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Utilization of Hepatitis C Virus RNA-Positive Donor Liver for Transplant to Hepatitis C Virus RNA-Negative Recipient

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TO THE EDITOR:

Herein, we report a hepatitis C virus (HCV) RNA-negative patient who deliberately received a liver transplantation (LT) from a HCV RNA-positive deceased donor, and we discuss the outcome.

A 57-year-old Caucasian woman with a history of Child-Turcotte-Pugh class A HCV cirrhosis, blood group A, was wait-listed 3 years prior for cadaveric LT, and she consented to include HCV-positive donors. The patient had signs of decompensation manifested by ascites with a Model for End-Stage Liver Disease (MELD) score of 12. HCV genotype was 1A and previously did not respond to peginterferon-based triple therapy with boceprevir. She completed 12 weeks of sofosbuvir/simeprevir combination therapy under an industry-sponsored clinical trial and achieved sustained virological response (SVR). Six months after SVR, she was diagnosed with hepatopulmonary syndrome (HPS), with room air partial pressure of arterial oxygen (PaO₂) of 59 mm Hg and granted 22 MELD exception points. Her resting oxygen requirement continued to increase, requiring continuous 4 L/minute through nasal cannula, causing further debilitation necessitating multiple hospitalizations. Living donor options were not available for the patient. She eventually received an offer from a HCV-positive donor. Given the worsening of her general condition and the drop in her oxygen saturation into the 50% range, the option of this HCV-positive liver allograft was discussed with the patient. With the knowledge that she was recently cured of HCV, the risks and benefits of receiving a HCV-infected allograft were reviewed in detail by the medical

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and surgical transplant teams. She was informed that she will experience HCV recurrence following LT and that there was a slight chance of developing the more aggressive form of hepatitis C: fibrosing cholestatic hepatitis C (FCHC). In addition, it was discussed that she had to be retreated with direct-acting antivirals (DAAs) following LT and was informed of the high costs. The patient agreed to accept this HCV-positive liver and signed the relevant consent form, with the knowledge of increased risk of HCV infection and the potential risk of liver failure and death. The donor was an 18-year-old high-risk male donor who died from intravenous heroin overdose. Donor laboratory tests showed aspartate aminotransferase (AST) of 128 U/L; alanine aminotransferase (ALT) of 33 U/L; albumin of 3.7 g/dL; total bilirubin (T.bili) of 1.7 mg/dL; international normalized ratio (INR) of 1.5; platelets of 141,000 per cu mm; negative HCV antibody (Ab); and positive HCV RNA nucleic acid amplification testing (NAT). The donor's liver biopsy showed moderate portal inflammation, mild interface hepatitis, and minimal fibrosis but did not show any evidence of cirrhosis, microvesicular or macrovesicular steatosis. The donor's HCV genotype was not reported by the organ procurement organization. Three days following LT, the recipient's HCV genotype was reported as 1A, and HCV RNA was quantified at 5,170,000 IU/mL. It was decided not to use ribavirin due to significant concurrent anemia and history of ribavirin-induced anemia. The recipient had normal renal function, and based on American Association for the Study of Liver Diseases (AASLD) guidelines, 24 weeks of ledipasvir/ sofosbuvir was requested through prior authorization process and was approved by insurance. The treatment was started on postoperative day 25. The HCV RNA at 4 weeks following therapy was 20 IU/mL and at 8 weeks was undetectable. The patient achieved SVR following this regimen. Two years following LT, the patient remains HCV RNA negative and has excellent graft function (Fig. 1A,B).

Discussion

LT remains a lifesaving treatment option for patients with decompensated cirrhosis. However, wait times can be significantly long due to limitations in organ availability. On the basis of the latest Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients (SRTR) data, more than 14,000 patients were awaiting LT, yet only 7127 received a LT in 2015.⁽¹⁾ Moreover, 1673 patients died while waiting on the list, and another 1227 patients were removed from the list, being too ill for a transplant.⁽¹⁾

With the availability of DAAs, recently the use of HCV RNA-positive donors to HCV RNA-negative recipients has been introduced. The use of HCV-infected donors can be considered among 3 groups of recipients, each with their own unique challenges:

1. HCV-viremic (HCV RNA-positive).
2. HCV-naïve (HCV Ab-negative/HCV RNA-negative).
3. HCV-resolved/cured (HCV Ab-positive/HCV RNA-negative).⁽²⁾

