001$ vs. recipients of 3-DAA without RBV). Mean hemoglobin reductions were significantly greater in patients with CKD1 or 2 versus CKD3: OBV/PTV/r + DSV, $P = 0.025$; OBV/PTV/r + DSV + RBV, $P < 0.001$; Figure 2).

Renal-Associated AEs

Renal-associated AEs were infrequent, with 67 events occurring in 2% (56/3567) of patients. The frequency of renal-associated AEs increased with decreasing renal function (CKD1: 17/1674 [1%]; CKD2: 34/1801 [2%]; CKD3: 5/92 [5%]; $P = 0.001$; Table 2). Renal-associated AEs in RBV recipients were reported in 1% (13/1221), 2% (24/1254), and 7% (4/59) of patients with CKD1, 2, and 3, respectively ($P = 0.002$). Among patients treated without RBV, the incidence was 1% (4/453), 2% (10/547), and 3% (1/33), respectively ($P =$ not significant; Table 2). Most renal-associated AEs were of mild-to-moderate intensity, with 7 patients (0.2%) experiencing severe events. The most common renal-associated AEs were decreased CrCl (33% [22/67]), proteinuria (15% [10/67]), and hyponatremia (13% [9/67]; Table 3). In total, 29 (52%) patients had renal-associated AEs (34 AEs in total) that were considered by the study investigator to be possibly related to either OBV/PTV/r + DSV or RBV. Of 20 patients with CKD4 or 5, 1 recipient (CKD4) of RBV experienced 2 renal-associated AEs (elevated SCr and blood urea nitrogen) during treatment. Two patients discontinued study drug treatment because of renal-associated AEs. Ninety-three percent of renal-associated AEs resolved during or after study drug treatment.

Effect of Treatment on Renal Function

We observed 2 distinct patterns of changes in kidney function from baseline to EOT among patients with CKD1, CKD2, and CKD3. Mean eGFR decreased among patients with CKD1 but increased among patients with CKD2 to 3 (Figure 3a). Similarly, mean SCr values increased among patients with CKD1 and decreased among patients with CKD2 or 3 (Figure 3b). Importantly, the largest gain in eGFR and decrease in SCr occurred in patients with the lowest baseline eGFR (CKD3). Mean eGFR increased from baseline to EOT in recipients of RBV with CKD2 (1.55 ml/min per 1.73

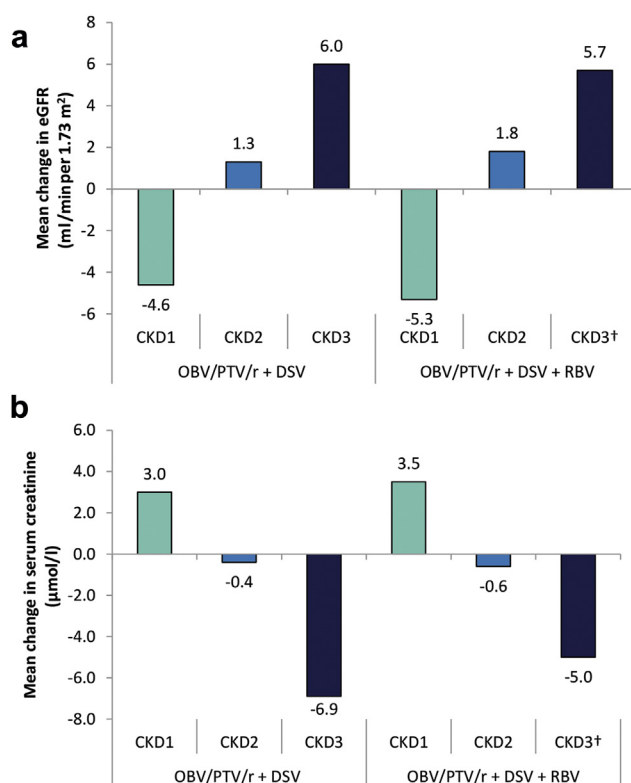


Figure 3. Mean change in eGFR (a) and serum creatinine (b) from baseline to end of treatment by CKD stage (CKD1: >90 ml/min per 1.73 m²; CKD2: >60 – 90 ml/min per 1.73 m²; CKD3: >30 – 60 ml/min per 1.73 m²). All patients with CKD1 to 3 across 11 clinical trials. Data on eGFR and serum creatinine were missing for 1 patient in the CKD3 group treated with OBV/PTV/r + DSV + RBV. CKD, chronic kidney disease; DSV, dasabuvir; eGFR, estimated glomerular filtration rate; OBV, ombitasvir; PTV/r, paritaprevir/ritonavir; RBV, ribavirin.

