

## OPEN

# Eight Weeks of Ledipasvir/Sofosbuvir in Kidney Transplant Recipients With Hepatitis C Genotype 1 Infection

Jennifer S. Husson, MD, MPH,<sup>1</sup> Bharath Ravichandran, PharmD, BCPS,<sup>2</sup> Srijana Jonchhe, PharmD, BCPS,<sup>2</sup> Shyamasundaran Kottitil, MD, PhD,<sup>1</sup> and Eleanor Wilson, MD, MHS<sup>1</sup>

**Abstract:** Short treatment duration of ledipasvir/sofosbuvir (LDV/SOF) has been successfully used to treat hepatitis C virus (HCV) genotype 1 infection in treatment-naïve noncirrhotic patients with viral loads (VLs) under 6 million IU/mL. However, this short duration has not been studied in renal transplant recipients (RTRs), a patient population on lifelong immunosuppression. Here, we describe 3 RTRs who received 8 weeks of LDV/SOF, meeting the standard criteria for shortened treatment duration. All 3 patients tolerated treatment well and achieved sustained virologic response at 12 weeks (SVR 12).

(*Transplantation Direct* 2017;3:e229; doi: 10.1097/TXD.0000000000000744. Published online 3 November, 2017.)

Shortened treatment strategies for chronic hepatitis C virus (HCV) genotype 1 infection have been explored using combination therapy and found to be effective in select patient populations. Currently, an 8-week regimen of ledipasvir/sofosbuvir (LDV/SOF) is approved for treatment-naïve noncirrhotic patients with HCV viral load (VL) of less than 6 million IU/mL.<sup>1</sup>

No studies to date have looked at using this 8-week treatment regimen in immunosuppressed patients. The prevalence of HCV in hemodialysis patients is higher than that of the general population.<sup>2</sup> Renal transplant recipients infected with HCV tend to have higher rates of cirrhosis and hepatocellular carcinoma as well as worse patient and graft survival after transplant.<sup>3,4</sup> Whereas the direct-acting antivirals (DAAs)

provide safer and more effective treatment options in this population, the optimal duration of treatment remains unknown.

Owing to the high cost of DAA therapy, there is often pressure to use approved shorter durations of therapy despite a paucity of data regarding treatment duration after renal transplant. Here, we describe 3 cases of treatment-naïve HCV genotype 1 infection successfully treated with 8 weeks of LDV/SOF after renal transplant. All patients received maintenance immunosuppression per standard protocol at our transplant center with a tacrolimus goal of 8 to 9 ng/mL, mycophenolate mofetil 2000 mg per day (or equivalent), and a 21-day steroid taper. This case series was approved by the institutional review board at the University of Maryland.

The first patient is a 57-year-old African American man with a pretreatment HCV VL of 620,260 IU/mL and fibrosis stage 1. He received a HCV-positive deceased donor renal transplant (DDRT) with alemtuzumab induction complicated by delayed-graft function for 3 weeks after transplant. As donor HCV genotype testing is not routinely performed by the local organ procurement organization before transplantation, we repeated his HCV genotype after transplant, which was found to be genotype 1a, and he was started on LDV/SOF 146 days after transplant for 8 weeks. His tacrolimus level before treatment start was above goal and he required continued tacrolimus dose reduction during his HCV treatment, although it was not felt to be related to his HCV treatment. The patient achieved sustained virologic response at 12 weeks (SVR 12) with a stable serum creatinine (Cr) level and estimated glomerular filtration rate (eGFR) from initiation (Cr, 3.08 mg/dL; eGFR, 25 mL/min per 1.73 m<sup>2</sup>) to SVR 12 (Cr, 2.47 mg/dL; eGFR, 32 mL/min per 1.73 m<sup>2</sup>), with improvement in his baseline proteinuria during treatment.

The second patient is a 64-year-old African American man with a pretreatment HCV genotype 1b VL of 2,228,293 IU/mL

Received 7 July 2017. Revision requested 29 August 2017.

Accepted 11 September 2017.

