Hepatitis C virus infection in nonliver solid organ transplant candidates and recipients

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Purpose of review
Transplantation is the best treatment for many patients with end-stage organ failure. Hepatitis C infection is prevalent among solid organ candidates and recipients and continues to represent a major source of morbidity and mortality. Prior interferon (IFN)-based therapies have been associated with limited efficacy and high rates of adverse events. Furthermore, prior IFN-based regimens are associated with high rates of allograft rejection limiting their use post-transplant. This review will outline the limited experience with current treatment regimens and how to incorporate the new hepatitis C virus (HCV) treatment regimens.

Recent findings
The introduction of new direct-acting antiviral (DAA) agents against HCV has dramatically altered the landscape of treatment for HCV. Different all-oral regimens are currently available and are rapidly becoming the standard for treating patients with chronic hepatitis C. Excluding patients with liver disease or those who received liver transplant, those regimens have not been studied in patients awaiting solid organ transplant, or those transplanted.

Summary
The safety and efficacy of DAAs in patients awaiting liver transplant and liver transplant recipients provide us with some insight and guidance on how to use those all-oral IFN-free regimens to allow effective treatment for patients who received or are awaiting nonliver solid organ transplants.

Keywords
direct-acting antiviral agents, end-stage kidney disease, hemodialysis, hepatitis C, solid organ transplant

INTRODUCTION

Hepatitis C virus (HCV) is the most common bloodborne infection with 170 million individuals chronically infected worldwide [1]. Approximately 3.4–4.9 million Americans are chronically infected with HCV and are at risk of developing cirrhosis, hepatocellular carcinoma (HCC) or both. Most patients are undiagnosed and may have been infected for more than 20 years. Prevalence of cirrhosis in patients with chronic hepatitis is directly related to the duration of the infection. Both decision modeling studies and US veterans national study estimated that 18–25% of HCV-infected patients will have cirrhosis at the time of diagnosis [2–4]. That estimate will most likely reach a peak of 45% in 2020, leading to progressive increase in the rates of hepatic decompensation and HCC in the next 2 decades [5,6]. As a result, HCV is the leading indication for liver transplantation in the United States.

Management of HCV infection in candidates and recipients of nonliver solid organ transplants continues to be a challenge. HCV infection in those patients is the source of significant morbidity and mortality. Prior interferon (IFN)-based therapies are not widely used because of limited efficacy and high rates of adverse events. IFN-free treatment regimens, with their greater efficacy and reduced toxicity, offer a promising and attractive treatment option in both candidates and recipients of nonliver solid organ transplants. Clinical trials and more experience are still required to evaluate their use in this patient population.

HEPATITIS C VIRUS IN PATIENTS WITH END-STAGE KIDNEY DISEASE

HCV is a major problem among patients on hemodialysis with an estimated prevalence at

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KEY POINTS

- HCV infection is common in solid organ allograft candidates and recipients and is a cause of significant morbidity and mortality.
- Prior IFN-based regimens should be avoided in those patients and should be replaced with a suitable all-oral regimens determined by genotype, stage of liver disease, and eGFR.
- Patients with HCV awaiting kidney transplant should be considered for HCV treatment (preferable within 1 year) after successful kidney transplant.
- HCV should not preclude patients from being candidates for heart or lung transplantation. Candidates can be treated, if feasible, prior to transplant or promptly after transplantation.

approximately 10–23% [7,8]. The natural history of HCV in patients with chronic kidney disease remains incompletely defined [9]. Several studies including a recent large meta-analysis of 14 observational studies found an independent and significant relationship between HCV infection and reduced patient survival in the dialysis population [10]. The adjusted relative risk for all-cause mortality in patients with HCV was 1.35 [11]. Furthermore, a recent prospective observational study of hemodialysis patients from western countries (DOPPS) showed similar results [11]. The relative risk of liver disease-related death was significantly high at 3.82 (95% confidence interval 1.92–7.61). Most of the liver-related mortality in this population was related to cirrhosis complications and HCC. Furthermore, HCV patients on hemodialysis had an additional increase in the cardiovascular-related mortality compared with matched group of patients who are HCV negative [12]. This observation was confirmed by several other studies supporting the additional role of HCV in the overall mortality of patients with end-stage kidney disease (ESKD) [13].

