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Treatment of HCV in Renal Disease: Subtle Management Considerations in the Era of Direct-acting Antivirals

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Abstract

Chronic hepatitis C virus (HCV) infection is burdensome in patients with chronic kidney disease and contributes to substantial liver-related and all-cause morbidity and mortality. HCV infection itself may cause kidney dysfunction, as exemplified through mixed cryoglobulinemic vasculitis. HCV is more prevalent in patients with significant kidney disease compared to the general population, and recent reports have shown inadvertent HCV transmission in U.S. hemodialysis centers. Further, HCV has been demonstrated to accelerate kidney dysfunction and is associated with worse clinical outcomes in patients with kidney disease. As such, the HCV-infected population with concurrent kidney disease is an important patient subgroup that warrants focused medical care and attention. With the advent of direct-acting antivirals (DAAs), the successful treatment of HCV is now a medical reality for many patients. Nuances in regimen selection and timing need to be considered when treating those with kidney dysfunction, particularly for those considering kidney transplantation.

Keywords

Hepatitis C virus; Direct-acting antivirals; Chronic kidney disease

Introduction

Hepatitis C virus (HCV) infection is one of the most common causes of chronic liver disease worldwide affecting >185 million people with an estimated seroprevalence of 2.8% [1]. HCV infection may result in extrahepatic disease manifestations including kidney dysfunction, such as that caused by mixed cryoglobulinemic vasculitis. Additionally, patients with known kidney disease are frequently burdened with HCV infection; a recent study found a 9.5% HCV prevalence among 49,762 end-stage renal disease (ESRD) patients on hemodialysis across 12 countries [2]. Furthermore, chronic kidney disease (CKD)

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Compliance with Ethics Guidelines

Conflict of Interest

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patients with HCV infection have been demonstrated to suffer a more rapid rate of kidney dysfunction and progression to ESRD as compared to the general population [3–8]. Additionally, liver-related and all-cause mortality are significantly worse in HCV patients with significant renal disease, further emphasizing the need to target and effectively treat this patient population [9–12]. With the advent of DAAs the ability to effectively treat and cure HCV patients is now a medical reality, though subtleties in management are important to address in those with HCV-related kidney disease or concurrent kidney disease in general. This review will discuss HCV-related kidney disease, the evaluation of HCV infection in kidney disease patients on hemodialysis, and the treatment of HCV infection in kidney disease patients, including in patients considering kidney transplant and those who have received a kidney transplant.

HCV-related Kidney Disease

Mixed Cryoglobulinemic Vasculitis

Chronic HCV infection may result in kidney disease through mixed cryoglobulinemic vasculitis, a small-vessel vasculitis that typically presents with palpable purpura, arthralgias, fever, and neuropathy in addition to renal impairment [13, 14]. Mixed cryoglobulinemic vasculitis is due to type II/III cryoglobulins and is attributable to HCV in 70–90% of cases [13]. HCV-containing immune complexes are directly involved in disease pathogenesis resulting in glomerular dysfunction [13]. In addition to functional renal impairment, patients may suffer from hematuria and proteinuria, which may be nephrotic range [13]. The disease process of HCV-induced mixed cryoglobulinemic vasculitis typically responds to HCV clearance, and has been found to recur with relapse of HCV [15].

The decision to treat patients HCV-induced mixed cryoglobulinemic vasculitis is based on the goals to eliminate the immunologic stimulus that results in glomerular disease and other extrahepatic manifestations in addition to preventing future liver complications due to HCV. Further, HCV clearance may lead to improvement in renal function, as some studies demonstrate decreased plasma creatinine and proteinuria after successful treatment [16, 17]. In patients with mild to moderate HCV-induced mixed cryoglobulinemic vasculitis, an optimized direct-acting antiviral regimen should be utilized [13]. In patients with severe or catastrophic disease, rituximab and a rapidly tapered glucocorticoid course with or without plasmapheresis should be employed prior to initiation of an optimized antiviral therapy [13]. If rituximab is not available, cyclophosphamide may be used for immunosuppression prior to antiviral therapy [18]. As the treatment paradigm of HCV has shifted away from interferon-containing regimens and towards newer direct-acting antivirals, case series are emerging demonstrating the efficacy of using these regimens for viral clearance in these patients [19–22]. The particular DAA regimen options that should be considered depend on renal function, HCV genotype, and status and severity of concurrent liver disease. These are discussed in later sections of this review.

