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INVITED COMMENTARY

Hepatitis C treatment in kidney transplant recipients: the need for sustained vigilance after sustained viral response

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Hepatitis C virus (HCV) infection is a global health problem with an estimated 71 million people infected worldwide. Approximately 400 000 people die each year from HCV, primarily from cirrhosis and hepatocellular carcinoma (Global Hepatitis Report, 2017, WHO) (http://www.who.int/hepatitis/publications/global-hepatitis-report2017). HCV infection in kidney transplant recipients is associated with increased morbidity and mortality [1–3]. Compared with noninfected patients, HCV is associated with increased risk of allograft loss due to higher rate of rejection, transplant glomerulopathy [4], and de novo post-transplant glomerular disease [5].

Historically, interferon-based HCV treatment in transplant recipients was limited by poor tolerability and low efficacy [6,7] and was associated with higher rates of allograft loss [8,9]. HCV treatment has been revolutionized by the development of interferon-free direct-acting antivirals (DAAs). The HCV genome encodes a single ~3000 amino acid polyprotein, from which 10 viral proteins are cleaved by the action of viral and host proteases. The identification of the nonstructural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B) has been crucial for the development of DAAs. Currently, three major classes of antiviral HCV drugs exist: inhibitors of the NS3/NS4A protease, for example Simeprevir; inhibitors of the NS5A complex, for example Ledipasvir (LDV); and inhibitors of the NS5B polymerase, which are further subdivided into nucleoside inhibitors (NI), for example Sofosbuvir (SOF) (coformulation as Harvoni® containing 400 mg SOF and 90 mg LDV per tablet), and non-nucleoside inhibitors (NNI), for example Dasabuvir [10]. The advent of interferon-free DAAs has provided a breakthrough with an all oral-based therapy, and more than 95% sustained virologic response (SVR) in kidney transplant

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recipients [11]. Although a number of small-sample-size studies reported a favorable outcome in HCV-infected kidney recipients at least in the short and medium term, the long-term outcomes are still unclear. The assumption, although unproven, is that eradication of HCV with DAAs after kidney transplantation will lead to a reduction in risk and improved outcomes overall.

In their article in this month's journal, Fernandez-Ruiz and colleagues present outcomes from a single center study of 49 kidney transplant recipients treated with DAAs [12]. Notably, median initiation of treatment was years beyond kidney transplant, average 155.5 months, and patients were followed up for a median of 12.7 months after completion of therapy. There were varied treatment regimens and durations, with the most common regimen of SOF plus LDV along with Ribavirin (RBV) in 51%. The authors report an impressive SVR rate of 95.8% at 12 weeks of treatment, in line with other studies [13–15]. Calcineurin inhibitor (CNI) and everolimus levels dropped on average, and 80.6% of patients on tacrolimus required dose escalation while on DAA therapy. The need to adjust CNI doses during treatment was similar to previous reports [15–17].

While drug interactions with DAAs have been implicated in the drop in CNI drug levels [18], the significant decrease in tacrolimus levels persisting at 3 months after completion of therapy in this study suggests that changes in metabolism may have been independent of drug–drug interactions. Improvement in hepatic synthetic function may have led to improved CNI metabolism, as serum transaminase and bilirubin levels decreased after treatment. Intriguingly, a lower degree of fibrosis on pretreatment liver biopsy was associated with a trend for tacrolimus dose escalation and amount of dose change after DAA therapy, suggesting a link related to residual hepatic function and increased drug metabolism after viral clearance. Hemoglobin A1c improved as well, demonstrating a potential benefit of improved glycemic control after achieving SVR which may attenuate the well-described association of HCV and post-transplant diabetes [19].

The investigators next compared pre- and post-treatment 12-month trajectories of estimated glomerular filtration rate (ΔeGFR) and 24-h proteinuria (Δ24-h proteinuria) and found significant changes in both. In the 12 months pre- and post-treatment, median ΔeGFR was 3.9% and −6.1% ($P = 0.002$) and median Δ24-h proteinuria was −5.3% and 26% ($P = 0.057$). The authors thus offer a note of caution and expand upon a previous report that described a trend in decreased eGFR with an increase in proteinuria in a subset of patients after DAA treatment [20]. In that prior study, there was no link to rejection in the subset of patients biopsied. In the study herein, two cases of cellular rejection were noted in the first year after treatment, along with a case of transplant glomerulopathy (TG) on biopsy. No episodes of antibody-mediated rejection or donor-specific antibodies were described.

