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Living Donor Liver Transplant from a Hepatitis C–Seropositive Donor into a Seronegative Recipient: A Case Report

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Abstract

Liver transplant is a lifesaving therapy for patients with end-stage liver disease who exhibit massive ascites, hepatic encephalopathy, and a high risk of esophageal bleeding due to liver decompensation. The shortages in liver donations leave these patients waiting in despair. Prior to the approval of direct-acting antiviral agents (DAAs), Hepatitis C Virus (HCV)–positive liver grafts were discarded three times more than HCV-negative grafts. However, with the use of DAAs, transplants from HCV-positive donors into HCV-negative recipients have become feasible and safe. The high serum virologic response rate obtained with DAA therapy is a milestone in the treatment of HCV infection.

Few studies have focused on living HCV-positive donor liver transplants to HCV-negative recipients. We present an HCV-positive donor who received 8-week DAA therapy before donating the liver to her seriously ill HCV-negative relative. The donor's recovery was uneventful, and the recipient was stable during the perioperative period and postoperative follow-up.

Keywords: Living donor liver transplant; Hepatitis C-seropositive donor; Seronegative recipients

Introduction

Liver transplant is a lifesaving therapy for patients with end-stage liver disease who have massive ascites, hepatic encephalopathy, and a high risk of esophageal bleeding due to decompensation. Advances in organ preservation, surgical techniques, and immunosuppressive agents in the past few decades have extended the life expectancy of these patients. However, the shortage of cadaveric donors remains a major concern. A Living Donor Liver Transplant (LDLT) is an option; however, the supply of donated livers is very low relative to the demand. According to the Taiwan Organ Registry and Sharing Center database, although 6,211 liver transplants were performed in Taiwan from 2005 to 2018, the organ shortage led to a long wait, with a cumulative dropout probability within 3 years of up to 24% [1]. In 2021, more than 1,169 patients were awaiting a liver transplant in Taiwan. However, only 107 cadaveric and 436 LDLTs were performed in 2020, with many patients dying on the waiting list [2]. Therefore, the extension of the organ pool may benefit more people.

Prior to the approval of Direct-Acting Antivirals (DAAs), Hepatitis C Virus (HCV) –positive liver grafts were discarded three times more than HCV-negative grafts [3]. A liver transplant from an HCV-positive donor into an HCV-negative recipient has become possible because of the remarkable success rate of DAA therapy, with ASTRAL studies reporting an overall Sustained Virologic Response (SVR) of 99% in 624 patients [4]. However, most of such case series focused on cadaveric liver transplants, leading to the lack of information on LDLTs.

We present a novel procedure to treat an HCV-seropositive donor with 8 weeks of DAA therapy before liver donation to her seriously ill relative; moreover, we evaluated the long-term outcomes of the treatment in both donor and recipient.

Materials and Methods

Recipient

A 39-year-old man with blood type B and alcoholic liver cirrhosis was transferred to our division for liver transplant evaluation. He had a weight of 75 kg and a height of 177 cm. The patient's Body Mass Index (BMI) was 23.9, and Body Surface Area (BSA) was 1.92. According to the medical

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Table 1: Donor and recipient pretransplant laboratory data.

Variable	Reference range	Recipient	Donor
Hemoglobin (g/dl)	12.0-16.0	8.3	13.9
Hematocrit (%)	36.0-46.0	24.1	40.8
White-cell count (per mm^3)	4500-11,000	5500	8.8
Platelet count (per mm^3)	150,000-400,000	47000	243000
Sodium (mmol/liter)	135-145	131.1	136.5
Potassium (mmol/liter)	3.4-5.0	3.79	4.26
Creatinine (mg/dl)	0.60-1.50	0.82	0.62
Alanine aminotransferase (U/liter)	7-33	13	11
Aspartate aminotransferase (U/liter)	9-32	39	16
Albumin (g/dl)	3.3-5.0	2.7	3.5
Total bilirubin (mg/dl)	0-1.0	7.45	0.9
Ammonia (µmol/liter)	12-48	21	6.8
Prothrombin time (sec)	11.0-14.0	18.7	10
Prothrombin-time (INR)	0.9-1.1	1.79	0.92
HBsAg (IU/ml)	<0.05	<0.05	<0.05
Anti-HBs Ab (mIU/ml)	>10	153.3	<1.0
HbeAg	Negative	Negative	Negative
Anti-Hbe	Negative	Positive	Negative
Anti-HCV (qualitative)	Negative	Negative	Positive
Anti-HCV (qualitative)[@]	Negative	positive	positive
Anti-HCV (qualitative)[#]	Negative	Negative	Positive
Anti- HBc T	Negative	Positive	Negative
HCV-RNA (IU/ml)	<15 IU/ml	<15 IU/ml	32,100 IU/ml
HCV-RNA (IU/ml)[*]	<15 IU/ml	NA[+]	<15 IU/ml
HCV-RNA (IU/ml)[#]	<15 IU/ml	<15 IU/ml	<15 IU/ml