HCV treatment should be strongly considered in all patients with ESKD especially those who are potential candidates for kidney transplant, as those patients will be at risk of progressive liver disease post-transplantation, and IFN-based treatment regimens can be associated with high risk of acute graft rejection.

HEPATITIS C VIRUS TREATMENT IN PATIENTS WITH KIDNEY DISEASE

The goal of HCV therapy is to achieve a virological cure, often referred to as a sustained virological response (SVR) and defined as the continued absence of detectable HCV RNA for at least 12 weeks after completion of therapy. SVR of at least 12 weeks after the end of treatment has been shown to be indefinitely durable for more than 99% of patients [14,15]. Documentation of SVR requires a quantitative or qualitative nucleic acid test with a detection level of 25 IU/ml or lower.

The introduction of new direct-acting antiviral (DAA) agents against HCV has dramatically altered the landscape of treatment for HCV. Several regimens are currently available and are considered to be the first line of therapy in patients with HCV infection. Table 1 outlines the currently approved regimens, mode of metabolism, and the recommended use in patients with kidney disease.

PATIENTS WITH MILD–MODERATE RENAL IMPAIRMENT (ESTIMATED GLOMERULAR FILTRATION RATE HIGHER THAN 30 ML/MIN)

DAAs can be used safely in this patient population, and treatment should be considered for most patients with an effective all-oral regimen determined by the prior treatment status and stage of liver disease [16▪,17,18,19▪,20▪]. Those regimens are shown in Table 1.

PATIENTS WITH SEVERE RENAL IMPAIRMENT AND PATIENTS ON HEMODIALYSIS

Treatment of patients with estimated glomerular filtration rate (eGFR) lower than 30 ml/h and those on hemodialysis is a challenging dilemma. Most of the available data are based on small case series of patients treated with pegylated IFN-based regimens. Studies that address the safety of the new DAAs are still undergoing, and we expect few of those agents to be available for use in this population in the future.

Current published guidelines including those of the Kidney Disease Improving Global Outcomes recommend treating HCV in patients with ESKD based on the safety of the HCV regimen, comorbidities, and candidacy for kidney transplantation [9]. The timing of treating those patients is rapidly changing with the availability of the new effective all-oral treatment regimens.

Prior IFN-based regimens are no longer used to treat patients with HCV. Studies that looked at the efficacy of IFNα monotherapy in patients on hemodialysis reported SVR rates of approximately 40% [21]. Most of those studies were small case series, with high drop rate of 25% and long treatment duration of 12 months, thus precluding the use of

Table 1. Dose adjustments of hepatitis C virus treatment regimens in patients with renal impairment

	Mild–moderate renal impairment (eGFR 30–80 ml/min)	Severe renal impairment (eGFR < 30 ml/min)	ESKD/Hemodialysis
Sofosbuvir/ledipasvir	Standard dosing	Data not available	Data not available
		Avoid use	Avoid use
Paritaprevir/ritonavir/ombitasvir along with dasabuvir ± RBV	Standard dosing	Can be used with caution	Data not available
		RBV dose adjustment	Avoid use
Simeprevir/sofosbuvir ± RBV	Standard dosing	Data not available	Data not available
		Avoid use	Avoid use
Sofosbuvir ± RBV	Standard dosing	Data not available	Data not available
		Avoid use	Avoid use

eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; RBV, ribavirin.

this regimen in this era of shorter treatment duration.

Pegylated IFNα with or without ribavirin (RBV) has been used in patients with ESKD and those on hemodialysis. RBV use in patients with ESKD should be done with extreme caution and using much lower doses that is used in patients with normal kidney function (200 mg three times weekly to 200 mg daily). As RBV elimination is predominantly through the kidneys, it can accumulate in patients on hemodialysis and can lead to severe anemia and catastrophic adverse events [22]. Treatment with pegylated IFNα-2a combined with low-dose RBV (200 mg/day) for 6–12 months (based on genotype) was associated with SVR rates of 40–63%. Although this regimen is still being used for patients on hemodialysis and awaiting kidney transplant, it is frequently associated with high rates of serious adverse events (especially anemia), high dropout rates, and high rates of growth factor use [23,24▪▪].

