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Use of a hepatitis C virus (HCV) RNA-positive donor in a treated HCV RNA-negative liver transplant recipient

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Abstract

The shortage of livers has led most transplant centers to use extended criteria donors. Hepatitis C virus (HCV) RNA-positive donor organs are typically not given to patients who have cleared HCV. A 64-year-old male with chronic hepatitis C, genotype 1b was listed for LT with hepatocellular carcinoma. While on the waiting list, the patient was treated with sofosbuvir, ledipasvir, and ribavirin and achieved an HCV RNA <15 IU/mL by week 10. At week 18 of a planned 24-week treatment course, the patient under-went deceased-donor LT and received an organ from an anti-HCV-positive donor. Treatment was stopped at LT. At week 3 post LT, HCV RNA was detectable and revealed a genotype 3 HCV infection, compatible with transplantation of an organ with established infection. With retreatment with sofosbuvir, daclatasvir, and ribavirin for 12 weeks, the patient achieved a sustained virologic response. This report highlights how antiviral therapies can be used to optimize the outcomes of HCV-infected transplant patients.

Keywords

antiviral treatment; genotype 1; genotype 3; hepatocellular carcinoma; sustained virologic response

1 | INTRODUCTION

Hepatitis C virus (HCV) is the leading indication for liver transplantation (LT) in the United States.[1] As the wait-list registrants far outnumber the available organs, most transplant

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

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programs utilize extended-criteria donors.[2,3] HCV RNA-positive donors are typically used in HCV-infected recipients, as prior studies have shown excellent outcomes as long as older donors or those with significant fibrosis (F2 or greater) are avoided.[4] The use of anti-HCV-positive donors has increased from 6.2% in the interferon-only era, to 9.1% in 2013 and to 16.9% in 2015, which may reflect the greater availability of young anti-HCV-positive donors related to the epidemic of opioid use in the U.S.[5,6] As more anti-HCV-positive donors become available and with more HCV-positive patients with cirrhosis being treated for HCV, the possibility of using HCV-positive donor organs in HCV RNA-negative recipients arises. Direct-acting antivirals (DAAs) open the door to considering the use of organs from HCV-positive donors in HCV RNA-negative recipients.

Here, we report the use of an anti-HCV-positive donor in a patient who was treated for HCV pre-transplant. This case serves to highlight how HCV therapies are likely to change the landscape of using anti-HCV-positive donors.

2 | CASE REPORT

A 64-year-old male with HCV cirrhosis, genotype 1b infection, with no history of previous decompensation, Child-Pugh score of 7, and laboratory Model for End-stage Liver Disease (MELD) score of 11, was listed for LT with hepatocellular carcinoma (HCC) as the primary indication. He was HCV treatment-experienced, with prior treatment with interferon in 1997 with partial response and boceprevir, peginterferon, and ribavirin in 2013, but with treatment stopped after just 1 month because of side effects.

Regarding his HCC, he was first diagnosed on 2013, when three lesions measuring 2.1, 3.5, and 2.7 cm were identified. As the patient was outside Milan criteria, transarterial chemoembolization (TACE) and percutaneous ethanol injection were used to downstage tumor burden to within Milan criteria. The patient underwent two courses of TACE and three courses of ethanol injection with computed tomography-documented response (Figure 1). Alpha-fetoprotein (AFP) level pre-TACE was 17.4 ng/mL, and after the five procedures and before LT was 5.5 ng/mL. Because of the concerns about HCC progression and because of the anticipated waiting list time of >1 year, the patient was consented for receipt of extended-criteria donors, initially excluding anti-HCV-positive donors, but subsequently changed to acceptance of anti-HCV-positive donors to further broaden donor options, when no offers were forthcoming and concern for tumor progression increased.