Other HCV-related Kidney Disease

Other types of glomerular disease associated with HCV include non-cryoglobulinemic membranoproliferative glomerulonephritis, membranous nephropathy, polyarteritis nodosa,

IgA nephropathy, and focal segmental glomerulosclerosis, among others [23]. The potential for renal involvement in HCV infection emphasizes the importance of evaluating for proteinuria, hematuria, hypertension, and kidney function in chronically infected patients. Further in-depth discussion of HCV-related kidney disease manifestations is beyond the scope of this review. For reference, Ozkok et al. [23] provide a thorough evaluation of other types of HCV-related kidney disease manifestations beyond mixed cryoglobulinemic vasculitis.

Evaluation of HCV Infection in Kidney Disease Patients on Hemodialysis

Given increased reports of newly acquired HCV infection in ESRD patients on hemodialysis in the United States, the Centers for Disease Control and Prevention (CDC) has released a health advisory in 2016 for hemodialysis providers to reduce the risk of inadvertent transmission between patients [24]. At least 36 cases across 19 different hemodialysis centers were identified between 2014 and 2015 [24]. Lapses in infection control, such as involving injection safety, were commonly identified at such facilities and are thought to have contributed to this elevated incidence. Increased screening and awareness of HCV may also have influenced the rise in reported new infections that have occurred in this setting. Regardless, recommendations including evaluating and addressing gaps in infection control practices at hemodialysis centers, ensuring proper staff training regarding infection control guidelines, and routinely obtaining HCV antibody for chronic hemodialysis patients upon admission and every 6 months if susceptible to HCV infection were emphasized [24].

Treatment of HCV Infection in Kidney Disease Patients

Patients with CKD or ESRD

Prior to this decade, peginterferon and ribavirin were the backbone of HCV therapy in patients with kidney dysfunction, despite frequent side effects and poor tolerability. With the advent of DAA therapy the approach to treating HCV in patients with renal impairment has been revolutionized for a large segment of this patient population, particularly given excellent efficacy and tolerability. Both the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) currently recommend treatment for patients with chronic HCV infection except for those with short life expectancies that cannot be remediated by successful HCV clearance [25]. Table 1 provides currently recommended treatment regimens by genotype for patients with creatinine clearance less than 30 mL/min.

For patients with HCV genotype 1a, 1b, or 4 infection and creatinine clearance less than 30 mL/min, fixed dose NS5A inhibitor elbasvir (50 mg) and second-generation NS3/NS4A inhibitor grazoprevir (100 mg) for 12 weeks is a recommended regimen [25]. Treatment is limited to patients with at most Child-Pugh class A chronic liver disease. The recommendation for this regimen is due largely to excellent results of the C-SURFER phase 3 randomized clinical trial, which reported a sustained virologic response (SVR) at 12 weeks of 99% (115/116 patients) for 12 weeks of elbasvir/grazoprevir in genotype 1 patients with CKD stage 4/5 (with or without hemodialysis dependence) and minimal side effects [26]. The development program for elbasvir/grazoprevir found that certain NS5A resistance

associated variants (RAVs) in genotype 1a patients led to virologic failure, and the Food and Drug Administration therefore recommended testing for RAVs and a longer 16-week course of treatment with the addition of ribavirin if present. Ribavirin is renally cleared and therefore must be given at reduced doses with CKD. Even with reduced doses, patients will be at risk for hemolytic anemia and will require close monitoring. Interestingly, none of the genotype 1a patients in C-SURFER with NS5A resistance associated variants (RAVs) suffered from viral relapse. Given these compelling results and the risks of ribavirin in patients with CKD, the AASLD and IDSA do not routinely recommend NS5A resistant testing prior to treatment as recognition of these variants would not change treatment strategy with this regimen [25]. Although the addition of ribavirin and extended duration are reasonable approaches for the patient who is closely monitored and can tolerate the anemia of ribavirin, our clinical practice has been to follow the AASLD/IDSA recommendation given the C-SURFER results. Though C-SURFER did not evaluate patients with genotype 4 infection, the high efficacy of elbasvir/grazoprevir in genotype 4 infection patients with normal renal function was extrapolated to those with CKD stage 4/5 [26].

