

Hepatitis C in non-hepatic solid organ transplant candidates and recipients: A new horizon

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Author contributions: Belga S and Doucette KE contributed equally to this work, including review of the literature, writing and editing of the manuscript.

Conflict-of-interest statement: Belga S has no conflict of interest to declare; Doucette KE has received speaker honoraria from Bristol-Myers Squibb and Gilead and has received research support from Bristol-Myers Squibb, Gilead, Merck, AbbVie.

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Received: July 31, 2015

Peer-review started: July 31, 2015

First decision: August 31, 2015

Revised: September 20, 2015

Accepted: November 24, 2015

Article in press: November 24, 2015

Published online: January 28, 2016

Abstract

Hepatitis C virus (HCV) infection is estimated to affect 130-150 million people globally which corresponds to

2%-3% of the total world population. It remains the leading indication for liver transplant worldwide and has been demonstrated to negatively impact both patient and graft survival following non-hepatic organ transplantation. In the era of interferon-based therapy, although treatment and cure of HCV prior to non-hepatic transplant improved survival, tolerability and low cure rates substantially limited therapy. Interferon (IFN)-based therapy following non-hepatic solid organ transplant, due to the risk of allograft rejection, is generally contraindicated. Rapid advances in IFN-free therapy with direct acting antivirals (DAAs) in the last few years have completely changed the paradigm of hepatitis C therapy. Compared to IFN-based regimens, DAAs have less frequent and less severe adverse effects, shorter durations of therapy, and higher cure rates that are minimally impacted by historically negative predictors of response such as cirrhosis, ethnicity, and post-transplant state. Recent studies have shown that liver transplant (LT) recipients can be safely and effectively treated with DAA combination therapies; although data are limited, many of the principles of therapy in LT may be extrapolated to non-hepatic solid organ transplant recipients. Here we review the data on DAA combination therapies in transplantation, discuss the advantages and disadvantages of pre- vs post-transplant HCV therapy and future directions.

Key words: Hepatitis C; Chronic; Kidney transplantation; Heart transplantation; Lung transplantation; Liver transplantation; Kidney failure; Chronic; Antiviral agents

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Core tip: Direct acting antiviral (DAA) therapy has the potential to eliminate hepatitis C virus (HCV) from the population of organ transplant candidates and recipients and thereby the negative impact of HCV

on outcomes. Among non-hepatic organ transplant patients, the biggest barriers currently are limited safety and efficacy data in this population, particularly in those with advanced renal disease, and global variability of access and reimbursement for DAAs. Future research is needed to better assess safety, efficacy and impact of DAA therapy in non-hepatic solid organ transplant, as well as to explore the safety of using HCV infected donors, with prophylactic therapy, to expand the donor pool.

Belga S, Doucette KE. Hepatitis C in non-hepatic solid organ transplant candidates and recipients: A new horizon. *World J Gastroenterol* 2016; 22(4): 1650-1663 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i4/1650.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i4.1650>

INTRODUCTION

Hepatitis C virus (HCV) infection affects 130-160 million people globally which corresponds to about 2%-3% of the total world population^[1-3]. After acute infection, which is usually asymptomatic, 55% to 85% of the patients go on to develop chronic hepatitis C with a risk of progression to cirrhosis is 15%-45% over 20 to 30 years^[1]. Those who develop HCV-related cirrhosis are then at risk of end-stage liver disease and/or hepatocellular carcinoma (HCC) and hepatitis C remains the leading indication for liver transplantation worldwide.

Among candidates for non-hepatic solid organ transplant (SOT), the prevalence of HCV infection varies by organ group and regional epidemiology. In the hemodialysis population, worldwide estimates of prevalence vary between 5% and 60%^[4]. Patients with end-stage renal disease (ESRD) on hemodialysis (HD) are at higher risk compared to patients on peritoneal dialysis^[5]. The prevalence in dialysis patients is directly related to the duration of dialysis, the type of dialysis and the total volume of blood and blood products transfused^[6,7]. The prevalence of HCV in dialysis patients, in Western countries in particular, has declined over the last two decades largely due to blood product screening implemented in the early 1990's and adherence to infection control practices^[8]. Despite this, the prevalence remains higher than in the general population and in 2002 the seroprevalence of HCV in US hemodialysis units was 7.8%^[9], at least 4-fold higher than the background rate^[1,9,10].

Substantial variability in HCV prevalence exists by country and amongst different dialysis centers within a single country^[9,10]. Available data suggest that the prevalence of HCV in hemodialysis units in Asia remains high, at up to 32%^[11], even in the era since 2010.

The prevalence of HCV infection in thoracic organ transplant candidates has been less rigorously assessed,

but appears to approximate the background population prevalence^[12,13]. Based on older studies, the prevalence of HCV infection in cardiac transplant recipients was 11%-18%^[14-16]. As in those with end-stage renal disease, the prevalence of HCV in cardiac transplant candidates has likely declined over time since the implementation of routine screening of blood products.

