Kidney360

Curative Therapies for Hepatitis C Virus Infection in Patients with Kidney Disease

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Abstract

Through the discovery of direct-acting antiviral therapies over the last decade, hepatitis C virus (HCV) has been transformed from a highly morbid and potentially fatal chronic viral infection to a curable illness. HCV is common in patients with kidney disease, is a risk factor for progression of CKD, is associated with higher morbidity and mortality in patients receiving dialysis, and leads to worse allograft and patient outcomes in recipients of kidney transplants. Clinical trial and real-world data of direct-acting antivirals in patients with kidney disease demonstrate extremely high cure rates and favorable adverse event profiles. This review covers the transformative effects of curative HCV therapies on patients with kidney disease, including patients with CKD, ESKD, and those who have received a kidney transplant.

KIDNEY360 2: 1316–1325, 2021. doi: https://doi.org/10.34067/KID.0001812021

Introduction

Untreated hepatitis C virus (HCV) infection is a major cause of chronic and end stage liver disease in both the developed and developing world. Beyond causing liver disease, HCV can affect multiple organ systems and is both a cause and complication of CKD. In fact, up to 10% of the patients infected with HCV in the United States have CKD (1). HCV infection also has important implications for patients with ESKD and recipients of kidney transplants (Figure 1). Direct-acting antiviral (DAA) therapies for HCV, which have been discovered and widely deployed over the last decade, have rapidly changed HCV from a chronic, potentially deadly disease to a readily curable illness. A recent, large, prospective cohort study of nearly 10,000 patients showed that DAAs decreased all-cause mortality and hepatocellular carcinoma risk (2). This review covers the far-reaching effect of curative HCV therapies on patients with kidney disease.

Evolution of Modern DAA Treatments for HCV

Historically, HCV drug therapy depended on the combination of IFN-α, in standard form or pegylated form, and ribavirin. IFN and ribavirin-based therapies required 6–12 months of treatment with suboptimal efficacy (<50%) and commonly resulted in severe side effects, including neuropsychiatric changes, hematologic abnormalities, flulike symptoms, and autoimmune toxicities (3–6). In 2011, the first-generation DAAs, boceprevir and telaprevir, were approved in combination with ribavirin; however, despite increased effectiveness, these medications were poorly tolerated (7–10). Boceprevir and telaprevir were quickly supplanted by sofosbuvir, a nonstructural protein 5B (NS5B) polymerase approved in 2013, which was paired with ribavirin and led to outstanding cure rates and significantly fewer side effects (11,12). Quickly, the field moved to combination DAA therapies; by pairing agents that target multiple components of HCV's replicative machinery, including HCV's NS3/4A protease, NS5A protein, and NS5B polymerase, combination DAA therapy can overcome resistance (Figure 2). Combination DAA therapy allows for IFN- and ribavirin-free regimens and are extremely well tolerated. Because DAAs do not rely on the host immune response, they have demonstrated outstanding cure rates across essentially all previously difficult-to-treat populations, including patients who are immunosuppressed due to organ transplantation or HIV coinfection.

DAAs are largely considered non-nephrotoxic, with large series showing extremely low rates of AKI attributed to DAA therapy (13). However, small case series have linked DAA use with lupus-like GN and podocytopathies, and there have also been case reports of acute interstitial nephritis (14–17). However, these rare reports should not deter the use of DAAs in patients with CKD.

DAAs in Patients with an eGFR of <30 ml/min per 1.73 m^2

Sofosbuvir, the first modern DAA, is a uridine nucleotide analogue prodrug whose active metabolite inhibits HCV's NS5B polymerase and is active against all genotypes of HCV (18). Because sofosbuvir and its active metabolite are renally eliminated, patients with an eGFR of <30 ml/min per 1.73 m^2 were excluded from the initial registrational trials of all sofosbuvir-based DAA combinations. The first DAA combination studied in patients with advanced CKD and ESKD was grazoprevir (NS3/4A protease inhibitor) combined

