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 and is a risk factor for progression of chronic kidney disease, is associated with higher morbidity and mortality in dialysis patients and leads to worse allograft and patient outcomes in kidney transplant recipients. 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 chronic kidney disease, end-stage kidney disease, and kidney transplant recipients.
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 chronic kidney disease (CKD). In fact, up to 10% of the HCV-infected patients in the United States have CKD (1). HCV infection also has important implications for patients with end-stage kidney disease (ESKD) and kidney transplant recipients (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 interferon-α (IFN-α), in standard form or pegylated form (PEG-IFN), 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, flu-like 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 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 human immunodeficiency virus (HIV) co-infection.

DAAs are largely considered non-nephrotoxic; with large series showing extremely low rates of acute kidney injury attributed to DAA therapy (13). However, small case series have linked DAA use with lupus-like glomerulonephritis 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 estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m²**

Sofosbuvir, the first modern DAA, is a uridine nucleotide analog 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 eGFR < 30mL/min/1.73m² 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 with elbasvir (a NS5A) inhibitor. Both of these agents are hepatically metabolized, and their exposure in patients with kidney failure is not substantially increased. The C-SURFER study, published in 2015, was a phase 3 trial that enrolled 235 patients with genotype 1 HCV infection and CKD stage 4 or 5 or 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 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 demonstrating outstanding safety and efficacy and ultimately led to expansion of the FDA label for sofosbuvir-based DAAs to include patients with all levels of kidney function, including dialysis dependence (Table 1). The first was a phase 2, open-label study of 95 dialysis patients 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 (IDSA) 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 chronic kidney disease**

HCV infection is a major cause of mixed (type II) cryoglobulinemia syndrome (MCS), a systemic vasculitis characterized by involvement of small-to-medium sized vessels that causes palpable purpura, neuropathy, arthralgia, and glomerulonephritis. The pathogenesis of HCV-triggered MCS is hypothesized to be due to chronic stimulation of B lymphocytes with excess production of autoantibodies and cryoglobulins. Cryoglobulinemic glomerulonephritis 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 demonstrates membranoproliferative pattern of injury with mesangial hypercellularity and expansion, endocapillary proliferation, monocytic infiltration, thickened capillary loops, large eosinophilic and PAS-positive intraluminal deposits referred to as “pseudothrombi” as 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 glomerulonephritis range from asymptomatic microscopic hematuria to acute kidney injury from rapidly progressive glomerulonephritis, 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 glomerulonephritis 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% (27, 28).

Because IFN and ribavirin-based therapies for HCV were rarely efficacious in curing HCV in patients with cryoglobulinemic glomerulonephritis, it was customary that rituximab and corticosteroids were used to treated HCV-related cryoglobulinemic glomerulonephritis. However, given that multiple studies have shown the DAAs are efficacious in patients with CGN (29, 30), it is now recommended per KDIGO guidelines that DAAs be used as first line treatment for cryoglobulinemic glomerulonephritis and that immunosuppression with rituximab-based therapy be reserved for patients with severe manifestations of vasculitis (rapidly-progressive glomerulonephritis, pulmonary hemorrhage) or those with persistent glomerulonephritis after completing DAAs (31). It is important to note that de novo cryoglobulinemic glomerulonephritis can occur after cure of HCV with DAAs, though 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, focal segmental glomerulosclerosis, fibrillary glomerulonephritis, immunotactoid glomerulonephritis, 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 co-infection (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 suggests 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 in order to stabilize or improve eGFR in patients with HCV (39, 40).

**HCV and dialysis**

Hepatitis C virus infection is more commonly seen in patients on dialysis than in the general patient, estimated to be 3-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 dialysis patients (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 6 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 dialysis patients received treatment for HCV infection due to the low response rate and poor tolerability of interferon and ribavirin-based
therapies (45). However, DAAs have now been prospectively 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, as the current AASLD guidelines suggest that anyone with >1 year life expectancy should be treated with 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 dialysis patients. In 2016, the WHO 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 that 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 transplant waitlist patients should involve a discussion with local transplant center physicians.