IMPACT OF HEPATITIS C ON OUTCOMES OF NON-HEPATIC SOT

The impact of HCV on the outcomes of non-hepatic SOT has been studied most extensively in renal transplant recipients. The majority of studies demonstrate that in patients with HCV infection, immunosuppression post-transplant accelerates progression and is associated with earlier onset and higher rates of cirrhosis and its complications^[17,18]. Nevertheless, some studies have failed to show a clear correlation with fibrosis progression^[19-21]. This may be explained by differences in immunosuppressive regimens used in the populations studied as well as small numbers and relatively short duration of follow up in most of these studies^[22].

Although hepatitis C does not appear to impact overall survival in renal transplant recipients in the first 5 years post-transplant. Early post-transplant deaths occur in about 1%-2%, up to 5% in older studies, of recipients as a consequence of rapidly progressive fibrosing cholestatic hepatitis and liver failure^[18,23-25]. By 10 years after transplant however, survival is decreased in HCV-infected recipients by approximately 15% compared to HCV-uninfected recipients^[17,26-32]. The dominant causes of death are due to liver disease^[17,20,30] and sepsis^[33]. In addition, there is an increased incidence of new onset diabetes, infectious complications, chronic rejection, and proteinuria and membranoproliferative glomerulonephritis in those with HCV^[17,29,34].

When the data are examined more closely, the risk of accelerated progression of fibrosis and development of end-stage liver disease and its complications appear to be limited largely to those with advanced fibrosis or cirrhosis at the time of transplant^[17,35,36]. As HCV has also been demonstrated to be an independent risk factor for mortality in hemodialysis patients^[37,38], the overall survival in those with moderate (METAVIR stage 2) fibrosis or less, is generally improved with renal transplantation compared to remaining on dialysis^[39]. In addition, pre-transplant therapy and cure of HCV prior to transplant has been demonstrated to mitigate the impact on post-transplant morbidity and survival^[40].

There are no long term studies regarding the impact of HCV on outcomes of heart or small bowel or pancreas recipients. Studies in these populations have suggested no difference in patient and graft

survival, likely due to short term follow up and/or the relatively small numbers studied^[16,41,42]. A retrospective study done between 1987 and 2010 that included 20 patients, showed that hepatitis C did not impact short-term patient and graft survival in cardiac transplant recipients^[43]. In the short-term there was also no increased risk of liver failure or accelerated transplant-related coronary artery disease. Another study with 10 patients and mean follow-up of 58 mo, showed similar results^[44]. However, there has been some contradictory evidence suggesting that hepatitis C can independently increase the risk of mortality and allograft vasculopathy in cardiac transplant recipients^[12,45].

In lung transplant recipients, a recent analysis of the OPTN/UNOS database demonstrated a similar 5 year survival amongst HCV-seropositive and seronegative recipients^[46]. The results of this study however are limited by the lack of data on HCV RNA status in the database and the likelihood that the majority of the seropositive recipients were RNA negative based on the authors' survey of practices amongst US lung transplant centers. Given the data in renal transplant, however there may be an increased risk of HCV-related death beyond 5 years post-transplant in other non-hepatic SOT recipients.

In a single center study of 14 HCV-RNA positive lung transplant recipients, the 5 year survival was similar to HCV negative recipients^[47]. Another small retrospective study from Sahi *et al.*^[48], also showed no difference in short-term survival between HCV-positive and HCV-negative lung transplant recipients. Despite the limited data on survival of lung transplant recipients with chronic hepatitis C with only small studies and conflicting evidence on outcomes^[13,49], hepatitis C remains a relative contraindication to lung transplantation in the update of the International Society for Heart and Lung Transplantation guidelines for the selection of lung transplant candidates, recently published in January of 2015. These suggest that transplant can be considered in patients "without evidence of cirrhosis" and who are on "appropriate therapy" and that such patients be managed in centers with expertise in viral hepatitis. There is no evidence cited to support this recommendation and it gives little guidance to physicians and lung transplant programs as to how best select and manage such patients^[50].

The available data on pancreas and pancreas-kidney transplant recipients with hepatitis C is scarce but these patients appear to be at higher risk of graft dysfunction and morbidity^[51]. No data exists regarding survival for small bowel transplant recipients with hepatitis C.

INTERFERON ERA OF HCV THERAPY

Treatment of hepatitis C with interferon based therapy following non-hepatic SOT is generally contraindicated due to a significant risk of rejection, although more

recent studies, suggest this risk is only about 5% in renal transplant recipients^[52-55]. In life-sustaining (e.g. heart, lung) transplants, however, IFN-based therapy is not recommended and the risks and benefits must be carefully weighed if considering therapy in renal transplant recipients^[56,57]. As a result of the risks of therapy post-transplant, focus has largely been on treatment of HCV prior to transplantation. Most of the data on hepatitis C management in non-hepatic organ transplantation is in kidney transplant with very limited evidence in heart and lung transplantation^[37].

Table 1 summarizes the results of 3 recently published meta-analyses^[58-60] examining the outcomes of HCV therapy in ESRD and predictors of sustained virologic response (SVR). Overall, SVR rates for IFN-based therapy in dialysis patients in these analyses were about 40%. There was no benefit of pegylated over standard interferon in the meta-analyses, although some studies have demonstrated this^[61,62]. Although ribavirin is by label contraindicated in those with a creatinine clearance less than 50 mL/min, ribavirin has been used at reduced doses in hemodialysis patients. There is little data however on the benefit of adding ribavirin to interferon-based therapy in this setting and it carries an significant risk of severe anemia^[4].