<sup>1</sup> The Institute of Human Virology, School of Medicine, University of Maryland, Baltimore, MD.

<sup>2</sup> Department of Pharmacy, University of Maryland, Baltimore, MD.

The authors declare no funding or conflicts of interest.

J.H. contributed to the collection of the cases and writing of the paper. B.R. contributed to the collection of data and writing of the paper. S.J. contributed to the collection of data and writing of the paper. K.S. and E.W. contributed to the writing of the paper.

Correspondence: Jennifer Husson, MD, MPH, Division of Clinical Care and Research, The Institute of Human Virology, University of Maryland School of Medicine, 725 W Lombard St, N151, Baltimore, MD 21201. (jhusson@ihv.umaryland.edu).

Copyright © 2017 The Author(s). *Transplantation Direct*. Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000000744

and fibrosis stage 0. He received a HCV-negative living related renal transplant (LRRT) with antithymocyte globulin induction and experienced immediate graft function. His medical history is notable for a failed DDRT and LRRT, the last of which was lost owing to rejection. He started HCV treatment 1220 days after transplant with LDV/SOF for 8 weeks. No dose adjustment of his tacrolimus during the treatment period was required. He attained SVR 12 with a stable Cr level of 1.83 mg/dL and an eGFR in the 40-mL/min/1.73 m<sup>2</sup> range throughout treatment and at SVR 12 with significant improvement in his baseline proteinuria.

The third patient is a 53-year-old African American woman with a pretreatment HCV VL of 270,760 IU/mL and fibrosis stage 0. She received a HCV-positive DDRT with alemtuzumab induction, complicated by delayed-graft function requiring 1 dialysis session after transplantation. Her genotype both before and after transplant was 1a, and she started treatment 119 days after transplant with LDV/SOF for 8 weeks. She maintained a stable Cr level of 1.1 mg/dL and an eGFR of more than 60 mL/min per 1.73 m<sup>2</sup> with minimal proteinuria throughout treatment, also attaining SVR12 (Table 1, Figure 1, Figure 2). Owing to tacrolimus levels being below goal, she required tacrolimus dose increases twice during the treatment and follow-up period.

Each of these patients met the current criteria for shortened 8-week treatment durations with LDV/SOF at the time of their treatment.<sup>5</sup> Data are conflicting, however, regarding the efficacy of the 8-week regimen in certain subgroups, such as African Americans and those with higher fibrosis stages. Recently, the American Association for the Study of Liver Disease and Infectious Disease Society of America joint guidelines have been updated to recommend an 8-week duration only for nonblack, nonhuman immunodeficiency virus-infected, treatment-naïve, noncirrhotic patients with a HCV VL of less than 6 million.<sup>5</sup> Despite this change, a recent study found that 8 weeks of LDV/SOF had SVR rates of approximately 94% or greater for most subgroups, African Americans and those with fibrosis stage 0 to 3.<sup>6</sup>

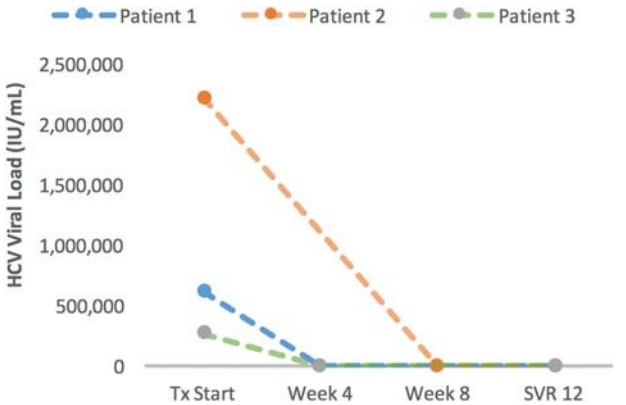


FIGURE 1. Hepatitis C viral load during DAA treatment through SVR 12.

