REVIEW ARTICLE

Use of Direct-Acting Antivirals for the Treatment of Chronic Hepatitis C Virus Infection in the Perspective of Kidney Transplantation

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ABSTRACT

Hepatitis C virus (HCV) is more prevalent in patients with end-stage kidney disease on hemodialysis and, consequently leading to a higher prevalence of HCV infection among kidney transplant recipients than in the general population. Chronic HCV infection can contribute to increased morbidity and mortality in both the pretransplant and post-transplant settings. After transplantation, HCV infection also has adverse impacts on both patient and graft survival in kidney transplant recipients compared to those with HCV-negative including higher risks of cardiovascular disease, sepsis, and liver disease. In the recent years, notable advancement has been made in the development of oral anti-HCV agents that directly inhibit and target various HCV viral proteins with direct acting antiviral (DAA) therapies with reported excellent sustained virologic response, resulting in a paradigm shift in the management of HCV-infected patients undergoing kidney transplantation in the era of DAA therapies. In this review, we present the perspectives of use of direct-acting antivirals for the treatment of chronic hepatitis C virus infection in kidney transplant recipients.

Key words: Direct-acting antivirals, hepatitis, kidney transplantation, renal transplantation

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INTRODUCTION

Hepatitis C virus (HCV) infection affects nearly more than 200 million people worldwide.[1] Transmission of HCV happens primarily via blood contact. Hence, the prevalence of HCV infection is higher in hemodialysis (2.6-22.9% in Western countries) and, consequently, in kidney transplant patients (1.8%-8% in developed countries) than in the general population (~1% in the United States), arbitrarily associated with time on hemodialysis and a previous history of multiple previous blood transfusions.[2-5] Most kidney transplant patients have received HCV infection while on dialysis. Transmission from organ transplantation is a scarcity in this current era due to decent donor screening.[6]

Liver failure and hepatocellular carcinoma are the important long-term complications in chronic HCV-infected patients, particularly after transplantation.[7] In addition to liver complications, several extra hepatic complications lead to lessened patient and allograft survival in HCV-infected kidney patients.[6] Nevertheless, HCV infection should not be regarded as a contraindication for renal transplantation since patient mortality has been explicitly shown to improve following transplantation compared to continuing on dialysis.[8]

In the recent years, notable progress has been made in the development of oral anti-HCV agents that directly inhibit and target various HCV viral proteins with direct acting antiviral (DAA) therapies with reported excellent sustained virologic response (SVR).[1,9] In this review, we present the perspectives of a paradigm shift in the management of HCV-infected patients undergoing kidney transplantation in the era of DAA therapies.

KIDNEY TRANSPLANTATION IN PATIENTS WITH HCV

Impacts of HCV infection on kidney transplant candidates and recipients

HCV infection among kidney transplant candidates is not infrequent with the geographically varying prevalence ranging between 6% and 40%[10], and most of the patients are viremic.[11,12] Thus, Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline has recommended all kidney transplant candidates be tested for HCV infection.[7]

Chronic HCV infection can contribute to increased morbidity and mortality in both the pretransplant and post-transplant settings.[10] In candidates on kidney transplant waiting list, studies have demonstrated an association between chronic HCV infection and higher mortality risk attributed to cardiovascular disease.[8,10]

After transplantation, HCV infection also has adverse impacts on both patient and graft survival in kidney transplant recipients compared to those with HCV-negative including higher risks of cardiovascular disease, sepsis, and liver disease.[10,13,14] Besides, HCV-infected kidney transplant recipients may also develop HCV-related extra hepatic complications including de novo or recurrent glomerulonephritis, new onset diabetes mellitus after transplant (NODAT), nephrotoxicity related to excessive exposure to cyclosporine, malignancy, greater incidence of humoral rejection, and chronic allograft nephropathy.[2,4,9,15-19] A recent meta-analysis of 18 observational studies including 133,530 kidney transplant recipients showed a 1.85-fold increased risk of all-cause mortality and a 1.76-fold increased risk of graft loss in HCV-infected kidney transplant patients.[11] The link between HCV and lower graft survival after kidney transplant was demonstrated irrespective of the reference year, country of origin or size of the study group.[11]