The first-generation NS3A protease inhibitors, telaprevir and boceprevir, do not require dose adjustment in renal failure, however, their use in combination with peginterferon and ribavirin is associated with additive side effects, with more anemia and declining renal function of particular concern, and very limited data on safety and efficacy in this population^[63,64]. These agents have now been discontinued from most markets worldwide and are listed as contraindicated therapies in international guidelines^[65-67]. Although there is no dose adjustment needed for the protease inhibitor simeprevir in advanced renal disease, there are no published data on the efficacy and safety of simeprevir in combination with peginterferon and ribavirin in this population. The combination of sofosbuvir with peginterferon and ribavirin is listed as an interferon containing option for therapy in the 2015 European Association for the Study of the Liver (EASL) guidelines^[66], however in those with a creatinine clearance less than 30 mL/min, sofosbuvir is contraindicated due to a lack of safety data.

Dropout rates on interferon-based therapy are high in those with end-stage renal disease, ranging from 19% to 28% in the meta-analyses, and largely due to adverse effects, particularly flu-like symptoms. The positive predictors of response found, were those associated with response in the general population, including low baseline HCV viral load, lesser degrees of hepatic fibrosis, non-1 HCV genotype and age less than 40^[59,60]. It has been suggested that specific types of immunosuppressants can have an impact on virological outcomes; however, these data are conflicting and largely examined in the setting of liver

Table 1 Outcomes of interferon-based therapy in hemodialysis patients

Author	Number of studies included	Patients (n)	Regimen	SVR	Treatment discontinued for adverse effects	Predictors of SVR
Alavian <i>et al</i> ^[60]	21	491	IFN α 2a or 2b	39.1%	29.7%	Age < 40
Gordon <i>et al</i> ^[59]	12	279	PegIFN α 2a or 2b	39.3%	22.6%	Lower HCV RNA non-cirrhotic elevated ALT genotype 1 N/A
	20	459	IFN	41%	26%	
	3	38	PegIFN	37%	28%	
Fabrizi <i>et al</i> ^[58]	2	49	PegIFN/RBV	43%-97%	¹ OR dropout 0.389 (0.155-0.957)	N/A
	13	539	IFN	¹ OR of no SVR 0.081 (0.029-0.230)		
			(10 studies) IFN + RBV (3 studies)			

¹This analysis only reported the OR, rather than %SVR and dropout; data support relative benefit of IFN-based therapy on SVR, but do not provide absolute benefit. IFN: Interferon; PegIFN: Pegylated interferon; RBV: Ribavirin; OR: Odds ratio; SVR: Sustained virologic response.

transplant^[68].

In patients with end-stage heart failure IFN-based therapy, with or without RBV, is contraindicated due to the increased risk of arrhythmias, cardiotoxicity and the risk of RBV-induced anemia can also worsen any underlying cardiac ischemia^[41,43,57,69-71]. In lung transplant candidates with end-stage disease, this has been considered by some to be a contraindication to IFN-based therapy due to concerns of intolerability^[72]. In carefully selected lung transplant candidates however a small single center study demonstrated the efficacy and safety of IFN and RBV therapy prior to lung transplantation^[73].

The epidemiologic, natural history and treatment outcomes data led to the development of international guidelines on the management of hepatitis C in renal and non-hepatic transplant candidates and recipients^[56,57]. As part of the evaluation for transplantation candidacy, liver biopsy is recommended in current guidelines to confirm or exclude the presence of cirrhosis, unless the latter has already been documented on clinical, radiographic and/or biochemical grounds. All non-hepatic, non-cardiac organ transplant candidates, should be considered potential candidates for therapy of HCV. With interferon-based therapy however, the numerous adverse effects, particularly in those with end-stage organ disease, along with the overall poor responses to therapy requires careful consideration of the risks and benefits in the individual. There is clearly a greater urgency for therapy in those with more advanced fibrosis, but the success and tolerability in such patients is decreased. Figure 1 summarizes the current recommendations for assessment, transplant listing and HCV therapy in non-hepatic SOT.

NEW ERA OF HEPATITIS C TREATMENT - INTERFERON FREE

IFN-free regimens with direct acting antivirals (DAAs) have numerous advantages including, shorter duration of therapy, far fewer adverse effects and higher cure rates when compared to interferon-based therapy.

There are now data on DAA regimens for all HCV genotypes with recommendations published in international guidelines^[65,66]. Recommendations from EASL and AASLD/IDSA guidelines for treatment of naïve patients with chronic HCV, by genotype, with interferon free regimens are summarized in Table 2.

Current DAAs target three viral non-structural proteins that are vital in viral replication: the NS3/4A protease, the NS5A protein and the NS5B polymerase^[74]. Simeprevir (SMV)^[75] and paritaprevir (PTV)^[76] are NS3/4A protease inhibitors, ledipasvir (LDV)^[77], daclatasvir (DCV)^[78] and ombitasvir (OMV)^[76] are NS5A inhibitors and sofosbuvir (SOF)^[77] and dasabuvir (DSV)^[76] are nucleoside and non-nucleoside, respectively, NS5B polymerase inhibitors. Ritonavir (RTV), used in combination with PTV acts as a booster *via* CYP3A inhibition^[76]. The most robust data are in genotypes 1, 2 and 3, however there are limited data in genotype 4, 5 and 6 with additional studies ongoing, including with next generation molecules^[79].