Notes: *: HCV viral load after 8-week DAA therapy; +: NA: Not Available; @: 2 weeks after transplant; #: 3 months after transplant

record, the patient was an alcoholic for decades; however, he had quit alcohol recently and had massive ascites and bleeding secondary to esophageal varices. His initial Model for End-Stage Liver Disease (MELD) score was 25, and the total bilirubin level was 7.45 mg/dL (normal range: 0.2 mg/dL to 1.2 mg/dL). Serological tests revealed a negative hepatitis B and C status (Table 1). Imaging tests, including Panendoscopy, colonoscopy, abdominal Computed Tomography (CT), and liver magnetic resonance imaging, were performed to rule out malignancies and major vascular anomalies. Subsequently, the patient was referred to the waiting list for a liver transplant. However, his liver function deteriorated rapidly after several episodes of bleeding from esophageal varices, with the MELD score escalating to 34. On the basis of the MELD score, the estimated 3-month mortality rate was 52.6% [5]. Because of the recent high mortality without liver transplants in time attributing to the cadaveric liver shortage, we discussed the possibility of an LDLT with his family. His younger sister expressed willingness to be a donor; therefore, an LDLT was initiated.

Donor

The living donor was a 39-year-old woman with blood type B. She had a weight of 61 kg and a height of 163 cm; moreover, her BMI was 23.0, BSA was 1.66, and history was noncontributory. Her pretransplant serological test results were normal; however, HCV-RNA was more than 4 log 10, with a sub-genotype of 1b (Table 1). Abdominal CT and magnetic resonance cholangiopancreatography revealed neither vascular variation nor bile duct anomalies. Although the risk of postoperative hepatic insufficiency is influenced by multiple factors, the preoperative Future Liver Remnant (FLR) volume is a key determinant for ensuring adequate functional remnant liver [6,7]. CT liver volumetry revealed a total liver volume of 1266.1 mL, with 753.4 mL in the right liver lobe without the middle hepatic vein and 512.7 mL in the left liver lobe with the middle hepatic vein. The results suggested an acceptable volume for the recipient and indicated that harvesting the right liver lobe without the middle hepatic vein was safe for the donor. Regardless of HCV infection, the donor's clinical condition was suitable for right lobe liver donation, with a graft-to-recipient weight ratio of 0.978 and the donor's liver remnant of 39.76%. The estimated FLR, calculated using the Urata formula (SLV = 2.4 + 706.2 × BSA), was 55.48% and 43.57% for the recipient and donor, respectively. The donor was informed of the risks associated with the procedure, and coercion was excluded during an independent, confidential evaluation. Surgical agreement was approved by the medical ethics committee followed by the discussions with hepatologists, hepatobiliary surgeons, and intensive care staff. Informed consent was obtained from the patients.

Results

We developed a novel protocol for LDLTs from HCV-positive donors into HCV-negative recipients. According to the Treatment of Hepatitis C 2018 recommendations of the American Association for the Study of Liver Diseases and European Association for the Study of the Liver, treatment-naïve patients with HCV genotype 1b infection and without cirrhosis can be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 8 weeks (grading B1; moderate evidence quality and strong recommendation) [8,9]. We initiated DAA therapy for the donor with a daily fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg; Harvoni) for 8 weeks [10]. The presence of HCV-RNA was evaluated at 4, 8, and 12 weeks posttherapy (Table 1), and the Rapid Virologic Response (RVR), SVR12, posttherapy SVR, and posttransplant SVR suggested that the disease was cured. The donor HCV-RNA diminished from 4 log 10 to less than 15 IU/mL, which is below the lower limit of quantification. Although the HCV-RNA was not detected post transplantation, anti-HCV seropositivity was detected before and after the transplant. The LDLT was performed after the end of DAA therapy. To ensure donor safety, physicians requested a preoperative liver biopsy that was suggested using the options of laparoscopic or conventional percutaneous procedure because of the latter process-related bleeding risks, as informed by the radiologist. Subsequently, an intraoperative laparoscopic liver wedge biopsy was performed before the liver harvest surgery. The frozen section of the bilateral liver lobes revealed a minimal fatty change of less than 5% and no fibrosis. The laparoscopic liver biopsy was converted to an open donor right hepatectomy, with an uneventful perioperative period. The donor developed transient postoperative hyperbilirubinemia, however, the level decreased to normal range 1 week later. The donor was discharged in stable condition on postoperative day 7. Currently, the donor is undergoing regular follow-ups by the hepatologist and surgeons in the outpatient department. The donor resumed her job 3 months post-donation. No other complications have been noted during the 3-year follow-up period.

