

79270\_Auto\_Edited.docx

**Name of Journal:** *World Journal of Transplantation*

**Manuscript NO:** 79270

**Manuscript Type:** MINIREVIEWS

## **A Review of Heart Transplantation from Hepatitis C-positive Donors**

Palak Patel, Nirav Patel, Fahad Ahmed, Jason Gluck

### **Abstract**

Significant scarcity of donor pool exists for heart transplantation (HT) as the prevalence of patients with end-stage refractory heart failure is increasing exceptionally with constant rate of HT being performed. With the discovery of effective direct-active antiviral (DAAs) and favorable short-term outcomes following HT, the hearts from hepatitis C virus (HCV) are being utilized to increase the donor pool. Short-term outcomes with regards to graft function, coronary artery vasculopathy, kidney and liver disease is comparable in HCV-negative recipients undergoing HT from HCV-positive donors compared to HCV-negative donors. Significant high incidence of donor derived HCV transmission was observed with great success of achieving sustained viral response with use of DAAs. By accepting HCV-positive organs, the donor pool has expanded with younger donors, shorter waitlist time and reduction in waitlist mortality. However, the long-term outcomes and impact of specific HCV genotype remains to be seen. We are reviewing current literature of HT from HCV-positive donors.

### **INTRODUCTION**

Heart failure (HF) prevalence is increasing with 6.2 million adults from 2013 to 2016 compared to 5.7 million from 2009 to 2013 and estimated to increase by more than 8 million by 2030.<sup>[1,2]</sup> 10-15% of patients will develop end-stage refractory HF requiring

advanced therapies including orthotopic heart transplantation (OHT) or durable mechanical support therapies.<sup>[2,3]</sup> There is a substantial mismatch between donors and recipients as there is increasing prevalence of HF over the years with a constant rate of OHT performed. During 2018, 268 patients died while waiting for OHT with 3883 patients being added to the transplant list and 3440 OHTs performed.<sup>[4]</sup> Expanding the donor pool with utilization of organs from hepatitis C virus (HCV)-positive individuals seems an opportunity to close this gap.

Historically, HCV-positive donors were not considered due to high risk of HCV transmission, ineffective and unsafe HCV treatments, and overall inferior survival following HT.<sup>[5,6]</sup> With the discovery of direct-acting antivirals (DAAs), the donor pool has expanded with an addition of HCV-positive donors due to great success of treating HCV, limited interaction with immunosuppression and optimal short-term outcomes following HT. Data of long-term outcomes are scarce and there is wide variation with use of different DAAs agents and optimal initiation among the studies. Therefore, we aim to review the current literature of HT from HCV-positive donors in HCV-negative recipients and discuss the epidemiology, outcomes of HT in pre- and post-DAA era, complications, and potential barriers for more widespread utilization of HCV-positive donors.

## **METHODS**

We searched the terms “heart transplant”, “organ transplant”, “transplant”, and “hepatitis C” in various combinations in Medline up to November 2021.

## **DONOR HCV STATUS CLASSIFICATION**

HCV infection in donors can be classified using two serological markers. HCV antibodies (Ab) which typically present after 6-8 wk of exposure to HCV<sup>[7]</sup>, and nucleic acid testing (NAT) which is present during an active infection occurring after three to four days of exposure to HCV.<sup>[8,9]</sup>

HCV Ab-positive NAT-negative

These donors have spontaneously cleared the virus or treated with antiretrovirals. There is low to no risk of transmission of the virus to the recipient.<sup>[10,11]</sup>

HCV Ab-positive NAT-positive

These donors have an ongoing infection or chronic active hepatitis, high risk of transmission of HCV to the recipient.

HCV Ab-negative NAT-positive

This occurs in acute HCV infection without adequate time for Ab production against HCV. High risk of transmission in solid organ transplant.

