Editorial Commentary

Expanding the donor pool for lung transplantation using HCV-positive donors

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Despite the increasing numbers of heart and lung transplants within the United States and worldwide and an increased awareness regarding organ donation, there remains a global shortage of donor organs. As a result, the waitlist mortality rate for lung transplantation is approximately 15.3% for all diagnoses in the United States despite introduction of the lung allocation score (1,2), and is higher among those patients listed in areas of low local lung availability (3). These statistics are similar worldwide (13–37% waitlist mortality rate), with as many as 1 in 3 patients with pulmonary fibrosis dying on the waitlist in the United Kingdom (4). As a result, extended criteria donors are considered to maximize organ availability for thoracic transplantation (5,6). The spectrum of extended criteria donors includes those aged >55 years, PaO_2/FiO_2 <300 mmHg on PEEP 5 cmH_2O at time of offer, presence of abnormalities on chest radiography, smoking history, presence of aspiration, presence of chest trauma, or donation after circulatory death. However, extended criteria donors have historically not included "increased-risk donors", whose organs are associated with an increased risk of disease transmission to potential transplant recipients [for example, those with human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infection] (7). As a result, most studies on outcomes of transplants utilizing lungs from extended criteria donors have excluded these recipients (7).

A major hurdle to accepting organs from "increased-risk donors" has been whether these donors can be correctly and rapidly identified, thus increasing the donor pool for transplantation while simultaneously preventing donor-transmitted infections. The HIV Organ Policy Equity (HOPE) Act, enacted on November 21, 2013, calls for the development and publication of research criteria relating to transplantation of HIV positive organs into HIV positive individuals (8). Since then, there have been increasing reports of lung transplants in HIV-positive recipients with controlled HIV infection, while understanding caveats such as the increased risk of acute cellular rejection (9). However, there remains a paucity of data on lung transplantation, either in HCV-positive recipients, or in those who receive organs from HCV-positive donors.

Two clinical trials in renal transplantation have previously demonstrated safety of transplants from donors with hepatitis C infection (D+) into HCV-negative recipients (R–). Specifically, the EXPANDER-1 trial showed that a minimum of 12-week of the direct-acting antivirals (DAA) elbasvir/grazoprevir started immediately before transplantation resulted in no treatment-related adverse events (primary outcome) and hepatitis C RNA (HCV RNA) was undetectable in all ten recipients 12 weeks after the completion of DAA therapy (10). Subsequently, all 20 HCV-negative transplant recipients who received kidneys in the THINKER trial met the primary outcome of treatment cure (11). All of these participants in the THINKER trial received kidneys infected with genotype 1 HCV and were treated with 12–16 weeks of elbasvir-grazoprevir (the duration of therapy being based on the

presence of resistance-associated substitutions in the viral genome). At the 12-month follow-up, serum HCV RNA was undetectable, they maintained a good quality of life, and had good renal function. These two trials suggested that organs from HCV-infected donors may form a valuable resource in the setting of organ shortage.

Based on these studies, the DONATE HCV trial was conducted for the transplantation of hearts and lungs from donors with HCV infection, irrespective of HCV genotype, to HCV-negative recipients (12). A total of 217 potential recipients were screened from March 1, 2017, to July 31, 2018, of whom 75 were eligible for enrollment, and 44 (36 lungs, 8 hearts) received an organ from a donor with hepatitis C viremia (HCV NAT-positive). The recipients were pre-emptively started on sofosbuvir-velpatasvir, a once daily, pan-genotypic DAA. Treatment was initiated within hours post-transplant and continued for a total of 4 weeks. The DAA was crushed and mixed with saline and administered via an enteral (nasogastric, orogastric, or percutaneous endoscopic gastrostomy) tube prior to extubation, and transitioned to a pill when patients recovered their ability to swallow. Sofosbuvir/velpatasvir was also given at least four hours prior to a proton pump inhibitor, or simultaneously with or 12 hours apart from an H2-receptor antagonist, so as not to decrease velpatasvir concentrations. The primary outcome was a composite of (I) a sustained virologic response at 12 weeks after completing antiviral therapy for HCV infection and (II) graft survival at 6 months after transplantation.

