Safety and Efficacy of Paritaprevir/Ritonavir, Ombitasvir, and Dasabuvir for Hepatitis C Virus Infection Across All Levels of Kidney Function

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Hepatitis C virus (HCV) infection affects approximately 71 million people worldwide, and is an important cause of end-stage liver disease, hepatocellular carcinoma, and death. HCV may cause systemic vasculitis leading to cryoglobulinemic glomerulonephritis, and HCV has been associated with incident chronic kidney disease (CKD) and accelerated progression to end-stage renal disease.[1] HCV infection is common in patients on dialysis because of shared risk factors and nosocomial HCV transmission.[2] HCV-infected dialysis patients have a 15% to 34% increased risk of mortality compared with those without HCV.[3] Direct-acting antiviral therapies (DAAs) have revolutionized the management of HCV, trans-

forming it into a curable illness. However, because the first DAA approved by the Food and Drug Administration, sofosbuvir, is renally eliminated and was not approved in patients with estimated glomerular filtration rate (eGFR) <30 ml/min per 1.73 m^2, studies using DAAs in patients with kidney disease have lagged behind the general population.

This issue of *Kidney International Reports* features the results of 2 important studies using DAAs in patients with kidney disease.[4,5] In both studies, the DAA regimen evaluated is paritaprevir with the pharmaco-enhancer ritonavir, ombitasvir, and dasabuvir (PROD), a combination DAA therapy that includes 1 drug from each of the major DAA classes (protease inhibitors, polymerase inhibitors, and NS5A protein inhibitors). PROD was the first DAA regimen approved by the Food and Drug Administration that included agents primarily metabolized by the liver with minimal renal

elimination. According to the Food and Drug Administration label, the addition of ribavirin was necessary in patients with genotype 1A, but not in those with genotype 1B. Of note, those with genotype 4 infection can be treated with paritaprevir with the pharmaco-enhancer ritonavir, and ombitasvir with ribavirin. PROD ± ribavirin is not effective at treating HCV genotypes 2, 3, 5, or 6.

Bernstein and colleagues[5] pooled the results for 11 phase 3 clinical trials ($N = 3567$ patients) to examine the effect of PROD on patients with "early-stage" CKD. They compare the rates of HCV cure and adverse events (AEs) stratified by CKD stage, as defined by eGFR (Table 1). Very few patients actually had evidence of true CKD, and it is likely that the vast majority of this cohort could be considered to have normal kidney function; however, the comparison of safety and efficacy in the 92 (2.6%) patients with stage 3 CKD compared with those with normal kidney function demonstrates that cure rates are similar (93%–98%); however, anemia-related side effects and renal AEs were higher in patients with stage 3 CKD, particularly if they received ribavirin (Table 1). The vast majority (93%) of renal AEs were transient. It is important to note that making conclusions about renal safety based on numbers of "renal AEs" versus evaluating actual changes in serum creatinine during therapy has limitations.

In a *post hoc* analysis of 7 trials that included baseline proteinuria, Bernstein and colleagues[5] also performed a logistic regression to determine what factors predict a 10 ml/min per 1.73 m^2 rise in eGFR from the baseline to end of treatment (either 12 or 24 weeks later,

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Table 1. Summary of cohorts and outcomes in each study

Early CKD: Bernstein et al.[5]	Ribavirin (Yes/No)	Cure Rate, %	Anemia, %[a]	Renal AEs, %	All SAEs, %
eGFR ≥90 (n = 1221)	Yes	96	49	1	3
eGFR 60–89 (n = 1254)	Yes	96	61	2	3
eGFR <60 (n = 59)	Yes	93	78	7	10
eGFR ≥90 (n = 453)	No	97	2	1	1
eGFR 60–89 (n = 547)	No	98	2	2	1
eGFR <60 (n = 33)	No	97	2	3	6
Advanced CKD: Lawitz et al.[4]	**%Dialysis**	**DAA regimen**	**Duration, wk**	**Cure rate, %**	**Anemia**
Ruby-I cohort					
GT1A without cirrhosis (n = 28)	68	PROD + ribavirin	12	96	Grade 2–3 in 71%
GT1A with cirrhosis (n = 9)	89	PROD + ribavirin	24	89	Grade 2–3 in 75%
GT1B with or without cirrhosis (n = 11)	73	PROD	12	100	Grade 2 in 27%, no grade 3
Ruby-II cohort					
GT1A without cirrhosis (n = 13)	100	PROD	12	100	Grade 2 in 31%, no grade 3
GT4 without cirrhosis (n = 5)	80	PRO	12	80	Grade 2 in 40%, no grade 3

AE, adverse event; CKD, chronic kidney disease; DAA, direct-acting antiviral; GT, genotype; PRO, paritaprevir, ritonavir, ombitasvir; PROD, paritaprevir, ritonavir, ombitasvir, and dasabuvir; SAE, serious adverse event.
[a]Anemia defined as hemoglobin decrease to <10 g/dl or ≥2 g/dl from baseline to end of treatment. Unable to determine from text the breakdown of anemia by CKD stage in those treated with regimens that did not include ribavirin; text notes only 2% had comparable hemoglobin reductions.

depending on the duration of the DAA regimen). Eighteen percent of patients (486 of 2663) experienced a >10 ml/min per 1.73 m^2 increase in eGFR from baseline to end of treatment. Of note, this rate of "eGFR improvement" was similar to what was seen in the placebo arms of these trials, suggesting some fluctuation in kidney function over a 12- to 24-week period is inherent, especially in patients with normal eGFR, in whom small changes in serum creatinine translate into large eGFR changes. Baseline proteinuria (detected by dipstick), lower body mass index, nonblack race, and history of diabetes were associated with improved eGFR. These baseline predictors were not associated with eGFR improvement in the placebo groups. This result is intriguing; future studies with extended follow-up of kidney function beyond 3 to 6 months are needed to identify which patients are likely to have improvement in kidney function with DAAs.