HCV Ab-negative NAT-negative

This occurs in the eclipse period (within a week) of acquisition of HCV when NAT is not detectable with negative HCV Ab. This typically includes high-risk donors, intravenous drug users (IVDU), the potential of such donors is 32.4 per 10,000 in the United States (US).<sup>[12]</sup>

### **EPIDEMIOLOGY AND HCV-POSITIVE DONOR POOL**

HCV, single-stranded RNA virus, is the most frequent blood-borne infection common among IVDU.<sup>[13,14]</sup> The World Health Organization reports a worldwide prevalence of HCV is 71 million with an annual incidence of 50,300 in 2018 in the US and a 3-fold increase from 2009 to 2018 with a rate of 0.3 to 1.2 per 100,000 population.<sup>[15]</sup>

The prevalence of HCV infection among IVDU increased from 28% in 2008 to 40% in 2015 in North America,<sup>[14,16]</sup> and it is estimated to increase by 43% by 2030.<sup>[17]</sup> The donor pool of HCV-positive is increasing by 10-fold due to the current opioid epidemic in the US and increase in deaths related to overdose since 2000 which is on the rise from 15.1% in 2010 to 26.1% in 2018.<sup>[18]</sup> In 2020, 12 mo period ending May 2020 81,230 deaths due to opioid overdose increased by 38.4% since June 2019 and these are younger victims without significant comorbidities with potential for prolonged organ survival following HT.<sup>[19,20]</sup> The United Network of Organ Sharing reported HT from HCV-positive donors is on the rise from 247 to 362 HT from HCV-positive donors from 2018 to 2019. A single center reported doubling their transplant volume by utilizing HCV-positive hearts from

130 to 260 from 2013 to 2018, with a reduced mean waiting period of four days.<sup>[21]</sup> Nationwide utilization of HCV-positive donors can increase the number of HT resulting in reduction in the waiting period and closing gap between donors and recipients.

### **HCV-POSITIVE TRANSPLANT IN PRE-DAA ERA**

Limited data are available of HT from HCV-positive donors in the pre-DAA era (**Table 1**). Studies reported a high transmission rate of HCV with an inferior survival rate of 70% at 1-year compared to 89% in controls,<sup>[5]</sup> at 10 year survival rate of 25% in HCV-positive group *vs* 53% in controls.<sup>[22]</sup> Due to higher incidence of cardiac allograft rejections, cardiac allograft vasculopathy, progression to chronic HCV infection, and liver disease.<sup>[5]</sup> Haji *et al* reported HCV seropositivity as an independent risk factor for overall mortality by 2.8-fold and increased incidence of CAV by 3-fold.<sup>[23]</sup> Historically, Interferon-based therapy was being utilized for HCV infection which demonstrated poor tolerability and risk of interactions with immunosuppressants.<sup>[24]</sup> Due to these complications and decreased overall survival, the use of HCV-positive donors diminished until recent years following the discovery of DAAs.

### **HCV-POSITIVE TRANSPLANT IN POST-DAA ERA**

In 2011, DAAs were introduced, demonstrating high efficacious in eradicating HCV and achieving remission.<sup>[25]</sup> In 2013, the combination of Sofosbuvir and Simeprevir achieved 92% sustained virologic response (SVR) at 12-weeks after completion of antiretroviral regimen without the addition of historical medications such as Interferon and Ribavirin.<sup>[26]</sup> In 2014, a four-drug combination was approved for acute HCV infection with Ombitasvir, Paritaprevir, Ritonavir, and Dasabuvir which achieved 100% SVR,<sup>[27]</sup> and these DAAs used in post-transplant recipients and achieved comparable SVR to non-transplanted patients.<sup>[11,25,28–30]</sup> The overall survival in HCV-negative recipients receiving hearts from HCV-positive donors are comparable HCV-negative donors and we described these studies in (**Table 2**).

## **POTENTIAL COMPLICATIONS OF HEART TRANSPLANTATION IN HCV-NEGATIVE RECIPIENT FROM HCV-POSITIVE DONOR**

### **HCV Contraction**

HCV contraction is 82 to 100% from HCV NAT-positive donors. Schlendorf *et al* demonstrated 95.7% of donor-derived HCV (dd-HCV) from HCV NAT-positive donors<sup>[11]</sup>, and the risk of acquiring HCV from HCV Ab-positive and NAT-negative donors are low. One study demonstrated no viremia up to 1-year in ten HCV-negative recipients receiving hearts from NAT-negative donors.<sup>[11]</sup> The risk of developing HCV is variable across all the studies, but it appears it is reduced with the use of HCV NAT-negative donors compared to HCV NAT-positive donors. All patients with dd-HCV achieved SVR across all studies with DAAs treatment.

