Hepatitis C Virus Treatment in Patients With Chronic Kidney Disease and in Kidney Transplant Recipients

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Abstract: An important interplay exists between hepatitis C virus (HCV) infection and chronic kidney disease (CKD). HCV infection is associated with an increased risk of morbidity and mortality in patients coinfected with CKD, and patients with CKD have an increased risk of HCV infection. Direct-acting antiviral (DAA) agents have changed the landscape of treatment with excellent sustained virologic response rates and fewer side effects than previously seen. An increasing number of studies demonstrate that DAA agents are efficacious and safe both in patients on dialysis and in patients who have undergone kidney transplantation. This article reviews the current literature on approved DAA agents for the treatment of HCV infection in patients on dialysis and in kidney transplant recipients.

Hepatitis C virus (HCV) infection is an important cause of morbidity and mortality in the United States. An estimated 2.7 to 3.5 million people in the United States have HCV infection, and its prevalence is rising; the reported cases of acute HCV infection increased more than 2.9-fold from 2010 to 2015.[1] Chronic HCV infection is also one of the leading indications for liver transplantation in the United States.[2] There are 6 major HCV genotypes, with HCV genotype 1 being the most prevalent worldwide.[3]

A unique relationship exists between HCV infection and chronic kidney disease (CKD), in that the natural history of either disease entity can lead to the other. For example, HCV infection can cause CKD through several mechanisms, including cryoglobulinemic vasculitis with renal involvement and immune complex–mediated glomerulonephritis (eg, membranous nephropathy).[4] HCV infection can also lead to CKD via extrahepatic manifestations of cirrhosis such as hepatorenal disease. Recently, it has been demonstrated that the higher the viral load of HCV, the higher the risk of developing end-stage renal disease. Compared to patients who are not chronically infected with HCV, patients with a HCV viral load greater than 167,000 IU/mL are 3 times as likely to develop end-stage renal

disease, whereas patients with lower viral loads (≤167,000 IU/mL) are twice as likely.[5] On the other end of the spectrum, HCV infection can be seen as a consequence of CKD treatment. Dialysis is a significant risk factor for HCV infection. Prior to universal precautions, this risk was likely related to inadequate sterilization techniques and a lack of screening of blood transfusion products.[6] A study conducted between 1990 and 1991 assessed the incidence and prevalence of antibodies to HCV in 499 patients on dialysis.[7] Antibodies to HCV were detected in 10% of patients on dialysis, and the cumulative incidence of HCV infection over an 18-month period was 4.6%.[7] The study also demonstrated that an antibody-to-HCV–positive serology was associated with the length of time on dialysis (≥3 years). Furthermore, CKD can impact the natural history of HCV infection. In a cohort of more than 4000 patients with HCV infection between 2006 and 2016, patients coinfected with CKD had a significantly higher rate of liver fibrosis progression based on the Fibrosis-4 Index than patients without CKD (43% vs 26%, respectively).[8]

Chronic HCV infection is a significant risk factor for poor outcomes in patients with CKD. An analysis of a cohort of more than 70,000 patients on dialysis between 1996 and 2015 demonstrated that HCV-positive patients had an increased risk of death and hospitalization, and worse quality-of-life scores.[9] HCV infection has also been associated with CKD stage progression. In a cohort of more than 1000 patients with CKD between 2006 and 2016, patients with HCV infection had a significantly lower mean time to CKD progression than patients without HCV infection (506 vs 676 days, respectively).[8]

HCV treatment has changed the landscape of the management of HCV infection in transplant patients. It has been shown that HCV infection is an independent predictor of graft loss and is associated with de novo immune-mediated glomerulonephritis in the graft kidney.[10] The efficacy and safety of direct-acting antiviral (DAA) agents have been studied, with promising results in which sustained virologic response (SVR) rates are comparable to the SVR rates of nontransplant patients, allowing an entire population access to HCV treatment. This article reviews the current literature on different treatment options for HCV infection and their efficacy in patients on dialysis, as well as the clinical complexities in treating patients undergoing kidney transplantation.