Before the patient consented for receipt of extended-criteria donors, he was started on treatment with sofosbuvir 400 mg, ledipasvir 90 mg, and weight-based ribavirin for an intended 24 weeks of treatment. HCV RNA was <15 IU/mL by week 10 and undetectable at week 14 (Table 1). At week 18 of antiviral therapy and 4 weeks after having achieved undetectable HCV viral load, but still under treatment, the patient underwent deceased-donor LT from a 42-year-old female anti-HCV-positive donor. Pre-implantation liver biopsy showed no fibrosis and 20% steatosis. The donor was also anti-hepatitis B core positive. At the time of LT, the patient's laboratory MELD was 11, but MELD score based on exception points for HCC was 31. The immediate post-LT course was uneventful and the patient was discharged on postoperative day 7, with near-normal liver enzymes and function tests. The

explant revealed tumor burden outside Milan criteria with three foci of HCC of 3.5, 2.8, and 2.5 cm with no or incomplete necrosis. No extrahepatic disease was identified.

Testing of a retrieved serum sample from the donor confirmed HCV RNA positive and HCV genotype 3 infection. At week 3 post LT, HCV RNA was quantifiable and genotyping of the recipient revealed genotype 3 HCV, compatible with graft infection from a donor source. His immunosuppressive regimen consisted of tacrolimus, everolimus, and corticosteroids. He was also on lamivudine for hepatitis B virus prophylaxis.

Retreatment of HCV infection was undertaken 4 months after LT with sofosbuvir, daclatasvir, and ribavirin (1000 mg) daily for an intended duration of 12 weeks. No baseline NS5a resistance testing was performed pre-treatment, as it was not available for HCV genotype 3 at that time. His initial HCV viral load was 11 670 801 IU/mL. HCV RNA was <15 IU/mL by week 8 and became undetectable at week 12 of treatment (Table 1). Treatment was well tolerated and no side effects were reported. No adjustments of immunosuppression were required during treatment or in the 12 weeks after end of treatment. Neither erythropoiesis-stimulating agents nor blood transfusions were required. His post-treatment week 12 HCV RNA remained undetectable, indicating achievement of sustained virologic response (SVR) 12. Regarding HCC, the patient is receiving HCC surveillance post LT with abdominal imaging and AFP every 6 months. After 1 year, no signs of recurrence are apparent.

3 | DISCUSSION

This case report highlights the expanded use of anti-HCV-infected organs in the current era of DAAs. Early antiviral treatment after LT minimizes the risks of post-LT HCV-related complications. Uniquely, our case was a patient who had already been treated for HCV pre-LT and, in the absence of receiving an anti-HCV-positive donor, would likely have been cured of his HCV, as prior studies of pre-transplant HCV treatment with sofosbuvir and ribavirin showed that achievement of HCV RNA <15 IU/mL for at least 4 weeks prior to LT was associated with a 95% chance of being HCV-free post LT.[7] In our case, the patient met this benchmark of HCV RNA <15 IU/mL 8 weeks prior to LT. Moreover, a change in genotype was noted post LT consistent with a donor source for infection, rather than recurrence of his original infection. While it is atypical to give an anti-HCV-positive donor organ to a patient already treated for HCV, when need for transplant is high, this is an option that can be considered.

Within this framework, no recommendation is clear and the decision needs to be individualized. In this particular case, concern for the wait-list drop off owing to HCC progression was the primary reason to consider use of the anti-HCV-positive donor organ. In retrospect, deferral of treatment until after transplantation would have saved one treatment course, but the course of both HCC and decompensation can be unpredictable, and treatment is often considered to maintain clinical stability while on the waiting list.[8,9] A third possibility might have been to treat HCV and not to accept a high-risk donor; in that case, the waiting list time delay might have had costly consequences for the patient, in light of the explant findings.

The relevance of the discussion is related to the organ discard rates, which have decreased over time, for both HCV-negative and - positive livers; however, it is still 1.7 times higher for HCV-positive livers.[5] The use of HCV-positive organs might have more interest because of the observed rise in the number of HCV-positive potential donors.[6] To date, the main concern was the risk of transmission of HCV to the recipient and the quality of HCV-positive donors, and subsequently the outcome of such grafts. For HCV-positive donors, a donor age >45 years was an independent factor of fibrosis progression. Also, transplantation with HCV-positive donor organs was associated with a 58% increase risk of advanced fibrosis. One limitation of previous studies is the lack of detailed information regarding donor HCV status, including degree of fibrosis and HCV RNA at the time of LT.[10] In the current period of therapy with DAAs, a modest increase in the age and/or fibrosis criterion for use of HCV-positive donors may be possible, as experience in treating HCV infection early post-transplantation increases.[11]