The majority of the data on HCV therapy in transplantation are in liver transplant candidates and recipients. The safety and tolerability in addition to high efficacy have been demonstrated for several interferon-free regimens in decompensated cirrhotics awaiting liver transplant and are currently recommended in international guidelines^[65,66]. These include LDV/SOF with RBV for 12 wk or LDV/SOF for 24 wk in genotype 1, 4, 5 or 6^[80,81] and SOF/RBV for up to 48 wk in genotypes 2 and 3^[82].

In those with recurrent HCV following liver transplant, and genotype 1, 4, 5 or 6, LDV/SOF with RBV for 12 wk is recommended^[65,66]. In the SOLAR 1 and 2 studies, the SVR12 in genotype 1 was 96%-98% in those with F0-3 or Child Pugh A cirrhosis and 88%-89% in those with Child Pugh B or C cirrhosis^[83,84]. Adverse effects, largely attributable to RBV, are seen with this regimen, so the alternative of LDV/SOF for 24 wk can be considered, particularly in those with decompensated liver disease. Although data are limited, on the combination of SOF and DCV post-transplant, overall SVR has been more than 90%, including in those with

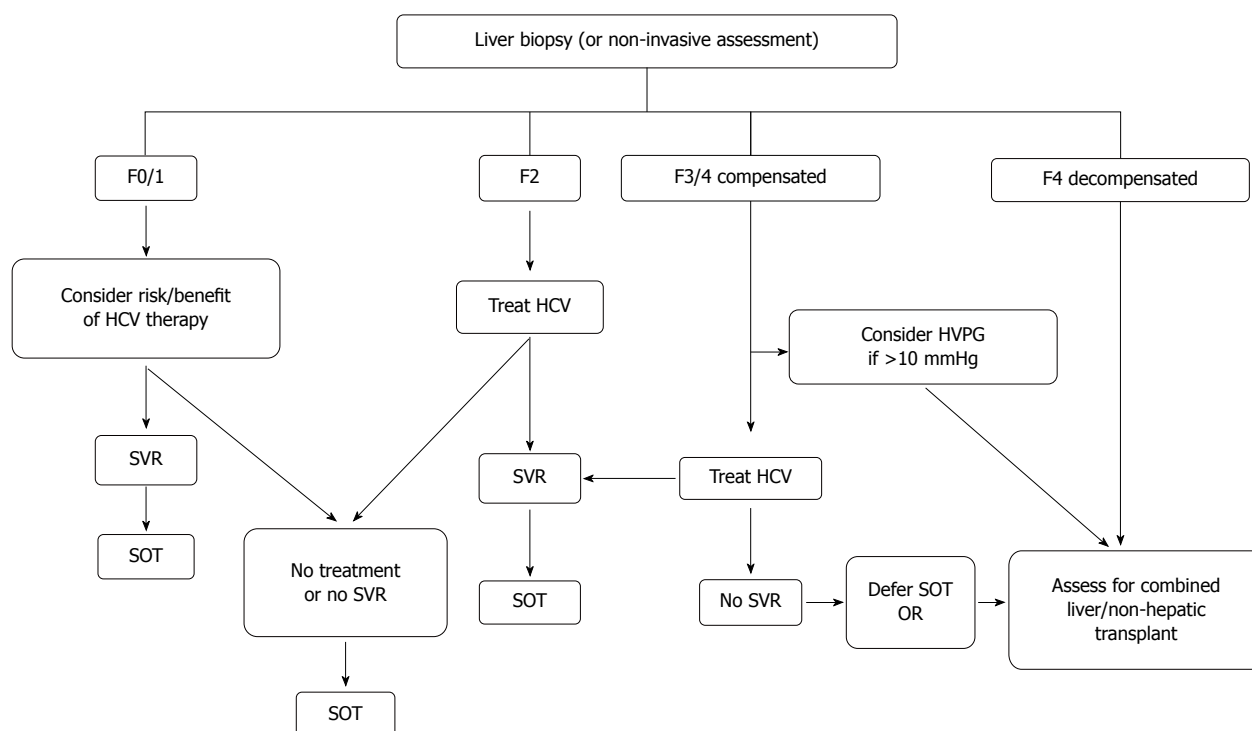


Figure 1 Approach to assessment of hepatitis C virus in non-hepatic solid organ transplant candidates in interferon era. HCV: Hepatitis C virus; F: Fibrosis stage; SVR: Sustained virologic response; SOT: Solid organ transplant; HVPG: Hepatic venous pressure gradient.