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HCV INFECTION AND IMMUNOSUPPRESSION AFTER KIDNEY TRANSPLANTATION

Despite concerns regarding a permissive effect on viral replication due to immunosuppression leading to reactivation of HCV infection, acute hepatitis, and progression of liver disease after kidney transplantation.[7,15,20] data from the United Network for Organ Sharing (UNOS) database of 3,708 HCV-infected and 75,629 HCV negative kidney transplant recipients did not show an association between the use of induction therapy and increased mortality risk after transplantation.[21] Moreover, a lower mortality risk with induction therapy was observed beyond the first two years after transplantation. Besides, the type of Calcineurin Inhibitors (CNIs) including cyclosporine or tacrolimus and the use of steroids had no effect on mortality in HCV-infected kidney transplant recipients. Interestingly, the use of mycophenolate mofetil (MMF) was associated with a significantly reduced mortality.[21]

TREATMENT OF HCV INFECTION AND KIDNEY TRANSPLANTATION

Treatment options for HCV infection until recently have revolved around Interferon (IFN)-based regimens, a mainstay of treatment for HCV infection for the past 30 years, which provided limited efficacy and safety among chronic kidney disease (CKD) patients, particularly patients with advanced CKD (stage 4 to 5) or end-stage kidney disease (ESRD).[9] The use of IFN-based therapy has been restricted to pretransplant administration due to concerns related to acute allograft injury, immune stimulation related allograft rejection, allograft loss, and poor tolerability.[1,10] Furthermore, meta-analyses have demonstrated a poor SVR rate (18% to 26.9%) and a high dropout rate between 21.1% and 35% with alpha IFN[22,23] and 40.6% with pegylated IFN[23] in kidney transplant recipients. Thus, the HCV KDIGO workgroup recommended IFN not be administered to kidney recipients except in cases of fibrosing cholestatic hepatitis or life-threatening vasculitis, and the treatment should be provided for those HCV-infected candidates on the waiting list for renal transplant.[7,10]

Despite the recommendation for treatment before transplantation, IFN-based regimens have unfortunately been limited in efficacy and poorly tolerated in the ESRD patients [10], resulting in a subtle number of dialysis patients being treated for HCV of less than 5%.[24] A previous clinical study demonstrated promising efficacy and safety profiles of pegylated IFN alfa-2a (40 kDa) low-dose ribavirin (200 mg/d) in 70 HCV-infected hemodialysis patients awaiting kidney transplantation. In this study, pegylated IFN plus low-dose ribavirin provided a rate of SVR of 97%, with a low dropout rate of 14%.[25] The findings from this study suggested that combination antiviral therapy with pegylated IFN plus low-dose ribavirin can be effective and safe when given to selected patients since renal transplant candidates are younger with a lower frequency of comorbidities compared to overall dialysis population.

Nevertheless, subsequent studies including a few meta-analyses have shown the overall poor SVR rate of 33%to 39% in ESRD patients treated with pegylated IFN plus ribavirin, especially in HCV genotype 1 infected ESRD patients with high dropout rates.[26-28] The most common sources of dropouts were anemia (23%) and infections (13%).[26] Recently, two large randomized controlled clinical trials (RCTs) demonstrated higher than expected efficacy and tolerability of pegylated IFN plus low-dose ribavirin (200 mg daily) in HCV-infected ESRD patients on hemodialysis with SVR ~70%, especially in treatment-naïve patients with HCV-2 infection.[29,30]

Regarding the safety of ribavirin in patients with CKD, ribavirin is renally excreted and, according to the summary of product characteristics, is not recommended in patients with advanced CKD, as it can cause hemolytic anemia by an accumulation of ribavirin metabolites in erythrocytes and erythroblasts. However, low-dose ribavirin in hemodialysis patients reported encouraging results regarding efficacy and tolerability.[6] The recent international guidelines, the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) recommend cautious and individualized dosing of ribavirin in dialysis patients under proper safety precautions such as weekly hemoglobin monitoring.[31,32]