Past Treatment of Hepatitis C Virus Infection in Patients With Chronic Kidney Disease and in Kidney Transplant Recipients

Prior to DAA agents, initial regimens consisted of interferon and ribavirin.[11] However, both of these therapies rely on renal clearance for elimination and require dose reductions in patients undergoing dialysis. In particular, ribavirin is a nucleoside analog that can accumulate in red blood cells and lead to hemolytic anemia. This toxicity increases significantly when the creatinine clearance is more than 50 mL/min.[12] Due to these barriers, the treatment of HCV infection among patients on dialysis has been historically low. For example, 49,762 patients were enrolled in the observational Dialysis Outcomes and Practice Patterns Study[13] across 12 countries. In a subsequent study that examined this large dialysis population, it was reported that 4735 patients (9.5%) were HCV-positive. However, despite increased morbidity and mortality of HCV infection in this patient population, only 48 patients (1%) with HCV infection were receiving antiviral medication.[14]

Among patients on dialysis who are treated with interferon and/or ribavirin, the SVR rate is substantially lower than what is described with DAA agents. In a 2008 meta-analysis, treatment with interferon in patients on dialysis resulted in a SVR rate of 41%.[15] A significant treatment discontinuation occurred due to poor tolerability among patients on dialysis (interferon, 26%; pegylated interferon, 28%). Reported adverse events included influenza-like illness, anemia, depression, symptomatic rejection of a nonfunctioning kidney allograft, leukopenia, confusion, diarrhea, thrombocytopenia, and seizures. The overall rate of adverse events was 50%.[15]

Interferon therapy has also shown unfavorable outcomes in kidney transplant recipients. In a study conducted by Gane and Pilmore, interferon treatment was characterized by a clearance in only 25% to 50% of patients, relapse after treatment withdrawal, and an increased rate of allograft rejection.[16] According to the 2008 Kidney Disease: Improving Global Outcomes guidelines, kidney transplantation is not recommended in patients who are being treated with interferon due to the immunomodulatory properties of the drug that increase the rates of both cell- and antibody-mediated rejection.[17]

Direct-Acting Antiviral Therapies in Patients With Chronic Kidney Disease

With the advent of DAA therapies, SVR rates have made substantial progress over the past 2 decades. Designed to block critical steps in the HCV replication cycle, DAA agents now have a SVR rate of more than 95%.[18] There are currently 3 major classes of DAA therapies: nonstructural (NS) 3/4 protease inhibitors (-previr), NS5A complex inhibitors (-asvir), and NS5B polymerase inhibitors (-buvir).[19] Among the DAA agents currently approved by the US Food and Drug Administration, sofosbuvir (Sovaldi, Gilead) is the only drug that is

contraindicated in patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min or in patients with CKD on dialysis due to an accumulation of the medication's metabolite. Sofosbuvir is metabolized by the liver into the pharmacologically active metabolite GS-461203, which is then dephosphorylated into the inactive metabolite GS-331007 that is primarily excreted by the kidney.[20] Administration of sofosbuvir to patients with renal impairment is associated with more frequent anemia-related adverse events, transfusion requirements, and worsened renal function.[21] However, for patients with CKD stage 4 or 5 and for patients on dialysis, only 2 regimens have been approved in the most recent guidelines[22] published by the American Association for the Study of Liver Diseases: the combinations elbasvir/grazoprevir (Zepatier, Merck) and glecaprevir/pibrentasvir (Mavyret, AbbVie; Figure 1).

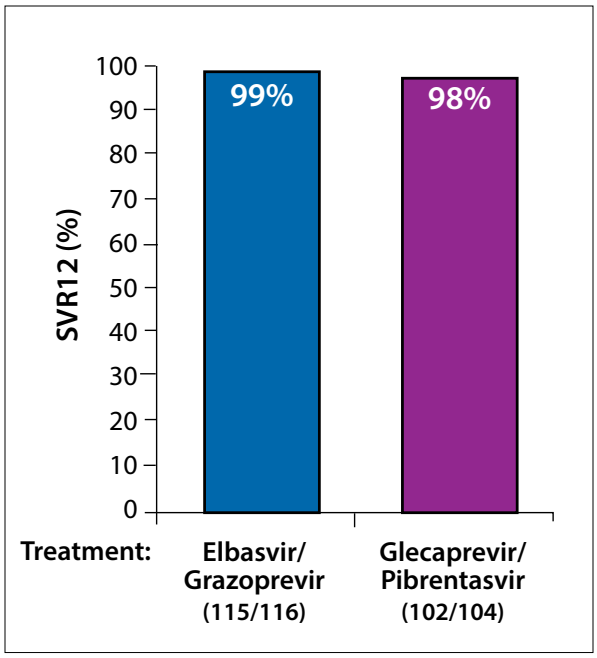

Figure 1. The sustained virologic response rates of direct-acting antiviral regimens in patients with chronic kidney disease (stage 4 or 5).[23,25] The ratios represent the cured patients of the total number of patients with combined stage 4 or 5 chronic kidney disease for each regimen.

