reports

Brief Report

Liver Transplantation from a Human Leukocyte Antigen-Matched Sibling Donor: Effectiveness of Direct-Acting Antiviral Therapy against Hepatitis C Virus Infection

Tatsuo Kanda [1,*], Naoki Matsumoto [1], Tomotaka Ishii [1], Shuhei Arima [1], Shinji Shibuya [1], Masayuki Honda [1], Reina Sasaki-Tanaka [1], Ryota Masuzaki [1], Shini Kanezawa [1], Masahiro Ogawa [1], Shintaro Yamazaki [2], Osamu Aramaki [2], Hirofumi Kogure [1] and Yukiyasu Okamura [2]

[1] Division of Gastroenterology and Hepatology, Department of Medicine, Nihon University School of Medicine, 30-1 Oyaguchi-kamicho, Itabashi-ku, Tokyo 173-8610, Japan
[2] Division of Digestive Surgery, Department of Surgery, Nihon University School of Medicine, Tokyo 173-8610, Japan
* Correspondence: kanda.tatsuo@nihon-u.ac.jp

Abstract: Through living-donor liver transplantation (LDLT) from a human leukocyte antigen (HLA)-matched sibling donor, it may be possible to stop the use of immunosuppressants. It is possible that acute antibody-mediated rejection and chronic active antibody-mediated rejection through the positivity of donor-specific anti-HLA antibodies and/or T cell-mediated rejection may affect the prognosis of liver transplantation. The etiologies of liver diseases of the recipient may also affect the post-transplantation course. Herein, we report on the successful re-treatment with direct-acting antiviral (DAA) therapy against hepatitis C virus (HCV) infection in a patient who underwent a LDLT from HLA-matched sibling donor. After liver transplantation for HCV-related liver diseases, it is easy for HCV to re-infect the graft liver under a lack of immunosuppressants. DAA therapy against HCV re-infection immediately after transplantation should be commenced, and it is important to eradicate HCV for better prognosis of the recipients in LDLT for HCV-related liver diseases.

Keywords: DSA; HCV; LDLT; liver transplant; sibling donor; SVR

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1. Introduction

There have been several reports on successful liver transplantation from human leukocyte antigen (HLA)-matched sibling donors [1–4]. These reports discussed living-donor liver transplantation (LDLT) from human leukocyte antigen (HLA)-matched sibling donors, although long-term observations from these LDLT cases have not yet been reported. In general, identical HLA matching has enabled successful transplantation along with the stopping of immunosuppressants. These cases may bring useful knowledge for immunosuppressant withdrawal after liver transplantation.

In Japan, compared with other countries, due to the legal difficulties associated with cadaveric donation, LDLT is performed more often than brain death liver transplantation for end-stage liver diseases [5]. In Japan, chronic hepatitis C virus (HCV) infection is still one of the major etiologies of end-stage liver diseases [6,7]. It is unknown whether immunosuppressant-free liver transplantation has effects on HCV re-infection of the graft liver.

However, the liver diseases of recipients occasionally affect the clinical course after liver transplantation [8–10]. The development of antiviral therapies for hepatitis B virus (HBV) and HCV, respectively, could prevent the occurrence of complications accompanying HBV- and HCV-associated liver diseases, such as fibrosing cholestatic hepatitis. The development of direct-acting antivirals (DAAs) against HCV could lead to higher sustained

virological response (SVR) rates with less adverse events, even in patients with liver transplantation, compared to interferon therapy, resulting in better survival [11–13].

Another problem is that recurrent autoimmune hepatitis (AIH) following liver transplant is frequent, as associated with some recipient features and/or the type of immunosuppressive medications used [14]. De novo donor-specific anti-HLA antibodies (dnDSAs) in pediatric liver transplant recipients have been associated with liver transplant rejection and liver fibrosis [15]. Donor-specific antibodies (DSAs) play a role in acute antibody-mediated rejection (AAMR) and chronic active antibody-mediated rejection (CAAMR) [16,17].