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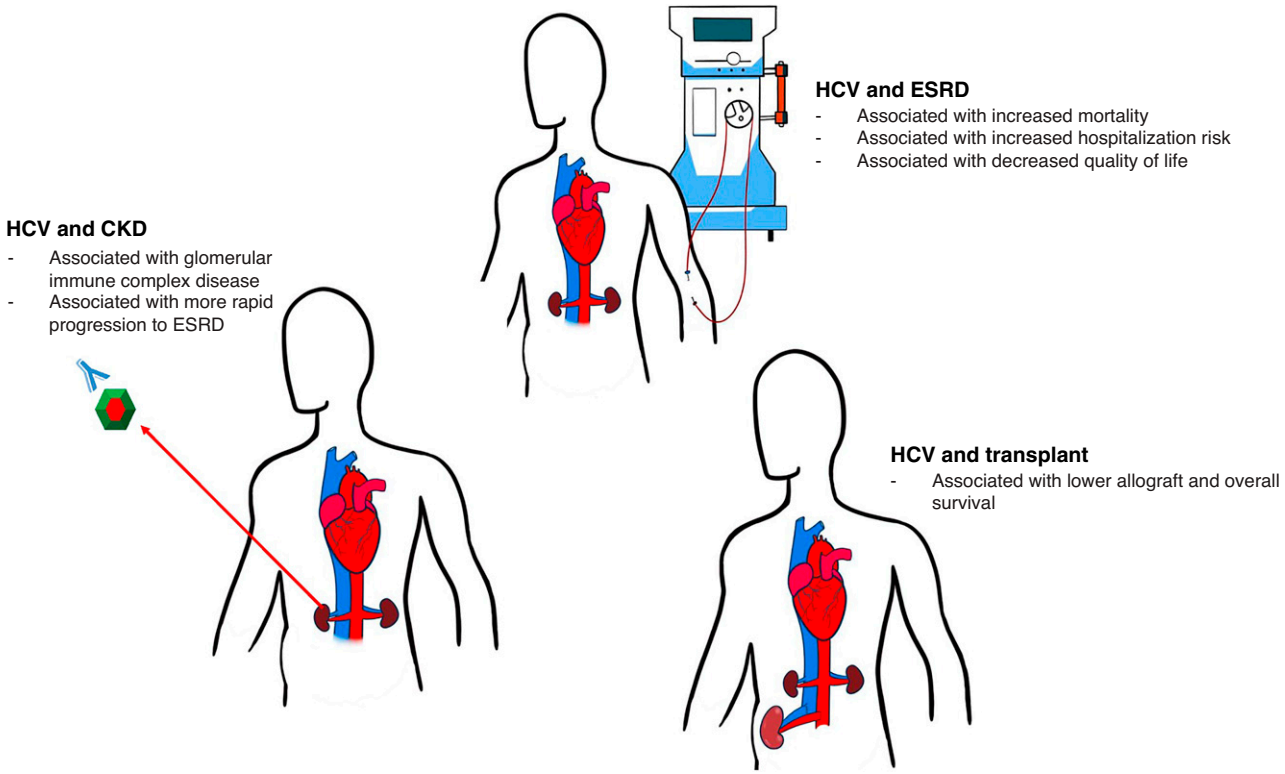

Figure 1. | **HCV and kidney disease.** HCV, hepatitis C virus; ESRD, end-stage renal disease; CKD, chronic kidney disease.

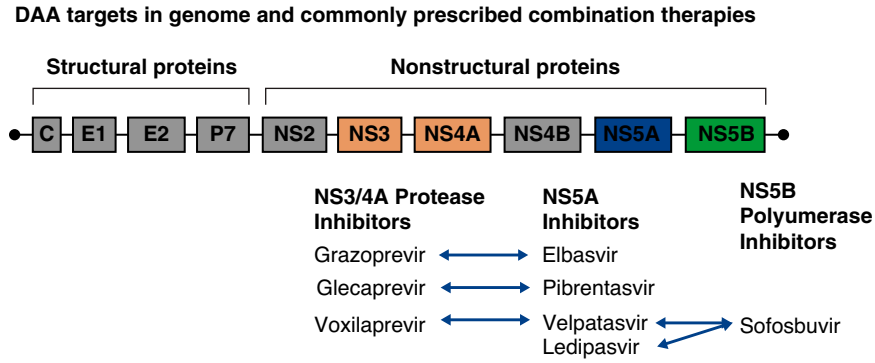

Figure 2. | **DAA targets in genome and commonly prescribed combination therapies.** Combination DAAs pair agents from two or three classes. Two-drug combinations include sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, elbasvir/grazoprevir, and glecaprevir/pibrentasvir. Three-drug regimens (for prior treatment failures) include sofosbuvir/velpatasvir/voxilaprevir. Up-to-date HCV treatment recommendations can be found at HCVguidelines.org. DAA, direct-acting antiviral; NS2, nonstructural protein 2; C, core protein; E1, envelope glycoprotein 1; E2, envelope glycoprotein 2; P7, P7 ion channel protein.