m²) or CKD3 (5.85 ml/min per 1.73 m²) at baseline and decreased in patients with CKD1 (-4.95 ml/min per 1.73 m²; Figure 3a). Similarly, mean SCr decreased from baseline to EOT with OBV/PTV/r + DSV ± RBV in patients with CKD2 (-0.50 μmol/L) or CKD3 (-5.95 μmol/L), whereas it increased in patients with CKD1 (3.25 μmol/L; Figure 3b). Given that the risk of CKD is higher in patients with cirrhosis,⁴ we assessed the impact of cirrhosis on renal function (Figure 4). Among patients without cirrhosis with CKD3 at baseline, a mean increase in eGFR of 4.5 ml/min per 1.73 m² and 6.9 ml/min per 1.73 m² was observed in patients treated with or without RBV, respectively. In patients with cirrhosis with CKD3 at baseline, a mean increase in eGFR of 8.0 ml/min per 1.73 m² and 3.6 ml/min per 1.73 m² was observed in patients treated with or without RBV, respectively (Figure 4). By contrast, the largest mean decreases in eGFR were observed in patients with cirrhosis with CKD1. No substantial change was reported in eGFR in patients with CKD4 (0.9 ml/min per 1.73 m²) or CKD5 (-0.4 ml/min per 1.73 m²) treated with or without RBV.

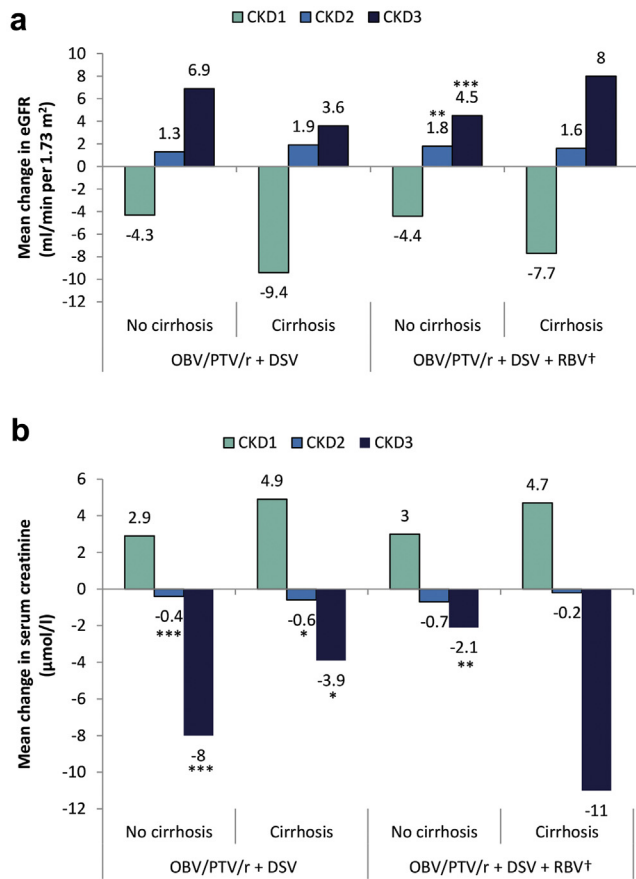


Figure 4. Mean change in eGFR (a) and serum creatinine (b) from baseline to end of treatment according to CKD stage (CKD1: >90 ml/min per 1.73 m²; CKD2: >60–90 ml/min per 1.73 m²; CKD3: >30–60 ml/min per 1.73 m²) and presence of cirrhosis. All patients with CKD1 to 3 across 11 clinical trials. Data on eGFR and serum creatinine were missing for 1 patient in the CKD3 group treated with OBV/PTV/r + DSV + RBV. *P* values represent a comparison with CKD1. ***, **, and * denote *P* values statistically significant to 0.001, 0.001, and 0.05 levels, respectively. CKD, chronic kidney disease; DSV, dasabuvir; eGFR, estimated glomerular filtration rate; OBV, ombitasvir; PTV/r, paritaprevir/ritonavir; RBV, ribavirin.