Few case series addressed the efficacy of the first-generation protease inhibitors (telaprevir and boceprevir) combined with pegylated IFN and RBV in patients with ESKD. Treatment was associated with SVR rates of 50–60% but was associated with high rates of adverse events and anemia. Studies in clinical trial registries still show activity in these areas (NCT02112630). The use of those first wave agents has been abandoned in favor of the newer class of direct-acting agents that are more effective and less toxic [25▪,26,27▪].

Simeprevir is a second-generation protease inhibitor that is primarily metabolized through the liver with negligible renal elimination. Theoretically, a regimen of pegylated IFNα combined with simeprevir and RBV can be used in patients with

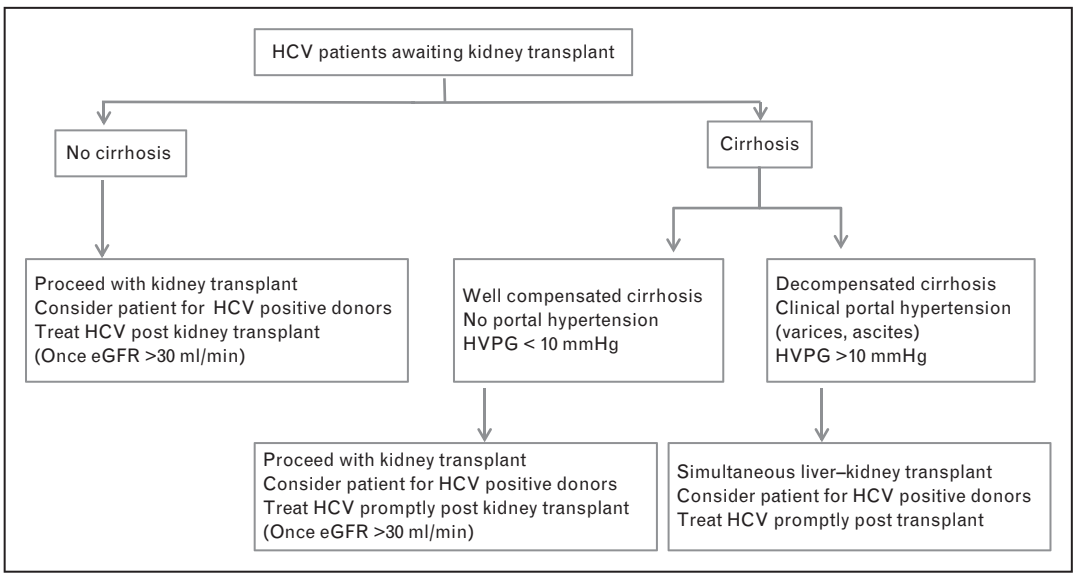

FIGURE 1. Treatment algorithm of hepatitis C virus infection in patients with end-stage kidney disease on hemodialysis. eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HVPG, hepatic venous pressure gradient.

ESKD but so far the safety and efficacy of such regimen has not been studied.

Sofosbuvir and the coformulation of ledipasvir/sofosbuvir have no safety data in patients with ESKD and their use should avoided until further studies (NCT02251717) are available that will give guidance regarding dosing adjustment in this patient population. Furthermore, the recently approved paritaprevir/ritonavir/ombitasvir along with dasabuvir and RBV is currently being studied in patients with renal impairment (NCT02207088). Grazoprevir and elbasvir (PI and NS5A inhibitor) are also being tested in this patient population (NCT02092350). Data from those studies will help to guide future treatment approaches.

A practical approach for now invokes that all patients with HCV and ESKD be evaluated for HCV therapy. Treatment decisions should be based on several variables including HCV genotype, comorbidities, candidacy for kidney transplantation, and the presence of cirrhosis or portal hypertension. Patients with early liver disease who are not candidates for kidney transplantation should be treated on a case-by-case basis, and preferably should wait for the availability of effective, all-oral regimens that can be used safely in the setting of ESKD. Figure 1 outlines the management algorithm for HCV patients awaiting kidney transplantation. In the absence of significant liver disease (cirrhosis with portal hypertension), those patients will likely be best served by proceeding with kidney transplantation, and then treated promptly post-transplantation with an all-oral regimen that will be determined by their genotype, and prior treatment status. In patients with decompensated cirrhosis and those with portal hypertension, we recommend that those patients be listed for simultaneous liver–kidney transplant and we treat HCV post-transplantation with an all-oral regimen. Patients with well compensated cirrhosis (no portal hypertension and hepatic venous pressure gradient less than 10 mmHg) can be either treated with an all-oral regimen once safety and efficacy data is available, or can proceed with kidney transplantation. Treatment with all oral-regimen can be pursued promptly post-kidney transplantation.

