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Hepatitis C virus infection in kidney transplantation-changing paradigms with novel agents

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Abstract

Hepatitis C virus (HCV) is a common cause of increased morbidity and mortality in kidney transplant patients. It is associated with posttransplant glomerulonephritis, chronic allograft nephropathy, and New Onset Diabetes after Transplant (NODAT). In the past, HCV was difficult to treat due to the presence of interferon alpha-based therapies that were difficult to tolerate and were associated with adverse side-effects, such as the risk of rejection. With the advent of oral directly acting antiviral therapies, the landscape for HCV and transplantation has changed. These agents are highly effective and well tolerated with minimal side-effects. Sustained viral response rates in excess of 90% are achieved with most current treatment regimens active against all HCV genotypes. These new agents may show an improvement in graft and patient survival while essentially eliminating the risk of acute rejection from the use of prior interferon-based HCV therapies. These agents may also result in an improvement in organ allocation for HCV donor/HCV recipient transplantation. This review is meant to discuss the epidemiology of HCV, the new oral direct-acting antiviral agents (DAAs) and future opportunities for research in the field of HCV related transplantation.

Keywords

Hepatitis C; Kidney transplantation; immunosuppression

INTRODUCTION

Hepatitis C virus (HCV) is one of the most common chronic viral infections worldwide and remains challenging with a major health care impact.[1] In 2015, it was estimated that there were about 71 million individuals already infected with HCV and approximately 1.75 million new cases are expected to add to the disease pool annually.[2] This pattern is also

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reflected in the United States of America, where the incidence of HCV infection has doubled between 2010 and 2014.[3] While HCV-mediated diseases pose colossal problems in the general population, they present with a unique set of manifestations and complicate the management of organ transplant recipients.

According to the Global Observatory on Donation and Transplantation, 126,670 organs were transplanted in 2015 internationally and this is likely to grow as the number of transplanted organs increase.[4] HCV is a prevalent infection in transplant recipients. The prevalence of HCV infection in (kidney) transplant recipients varies from 5% to 50% in the developed world and varies according to factors such as the prevalence of HCV infection in dialysis units, the type of dialysis (Hemodialysis vs. Peritoneal dialysis), and the duration of dialytic therapy.[5–7]

In most instances, HCV infection in transplant recipients is acquired during the pre-transplant period.[7,8] In prospective renal transplant recipients, HCV complicates their course on dialysis and is associated with increased mortality and morbidity in end-stage renal disease (ESRD) patients.[7,9] It can result in the development of cirrhosis and related sequela as well as hepatocellular carcinoma in ESRD as well as posttransplantation.[10,11]

HCV treatment is complicated both in ESRD and renal transplant recipients. Historically, HCV has been difficult to treat in the ESRD population due to several reasons including intolerable side-effects, the lack of oral regimens, poor efficacy of regimens, and complications such as symptomatic anemia with the use of some anti-HCV agents such as ribavirin.[9,12] In the transplant population, HCV regimens were complicated by an increased risk of acute rejection and were associated with worse graft and patient survival. This was predominantly due to the existence of interferon alpha-based therapies that had intolerable side-effects that limited patient compliance as well as an increased risk of acute graft rejection.[7,9,12,13] Nonetheless, the landscape of HCV therapy changed with the emergence of direct-acting antiviral (DAA) therapies. These agents specifically target HCV viral replication without affecting host immunity and are thus well suited to the treatment of a posttransplant population. In general, these regimens are well tolerated with minimal side-effects and typically require 8–24 weeks of treatment.[9,12,13] Clinical trials and large scale observational studies have supported their efficacy by demonstrating sustained viral response (SVR) rates of >95% across all HCV genotypes in the general population.[12]

DAAs are well tolerated in the posttransplant population with similar rates of SVR without the risk of precipitating acute rejection. These DAA agents have also resulted in an expanded pool of potential organ donors such as HCV positive donor kidneys for transplantation and could lead to improved outcomes for HCV-infected patients. Overall, the advent of DAAs has essentially revolutionized the management of HCV in transplant patients, which remains the focus of the current review. Here, we will summarize the different anti-HCV agents including interferon-based therapies and DAAs in kidney transplant recipients, the role of DAAs in HCV mismatch transplantation and will provide recommendations for current management based on the existing literature and highlight areas for future research.

