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INVITED COMMENTARY

Reclaiming missed opportunities: a strategy of targeted direct-acting antiviral prophylaxis for HCV-seronegative recipients of HCV-seropositive donor kidneys

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Direct-acting antivirals (DAAs) have cured millions of individuals living with chronic hepatitis C virus (HCV) infection [1]. They have also been shown to be effective and tolerable in transplant recipients [2], with good outcomes using HCV-infected (HCV+) donor organs for HCV+ recipients [3]. Despite these advances, HCV+ donor organs continue to be discarded in the face of a severe organ shortage [4].

An epidemic of opioid overdose deaths in the United States has compounded the HCV+ donor organ discard problem; in 2017, more than one of every eight deceased donors had drug overdose as a cause of death and 30% were HCV-antibody positive (Ab+) [5]. In Europe, although the proportion of overdose death donors has remained stable at <1% [6], high-quality HCV Ab+ donor organs are still declined at higher than expected rates [7]. To address this lost potential, an innovative practice of HCV+ donor to HCV− seronegative (HCV−) recipient transplantation in combination with DAAs is being explored.

In this issue of *Transplant International*, Franco and colleagues report a novel protocol to utilize HCV+ donor kidneys for HCV− recipients using a strategy of targeted DAA prophylaxis based on the risk of donor-derived HCV transmission [8]. The risk depends on whether the donor is viremic, that is, HCV nucleic acid test positive (NAT+). HCV NAT+ donors universally transmit infection whereas HCV NAT-negative (NAT−) kidney donors pose a near-zero risk of transmission except in donors with very recent injection drug use; even in these cases, the risk remains extremely low at 0.32% [9]. In the United States, all deceased donors have HCV NAT performed; however, in Europe, only HCV Ab testing is performed. Accordingly, Franco and colleagues performed rapid HCV NAT for all HCV Ab+ donors to manage the risk of HCV transmission to recipients.

At three centers in Spain, six HCV Ab+ genotype 1 donors were identified over 9 months: two were NAT+ and four were NAT−. Interestingly, one of the NAT+

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donors had recently initiated DAA treatment before death and had a low viral load at 100 IU/ml. The four recipients of HCV NAT+ donor kidneys received one dose of glecaprevir/pibrentasvir 6 h before transplant as prophylaxis and for 8 weeks thereafter. These recipients had no episodes of viremia—even with testing as early as postoperative day 1—and there were no adverse events related to treatment. In addition, there were seven kidney recipients from the four HCV Ab+/NAT− donors; three donors had been cured with DAAs and one presumably cleared infection spontaneously. These recipients were monitored without DAA therapy and also had no evidence of viremia at any timepoint. There were no episodes of rejection. One recipient of an HCV NAT− donor kidney had graft failure unrelated to HCV and the remaining 10 recipients had acceptable graft function with 6–16 months of follow-up.

This is the first study of HCV NAT+ donor kidney transplantation to HCV− recipients in Europe. The practice was first investigated in two clinical trials of kidney transplantation in the United States using distinct DAA strategies [10,11]. The THINKER trial employed a "transmit and treat" approach: HCV genotype 1 NAT+ donor kidneys were transplanted to HCV- recipients who were treated with DAAs (grazoprevir/elbasvir) once viremia was detected. In that study, all 20 patients were viremic by day 3, successfully treated and cured [10]. The EXPANDER trial investigated a pre- and post-transplant DAA prophylaxis approach for recipients of kidneys from HCV NAT+ donors of all genotypes, utilizing grazoprevir/elbasvir and adding sofosbuvir for genotype 2 or 3. None of the 10 recipients demonstrated evidence of chronic HCV [11].

The present study is unique in that HCV NAT+ donor kidney recipients received glecaprevir/pibrentasvir which was not available at the time of THINKER or EXPANDER. Glecaprevir/pibrentasvir is an ideal DAA regimen for a prophylaxis approach since it has activity against all HCV genotypes and HCV genotype is not part of standard deceased donor testing. Furthermore, glecaprevir/pibrentasvir is not renally metabolized, and therefore, it is safe to use even in cases where there is delayed renal allograft function.

In addition to kidney transplantation, there have been several single-center reports of HCV NAT+ donor to HCV-seronegative recipient transplantation with other organs, including observational studies of the "transmit and treat" approach in heart [12] and liver [13] and a clinical trial in heart transplantation [14]. Another pangenotypic DAA regimen, sofosbuvir/velpatasvir, is being investigated as prophylaxis with HCV NAT+ donor to HCV− recipient lung transplantation (ClinicalTrials.gov NCT03086044).

Franco and colleagues decided to use a DAA prophylaxis strategy rather than a "transmit and treat" approach. There remains equipoise over which strategy is optimal for transplant recipients. Proponents of "transmit and treat" strategy have suggested that this approach is more real world since currently, most insurers in the United States require evidence of chronic HCV before approving treatment. This was not an issue in the present study since Spain provides DAAs universally for patients. Other arguments for delaying treatment include the ability to wait until a recipient can reliably take oral medications postoperatively. Administering DAAs via a nasogastric tube may overcome this issue and this was done successfully in the heart transplant trial in one recipient [14]. Prophylaxis has the potential to avoid any clinical consequences of acute HCV in an immunosuppressed patient. The most feared complication would be fibrosing cholestatic HCV which can be fatal post-transplant [15]. Another advantage of prophylaxis is that recipients might not be as concerned about HCV transmission to partners or household members. Finally, it offers the potential advantage of reducing the duration of DAA therapy and the cost of this strategy. In fact, in the present study, Franco and colleagues used 8 weeks of glecaprevir/pibrentasvir rather than the approved 12-week duration for kidney transplant recipients.

In conclusion, Franco and colleagues report the first successful experience of HCV NAT+ donor kidney transplantation to HCV− recipients in Europe, using targeted direct-acting antiviral prophylaxis with a pangenotypic regimen. Future studies of this approach in other settings and with other organs are eagerly anticipated.

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