PATIENTS WHO HAVE RECEIVED RENAL TRANSPLANTATION

There is strong evidence that HCV-positive kidney transplant recipients have worse patient and graft survival after transplantation compared with HCV-negative kidney transplant recipients [10,12]. Cardiovascular disease, malignancy, and hepatic decompensation are the leading causes of death in this population [8]. Furthermore, those patients have higher rates of HCV-related morbidity, such as new-onset diabetes after transplant, post-transplant glomerulonephritis, and sepsis that can further negatively impact both graft and patient survival [28▪▪]. Therefore, those patients should be treated promptly after successful kidney transplant, and we currently recommend treating those patients once eGFR is higher than 30 ml/min and within 3–6 months after kidney transplant.

In general, IFN-based regimens are contraindicated in patients with HCV who have undergone kidney transplantation [9]. Although some authors reported successful use of IFN in few long-term kidney transplant recipients, several studies have confirmed that the use of IFN in this clinical setting can be associated with high rates of acute cellular rejection (40–100%) that can result in graft loss. Therefore, prior IFN-based regimens should be avoided in recipients of kidney transplantation [29].

The availability of all-oral regimens represents a dramatic change in the field of HCV treatment post-kidney transplant. Kidney transplant recipients with good graft function should have an adequate eGFR to allow the use of those regimens post-transplantation. The current available treatment regimens are summarized in Table 2. Those regimens in general are well tolerated, highly effective, and should not increase the risk of acute cellular rejection. So far, there are no studies that addressed the treatment in this population, but the lessons learned from its use post-liver transplant should be applicable to HCV-infected kidney transplant recipients.

Table 2 outlines the different regimens that are currently used to treat HCV infection. The treatment regimen and duration of treatment is determined by the HCV genotype, prior treatment status and the presence or absence of cirrhosis.

The Federal Drug Administration (FDA) recently approved simeprevir/sofosbuvir combination for treating patients with genotype-1 HCV infection [20▪]. This regimen has been well studied in patients with recurrent post-liver transplant with SVR rates of 90%. It is well tolerated and was associated with no significant interactions with immunosuppression regimen. Interestingly, recent data from an interim analysis of an ongoing study, the concomitant use of simeprevir (along with daclatasvir and RBV) with cyclosporine at steady state, resulted in an approximately six-fold increase in plasma concentrations of simeprevir compared with historical data of simeprevir in the absence of cyclosporine. Therefore, this regimen should be avoided in kidney transplant recipients who are maintained on cyclosporine-based immunosuppression regimen. The approval of sofosbuvir/ledipasvir combination has

Table 2. Hepatitis C virus treatment post-kidney transplant

	Pros	Cons
GT-1, GT-4, GT-6		
Sofosbuvir/ledipasvir	Preferred regimen post-solid organ transplant	Critical interactions with acid-suppressing medications
	Effective and well tolerated	PPI should be avoided
	Minimal interaction with immunosuppression	
	RBV use not needed for majority of patients	
Paritaprevir/ritonavir/ombitasvir along with dasabuvir þïRBV	Effective regimen with high rates of SVR	10 pills daily in two divided doses
	RBV use not needed for GT-1b without cirrhosis	RBV use required in patients with GT-1a
		Significant interactions with immunosuppression regimens requires very close monitoring
Simeprevir/sofosbuvir ± RBV	Effective	Expensive
	Well tolerated	Simeprevir has potential interaction with cyclosporine
	High SVR rates in patients post-liver transplantation	RBV use may still be needed
		Patients with cirrhosis will need 24 weeks of treatment
GT-2, GT-5[a]		
Sofosbuvir ± weight-based RBV (12–16 weeks)	Effective	RBV-induced anemia
	Well tolerated	
GT-3		
Sofosbuvir ± weight-based RBV (24 weeks)	Well tolerated	Only treatment regimen
		RBV-induced anemia

GT, genotype; HCV, hepatitis C virus; PPI, proton pump inhibitor; RBV, ribavirin; SVR, sustained virological response.
[a]Few data available regarding treatment of HCV GT-5.

led to significant decline in the use of this regimen [17].