**HCV in kidney transplant recipients**

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 glomerulonephritis, thrombotic microangiopathy, proteinuria, and new-onset diabetes (50-53). In the pre-DAA period, HCV was associated with poorer outcomes and thus HCV-infected donors received a 20–25-point kidney donor profile index (KDPI) penalty. IFN-based therapies were largely avoided in the post-kidney transplantation setting as 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 kidney transplant recipient confirmed high cure rates (97%) and low acute rejection rates (3%) (50). HCV-related post-transplant glomerulonephritis is likely to be less common in
transplant recipients who have received DAAs, however it is important to note that *de novo* cryoglobulinemic glomerulonephritis has been described in HCV-infected patients 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 HCV-uninfected recipients followed by DAA therapy to eradicate HCV have been actively explored over the last five years. Single-center and multi-center clinical trials have demonstrated outstanding cure rates when DAAs are begun preemptively (just prior to surgery) or within the first few days of kidney transplant (Table 2) (64-72). While initial trials used a full treatment course, a recent pilot trial shortened DAA therapy to four 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; though one case of post-transplant focal segmental glomerulosclerosis 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 HCV viremic donors into HCV naïve recipients (66, 73, 74). Two recent analyses used UNOS data to show that there has been a rapid rise in the acceptance of HCV+ organs (75, 76). Potluri and colleagues noted that by 2019, HCV-seronegative patients received the majority of kidneys transplanted from HCV-viremic donors. Results of “real-world” studies that have transplanted HCV- viremic kidneys into HCV naïve donors 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.* showed that pre-emptive DAA strategies were cost effective
when increased utilization of HCV-infected donors 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. An analysis by Potluri et al. HCV-viremic kidneys when transplanted into HCV-seronegative recipients, matched to HCV-non-viremic had similar 1-year eGFR when matched on predictors of organ quality, except HCV, despite the much worse kidney donor profile index scores assigned to the HCV-viremic kidneys (76). Additionally, 1-year allograft outcomes for HCV-viremic kidneys were not meaningfully different if transplanted into HCV-seronegative versus HCV-seropositive recipients. These results provide important evidence that the current KDPI penalty for HCV status may not accurately assess the quality of kidneys from HCV-viremic donors 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 kidney transplant recipients. It is possible that in the near future, assuming long-term studies confirm that HCV donors 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 HCV naïve patients undergoing transplantation from an HCV viremic donor 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 as well as the high efficacy and tolerability of DAAs, curing HCV should be prioritized in patients with kidney disease.
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I Strohbehn: Visualization; Writing - original draft; Writing - review and editing
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M Lee: Visualization; Writing - original draft; Writing - review and editing
M Sise: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing - original draft; Writing - review and editing

References


Table 1. Clinical trials involving DAAs in patients with eGFR < 30 mL/min/1.73m² or on dialysis and in kidney transplant recipients

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>REGIMEN</th>
<th>NUMBER ENROLLED / STUDY DESIGN</th>
<th>PATIENT POPULATION</th>
<th>HCV CURE RATE</th>
<th>OVERALL SAE RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth, The Lancet, 2015 (C-Surfer)</td>
<td>Elbasvir/grazoprevir</td>
<td>235, randomized controlled trial</td>
<td>CKD 4/5, ESKD</td>
<td>94%</td>
<td>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.)</td>
</tr>
<tr>
<td>Gane, New England Journal of Medicine, 2017 (Expedition-4)</td>
<td>Glecaprevir/pibrentasvir</td>
<td>104, Single-arm</td>
<td>CKD 4/5, ESKD</td>
<td>98%</td>
<td>24% SAE, none treatment-related</td>
</tr>
<tr>
<td>Lawitz, Liver International, 2020 (Expedition-5)</td>
<td>Glecaprevir/pibrentasvir</td>
<td>101, Single-arm</td>
<td>CKD 3b/4/5, ESKD</td>
<td>97%</td>
<td>12% SAEs, none treatment-related</td>
</tr>
<tr>
<td>Borgia, Journal of Hepatology, 2019</td>
<td>Sofosbuvir/velpatasvir</td>
<td>59, Single-arm</td>
<td>ESKD</td>
<td>95%</td>
<td>19% SAEs, none treatment-related</td>
</tr>
<tr>
<td>Chuang, Journal of Hepatology, 2019</td>
<td>Sofosbuvir/ledipasvir</td>
<td>95, Single-arm</td>
<td>ESKD</td>
<td>94%</td>
<td>13% SAEs, none treatment-related</td>
</tr>
<tr>
<td>Colombo, Annals of Internal Medicine, 2017</td>
<td>Sofosbuvir/ledipasvir</td>
<td>114, randomized, open label study</td>
<td>Transplant recipients, eGFR ≥ 40 mL/min/1.73m²</td>
<td>100%</td>
<td>11% SAEs (3 treatment-related SAEs: syncope, pulmonary embolism, and serum creatinine increase)</td>
</tr>
<tr>
<td>Reau, Hepatology, 2018*</td>
<td>Glecaprevir/pibrentasvir</td>
<td>20 kidney transplants, single-arm, open label</td>
<td>Transplant recipients, no eGFR cutoff</td>
<td>100%</td>
<td>8% in overall cohort (n=20 kidney transplants, n=80 liver transplant; 2 treatment related SAEs: sinusitis and abnormal hepatic function)</td>
</tr>
</tbody>
</table>

