Lung Transplantation from Hepatitis C Viremic Donors to Uninfected Recipients

To the Editor:

The scarcity of donor lungs is a significant factor contributing to respiratory death while awaiting lung transplantation. The average waitlist mortality rate in the United States in 2015 was 16.5 deaths per 100 waitlist years (1). Current practice for the use of hepatitis C virus (HCV)-infected donor lungs has been to use them only for HCV-positive recipients, although this has not been broadly adopted by all centers. The recent development of direct-acting antivirals (DAAs) has now made HCV curable in virtually all those infected, leading to the consideration of using these infected organs to expand the donor pool. In addition, there are increasing numbers of HCV viremic donors associated with the opioid crisis, many of whom are young, with normal lung function, and otherwise excellent potential donors (2). A pilot trial of kidney transplants from HCV viremic donors to 10 HCV uninfected recipients demonstrated universal transmission with 100% sustained virologic response after 12 weeks of elbasvir/grazoprevir post-transplant (3). Current guidance identifies the use of HCV-infected donors as a priority for further research (4). To date, only one case of intentional transmission of HCV from a viremic donor to uninfected lung recipient has been described (5). Lung recipients receive higher-intensity immunosuppression than renal recipients, and can rarely be initiated on oral therapy immediately after transplant. Therefore, the safety of lung transplantation from infected donors to negative recipients with post-transplant DAAs requires further evaluation.

We present a case series describing outcomes of lung transplantation from five HCV viremic donors to negative recipients between November 2016 and February 2017 at the University of Alberta Hospital (University of Alberta Research Ethics approval Pro000075225) after informed consent and discussion of potential risks and benefits with patients/decision makers. All patients were rapidly deteriorating, with several being bridged to transplant with mechanical respiratory support, leaving only a small window of remaining transplant eligibility (Table 1). All the donors were female, and four of the five were aged 40 years or younger. Of these four donors, all were known to have chronic hepatitis C infection and had never been treated with antiviral therapy. They all continued to engage in high-risk behaviors in the 12 months before their death, including intravenous drug use, high-risk sexual contact, recent incarceration, and recent unprofessional tattoos. One additional donor, age 64 years, had positive serology and nucleic acid testing at the time of transplant workup. Despite a history of blood transfusion in 1982, the donor had never been previously screened for HCV. Donor HCV RNA viral load at the time of transplant ranged from 645 IU/mL to 2.1 million IU/mL, using the Abbott RealTime Assay (Abbott Laboratories). The ischemic time for the second lung to be implanted ranged from 363 to 663 minutes, with two out of five greater than 480 minutes because of retrieval from distant regions in Canada. In two cases (patients 1 and 2), HCV RNA was detected between Days 1 to 16 after transplant (Figure 1). In the two cases in which donor lungs were receiving *ex vivo* perfusion before transplant (patients 1 and 2), HCV RNA was first detected in the recipients at 8 and 16 days, respectively. The best *Pab*0, in donor arterial blood ranged from 300 to 479 mm Hg.

Three patients received basiliximab induction therapy and two received no induction therapy, as they were mismatched for Epstein-Barr virus (donor positive/recipient negative), and thus were at increased risk for post-transplant lymphoproliferative disease. All received maintenance immunosuppression with tacrolimus, mycophenolate, and prednisone. HCV RNA was first detected between Days 1 to 16 after transplant (Figure 1). In the two cases in which donor lungs were receiving *ex vivo* perfusion before transplant (patients 1 and 2), HCV RNA was first detected in the recipients at 8 and 16 days, respectively. These recipients, however, went on to have the highest peak viral loads, both higher than 7 log10 (Table 1). Three recipients had genotype 1a, one genotype 1b, and one genotype 2 infection. The four recipients with a genotype 1 infection received sofosbuvir/ledipasvir, and the patient with genotype 2 infection received sofosbuvir/velpatasvir, all for 12 weeks. Initiation of DAA therapy after transplant ranged from