THE NATURAL HISTORY OF HCV INFECTION AND OUTCOMES IN KIDNEY TRANSPLANT RECIPIENTS

HCV infection has direct associations with adverse outcomes in kidney transplant recipients.[14–16] It is associated with an increased risk of acute rejection, chronic allograft nephropathy (CAN), new onset diabetes after transplantation (NODAT) as well as other known syndromes such as HCV-associated cryoglobulinemic vasculitis, membranoproliferative glomerulonephritis and membranous nephropathy following kidney transplantation.[13,14] A study by Mahmoud et al. suggested that HCV-infected transplant recipients with chronic alanine aminotransferase level elevations have an increased risk of graft failure (odds ratio, 3; 95% confidence interval [CI], 1.4–6.7) compared with viremic transplant recipients with persistently normal liver function test results as well as noninfected patients.[15] They also demonstrated that the risk of CAN was 40.6% in HCV viremic patients compared to 5.6% in patients (successfully) treated with interferon prior to renal transplantation (P50.009). HCV viremic kidney transplant recipients also have a significantly greater frequency of proteinuria, and biopsy-proven CAN compared with noninfected transplant recipients.[15,17,18] A meta-analysis of just over 30,000 transplant recipients showed a marked increase in posttransplant diabetes in renal transplant recipients with HCV (relative risk [RR] 2.73 95% CI of 1.94–3.83) suggesting a potential contribution to the increased insulin resistance.[19]

Further, it is believed that the immunosuppression associated with transplant regimens can lead to clinical progression of HCV infection after kidney transplantation. This can result in an acute on chronic flare of hepatitis, and an increased risk of cirrhosis as well as hepatocellular carcinoma after transplantation. Also, HCV infection in renal transplant recipients impacts mortality.[17] HCV-infected transplant recipients with chronic alanine aminotransferase level elevations have an increased risk of death (odds ratio, 3.7; 95% CI, 1–13.7).[15] A recent meta-analysis demonstrated an adjusted relative risk for all-cause mortality of 1.85 in kidney transplant recipients with HCV infection when compared to HCV uninfected kidney transplant recipients.[18,20–22] Liver disease, cardiovascular disease, and infectious complications accounted for the top 3 causes of death.

Despite these risks, it is still recommended that ESRD patients with HCV undergo transplantation due to an improvement in mortality for HCV-infected kidney transplant recipients compared with those remaining on the waiting list while undergoing maintenance hemodialysis.[23] In fact, the current KDIGO guidelines recommend that anti-HCV positive donor kidneys be transplanted to HCV RNA positive recipients. This practice shortens the waiting time for HCV-positive kidney transplant candidates without an increase in the rate of allograft rejection, infectious complications, graft loss, or mortality.

THE HISTORY OF HCV THERAPY: INTERFERON ALPHA AND RIBAVIRIN

In the past, interferon-based regimens constituted the standard-of-care to treat HCV infections. However, they all suffered from several limitations such as neuropsychiatric and flu like symptoms, exacerbation of autoimmune diseases, poor efficacy, and increased the risk of acute graft rejection in transplant recipients. Interferon often required combination

with ribavirin, which is associated with a dose dependent hemolytic anemia. Since ribavirin is renally excreted, its use in patients with chronic kidney disease is severely limited.

A recent meta-analysis of interferon monotherapy in 140 kidney transplant recipients revealed a dismal HCV cure rate (less than 15%), which increased to 33% when combined with ribavirin.[24] However, this success was severely off set by poor patient compliance. Over 1 in 5 patients dropped out due to side-effects, the most common being graft dysfunction. One in 14 patients developed rejection on interferon therapy.[24,25] Interferon therapy is difficult to tolerate and data suggest that less than 5% of waitlisted ESRD patients with HCV ever received interferon-based therapy with only 1% internationally receiving interferon.[26,27] As a result, interferon-based therapy is currently only used in rare instances.[28]

DIRECT-ACTING ANTIVIRAL AGENTS:THE HERE AND NOW OF HCV THERAPY

DAAs were designed to target viral proteins involved in HCV replication. Several agents targeting 1 of 3 viral proteins have been identified. These include inhibitors of the NS3–4A protease, NS5A replication complex inhibitors and NS5B polymerase inhibitors. All currently recommended regimens include at least 2 agents of different classes, usually a NS5A inhibitor combined with a more potent polymerase inhibitor or a protease inhibitor. In some instances the addition of ribavirin is recommended for the management of difficult to treat sub-populations. In a study of 47 renal transplant recipients, 12–24 weeks of treatment led to SVR of greater than 90% in most cases. The only serious adverse effect was anemia in patients receiving ribavirin (8 patients).[12]

FDA approved HCV treatment regimens are shown in Table 1. Sofosbuvir-based regimens (sofosbuvir/ledipasvir or sofosbuvir/velpatasvir) are highly effective, well tolerated and have relatively few drug-drug interactions including immunosuppressive agents. Sofosbuvir has a very high barrier to resistance and is active against all HCV genotypes. Since sofosbuvir and its metabolites are renally cleared, it is not recommended in patients with a GFR <30 mL/min/1.73 m^2 and has been associated with increased proteinuria, collapsing glomerulopathy and with decrease in GFR.[34] This limits its use in prekidney transplant, or immediate posttransplant patients until graft function improves. As a result, it has been used extensively several months postkidney transplant once eGFR is >30 mL/min/1.73 m^2.