Sofosbuvir/ledipasvir combination (Harvoni Gilead Sciences, California) is becoming the most widely used regimen to treat patients infected with genotypes 1 and 4. It is highly effective and well tolerated in all patients including those treated post-liver transplant. High SVR rates (90%) in the post-liver transplant setting combined with the lack of any significant interactions with various immunosuppressive medications (calcineurin inhibitors, mycophenolate mofetil, or rapamycin) makes this regimen the preferred one to use currently in kidney transplant recipients with HCV infections. Patients receiving this regimen should be counseled to avoid the use of proton pump inhibitors while on treatment.

Paritaprevir/ritonavir/ombitasvir along with dasabuvir and RBV regimen (Viekira Pak ± RBV, AbbVie, Illinois) was also recently approved by the FDA for treatment of genotype-1 HCV infection [30▪]. This regimen proved to be effective in patients post-liver transplantation, but its use was associated with significant interactions with calcineurin inhibitors requiring very close monitoring of drug level and significant dose reduction in both tacrolimus and cyclosporine. The complexity associated with the use of this regimen in patients with solid organ transplantation may make its use for patients' post-kidney transplantation more complex and risk of calcineurin toxicity or rejection higher than the sofosbuvir-based regimens [31▪▪]. If this regimen to be used, we recommend to use in patients with genotype-1b infection, with preemptive monitoring of immunosuppression levels alterations. In addition, patient education and engagement in their treatment may be warranted.

HCV-positive kidney transplant recipients with functional graft should be assessed and considered for treatment promptly post-transplantation. The data regarding the negative impact of HCV on both graft and patient survival should make treating those patients a priority. Sofosbuvir/ledipasvir appears to be the best available regimen to treat those patients infected with genotypes 1, 4, and 6 (can be used in genotype-5 despite no strong data available). For genotypes 2 and 3 infection, sofosbuvir along with weight-based RBV should be used for 12–16 and 24 weeks, respectively.

HEART TRANSPLANTATION

There are very limited data regarding prevalence or treatment outcomes of HCV infection in patients awaiting heart transplant and those who are heart transplant recipients [32,33]. Only a few studies have demonstrated lower survival rates in heart transplant recipients infected with HCV [34]. Unfortunately, those studies are limited by small sample size, inclusion of both preexisting HCV infection and those acquired through transplant, and short follow-up [35,36]. Furthermore, those studies do not compare the transplant-related mortality to the high mortality rates the same patient will have remaining on the waiting list. Despite the paucity of data, several heart transplant programs use this data to exclude HCV-positive candidates from heart transplant [34].

As we have seen in the kidney transplant setting, the new era of an effective all-oral regimens will change the selection criteria for patients awaiting heart transplant, allow effective treatment for heart transplant recipients with HCV infection, and may in the future allow the safe use of HCV-positive heart donors in both HCV-positive and HCV-negative recipients [37].

Although HCV positivity is an independent risk factor for increased mortality and for the development of accelerated vasculopathy after cardiac transplantation, heart transplant candidates with HCV should not be excluded from heart transplant based on the current available data [38]. Those patients should be selected based on the stage of their liver disease. Patients without cirrhosis should be considered for antiviral therapy. Historically, prior IFN-based regimens should be avoided in those patients as IFN can exacerbate heart failure or arrhythmias and RBV-induced anemia may further increase the risk of decompensation. Although no studies have been done yet in this population to our knowledge, the new all-oral regimens should be used safely in heart transplant recipients with adequate kidney functions (eGFR $>$ 30 ml/min), as none of those regimens have been associated with cardiac adverse events. Similar to treatment post-kidney transplant, the regimen will be determined by HCV genotype, should have minimal interactions with immunosuppression, and avoid the use of the RBV whenever possible to minimize the risk of anemia and its negative impact on patients with advanced heart failure of ischemic cardiomyopathy [17]. Heart transplant candidates with HCV-related cirrhosis should not be excluded, but rather should be considered for combined transplantation with prompt treatment of HCV after transplantation.