For patients with HCV genotype 1b infection and creatinine clearance less than 30 mL/min, a fixed dose regimen of paritaprevir (150 mg)/ritonavir (100mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is a recommended regimen (known as the PrOD regimen) to consider in patients whom urgency to treat is high [25]. Twenty patients with HCV genotype 1 infection without cirrhosis and with stage 4/5 CKD were treated with PrOD regimen for 12 weeks in a phase IIb open label study and achieved an SVR at 12 weeks of 90% [27]. Genotype 1a patients (n=13) in this study also received ribavirin, though this was interrupted in 9 patients due to significant hemoglobin decline, making this regimen lose favor for treatment of genotype 1a patients [27]. However, a dose-adjusted ribavirin containing PrOD regimen can be considered as an alternate regimen for HCV genotype 1a infection for patients with creatinine clearance less than 30 mL/min in patients with baseline hemoglobin of 10 g/dL [25]. The PrOD regimen in general should be used with caution in treatment of Child-Pugh class A patients, and is not recommended for use in patients with more advanced liver disease such as Child-Pugh class B or C [25].

At this time, peginterferon with dose-adjusted ribavirin remains the recommended regimen for patients requiring urgent treatment with HCV genotype 2, 3, 5, or 6 infection and creatinine clearance less than 30 mL/min [25]. Caution with this therapy choice is required given the risk of hemolytic anemia due to diminished renal clearance [25]. Further, ribavirin should only be given to those with a baseline hemoglobin above 10 g/dL, and discontinued if the hemoglobin drops by more than 2 g/dL despite erythropoietin use [25]. Combination peginterferon and ribavirin therapy in large Taiwanese trials have reported SVR rates ranging from 62–74% in hemodialysis patients [28–30]. Restrictions due to medical tolerability and comparatively worse efficacy compared to direct-acting antivirals make the interferon and ribavirin-based regimens suboptimal as we await further advances in management for patients with these HCV genotypes and renal impairment.

For patients with mild to moderate renal impairment (creatinine clearance ranging from 30 to 80 mL/min), regimen selection is the same for patients without any renal impairment and no dose adjustments are warranted for renal function when using fixed-dose combination

ledipasvir (90 mg)/sofosbuvir (400 mg), daclatasvir (60 mg), fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg), paritaprevir (150 mg)/ritonavir (100mg)/ombitasvir (25 mg) with (or without for genotype 4) twice-daily dosed dasabuvir (250 mg), simeprevir (150 mg), or sofosbuvir (400 mg) to treat or retreat HCV infection as appropriate by genotyping [25].

Patients Considering Kidney Transplant

For patients under consideration for kidney transplant, the timing of treating HCV infection is often a strategic one. Despite overall health-related and liver-related benefit from treating chronic HCV infection as early as possible, successfully treating HCV infection in a kidney transplant candidate can prolong waitlist time by limiting the donor pool through exclusion of HCV-positive donors. A decision not to treat HCV infection in a kidney transplant candidate would more practically allow accepting allograft offers from HCV-positive donors with the goal to treat HCV after transplantation. A retrospective analysis of 1679 adult deceased-donor single-organ renal transplants found that HCV-recipient positive patients that received HCV-donor positive organs spent less time on the waitlist (mean 318 days) compared to HCV-recipient negative patients who received HCV-donor negative organs (mean 613 days) [31]. Furthermore, HCV recipient-positive, donor-positive patients had improved death censored graft survival compared to HCV recipient-positive, donor-negative patients, which was considered to be at least partially due to decreased waitlist time [31]. As such, many U.S. kidney transplant programs have adopted this strategy to hold pre-transplant HCV treatment to decrease wait-list time for HCV infected kidney transplant candidates that are willing to accept HCV-donor positive organs.