Furthermore, regardless of baseline eGFR, no difference was observed in the proportion of patients with either a decrease (Figure 5a) or increase (Figure 5b) in eGFR by ≥10 ml/min per 1.73 m² in the placebo (*n* = 255) and OBV/PTV/r + DSV + RBV (*n* = 769) arms of the SAPPHIRE-I and -II trials or the OBV/PTV/r + DSV ± RBV (*n* = 2663) arms of 7 clinical trials in which baseline urinalysis was performed.²¹

Baseline Factors Associated With eGFR Improvement

Stepwise logistic regression analysis was performed to identify baseline factors associated with ≥10 ml/min per 1.73 m² improvement in eGFR in 7 clinical trials with baseline urinalysis data. Overall, 18% of patients (486/2663) experienced ≥10 ml/min per 1.73 m² increase in eGFR at EOT (Figure 5b). Baseline factors

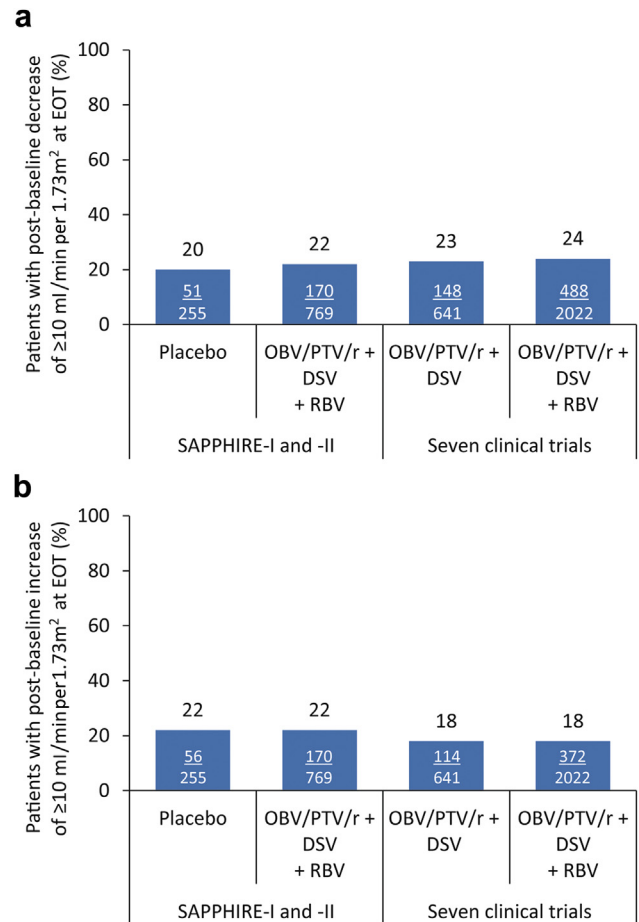


Figure 5. Post-baseline decrease (a) and increase (b) in eGFR by ≥10 ml/min per 1.73 m² at EOT. Patients were from 7 clinical trials (SAPPHIRE-I, SAPPHIRE-II, TURQUOISE-II, TOPAZ-II, PEARL-II, PEARL-III, PEARL-IV). DSV, dasabuvir; eGFR, estimated glomerular filtration rate; EOT, end of treatment; OBV, ombitasvir; PTV/r, paritaprevir/ritonavir; RBV, ribavirin.

significantly associated with this increase were body mass index (*P* < 0.001), nonblack race (*P* = 0.021), proteinuria (*P* < 0.001), and diabetes (*P* = 0.023; Table 4). When the analysis was done on the placebo group in SAPPHIRE-I and -II, changes in eGFR were not associated with any baseline factors.²¹

Table 4. Baseline factors associated with improvement in eGFR^a

Variable	≥10 ml/min per 1.73 m ² eGFR improvement		
	OR	95% CI	<i>P</i> value
Baseline proteinuria (positive vs. negative)	1.65	1.32–2.05	<0.001
Baseline BMI	0.95	0.93–0.97	<0.001
Race (black vs. nonblack)	0.60	0.38–0.92	0.021
History of diabetes (yes vs. no)	1.51	1.06–2.16	0.023

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

^aBaseline characteristics that were evaluated by linear regression analysis: urine blood (positive or negative), urine protein (positive or negative), fibrosis score (F0–1, F2, F3, F4), BMI (continuous, kg/m²), age (continuous, years), sex (male or female), race (black or nonblack), history of hypertension (yes or no), history of diabetes (yes or no), baseline hepatitis C virus RNA (continuous, log₁₀ IU/ml).