Table 2 Summary of recommendation for interferon-free hepatitis C virus therapy in naïve patients without (a) and with (b) cirrhosis^[65,66,90,91,94,115-126]

	SOF + RBV ^[65,66]	SOF + LDV ^[65,66]	PTV/r + OMB + DSV ^[65,66]	PTV/r + OMB ^[65,66]	SOF + SMV ^[65,66]	SOF + DCV ^[66]
	(SVR)	(SVR)	(SVR)	(SVR)	(SVR)	(SVR)
Without cirrhosis						
Genotype 1a		8-12 wk (93%-99%)	12 wk with RBV (95%-97%)		12 wk without RBV (93%-100%)	12 wk without RBV (95%-100%)
Genotype 1b		8-12 wk (93%-99%)	12 wk without RBV (98%-99%)		12 wk without RBV (93%-100%)	12 wk without RBV (95%-100%)
Genotype 2	12 wk (97%)					
Genotype 3	24 wk (94%)					12 wk without RBV (89%-97%)
Genotype 4		12 wk (95%)		12 wk with RBV	12 wk without RBV	12 wk without RBV (89%-97%)
Genotype 5 or 6		12 wk				12 wk without RBV (89%-97%)
With cirrhosis						
Genotype 1a		12 wk without RBV (95%)	24 wk with RBV (92%)		12 wk without RBV (93%)	12 wk with or 24 wk without RBV
Genotype 1b		12 wk without RBV	12 wk with RBV (96%)			
Genotype 2	16-20 wk (78%-83%)					12 wk without RBV
Genotype 3	24 wk (92%)					24 wk with RBV
Genotype 4		12 wk with RBV or 24 wk without RBV		24 wk with RBV	12 wk without RBV	12 wk with RBV or 24 wk without RBV
Genotype 5 or 6		12 wk with RBV or 24 wk without RBV				12 wk with RBV or 24 wk without RBV

HCV: Hepatitis C virus; Peg: Pegylated interferon; RBV: Ribavirin; SOF: Sofosbuvir; SMV: Simeprevir; LDV: Ledipasvir; PTV: Paritaprevir; r: Ritonavir; OMB: Ombitasvir; DSV: Dasabuvir; DCV: Daclatasvir.

Table 3 Drug interactions with immunosuppressants and other common post-transplant medications

	SOF	SMV	LDV	PTV/r + OMB + DSV	DCV
Cyclosporine	*	***	**	**	*
Tacrolimus	*	**	**	**	*
Sirolimus	*	**	**	**	*
MMF	*	*	*	**	*
Azathioprine	*	*	*	*	*
Prednisone	*	**	*	**	*
Fluconazole	*	***	*	*	*
Voriconazole	*	***	*	***	**
Posaconazole	*	***	*	***	**
PPI	*	*	**	**	*

SOF: Sofosbuvir; SMV: Simeprevir; LDV: Ledipasvir; PTV: Paritaprevir; r: Ritonavir; OMB: Ombitasvir; DSV: Dasabuvir; DCV: Daclatasvir; PPI: Proton pump inhibitor. ***Contraindicated, do not co-administer;

**Potential for interaction, use with caution; may require altered dosing;

*No clinically significant interaction.

fibrosing cholestatic HCV^[85-87] and this combination can be considered in all genotypes^[66]. All of these combinations can be used post-transplant without concerns regarding drug interactions and the need to adjust immunosuppressant doses (Table 3).

Based on the real world data from observational studies^[88,89], the combination of SOF/SMV can be considered, however, there is a significant interaction with cyclosporine, which must not be used in combination, and the relatively poor performance of this regimen in the phase 3 trials in non-transplant patients^[90,91], raises concerns that this combination may not be as potent as others. The combination of OMV/PTV/RTV with DSV and ribavirin has been studied in 34 post-liver transplant patients with genotype 1 HCV recurrence and mild to moderate fibrosis (Metavir F0-2)^[92]. Dose adjustments were needed for cyclosporine and tacrolimus due to the drug-drug interactions between ritonavir. There are several other drug interactions with ritonavir and other medications commonly taken by liver transplant recipients (Table 3) and these must be carefully considered if this regimen is used for treatment in this population. Although the efficacy and tolerability of this regimen in the study was excellent, with an SVR achieved in 33 of 34 and only 1 discontinuation for adverse effects, the safety and efficacy in patients with more advanced HCV infection post-liver transplant are unknown.

Of the interferon free DAA combinations studied to date in the post liver transplant population, all have an excellent safety and tolerability profile and hence a significantly lower discontinuation rate when compared to IFN-based regimens^[93]. SMV may cause rash, pruritus, gastrointestinal upset and muscle pain, but these rarely lead to discontinuation^[75]. Photosensitivity can occur, but usually when SMV is combined with IFN and RBV^[75]. Fatigue and headache are the most common side-effects of LDV/SOF, but are generally mild and occur in at most 10%-20%^[77]. OMV/PTV/

RTV + DSV as well as DCV can lead to fatigue, gastrointestinal symptoms, pruritus, skin reactions and insomnia, but again, discontinuations for adverse effects are uncommon^[76,78]. When RBV is, or must be, used as part of an interferon-free regimen, significant anemia (hemoglobin < 100 g/L)^[94] is more common and quality of life decreased compared to the RBV-free regimens^[95,96]. This is an important consideration, particularly in those with end-stage organ disease.