Protease inhibitor-based regimens include glecaprevir/ pibrentasvir and elbasvir/grazoprevir. The former has pangenotypic activity while the latter is limited to use in patients with HCV genotypes 1 and 4. These agents are hepatically metabolized and can be used safely in patients with advanced chronic kidney disease including those on renal replacement therapy (Expedition 4 trials and C-Surfer, respectively).[29,42]

Currently, increasing evidence support the safety and the efficacy of treatment of HCV in Chronic Kidney Disease4–5 and ESRD patients and particularly in pre and posttransplant patients with minimal side-effects.[43–47] Virtually, all patients with HCV can be treated with DAAs. The few patients who fail to achieve SVR after the use of the first generation of

agents can be successfully treated with newer, more potent combinations including glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir. Ribavirin is combined with DAAs in some instances, specifically when treating HCV liver-kidney transplants or in patients with decompensated cirrhosis.[34]

DAAS IN KIDNEY TRANSPLANT RECIPIENTS: CURRENT EXPERIENCE AND SAFETY

There are 3 prospective trials involving DAAs in kidney transplant recipients and several retrospective studies documenting the efficacy of therapy in these patients. These studies are reviewed in Table 1 and we emphasize a few important trials with each of the major regimens.[12,29–41]

Colombo et al. conducted a randomized, phase 2 open label trial where 114 adult patients, at least 6 months postkidney transplant with baseline eGFR >40 mL/min/ 1.73 m^2 received sofosbuvir/ledipasvir 400 mg/90 mg combination therapy for either 12 or 24 weeks.[32] The patients had HCV genotype 1b (75%), 1a (16.5%) or 4 (8.5%) only. They were a median of 53 years of age, 58% male and 15% had compensated cirrhosis. Hundred percent of patients in both arms achieved SVR. The most frequent adverse events were headache (19%), asthenia (14%), and fatigue (10%) Serious adverse events were reported in 13 patients (11%), of which 3 events—syncope, pulmonary embolism, and serum creatinine increase to CKD Stage 5 were determined to be treatment related. Although 19% of patients required dose adjustment in their immunosuppressive medications, it is unclear if this was potentially related to DAA treatment and related improvement in hepatic function.

Reau et al. conducted an open label, multinational, multicenter Phase 3B study (MAGELLAN-2) to investigate the safety and efficacy of glecaprevir/pibrentasvir in chronic HCV infection without cirrhosis in liver and kidney transplant recipients.[29] They used glecaprevir/pibrentasvir at a dose of 300 mg/120 mg for 12 weeks and included all HCV genotypes (although they were unable to recruit HCV 5 genotype patients). In the cohort of 100 patients, 78% were white, 75% male, the median age was 60 years, and the median time following transplantation was 55.6 months. Only 20 patients of the full cohort were kidney transplant recipients. SVR was achieved in 99% of patients overall and 100% of the kidney transplant recipients. Otherwise, serious adverse events were rare (8/100 patients). Adverse events that occurred more commonly were headache (22%), fatigue (22%), nausea (12%), pruritic (12%), and diarrhea (10%).[29]

The previous 2 trials described were in transplant recipients with eGFR>30 mL/min/1.73 m^2 who are chronically infected with HCV. Little data exists on the use of DAA in kidney transplant patients with eGFR <30 mL/min/1.73 m^2 and in acute hepatitis C infection. Another prospective pilot trial is focusing on the use of DAAs in acute hepatitis C through transplantation of HCV positive donor kidneys into HCV negative recipients. Goldberg et al. have published the initial results of an open-label, single center, prospective trial of elbasvir/grazoprevir immediately posttransplantation for HCV negative recipients who elected to receive an HCV genotype 1 infected kidney, the THINKER trial with a pilot of 10 patients.[41] All recipients had detectable HCV viral RNA on day 3 after transplantation. The median

age was 59, half the recipients were men and 2 were black. Median waiting time was 58 days. One recipient had delayed graft function, 2 had elevated aminotransferase levels, 1 had a transient new class I donor-specific antibody level and 1 patient with IgA nephropathy developed proteinuria (2 g/ day) with FSGS on biopsy. All 10 patients achieved SVR with no drug-related serious adverse events reported. This study provides indirect preliminary evidence for the use of DAAs with eGFR <30 mL/min/1.73 m^2.

