Hepatitis C Virus Infection in Chronic Kidney Disease

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ABSTRACT

Soon after the hepatitis C virus (HCV) was identified in 1989, it was recognized that the prevalence of infection in patients with ESRD far exceeded that in the general population. Infection with HCV predisposes to the hepatic complications of cirrhosis and hepatocellular carcinoma. However, important extrahepatic manifestations include immune complex glomerular disease, accelerated progression of CKD, increases in cardiovascular event risk, and lymphoproliferative disorders. Advances in understanding the molecular biology of HCV have ushered in a new era in the treatment of this infection. Second generation direct–acting antiviral agents have revolutionized therapy, with sustained virologic response rates (undetectable viral load 12 weeks after completing therapy) of >90% in most patients. Studies using direct-acting antivirals in patients with CKD and those on dialysis are showing excellent safety and efficacy as well. In this context, it is imperative that nephrologists become familiar with this literature, reviewed here, so that the important decisions, including which patients should be treated and the optimal timing to initiate therapy, are vetted in association with the compounding issues of CKD, ESRD, and kidney transplantation.


In the quarter century that has passed since hepatitis C virus (HCV) was identified,1 an extensive literature has defined the epidemiology, viral kinetics, and clinical manifestations of this infection. Soon after its discovery, HCV was recognized to be a public health issue of global significance that is estimated to affect approximately 170 million individuals worldwide,2–5 many of whom remain undiagnosed. Furthermore, it has become clear that the consequences of HCV infection extend well beyond the liver, defining more of a systemic disease with a multitude of clinical consequences.6–8

As different populations of patients were screened for anti-HCV antibodies, it became evident that the prevalence of HCV infection in patients with ESRD far exceeded that of the general population. Early reports noted prevalence rates as high as 25% in urban hemodialysis units in the United States and in excess of 50% in less developed countries. Moreover, it was unequivocally shown that HCV was transmissible by kidney transplantation (KT)9 as well as within dialysis units as a consequence of a breakdown of universal precautions.10 HCV infection was also shown to be the etiology of most cases of what had previously been referred to as essential mixed cryoglobulinemia as well as some cases of idiopathic membranoproliferative GN.7,10

Recognizing that an extensive literature had accumulated on the effect and treatment of HCV infection, the first Kidney Disease Improving Global Outcomes (KDIGO) workgroup was organized in 2007 with a focus on developing clinical guidelines for the diagnosis and treatment of HCV infection.6 It was evident to the KDIGO investigators that patients with CKD and patients with ESRD had been systematically excluded from all of the phase 3 HCV treatment trials and as a consequence, that they represented a population with a substantial unmet clinical need.

This review will focus on HCV infection in patients with CKD, patients with ESRD, and patients with transplants and summarizes new information pertaining to the use of direct–acting antiviral (DAA) agents in these patients. The availability of safe and effective antiviral medications requires the development of treatment paradigms that take into account the unique needs of this patient population.

THE HCV

HCV is a small (50 nm) enveloped virus that was first isolated and cloned in 1989.1 It has a positive single–stranded RNA with approximately 9600 nucleotides11 and a genome composed of structural and nonstructural proteins (Figure 1). Seven genotypes have been identified, with each divided into subtypes and strains.12,13 Genotypes 1–3 are distributed...
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12 weeks after completion of treatment to obtain a sustained virologic response important question of whether treating rate of progression to ESRD, raising the increased mortality and an accelerated infected patients with CKD had an in-

Figure 1. The HCV genome and target sites of action for the direct acting antiviral agents. Combining agents with different mechanisms of viral interference has resulted in the achievement of very high sustained viral response rates. NTR, nontranslated region.

globally, with 1a and 1b being the most common (60% of the infections worldwide). Genotype 1a is the dominant genotype in northern Europe and North America, whereas 1b is distributed worldwide. In contrast, genotypes 2 (Europe and Mediterranean region), 3 (Asia), 4 (Middle East and central Africa), 5 (South Africa), 6 (Asia) and 7 (Central Africa) have a penetration that is more geographically specific.11,13

