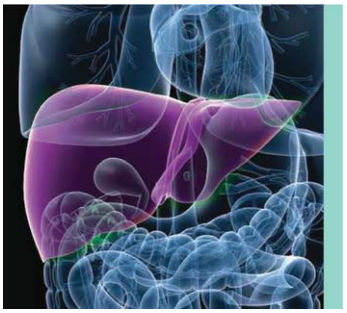

Treating Hepatitis C Viral Infection in Patients with Chronic Kidney Disease: When and How

Fernando E. Pedraza, M.D., Marco A. Ladino Avellaneda, M.D., and David Roth, M.D.

Hepatitis C virus (HCV) is recognized to be an incremental contributor to the morbidity and mortality of patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD).[1,2] Recent data suggest that HCV-infected patients with CKD have an accelerated rate of CKD progression to ESRD.[3-5] Furthermore, HCV has also been associated with adverse outcomes in kidney transplant recipients, including diminished graft survival to increased mortality.[6] Advances in the treatment of HCV infection have been accomplished in the last several years both for the general population and for those with CKD, although the data for the CKD population remain limited. This review will summarize the most relevant information regarding the use of direct-acting antivirals (DAAs) in patients with CKD.

HCV AND CKD

A higher prevalence of HCV infection in patients with ESRD compared with the general population has been well established.[7] In a meta-analysis by Fabrizi et al., HCV-infected patients with ESRD were demonstrated to have a higher risk for either liver- or cardiovascular disease–related mortality compared with the HCV-negative cohort.[1] In addition, HCV infection has been causally linked with mixed cryoglobulinemia[8] and several immune-complex forms of glomerular disease, including membranoproliferative[8] and membranous glomerulonephritis.[9]

DAA DRUGS AND CKD

The options available for the treatment of HCV infection have dramatically evolved in recent years. The introduction

Abbreviations: CKD, chronic kidney disease; CyA, cyclosporine; DAA, direct-acting antiviral; EBR/GZR, elbasvir/grazoprevir; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GFR, glomerular filtration rate; GI, gastrointestinal; HCV, hepatitis C virus; LDV, ledipasvir; OMV/PTV/r/DSV, ombitasvir/paritaprevir/ritonavir/dasabuvir; SMV, simeprevir; SOF, sofosbuvir; SRL, sirolimus; SVR, sustained viral response; SVR12, sustained viral response rates at 12 weeks; TAC, tacrolimus.

From the University of Miami Miller School of Medicine, Division of Nephrology and Hypertension and the Miami Veterans Administration Hospital, Miami, FL.

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of DAAs that target varying sites of the HCV genome has translated into sustained viral response (SVR) rates at 12 weeks (SVR12) that routinely exceed 95%. Differing groups of HCV-infected patients may now be cured including decompensated cirrhotics, patients with prior treatment failures, and patients infected with all genotypes. Additional cohorts with long-standing unmet medical needs, including those coinfected with HIV[10] and the CKD population, have also been examined.[11,12]

In this context, several studies have evaluated the use of DAAs in the HCV-infected patient with CKD/ESRD (Table 1). The HCV-TARGET, a longitudinal real-world observational study, reviewed the use of sofosbuvir-based regimens in HCV-infected patients with CKD (defined as an estimated glomerular filtration rate [eGFR] $\leq$ 45 mL/min).[13] The results demonstrated that patients receiving a regimen that included sofosbuvir had an SVR12 of approximately 80% to 85%, higher rates of anemia, worsening kidney function, and increased adverse events. The authors recommended that close monitoring of patients on sofosbuvir with renal dysfunction was advisable.[13] The RUBY-I trial reported results using ombitasvir, paritaprevir/ritonavir, and dasabuvir, and showed that this combination can be safely used in patients with advanced CKD (stages 4/5) with SVR rates of 90%, and 70% of patients were on dialysis.[14,15] The randomized, prospective, phase III C-SURFER trial demonstrated that treatment with grazoprevir and elbasvir resulted in SVR12s of 99% with minimal adverse events in a population of genotype 1–infected patients with advanced CKD, including a majority of patients receiving maintenance hemodialysis.[16]