with elbasvir (an NS5A inhibitor). Both of these agents are hepatically metabolized, and their exposure in patients with kidney failure is not substantially increased. The C-SURFER (Hepatitis C: Study to Understand Renal Failure's Effect on Responses) stu dy, published in 2015, was a phase 3 trial that enrolled 235 patients with genotype 1 HCV infection and CKD stage 4 or 5 or those on dialysis (19). Sustained virologic response at 12 weeks (virologic cure) was 94%. The most common adverse events were headache, nausea, and fatigue, occurring at similar frequencies in patients receiving active and placebo drugs. Two trials in the advanced CKD and dialysis population using glecaprevir and pibrentasvir (a hepatically metabolized NS3/4A protease and NS5A inhibitor combination that treats all genotypes of HCV infection) have also shown outstanding cure rates and excellent safety profiles in patients with kidney failure, with no treatment-related severe adverse events in either trial (20,21).

Despite early concerns about accumulation of sofosbuvir and its active metabolite (22), multiple "real-world" studies showed that sofosbuvir-based DAAs were effective and

Table 1. Clinica l trials involving DAAs in patients with an eGFR of <30 ml/min per 1.73 m^2 or those on dialysis and in recipients of kidney transplants

Trial	Regimen	Number Enrolled, Study Design	Patient Population	HCV Cure Rate (%)	Overall SAE Rate
C-SURFER; Roth *et al.* (19)	Elbasvir/grazoprevir	235, randomized controlled trial	CKD 4/5, ESKD	94	14% in immediate treatment group; 17% in deferred treatment group (no SAE considered treatment related in immediate treatment group; treatment-related SAE in deferred treatment group was increased lipase)
Expedition-4; Gane *et al.* (20)	Glecaprevir/pibrentasvir	104, single arm	CKD 4/5, ESKD	98	24% SAE, none treatment related
Expedition-5; Lawitz *et al.* (21)	Glecaprevir/pibrentasvir	101, single arm	CKD 3b/4/5, ESKD	97	12% SAEs, none treatment related
Borgia *et al.* (26)	Sofosbuvir/velpatasvir	59, single arm	ESKD	95	19% SAEs, none treatment related
Chuang *et al.* (46)	Sofosbuvir/ledipasvir	95, single arm	ESKD	94	13% SAEs, none treatment related
Colombo *et al.* (56)	Sofosbuvir/ledipasvir	114, randomized, open-label study	Transplant recipients, eGFR ≥40 ml/min per 1.73 m^2	100	11% SAEs (three treatment-related SAEs: syncope, pulmonary embolism, and serum creatinine increase)
Reau *et al.* (57)[a]	Glecaprevir/pibrentasvir	20 kidney transplants, single arm, open label	Transplant recipients, no eGFR cutoff	100	8% in overall cohort (n=20 kidney transplants, n=80 liver transplant; two treatment-related SAEs—sinusitis and abnormal hepatic function)

DAA, direct-acting antivir al; HCV, hepatitis C virus; SAE, serious adverse event; C-SURFER, Hepatitis C: Study to Understand Renal Failure's Effect on Responses; Expedition-4, A Study to Evaluate the Efficacy and Safety of ABT-493/ABT-530 in Renally Impaired Adults With Chronic Hepatitis C Virus Genotype 1 - 6 Infection; Expedition-5, A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Glecaprevir/Pibrentasvir in Renally-Impaired Adults With Chronic Hepatitis C Virus Genotype 1 - 6 Infection.

[a]In this study, overall cohort was n=100, out of which 80 patients had liver transplant and 20 patients had a kidney transplant. The HCV cure rate was 20 out of 20 for patients with a kidney transplant, and the SAEs were 8% for the overall cohort.

well tolerated in the dialysis populations (23,24), and other analyses showed extremely low rates of kidney injury in patients receiving sofosbuvir-based DAAs (13,25). In 2019, the results of two clinical trials of sofosbuvir-containing therapies, conducted in patients with ESKD on dialysis, demonstrated outstanding safety and efficacy and ultimately led to expansion of the Food and Drug Administration label for sofosbuvir-based DAAs to include patients with all levels of kidney function, including those with dialysis dependence (Table 1). The first was a phase 2, open-label study of 95 patients on dialysis who were treated with sofosbuvir and ledipasvir for 12 weeks, in which 89 patients (94%) were cured. Another was a study of sofosbuvir/velpatasvir in 59 patients on dialysis, in which 56 patients (95%) were cured (26). In both trials, there were no treatment-related serious adverse events.