There are very limited data on the treatment of HCV following non-hepatic transplant, with to our knowledge only 1 published case report using SMV/SOF and a case series of 17 patients treated with SOF and RBV^[97,98]. However, these 2 reports and all of the data in historically "difficult-to-cure" populations in the interferon era, such as cirrhotics, HIV co-infected, prior null responders, and post-liver transplant patients, demonstrate cure rates comparable to uncomplicated HCV treatment naive patients when interferon free DAA therapy is used. This supports the extrapolation of data in liver transplantation to the treatment of hepatitis C in non-hepatic solid organ transplant recipients. In liver transplant, there remains controversy as to the optimal timing of HCV therapy, pre or post-transplant in order to maximize survival benefit and quality of life. The timing of therapy is also a major consideration in non-hepatic SOT. Considerations include the degree of hepatic fibrosis, the HCV genotype, treatment history and access to interferon free therapy, the presence or absence of renal dysfunction; for those pre-transplant the degree of sensitization and anticipated wait time as well as the immunosuppressive plan. Figure 2 summarizes these considerations in the non-hepatic SOT candidate or recipient with HCV and the advantages and disadvantages of HCV therapy prior to or after transplant.

Renal dysfunction is the primary barrier to therapy prior to renal transplant. Most of the currently recommended interferon free regimens are sofosbuvir-based and the safety of sofosbuvir in those with a creatinine clearance under 30 mL/min is under investigation^[99], but remains uncertain at this time. Table 4 summarizes the dosing considerations for DAA therapy in those with renal dysfunction. OMV/PTV/RTV with DSV, and with or without RBV was recently shown to be effective in patients with HCV genotype 1 and stage 5 chronic kidney disease (creatinine clearance less than 15 mL/min)^[100]. Data on the investigational combination of grazoprevir, an NS3 protease inhibitor and elbasvir, an NS5A inhibitor, was recently presented from the phase III trial examining the efficacy and safety of for 12 wk in patients with stage 4 or 5 chronic kidney disease, most of whom were on hemodialysis^[101]. The SVR12 was 94% overall and adverse effects in the treatment group were similar to placebo. These data are extremely encouraging in this historically difficult to cure population who experienced numerous adverse effects of therapy. As a result of

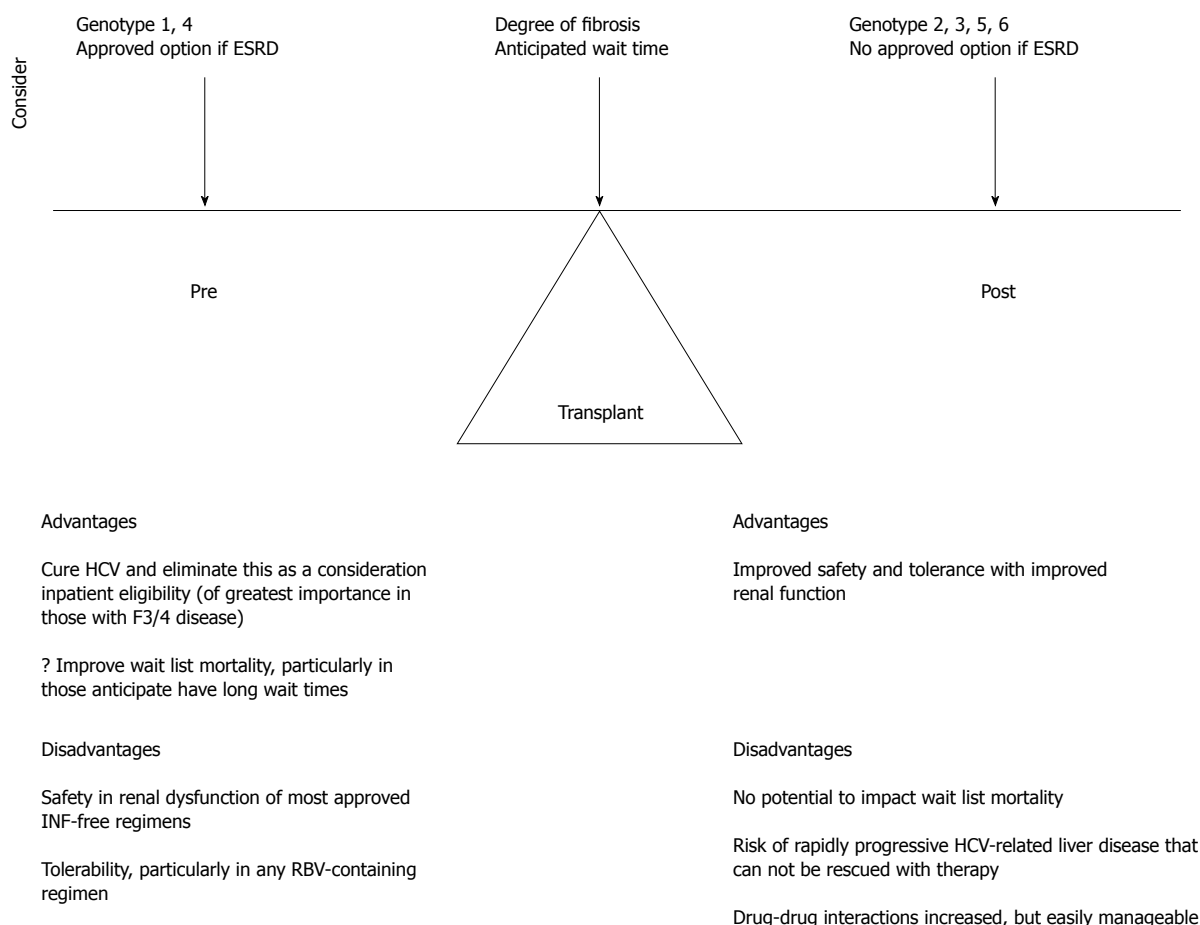


Figure 2 Considerations, advantages and disadvantages of hepatitis C virus therapy before or after non-hepatic solid organ transplant.