In the pre-DAA era, use of anti-HCV-positive donors in HCV-negative recipients was avoided, owing to the risk of progressive HCV disease post LT and limited therapies to treat recurrent disease.[4,10] Now, most HCV-infected transplant recipients can be cured with DAA combination therapy. Nonetheless, a small percentage of patients fail DAA therapy, and among the more “difficult-to-cure” groups are those with genotype 3 and cirrhosis and those with resistance-associated substitutions (RASs). It is conceivable that, in the near future, both donors and recipients might be DAA treatment-exposed. Presence of baseline or treatment emergent RASs may lead to reduced efficacy of DAA therapy.[12] In particular, the presence on NS5A RASs may compromise future treatment success and limit post-LT treatment options.[13] Thus, in future, pre-treatment assessment of baseline RASs may be useful in choosing the post-LT regimen. HCV genotype may be the other source of concern. Currently, HCV genotype 3 represents the more difficult-to-treat genotype, with suboptimal rates of SVR in those with cirrhosis and prior treatment experience and may influence post-LT outcomes.[14,15] As genotyping of the donor is not typically done pre LT, the possibility of transplanting a patient with a slightly less favorable genotype, in terms of treatment response, is possible. However, for patients with mild liver disease, SVR rates are high across all genotypes in the non-transplant setting, so assuming similar effects post LT, treatment of patients with anti-HCV-positive donors early post LT, before the development of significant fibrosis, would be expected to provide equally high chances to achieve viral clearance.[16,17] It could be argued that we could have continued anti-viral treatment through transplant as an alternative strategy. This was not the elected approach, because of the absence of donor genotype, and the risk of RASs development. However, this option might be considered under these circumstances.

In summary, long waiting times and the risk of being removed from the list or dying before getting to transplantation remain a stimulus for continued expansion of donor options. The availability of safe and highly effective DAA therapies allows for a broader use of anti-HCV-positive donors to be considered and expands the arena for discussion.

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Abbreviations

AFP	alpha-fetoprotein
DAAs	direct-acting antivirals
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
LT	liver transplantation
MELD	Model for End-Stage Liver Disease
RASs	resistance-associated substitutions
SVR	sustained virologic response
TACE	transarterial chemoembolization

References

1. Kim WR, Terrault NA, Pedersen RA, et al. Trends in waiting list registration for liver transplantation for viral hepatitis in the United States. Gastroenterology. 2009; 137:1680–1686. [PubMed: 19632234]
2. Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2013 Annual Data Report: Liver. Am J Transplant. 2015; 15(Suppl 2):1–28.
3. Rana A, Gruessner A, Agopian VG, et al. Survival benefit of solid-organ transplant in the United States. JAMA Surg. 2015; 150:252–259. [PubMed: 25629390]
4. Khapra AP, Agarwal K, Fiel MI, et al. Impact of donor age on survival and fibrosis progression in patients with hepatitis C under-going liver transplantation using HCV+ allografts. Liver Transplant. 2006; 12:1496–1503.
5. Bowring MG, Kucirka LM, Massie AB, et al. Changes in utilization and discard of hepatitis C-infected donor livers in the recent era. Am J Transplant. 2017; 1:519–527.
6. Suryaprasad AG, White JZ, Xu F, et al. Emerging epidemic of hepatitis C virus infections among young nonurban persons who inject drugs in the United States, 2006–2012. Clin Infect Dis. 2014; 59:1411–1419. [PubMed: 25114031]
7. Curry MP, Forns X, Chung RT, et al. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: An open-label study. Gastroenterology. 2015; 148:100–107. [PubMed: 25261839]
8. Reig M, Marino Z, Perello C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol. 2016; 65:719–726. [PubMed: 27084592]
9. ANRS Collaborative Study Group On Hepatocellular Carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts). Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts. J Hepatol. 2016; 65:734–740. [PubMed: 27288051]
10. Lai JC, O'Leary JG, Trotter JF, et al. Risk of advanced fibrosis with grafts from hepatitis C antibody-positive donors: A multicenter cohort study. Liver Transplant. 2012; 18:532–538.