The use of HCV-positive donor to HCV-positive recipient has been the standard of practice and is advocated. LT outcomes for HCV recipients who receive HCV-positive donors are comparable with those who receive HCV-negative allografts.⁽³⁾ The use of HCV-positive livers can potentially increase organ availability and decrease wait times on the LT list,

without negatively affecting the outcomes.⁽⁴⁾ However, there are limited data on the use of HCV-viremic liver allografts to HCV RNA-negative recipients.⁽²⁾

In this report, we present a case of a previously cured HCV RNA-negative patient who intentionally received a LT from a HCV-infected donor. Although the recipient had a low biological MELD score, she had significant HPS requiring oxygen, and ultimately, with this approach, she was able to undergo LT at an earlier time. The recipient subsequently completed HCV treatment with DAAs following LT and was cured for the second time with excellent graft function within the 2-year follow-up period. This report is a proof of concept with an actual case and introduces the idea of expanding transplantation by using HCV RNA-positive liver allografts for HCV RNA-negative recipients. However, this is a report of only 1 case, and this approach poses significant challenges that require further evaluation in prospective clinical trials.

Various aspects of the use of HCV-viremic donors in solid organ transplantation was comprehensively reviewed by the American Society of Transplantation Consensus conference in Dallas, TX, in January of 2017.⁽²⁾ Currently, there are no OPTN policies restricting transplantation of HCV-infected donors to HCV-positive or HCV-negative recipients. Because of the increase in mortality from drug overdose, it is estimated that this will be the main source of available HCV-infected livers in the next decade.⁽²⁾ Similar to our donor, these organs are from young donors, without major underlying diseases, and with no or minimal liver fibrosis. These allografts are considered to be of better quality than organs from older HCV-viremic donors that can potentially have advanced liver fibrosis.⁽²⁾

Who are the appropriate HCV RNA-negative recipients for LT—from a HCV-infected donor? Who should be prioritized? These are important questions with unclear answers and will need to be investigated in future studies. The idea is to provide LT for “sick” liver patients who are awaiting LT on the waiting list and who will potentially deteriorate or die if they do not receive an organ in a timely fashion. This might vary in each region based on the HCV-infected donor pool, the overall organ supply and demand, MELD score, and the blood type. Overall, this approach can be relevant in a few recipient scenarios.

1. Patients with acute liver failure in whom the timing of LT becomes extremely critical.
2. Patients with hepatocellular carcinoma in whom there is the risk of dropout.
3. Patients with low MELD score but with significant complications from portal hypertension, where their native MELD does not reflect the degree of their illness, such as the patient presented in our case with debilitating HPS.

The type and duration of DAA therapy in the post-LT period are dependent on the recipient's newly acquired genotype. The recommendations for post-LT HCV patients are reported in the AASLD and Infectious Diseases Society of America guidelines⁽⁵⁾ In treatment-naïve and treatment-experienced genotype 1 patients, fixed daily doses of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin for a total of 12 weeks is recommended, as first-line treatment. In patients who are ribavirin ineligible, such as patients with significant anemia, daily doses of ledipasvir (90 mg)/sofosbuvir (400 mg) for

24 weeks is recommended.⁽⁵⁾ In an effort to decrease the risk of development of FCHC and potential for graft failure, preemptive treatment should be considered in the immediate post-LT phase. However, there are not sufficient data on this topic, and this should be further evaluated in future clinical trials.

In conclusion, following the discovery of DAAs, there are ongoing discussions regarding the use of HCV RNA-positive livers to HCV RNA-negative donors. This idea deserves further consideration and should be investigated in carefully designed clinical trials. Various challenges remain unanswered, including the cost, donor and recipient selection, and ideal timing of DAA therapy. If successful, expanding organ availability through the intentional use of liver allografts from HCV RNA-positive donors is achievable.

Abbreviations:

AASLD	American Association for the Study of Liver Diseases
Ab	antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
DAA	direct-acting antiviral
FCHC	fibrosing cholestatic hepatitis C
HCV	hepatitis C virus
HPS	hepatopulmonary syndrome
INR	international normalized ratio
LT	liver transplantation
MELD	Model for EndStage Liver Disease
NAT	nucleic acid amplification testing
OPTN	Organ Procurement and Transplantation Network
PaO₂	pressure of arterial oxygen
SRTR	Scientific Registry of Transplant Recipients
SVR	sustained virological response
T.bili	total bilirubin

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FIG. 1.

(A) Pre- and post-LT trend of ALP, AST, and ALT (IU/L) in the recipient. Note that the DAA regimen was started 25 days following LT. (B) Pre- and post-LT trend of T.bili (mg/dL) in the recipient. Note that the DAA regimen was started 25 days following LT.