Current treatment guidelines, endorsed by the American Association of Liver Disease (AASLD) and Infectious Diseases Society of America, are available at HCVguidelines.org. Guidelines recommend the use of a pan-genotypic regimens when possible, with no dose adjustments needed for kidney disease.

HCV and CKD

HCV infection is a major cause of mixed (type II) cryoglobulinemia syndrome, a systemic vasculitis characterized by involvement of small to medium-sized vessels that causes palpable purpura, neuropathy, arthralgia, and GN. The pathogenesis of HCV-triggered mixed cryoglobulinemia syndrome is hypothesized to be due to chronic stimulation of B lymphocytes, with excess production of autoantibodies and cryoglobulins. Cryoglobulinemic GN may result due to the affinity of IgM rheumatoid factor for cellular fibronectin in the mesangial matrix. Immune complex deposition leads to complement activation, inflammatory cytokine release, vasculitis, fibrinoid necrosis, and crescent formation. Kidney biopsy specimens demonstrate a membranoproliferative pattern of injury with mesangial hypercellularity and expansion, endocapillary proliferation, monocytic infiltration, thickened capillary loops, large eosinophilic, and intraluminal deposits showing positive staining for Periodic acid–Schiff, which are referred to as "pseudothrombi" because they may fill the entire capillary lumen. Vasculitis of small and medium-sized renal arteries is present in some cases. Immunofluorescence typically shows C3, IgM, and IgG granular deposits in the capillary wall and mesangium. The subendothelial deposits seen on electron microscopy may have tubular and crystalline patterns typical of cryoglobulinemia. Clinical manifestations of GN range from asymptomatic microscopic hematuria to AKI from rapidly progressive GN, or even nephrotic syndrome. Laboratory evaluation demonstrates marked hypocomplementemia, with a greater reduction in C4 than C3, and the majority of patients have an elevated rheumatoid factor. Despite the fact that cryoglobulinemic GN is only found in approximately 1%–2% of patients with HCV, biopsy and autopsy series in patients with advanced liver disease have shown that subclinical glomerular abnormalities are actually much more common, found in >50% of patients with HCV (27,28).

Because IFN- and ribavirin-based therapies for HCV were rarely efficacious in curing HCV in patients with cryoglobulinemic GN, it was customary that rituximab and corticosteroids were used to treat HCV-related cryoglobulinemic GN. However, given that multiple studies have shown the DAAs are efficacious in patients with cryoglobulinemic GN (29,30), the Kidney Disease Improving Global Outcomes guidelines now recommend that DAAs be used as first-line treatment for cryoglobulinemic GN and that immunosuppression with rituximab-based therapy should be reserved for patients with severe manifestations of vasculitis (rapidly progressive GN, pulmonary hemorrhage) or those with persistent GN after completing DAAs (31). It is important to note that *de novo* cryoglobulinemic GN can occur after cure of HCV with DAAs, although the incidence is rare (32). In this instance, rituximab-based immunosuppression treatment should be used.

Various other histologic types of kidney diseases are reported in association with HCV infection, including membranous nephropathy, FSGS, fibrillary GN, immunotactoid GN, IgA nephropathy, thrombotic microangiopathy, renal vasculitis, and interstitial nephritis (33–35). The effect of DAAs on these lesions is less well studied.

Beyond causing glomerular disease, HCV is associated with an increased risk of progression to ESKD in patients with CKD. Population studies in multiple settings have highlighted this important association, particularly in patients with HIV coinfection (33,36–38). This is likely due to systemic effects of HCV, which include promoting immune activation, worsening insulin resistance, and accelerating atherosclerosis, each of which could affect the development and progression of CKD. Recent data suggest that DAAs therapy may slow eGFR decline in patients with CKD and decrease the risk of ESKD (13,25). Two recent studies have highlighted the importance of curing HCV to stabilize or improve eGFR in patients with HCV (39,40).