In addition to concerns regarding efficacy and safety profiles, there has also been a caution of IFN-based therapy that guidelines recommend that candidates be inactivated on the kidney transplant waiting list during treatment of IFN therapy and for 4 weeks after cessation of IFN-based therapy due to concerns regarding the higher risk of allograft injury and graft loss.[6,7,10]

Direct acting antiviral (DAA) and kidney transplantation

The introduction of DAAs into the clinical arena in 2011 of protease inhibitors, especially telaprevir and boceprevir (first-generation DAAs) has spawned a paradigm change in treating HCV-infected patients and is anticipated to have a significant impact on the ESRD population as well. They have inhibitory activity against NS3/4A protease. No dose adjustment of boceprevir or telaprevir is required since the pharmacokinetic properties are not changed in patients with CKD. Unfortunately, they still require the use of pegylated IFN, and ribavirin as monotherapy with boceprevir or telaprevir is associated with the development of viral resistance (9). Subsequently, significant accumulation of sufficient knowledge has recently been made on the mechanisms of HCV entry and release and the characterization of viral proteins involved in the replication of HCV.[31,33] This advancement has led to the development of interferon-free direct acting antiviral (DAA) that target and directly inhibit different nonstructural HCV viral proteins including NS3 serine protease (and its cofactor, NS4A), NS4B, NS5A, and NS5B RNA polymerase[32], as demonstrated in Table 1.[31,33]

The approval of oral DAAs revolutionized the treatment of HCV by leading to high rates of SVR at 12 weeks with fewer side effects.[34] The current generation of all-oral therapies began with the approval of sofosbuvir (SOF), a nucleotide NS5B polymerase inhibitor in 2013 (1, 9). Subsequently, the newer DAAs for the treatment of HCV [Table 1] have been available. Three all-oral regimens approved by the US Food and Drug Administration have been available since 2015 including SOF/ledipasvir (LDV), SOF/simeprevir (SIM), and ombitasvir (OBV)/ paritaprevir-ritonavir (PTV-r)/ dasabuvir (DBV). The advent of these combination regimens of new DAAs has given the opportunity to reach SVR rates exceeding 90% for many patient groups even among "difficult-to-treat" patients including posttransplant as well.[1,9,35]

Use of DAAs in Pre-transplantation setting

It has been confirmed that renal clearance is the major elimination pathway for GS-331007, which is the predominant circulating metabolite of SOF.[34] The risk of drug accumulation and incidence of adverse side effects in patients with stage 4-5 CKD should be regarded, and SOF dose adjustments are advised for patients with an estimated glomerular filtration rate (eGFR) <30 mL/min.[9] Several other DAAs, such as grazoprevir (GZR) and elbasvir (EBR)[36], daclatasvir (DCV) and asunaprevir[37,38], which are not eliminated by the kidney, have also been used for the treatment of HCV patients with stage 4-5 CKD.[9]

Studies have demonstrated that DAA-based antiviral therapies are efficient and well-tolerated for HCV patients with stage 4–5 chronic kidney disease.[34] Recently, Roth *et al.*[36] published their findings of a phase 3 RCT (the C-SURFER study) on efficacy and safety of GZR -EBR for the treatment of HCV genotype 1 in patients with CKD (stage 4-5 with or without hemodialysis dependence; 76% were hemodialysis-dependent). In this RCT, GZR-EBR (100 mg/50 mg) combination

Table 1: Characteristics of DAA against HCV and options for each genotype[31,33]