Table 1. *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 20/20 for patients with a kidney transplant and the SAEs were 8% for the overall cohort. Abbreviations: HCV = hepatitis C virus; SAE = serious adverse event; AE = adverse event; CKD = chronic kidney disease; ESKD = end-stage kidney disease.
Table 2. Clinical trials involving DAAs in HCV-naïve transplant recipients of kidneys from HCV-viremic donors

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>REGIMEN</th>
<th>NUMBER ENROLLED / STUDY DESIGN</th>
<th>TIMING OF DAA</th>
<th>HCV CURE RATE</th>
<th>STUDY NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldberg, New England Journal of Medicine, 2017 (THINKER-1)</td>
<td>Elbasvir/grazoprevir</td>
<td>10, Single-arm</td>
<td>POD3</td>
<td>100%</td>
<td>1 case of FSGS (proteinuria adjudicated as being possibly related to HCV and with substantial improvement after treatment)</td>
</tr>
<tr>
<td>Reese, Annals of Internal Medicine, 2018 (THINKER-2)</td>
<td>Elbasvir/grazoprevir</td>
<td>10, Single-arm</td>
<td>POD3</td>
<td>100%</td>
<td>5 DGF (THINKER-1 group) 1 treatment failure with successful re-treatment with DAAs</td>
</tr>
<tr>
<td>Durand, Annals of Internal Medicine, 2018 (EXPANDER)</td>
<td>Elbasvir/Grazoprevir*</td>
<td>10, Single-arm</td>
<td>Pre-op</td>
<td>100%</td>
<td>No AEs related to treatment</td>
</tr>
<tr>
<td>Sise, Kidney International Reports, 2020</td>
<td>Elbasvir/grazoprevir</td>
<td>8, Single-arm</td>
<td>Pre-op</td>
<td>100%</td>
<td>1 immediate graft failure, 3 DGF</td>
</tr>
<tr>
<td>Durand, Annals of Internal Medicine, 2021</td>
<td>Glecaprevir/Pibrentasvir**</td>
<td>10, Single-arm</td>
<td>Pre-op</td>
<td>100%</td>
<td>1 graft failure</td>
</tr>
<tr>
<td>Sise, Journal of the American Society of Nephrology, 2020</td>
<td>Glecaprevir/pibrentasvir</td>
<td>30, Single-arm</td>
<td>POD3</td>
<td>100%</td>
<td>3 acute rejection within first 6 months, 7 DGF</td>
</tr>
<tr>
<td>Terrault, Hepatology, 2020</td>
<td>Sofosbuvir/velpatasvir</td>
<td>11, Single-arm</td>
<td>Started once viremia detected, median POD 17</td>
<td>100%</td>
<td>2 w/ delayed graft function, 3 w/ transaminase elevations 4-7x ULN10 treated with DAA (1 never developed viremia). Included liver and kidney transplants.</td>
</tr>
<tr>
<td>Feld, Lancet Gastroenterology and Hepatology, 2020</td>
<td>Glecaprevir/Pibrentasvir plus Ezetimibe</td>
<td>10, Single-arm</td>
<td>Pre-op</td>
<td>100%</td>
<td>1 grade 3 elevated ALT (peak 650 U/L) possibly related to treatment. Included lung, heart, kidney and pancreas transplants.</td>
</tr>
</tbody>
</table>

Table 2. *In patients with genotype 1a with NS5a resistance associated substitutions ribavirin was added to grazoprevir/elbasvir and therapy duration extended to 16 weeks as per standard of care. ** In this study, patients received only 4 weeks of glecaprevir/pibrentasvir.

Abbreviations: HCV = hepatitis C virus; DAA = direct acting antiviral; FSGS = focal segmental glomerulosclerosis; AE = adverse event; DGF = delayed graft function; POD = post-op day; ULN = upper limit of normal; ALT = alanine aminotransferase.
Figure 1. HCV and kidney disease

Abbreviations: HCV = hepatitis virus; CKD = chronic kidney disease; ESKD = end-stage kidney disease; GN = glomerulonephritis.

Figure 2. DAA targets in genome and commonly prescribed combination therapies

Combination DAAs pair agents from 2 or 3 classes. Two-drug combinations include Sofosbuvir/Ledipasvir, Sofosbuvir/Velpatasvir, Elbasvir/Grazoprevir, 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.
HCV and CKD
- Associated with glomerular immune complex disease
- Associated with more rapid progression to ESRD

HCV and ESRD
- Associated with increased mortality
- Associated with increased hospitalization risk
- Associated with decreased quality of life

HCV and transplant
- Associated with lower allograft and overall survival
Figure 2. Combination DAAs pair agents from 2 or 3 classes. Two-drug combinations include Sofosbuvir/Ledipasvir, Sofosbuvir/Velpatasvir, Elbasvir/Grazoprevir, 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.