### **Cardiac Allograft Rejection**

Transplant allograft rejection, either cellular or antibody-mediated, is associated with poor allograft survival and increased mortality.<sup>[31]</sup> Pre-DAA era, the studies have demonstrated an increased rate of allograft rejection in heart transplant recipients from HCV-positive donors, and the risk is directly associated with viremia post HT.<sup>[5,32,33]</sup> Two potential pathways are linked with allograft rejection from HCV infection. The first is the activation of lymphocytes predominately T-cells through direct and indirect pathways affecting the endothelium, and the second is direct allograft injury is mediated with upregulation of interferon-alpha, apoptotic and proliferative genes.<sup>[34]</sup> The incidence of allograft rejection was 58% in 12 HCV-negative recipients undergoing HT from HCV NAT-positive donors compared to 30% in 13 HCV NAT-negative donors with mean follow up of 147 days.<sup>[35]</sup> Another study demonstrated allograft rejection of 12% and 3% in HCV-negative recipients from HCV Ab-positive NAT-positive compared to HCV Ab-positive NAT-negative donors at 180 days follow-up, respectively. The time to first-event of rejection was earlier in recipients with NAT-positive compared to NAT-negative donors demonstrating viremia directly plays a role in acute allograft rejection.<sup>[33]</sup> Schlendorf *et al* reported two events of acute cellular rejection requiring treatment in recipients who became viremic at mean of 4 days

and the initiation of DAAs were delayed as they were introduced on outpatient basis at mean of 33 days.<sup>[36]</sup> Therefore, early detection and aggressive implementation of DAAs are required to decrease the incidence of allograft rejection. Overall short-term survival in the current era is similar, but the long-term risk of allograft rejection remains to be seen.

2

### Cardiac Allograft Vasculopathy

CAV is the major cause of morbidity and mortality following HT with an incidence of 8% at 1-year and 50% at 10-year<sup>[37]</sup>, and the risk of CAV is increased by 3-fold in donor derived HCV recipients.<sup>[23]</sup> The pathophysiology of CAV is not completely understood, but presumed to be immune-mediated endothelial injuries observed with elevated intracellular adhesion molecule-1 in HCV infected patients.<sup>[38]</sup> The risk was observed to be further increased with B cell cross reactivity in HCV positive heart recipients.<sup>[23]</sup> CAV has been associated with increased alloimmune response.<sup>[39,40]</sup> CAV directly affects the longevity of the graft, but treatment of DAAs rapidly clears viremia and studies have demonstrated no statistically significant risk of CAV at 1-year following HT from HCV-positive donors.<sup>11,39</sup> Zalawadiya *et al* reviewed intracoronary ultrasound on 54 HCV-negative recipients from HCV-positive hearts treated with ledipasvir-sofosbuvir for 12 or 24 wk following HT and up to 1-year follow up, and they found no significant difference of CAV compared to control group.<sup>[41]</sup> Schlendorf *et al* also showed 29 recipients receiving hearts from HCV-positive had no statistically significant incidence of CAV compared to HCV-negative donors.<sup>[11]</sup> All current studies are single-centered, small sample size with short term follow-up of 1 year. However, compared to the pre-DAA era, the evidence shows that there is decreased reduction in incidence of CAV secondary to rapid and effective clearance of HCV with DAA-based therapy. Long term risk of CAV and its impact on graft survival remains to be explored.

### Liver Disease

A higher incidence of liver disease was noted in the pre-DAA era attributing to increased mortality in HCV-positive recipients.<sup>[22]</sup> HCV is a known cause of progressive

liver disease leading to liver cirrhosis and risk for hepatocellular carcinoma (HCC)<sup>[42]</sup>, early eradication of HCV reverses the liver damage that is caused by inflammation from HCV and decrease the incidence of downstream effects. Untreated HCV in transplant patients resulted in fulminant liver failure, cholestatic liver disease and chronic hepatitis.<sup>[43–45]</sup>

Pre-DAA recipients receiving hearts from HCV-positive donors had higher liver-related mortality with hazard ratio of 5.9.<sup>[46]</sup> In immunocompromised hosts, the progression to advanced liver disease and cirrhosis is accelerated by a median of 2 to 10-years compared to 30 years in immunocompetent individuals,<sup>[47]</sup> and the recipients receiving antilymphocyte preparation peri-transplant has higher risk of liver disease.<sup>[48]</sup> HCV has 6 different genotypes with 1 to 4 being the most the common world-wide,<sup>[49,50]</sup> genotype 1b and 3b are associated to higher rate of liver disease compared to others,<sup>[51,52]</sup> and genotype 2 carries the improved overall survival with hepatocellular carcinoma (HCC) but others can lead to progressive liver disease to HCC as well<sup>[53]</sup> Both antiviral therapies including IFN or DAAs reduce the risk of HCC following achievement of SVR,<sup>[54]</sup> but DAAs are more tolerable and efficacious compared to IFN.<sup>[55]</sup> All HCV genotypes can be responsive with various combination of DAA treatment. Although, we did find two case reports of relapse with DAA treatment.<sup>[56,57]</sup>