DAA	Mechanism of action	Renal dose Adjustments
Simeprevir (SIM)	N3/4A protease inhibitor	No adjustment required
Sofosbuvir (SOF)	Nucleotide NS5B polymerase inhibitor	Safety and efficacy not established with estimated GFR ≤30 mL/min
Ledipasvir (LDV)	NS5A replication complex inhibitor	No adjustment required
Paritaprevir-ritonavir (PTV-r)	NS3/4A protease inhibitor	No adjustment required, (However, not well studied in CKD stage 5 and hemodialysis patients)
Ombitasvir (OBV)	NS5A replication complex inhibitor	No adjustment required
Dasabuvir (DBV)	Non-nucleoside NS5B polymerase inhibitor	No adjustment required
Daclatasvir (DCV)	NS5A replication complex inhibitor	No adjustment required
Grazoprevir-Elbasvir (GZR-EBR)	NS3/4A protease inhibitor- NS5A replication complex inhibitor	No adjustment required
Velpatasvir (VEL)	NS5A protein inhibitor	Mild or moderate: No adjustment necessary

Combination regimens	HCV genotype				
	1	2	3	4	5 and 6
SOF + ribavirin	No	Suboptimal	Suboptimal	No	No
SOF/LDV ± ribavirin	Yes	No	No	Yes	Yes
SOF/VEL ± ribavirin	Yes	Yes	Yes	Yes	Yes
OBV/PTV-r+ DBV ± ribavirin	Yes	No	No	No	No
OBV/PTV-r ± ribavirin	No	No	No	Yes	No
GZR-EBR ± ribavirin	Yes	No	No	Yes	No
SOF + DCV ± ribavirin	Yes	Yes	Yes	Yes	Yes
SOF + SIM ± ribavirin	Suboptimal	No	No	Yes	No

once daily for 12 weeks provided excellent efficacy with SVR of 94.3% with favorable safety and tolerability profile.[36] Also, evidence on the combined treatment of SOF 400 mg daily and SIM 150 mg daily, without ribavirin for 12 weeks has given SVR of 89% with no reported significant adverse events during treatment.[39] However, the size of the study group is small (38 patients with CKD 4-5; 28 patients were on hemodialysis, a patient was on peritoneal dialysis, and nine patients had GFR<30 mL/min).[39]

Recently, a clinical trial (ClinicalTrials.gov identifier: NCT02487199, last verified: December 2016) of 3-drug regimen including OBV/PTV-r/DBV with or without ribavirin for the treatment of HCV genotype 1 in patients with advanced CKD stage 4 or 5, including those on hemodialysis has been finished. The 3DAA (3D) includes OBV (25 mg daily)/PTV-r (150 mg/100 mg daily)/DBV (250 mg twice daily). Low-dose ribavirin (200 mg daily) was also administered to patients with HCV genotype 1a (65%) only. The 3D regimen is metabolized in the liver and does not require adjustment of doses in patients with renal impairment.[9] An interim analysis showed SVR at 12 weeks of 100% without virology failures. Adverse events were mild or moderate, and no study drug was discontinued.[40]

Investigations on effectiveness and safety profiles of SOF-based regimen approaches in patients with CKD are also ongoing [NCT02563665 (a prospective cohort study on safety and efficacy of SOF-based regimen for treating HCV in patients with moderate to advanced CKD and patients receiving renal replacement therapy, last updated: October 2016) and NCT01958281 (SOF plus ribavirin, or LDV/SOF in adults with HCV Infection and severe renal insufficiency (not on dialysis), last updated: December 2016).[9] These studies will likely provide us additional data regarding effectiveness and safety of SOF-based regimen in patients with advanced CKD.

These emerging DAA therapies have shown to elicit a rapid virological response with undetectable HCV RNA at 4four weeks of treatment. With these current rates of the efficacy of DAA treatment, kidney transplant candidates will likely not require more than three months of DAA treatment. Besides, since emerging therapies can be used after transplant and do not stimulate the host immune system without the risk of rejection, prolonging the waiting time on the transplant list because of an IFN based antiviral therapy is no longer required.[10] Also, the use of DAAs in pre-transplantation setting will also help prevent disease transmission and avoid drug-drug interactions with immunosuppression after transplantation and possible decrease risk of HCV-related complications.[10] At the same time, curative treatment with DAAs in pre-transplantation could delay transplantation by several years by eliminating the option of a kidney from an HCV+ donor.