Table 4 Considerations with direct acting antivirals in renal dysfunction

DAA agent or combination	Issues in renal dysfunction
Sofosbuvir	Contraindication in GFR < 30 mL/min due to insufficient safety data ^[127]
Simeprevir	No dose adjustment ^[75]
Ledipasvir	Limited data; no theoretical concerns ^[127]
PTV/r + OMB + DSV	Safe and effective and no dose adjustment in ESRD ^[100]
Daclatasvir	No dose adjustment ^[78]
Elbasvir/Grazoprevir	Safe and effective and no dose adjustment in ESRD ^[101]

DAA: Direct acting antiviral; ESRD: End stage renal disease; GFR: Glomerular filtration rate; PTV: Paritaprevir; r: Ritonavir; OMB: Ombitasvir; DSV: Dasabuvir.

these results, the combination was granted expedited breakthrough designation for this indication from the United States Food and Drug Administration.

In an ideal world, pretransplant therapy is preferable in order to document cure of HCV and improve patient eligibility for non-hepatic SOT. For most thoracic organ transplant candidates, this should be the goal. In renal transplant candidates, and any other non-hepatic SOT candidate with advanced renal dysfunction, until the licensing of therapies such as grazoprevir/elbasvir, with proven safety and efficacy in end stage renal disease, and/or additional data on the use of sofosbuvir in this population, in general therapy should be deferred until post-transplant. In those with genotype 1 or 4

and access to OMV/PTV/RTV, with or without DSV and RBV, as applicable to the HCV genotype, therapy can be considered prior to transplant, with cautious use of ribavirin and considerations of the drug interactions. Pre transplant therapy is of higher priority in those with advanced (F3 or Child Pugh A cirrhosis) fibrosis. In this group, deferral to post renal transplant therapy may carry the risk of rapidly progressive fibrosis, including fibrosing cholestatic hepatitis C, and decompensation. Although cure rates with current DAA therapy are high, the risk of failure remains highest in those with decompensated liver disease and there is concern that should this occur, patients may not be rescued with HCV therapy.

For those with genotype 2, 3, 5 and 6, as all currently available IFN-free therapies are SOF-based, until additional safety data are available, therapy should be deferred in those with creatinine clearance < 30 mL/min until after SOT. In the setting of advanced (F3 or Child Pugh A cirrhosis) fibrosis, the risks and benefits of deferral of therapy and transplantation must be carefully assessed. Non-hepatic SOT in this setting should be done in consultation with a liver transplant program and patients should be assessed for liver transplant candidacy as a back-up should they develop rapidly progressive HCV-related liver disease post non-hepatic SOT that cannot be rescued with therapy.

DRUG INTERACTIONS WITH IMMUNOSUPPRESSANTS

In post-transplant populations, the other key consideration influencing the choice of therapy is the potential for drug interactions; although renal dysfunction may also be a concern in this group. Most novel DAAs are metabolized *via* cytochrome P 450 3A (CYP3A) and therefore drug interactions, particularly with calcineurin inhibitors, remain a concern^[102].

SMV should not be co-administered with cyclosporine as previous studies have shown a significant increase in SMV levels due to inhibition of organic anion transporting polypeptide 1B1 (OATP1B1), P-glycoprotein and CYP3A by cyclosporine^[75]. However, SMV can be used concomitantly with tacrolimus, despite up to 2-fold increase in SMV concentrations with the latter, requiring close drug monitoring^[102]. SMV can increase or decrease sirolimus levels; therefore, close monitoring of sirolimus levels is also recommended^[75,102]. SMV can be safely used with mycophenolate mofetil (MMF) and azathioprine^[102].

SOF can be safely co-administered with all immunosuppressants used in the transplant setting, including tacrolimus, cyclosporine, sirolimus, MMF and azathioprine^[77,102]. When SOF is used in combination with LDV, monitoring is required for co-administration with tacrolimus, sirolimus and cyclosporine as there is theoretical possibility of an interaction, and data are insufficient^[102]. There have been no clinically relevant drug interactions seen in studies to date, however in those treated with advanced liver disease, calcineurin inhibitor levels have been noted to drop and require increased dosing, an effect thought to be related to improved liver function and metabolism. No dose adjustment is necessary for when DCV is co-administered with cyclosporine, tacrolimus, sirolimus and MMF^[78].