SVR12, sustained virologic response at 12 weeks.

Elbasvir and Grazoprevir

The combination elbasvir (a NS5A inhibitor) and grazoprevir (a NS3/4 protease inhibitor) is currently 1 of the 2 recommended regimens for patients with CKD stage 4 or 5. The recommended dosage is a daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) and treats patients with HCV genotype 1a, 1b, and 4 infections.

A landmark study highlights the potential of this regimen in patients on dialysis. The C-SURFER (Hepatitis C: Study to Understand Renal Failure's Effect on Responses) study was a phase 3, randomized study involving 224 patients with CKD stage 4 or 5 with or without dialysis dependence and with HCV genotype 1 infection.[23] Seventy-six percent of patients were dialysis-dependent, 81% had CKD stage 5 at baseline, and 80% were naive to treatment. Patients were randomly assigned to receive elbasvir 50 mg and grazoprevir 100 mg (immediate treatment group) or placebo (deferred treatment group) once daily for 12 weeks. The deferred treatment group was used as an internal control for potential safety signals in the immediate treatment group and started active treatment at week 16. The primary outcome was a SVR at 12 weeks, which was achieved by 94% of patients in the intention-to-treat analysis. In the modified full analysis (in which 6 patients were excluded due to reasons other than virologic failure), the SVR rate at 12 weeks was 99% (Figure 1). The most common adverse events were headache, nausea, and fatigue. Elevated lipase was the only drug-related adverse event reported. There was no consistent change in mean eGFR or creatinine.[23]

Another retrospective study further demonstrated that the combination elbasvir/grazoprevir does not worsen kidney function in patients with preexisting renal disease and HCV infection.[24] Patients with CKD stage 3 at baseline who were enrolled in elbasvir/grazoprevir phase 2/3 clinical trials with chronic HCV infection with or without ribavirin were included in the study (N=32). Thirty-one patients (97%) achieved SVR at 12 weeks. There was no decline in median eGFR at the end of treatment or at 12 weeks follow-up. In fact, many patients had an improvement in their CKD stage. All 32 patients had a glomerular filtration rate (GFR) of less than 60 mL/min at baseline; however, at the end of treatment, 12 patients had a GFR of at least 60 mL/min. Of note, this improvement was consistent regardless of the presence of cirrhosis, treatment with ribavirin, or HIV coinfection.

Glecaprevir and Pibrentasvir

The combination glecaprevir (a NS3/4 protease inhibitor) and pibrentasvir (a NS5A inhibitor) has activity against all 6 major HCV genotypes with a recommended fixed daily dose of 300 mg and 120 mg, respectively. In the EXPEDITION-4 (Efficacy and Safety of ABT-493/ABT-530 in Renally Impaired Adults With Chronic Hepatitis C Virus Genotype 1-6 Infection) phase 3 trial, Gane and colleagues assessed the efficacy and safety of the combination regimen in patients with severe renal impairment (stage 4 or 5).[25] One hundred and four patients who had