#### DAA in Heart Transplant Recipients

No data are available about the optimal initiation for DAA-therapies following HT, but recent studies report increased risk of rejection with delayed treatment<sup>[33]</sup>. Empirical initiations of DAAs have shown to decrease the viral load and rapid clearance of HCV in 10 days,<sup>[58]</sup> hence, early initiation of DAAs post-transplant, while in the hospital, should be highly encouraged.<sup>[11,59]</sup> Fluctuating kidney function following HT limits the use of DAAs as some agents like Sofosbuvir may adversely affect kidney function, but DAAs have been used successfully in renal transplant recipients with no impact on renal function.<sup>[60]</sup>

DAAs are well tolerated with no major adverse effects, recipients typically suffered from self-limiting constitutional symptoms like headaches, fatigue, or insomnia.<sup>[59]</sup>

Overall cost of a 12-week course of DAAs are concerned, ranging from \$80,000 to \$100,000, but recently the cost has been reduced to as low as \$30,000 in 2020.<sup>[25,61,62]</sup> This is far less compared to the cost of a mechanical cardiac support device with an average cost of hospitalization of \$726,000 and a yearly cost ranging from \$30,000 to \$80,000 for follow-up and maintenance.<sup>[24,63]</sup> As well as the burden of caring for durable mechanical support by the patient and their families.

#### Overall Survival

Pre-DAA era, the overall mortality was increased by 2-fold in recipients receiving hearts from HCV-positive donors,<sup>[5,6]</sup> with the effective treatment against HCV with DAAs, the one-year survival rate is 90.4% in HCV-positive recipients similar to HCV-negative recipients.<sup>[29,41,64]</sup> However, there is a scarcity of available data beyond 1-year, larger studies are currently ongoing for evaluating long-term outcomes.<sup>[11,29]</sup> The average waiting period for HT is reduced, and thereby decreasing waiting list mortality.<sup>[11,29]</sup> Data on multi-organ transplants are limited. McMaster *et al* demonstrated equivalent survival rates in combined heart and kidney transplants with preservation of renal function.<sup>[64]-[65]</sup>

#### Future of HCV-positive Donor Utilization

The studies have demonstrated comparable 1-year outcomes following heart transplantation from HCV-positive compared to HCV-negative donors with potential younger donors.<sup>[66]</sup> Generally, the recipients have an uncomplicated course following HT with rapid clearance of viremia with use of DAAs with minimal interactions with immunosuppressant and side effects.<sup>[67,68]</sup> One-year outcomes of heart transplant recipients from HCV-positive donors are encouraging, but further studies are needed to evaluate the risk of allograft rejection, development of CAV, long-term sequela of liver disease and potential HCC risk, HCV genotype specific effects, recurrence of HCV and its impact on morbidity and mortality beyond the first year. In 2020, only 28% of the transplant centers were utilizing HCV-positive hearts,<sup>[21]</sup> but with more experience and reassuring long-term outcome will lead more transplant centers to accept HCV-positive organs.

## **CONCLUSION**

As the IVDU and opioid epidemic is on the rise in the US, the donor pool with HCV-positive hearts is going to increase in upcoming years. With highly effective DAA therapy and comparable short term outcomes following HT, it is reasonable to utilize these organs to meet the increasing prevalence of end-stage refractory HF patients. However, multidisciplinary team approach and close monitoring of these recipients needed with close observation for long-term sequelae.

ORIGINALITY REPORT

1 %

SIMILARITY INDEX

PRIMARY SOURCES

- 1

Lindsay A. Sobotka, Khalid Mumtaz, Michael R. Wellner, Sean G. Kelly et al. "Outcomes of hepatitis C virus seropositive donors to hepatitis C virus seronegative liver recipients: A large single center analysis", Annals of Hepatology, 2021

Crossref

13 words — < 1 %
- 2

cardiab.biomedcentral.com

Internet

13 words — < 1 %