The exact reason for renal functional decline in this cohort was unclear. There may have been direct renal toxicity exhibited by DAAs, although this has not been reported in the nontransplant population. Some patients may have developed CNI toxicity, as tacrolimus levels increased after completion of treatment, and dose escalation correlated independently with decline in eGFR. However, CNI levels at twelve months post-treatment appeared to be similar to pretreatment levels. RBV was also used in the majority of patients and was associated with a drop in hemoglobin. RBV also commonly causes leucopenia, and, while not reported, this may have led to a reduction in the dosing of adjunct mycophenolate-based immunotherapy, increasing the risk of immunologic injury after treatment.

The differential diagnosis in renal dysfunction after HCV treatment could also include a form of "immune reconstitution syndrome," which has been described with treatment of HIV leading to an *autoimmune* response or response to another infection [21]. Alternatively, HCV treatment in transplant patients may increase the risk of an *alloimmune* response. Cellular immunity has been shown to be impaired with active HCV infection [22,23] and may explain the heightened infectious mortality seen in HCV-infected transplant recipients [24]. HCV-specific $CD8^+$ T cells are restored to normal levels after DAA therapy [25]. It is unknown whether alloimmune T-cell response is also altered by HCV eradication, but the two cellular rejection episodes in this cohort, as well as the case of TG [26], may have been related to an accelerated T-cell response after therapy.

Weaknesses of the study relate to the heterogeneity of the patient population in terms of immunosuppressive therapy and DAA regimens, as well as a lack of a non-treated control group for comparison. Secondly, differences in proteinuria and eGFR on average were modest and of unclear clinical significance. Another acknowledged weakness was the lack of uniform histologic data with biopsy on all patients with allograft deterioration post-treatment.

Regardless, Fernandez-Ruiz and colleagues should be commended for reporting on longer term follow-up beyond the early post-treatment phase of HCV with

Transplant International 2018; 31: 867–869

DAA. Changes in renal function were not noted until 4 months beyond completion of HCV treatment in this cohort. After DAA therapy, a combination of increased drug metabolism and perhaps alteration in cellular immunity may converge to increase immunologic risk. These data show that sustained vigilance is required following DAA therapy, with the need for frequent bloodwork and drug monitoring even in patients out years from transplantation. Future studies with systematic biopsy data may help to further define the etiology of allograft deterioration in some patients after DAA treatment for HCV.