TREATMENT OF HCV INFECTION IN PATIENTS WITH CKD, INCLUDING KIDNEY TRANSPLANT CANDIDATES AND RECIPIENTS

The Patient With Acute Glomerulonephritis With or Without Cryoglobulinemia. HCV has a tropism for B cells and is associated with both lymphoproliferative disorders and several histological forms of immune-complex glomerular disease and cryoblobulinemia.[18,19] In this setting, treatment for eradication of virus would be appropriate because clearance of the virus would be expected to be accompanied by decrease in the ongoing immune-complex injury to the kidney. The recently published article ''Sofosbuvir Plus Ribavirin for Hepatitis C Virus-Associated Cryoglobulinaemia Vasculitis: VASCUVALDIC Study''[20] reported that patients with a HCV vasculitis syndrome and cryoglobulinemia who received sofosbuvir (400 mg/day) and ribavirin (200-1400 mg/day) had a high rate of a complete clinical response, SVR12 of about 75%, and a low rate of adverse events. Some patients may present with a more aggressive vasculitic syndrome accompanied by cryoglobulinemia. In these cases, antiviral therapy should be preceded by interventions designed to reduce the inflammatory activity involving the endothelium, including corticosteroids, rituximab, and possibly therapeutic plasma exchange.[21-23]

The HCV-Infected Patient With Stage 1 to 3a CKD. HCV-infected patients with CKD and GFR greater than 45 mL/min should be considered for DAA therapy. From a strictly renal perspective, the major indication for treatment in this group would be slowing the progression of the CKD. HCV infection has been associated with an accelerated rate of CKD progression, as demonstrated in several recently published reports.[3,5] If this finding is confirmed in additional studies, this would represent a compelling indication for treatment.

The Patient With Advanced Stage 3 and 4/5 CKD. This group of patients must be viewed differently because they are clearly progressing into later stages of CKD and the issue of renal replacement therapy begins to enter into the decision tree. In this situation, the nephrologist and hepatologist must work closely and consider whether treatment before or after kidney transplant is advisable. For the patient with a living kidney donor it would be reasonable to treat for a cure before transplant. However, if the patient is going to be placed on the deceased donor waiting list, then other options might be available. For example, delaying antiviral treatment and transplanting with a kidney from an anti-HCV-positive donor is an option at some centers. Programs using this approach have reported dramatically shortened waiting times for a deceased donor kidney.[11,24,25] In this setting, treatment with DAA can be introduced early after transplantation. Sawinski et al.[26] recently reported the outcomes of 20 kidney recipients who received DAAs posttransplant; the DAA therapy achieved an SVR of 100% and was well tolerated without affecting allograft function. Kidney transplant candidates with compensated METAVIR stage 4 liver disease without portal hypertension require close

TABLE 1. DAA AGENTS: DOSE, CLEARANCE, AND USE IN CKD AND ESRD PATIENTS

Medication	Clearance	Use in CKD Stages IV and V	Use in ESRD
Sofosbuvir	Renal: 81% GI: 15%	eGFR 15-29 mL/min: not recommended eGFR < 15 mL/min: not recommended	Limited data available;higher rates of anemia, worsening renal dysfunction, and increased adverse events[13]
Simeprevir	Renal: <1%	eGFR 15-29 mL/min: dose adjustment not required eGFR < 15 mL/min: not recommended	Limited data available
Daclatasvir	Renal: 7% GI: 88%	eGFR 15-29 mL/min: dose adjustment not required eGFR < 15 mL/min: dose adjustment not required	Limited data available; patient on dialysis; no serious adverse events[14]
Ledipasvir	Renal: 1% GI: 86%	eGFR 15-29 mL/min: dose adjustment not required eGFR < 15 mL/min: not recommended	Limited data available
Ombitasvir/Paritaprevir/ Ritonavir	Renal: <2% GI: 90%	eGFR 15-29 mL/min: dose adjustment not required eGFR < 15 mL/min: dose adjustment not required	Dialysis patients studied;safely used in patients with advanced CKD[15]
Dasabuvir			
Grazoprevir/Elbasvir	Renal: <1%	eGFR 15-29 mL/min: dose adjustment not required eGFR < 15 mL/min: dose adjustment not required	Dialysis population studied;minimal adverse events in patients with advanced CKD and ESRD on hemodialysis[16]
Sofosbuvir/Velpatasvir	Renal: 81% GI/Renal: 15%/0.4% GI: 94%	eGFR 15-29 mL/min: not recommended eGFR < 15 mL/min: not recommended	Limited data available; no dosage recommendation for patients with severe renal impairment[17]