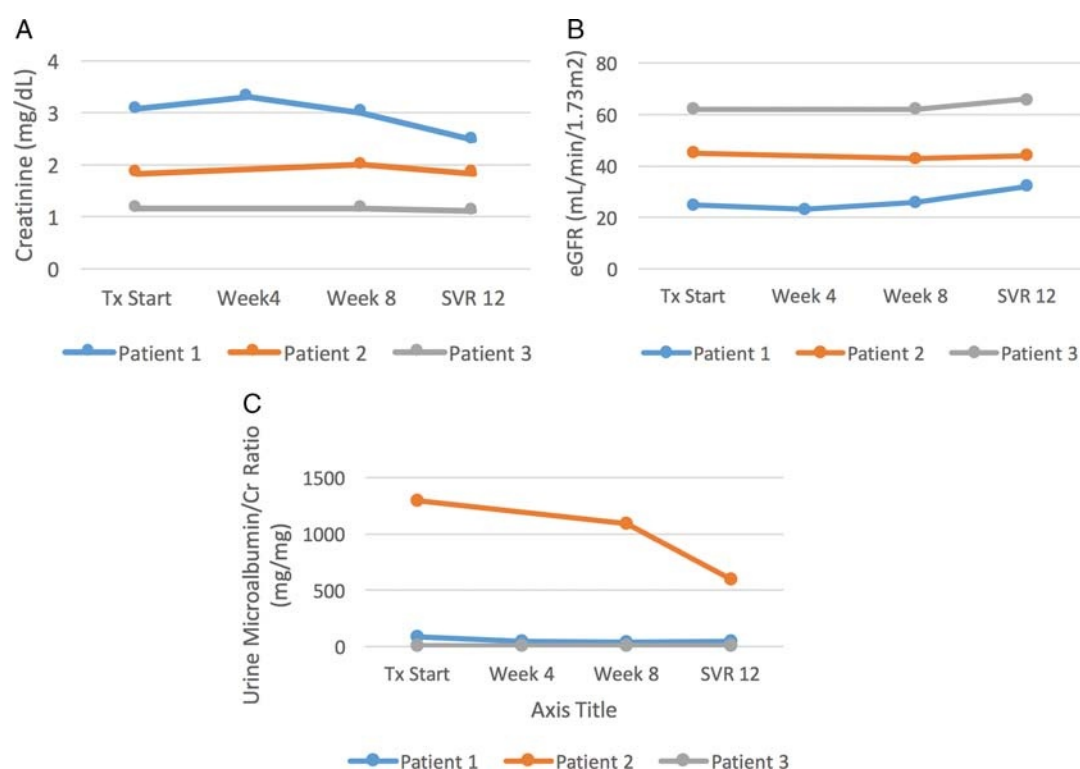
A low baseline HCV VL is a good predictor of SVR, even with 8 weeks of therapy. However, its efficacy in an immunocompromised population has not yet been explored. Although DAAs are critical in clearing HCV infections, the immune system may also play an important role, especially through interferon-stimulated gene expression.<sup>7</sup> This response may be altered in immunocompromised patients, especially early after transplantation. In fact, the relative efficacy of treating renal transplant candidates before or after transplant has not been established, although several groups have reported good outcomes in renal transplant recipients (RTRs) treated with standard 12-week regimens after transplant.<sup>8</sup>

The potential cost savings associated with expanding the population eligible for shortened treatment durations could affect the feasibility of treating these patients as well as lower the total health care costs associated with these patients. In fact, keeping HCV treatment costs down may also shorten the time to treatment for these patients by improving the insurance approval process. In addition, cost savings on a larger group of people may make it more feasible in the future

TABLE 1.  
Description of cases

	Patient 1	Patient 2	Patient 3
Age	57	64	53
Race	African American	African American	African American
Sex	Male	Male	Female
Prior HCV treatment	No	No	No
HCV VL pretreatment	620,260 IU/mL	2,228,293 IU/mL	270,760 IU/mL
Genotype	1a	1b	1a
Fibrosis stage	1	0	0
Transplant type	DDRT	LRRT	DDRT
Induction	Alemtuzumab	ATG	Alemtuzumab
HCV+ donor kidney	Yes	No	Yes
Days from transplant to Tx start	146	1220	119
SVR 12	Yes	Yes	Yes
Tx start GFR (mL/min/1.73 m <sup>2</sup> ) (Cr (mg/dL))	25 (3.08)	45 (1.83)	62 (1.16)
Tx end GFR (mL/min/1.73 m <sup>2</sup> ) (Cr (mg/dL))	32 (2.47)	44 (1.83)	66 (1.10)
Tx start urine microalbumin/Cr ratio (mg/mg)	85.2	1293.6	<3.7
Tx end urine microalbumin/Cr ratio (mg/mg)	46.7	569.6	4.7
Tacrolimus dose adjustment	Decrease	None	Increase