Patients After Kidney Transplant

For HCV patients that have received a kidney transplant, several different studies have shown efficacious outcomes with DAA therapies in clearing virus. Kamar et al reported 100% SVR in treating 25 HCV-infected kidney transplant recipients with sofosbuvir-based regimens, 76% of which were genotype 1 and 44% of which had advanced liver fibrosis [32]. Patients were reported to have tolerated therapy without any discontinuations, dose reductions, or graft-related dysfunction [32]. Sawinski et al. similarly reported 100% SVR after treatment of 20 HCV-infected kidney transplant recipients with sofosbuvir-based regimens, 60% of which were treatment experienced, 88% genotype 1, and half of which had advanced liver fibrosis [33]. No significant changes in renal graft function were noted after treatment, though 45% of patients did require dose reduction of immunosuppression while on therapy, and two patients required dose reductions of ribavirin due to anemia during therapy [33]. Hussein et al. in an additional series noted 100% SVR in 3 HCV genotype 4 patients treated with sofosbuvir plus ribavirin for 24 weeks [34]. Anemia was reported in 2 of the patients due to ribavirin requiring dose reduction and blood transfusion though no other adverse effects were noted [34]. A recent abstract presented by Colombo et al. at the 51st European Association for the Study of the Liver (EASL) meeting in April 2016 demonstrated 96% SVR for 114 HCV genotype 1 or 4 patients treated more than 6 months after kidney transplant with ledipasvir/sofosbuvir for 12 or 24 weeks [35]. Less than one percent discontinued therapy due to adverse events, though adverse events were notably commonly reported at 64% [35]. This promising ability to effectively treat HCV after kidney

transplantation further makes the decision to hold on HCV treatment until after transplantation more attractive as a means to reduce individual waitlist time from an individual viewpoint and expand the donor pool from a systems viewpoint.

Conclusions

Chronic HCV infection may directly cause kidney dysfunction and is often found in patients with chronic kidney disease or ESRD. Multiple studies have shown that chronic HCV infection in patients with significant kidney disease results in worse clinical outcomes, making treatment of HCV paramount in importance. At this time, treatment of HCV genotype 1 and 4 patients with CKD stage 4/5 and up to Child Pugh class A chronic liver disease is possible with DAA regimens with superb efficacy, safety, and SVR. Currently, treatment of HCV genotype 2, 3, 5, and 6 in patients with CKD stage 4/5 is limited to peginterferon and ribavirin regimens, which may be problematic due to side effects and notably worse SVR as compared to DAA regimens. For patients considering kidney transplant, a practical strategy of holding off on HCV treatment and accepting HCV donor-positive organs has been found to effectively decrease waitlist time, and makes sense from a systems perspective in expanding the donor pool. Furthermore, recent studies have shown promising efficacy and tolerability in treating HCV patients after kidney transplant with direct-acting antivirals.

Abbreviations

CDC	Centers for Disease Control and Prevention
CKD	Chronic Kidney Disease
DAAs	Direct-acting Antivirals
ESRD	End Stage Renal Disease
HCV	Hepatitis C Virus
PrOD	Paritaprevir/ritonavir/Ombitasvir/Dasabuvir
RAVs	Resistance Associated Variants
SVR	Sustained Virologic Response

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Table 1

Current recommended HCV treatment regimens for chronic kidney disease patients with creatinine clearance less than 30 mL/min

Genotype 1a
Fixed-dose Elbasvir (50 mg)/ Grazoprevir (100 mg) for 12 weeks (Up to Child Pugh class A cirrhosis)
<i>Alternate:</i> Fixed-dose combination Paritaprevir (150 mg)/ Ritonavir (100mg)/ Ombitasvir (25 mg) plus twice-daily dosed Dasabuvir (250 mg) and dose-adjusted Ribavirin ^{**} (200 mg) daily for 12 weeks (without cirrhosis) and 24 weeks (with Child Pugh class A cirrhosis)
Genotype 1b
Fixed-dose Elbasvir (50 mg)/ Grazoprevir (100 mg) for 12 weeks (Up to Child Pugh class A cirrhosis)
Fixed-dose combination Paritaprevir (150 mg)/ Ritonavir (100mg)/ Ombitasvir (25 mg) plus twice-daily dosed Dasabuvir (250 mg) for 12 weeks (Up to Child Pugh class A cirrhosis)
Genotype 4
Fixed-dose Elbasvir (50 mg)/ Grazoprevir (100 mg) for 12 weeks (Up to Child Pugh class A cirrhosis)
Genotype 2, 3, 5, or 6
Peginterferon and dose-adjusted Ribavirin ^{**} (Up to Child Pugh class A cirrhosis)

^{**} Restricted to baseline hemoglobin greater than 10 g/dL.