HCV IN PATIENTS WITH KIDNEY DISEASE

HCV and CKD

Patients with CKD have a higher prevalence of HCV infection compared with the general population.10 Recent studies suggest that HCV-infected patients with CKD have an accelerated rate of kidney function loss and an increased risk of progressing to ESRD.14–19 In one study, Molnar et al.19 showed that HCV-infected patients with CKD had an increased mortality and an accelerated rate of progression to ESRD, raising the important question of whether treating to obtain a sustained virologic response defined as an undetectable viral load 12 weeks after completion of treatment (SVR12) would diminish the rate of decline in GFR.

Infection with HCV has been implicated as being causative in most patients with mixed cryoglobulinemia and several histologic forms of glomerular injury, including membranoproliferative and membranous GN.7,20 Patients coinfected with HIV have been reported to have an increased mortality and overall worse prognosis.21,22

HCV in the Patient with ESRD

The prevalence of HCV in patients with ESRD has always exceeded that of the general population, and transmission of the virus within dialysis clinics has been unequivocally shown.10 The risk of transmission is an ongoing hazard as emphasized in a recent Centers for Disease Control and Prevention (CDC) health advisory that noted an increased number of acute HCV infection events among patients undergoing maintenance hemodialysis.23 Lapses in universal precautions were identified at these dialysis clinics, emphasizing the need for continuously improving infection control practices and environmental disinfection procedures accompanied by adherence to recommended CDC HCV screening protocols.24 Studies have consistently shown that HCV infection is associated with an increased mortality in patients with ESRD.25–29 In a meta-analysis by Fabrizi et al.,26 the relative risk of mortality was 1.35 (95% confidence interval, 1.25 to 1.47) among HCV-infected patients with ESRD. Analysis of cause-specific death showed an increased burden of cardiovascular risk, supporting the concept that HCV is a systemic disease with important extrahepatic consequences.26 Of interest, transplanting an anti-HCV–positive patient with ESRD is accompanied by a significantly decreased risk of death compared with remaining on the waiting list. This survival benefit is largely attributable to a decrease in cardiovascular events within the first year post-transplant.30 Thus, although it is important to recognize that HCV–infected kidney recipients have an increased hazard ratio for death, transplant continues to offer these patients a significantly improved survival compared with remaining on dialysis.25–29,31

HCV and KT

HCV infection is the primary cause of liver disease in KT recipients; however, it has also been associated with important extrahepatic manifestations that contribute to increased morbidity and mortality after transplantation.33 HCV-infected recipients are at increased risk of de novo and recurrent membranous nephropathy, membranoproliferative GN,34–36 and transplant glomerulopathy.37 Infection with HCV has also been associated with an increased risk for insulin resistance and diabetes mellitus in wait-listed candidates and kidney recipients, similar to that reported for the general population.38–43 Although prospective studies are lacking, it is reasonable to assume that the increased incidence of diabetes in the HCV–infected KT candidate/recipient would translate into an increased burden of cardiovascular event risk.

The presence of anti-HCV antibody is associated with lower patient and graft survival among KT recipients.44,45 In a large meta-analysis, Fabrizi et al.44 showed a significant increase in both...
mortality and graft loss among HCV-infected recipients. However, in a retrospective study of 230 patients, Roth et al. showed that KT in HCV-infected patients conferred a long-term survival benefit compared with remaining on the waitlist. Thus, chronic HCV infection should not be considered a contraindication to KT, because the long-term survival advantage associated with transplantation can still be shown in these patients.  

**DAA AGENTS IN PATIENTS WITH CKD**

Patients achieving an SVR12 are considered cured of the infection. Using the latest generation DAAAs, rates of SVR12 in clinical trials conducted in the general population exceed 90% across all genotypes, with the lowest response rates being reported in cirrhotics and patients with genotype 3. The evolution from IFN-based therapy to DAAAs is a remarkable accomplishment of the last decade and offers the possibility of life-saving treatment for millions of patients.