CONCLUSION

Given that HCV infection is implicated in the development and progression of CKD, it is important to identify and treat HCV in patients with CKD. However, given that patients with CKD were generally excluded from registration trials, more data are needed to confirm the safety and efficacy of DAAs in patients with CKD.²²

In the present analysis, the safety and efficacy of OBV/PTV/r + DSV ± RBV were assessed in 3567 GT1b-infected patients with CKD stages 1 to 3 across 11 phase 3 studies. It should be noted that some patients received regimens not presently recommended in product labeling. For example, some GT1b-infected patients with cirrhosis received OBV/PTV/r + DSV with RBV for 12 weeks, whereas European Union and US product labeling recommends OBV/PTV/r + DSV alone for all GT1b-infected patients, including those with compensated cirrhosis. Similarly, the approved regimens for GT1a-infected patients are OBV/PTV/r + DSV + RBV for 12 weeks in patients without cirrhosis and 24 weeks in patients with compensated cirrhosis. However, this analysis includes GT1a-infected patients who received OBV/PTV/r + DSV without RBV, in whom the SVR12 rate was 90%. Among patients who received the label-recommended regimen based on HCV subtype, SVR rates across CKD strata were similar to those reported in the registration trials. Regardless of GT1 subgroup or receipt of RBV, high overall SVR rates (93%–98%) were achieved and were similar across CKD stages. In addition, SVR rates were consistently high in subgroups defined by cirrhosis status, irrespective of CKD stage.

OBV/PTV/r + DSV ± RBV was generally well tolerated irrespective of CKD stage. Relatively few patients (3%) had a serious AE, and AEs leading to treatment discontinuation occurred in <1% of patients and did not differ by CKD stage.

The safety profile of OBV/PTV/r ± RBV in patients with CKD3 was largely similar to that in patients with CKD1 or CKD2. However, serious AEs and renal-associated AEs were more common in patients with CKD3 than in patients with CKD1/2. Many were considered unrelated to DAA therapy, suggesting that this difference reflects the greater underlying morbidity in patients with CKD3.

No worsening of eGFR was observed with OBV/PTV/r + DSV + RBV, regardless of baseline CKD stage in placebo-controlled trials (SAPPHIRE-I/II). eGFR increased and SCr decreased from baseline to EOT in patients with CKD2 or 3 treated with OBV/PTV/r + DSV ± RBV, suggesting that this regimen does not

affect renal function in patients with moderate CKD. Although these parameters improved in patients with CKD3, these data are insufficient to conclude that renal function improves in patients with moderate renal impairment. A large, community-based study showed a correlation between decreasing eGFR and increasing risk of death, cardiovascular events, and hospitalization²³; however, it is unknown whether improvements in eGFR observed in this analysis persist after treatment and translate into improved clinical outcomes. Several factors (positive baseline proteinuria, lower baseline body mass index, nonblack race, and a history of diabetes) were associated with improved eGFR in the subanalysis of baseline urinalysis data and may be used to identify patients likely to benefit from treatment. Studies with prolonged observation periods are needed to assess whether eradication of HCV affects the progression of kidney disease and improves survival in patients with renal impairment.

The results of this study are supported by a German real-world study of more than 1000 GT1- or GT4-infected patients with or without renal impairment who received OBV/PTV/r ± DSV ± RBV.²⁴ The SVR12 rate among patients with moderate-to-severe renal impairment (eGFR <60 ml/min per 1.73 m²) was 100% (34/34), and the safety profile among patients with any degree of renal impairment (eGFR ≤90 ml/min per 1.73 m²; n = 326) was similar to the overall population.²⁴ In addition, no clinically relevant changes in eGFR from baseline to EOT were observed for the overall population or for any CKD subgroup.²⁴