The stopping boundary for efficacy was met by February 2018, at which point 35 recipients had been enrolled. The initial manuscript reported data on 44 patients enrolled by July 2018, at which point they had a median follow-up of 284 days (interquartile range, 171–365 days). Of these, 35/44 (79.5%) had follow-up for at least 6 months with monitoring of HCV viral load, anti-HCV antibodies, and liver-function tests after treatment. Basiliximab induction was used at day 0 and day 4 after transplantation. Post-transplant immunosuppression consisted of tacrolimus (goal trough 8–12 ng/mL), mycophenolate mofetil 1,000–1,500 mg twice daily, and prednisone (tapered over 3–6 months to 5 mg daily, assuming no episodes of rejection). Surveillance bronchoscopies with transbronchial biopsies were done at 1, 3, 6, and 12 months and thereafter, based on the recipient's clinical status.

There were no reported issues with the enteral administration of sofosbuvir/velpatasvir in the participants. HCV RNA was detected in the circulation in 42/44 (95%) recipients soon after transplantation. The viral load in the recipient was proportional to that of the donor (median 1,800 IU/mL, IQR 800–6,180 IU/mL), but was undetectable within 2–3 weeks (n=44), and remained undetectable at 12 and 24 weeks after transplantation (n=35). Among study subjects with documented virologic remissions at week 24 post-completion of DAA therapy, the rate of anti-HCV positivity decreased from 27/35 (77%) within 1 week after transplantation, to 17/35 (49%) at 6 months after transplantation. In addition to having a sustained virologic response at 12 weeks, only 2 recipients of HCV NAT-positive lungs had liver function results >3 times the upper limit of normal range within 30 days of transplantation (7% *vs.* 11% in recipients from HCV-negative donors) and after 30 days of transplantation (7% *vs.* 16% in recipients from HCV-negative donors). No adverse events were attributed to the antiviral regimen, and were similar in the two groups at 30 days and 6 months after transplantation. In the first 30 days post-transplantation, 7 recipients developed Grade III atrial fibrillation, 3 of whom received amiodarone. No clinically significant arrhythmia was observed in these patients, despite the risk of symptomatic bradycardia associated with the co-administration of amiodarone and sofosbuvir (13). There were also no significant differences in Stage 4 or 5 chronic kidney disease at 6 months between either group (29% *vs.* 20%) or overall survival at 6 months (100% *vs.* 98% in HCV-negative donors).

A majority of the donors had HCV genotype 1 (61% donors, of which 96% had genotype 1a). Genotype 2 and 3 were present in 17% of donors (each) and the genotype was indeterminate in 5% of the donors. There were also differences in recipients demographics; those who received a lung from HCV NAT-positive donors were less likely to be male (39% *vs.* 66%, P=0.03), had a lower lung-allocation score (median LAS 33.3–38.16, P<0.001) and were less likely to have restrictive lung disease (29% *vs.* 68%, P<0.0001). Understandably, donors with HCV NAT-positive lungs were more likely to be considered "increased risk donors" (100% *vs.* 20%, P<0.0001).

The results of this trial bring up at least three questions for the lung transplant community.

Is this the right approach to ensure recipients can get lungs from increased risk donors while minimizing the risk of donor transmitted HCV infection?

Acute HCV infection occurs within the first 6 months of

transmission and is recognized by detectable HCV RNA with either a negative anti-HCV antibody, or evidence of anti-HCV seroconversion within the past 12 months. In comparison, chronic HCV infection is defined as persistence of HCV RNA in the bloodstream for greater than 6 months (14). When utilizing a pre-emptive strategy as used in the DONATE HCV trial, most (95%) of the recipients had a detectable HCV viral load, but this became undetectable within 3 weeks of treatment, and these recipients had a sustained virologic response at 12 weeks following the end of therapy. Additionally, epidemiological data would suggest that HCV does not recur in greater than 99% of the cases with a sustained virologic response, regardless of immunosuppression (15). Thus, this strategy ensures HCV infection, even if it occurs, can be cured in transplant recipients. The bigger issue is whether a pre-emptive strategy—such as what was used in the DONATE HCV trial—is a more effective approach than delayed treatment. Pre-emptive treatment carries the primary benefit of minimizing the risk of viremia; however, 10% of organ recipients do not get infected with HCV; and the behavior of DAAs has not been comprehensively evaluated in the perioperative setting. These issues would suggest that the efficacy of delayed treatment should be evaluated, while understanding that such an approach carries at least some risk of acute hepatitis. Based on data from cardiac transplantation using such an approach, a majority of these recipients (9 of 13, 69%) develop HCV viremia after heart transplantation. Among these, most, if not all, have a sustained virologic response within 12 weeks after transplant (16). Such studies are ongoing in the lung and the final results are eagerly awaited.