HCV and Dialysis

HCV infection is more commonly seen in patients on dialysis than in the general patient, it is estimated to be three-fold higher than the general population (41). Patients on dialysis may be more likely to acquire HCV from blood transfusions, prior transplantation, prior or current intravenous drug use, and nosocomial infection. Dialysis vintage is associated with risk of HCV infection in patients on dialysis (41). Unfortunately, even in the current era, breakdown in infection control practices and universal precautions have led to HCV outbreaks in dialysis centers (42,43). Patients on dialysis infected with HCV have high mortality rates, and are six times more likely to die of liver disease; they are also more likely to be hospitalized and have lower quality-of-life scores (44) Historically, only 1% of patients on dialysis received treatment for HCV infection due to the low response rate and poor tolerability of IFN- and ribavirin-based therapies (45). However, DAAs have now prospectively been studied in patients on dialysis (Table 1) and are safe and efficacious (19–21,26,46). Nephrologists who manage patients on dialysis must identify HCV infection and advocate for their patients to undergo treatment, because the current AASLD guidelines suggest that anyone with >1 year life expectancy

Table 2. Clinical trials involving DAAs in transplant recipients without HCV who have received kidneys from donors with HCV

Trial	Regimen	Number Enrolled, Study Design	Timing of DAA	HCV Cure Rate (%)	Study Notes
THINKER-1; Goldberg *et al.* (72)	Elbasvir/grazoprevir	10, single arm	POD3	100	1 case of FSGS (proteinuria adjudicated as being possibly related to HCV and with substantial improvement after treatment)
THINKER-2; Reese *et al.* (71)	Elbasvir/grazoprevir	10, single arm	POD3	100	5 DGF (THINKER-1 group); 1 treatment failure with successful retreatment with DAAs
EXPANDER; Durand *et al.* (61)	Elbasvir/grazoprevir (sofosbuvir if not genotype 1 or 4)[a]	10, single arm	Preoperative	100	No AEs related to treatment
Sise *et al.* (69)	Elbasvir/grazoprevir	8, single arm	Preoperative	100	1 immediate graft failure, 3 DGF
Durand *et al.* (67)	Glecaprevir/pibrentasvir[b]	10, single arm	Preoperative	100	1 graft failure
Sise *et al.* (68)	Glecaprevir/pibrentasvir	30, single arm	POD3	100	3 acute rejection within first 6 months, 7 DGF
Terrault *et al.* (64)	Sofosbuvir/velpatasvir	11, single arm	Started once viremia detected, median POD17	100	2 with delayed graft function, 3 with transaminase elevations 4–7× ULN; 10 were treated with DAA (1 never developed viremia); included liver and kidney transplants
Feld *et al.* (65)	Glecaprevir/pibrentasvir plus ezetimibe	10, single arm	Preoperative	100	1 grade 3 elevated ALT (peak 650 U/L), possibly related to treatment; included lung, heart, kidney, and pancreas transplants

DAAs, direct-acting antivirals; HCV, hepatitis C virus; POD, postoperative day; DGF, delayed graft function; AE, adverse event; ULN, upper limit of normal; ALT, alanine am inotransferase; THINKER, Transplanting Hepatitis C kidneys Into Negative KidnEy Recipients; EXPANDER, Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV-negative Recipients.
[a]In patients with genotype 1a with nonstructural protein 5A resistance-associated substitutions, ribavirin was added to grazoprevir/elbasvir and therapy duration was extended to 16 weeks, as per standard of care.
[b]In this study, patients received only 4 weeks of glecaprevir/pibrentasvir.

should be treated DAAs (47). Future research will be needed to determine if DAAs mitigate the known adverse association of HCV on quantity and quality of life for patients on dialysis. In 2016, the World Health Organization established the goal of eliminating HCV by 2030 (48). Strategies to eradicate HCV from dialysis units should consider DAA treatment as prevention. Indeed, reports of targeted outreach efforts to screen and treat HCV in dialysis have resulted in elimination of HCV entirely from dialysis units, demonstrating these efforts can be successful (49). However, it is important to note that, in some regions, being infected with HCV can shorten transplant waitlist times, so HCV treatment decisions in patients on the transplant waitlist should involve a discussion with local transplant center physicians.

HCV in Recipients of Kidney Transplants

Untreated HCV has been linked to lower graft and patient survival after kidney transplantation. HCV-associated liver disease increases the risk of acute rejection, *de novo* GN, thrombotic microangiopathy, proteinuria, and new-onset diabetes (50–53). In the pre-DAA period, HCV was associated with poorer outcomes and, thus, donors infected with HCV received a 20- to 25-point Kidney Donor Profile Index (KDPI) penalty. IFN-based therapies were largely avoided in the post–kidney transplantation setting because IFN can induce acute graft rejection (54,55). Fortunately, dedicated clinical trials in transplant recipients have shown that DAAs can be used safely after kidney transplantation, with excellent cure rates and without causing allograft dysfunction or acute rejection (Table 1**)** (56,57). A summary of real-world use of DAAs in recipients of kidney transplants confirmed high cure rates (97%) and low acute rejection rates (3%) (50). HCV-related, post-transplant GN is likely to be less common in transplant recipients who have received DAAs; however, it is important to note that *de novo* cryoglobulinemic GN has been described in patients infected with HCV who have been cured of HCV (32).