In addition to the above prospective trials, several centers have retrospective experience with DAAs with a total of 321 liver and renal transplant recipients (see Table 1).[12,29–41] The majority of patients received sofosbuvir regimens several months to years posttransplantation with an eGFR >30 mL/min/1.73 m^2. To date, only 7 failures were reported in the retrospective data, with 2 of them being retreated with next generation DAA regimens and subsequently achieving SVR.[29–33,35–38,40,48] These retrospective studies reported anemia in 11% of patients, largely attributed to the use of ribavirin.

DAAS AND CALCINEURIN INHIBITORS: INTERACTIONS AND MONITORING

While the DAAs are associated with few side-effects, data on their potential interactions with calcineurin inhibitors is still limited (see Table 1). The elbasvir/grazoprevir and simeprevir/sofosbuvir regimens are contraindicated in patients treated with cyclosporine as the combination results in unpredictably high levels of these DAAs through inhibition of various enzymes such as CYP3A, OATP1B1/3 and BCRP.[38,49] However, the elbasvir/ grazoprevir and simeprevir/sofosbuvir regimens can be used with tacrolimus but require close monitoring of tacrolimus levels, as grazoprevir may result in a 40%–50% increase in tacrolimus levels.[50] The glecaprevir/pibrentasvir regimen is not recommended in patients treated with cyclosporine doses greater than 100 mg, but this regimen may be used in tacrolimus-treated patients with close monitoring of therapeutic drug levels. Daclatasvir/ sofosbuvir and ledipasvir/ sofosbuvir regimens have not been associated with significant impact on the area under the curve of either calcineurin inhibitor but close monitoring of levels is still recommended. Currently, insufficient data exists on the impact of the velpatasvir/sofosbuvir regimen on calcineurin inhibitor levels but as with other DAA regimens, close monitoring of drug levels is advised.

In the studies reviewed above, acute allograft rejection was reported in 7 kidney transplant recipients.[27–38,40,42–48] Approximately 36% of patients required calcineurin inhibitor dose adjustments during or shortly after DAA therapy; however, whether this is a direct effect of DAA is still unknown.[27–38,40,42–48] Nevertheless, we recommend close monitoring of calcineurin inhibitor levels during and shortly after DAA therapy until further evidence is available.

TIMING OF ANTI-HCV THERAPY IN TRANSPLANTATION

Currently the optimal timing of therapy for kidney transplant candidates and recipients remains uncertain. We will first discuss the issues of whether treatment should be performed before or after transplantation and subsequently the timing of treatment following transplantation.

With DAAs, patients can achieve SVR rates of 94%–100% prior to transplantation with minimal adverse effects, particularly if ribavirin is avoided.[46,51] However, debate continues about the timing of DAA therapy in these patients. Currently, waiting until after a kidney transplant allows patients the opportunity to accept an HCV positive kidney which can reduce wait time and wasting of organs and will lower the health care costs of managing patients on dialysis.[52] For example, in 2010, the wait time of an HCV positive recipient was reduced by 310 days by accepting an HCV positive donor kidney compared to the generally considerably longer wait time on the non-HCV waiting list.[53] Currently, many centers that utilize HCV positive donors have wait times of less than 6 months for kidney transplant candidates willing to accept an HCV positive donor kidney. This in part, is due to the increase in HCV positive deceased donors secondary to the opioid overdose epidemic.[54] Thus, it is often beneficial for HCV positive patients to wait until after transplantation to receive therapy. Patients who receive therapy prior to transplantation do so due to personal preference, risk of progression of liver disease, or other HCV related complications such as vasculitis.

The timing of treatment in patients selected for treatment after transplantation is uncertain. Currently, most patients are treated months to years after transplant because of the only recent availability of DAA and previously no effective and safe treatment options. Currently, some centers delay HCV treatment for approximately 6 months after transplantation to confirm stability of kidney function and calcineurin inhibitor dosing. This is done so because retrospective data has suggested that up to 1/3rd of patients have required dose adjustment of their immunosuppressive regimen to remain within therapeutic range.[48] However, some studies have demonstrated a decline in proteinuria in kidney transplant patients following SVR, suggesting the potential for short and long-term improvement in graft survival.[48] This finding suggests that earlier treatment might offer a greater benefit by limiting HCV-associated glomerular disease. In addition, early treatment might prevent HCV-associated NODAT which often develops within 6 months of transplantation.[55,56] Thus, there may be a case for the earlier use of anti-HCV treatment after renal transplantation.