Lawitz and colleagues[4] determined the safety and efficacy of PROD in patients with advanced CKD (eGFR <30 ml/min per 1.73 m^2), reporting the combined results of 2 small phase 3, open-label

clinical trials: Ruby-I, Cohort 2 (NCT02207088) and Ruby-II (NCT 02487199). A total of 66 patients were included, most (76%) were on dialysis. Regimen selection in Ruby-I, Cohort 2, summarized in Table 1, followed guidelines published for patients without CKD; patients with genotypes 1A began dose-adjusted ribavirin (200 mg daily) at the time of treatment initiation. The presence or absence of cirrhosis dictated whether a 24- or 12-week treatment course was used, respectively. Patients with genotype 1B were treated with PROD alone for 12 weeks regardless of cirrhosis status. The combined HCV cure rates were 95%. The high rate of AEs leading dose modification or discontinuation (73%) of ribavirin highlights how difficult it is to use ribavirin in this population, even when it is appropriately dose adjusted and closely monitored. Thus, Ruby-II was designed to test whether the DAA combinations (PROD for genotype 1A or paritaprevir, ritonavir, and ombitasvir for genotype 4) could be used *without* ribavirin in patients without cirrhosis; to test whether it was safer and just as efficacious. PROD alone did not lead to any anemia-related AEs and the cure

rate was 94%. The authors concluded that ribavirin coadministration may not be needed in patients with advanced CKD. They, like others have previously,[6] speculated that it may be easier to cure HCV infection in patients on dialysis than in the general population, given that dialysis patients have lower HCV RNA levels and potentially have higher drug exposure due to renal failure. The trial is important given its attempts to minimize side effects without sacrificing efficacy for dialysis patients. It is also one of the first trials to include a substantial number of patients on peritoneal dialysis (n = 7 total across both studies).

Despite high overall cure rates (93%–98%) and low rates of serious AEs, because of the complexity of the regimen, its need for ribavirin coadministration in patients with genotypes 1A and 4, and the potential drug-drug interactions caused by ritonavir-boosting, new HCV DAA drug development has led to PROD being removed from the list of first-line recommended DAA therapies by both the American Association for the Study of Liver Disease and the European Association for the Study of the Liver. Current

recommended therapies for patients with advanced CKD or end-stage renal disease are elbasvir and grazoprevir, which treat genotype 1A, 1B, or 4 infection, or glecaprevir and pibrentasvir which treat all genotypes of HCV infection. Both of these combinations are primarily metabolized by the liver, and their safety and efficacy were studied in larger clinical trials in patients with advanced CKD and end-stage renal disease.[7,8]

It is important to note that any decision to treat a patient on or approaching dialysis who is on the kidney transplant waiting list should be done in conjunction with the input of the patient's transplant center. In parts of the world in which HCV-infected organ donors are common and organs are often discarded, such as the United States, allowing a waitlisted patient to accept an organ from an HCV-infected donor may dramatically shorten transplant waiting time.[9,10] In the United States, HCV-infected donors are younger and have fewer comorbidities.[9] Where HCV-infected donors are not common, immediate treatment of dialysis patients with HCV infection is warranted. More data are needed to determine the effect of curative DAA therapy on important kidney outcomes, such as doubling of serum creatinine and progression to end-stage renal disease in patients with CKD, and to determine if curing HCV affects morbidity and mortality in patients on dialysis.

DISCLOSURE

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REFERENCES

1. 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.

2. Nguyen DB, Gutowski J, Ghiselli M, et al. A large outbreak of hepatitis C virus infections in a hemodialysis clinic. *Infect Control Hosp Epidemiol*. 2016;37:125–133.

3. Goodkin DA, Bieber B, Gillespie B, et al. Hepatitis C infection is very rarely treated among hemodialysis patients. *Am J Nephrol*. 2013;38: 405–412.

4. Lawitz E, Gane E, Cohen E, et al. Efficacy and safety of ombitasvir/paritaprevir/ritonavir in patients with hepatitis C virus genotype 1 or 4 infection and advanced kidney disease. *Kidney Int Rep*. 2019;4:257–266.

5. Bernstein DE, Tran A, Martin P, et al. Ombitasvir, paritaprevir, ritonavir, and dasabuvir with or without ribavirin in patients with kidney disease. *Kidney Int Rep*. 2019;4:245–256.

6. Gordon CE, Uhlig K, Lau J, et al. Interferon for hepatitis C virus in hemodialysis—an individual patient meta-analysis of factors associated with sustained virological response. *Clin J Am Soc Nephrol*. 2009;4:1449–1458.

7. Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naive 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.

8. 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.

9. Chute DF, Sise ME. Effect of the opioid crisis on the donor pool for kidney transplantation: an analysis of national kidney deceased donor trends from 2010–2016. *Am J Nephrol*. 2018;47:84–93.

10. Mehra MR, Jarcho JA, Cherikh W, et al. The drug-intoxication epidemic and solid-organ transplantation. *N Engl J Med*. 2018;378:1943–1945.