Grazoprevir plus elbasvir and other treatment options in hepatitis C infected patients with stage 4–5 chronic kidney disease

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The prevalence of Hepatitis C (HCV) in patients with advanced renal disease and dialysis is higher than that of general population with rates around 5–10% in Europe and USA (1,2). The prevalence of HCV also correlates with the duration or number of years on hemodialysis (3). Furthermore, HCV-infected patients receiving maintenance dialysis have an increased mortality when compared to the uninfected population (4). HCV is not only associated with the development and progression of chronic kidney disease in non-dialysis patients but also with progressive liver disease in dialysis patients (5). For decades, treatment of the HCV-infected end stage renal disease (ESRD) patient was limited by the low efficacy and poor tolerability of interferon and ribavirin (6). The availability of direct-acting antiviral (DAA) agents to treat chronic HCV infection has dramatically changed the way patients with this disease is managed and offers the opportunity for cure in most cases. Several pivotal phase III clinical trials conducted in the general population have demonstrated sustained viral response rates (SVR12; undetectable viral load 12 weeks after completing therapy) exceeding 90% for most HCV genotypes (7). Until recently, all of these trials excluded patients with CKD stage 4–5 from enrollment, mostly due to a lack of reliable pharmacokinetic and safety data in patients with reduced kidney function. This is reflected in the HCV Guidelines which had formerly endorsed the use of initially available DAA regimens only in patients with GFR >30 mL/min and clearly precluded the hemodialysis patients from therapy. Among the direct acting antivirals (DAAs) that are currently approved, Sofosbuvir (nucleotide NS5B analogue) is the only drug that is contraindicated in patients with GFR <30 mL/min. DAA regimens that require ribavirin have posed a particular concern due to poor tolerance of ribavirin in patients with advanced renal disease. Despite these limitations, a number of groups had reported smaller case series of successful treatment with interferon or DAAs with or without ribavirin (8-10). Fortunately, this situation has evolved in a more favorable way as studies like C-SURFER and RUBY demonstrated safety and efficacy of newer DAAs in the CKD stage 4–5 and dialysis setting (11,12).

The C-SURFER (Hepatitis C: Study to Understand Renal Failures' Effect and Responses) study is the first randomized trial in the advanced renal disease cohort that evaluated Grazoprevir and Elbasvir for HCV treatment (12). Although DAAs were available to treat HCV in patients with normal kidney function, the only HCV agents approved in patients with GFR <30 mL/min at the time of the study enrollment were pegylated interferon and ribavirin. Patients with advanced renal disease (CKD stage 4–5) therefore had limited HCV treatment options. This is the largest trial published to date that included all-oral HCV treatment which is free of interferon and ribavirin. In this multicenter trial, 224 patients were randomly assigned to two groups, immediate treatment group (n=111) or the deferred treatment group (n=113). The study population comprised of 46% Whites, 46% African Americans, 80% diabetics, 76% hemodialysis patients and 6% overall with cirrhosis (Metavir F4 fibrosis). This is a HCV genotype 1 study that included almost equal proportion of subtypes 1a and 1b and 80% of them were treatment naïve. Each group received Grazoprevir, NS3/4 protease inhibitor of 100 mg/Elbasvir, NS5A inhibitor (fixed dose combination pill) or placebo once daily for 12 weeks based on their randomization. At

week 16, the deferred treatment arm initiated the study drug for another 12 weeks. HCV resistance testing was performed with population-based sequencing at baseline in almost half of the patients, which detected NS3/4A RAVs in 32% and NS5A RAVs in 15%. No additional interventions were administered in those who harbored the RAVs.

The primary efficacy outcome of SVR12 was achieved in 94% on full analysis set and in 99% the modified full analysis set. Six patients discontinued the study for non-virologic failure reasons and 1 non-cirrhotic patient with HCV genotype 1b with baseline L31M NS5A RAV had a true relapse. Interestingly, 1 patient in the deferred treatment group had spontaneous HCV clearance while receiving the placebo. The SVR12 was 100% among African Americans and in cirrhotics. None of the patients experienced on-treatment virologic breakthrough.

HCV therapy is associated with several extrahepatic symptoms but HCV itself and the patients' comorbid conditions might accentuate these symptoms (13). The study was therefore uniquely designed with a deferred treatment group that would serve as a comparator to analyze the safety data and to determine whether the symptoms were related or unrelated to HCV therapy. The frequency of adverse events (AEs) was comparable in both immediate and deferred treatment groups, typically mild and moderate in intensity. Most frequent AEs were headache, nausea and fatigue. Serious AEs also occurred at comparable frequencies in both groups which were deemed unrelated to the study drugs, and did not lead to drug discontinuation in the immediate treatment group. There was no significant renal or hepatic impairment noted in either group.

The limitations of the study include small sample size in the sub groups, specifically cirrhosis (only 6%) and prior HCV treatment experience (20%). The authors also admit that excluding patients on peritoneal dialysis and decompensated cirrhosis were their study limitations. Exclusion of HCV genotype 4 in this study could also be considered as a limitation as Grazoprevir and Elbasvir have good coverage against the genotype. The prevalence of HCV genotype 1a in USA is higher than that of genotype 1b and the prevalence of baseline NS5A RAVs is around 10-15% (7). HCV genotype 1b appears to be over-represented in this study which may have led to under-estimation of the effect of baseline NS5A RAVs on SVR12. The study regimen does not include NS5B nucleotide analogue which typically has high genetic barrier for resistance. Prior studies in the non-renal setting have shown that Grazoprevir and Elbasvir therapy for 12 weeks in HCV genotype 1a patients with baseline NS5A RAVs has significantly lower SVR12 rate than those without NS5A RAVs (14). The regimen can however be optimized to improve the SVR12 rates by adding ribavirin and prolonging the duration of therapy to 16 weeks (7). Such a strategy would seem appropriate in real world practice but it should be noted that a diminished response was not observed in genotype 1a NS5A RAVs in the study.