Using HCV-positive heart should be considered in the appropriately selected recipients. The use of those donors in HCV-positive recipients should be appropriate (similar to the practice used for kidney and liver allocation), but extending their use to HCV-negative recipients continues to be controversial [39]. The reported rate of transmission of HCV is (25–82%), which is lower than that reported with the use of liver and kidney, possibly as the heart is not believed to serve as a viral reservoir (in contrast to liver) [40]. As the American Heart Association Consensus Conference in 2001 recommended that HCV-positive donors could be utilized in highly selected high-risk recipients, some studies reported acceptable outcomes using those donors in elderly recipients who tend to require lower burden of immunosuppression [33]. Unfortunately, the limited number of studies, small sample size, and poor documentation of the recipient HCV status prior to transplant makes it hard to draw any conclusions regarding the outcomes of those organs in heart transplant recipients. Furthermore, most of those studies are old and preceded the currently available effective HCV therapy that can be used safely post-heart transplant [34].

Similar to what has been reported in recipients of kidney transplant, prior IFN-based regimens are rarely used in recipients of heart transplant as those regimens carry the potential risk of heart failure, arrhythmias, and graft rejection. Treatment with an all-oral regimen should be considered in all HCV-positive heart transplant recipients with adequate kidney functions [18]. Those patients will be best served by using a treatment regimen that lacks any significant interactions with various immunosuppressant agents used post-heart transplant and does include the use of RBV, if possible. We recommend the use sofosbuvir/ledipasvir as first-line regimen for genotypes 1, 4, and 6. Paritaprevir/ritonavir/ombitasvir along with dasabuvir and RBV regimen can be still be used, but with extreme caution and with close monitoring of immunosuppression levels. For genotypes 2 and 3, sofosbuvir along with weight-based RBV continues to be the only option available for now (Table 2).

LUNG TRANSPLANTATION

Most lung transplant centers consider HCV viremia a contraindication for lung transplant, limiting the data that defines the outcome of lung transplant in HCV-positive recipients, and the availability of any studies that address the HCV treatment in this setting [41▪▪]. The policy and guidelines outlined by the American Society for Transplant Physicians and the International Society for Heart and Lung Transplantation identify HCV-related liver disease as a contraindication for lung transplant. Those guidelines are based on very few published studies.

A recent survey of 29 US lung transplant centers showed that only five programs would consider lung transplant in HCV-positive candidates. Between 2000 and 2007, United Network for Organ Sharing data show that only 1.2–2.1% of lung transplant recipients were HCV seropositive at the time of transplant. Despite the lack of any information regarding presence of viremia or liver histology at time of transplantation, the study showed that those patients had similar survival to those who are HCV negative at the time of transplant [35]. Those encouraging results, combined with presence of effective HCV treatment regimens, do support wider consideration of HCV-seropositive patients for lung transplant [42].

Treatment of HCV before or after lung transplant has not been reported. The side-effect profile of prior IFN-based regimens especially with RBV should limit their use in lung transplant candidates and will preclude their use post-successful lung transplant. As with other solid organ transplants, an all oral-regimen determined by genotype should allow the well tolerated and effective treatment of those patients (Table 2). Whenever possible, RBV use should be avoided as RBV-induced anemia will be poorly tolerated in patients with advanced lung disease.

CONCLUSION

The new DAA agents against HCV infection have dramatically altered the landscape of treatment for this chronic infection. Several IFN-free regimens are currently approved to treat the different genotypes and are included in the treatment protocols in the United States. The pace of change is expected to increase, with numerous new drugs with different mechanisms of action that will likely become available over the next few years. Those regimens should become the standard treatment regimens in patients awaiting solid organ transplants, when feasible, and should be used promptly after transplant in those who could not be treated prior to transplant. The high rates of SVR achieved with those regimens should allow expansion of current selection criteria for solid organ transplant to include those patients who have HCV.

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Conflicts of interest

There are no conflicts of interest.

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