**DAs**

**Sofosbuvir**

Sofosbuvir is a nucleotide analog NS5B polymerase inhibitor that targets the nonstructural protein 5B RNA-dependent RNA polymerase, thus effectively terminating viral replication. (Figure 1, Table 1). Sofosbuvir is a pro-drug that is phosphorylated into the active metabolite GS-461203, with subsequent dephosphorylation into the inactive metabolite GS-331007. Sofosbuvir and GS-331007 are cleared by the kidneys, resulting in significant accumulation of both in patients with CKD. In this context, the safety and efficacy of sofosbuvir in patients with advanced CKD or ESRD have not been established, and the drug is not recommended for use in patients with a creatinine clearance of <30 ml/min. Nevertheless, two recent studies using open-label treatment with simeprevir and dose-adjusted sofosbuvir in patients with advanced CKD/ESRD showed safety and high rates of SVR12. Additional experience with sofosbuvir in HCV-infected patients with CKD has been reported from the HCV-TARGET Study, a longitudinal real world observational study of DAAs. SVR12 rates of 85%–90% were achieved across all patient groups; however, increased adverse events were reported in patients with more advanced kidney disease (eGFR<45 ml/min). Current guidelines from the American Association for the Study of Liver Disease (AASLD) recommend that sofosbuvir only be considered as an option for patients with a creatinine clearance of <30 ml/min when expert opinion is obtained before initiating therapy.

**Simeprevir**

Simeprevir is a nonstructural protein 3/4A protease inhibitor that is metabolized in the liver (>90%) with insignificant renal clearance (<1%). The drug is highly protein bound, and it is not cleared by dialysis; thus, no dosing adjustments are required for patients with CKD or ESRD. Limited data are available on the safety and efficacy of simeprevir in the CKD and ESRD population. Bhamidimarri et al. reported the use of full-dose simeprevir combined with half-dose sofosbuvir in patients with advanced CKD/ESRD. This combination was found to be well tolerated, with limited adverse events and excellent efficacy.

**Ledipasvir**

Ledipasvir is a nonstructural protein 5A inhibitor (NS5A) that is marketed in combination with sofosbuvir (Harvoni). The drug is hepatically metabolized with minimal renal clearance, and as a consequence, the AASLD does not recommend dose adjustments for patients with CKD or ESRD. However, because it is prepared in combination with sofosbuvir, caution must be used in patients with GFR<30 ml/min.

**Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir (3D Regimen)**

The combination of ombitasvir-paritaprevir (ritonavir boosted) and dasabuvir is marketed as Viekira Pak. Ombitasvir is an inhibitor of the nonstructural protein 5A (NS5A), whereas paritaprevir is a nonstructural protein 3/4A protease inhibitor that is combined with low-dose ritonavir to boost paritaprevir drug levels. These three drugs are administered with dasabuvir, an inhibitor of the nonstructural protein 5B RNA-dependent RNA polymerase (NS5B). This combination was studied in the RUBY-I Trial, a multicenter, phase 3b study assessing the safety and efficacy of the three-dimensional regimen in patients with CKD stage 4/5. In preliminary reports, 17 of 17 patients achieved an SVR12, and no treatment-related serious adverse events were noted. No dose adjustments of ombitasvir-paritaprevir/ritonavir and dasabuvir are required in patients with advanced CKD; however, insufficient data are available to recommend their use in patients on dialysis.

**Daclatasvir**

Daclatasvir is a nonstructural protein 5A (NS5A) inhibitor that blocks both RNA replication and virion assembly. As a consequence of the drugs hepatic metabolism, no dosing adjustments are necessary in patients with CKD. Daclatasvir has been used mostly in combination with sofosbuvir for patients with advanced CKD; however, insufficient data are available in patients with mild to moderate CKD and ESRD. Daclatasvir was well tolerated with good efficacy.

