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Treatment of Hepatitis C Infection in Renal Transplant Recipients: The Long Wait is Over

Varun Saxena and Norah A. Terrault*

University of California San Francisco, San Francisco

The reported prevalence of chronic hepatitis C virus (HCV) infection in hemodialysis (HD) patients, at 2.6% – 22.9% in Western countries, is greater than in the general population and is significantly correlated with the duration of HD.¹ As a result, chronic HCV infection among kidney transplant (KT) recipients, is not infrequent and there is also substantial evidence that HCV-infected KT recipients have worse survival after transplantation compared with HCV-negative KT recipients driven by new-onset diabetes after transplant resulting in cardiovascular disease, post-transplant glomerulonephritis, malignancy and hepatic failure.^{1,2} Thus, treatment of HCV infection post-KT with the goal of eliminating the risk of these complications is highly desirable, but up until recently was difficult to achieve. HCV treatment in the era of interferon-containing regimens was fraught with poor tolerability, concern for IFN-induced acute allograft rejection and ultimately very modest success in achieving viral eradication.^{1, 2}

The availability of current direct acting antivirals (DAAs) against HCV (Table 1), has revolutionized the treatment of HCV and for the first time offers a safe and highly effective antiviral option for transplant recipients. The efficacy of DAA therapy in liver transplant recipients is well-established,³ and while similar outcomes would be predicted in KT patients, specific experience with new HCV therapies in the post-KT setting was lacking until recently. In this edition of *American Journal of Transplantation*, early experiences with HCV DAA therapy in KT recipients are reported from two centers in the US and France. In a U.S. cohort of 20 KT recipients, the majority of whom had genotype 1 infection with baseline advanced fibrosis (Metavir fibrosis stage 3) and prior treatment experience, Sawinski et al. showed that 100% (95% CI: 83%–100%) attained a sustained virologic response at week 12 post-treatment (SVR12), with no serious adverse events (SAEs) including no episodes of acute rejection.⁴ Treatment regimens were heterogeneous, preventing conclusions about the efficacy of specific DAA combinations and the median time from KT to HCV treatment initiation was 888 days (IQR: 341–1621).⁴ There were no significant changes in serum creatinine before and after treatment, though follow-up post-treatment may have been too short to observe potential benefits of HCV clearance on renal outcomes. Similarly, in the French cohort of 25 KT recipients, of whom 76% were genotype 1 and 25% had baseline advanced fibrosis, Kamar et al. showed a 100% (95% CI: 86%–

*Corresponding Author: Norah A. Terrault, norah.terrault@ucsf.edu.

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100%) SVR12 rate without any SAEs.⁵ Again, drug treatment regimens were diverse, though all were sofosbuvir-based. All patients had baseline eGFR ≥ 30 mL/min without significant changes on treatment.⁵ The median time from KT to HCV treatment initiation was shorter in this study at 146 months with some patients treated early after KT (range: 1–329 months).⁵ In both studies, RBV was infrequently used and when it was utilized, dose-reductions for anemia and for changes in eGFR were required.^{4, 5} Overall, these results are reassuring and provide confidence that sofosbuvir-based therapy can be safely and effectively used in the KT population. While this is great news for the kidney transplant community, a few words of caution are warranted as clinicians look to expand the treatment of HCV to a larger group of HCV-infected KT recipients.

First, drug-drug interactions (DDIs) need to be carefully considered (Table 2). The calcineurin inhibitors (CNI), tacrolimus and cyclosporine, as well as the mammalian target of rapamycin inhibitors (mTORi), sirolimus and everolimus, are frequent components of modern immunosuppression (IMS). Both of these drug classes are substrates of cytochrome P450 (CYP) isoenzymes 3A4/5 and the drug-transporter, P-glycoprotein (P-gp). While administration of sofosbuvir and/or daclatasvir do not interact with *CYP3A4/5* or *P-gp* and therefore do not result in clinically significant DDIs with immunosuppressants, simeprevir, ledipasvir and ombitasvir/ritonavir-boosted paritaprevir do have significant interactions (Table 2). Careful monitoring of IMS levels are required to avoid either sub- or supra-therapeutic IMS. Additionally, we learned from treatment of liver transplant recipients, that IMS levels could decline with viral clearance, presumably reflecting improvements in hepatic function and enhanced metabolism of CNI/mTORi drugs. Sawinski et al.⁴ reported that 45% of patients required dose adjustment of CNIs during DAA treatment. Both Sawinski et al.⁴ and Kamar et al.⁵ pointed out that CNI levels decreased on and after treatment, regardless of CNI dose alterations. These changes emphasize the need for close monitoring and dose adjustments of IMS to minimize toxicity and avoid precipitation of rejection.