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Conflict of interest

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REFERENCES

1. Pereira BJ, Natov SN, Bouthot BA, *et al.* Effects of hepatitis C infection and renal transplantation on survival in end-stage renal disease. The New England Organ Bank Hepatitis C Study Group. *Kidney Int* 1998; **53**: 1374.
2. Roth D, Gaynor JJ, Reddy KR, *et al.* Effect of kidney transplantation on outcomes among patients with hepatitis C. *J Am Soc Nephrol* 2011; **22**: 1152.
3. Scott DR, Wong JK, Spicer TS, *et al.* Adverse impact of hepatitis C virus infection on renal replacement therapy and renal transplant patients in Australia and New Zealand. *Transplantation* 2010; **90**: 1165.
4. Baid-Agrawal S, Farris AB, Pascual M, *et al.* Overlapping pathways to transplant glomerulopathy: chronic humoral rejection, hepatitis C infection, and thrombotic microangiopathy. *Kidney Int* 2011; **80**: 879.
5. Cruzado JM, Carrera M, Torras J, Grinyo JM. Hepatitis C virus infection and de novo glomerular lesions in renal allografts. *Am J Transplant* 2001; **1**: 171.
6. Fabrizi F, Martin P, Dixit V, Messa P. Meta-analysis of observational studies: hepatitis C and survival after renal transplant. *J Viral Hepat* 2014; **21**: 314.
7. Russo MW, Goldsweig CD, Jacobson IM, Brown JS. Interferon monotherapy for dialysis patients with chronic hepatitis C: an analysis of the literature on efficacy and safety. *Am J Gastroenterol* 2003; **98**: 1610.
8. Ozgur O, Boyacioglu S, Telatar H, Haberal M. Recombinant alpha-interferon in renal allograft recipients with chronic hepatitis C. *Nephrol Dial Transplant* 1995; **10**: 2104.
9. Rostaing L, Izopet J, Baron E, *et al.* Treatment of chronic hepatitis C with recombinant interferon alpha in kidney transplant recipients. *Transplantation* 1995; **59**: 1426.
10. Spengler U. Direct antiviral agents (DAAs) – a new age in the treatment of hepatitis C virus infection. *Pharmacol Ther* 2017; **5**: 2433.
11. Rostaing L, Alric L, Kamar N. Use of direct-acting agents for hepatitis C virus-positive kidney transplant candidates and kidney transplant recipients. *Transpl Int* 2016; **29**: 1257.
12. Fernandez-Ruiz M, Polanco N, Garcia-Santiago A, *et al.* Impact of anti-HCV direct antiviral agents on graft function and immunosuppressive drug levels in kidney transplant recipients: a call to attention in the mid-term follow-up in a single-center cohort study. *Transpl Int* 2018; **31**: 887.
13. Beinhardt S, Al Zoairy R, Ferenci P, *et al.* DAA-based antiviral treatment of patients with chronic hepatitis C in the pre- and postkidney transplantation setting. *Transpl Int* 2016; **29**: 999.
14. Kamar N, Marion O, Rostaing L, *et al.* Efficacy and safety of sofosbuvir-based antiviral therapy to treat hepatitis C virus infection after kidney transplantation. *Am J Transplant* 2016; **16**: 1474.
15. Sawinski D, Kaur N, Ajeti A, *et al.* Successful treatment of hepatitis C in renal transplant recipients with direct-acting antiviral agents. *Am J Transplant* 2016; **16**: 1588.
16. Eisenberger U, Guberina H, Willuweit K, *et al.* Successful treatment of chronic hepatitis C Virus infection with sofosbuvir and ledipasvir in renal transplant recipients. *Transplantation* 2017; **101**: 980.
17. Bhamidimarri KR, Ladino M, Pedraza F, *et al.* Transplantation of kidneys from hepatitis C-positive donors into hepatitis C virus-infected recipients followed by early initiation of direct acting antiviral therapy: a single-center retrospective study. *Transpl Int* 2017; **30**: 865.
18. Gutierrez JA, Carrion AF, Avalos D, *et al.* Sofosbuvir and simeprevir for treatment of hepatitis C virus infection in liver transplant recipients. *Liver Transpl* 2015; **21**: 823.
19. Fabrizi F, Martin P, Dixit V, *et al.* Post-transplant diabetes mellitus and HCV seropositive status after renal transplantation: meta-analysis of clinical studies. *Am J Transplant* 2005; **5**: 2433.
20. Lubetzky M, Chun S, Joelson A, *et al.* Safety and efficacy of treatment of hepatitis C in kidney transplant recipients with directly acting antiviral agents. *Transplantation* 2017; **101**: 1704.
21. Lankisch P, Laws HJ, Wingen AM, *et al.* Association of nephrotic syndrome with immune reconstitution inflammatory syndrome. *Pediatr Nephrol* 2012; **27**: 667.
22. Lauer GM, Barnes E, Lucas M, *et al.* High resolution analysis of cellular immune responses in resolved and persistent hepatitis C virus infection. *Gastroenterology* 2004; **127**: 924.
23. Li GY, Zhou Y, Ying RS, *et al.* Hepatitis C virus-induced reduction in miR-181a impairs CD4(+) T-cell responses through overexpression of DUSP6. *Hepatology* 2015; **61**: 1163.
24. Maluf DG, Fisher RA, King AL, *et al.* Hepatitis C virus infection and kidney transplantation: predictors of patient and graft survival. *Transplantation* 2007; **83**: 853.
25. Spaan M, van Oord G, Kreefft K, *et al.* Immunological analysis during interferon-free therapy for chronic hepatitis C virus infection reveals modulation of the natural killer cell compartment. *J Infect Dis* 2016; **213**: 216.
26. Hayde N, Bao Y, Pullman J, *et al.* The clinical and genomic significance of donor-specific antibody-positive/C4d-negative and donor-specific antibody-negative/C4d-negative transplant glomerulopathy. *Clin J Am Soc Nephrol* 2013; **8**: 2141.