Use of DAAs in Post-transplantation setting

IFN-free DAAs regimens offer promising new perspectives for kidney transplant recipients. Apart from their potential for greater efficacy, the reduced toxicity makes them an attractive therapeutic option after kidney transplantation. Since DAAs do not stimulate the host immune system, which is one of the concerns with IFN therapy, studies have suggested that DAAs can be used for the treatment of HCV infection after kidney transplantation.[1,10,41,42] Besides, for patients with HCV genotypes 2 and 3 for whom SOF-based regimens are recommended, based on current evidence, DAA treatment with SOF-based regimens should still be treated after kidney transplantation while awaiting new pan-genotypic combinations.[3,36]

Sawinski *et al.*[42] reported their successful experience of the use of interferon-free DAA treatment regimens for HCV in 20 consecutive kidney recipients. 88% of patients were infected with genotype 1, 50% of patients had biopsy-proven advanced hepatic fibrosis (Metavir fibrosis stage ≥ 3) on most recent liver biopsy, and 60% of patients had prior treatment experience with interferon-based therapy. The median time after kidney transplantation to HCV treatment with DAAs was 888 days. All patients cleared their HCV virus quickly while on treatment with 100% SVR at 12 weeks after completion of DAA therapy with no serious adverse events including no episodes of acute rejection.[42] Although treatment regimens were heterogeneous, most commonly used regimen included SOF 400 mg and SIM 150 mg daily.[42] Besides, Kamar *et al.*[43] also showed a 100% SVR at12 after DAA therapy without any serious adverse events in the French cohort of 25 kidney transplant patients. 76% of patients had genotype 1 and 25% of

patients had baseline advanced liver fibrosis. The median time between the last renal transplantation and the initiation of DAA therapy was 146 months (range 1-329 months). In both studies, ribavirin was not commonly used, and when it was used, dose reductions for anemia and changes in estimated GFR were also required.[42,43]

Lin *et al.*[1] recently reported their findings from their historical review with prospective clinical follow-up of post-kidney transplant recipients treated with DAAs at three major hospitals in Boston, MA. A total of 24 kidney recipients with HCV infection received all-oral DAA therapy post-transplant. Median baseline creatinine was 1.2 mg/dL (range 0.66-1.76). 42% of patients had advanced fibrosis or cirrhosis, and 58% of patients had HCV genotype 1a infection. All patients received full-dose SOF; it was paired with SIM ± ribavirin, LDV ± ribavirin or ribavirin alone. The overall SVR at 12 weeks was 91%. Adverse events were reported in 46% of patients and were managed clinically without discontinuation of DAA therapy. In this multi-center study of kidney transplant patients, all-oral DAA therapy seems to be safe and efficient in post-kidney transplant recipients with chronic HCV infection.[1]

Very recently, Colombo *et al.* conducted a phase 2, open-label multicenter European RCT study of HCV treatment with LDV-SOF for 12 or 24 weeks in 114 kidney transplant patients with chronic HCV Virus genotype 1 or 4 (91% of patients had genotype 1 infection).[42] The median eGFR was 56 mL/min (range 35-135 mL/min). Treatment with LDV-SOF for 12 or 24 weeks was well-tolerated and appeared to have an acceptable safety profile among kidney transplant patients with HCV genotype 1 or 4, all of whom reached 100% SVR at 12 weeks. Severe adverse events were reported in 11% of patients (13 patients). Of these, three events including syncope, pulmonary embolism, and serum creatinine increase were reported in 3 patients and were determined to be DAA treatment related. One patient permanently discontinued treatment because of bradycardia leading to syncope, which was temporally associated with the coadministration of amiodarone. The most frequent unfavorable events were headache (19%), asthenia (14%), and fatigue (10%), respectively. [41]

Overall, these results are encouraging and providing confidence that SOF-based DAA therapy can be safely and efficiently used with excellent SVR in the kidney transplant recipients. However, the ideal timing for HCV treatment after kidney transplantation is still unclear. While achievement of HCV cure earlier in the post-transplantation course may have many theoretical benefits of reduction of HCV-related complications, including both hepatic or extra hepatic complications[33], these advantages need to be balanced with higher risk of rejection early after kidney transplantation due to the potential drug-drug interactions between DAAs and immunosuppression.[42,43]