11. Levitsky J, Verna EC, O'Leary JG, et al. Perioperative ledipasvir– sofosbuvir for HCV in liver-transplant recipients. N Engl J Med. 2016; 375:2106–2108. [PubMed: 27959735]
12. Itakura J, Kurosaki M, Hasebe C, et al. Complex pattern of resistance-associated substitutions of hepatitis C virus after daclatasvir/asunaprevir treatment failure. PLoS One. 2016; 11:e0165339. [PubMed: 27776192]
13. Macartney MJ, Irish D, Bridge SH, et al. Telaprevir or boceprevir based therapy for chronic hepatitis C infection: Development of resistance-associated variants in treatment failure. Antiviral Res. 2014; 105:112–117. [PubMed: 24594347]
14. Campos-Varela I, Lai JC, Verna EC, et al. Hepatitis C genotype influences post-liver transplant outcomes. Transplantation. 2015; 99:835–840. [PubMed: 25211520]
15. Feld JJ, Maan R, Zeuzem S, et al. Effectiveness and safety of sofosbuvir-based regimens for chronic HCV genotype 3 infection: Results of the HCV-TARGET study. Clin Infect Dis. 2016; 63:776–783. [PubMed: 27325691]
16. Gane E, Poordad F, Wang S, et al. High efficacy of ABT-493 and ABT-530 treatment in patients with HCV genotype 1 or 3 infection and compensated cirrhosis. Gastroenterology. 2016; 151:651–659. [PubMed: 27456384]
17. Gane EJ, Schwabe C, Hyland RH, et al. Efficacy of the combination of sofosbuvir, velpatasvir, and the NS3/4A protease inhibitor GS-9857 in treatment-naive or previously treated patients with hepatitis C virus genotype 1 or 3 infections. Gastroenterology. 2016; 151:448–456. [PubMed: 27240903]

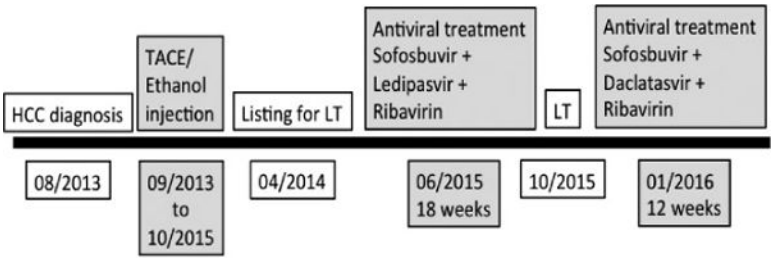

FIGURE 1.

Timeline of diagnosis and treatment procedures. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; LT, liver transplantation

TABLE 1

Laboratory data and virological response

	Sofosbuvir + Ledipasvir+ Ribavirin				
Pre-LT treatment course	**Baseline**	**Week 4**	**Week 10**	**Week 14**	**Week 18**
HCV RNA (lU/mL)	838 335	205	Detected	Undetectable	Undetectable
ALT (IU/L)	134	29	26	26	26
Bilirubin (mg/dL)	1.7	2.3	2.2	2.2	3.3
Direct bilirubin (mg/dL)	0.7	0.7	0.7	0.7	0.8
Creatinine (mg/dL)	0.8	0.8		0.7	0.8
INR	1.1	1.2		1.3	1.4
Albumin (mg/dL)	3.0	3.0	3.1	3.1	3.4
	Sofosbuvir + Daclatasvir + Ribavirin				**Off treatment**
Post-LT treatment course	**Baseline**	**Week 3**	**Week 8**	**Week 12**	**Week 12 SVR-12**
HCV RNA (lU/mL)	11 670 801	224	Detected	Undetectable	Undetectable
Hemoglobin (g/dL)	13.9	13.4	11.2	11.8	16.1
ALT (IU/L)	18	10	13	12	12
Bilirubin (mg/dL)	0.8	1.3	1.6	1.0	0.5
Creatinine (mg/dL)	1.08	1.06	1.22	1.03	1.22
INR	1.0	1.0	1.0	0.9	0.9
Albumin (mg/dL)	4.3	4.2	4.0	4.2	4.3

HCV, hepatitis C virus; ALT, alanine aminotransferase; INR, international normalized ratio; LT, liver transplantation; SVR, sustained virologic response.