CONCLUSION

There are several potential areas for future research in this field. First, the optimal regimen for patients with eGFR <30 mL/min/1.73 m^2 is not clearly defined. Sofosbuvir is not approved in this setting, but studies are ongoing to determine if there is a role for sofosbuvir with advanced CKD.[51] Such a study in the transplant population would expand the use of sofosbuvir to the immediate posttransplantation period.

Glecaprevir/pibrentasvir requires cyclosporine monitoring but has not been reported to require tacrolimus dose adjustment. Thus, it may be more useful in patients on tacrolimus as a pangenotypic agent and would be another area of interest that requires further study.[29]

There is currently a prospective study of a pangenotypic sofosbuvir-based regimen (sofosbuvir+velpatasvir; NCT02781571) in liver transplant recipients to address the question of the safety and efficacy of pangenotypic agents in this population. A similar prospective

study of sofosbuvir+velpatasvir in renal transplant recipients would be needed to address its safety in renal dysfunction as well as monitoring of immunosuppression.

Like the general population, chronic HCV viremia is curable in ESRD and renal transplant patients with the advent of DAAs with >95% success and minimal side-effects. While there are clear short-term benefits, studies are warranted to confirm the long-term benefits of HCV therapy on graft and patient survival, and reduced predilection to chronic liver disease. A concerted effort is needed to determine the optimal timing for HCV therapy in renal transplant patients. Overall, we are the cusp of a major change in anti-HCV therapy, where agents such as DAAs allows expansion of the donor pool and novel strategies to improve organ matching and reduce discard rates of organs.

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Table 1

FDA approved regimens with data in kidney and liver transplant patients

Regimen	Mechanism of action	Genotype	Dosage	Data in transplant recipients	Comments	CNI dose adjustment	Contraindications
Daclatasvir + Sofosbuvir	NS5A inhibitor + NS5B polymerase inhibitor	1,3	60 mg + 400 mg for 12 wks	Single prospective trial with 20 kidney transplant and 80 liver transplant recipients[29]	Can be used in cirrhotics	No dose adjustments reported	Sofosbuvir contraindicated in eGFR <30 mL/ min/1.73 m^2
Velpatasvir + Sofosbuvir	NS5A inhibitor +polymerase inhibitor	1–6	100 mg + 400 mg for 12 wks	No published data. 79 liver transplant patients under trial (NCT02781571)	Can be used in decompensated cirrhosis	No data	
Ledipasvir + Sofosbuvir	NS5A inhibitor + NS5B polymerase inhibitor	1	90 mg + 400 mg for 12 wks	Prospective trials with combined sample size of 210 [12,30–33] and retrospective data of 105 patients[34–39] (53 with ribavirin)	Preferred regimen for genotype 1 HCV in liver transplant ± ribavirin	No dose adjustments reported	
Simeprevir + Sofosbuvir	NS3/4A protease inhibitor + NS5B polymerase inhibitor	1,4	150 mg + 400 mg daily for 12 wks	Retrospective studies with combined sample size of ~37 patients with 7 of those patients on ribavirin[30,34,35,38,40]	Studied for use in cirrhosis	Not used with cyclosporine; acceptable use with tacrolimus but must monitor levels	
Glecaprevir + Pibrentasvir	NS3/4A protease inhibitor + NS5A inhibitor	1–6	300 mg + 120 mg for 8–12 wks	Single prospective trial with 20 kidney transplant and 80 liver transplant recipients[29]	Can use shorter 8 wk course if no cirrhosis; Not studied in decompensated cirrhosis	Cyclosporine levels increased; No tacrolimus dose adjustment	Okay to use with advanced kidney disease including patients on dialysis
Elbasvir + Grazoprevir	NS5A inhibitor + NS3/4A protease inhibitor	1,4	50 mg + 100 mg for 12 wks	10 patients in prospective trial (genotype 1)[41]	FDA approved for immediate posttransplant use in clinical trials (THINKER Trial)	Not used with cyclosporine; acceptable use with tacrolimus but must monitor levels	Safe and effective in ESRD
Telaprevir	NS3/4A protease inhibitor	1	Discontinued in 2014 after newer agents were developed				