These results contrast with those obtained with sofosbuvir-based regimens. Sofosbuvir, a nucleoside analog HCV polymerase inhibitor, and its principal metabolite GS-331007 are renally excreted.²⁵ Sofosbuvir and GS-331007 exposures are 171% and 451% higher, respectively, in patients with an eGFR of <30 ml/min per 1.73 m² than in patients with normal renal function.²⁶ The incidence of serious AEs and worsening renal function in patients with eGFR ≤45 ml/min per 1.73 m² (moderate renal impairment or worse) was 3.5-fold higher than that in patients with eGFR >45 ml/min per 1.73 m² in a cohort of 1789 sofosbuvir recipients.²⁵ Similarly, patients with eGFR <60 ml/min per 1.73 m² were more likely to experience worsening of eGFR than patients with normal renal function after controlling for age, fibrosis stage, and treatment duration in a retrospective study of recipients of ledipasvir/sofosbuvir.²⁷ In another report, sofosbuvir plus simeprevir were well tolerated in patients with severe CKD or ESRD.²⁸ It is not known if sofosbuvir or its metabolite have a pathogenic effect; however, guidelines do

not recommend use of sofosbuvir in patients with severe renal impairment (eGFR <30 ml/min per 1.73 m²) or ESRD requiring hemodialysis.^{8,9}

Grazoprevir (NS3 protease inhibitor) and elbasvir (NS5A inhibitor) are hepatically metabolized; thus, dose adjustments are unnecessary in patients with renal impairment.²⁹ This regimen was well tolerated, with an SVR12 rate of 94% to 99% in GT1-infected patients with CKD4 or 5, including hemodialysis patients.³⁰ In addition, the pan-genotypic regimen of glecaprevir (NS3 protease inhibitor) and pibrentasvir (NS5A inhibitor) is approved for patients with any degree of renal impairment without dosage adjustment³¹; this regimen achieved an SVR12 rate of 98% in patients infected with GT1 to 6 with CKD4 or 5, including patients requiring hemodialysis, and was well tolerated.³² Separate integrated analyses of grazoprevir plus elbasvir and glecaprevir plus pibrentasvir showed no worsening of eGFR from baseline with either regimen in patients with renal impairment.^{33,34}

Few patients with CKD4 or 5 were included in this analysis; however, the safety profile of OBV/PTV/r + DSV ± RBV in these patients was generally similar to that in patients with CKD1 to 3. In RUBY-I, OBV/PTV/r + DSV ± RBV achieved an SVR12 rate (by intention-to-treat analysis) of 90% in the initial cohort of GT1-infected patients without cirrhosis with CKD4 or 5.¹¹ The safety profile was generally similar to that in patients with normal renal function, with the exception of a higher incidence of RBV treatment interruptions therapy owing to anemia,¹¹ similar to the current analysis. SVR12 rates of 96% (46/48; 95% in GT1a [35/37] and 100% in GT1b [11/11] patients) were achieved in a second cohort of patients with CKD4 or 5 with or without compensated cirrhosis (including treatment-experienced patients). Most AEs were mild or moderate in severity, and only 1 patient discontinued treatment due to DAA-related serious AE (diarrhea).³⁵ Similarly, real-world studies of OBV/PTV/r ± DSV ± RBV in GT1- and GT4-infected patients with CKD4 or 5, including patients who require hemodialysis, have shown SVR12 rates >95% and good tolerability.^{36–38} In this study, the frequency of serious AEs was higher in the small group of patients with CKD4 or 5 than in patients with CKD1 to 3. This was also observed in an integrated analysis of more than 2000 patients with GT1 to 6 treated with glecaprevir and pibrentasvir, with an increased rate of serious AEs, as well as a higher frequency of the AE of pruritus, among patients with CKD4 or 5 ($n = 103$).³⁴

RBV is eliminated by renal excretion; thus, exposure to RBV and the risk of dose-related AEs is increased in patients with renal impairment. The incidence of renal-associated AEs was generally low across CKD groups,

but was higher in patients treated with RBV. For example, anemia occurred in 25% of ribavirin recipients with CKD3, compared with 4% to 8% in those with CKD1 or 2. Similarly, AEs resulting in RBV dose reductions occurred in 39% of patients with CKD3 and 7% to 11% of those with CKD1 or 2. The collective results of the present study and RUBY-I suggest dose adjustments do not completely abrogate the risk of RBV-associated toxicity. Thus, dose reductions and frequent hematologic monitoring are warranted in patients with CKD ≥3 who require RBV. It is noteworthy that SVR12 rates were not affected by RBV dose reductions in any CKD stratum.