How likely are "HCV mismatched" lung transplants to have worse outcomes compared to those transplants from donors without HCV infection?

The existing data from the DONATE HCV trial would suggest there were no major differences in outcomes in those receiving lungs from NAT-positive donors compared to those from HCV-negative donors (12). Despite the mean donor ischemic time being higher when transplanting HCV NAT-positive lungs (328 *vs.* 281 min), there was no grade 3 primary graft dysfunction at 72 hours in recipients of lungs from HCV NAT-positive donors. While the proportion of acute cellular rejection (ACR) necessitating treatment was lower in recipients receiving lungs from HCV-negative donors [30% *vs.* 54%, OR 0.37 (0.12–1.09)], none of the patients receiving HCV NAT-positive lungs had high-grade ACR, it was unrelated to the initial HCV load, and all responded to the initial treatment of pulse-dose steroids. There was also no difference in overall survival. However, the follow-up period has been modest (often less than or equal to 12 months) and the long-term results are awaited. Importantly, we do not fully understand how hepatitis C viremia modulates the alloimmune response (17). This is especially important in the delayed treatment strategy, where the viral load may be higher, even transiently. The effect of viral replication on long-term outcomes after lung transplantation has been most appreciated for cytomegalovirus (CMV), and to some extent, with Epstein Barr virus (EBV) (18,19). Transplant centers have used either a pre-emptive or delayed strategy for patients who receive an organ from a CMV positive donor, with varying durations of prophylaxis (20-22), with the goal of minimizing the risk of CMV disease, which is associated with chronic lung allograft dysfunction and an independent risk of death (22). Unlike CMV, however, HCV is curable. Yet, we will need an adequate follow up with both the pre-emptive and delayed treatment strategy for HCV to ensure there are no adverse events on the immune response and thus, on long-term transplant outcomes. This is especially important given the uncertainty whether a delayed treatment strategy carries an increased risk for relapse despite achieving an undetectable viral load short-term.

How much does include HCV+ donors truly expand the donor pool in lung transplantation?

There is evidence that declining lungs from "increased-risk donors" results in a longer time on the waiting list (23) and a higher waitlist mortality, even though the post-transplant survival appears to be the same. In 2018, our organ procurement organization was presented with 21 organ donors of which 12 had detectable HCV RNA (with or without anti-HCV positivity) and 9 had a reactive anti-HCV test but undetectable HCV RNA. In this group of 42 potential lungs, only 10 were recovered for transplant. It is, thus, conceivable that strategies like those employed in the DONATE HCV trial could have increased organs available for transplant within our OPO alone.

However, there are multiple questions that remain, such as whether preemptive DAA therapy be covered by third party payers in the way that antiviral therapy for the

prevention of CMV infection is covered. In cases of CMV, historically insurance providers have agreed to provide coverage; however, this is with the understanding that untreated CMV infection has clear detrimental long-term outcomes post-transplant (18,19,22). Second, the current studies are too small to know whether pre-emptive therapy is better than delayed therapy. In addition to the risk of acute hepatitis, cases of relapse are rare but possible (24,25). We hope to see the data on relapse rates in thoracic organ transplantation as these recipients are followed up over longer periods of time. Lastly, these initial studies have been in small numbers of subjects and as the practice expands, instances of potential viral resistance or unusual scenarios may arise that preclude treatment. This is complicated by the fact that the pharmacokinetics and pharmacodynamics of administration of non-pill forms of DAA therapy are not known for many of the DAAs. Hence, while we continue to aim to expand the donor pool, we as a field need to continue our endeavors where we find different methods to improve the utilization of marginal organs.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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