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<th>Case Number 1</th>
<th>Case Number 2</th>
<th>Case Number 3</th>
<th>Case Number 4</th>
<th>Case Number 5</th>
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<tr>
<td><strong>Age, yr</strong></td>
<td>65</td>
<td>65</td>
<td>43</td>
<td>40</td>
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<tr>
<td><strong>Sex</strong></td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>M</td>
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<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>31.6</td>
<td>26.9</td>
<td>21.3</td>
<td>28.5</td>
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<tr>
<td><strong>Primary diagnosis</strong></td>
<td>Idiopathic pulmonary fibrosis</td>
<td>Sjögren’s-related pulmonary fibrosis</td>
<td>Idiopathic pulmonary arterial hypertension</td>
<td>Alpha-1 antitrypsin deficiency</td>
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<tr>
<td><strong>Lung allocation score at transplant</strong></td>
<td>43.2</td>
<td>33.2</td>
<td>37.3</td>
<td>58.4</td>
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<tr>
<td><strong>Type of transplant</strong></td>
<td>Double lung</td>
<td>Double lung</td>
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<tr>
<td><strong>Ex vivo lung perfusion (min)</strong></td>
<td>Yes (195)</td>
<td>Yes (315)</td>
<td>No</td>
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<td><strong>Induction therapy</strong></td>
<td>Basiliximab</td>
<td>Basiliximab</td>
<td>Basiliximab</td>
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<td><strong>Post-transplant immunosuppression</strong></td>
<td>Tacrolimus, prednisone, and mycophenolate</td>
<td>Tacrolimus, prednisone, and mycophenolate</td>
<td>Tacrolimus, prednisone, and mycophenolate</td>
<td>None</td>
</tr>
<tr>
<td><strong>HCV genotype</strong></td>
<td>2</td>
<td>1b</td>
<td>1a</td>
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<tr>
<td><strong>Baseline liver stiffness measured by FibroScan, kPa</strong></td>
<td>12.2</td>
<td>4.4</td>
<td>6.8</td>
<td>16.9</td>
</tr>
<tr>
<td><strong>Recipient peak HCV viral load, IU/mL, and days to peak</strong></td>
<td>22,507,604 IU/mL at 22 d</td>
<td>62,163,571 IU/mL at 52 d</td>
<td>1,935,026 IU/mL at 31 d</td>
<td>1,204,344 IU/mL at 23 d</td>
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<tr>
<td><strong>Time to HCV therapy start post-transplant, d</strong></td>
<td>28</td>
<td>94</td>
<td>83</td>
<td>24</td>
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<tr>
<td><strong>Antiviral regimen</strong></td>
<td>Sofosbuvir/velpatasvir</td>
<td>Sofosbuvir/ledipasvir</td>
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<td><strong>Duration of treatment, wk</strong></td>
<td>12</td>
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<tr>
<td><strong>SVR12</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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(Continued)
Table 1. (Continued)