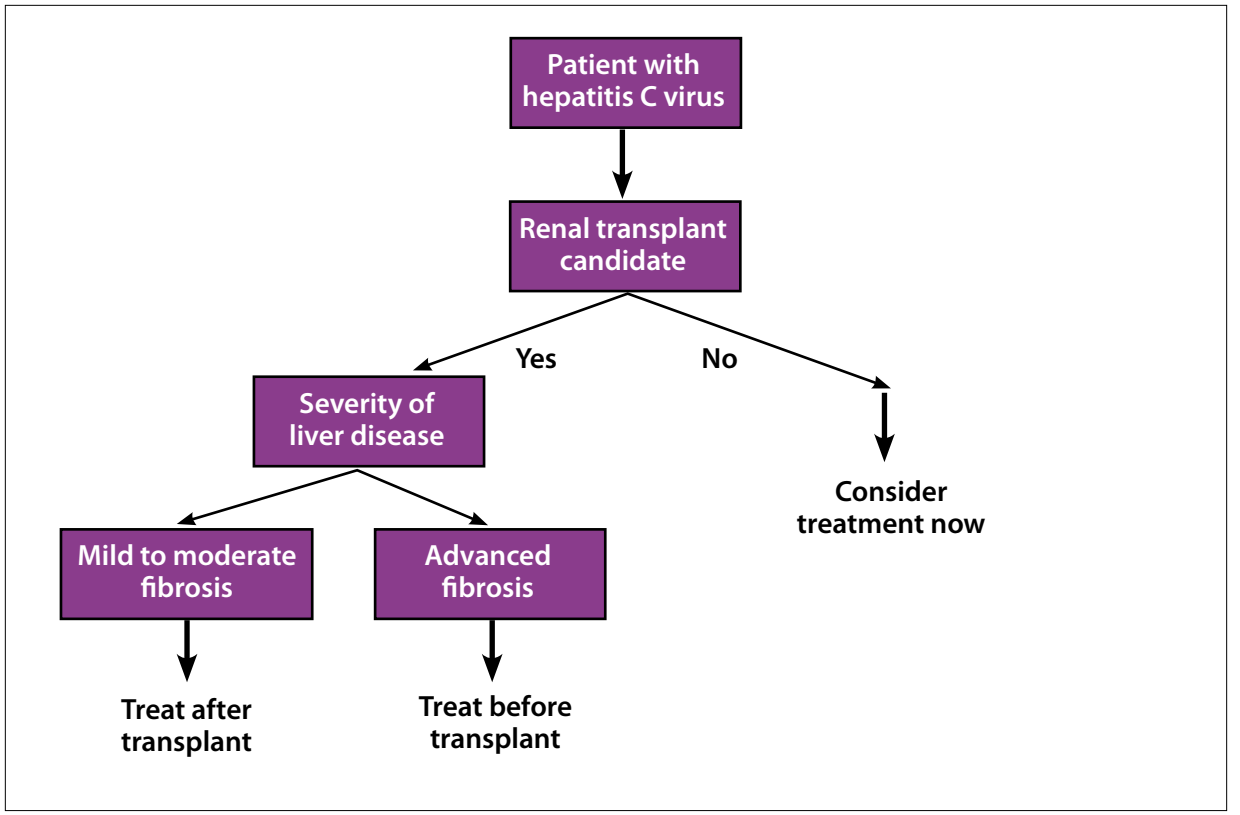

Figure 2. The timing of direct-acting antiviral therapy in patients on dialysis.

chronic HCV genotypes 1 through 6 infections were enrolled and received the combination antiviral therapy for 12 weeks. Fifty-eight percent of patients had no prior treatment history, 81% had compensated cirrhosis, and 82% were on dialysis. The SVR rate at 12 weeks was 98% (102/104; Figure 1). The most common adverse events were pruritus, fatigue, and nausea, and the rates of adverse events between patients on dialysis vs patients not undergoing dialysis were similar (72% vs 68%, respectively). Four patients discontinued treatment due to adverse events; none of the serious adverse events were considered to be drug-related. Of note, 3 of the 4 patients who discontinued the treatment achieved SVR at 12 weeks. Pre- and postdialysis drug levels were similar for both drugs, with only a 3% to 6% difference.

Direct-Acting Antiviral Therapies in Kidney Transplant Recipients

Although treatment of HCV infection in patients on dialysis has been shown to be efficacious, many clinicians also face the questions of when and if to treat patients who have undergone kidney transplantation. The decision to treat before or after transplantation involves evaluating the extent of liver damage as well as the need for expedited transplantation (Figure 2). Data suggest that DAA agents are safe and effective in patients following kidney transplantation without increasing the risk of allograft rejection. This is most highlighted by the safety of using HCV-positive organs in HCV-negative recipients. Goldberg and colleagues performed the THINKER (Transplanting Hepatitis C Kidneys Into Negative Kidney Recipients) trial, an open-label, single-group, pilot trial conducted at the University of Pennsylvania, in which 10 HCV genotype 1–infected donor kidneys were given to HCV-negative patients.[26] On day 3 post-transplantation, all recipients had detectable HCV RNA viral loads. The patients were given elbasvir/grazoprevir, and every recipient was cured of HCV infection with SVR at 12 weeks following the end of treatment. This paradigm shift in the utility of HCV-positive donors is especially relevant because of the increased number of HCV-positive donors owing to the opioid epidemic. For example, due to the surge in intravenous drug use, the median age of HCV-positive donors dropped from 47 years to 35 years between 2012 and 2016.[27] By using HCV-infected organs, wait times can be shortened and more patients can have access to kidney transplants. A study comparing the wait times between patients who are HCV-positive and received HCV-negative kidneys vs

Table. Drug Interactions Between Immunosuppressants and Direct-Acting Antiviral Regimens

Regimens	Common Immunosuppressant Medications				
	Prednisone	Tacrolimus	Mycophenolate Mofetil	Cyclosporine	Sirolimus
Ledipasvir/sofosbuvir	–	–	–	–	–
Glecaprevir/pibrentasvir	–	–	–	+[a]	–
Sofosbuvir/daclatasvir plus ribavirin	–	–	–	–	–