Cautions and drug-drug interactions: daas and immunosuppressions

Based on existing knowledge, no absolute contraindications to the DAAs approved in the EU region in 2016 exist.[31] Nevertheless, SOF should not be used in patients receiving amiodarone who cannot switch to another therapy. Amiodarone is a well-known P-GP transport inhibitor, and SOF is somewhat cleared via the P-GP system. [44] A reduction in P-GP activity indicates patients taking amiodarone could be endangered to greater levels of SOF, which is thought to be the cause of bradycardia. Also, SOF should be used with caution in patients with CKD, especially eGFR <30 ml/min/1.73 m^2 without other treatment options, as the pharmacokinetics and safety of SOF derived metabolites in patients with severe renal dysfunction are still being ascertained. It has been confirmed that renal clearance is the major elimination pathway for GS-331007, which is the predominant circulating metabolite of SOF.[34]

Compared with those with normal kidney function, the risk of drug accumulation and incidence of adverse effects in patients with stage 4-5 CKD should be concerned. In fact, experience with SOF-containing regimens in patients with CKD (eGFR ≤ 45 ml/min/1.73 m^2) resulted in an increase in adverse outcomes including higher rates of anemia, worsening renal dysfunction and serious adverse events regardless of the use of ribavirin.[45] Whether these negative effects reflected the natural history of CKD in those treated or represented toxicity from SOF metabolites is currently unknown and pending more data from future studies. As mentioned prior, several other DAAs, such as GZR and EBR[36], DCV and asunaprevir[37,38], which were not eliminated by the kidney, have also been used for the treatment of HCV patients with stage 4-5 CKD.[34]

DAA treatment regimens comprising an NS3-4A protease inhibitor, such as SIM, PTV-r or GZR, should not be utilized in patients with Child-Pugh B decompensated cirrhosis or with compensated cirrhosis but with previous episodes of decompensation and are contraindicated in patients with Child-Pugh C decompensated cirrhosis, due to the considerably higher protease inhibitor levels in these patients. [31-34] Ribavirin is also commonly used in combination regimens of DAA therapy. Although ribavirin use is associated with anemia, as demonstrated in previous reports,[1,10,41,42] just a small number of patients who received ribavirin developed notable anemia, and these patients did not need any blood transfusion and their anemia improved after treatment.

In addition to the cost of DAA therapies[9], drug-drug interactions between DAA and immunosuppression need to be carefully considered [Table 2]. Various and complicated drug-drug interactions are conceivable with the DAAs. Thus, the potential for drug-drug interactions should be regarded in all patients undergoing treatment with DAAs. This requires a thorough drug-drug interaction risk assessment before starting therapy and before starting other medications during treatment.[31]

The CNIs including tacrolimus and cyclosporine, and the mammalian target of rapamycin (mTOR) inhibitors including sirolimus, and everolimus are typical components of modern immunosuppression. Both of these drug classes are substrates of cytochrome (CYP) P450 isoenzymes 3A4/5 [Table 2] and the drug transporter P-glycoprotein (P-gp). CNI levels have been shown to fluctuate during and even after DAA treatments are completed. Need for careful monitoring of kidney function and CNI drug levels both during and after therapy. While administration of SOF and/or DCV do not interact with CYP3A4/5 or P-gp and thus do not result in clinically significant DDIs with immunosuppressants, SIM, LDV, GZV/EBR and ombitasvir (OBV)/PTV-r do have significant interactions.[33] Additionally, immunosuppression levels could also decline with viral clearance, presumably reflecting improvements in hepatic function and enhanced the metabolism of CNI/mTOR inhibitor drugs. Sawinski *et al.*[42] reported that 45% of patients required dose adjustment of CNIs during DAA treatment. Both Sawinski *et al.*[42] and Kamar *et al.*[43] denoted that CNI levels lowered on and after DAA treatment, regardless of CNI dose alterations. These changes emphasize the need for close monitoring and dose adjustments of immunosuppression to minimize toxicity and avoid precipitation of rejection. Careful monitoring of immunosuppression levels is required to prevent either subtherapeutic or supratherapeutic immunosuppression.[42,43,46] Combined efforts by hepatologists and transplant nephrologists.[10]

