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INVITED COMMENTARY

Should organs from hepatitis C virus-infected donors be used for transplantation in the era of DAAs?*

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*Invited commentary on "Benefits of transplanting 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" by Roth D *et al.*

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Hepatitis C virus (HCV) infection has been demonstrated to deleteriously impact both patient and graft survival following nonhepatic organ transplantation [1,2]. Interferon (IFN)-based therapies prior to nonhepatic transplant in HCV-infected patients improved their survival; however, tolerability and low cure rates practically limited those therapies [3]. In addition, due to the risk of allograft rejection, IFN-based therapy following nonhepatic solid organ transplant is not generally recommended.

The recent appreciation of IFN-free therapy with direct-acting antiviral agents (DAAs) dramatically changes the landscape of HCV infection treatment. Compared to IFN-based regimens, DAAs have less incidence and severity of adverse effects, shorter durations of therapy, and higher cure rates. The advent of safe and highly effective DAA had significant implications for the HCV transplant field and improved the management of both patients on the waiting list and those with HCV graft reinfection after liver transplantation (LT) [4]. Of the IFN-free DAA combinations studied to date in the post-LT population, all have an excellent safety and tolerability profile and hence a significantly lower discontinuation rate when compared to IFN-based regimens [5], although some DAAs would have a limited use due to the frequent drug–drug interactions with various immunosuppressants and the many other drugs LT recipients are frequently prescribed. Those principles of DAA therapy in LT are currently extrapolated to nonhepatic solid organ transplant recipients.

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Although there are currently limited data on the treatment of HCV with DAA following nonhepatic transplant, DAA therapy has the potential to cure HCV-infected candidates and recipients of nonhepatic organ transplant, thereby improving outcomes [3]. A further challenge in nonhepatic organ transplant would a use of HCV-infected donors, with prophylactic therapy using DAAs, to expand the donor pool. The decision to transplant grafts from HCV antibody-positive donors should be a balance between the risk of *de novo* virus transmission and the benefit of expanded access to transplantation. Hence, transplantation of nonhepatic organs from HCV-positive donors should be restricted to HCV-positive recipients as it is associated with a reduced time waiting for a graft and may not affect post-transplant outcomes. Patients with end-stage renal disease (ESRD) without cirrhosis and selected patients with early-stage cirrhosis can be considered for kidney transplant [6]. The use of kidneys from HCV-positive donors likely leads to shorter waiting time for HCV-infected kidney transplant candidates [7]. The risk of HCV transmission may depend on the quality of screening of the donor and the presence/absence of viral replication in the donor at the time of transplantation. Hence, universal use of nucleic acid amplification testing and/or quantify HCV core antigen for the screening of potential organ donors should be reserved to high-risk donors [2]. The risk of HCV superinfection with a second strain of HCV from donors infected with different genotypes may be also taken into account to predict the clinical consequences.

Roth D *et al.* in this issue [8] have performed a single-center retrospective study to investigate the benefits of transplanting kidneys from HCV-positive donors into HCV-infected recipients followed by early initiation of DAA therapy among a cohort of 25 HCV-infected ESRD patients. They found that mean wait-time for kidney transplantation was markedly shortened, and 24 of the 25 patients achieved sustained viral response (SVR) at 12 weeks. Even a case suffering from superinfection with donor HCV strain obtained a SVR with the DAA treatment. Most recently, the similar retrospective studies with small cohorts demonstrated that HCV-positive ESRD patients receiving an HCV-positive donor's kidney could receive DAA therapy and achieved SVR [9,10]. The results of those studies suggest that kidneys from anti-HCV-positive donors should be considered for transplant into HCV-infected recipients followed by early post-transplant treatment with DAA agents. One of the drawback of those studies might be rather short follow-up; hence, no significant conclusions could be drawn regarding long-term clinical benefits to patient and graft survival from viral early eradication. To determine whether the SVR remains durable in patients receiving maintenance immunosuppressive therapy and whether other adverse outcomes associated with HCV infection, such as post-transplant diabetes mellitus and immune-complex glomerular injury to the allograft, are favorably impacted or not, as pointed out by the authors themselves, further prospective studies with larger cohorts investigating long-term outcomes might be needed. Another concern of the early post-transplant treatment with DAAs might be drug–drug interaction with calcineurin inhibitors (CNI). In the study by Roth D *et al.*, tacrolimus dose adjustments were necessary in nearly half patients and some patients developed antibody-mediated rejection during DAA treatment, which was associated with tacrolimus mis-dosing. The mechanism of such altered CNI pharmacokinetics has not be wholly elucidated. The CYP3A genotype status, which has been linked to interindividual variability in dose requirements of CNIs, might also influence drug–drug interaction in patients treated with DAAs. Nevertheless, dosage of CNIs must be monitored closely to prevent mis-dosing in patients treated with DAAs.

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Conflicts of interest

The author discloses no conflicts.

REFERENCES

1. Chan SE, Schwartz JM, Rosen HR. Treatment of hepatitis C in solid organ transplantation. *Drugs* 2004; **64**: 489.
2. Carbone M, Mutimer D, Neuberger J. Hepatitis C virus and non-liver solid organ transplantation. *Transplantation* 2013; **95**: 779.
3. Belga S, Doucette KE. Hepatitis C in non-hepatic solid organ transplant candidates and recipients: a new horizon. *World J Gastroenterol* 2016; **22**: 1650.
4. Belli LS, Duvoux C, Berg T, Strazzabosco M, *et al.* ELITA consensus statements on use of DAAs in liver transplant

candidates and recipients. *J Hepatol* 2017; pii: S0168-8278(17)30140-X.
5. Gane EJ, Agarwal K. Directly acting antivirals (DAAs) for the treatment of chronic hepatitis C virus infection in liver transplant patients: "a flood of opportunity". *Am J Transplant* 2014; **14**: 994.
6. Szer S, Ozdemir FN, Akcay A, *et al.* Renal transplantation offers a better survival in HCV- infected ESRD patients. *Clin Transplant* 2004; **18**: 619.
7. Coilly A, Samuel D. Pros and Cons: usage of organs from donors infected with hepatitis C virus - Revision in the direct-acting antiviral era. *J Hepatol* 2016; **64**: 226.
8. Bhamidimarri KR, Ladino M, Pedraza F, Guerra G, *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.
9. Gallegos-Orozco JF, Kim R, Thiesset HF, Hatch J, *et al.* Early results of pilot study using hepatitis c virus (HCV) positive kidneys to transplant HCV infected patients with end-stage renal disease allowing for successful interferon-free direct acting antiviral therapy after transplantation. *Cureus* 2016; **8**: e890.
10. Sawinski D, Patel N, Appolo B, Bloom RD. Use of HCV+ donors does not affect HCV clearance with directly acting antiviral therapy but shortens the wait time to kidney transplantation. *Transplantation* 2017; **101**:968.