In this article, we present a case with liver transplant from HLA-matched sibling donor and successful re-treatment with DAA therapy against HCV infection, including follow-up with this patient up to about 8.5 years. We also discuss relevant topics.

2. Successful Re-Treatment with Direct-Acting Antiviral (DAA) Therapy against Hepatitis C Virus (HCV) Infection in a Patient Who Underwent a Living-Donor Liver Transplantation (LDLT) from a Human Leukocyte Antigen (HLA)-Matched Sibling Donor

2.1. Case

A man in his 40s underwent LDLT at our institution in 2014 for decompensated HCV-related cirrhosis. His height and weight were 170 cm and 69.9 kg, respectively. The organ donor was the patient's identical older twin brother. The recipient's diagnosis was HCV genotype (GT) 1b infection and decompensated cirrhosis. Before LDLT, the international normalized ratio was 1.38, platelet count 21,000/μL, albumin 2.3 g/dL, and total bilirubin 1.8 mg/dL. Child–Pugh score and grade were 8 and B, respectively. Model for end-stage liver disease (MELD) and MELD-Na scores were 11 and 12, respectively. α-fetoprotein and protein induced by vitamin K absence or antagonist-II (PIVKA-II) levels were 17.7 ng/mL and 33 mAU/mL, respectively. HCV RNA level was 6.5 LC/mL. HBV surface antigen and HBV DNA were negative and undetectable, although antibody to HBV core antigen was positive. His laboratory data and computed tomography (CT) images before liver transplantation are shown in Table 1 and Figure 1A, respectively.

Table 1. Laboratory data of recipient before living-donor liver transplantation (LDLT).

Item	Values	Item	Values	Item	Values
WBC	2000/μL	TP	5.1 g/dL	HBsAg	Negative
RBC	2,500,000/μL	Albumin	2.3 g/dL	Anti-HBs	Negative
Hemoglobin	8.5 g/dL	T.CHO	117 mg/dL	Anti-HBc	Positive
Hematocrit	26.1%	TG	34 mg/dL	HBV DNA	Undetectable
Platelets	21,000/μL	BUN	8.6 mg/dL	Anti-HCV	Positive
PT	59%	Creatinine	0.95 mg/dL	HCV RNA	6.5 LC/mL
PT-INR	1.38	CK	49 IU/L	HCV GT	GT1b
AST	63 IU/L	Amylase	39 IU/L	Anti-HIV	Negative
ALT	30 IU/L	BS	87 mg/dL	IgG	2250 mg/dL
LDH	187 IU/L	HbA1c	3.9%	IgA	191 mg/dL
γ-GTP	20 IU/L	NH3	54 μg/dL	IgM	98 mg/dL
ALP	231 IU/L	CRP	<0.10 mg/dL	ANA	Negative
T. Bil	1.8 mg/dL	AFP	17.7 ng/mL	AMAM2	Negative
D. Bil	1.0 mg/dL	PIVKA-II	33 mAU/mL	Anti-LKM1	Negative

WBC, white blood cell count; RBC, red blood cell count; PT, prothrombin time; PT-INR, PT international normalized ratio; AST, aspartate aminotransferase; ALT, alanine transaminase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyltransferase; ALP, alkaline phosphatase; T. Bil, total bilirubin; D. Bil, direct bilirubin; TP, total protein; T.CHO, total cholesterol; TG, triglyceride; BUN, blood urea nitrogen; CK, creatine kinase; BS, blood sugar; HbA1c, hemoglobin A1c; NH3, ammonia; CRP, C-reactive protein; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; HBsAg, hepatitis B virus (HBV) surface antigen; anti-HBs, anti-HBV surface antibody; anti-HBc, anti-HBV core antibody; anti-HCV, anti-hepatitis C virus (HCV) antibody; HCV GT, HCV genotype; anti-HIV, anti-human immunodeficiency virus antibody; Ig, immunoglobulin; ANA, anti-nuclear antibody; AMAM2, anti-mitochondrial M2 antibody; anti-LKM1, anti-liver/kidney microsome type 1 antibody.