The safety and efficacy of Sofosbuvir in patients with a creatinine clearance <30 mL/min has not been established. Nevertheless, few small open-label treatment studies (one of them by our group) using Simeprevir and full dose or dose-adjusted Sofosbuvir in patients with advanced CKD and ESRD did not demonstrate significant AEs while achieving high rates of SVR12 (8-10,15). However, until further studies with larger numbers of patients are available, Sofosbuvir based regimens are not recommended for HCV treatment in the CKD stage 4–5 setting. Paritaprevir/ritonavir/ombitasvir/dasabuvir (PrOD) was used in RUBY-1 trial to treat 20 HCV genotype 1 patients with favorable baseline patient characteristics (treatment naïve, non-cirrhotics) for 12 weeks (11). Ribavirin 200 mg daily was added to the PrOD regimen for patients with genotype 1a and an SVR12 rate of 90% was reported in the study. The PrOD regimen does not require dose adjustment but the need for Ribavirin in genotype 1a dialysis patients, especially those with baseline anemia may pose a challenge using this regimen.

Despite several advantages, a practical disadvantage of HCV eradication in a kidney transplant (KT) candidate is the prolonged time on the KT wait-list. A recent strategy adopted by most US transplant centers in order to reduce wait-listed time of HCV positive KT candidates is to offer them allografts from HCV positive donors (16). Such a strategy would not only increase the utilization of organs from expanded criteria donors but also improve death-censored graft survival. Therefore, it may be reasonable to defer HCV treatment until after KT. Experience in KT recipients confirms the efficacy and tolerability of Sofosbuvir based regimens in this setting as well. Two separate case series recently reported an SVR of 100% in KT recipients who were treated with Sofosbuvir based regimen for 12 or 24 weeks (17,18). Sofosbuvir dose reduction wasn't required after KT and the DAAs were well tolerated with minimal side effects.

Patients on maintenance hemodialysis with HCV continue to have higher mortality rates compared to those without HCV (3). Fortunately, the advent of well tolerated

oral regimens for HCV has expanded the treatment strategies in patients with severe CKD and hemodialysis. As HCV therapies continue to evolve, the management strategies for this difficult-to-treat cohort also continue to evolve which are geared towards individual patient outcomes. Clearly, with the availability of various HCV treatment options in both pre- and post-KT settings, the outcomes are expected to improve dramatically in this complicated cohort with the question now being, not how but when!

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Footnote

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Comment on: 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;386:1537-45.

References

1. Baid-Agrawal S, Pascual M, Moradpour D, et al. Hepatitis C virus infection in haemodialysis and kidney transplant patients. Rev Med Virol 2008;18:97-115.
2. Marinaki S, Boletis JN, Sakellariou S, et al. Hepatitis C in hemodialysis patients. World J Hepatol 2015;7:548-58.
3. Fabrizi F, Dixit V, Messa P. Impact of hepatitis C on survival in dialysis patients: a link with cardiovascular mortality? J Viral Hepat 2012;19:601-7.
4. Carbone M, Mutimer D, Neuberger J. Hepatitis C virus and nonliver solid organ transplantation. Transplantation 2013;95:779-86.
5. 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;61:1495-502.
6. McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009;361:580-93.
7. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. 2016. Available online: http://www.hcvguidelines.org
8. Bhamidimarri KR, Czul F, Peyton A, et al. Safety, efficacy and tolerability of half-dose sofosbuvir plus simeprevir in treatment of Hepatitis C in patients with end stage renal disease. J Hepatol 2015;63:763-5.
9. Nazario HE, Ndungu M, Modi AA. Sofosbuvir and simeprevir in hepatitis C genotype 1-patients with end-stage renal disease on haemodialysis or GFR <30 ml/min. Liver Int 2016;36:798-801.
10. Saxena V, Koraishy FM, Sise ME, et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. Liver Int 2016;36:807-16.
11. Pockros PJ, Reddy KR, Mantry PS, et al. Efficacy of Direct-Acting Antiviral Combination for Patients With Hepatitis C Virus Genotype 1 Infection and Severe Renal Impairment or End-Stage Renal Disease. Gastroenterology 2016;150:1590-8.
12. 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;386:1537-45.
13. Younossi Z, Park H, Henry L, et al. Extrahepatic Manifestations of Hepatitis C: A Meta-analysis of Prevalence, Quality of Life, and Economic Burden. Gastroenterology 2016;150:1599-608.
14. Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-Elbasvir Combination Therapy for Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C Virus Genotype 1, 4, or 6 Infection: A Randomized Trial. Ann Intern Med 2015;163:1-13.
15. Bhamidimarri KR, Martin P. Finally, safe and effective treatment options for hepatitis C in hemodialysis patients. J Hepatol 2016;65:7-10.
16. Scalea JR, Barth RN, Munivenkatappa R, et al. Shorter waitlist times and improved graft survivals are observed in patients who accept hepatitis C virus+ renal allografts. Transplantation 2015;99:1192-6.
17. Kamar N, Marion O, Rostaing L, et al. Efficacy and Safety of Sofosbuvir-Based Antiviral Therapy to Treat Hepatitis

C Virus Infection After Kidney Transplantation. Am J Transplant 2016;16:1474-9.
18. Sawinski D, Kaur N, Ajeti A, et al. Successful Treatment of Hepatitis C in Renal Transplant Recipients With Direct-Acting Antiviral Agents. Am J Transplant 2016;16:1588-95.

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