RBV-Free Regimens Are Preferred in Patients With ESRD

In the exploratory RUBY-II study, in which treatment-naïve patients infected with GT1a ($n = 13$) or GT4 ($n = 4$) without cirrhosis and with CKD4 or 5 received OBV/PTV/r ± DSV, the SVR12 rate was 100% (excluding 1 GT4-infected patient who withdrew from the study at week 2 for renal transplantation). The RBV-free regimen was well tolerated; no serious AEs were related to the study drugs. These results suggest that RBV may not be required in some GT1a and GT4 patients; however, larger trials are needed to confirm these results.³⁹

In conclusion, in this pooled analysis of 3567 GT1-infected patients with renal impairment across 11 phase 3 studies treated with OBV/PTV/r + DSV ± RBV for 12 or 24 weeks achieved high SVR rates independent of baseline renal function. Treatment was well tolerated across CKD groups, with low rates of renal-associated AEs and discontinuations. A gain in eGFR at the EOT was observed in patients with CKD2 or 3. Several baseline characteristics were associated with improved eGFR in a subset of 2663 patients who had urinalysis at baseline; however, the long-term benefit and durability of this improvement are yet to be determined. Patients treated with RBV were at higher risk of AEs; consequently, RBV doses should be reduced in and patients should be closely monitored for RBV-associated anemia during treatment with OBV/PTV/r + DSV + RBV.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Table S1. AEs in ≥10% of patients in any subgroup.

Table S2. Serious AEs possibly related to DAA study drug in patients treated with OBV/PTV/r + DSV + RBV.

Figure S1. SVR12 in patients treated with OBV/PTV/r + DSV without RBV (A) or with RBV (B) by CKD stage and genotype in the presence or absence of cirrhosis.

Figure S2. SVR12 rates in patients treated with OBV/PTV/r + DSV + RBV stratified by RBV dose modification.

Supplementary material is linked to the online version of the paper at <http://www.kireports.org/>.

REFERENCES

- Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl.* 2008;109:S1–S99.
- Cacoub P, Comarmond C, Domont F, et al. Extrahepatic manifestations of chronic hepatitis C virus infection. *Ther Adv Infect Dis.* 2016;3:3–14.
- Lee JJ, Lin MY, Chang JS, et al. Hepatitis C virus infection increases risk of developing end-stage renal disease using competing risk analysis. *PLoS One.* 2014;9:e100790.
- Chen YC, Lin HY, Li CY, et al. A nationwide cohort study suggests that hepatitis C virus infection is associated with increased risk of chronic kidney disease. *Kidney Int.* 2014;85:1200–1207.
- Molnar MZ, Alhourani HM, Wall BM, et al. Association of hepatitis C viral infection with incidence and progression of chronic kidney disease in a large cohort of US veterans. *Hepatology.* 2015;61:1495–1502.
- Patel PR, Thompson ND, Kallen AJ, Arduino MJ. Epidemiology, surveillance, and prevention of hepatitis C virus infections in hemodialysis patients. *Am J Kidney Dis.* 2010;56:371–378.
- Morales JM, Fabrizi F. Hepatitis C and its impact on renal transplantation. *Nat Rev Nephrol.* 2015;11:172–182.
- American Association for the Study of Liver Diseases and Infectious Diseases Society of America. HCV guidance: Recommendations for testing, managing, and treating hepatitis C. Updated 2018. Available at: <http://www.hcvguidelines.org/>. Accessed August 26, 2018.
- European Association for the Study of the Liver (EASL). EASL recommendations on treatment of hepatitis C 2016. *J Hepatol.* 2017;66:153–194.
- Copegus (ribavirin) [package insert]. South San Francisco, CA: Hoffmann-La Roche, Inc. 2011.
- Pockros PJ, Reddy KR, Mantry PS, et al. Efficacy of direct-acting antiviral combination for patients with HCV genotype 1 infection and severe renal impairment or end-stage renal disease. *Gastroenterology.* 2016;150:1590–1598.
- Andreone P, Colombo MG, Enejosa JV, 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;147:359–365.
- Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med.* 2014;370:1594–1603.
- Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med.* 2014;370:1983–1992.
- Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med.* 2014;370:1973–1982.
- Sulkowski MS, Eron JJ, Wyles D, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. *JAMA.* 2015;313:1223–1231.
- Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med.* 2014;370:1604–1614.
- Feld JJ, Moreno C, Trinh R, et al. Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12 weeks. *J Hepatol.* 2016;64:301–307.
- Dumas EO, Enejosa J, Ball G, et al. Phase 3B studies to assess long-term clinical outcomes in HCV GT1-infected patients treated with ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin. *J Hepatol.* 2015;62(suppl):S855.
- Reau N, Poordad F, Enejosa J, et al. Preliminary safety and efficacy results from TOPAZ-II: a phase 3b study evaluating long-term clinical outcomes in HCV genotype 1-infected patients receiving ombitasvir/paritaprevir/r and dasabuvir +/- ribavirin. *Hepatology.* 2015;62(suppl):732A.
- Bernstein DE, Tran A, Martin P, et al. Predictors of improvement in glomerular filtration rate among patients treated with