HCV, hepatitis C; VL, viral load; SVR, sustained virologic response; Tx, treatment; GFR, glomerular filtration rate; Cr, creatinine; DDRT, deceased donor renal transplant; LRRT, living related renal transplant; ATG, antithymocyte globulin; mL, milliliters; min, minute; m, meters; mg, milligrams; dL, deciliter.



**FIGURE 2.** A, Serum creatinine measurements for each patient over time during HCV treatment through SVR 12. B, Estimated glomerular filtration rate measurements for each patient over time during HCV treatment through SVR 12. C, Proteinuria as measured by urine microalbumin/creatinine ratios for each patient over time during HCV treatment through SVR 12.

to treat additional people who otherwise would be ineligible for treatment at this time.

Although all 3 patients at our institution achieved SVR 12 with an 8-week regimen that was well tolerated, further study is warranted before advocating for this approach. Several variables may affect treatment efficacy in this population, especially with a shortened duration. In our case series, the time from transplant to treatment ranged by chance from 119 days to 1220 days after transplant as patients were identified and referred for treatment once DAAs became available. In addition to the already established criteria, factors such as time from transplant or amount of immunosuppression could play a significant role and needs to be further explored.

Two patients in our case series received strong induction immunosuppression with alemtuzumab and there were significant differences in the overall lifetime immunosuppression (1 patient had a history of a prior transplant lost to rejection) and donor quality (our cases included both DDRTs and an LRRT) in our patients, which could affect treatment outcomes. Two of the 3 patients required adjustments in their tacrolimus dosing; however, in neither of these cases was the alteration in tacrolimus levels felt to be related to drug-drug interactions with the HCV medications. A larger sample size would be warranted to evaluate the impact of any drug-drug interactions between LDV/SOF and tacrolimus. Patients receiving DAAs in addition to tacrolimus should continue

to have close follow-up of their tacrolimus levels while on DAA therapy.

Treatment of RTRs with a low baseline HCV VL for 8 weeks may be safe and effective and should be further studied in larger clinical trials.

## REFERENCES

- Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med*. 2014;370:1879–1888.
- Fissell RB, Bragg-Gresham JL, Woods JD, et al. Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. *Kidney Int*. 2004;65:2335–2342.
- Sawinski D, Forde KA, Eddinger K, et al. Superior outcomes in HIV-positive kidney transplant patients compared with HCV-infected or HIV/HCV-coinfected recipients. *Kidney Int*. 2015;88:341–349.
- Xia Y, Friedmann P, Yaffe H, et al. Effect of HCV, HIV and coinfection in kidney transplant recipients: mate kidney analyses. *Am J Transplant*. 2014;14:2037–2047.
- HCV Guidance: Recommendations for testing, managing and treating hepatitis C. Available at: <http://www.hcvguidelines.org>. Accessed May 11, 2017. Published 2016.
- Kowdley KV, Sundaram V, Jeon CY, et al. Eight weeks of ledipasvir/sofosbuvir is effective for selected patients with genotype 1 Hepatitis C virus infection. *Hepatology*. 2017;65:1094–1103.
- Sun J, Rajsbaum R, Yi M. Immune and non-immune responses to hepatitis C virus infection. *World J Gastroenterol*. 2015;21:10739–10748.
- Fernandez I, Munoz-Gomez R, Pascasio JM, et al. Efficacy and tolerability of interferon-free antiviral therapy in kidney transplant recipients with chronic hepatitis C. *J Hepatol*. 2017;66:718–723.