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<th>Case Number 3</th>
<th>Case Number 4</th>
<th>Case Number 5</th>
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<tbody>
<tr>
<td>Serious adverse events and complications post-transplant</td>
<td>Primary graft dysfunction</td>
<td>Primary graft dysfunction</td>
<td>Primary graft dysfunction grade 3 requiring ECMO support</td>
<td>Large liver hematoma</td>
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<tr>
<td></td>
<td>Postoperative delirium</td>
<td>Persistent gastrointestinal bleeding</td>
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<td>Critical illness neuropathy with prolonged rehabilitation</td>
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<tr>
<td></td>
<td>Aspiration requiring reintubation</td>
<td>Clostridium difficile infection</td>
<td></td>
<td>Superficial wound infection with debridement</td>
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<td>Percutaneous endoscopic gastrostomy tube for swallowing dysfunction (now removed)</td>
<td>Antibody-mediated rejection treated with plasmapheresis, IVIG, and steroids</td>
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<td>Scedosporium sternal osteomyelitis requiring debridement</td>
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<tr>
<td></td>
<td>Critical illness polyneuropathy (legs predominantly)</td>
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<tr>
<td></td>
<td>PEG and tube feeds</td>
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**Definition of abbreviations:**
- BIPAP = bilevel positive airway pressure
- BMI = body mass index
- ECMO = extracorporeal membrane oxygenation
- HCV = hepatitis C virus
- IVIG = intravenous immunoglobulins
- MRSA = methicillin-resistant Staphylococcus aureus
- PEG = percutaneous endoscopic gastrostomy
- SVR12 = sustained virologic response 12 weeks after completion of therapy.
24 to 94 days (Table 1), starting as soon as recipients were judged to be clinically stable and able to complete oral therapy uninterrupted. All patients completed therapy without attributable adverse effects. All achieved sustained virologic response, were discharged from hospital, and are alive at 9–12 months after transplant.

There were no acute changes in kidney function or liver enzymes during the treatment course or follow up. None of the patients had clinical concerns regarding liver disease during work-up and listing for lung transplant. Baseline liver stiffness measurement was performed by FibroScan (Echosens, France; distributed by KNS Canada) on all patients after lung transplantation but before initiation of DAA therapy. The highest measurement was 16.9 kPa, seen in the transplant recipient who had underlying alpha-1 antitrypsin deficiency. Although no recipients developed HCV or DAA-related adverse effects, all had complicated postoperative courses mainly attributable to the severity of their underlying condition before transplant (Table 1). Major complications, each occurring in a single patient, included post-transplant lymphoproliferative disease, critical illness polyneuropathy, recurrent peptic ulcer–related gastrointestinal bleeding, recurrent pneumonia requiring intubation, post-transplant requirement for extracorporeal membrane oxygenation for primary graft dysfunction, lung infarction necessitating pneumonectomy, antibody-mediated rejection requiring plasmapheresis, intravenous gamma globulin and rituximab, and sternal osteomyelitis because of Scedosporium apiospermum.

This case series provides evidence to support the use of HCV viremic organs for HCV-negative lung recipients. Despite the severity of illness at transplant and numerous post-transplant complications resulting in delayed initiation of DAA therapy, all recipients were cured without any adverse effects attributable to either the acquired HCV infection or the DAA therapy. Routine use of such organs, when otherwise medically acceptable, has the potential to expand the donor pool.

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References


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**Disproportionate Right Ventricular Dysfunction and Poor Survival in Group 3 Pulmonary Hypertension**

To the Editor:

Pulmonary hypertension (PH) due to chronic lung disease, classified as World Health Organization (WHO) group 3 PH (1), is the second most common cause of PH after left-heart disease (2). Group 3 patients have a lower quality of life, higher medical costs, and worse survival compared with patients with chronic lung disease but without PH (3). Despite the large clinical burden and poor prognosis of group 3 PH, its long-term outcomes and clinical, echocardiographic, and hemodynamic characteristics are not well described. Furthermore, despite the large clinical burden of this disease, there are no approved therapies for patients with group 3 PH. Thus, we need to better understand the clinical characteristics and outcomes of group 3 PH to identify possible therapeutic targets.

We examined 122 patients with group 3 PH and 155 patients with group 1 PH from the University of Minnesota Pulmonary Hypertension Repository (4). Group 3 PH and group 1 PH were defined according to the WHO classification criteria (1, 5). In the group 3 population, PH was associated with interstitial lung disease in 55 patients, chronic obstructive pulmonary disease (COPD) in 45, obstructive sleep apnea or obesity-hypoventilation syndrome in 11, and combined pulmonary fibrosis and emphysema in 11. The etiology of PH in the group 1 population included idiopathic, heritable, or drug-induced disease (n = 48), connective tissue disease (n = 59), liver disease (n = 24), congenital heart disease (n = 18), human immunodeficiency virus infection (n = 2), and other causes (n = 4). Fifty-two group 3 patients (43%) and 65 group 1 patients (42%) were incident cases.