Second, the ideal timing for HCV treatment after KT is unclear from the limited data available. In the reports from Sawinski et al.⁴ and Kamar et al.⁵, the majority of patient's were several years after KT. However, one might argue that achievement of HCV cure earlier in the post-KT course may have many theoretical benefits including reduced rates of new-onset diabetes and resultant cardiovascular disease as well as cryoglobulin related and liver-related complications. Of course, these benefits need to be balanced with the risk of acute rejection early after KT and the potential for the HCV DAAs and immunosuppressants DDIs to confer a higher risk of rejection^{4, 5}.

Third, there is a need to be aware that many of the current HCV DAAs, specifically those including sofosbuvir, require a creatinine clearance level greater than 30 mL/min. In fact, experience with SOF-containing regimens in patients with reduced renal function resulted in an increase in adverse renal safety outcomes.⁶ Whether these adverse effects reflected the natural history of renal disease in those treated or represented a toxicity of sofosbuvir is unknown but pending more data, sofosbuvir is not recommended if eGFR is ≤ 30 mL/min. Thus, the status of renal recovery post-KT may influence the options for HCV treatment. In the future, this issue will be less important as alternative drugs that are safe and effective in

patients with significantly impaired renal dysfunction, such as combination of elbasvir/grazoprevir, become available.⁷

Looking ahead, the options for treatment of transplant recipients can only be anticipated to improve further. Future DAA combinations are expected to eliminate the need for ribavirin, reduce the duration of therapy and yet maintain high efficacy and safety. Thus, for all transplant recipients, the future looks bright and we can be confident that HCV will no longer be a contributor to reduced graft and patient survival in this population.

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Table 1

Characteristics of Approved Direct Acting Antivirals against Hepatitis C Virus

Direct Acting Antiviral	Mechanism of Action	Genotypic Coverage	Renal Considerations	Other Considerations
Simeprevir	NS3/4A protease inhibitor	1, 4	No adjustment	- Mild CYP3A inhibition - Indirect hyperbilirubinemia
Sofosbuvir	Nucleotide NS5B polymerase inhibitor	1, 4–6	Safety and efficacy not established with eGFR 30mL/min	--
Ledipasvir	NS5A replication complex inhibitor	1, 4–6	No adjustment	Co-formulated with SOF
Paritaprevir-ritonavir (PTV-r)	NS3/4A protease inhibitor	1, 4	No adjustment in mild to severe impairment, not well studied in eGFR 15mL/min and hemodialysis patients	- Co-formulated with OBV and co-administered with DBV - CYP3A inhibition - Indirect hyperbilirubinemia
Ombitasvir (OBV)	NS5A replication complex inhibitor	1, 4		Co-formulated with PTV-r
Dasabuvir (DBV)	Non-nucleoside NS5B polymerase inhibitor	1		Co-administered with OBV-PTV-r
Daclatasvir (DCV)	NS5A replication complex inhibitor	Pan-genotypic (approved for genotype 3)	No adjustment	--

Drug-Drug Interactions between Currently Approved Hepatitis C Virus Direct Acting Antivirals and Immunosuppressants

Table 2

	Simeprevir	Sofosbuvir	Sofosbuvir/ Ledipasvir	Ombitasvir/ Paritaprevir- Ritonavir/ Dasabuvir	Daclatasvir
ANTI-PROLIFERATIVE					
Azathioprine	•	•	•	•	•
Mycophenolate	•	•	•	•	•
CALCINEURIN INHIBITORS					
Cyclosporine	•	•	•	•	•
Tacrolimus	•	•	•	•	•
mTOR INHIBITORS					
Everolimus	•	•	•	•	•
Sirolimus	•	•	•	•	•
IL-2 RECEPTOR ANTAGONIST					
Basliximab	•	•	•	•	•

Color legend: lighter grey = no clinically significant drug-drug interaction, darker grey = potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring, black = co-administration of this drugs is not recommended.

The symbol (lighter grey, darker grey and black) used to rank the clinical significance of the drug-drug interaction is based on www.hep-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the referenced website.