- ombitasvir/paritaprevir/r and dasabuvir with or without RBV. *Hepatology*. 2016;64(suppl):456A.
22. Fabrizi F, Martin P, Messa P. New treatment for hepatitis C in chronic kidney disease, dialysis, and transplant. *Kidney Int*. 2016;89:988–994.
 23. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305.
 24. Welzel TM, Hinrichsen H, Sarrazin C, et al. Real-world experience with the all-oral, interferon-free regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir for the treatment of chronic hepatitis C virus infection in the German hepatitis C registry. *J Viral Hepat*. 2017;24:840–849.
 25. Saxena V, Korashy FM, Sise ME, et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C infected patients with impaired renal function. *Liver Int*. 2016;36:807–816.
 26. HARVONI (ledipasvir and sofosbuvir) [package insert]. Foster City, CA: Gilead Sciences, Inc. 2017.
 27. Rosenblatt R, Mehta A, Wagner M, Kumar S. Baseline creatinine clearance is a predictor of worsening renal function while on HCV treatment with sofosbuvir-ledipasvir. *J Hepatol*. 2016;64(suppl):S819.
 28. Nazario HE, Ndungu M, Modi AA. Sofosbuvir and simeprevir in hepatitis C genotype 1-patients with end-stage renal disease on haemodialysis or GFR. *Liver Int*. 2016;36:798–801.
 29. ZEPATIER (elbasvir and grazoprevir) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc. 2018.
 30. Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naïve and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. *Lancet*. 2015;386:1537–1545.
 31. MAVYRET (glecaprevir and pibrentasvir) [package insert]. North Chicago, IL: AbbVie, Inc. 2018.
 32. Gane E, Lawitz E, Pugatch D, et al. Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment. *N Engl J Med*. 2017;377:1448–1455.
 33. Reddy KR, Roth D, Bruchfeld A, et al. Elbasvir/grazoprevir does not worsen renal function in patients with hepatitis C virus infection and pre-existing renal disease. *Hepatol Res*. 2017;47:1340–1345.
 34. Pol S, Pockros P, Pugatch D, et al. Safety and efficacy of glecaprevir/pibrentasvir in adults with chronic hepatitis C virus infection genotype 1–6 as a function of chronic kidney disease stage. *J Hepatol*. 2017;66(suppl):S738.
 35. Vierling JM, Lawitz E, Reddy KR, et al. RUBY-I: Safety and efficacy of ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin in adults with genotype 1 chronic hepatitis C virus (HCV) infection with severe renal impairment or end-stage renal disease. *Hepatology*. 2016;64(suppl):441A.
 36. Munoz-Gomez R, Rincon D, Ahumada A, et al. Therapy with ombitasvir/paritaprevir/ritonavir plus dasabuvir is effective and safe for the treatment of genotypes 1 and 4 hepatitis C virus (HCV) infection in patients with severe renal impairment: a multicentre experience. *J Viral Hepat*. 2017;24:464–471.
 37. Sanai FM, Alghamdi AS, Afghani AA, et al. High efficacy of ombitasvir/paritaprevir/ritonavir plus dasabuvir in hepatitis C genotypes 4 and 1-infected patients with severe chronic kidney disease. *Liver Int*. 2018;38:1395–1401.
 38. Sperl J, Kreidlova M, Merta D, et al. Paritaprevir/ritonavir/ombitasvir plus dasabuvir regimen in the treatment of genotype 1 chronic hepatitis C infection in patients with severe renal impairment and end-stage renal disease: a real-life cohort. *Kidney Blood Press Res*. 2018;43:594–605.
 39. Gane EJ, Solà R, Cohen E, et al. RUBY-II: Efficacy and safety of a ribavirin-free ombitasvir/paritaprevir/ritonavir ± dasabuvir regimen in patients with severe renal impairment or end-stage renal disease and HCV genotypes 1a or 4 infection. *Hepatology*. 2016;64(suppl):470A–471A.