



More evidence that direct acting antiviral therapy is safe and effective in cirrhosis and chronic kidney disease including peritoneal dialysis

Paul Kwo and Deepti Dronamraju

Department of Gastroenterology and Hepatology, Stanford University, Redwood City, CA, USA

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Chronic hepatitis C virus (HCV) infection has an estimated prevalence of 1%, affecting 71 million people worldwide.¹ Multiple extrahepatic manifestations of hepatitis C have been reported including renal disease. Those infected with chronic hepatitis C are 70% more likely to develop chronic kidney disease (CKD) as compared to HCV seronegative patients. In addition, the presence of hepatitis C is associated with more rapid progression to end stage renal disease.^{2,3} Hepatitis C has also been shown to increase all-cause mortality for those on dialysis, and in the kidney transplant population, HCV also accelerates graft loss.⁴

While the introduction of direct acting antiviral (DAA) agents has changed the treatment landscape of HCV, with highly efficacious treatment and few difficult to treat populations, patients with advanced renal disease were not among those who initially benefitted from these therapeutic options.⁵ At first, sofosbuvir-containing regimens were not recommended for patients with advanced renal disease due to concern regarding renal clearance of

the drug's active metabolite, GS-331007.⁶ Combination therapies requiring co-administration of ribavirin were also suboptimal due to the side effect profile of ribavirin, which is renally cleared and associated with significant hemolysis in an already vulnerable population.

There are multiple recent trials that have since highlighted the success of DAAs in treating those with CKD. The C-SURFER trial was a randomized phase 3 study that showed that the efficacy and safety of elbasvir/grazoprevir in the treatment of genotype 1 patients with stage 4 and 5 CKD was similar to those with hepatitis C infection without CKD with a sustained virological response (SVR) rate of 99%.^{7,8} Similar results were demonstrated in the EXPEDITION-4 trial, a phase 3 trial that evaluated efficacy of the 12 weeks pangenotypic regimen glecaprevir/pibrentasvir which showed a SVR rate of 98%, again similar to what is achieved in those without CKD.⁹ Both of these combinations of DAAs are approved for treatment of hepatitis C in the CKD population. Two recent phase 2 trials have now demonstrated the safety and efficacy of sofosbuvir alone and in combination with other DAAs in the advanced kidney disease population.^{10,11} Both

Abbreviations:

HCV, hepatitis C virus; CKD, chronic kidney disease; DAA, direct acting antiviral; SVR, sustained virological response; PD, peritoneal dialysis

Corresponding author: Paul Kwo

Department of Gastroenterology and Hepatology, Stanford University, 430 Broadway, Pavilion C, 3rd Floor, Redwood City, CA 94063, USA
Tel: +1-650-498-6080, Fax: +1-650-498-5692
E-mail: pkwo@stanford.edu
<https://orcid.org/0000-0002-8234-4485>

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studies demonstrated that sofosbuvir was well tolerated and had a favorable safety profile without significant change in creatinine clearance despite exposure to higher levels of the active sofosbuvir metabolite GS-331007. Sustained response rates were again not different than what is achieved in non-CKD populations, 95–100% in both studies. In November 2019, the U.S. Food and Drug Administration approved the usage of sofosbuvir based therapy in patients with CKD stage 4 and 5 and in those on dialysis.

While these studies provide important insights into the treatment of hepatitis C in CKD, they also either excluded or had limited enrollment (<10%) of CKD patients receiving peritoneal dialysis (PD). Thus, much of the data on pharmacokinetics, efficacy and safety profile is extrapolated from the hemodialysis population receiving DAA therapy. However, in the real world setting, PD is an increasingly popular mode of dialysis encompassing 11% of the total dialysis population worldwide.¹² The rates of PD are increasing in Asia and the United States where it is recognized as a more cost-effective option.¹² In this issue of *Clinical and Molecular Hepatology*, Yap et al.¹³ provide additional data regarding the safety and efficacy of DAA therapy in CKD patients which includes a cohort of PD patients with advanced liver disease.

This prospective study identified patients from Hong Kong and Taiwan with well compensated HCV-related cirrhosis and CKD stage 4 or 5 (estimated glomerular filtration rate <30 mL/min) who then received treatment with glecaprevir/pibrentasvir for 12 weeks. A total of 21 patients with cirrhosis were included in the study with 33% of patients on PD, 43% on hemodialysis and 24% of patients not on dialysis. During the study, one patient died of a PD related peritonitis complication 3 months after completion of glecaprevir/pibrentasvir and two subjects were lost to follow up. Of the remaining 18 patients, 100% achieved SVR at 12 weeks. Treatment was well tolerated and renal function remained stable in treated patients who were followed for up to 24 weeks after therapy including those not on dialysis. One patient stopped therapy after 4 weeks due to personal preference, SVR was still achieved.

This study demonstrates that dialysis patients including those on PD with cirrhosis can be successfully treated, though the number of patients included in this study is still low and additional data is needed to understand the unique risks of treating patients who have underlying cirrhosis with PD. In any patient with compensated cirrhosis, there is a risk of subsequent hepatic decompensation, and in the population studied by Yap and colleagues¹³ who also had advanced renal disease careful follow up is required when treating with DAA therapy. Differentiating between the de-

velopment of ascites, which would indicate decompensation, and the dialysate used for PD may not be straightforward. The authors of this study did address these concerns by monitoring for liver decompensation the number of exchanges, net ultrafiltration and residual urine volume before and after antiviral treatment and documented these parameters in the PD patients. Moreover, these results highlight the need for these patients to be treated by specialists trained to recognize these potential decompensation events. It is important to note that in this small study there was a death of a PD patient due to fungal peritonitis, though this occurred 3 months after successful HCV treatment. This was attributed to a PD-related complication and highlights that those with cirrhosis and CKD represent a patient population that is at risk for infection and other complications. Fortunately, despite the significant comorbidities in this population, the combination of glecaprevir/pibrentasvir was both effective and generally well tolerated.

Efficacious, well tolerated pan-genotypic DAA therapy is now available to patients with advanced renal disease and HCV, including those who require hemodialysis and PD. Longer term follow up is needed to determine if successful treatment in this population may prevent development of further co-morbidities and prolonged life, as has been demonstrated in other populations achieving SVR.^{14,15} Currently, data in those with advanced liver disease on PD remains extremely limited. The study by Yap and colleagues¹³ does show that treatment can be successful in this particular population and a follow up report regarding longer term outcomes in this population will be valuable as well as future studies with larger PD populations. Given that PD is a modality that has gained significant traction in both Asia and in the USA over the years with comparable outcomes to hemodialysis, it is imperative to better understand the efficacy of DAAs and treatment risk in this population.

Authors' contribution

Deepti Dronamraju and Paul Kwo drafted the editorial, both provided critical revisions and approved of the final content.

Conflicts of Interest

Dr. Kwo reports grants and personal fees from Abbvie, grants from HCV Target Registries, grants and personal fees from Gilead, grants from BMS, personal fees from Syneos Health, outside the submitted work.

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