Abbreviation: GI, gastrointestinal.

collaboration between the hepatologist and transplant team to determine whether the patient is a candidate for a kidney-alone transplant and/or should receive DAA therapy pretransplant or posttransplant in the context of receiving a kidney from an anti-HCV-positive donor.

The Patient With ESRD Who Is on Dialysis. It has been reported that 5% to 10% of the US dialysis population is infected with HCV, many of whom still remain undiagnosed.[27] It is well established that the anti-HCV-positive patient with ESRD has increased mortality when compared with the negative cohort.[1] No prospective data, however, have demonstrated that clearance of the virus from these patients translates into improved outcomes. Because this is a population with multiple comorbidities, it would be difficult to demonstrate a change in hard outcomes, such as mortality. The decision to treat must be individualized, taking into account future transplant candidacy, magnitude of ongoing comorbidities, and expected survival.

The Kidney Transplant Recipient. There are large numbers of post-kidney-transplant patients with HCV infection that predates their transplantation. HCV has been clearly associated with an adverse impact on posttransplant patient and graft survival including immune-complex injury to the allograft and a higher incidence of posttransplant diabetes mellitus.[28] In contrast with the poorly tolerated interferons, the DAAs offer the opportunity of treatment for kidney recipients because early reports are demonstrating excellent safety and efficacy.[29] Importantly, there are several drug–drug interactions (Table 2) with some of the immunosuppressive agents commonly used, and early reports suggest that there may be changes in tacrolimus metabolism as the virus is cleared that would require doing adjustments to maintain therapeutic immunosuppression.[26,30] In this context, post-kidney-transplant patients being considered for DAA treatment should be under the care of a team familiar with these issues so that adequate immunosuppression is maintained.

In conclusion, the availability of DAA agents has dramatically altered the landscape of treatment for the HCV-infected patient with CKD/ESRD. A group of patients who had been largely left on the sidelines of antiviral therapy is now being studied more carefully, resulting in evolving strategies for treatment that take into account the unique needs of this patient population.

TABLE 2. INTERACTIONS OF DAAS WITH IMMUNOSUPPRESSIVE AGENTS

Medication	SOF/LDV	SOF	SMV	OMV/PTV/r/DSV	EBR/GZR
TAC	No changes in TAC levels	No changes in TAC levels	Decrease TAC levels Needs close monitoring of TAC levels	Increase TAC levels (ritonavir)	Increase TAC levels
CyA	No changes in CyA levels	No changes in CyA levels	Increase levels of both CyA and SMV	Increase CyA levels (ritonavir)	Increased levels of GZR, contraindicated to use together
SRL	No changes in SRL levels	No changes in SRL levels	Increase or decrease levels of SRL	Increase SRL levels (ritonavir)	Increase SRL levels

Abbreviations: CyA, cyclosporine; EBR/GZR, elbasvir/grazoprevir; LDV, ledipasvir; OMV/PTV/r/DSV, ombitasvir/paritaprevir/ritonavir/dasabuvir; SMV, simeprevir; SOF, sofosbuvir; SRL, sirolimus; TAC, tacrolimus.

CORRESPONDENCE

David Roth, M.D., 1120 NW 14th Street, Room 813, Miami, FL 33136. E-mail: d.roth@miami.edu

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