The recipient without hepatitis C history was not treated with DAAs all the time during the perioperative period. Transient anti-HCV antibodies were detected at the first serological follow-up

2 weeks post transplantation, with the antibodies disappearing 2 months later. No HCV-RNA was detected during follow-ups. Postoperative bile leak complicated with intraabdominal biloma formation was noted. The sono-guided Intra-abdominal pigtail drainage and the endoscopic retrograde cholangiopancreatography–guided biliary stent placement was performed. The recipient was discharged in a stable condition 1.5 months post-operation. The 2-year posttransplant liver biopsy revealed Ishak fibrosis stage 0 with a modified histology activity index score (neuroinflammatory score) of 2 (of 18) and no rejection. The recipient had a herpes zoster infection of the trigeminal nerve 1 year after the transplant, with the long-term neurological deficits of dizziness and vertigo that disabled him from the job. Currently, the patient is being followed up at our OPD, with no HCV flare-ups over 3 years.

Discussion

Here, we present an HCV-positive donor treated with DAAs before donating the right liver lobe to her elder brother. Few articles have discussed this topic. Prior to the approval of DAAs, HCV recurrence after liver transplant was the most common cause of graft failure and reduced recipient survival in HCV-positive patients compared with HCV-negative patients [11]. Chhatwal et al. demonstrated that HCV-seronegative patients have an increased life expectancy after accepting any liver graft regardless of HCV status if the MELD score is more than or equal to 20 [12].

The survival rates in HCV-positive donors and HCV-negative recipients are similar to those of HCV-negative donors and recipients because of the use of DAAs, with cure rates of nearly 100%. The use of HCV-positive organs in a selected group of recipients with and without HCV infection was reported by Dhaliwal et al. [13].

Because of the recipient's high 3-month mortality rate and the involved cost, the DAA therapy duration for the donor was shortened to 8 weeks. Under existing guidelines, most patients are prescribed 12-week DAA therapy, a treatment duration resulting in high rates of SVR across various viral and host characteristics [14]. Moreover, the guidelines do not encourage a treatment duration of less than 12 weeks [15,16]. However, increasing evidence suggests that many patients can achieve an SVR with only 8 weeks of therapy. In clinical practice, an SVR rate of 93% to 98% has been observed after treatment with ledipasvir and sofosbuvir for 8 weeks [17,18]. In Taiwan, the cost of DAA therapy is similar to that in the United States; however, it is not covered by National Health Insurance, making it unaffordable to ordinary people. The wholesale acquisition cost of ledipasvir and sofosbuvir is $1125 per pill, and the cost of a ledipasvir and sofosbuvir course reduces from $94,500 to $63,000 when the treatment duration is shortened from 12 to 8 weeks [19,20]. In Taiwan and neighboring countries, such as Japan and South Korea, routine pretransplant liver biopsies are not performed for living donors if CT and MRI images reveal no fibrosis, fatty change (less than 5%), or hemosiderosis. However, we performed a pretransplant laparoscopic liver biopsy for donor safety in the setting of treated HCV infection.

Although LDLTs have been performed in patients with fulminant liver failure or advanced liver disease categorized as the United Network of Organ Sharing (UNOS) status 2 A, posttransplant survival rates are low [21]. In a series, 1-year patient survival was 57%, with an average stay of 23 days in the intensive care unit [22]. By comparison, 1-year patient survival was 82% in cadaveric organ transplant recipients, with UNOS status 2 A at the time of the transplant [22]. With the advent of MELD, decisions on LDLTs are made on a case-by-case basis, and LDLTs are uncommon in patients with MELD scores above 25. In these patients, short-term mortality without liver transplants approaches 100% [23]. In regions such as East and South Asia with low cadaveric organ availability, the decreased posttransplant survival rates with LDLT may be superior to the high waiting list mortality, especially when the outcomes of LDLT are improving [24].

What mortality rate is acceptable when the donor understands the risks, and when coercion has been excluded? Even if the donor is willing to accept a potential mortality risk for the life of a loved one, would the medical community proceed with an LDLT? A balance should be achieved between the risk incurred by the donor and what is acceptable to society, the medical community, and the recipient.

Conclusion

In the DAA era, a transplant from deceased HCV-positive donors to HCV-negative recipients has become feasible and safe. Our study also revealed the feasibility and safety as well of HCV-seropositive LDLTs to seronegative recipients. However, some issues remain to be debated, and more studies are required to confirm the long-term outcome.

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