OMV/PTV/RTV + DSV requires dose adjustment with sirolimus, MMF, tacrolimus and cyclosporine^[76,102,103]. The cyclosporine dose needs to be decreased to one fifth the dose used prior to HCV therapy and tacrolimus decreased to 0.5 mg weekly or 0.2 mg

every 3 d with close monitoring of levels. No dose adjustment is necessary when used concomitantly with azathioprine^[102].

When protease inhibitor containing regimens (PTV/r or SMV) are used concomitantly with prednisone, a substrate of CYP3A4, prednisone exposure may increase due to CYP3A4 inhibition^[102]. No dose adjustments are recommended, but patients should be monitored clinically.

DRUG INTERACTIONS WITH OTHER DRUGS COMMONLY USED POST-TRANSPLANT

Importantly, a careful review of all patient medications and potential interactions should take place before starting any DAA regimen and special caution should be taken with certain drugs, particularly antibiotics, antifungals, antiretrovirals, anticonvulsants, antipsychotics, sedatives, oral contraceptives, antiarrhythmics and antihypertensives^[75-78,102].

Use of anti-infectives is particularly common following SOT. Most commonly used antibiotics can be administered safely with new DAA regimens with the exception of the macrolide clarithromycin which cannot be co-administered with OMV/PTV/RTV + DSV, and rifampin which is contraindicated with any all the current DAA regimens due to significant interactions^[75-78,102]. Antifungals such as fluconazole, posaconazole and voriconazole cannot be co-administered with SMV. OMV/PTV/RTV + DSV is contraindicated to be used with posaconazole or voriconazole and DCV must be used with caution in combination with these antifungal agents^[78,102]. Of note, proton-pump inhibitors, such as omeprazole and pantoprazole, by increasing the gastric pH, can lead to decreased absorption of LDV^[77].

USE OF HCV POSITIVE ORGAN DONORS

In patients with end-stage organ failure, donor organ shortage is a growing concern and there is increasing use of increased infectious risk, as well as otherwise medically marginal, donors. Transplantation of HCV-positive donor organs into HCV-negative recipients will almost invariably leads to chronic hepatitis C in the immunosuppressed host^[104-106] and historically this has been associated with an aggressive course with a high risk of death from infectious complications and fibrosing cholestatic HCV^[107,108]. As such, guidelines currently recommend against transplanting an HCV positive organ into an HCV negative recipient^[56,57].

In those already infected with HCV, some groups have found no difference in patient and graft survival when using HCV positive kidneys into HCV positive recipients^[109,110], while several recent large studies have demonstrated a significant increased risk of

death in HCV-positive recipients receiving an HCV-positive kidney or heart transplant^[12,109,111,112]. Despite the decrement in survival compared to receiving an HCV negative graft, there remains an overall survival advantage to receiving an HCV-positive kidney transplant over remaining on dialysis^[113]. The waiting time on the renal transplant list is also reduced significantly in the United States, by approximately 1 year. In spite of the overall benefit, HCV-positive kidneys continue to be underutilized in the United States^[114].

With highly effective interferon-free DAA therapy for HCV, it is easy to imagine an era on the horizon where HCV in donors will be approached in a manner similar to a donor with positive blood cultures; there may be a slightly increased risk of donor derived transmission of infection, but with safe effective therapy, this risk could be effectively mitigated and the donor pool further expanded. This approach however will require further data before such recommendations can be made.

CONCLUSION

Although historical data demonstrate that hepatitis C has a negative long-term impact in both patient and graft survival in non-hepatic solid organ transplant recipients, we are on the precipice of a new reality. Previous IFN-based regimens limited HCV treatment to pre-transplantation, and resulted in only a minority eligible for therapy, poor tolerability and resulted in only a small proportion of patients being able to complete treatment and achieve SVR.

The era of DAAs has been a major advance in hepatitis C management and prognosis, particularly in patients who were historically "difficult to cure". Recent studies show that liver transplant recipients can be safely and effectively treated with the new DAA regimens and although data are limited, there is every reason to believe these data can be extrapolated to non-hepatic solid organ transplantation recipients. This is expected to essentially eliminate the risk of hepatic and non-hepatic post-transplantation complications of hepatitis C. In patients with moderate to severe renal impairment, there are some emerging data on safety and efficacy of DAAs and further data are eagerly awaited. Until there are new licensed therapies, or additional data on current IFN-free therapies, those with ESRD should in general have HCV therapy deferred until post-transplant when renal function improves. This is a complete reversal of the historical paradigm of therapy restricted essentially to the pre-transplant period in non-hepatic SOT.

Despite some potential for drug-drug interactions remaining a concern, these are generally predictable and easily managed in a group of patients in whom management of drug interactions is a routine consideration.

In future directions, although dedicated prospective

studies on IFN-free therapies are unlikely to be undertaken in non-hepatic SOT, these patients will undoubtedly be treated based on the existing data. It will be important to see results of observational studies published in order to confirm the efficacy and safety in this population. The potential for utilization of HCV - positive organ donors, even into HCV - negative recipients is an intriguing possibility that will require future study. Within this defined population of non-hepatic SOT, it should be our goal, and easily achievable, to eradicate HCV.

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P- Reviewer: Boyacioglu AS, Grassi A, Song AT **S- Editor:** Gong ZM
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ISSN 1007-9327



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