Compared with group 1, the group 3 cohort was older, had a higher proportion of males, and had more comorbidities, including hypertension, diabetes, hyperlipidemia, coronary artery disease, obesity, and atrial fibrillation, resulting in a significantly higher Charlson comorbidity score (Table 1). There was no difference in WHO functional class between the groups. At the time of referral, group 3 patients were more likely to be on supplemental oxygen and digoxin, and less likely to be on pulmonary vasodilator therapy. Use of diuretics did not differ between the groups. Group 3 patients had lower 6-minute-walk distances and more exercise-induced hypoxemia. On pulmonary function tests, group 3 patients had lower lung volumes and lower DLCO values. There were no intergroup differences in serum N-terminal pro-B-type natriuretic peptide levels or serum creatinine (Table 1).

Group 3 patients had higher left ventricular mass and end-diastolic diameters (Table 1). There was no difference in right ventricular (RV) dimensions (Table 1), but group 3 patients had lower RV fractional area change (RVFAC) values (Figure 1A, top). When RVFAC was plotted against mean pulmonary artery pressure (mPAP), the rate of decline in RVFAC with increasing mPAP was similar between the two PH groups (Figure 1A, bottom). However, group 3 patients had lower RVFAC values for any given mPAP than group 1 patients (Figure 1A, bottom). Despite the lower RVFAC values, group 3 patients had a lower prevalence of right atrial enlargement and pericardial effusion than group 1 patients.

A hemodynamic evaluation showed that group 3 patients had lower mPAP and pulmonary vascular resistance, with higher pulmonary arterial compliance, pulmonary capillary wedge pressure, and cardiac output when compared with group 1 patients. Right atrial pressure and cardiac index did not differ between the two PH populations (Table 1).

The patients were followed routinely in the clinic every 3–6 months. Vital statistics were obtained from the Minnesota death index and chart review. No patient was lost to follow-up. There were 59 deaths in group 3 and 52 deaths in group 1 over a median follow-up of 2.3 years. Survival was significantly worse in group 3 patients compared with group 1 patients. The 1-, 3-, and 5-year survival rates in group 3 and group 1 patients were 80% and 95%, 48% and 82%, and 30% and 62%, respectively (hazard ratio [HR], 2.5 [95% confidence interval (CI), 1.7–3.7; P < 0.001]; Figure 1B, top). This remained significant after adjusting for age, sex, and Charlson comorbidity index (HR, 1.5 [95% CI, 1.0–2.3; P = 0.046]). The 1- and 2-year survival rates in the incident cohort were also worse in group 3 PH compared with group 1 PH (80% vs. 90%, and 55% vs. 82%, respectively; HR, 2.5 [95% CI, 1.1–5.6; P = 0.026]; Figure 1B, bottom).

In the group 3 PH population, there was no difference in survival when COPD PH was compared with interstitial lung disease PH.

Consequently, although they had less severe pulmonary vascular disease, group 3 patients had worse RV function, reduced exercise capacity, and worse survival than group 1 patients. The mechanisms underlying the worse RV function in group 3 PH are unclear, but there are several possible explanations. First, patients with COPD but without PH have impaired RV function (6). This airflow-dependent RV dysfunction is hypothesized to result from hypoxemia, inflammation, lung hyperinflation, and/or endothelial dysfunction (6). Thus, patients with group 3 PH may have additional, nonhemodynamic insults to the RV resulting in RV dysfunction that is disproportionate to the PH severity. Another possible reason for the worse RV function in group 3 patients is the higher proportion of males in this group. Consistent with this hypothesis, healthy males were found to have lower cardiac magnetic resonance–calculated RV ejection fraction values than females in the MESA (Multi-Ethnic...