**Grazoprevir and Elbasvir**

Grazoprevir is a nonstructural protein 3/4A protease inhibitor (NS3/4A) that has been combined with the nonstructural protein 5A (NS5A) inhibitor elbasvir. This product (Zepatier) recently received Food and Drug Administration approval for the treatment of HCV genotypes 1 and 4 infection and should be available in the United States within several months. Both grazoprevir and elbasvir are highly protein bound and thus, not cleared by dialysis. Additionally, they rely on hepatic metabolism and do not accumulate in patients with reduced kidney function. This combination was studied in the C-SURFER Trial,
the first prospective, randomized study of DAAs that focused exclusively on HCV-infected patients with CKD and HCV-infected patients with ESRD.67 In this phase 3 trial, 224 patients with HCV genotype 1 infection and stage 4 or 5/5D CKD were randomly assigned to an immediate treatment group (n=111) or a deferred treatment group (n=113) that initially received placebo and then, was offered active therapy. Data from an intensive pharmacokinetic group (n=11) showed no requirement for dose adjustment in patients on hemodialysis. Treatment with Zepatier resulted in SVR12s of 99%, with a low adverse event profile and no significant safety signals in this CKD population.67,68

Velpatasvir
Velpatasvir is a nonstructural protein 5A (NS5A) inhibitor with antiviral activity against genotypes 1–6.69 Two studies have shown that velpatasvir combined with sofosbuvir provided high rates of SVR12 in patients with all genotypes, including the difficult to treat patients with genotype 3.70,71 As has been the case in most pivotal trials of HCV infection in the general population, patients with kidney disease were not included in these studies; thus, there are no data on the safety and efficacy of this combination in patients with CKD and patients with ESRD.71

Special Considerations
HCV Infection in the KT Candidate
All patients being evaluated for KT should be screened for HCV infection. The KDIGO guidelines recommended ELISA testing in geographic regions with a low prevalence of HCV followed with nucleic acid testing confirmation of all positive results. Initial testing with nucleic acid testing was recommended in regions with a high prevalence of HCV.6 An accurate assessment of the extent of liver injury is necessary in all KT candidates with active viral replication. Liver biopsy has always been considered the gold standard; however, there are now several noninvasive tests that have shown promise in making this determination. These methods rely on distinct but complementary approaches: a biologic method that quantifies serum levels of biomarkers of fibrosis and a physical approach that measures liver stiffness by ultrasound or magnetic resonance elastography (FibroTest and FibroScan).72 Validation of these surrogate markers of liver fibrosis in the patient with ESRD will be needed. A liver biopsy should be considered in inconclusive cases or if there is a suggestion of advanced fibrosis (stage 3/4) on the noninvasive testing.

We have been using a management paradigm73,74 (Figure 2) similar to the one proposed by Sawinski et al.73 Patients with META-VIR stages 0–2 liver fibrosis who have a living donor should receive DAAs before transplant to achieve SVR12. For the patient without a living donor, there are two options available at the time of listing. In one scenario, the patient can delay DAA treatment (thus remaining viremic), with the intention of receiving a kidney from an HCV-positive donor. Of note, this option is not available at all transplant centers, and an informed consent should be obtained. This approach has been accompanied by significantly reduced waiting times compared with those for HCV-negative kidneys.75 In this scenario, DAA therapy can be initiated in the post-transplant period. We would recommend waiting 2–3 months post-transplant to achieve stable kidney function and immunosuppressive dosing (see below). The primary objective of transplanting a kidney from an HCV-positive donor would be to shorten waiting times and make transplantation more available by using kidneys that are often discarded.76 If this option was not available, the patient would be confronted with a waiting times that can often exceed 5 years. In this case, consideration should be given to pretransplant treatment with DAAs to achieve an SVR12, thus limiting the risk of progressive liver injury. In this scenario, the patient can wait to receive a kidney from an uninfected donor or consider transplantation of a kidney from an HCV-infected donor, with early initiation