Because of the rapid rise in HCV-infected donor kidneys in the last decade (58–63), and the high rate of discard of these potentially robust organs, research protocols transplanting HCV-infected kidneys into recipients not infected with HCV, followed by DAA therapy to eradicate HCV, have been actively explored over the last 5 years. Single-center and multicenter clinical trials demonstrated outstanding cure rates when DAAs are begun pre-emptively (just before surgery) or within the first few days of kidney transplant (Table 2) (64–72). Whereas initial trials used a full treatment course, a recent pilot trial shortened DAA therapy to 4 weeks post-transplant and still achieved 100% cure of HCV, suggesting a shorter course may be a viable approach (67). Overall 1-year allograft outcomes have been excellent, although one case of post-transplant FSGS was considered to be possibly related to HCV infection or DAAs by study investigators (72).

Because of these promising trial results, many centers are now transplanting donors with HCV into recipients without HCV (66,73,74). Two recent analyses used United Network for Organ Sharing data to show there has been a rapid rise in the acceptance of HCV+ organs (75,76). Potluri and colleagues (76) not ed that, by 2019, patients seronegative for HCV received the majority of kidneys transplanted from donors who were HCV viremic. Results of real-world studies that have transplanted HCV-viremic kidneys into donors who were HCV naive have encountered delays in initiation of DAAs, yet still report excellent cure rates (66,77). However, delay in access to DAAs, while awaiting insurance approval, led to substantial numbers of patients experiencing elevated liver function tests and even a few cases of fibrosing cholestatic hepatitis (66,77). These studies highlight the importance of starting DAAs immediately post-transplant. Using a Markov state transition simulation model, Eckman *et al.* showe d that pre-emptive DAA strategies were cost-effective when increased utilization of donors infected with HCV shortened waitlist time by at least 0.9 years (78) .

Many have questioned whether the "KDPI penalty" is still needed in the era of DAA therapy. The large KDPI penalty for kidneys from donors with HCV may discourage centers from transplanting these organs. In an analysis by Potluri *et al*. (76), HCV-viremic kidneys that were transplanted into recipients who were HCV seronegative had similar 1-year eGFRs to HCV-nonviremic kidneys when matched on predictors of organ quality, except HCV, despite the much worse KDPI scores assigned to the HCV-viremic kid neys. Additionally, 1-year allograft outcomes for HCV-viremic kidneys were not meaningfully different if transplanted into recipients who were HCV seronegative versus HCV seropositive. These results provide important evidence that the current KDPI penalty for HCV status may not accurately assess the quality of kidneys from donors with HCV in the era of curative DAAs (76,79).

Conclusions and Future Directions

The ability to cure HCV has led to dramatic changes in standard-of-care management of HCV in patients with kidney disease and important efforts to expand the kidney donor pool. Further research is needed to elucidate the effect of HCV eradication on CKD progression, dialysis morbidity and mortality, and recipients of kidney transplants. It is possible that, in the near future, assuming long-term studies confirm that donors with HCV do not lead to worse allograft survival, the KDPI penalty for HCV infection can be removed. Finally, standardizing the optimal timing and duration of DAA therapy for patients without HCV who undergo transplantation from a donor with HCV will hopefully move this practice to standard of care. In summary, considering the ample evidence demonstrating worse outcomes in patients who suffer from both comorbidities, and the high efficacy and tolerability of DAAs, curing HCV should be prioritized in patients with kidney disease.

Disclosures

M.E. Sise reports receiving research funding from Abbvie, Gilead Sciences, and Merck; and serving as a scientific advisory board member for Gilead Sciences. All remaining authors have nothing to disclose.

Funding

This work was supported by National Institutes of Health grants T32 DK007028 and K23 DK 117014, and a Massachusetts General Hospital Claflin Distinguished Scholars Award (to M.E. Sise).

Author Contributions

M.E. Sise conceptualized the study and was responsible for data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, and validation; and all authors were responsible for visualization, wrote the original draft, and reviewed and edited the manuscript.

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Received March 16, 2021 **Accepted** May 21, 2021