[a]Cyclosporine dosages of 100 mg or more increase the concentration of glecaprevir/pibrentasvir and may increase side effects.[35]

patients who received HCV-positive kidneys found that patients who received HCV-positive kidneys waited, on average, 310 days less.[28]

Evidence has shown that treating kidney transplant patients after their procedure can improve graft survival. When urine protein-to-creatinine ratios are compared in kidney transplant patients before and after treatment, there is a significant decrease in proteinuria after treatment, suggesting improved graft function.[29] In addition, patients with HCV infection with kidney transplants have a higher risk of death (hazard ratio, 1.5) and graft failure (hazard ratio, 1.26). They also have an increased risk of death from infection and liver failure and an increased risk of graft failure from recurrent disease.[30] Of note, the drug interaction profile between common immunosuppressants and DAA agents is very tolerable; however, as with all treatment regimens, patients should be monitored closely (Table). The approved regimens are ledipasvir/sofosbuvir (Harvoni, Gilead), glecaprevir/pibrentasvir, and sofosbuvir/daclatasvir plus a low initial dose of ribavirin, according to the 2017 guidelines from the American Association for the Study of Liver Diseases.[31]

Ledipasvir and Sofosbuvir

The combination ledipasvir (90 mg) and sofosbuvir (400 mg) is approved for the treatment of HCV genotype 1 or 4 infection in kidney transplant patients. Colombo and colleagues performed a phase 2, open-label study in which 114 patients were given this regimen; 91% of patients had genotype 1 infection, 69% were treatment-naive, 15% had compensated cirrhosis, and the median GFR was 56 mL/min.[32] Overall, 100% of patients achieved SVR at 12 weeks. Of note, only 4 patients had a decrease in GFR to less than 30 mL/min during therapy. In 3 of these patients, the GFR increased to more than 30 mL/min at the last visit recorded.[32]

Glecaprevir and Pibrentasvir

The combination glecaprevir (300 mg) and pibrentasvir (120 mg) is approved for the treatment of HCV genotypes 1 through 6 infections in kidney transplant patients. Reau and colleagues performed a phase 3, open-label, multicenter study in which patients without cirrhosis were treated for at least 3 months after either liver (80%) or kidney (20%) transplant.[33] The median GFR was 62.3 mL/min. In total, 100 patients were enrolled and treated with glecaprevir/pibrentasvir for 12 weeks. Of the available data, 89 of 90 patients achieved SVR at 12 weeks; 1 patient experienced virologic failure. Another patient had mild liver transplant rejection but continued with treatment and achieved SVR at 12 weeks.[33]

Sofosbuvir and Daclatasvir Plus Ribavirin

The combination sofosbuvir (400 mg) and daclatasvir (60 mg) plus a low initial dose of ribavirin (600 mg) has also been approved for kidney transplant patients. In the HCV-TARGET (Hepatitis C Therapeutic Registry and Research Network) study, 443 posttransplant recipients (60 kidney transplant patients, 347 liver transplant patients, and 36 dual liver-kidney transplant patients) were treated with several different regimens, including ledipasvir/sofosbuvir with or without ribavirin (85%), sofosbuvir/daclatasvir with or without ribavirin (9%), and ombitasvir/paritaprevir/ritonavir plus dasabuvir with or without ribavirin (Viekira Pak, AbbVie; 6%).[34] Overall, 42% of patients had cirrhosis, and 54% were treatment-experienced, including 28 patients (6%) with prior exposure to the first-generation protease inhibitors telaprevir and boceprevir. The SVR rates at 12 weeks were 96% for liver transplant recipients, 94% for kidney transplant recipients, and 90% for dual transplant recipients. There were 6 episodes of acute rejection. Of note, ribavirin did not affect SVR rates.

Summary

HCV infection in patients with CKD is an important risk factor for morbidity and mortality. Advancements have been made in the treatment of this high-risk patient population with the approval of DAA agents in the treatment of chronic HCV infection. Elbasvir/grazoprevir and glecaprevir/pibrentasvir are the 2 recommended drug

regimens for severe renal impairment and have SVR rates greater than 90%, which drastically change the opportunities for HCV eradication in this treatment population. For patients who are candidates for kidney transplantation, treatment after the procedure may be clinically reasonable; there are several regimens approved for such use. By increasing the number of patients treated for chronic HCV infection in both the dialysis and kidney transplant populations, a significant impact in global HCV eradication may be made.

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