### Table 1. DAA agents

<table>
<thead>
<tr>
<th>Medication agents</th>
<th>Dose</th>
<th>Clearance</th>
<th>Target of Action</th>
<th>Use in CKD Stages 4 and 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir</td>
<td>400 mg daily</td>
<td>Renal =81%; GI=15%</td>
<td>NS5B</td>
<td>eGFR=15–29 ml/min: not recommended; eGFR&lt;15 ml/min: not recommended; limited data available</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>150 mg daily</td>
<td>Renal &lt;1%; GI=91%</td>
<td>NS3A/4A</td>
<td>eGFR=15–29 ml/min: dose adjustment not required; eGFR&lt;15 ml/min: not recommended; limited data available</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>90 mg daily</td>
<td>Renal =1%; GI=86%</td>
<td>NS5A</td>
<td>eGFR=15–29 ml/min: dose adjustment not required; eGFR&lt;15 ml/min: not recommended</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir/dasabuvir</td>
<td>12.5/75/50 mg ×2 tablets; 250 mg ×2 tablets</td>
<td>Renal &lt;2%; GI=90%</td>
<td>NS5A/NS3A/4A/CYP3A; NS5B</td>
<td>eGFR=15–29 ml/min: dose adjustment not required; eGFR&lt;15 ml/min: dose adjustment not required; not studied in patients on dialysis; limited data</td>
</tr>
<tr>
<td>Grazoprevir/elbasvir</td>
<td>100/50 mg daily</td>
<td>Renal &lt;1%</td>
<td>NS3/4A NS5A</td>
<td>eGFR=15–29 ml/min: dose adjustment not required; eGFR&lt;15 ml/min: dose adjustment not required; dialysis population studied</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>60 mg daily; used with sofosbuvir</td>
<td>Renal =7%; GI=88%</td>
<td>NS5A</td>
<td>eGFR=15–29 ml/min: dose adjustment not required; eGFR&lt;15 ml/min: dose adjustment not required</td>
</tr>
</tbody>
</table>

GI, gastrointestinal.

Gl, gastrointestinal.
of DAAs in the post-transplant period. In a similar context, there is increased interest in transplanting kidneys from positive donors into negative recipients followed by early initiation of DAAs post-transplant. Reese et al. discussed this perspective in a recent editorial and propose this as a reasonable consideration for uninfected patients with high risk of health deterioration because of dialysis (elderly, cardiovascular morbidity, or access failure) or those with disadvantageous blood types. Any decision in this regard must be balanced against data suggesting that uninfected patients that receive HCV-positive kidneys have increased mortality. Furthermore, the ethics of knowingly infecting a patient with HCV must be carefully weighed against the knowledge that not all patients achieve an SVR with DAA treatment, and there is no certainty that payers will approve this costly therapy after transplantation.

Any discussion of knowingly infecting a patient with HCV at the time of transplantation must be with full understanding of the accompanying risk of fibrosing cholestatic hepatitis, an aggressive form of HCV seen after liver transplantation or KT during the period of maximal immunosuppression. This was a serious concern during the IFN/ribavirin era when SVRs were low, and the treatment was associated with an increased risk of renal allograft rejection. These concerns may be diminished by recent data from liver recipients showing successful treatment of fibrosing cholestatic hepatitis using current DAAs. These results are encouraging; however, we await confirmation of these outcomes in kidney recipients.

The second option for the HCV-infected transplant candidate would be to treat with DAAs before transplant. As mentioned earlier, this would be a reasonable plan for the patient with a living donor. This might also be an advisable approach for the patient with more advanced histologic liver injury (stage 3/4 liver disease with early cirrhosis) and without a living donor. These patients must be carefully evaluated to determine if a kidney-alone transplant is advisable or if a combined liver transplant/KT is necessary. Much of this decision will hinge on whether the patient has preserved synthetic liver function and/or portal hypertension. At our center, these patients have transjugular measurement of hepatic venous pressure gradient. Patients with a gradient $\leq 12$ mmHg with normal platelet count and synthetic liver function are treated with DAAs to achieve an SVR12 and subsequently, listed to receive a kidney from an HCV-negative donor. This will require the usual waiting times on the list; however, it seems prudent not to transplant a cirrhotic patient with active viral replication. Each of these options must be carefully reviewed with the patient, because the treatment strategy will have a significant effect on the patient’s clinical course.