Use of DAAs and use of HCV-positive kidneys

It is accepted that HCV-negative recipients should not receive HCV-positive, RNA-positive grafts because it negatively impacts morbidity and may also increase mortality. Over 6% of kidneys transplanted from 2001 to 2006 in the United States were from known HCV+ donors, resulting in the use of nearly 4800 kidneys that would have otherwise been discarded.[47] The KDIGO guidelines recommend utilizing kidneys

Table 2: Drug interactions between DAA against HCV and immunosuppression[10,31-33]

DAA	CYP3A4 inhibition
SIM	Yes
PTV-r	Yes
LDV	No
OBV	No
SOF	No
DBV	Yes

Drug-Drug Interactions							
Immunosuppression	SOF	SOF/LDV	SOF/VEL	3D	GZR/EBR	DCV	SIM
Antiproliferative							
Azathioprine	No	No	No	No	No	No	No
Mycophenolate	No	No	No	+	No	No	No
Calcineurin inhibitors							
Cyclosporine	No	No	No	+	*	No	*
Tacrolimus	No	No	No	+	+	No	+
Mammalian target of rapamycin inhibitors							
Everolimus	No	+	+	*	+	+	+
Sirolimus	No	No	No	+	+	No	+

No; no clinically significant interaction expected. +; potential interaction which may require dosage adjustment, altered timing of administration or additional monitoring. *; these drugs should not be co-administered

from HCV-positive donors for HCV-infected recipients due to the ongoing global organ shortage and to decrease the time on the waiting list[7] and accepting a kidney from an HCV-positive donor may decrease the waiting time for transplantation for the HCV-infected recipient by about one year.[6] It is usually limited to HCV-infected recipients with genotype 1. However, not every center accepts these HCV-positive kidneys due to the risk of super infection with other HCV genotypes, and genotype super infection is known to be associated with inferior patient and allograft survival compared to HCV+ recipients of kidneys from uninfected donors.[10] Thus, the safety of this approach is ideally by matching donors and recipients according to the HCV genotypes.[6] However, with emerging DAA treatment to cure HCV infection, there is currently no need to limit to genotype 1 infected recipient.

The use of DAAs affords HCV-infected candidates the option to accept kidneys from HCV+ donors.[10] This option may be particularly appealing for candidates with more limited expected post-transplant survival, those with limited health status that will likely result in their removal from the waiting list if they elect to wait longer for a kidney from an uninfected donor, or patients that are highly sensitized. Under this scenario, DAAs are initiated within the first few post-transplant weeks.

Recently, a reported case of successful transplantation of a kidney from a treated HCV-infected live donor (with SVR) in an uninfected recipient has constructed the proposal if this strategy should be considered (from either live or deceased donors), particularly with the emerging DAA treatments.[48] Accordingly, longitudinal investigations with close clinical and virologic monitoring of both live donors and recipients would be needed to examine the safety of such a strategy.

CONCLUSION

In summary, use of DAAs for the treatment of chronic HCV infection in patients with CKD, ESRD and after kidney transplantation is an active area of ongoing research. In developing new treatment algorithms for HCV-infected kidney transplant patients, it is important to consider whether viral eradication results in improved outcomes in candidates awaiting transplant as well as in kidney recipients. The prospects for treatment of HCV-infected CKD/ ESRD patients and kidney transplant recipients can only be contemplated to improve further. Future DAA combinations are expected to lessen the duration of HCV therapy but sustain high effectiveness and safety. Thus, for all HCV-infected patients with kidney diseases and kidney transplantation, the prospect favors brilliant that HCV infection will no longer be a contributor to poor kidney and patient outcomes in these patient population.

Author contributions

All authors had access to the data and a role in writing the manuscript.

Conflicts of interest

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