Critical decision points include whether the patient has a living donor and the extent of liver fibrosis. The option to accept a kidney from a HCV positive donor could significantly shorten wait times. HVPG, hepatic venous pressure gradient; Neg, negative; Pos, positive; SVR, sustained virologic response; DAA, direct antiviral agent.

<table>
<thead>
<tr>
<th>Immunosuppressant</th>
<th>SOF and LDV</th>
<th>OMV, PTV, r, and DSV</th>
<th>SMV</th>
<th>SOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporin</td>
<td>No changes in levels</td>
<td>† Cyclosporin levels (r)</td>
<td>† Levels of both cyclosporin and SMV</td>
<td>No changes in levels</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>No changes in levels</td>
<td>† Tacrolimus levels (r)</td>
<td>† Tacrolimus levels; monitor levels closely</td>
<td>No changes in levels</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>No changes in levels</td>
<td>† Sirolimus levels (r)</td>
<td>† or † Levels of sirolimus</td>
<td>No changes in levels</td>
</tr>
</tbody>
</table>

SOF, sofosbuvir; LDV, ledipasvir; OMV, ombitasvir; PTV, paritaprevir; r, ritonavir; DSV, dasabuvir; SMV, simeprevir.
that are currently being discarded and/or not being harvested.86

HCV Treatment in the KT Recipient
For the last two decades, the treatment of HCV infection in the post-transplant setting has not been an option in large part because of the unacceptable risk of rejection associated with the use of IFN-based regimens.84–87 Furthermore, the IFNs are poorly tolerated, and SVR rates are only in the 45%–50% range.88 As a consequence of this poor efficacy and high adverse event profile, treatment of HCV infection in the KT candidate and recipient has often been deferred.

In the era of DAAAs, there are several important caveats when opting to treat post-transplantation. There are potential drug-drug interactions that must be considered. Both the calcineurin inhibitors and mammalian target of rapamycin inhibitors are substrates of cytochrome p450 isoenzymes 3A4/5 and the drug transporter, P-glycoprotein (Table 2). Although sofosbuvir and/or daclatasvir do not interact with cytochrome p450 3A4/5 or P-glycoprotein, simprevir, ledipasvir, and Viekira Pak should be used with caution to avoid sub- or supratherapeutic immunosuppression. Recently reported studies from KT recipients have shown the need to adjust tacrolimus dosing in patients receiving DAAAs.89,90

With the availability of DAA agents that are safe and effective in transplant recipients, the important decisions will now focus on determining the safest and most effective DAs and their drug-drug interactions and provide guidance on the optimal timing for the initiation of therapy. Patients with kidney disease and HCV infection have waited decades for this opportunity, and as is often the case with other comorbidities, they will expect the nephrologist to orchestrate the nuances of the treatment decisions that will be necessary.

DISCLOSURES
M.L. and F.P. have no financial disclosures. D.R. has been a consultant for Merck GmbH (Darmstadt, Germany) and Abbvie and served on a Scientific Advisory Board for Merck GmbH.

REFERENCES

CONCLUSION
HCV infection is a global public health issue with important hepatic and extrahepatic manifestations. Although patients with CKD had been largely excluded from most phase 3 DAA trials, data are now becoming available that raise hopes for a cure in the patient with ESRD and the KT recipient. In this context, it will be essential that nephrologists become familiar with the different DAs and their drug-drug interactions and provide guidance on the optimal timing for the initiation of therapy. Patients with kidney disease and HCV infection have waited decades for this opportunity, and as is often the case with other comorbidities, they will expect the nephrologist to orchestrate the nuances of the treatment decisions that will be necessary.
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