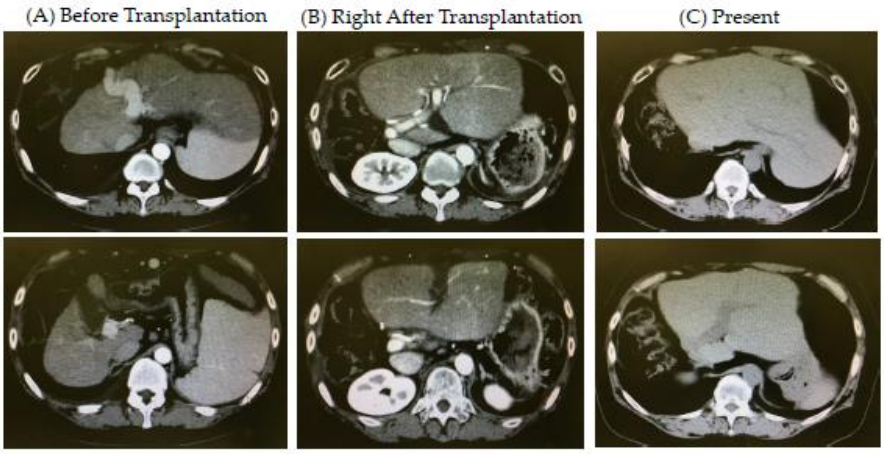

Figure 1. Computed tomography images before and after living-donor liver transplantation (LDLT): (**A**) before LDLT; (**B**) right after LDLT; and (**C**) present (about 8.5 years post-LDLT).

2.2. Donor and Living-Donor Liver Transplantation (LDLT)

HLA matching (A24, A31; B52, B35; C3:03, C12:02; and DR 15, DR4) was identical between the two siblings. HLA-A, B, and DR types were determined by PCR-sequence based typing (SBT) and PCR-reverse sequence specific oligonucleotide (rSSO) methods, respectively, and HLA-C were established by PCR-SBT. These tests were performed by SRL (Hachioji, Tokyo, Japan). A direct test of mixed-donor lymphocyte cultures with recipient sera was judged as negative [1].

The explanted liver and spleen weight of this recipient were 728 g and 1090 g, respectively. The left lobe graft from older brother was 406 g, 33% of the recipient's standard liver volume. The recipient underwent an uncomplicated LDLT, according to a previously described technique [18,19]. Intravenous methylprednisolone (600 mg) was administered intraoperatively. After post-operative day 7 (POD 7), the recipient received no immunosuppression. CT images right after liver transplantation are shown in Figure 1B.

2.3. Anti-HCV Therapies

After about 2 months post-transplantation, he was treated for his HCV with a 12-week combination of peginterferon α-2b (50–90 μg weekly), ribavirin (600 mg daily), and simeprevir (100 mg daily), followed by a 12-week combination of peginterferon α-2b and ribavirin [20]. HCV RNA was relapsed (7.2 LC/mL) after about 8 months of transplantation.

After 2 years of transplantation, he was retreated with a 12-week combination of sofosbuvir (400 mg daily) and ledipasvir (90 mg daily) [21]. Finally, he achieved SVR without HBV re-activation, although he had a history of HBV infection. Although almost 8.5 years have passed since transplantation, his HCV RNA and HBV DNA are now undetectable, and ultrasound sonography demonstrated no space occupying lesions and no advanced liver fibrosis (shear wave elastography, 5.64 kPa). His Child–Pugh score and grade were 5 and A, respectively (Table 2). The clinical course of this patient is shown in Figure 2.

Table 2. Laboratory data of recipient about 8.5 years after living-donor liver transplantation (LDLT).

Item	Values	Item	Values	Item	Values
WBC	7000 /μL	T. Bil	0.5 mg/dL	AFP	17.7 ng/mL
RBC	4,150,000 /μL	D. Bil	0.1 mg/dL	PIVKA-II	33 mAU/mL
Hemoglobin	12.6 g/dL	TP	7.0 g/dL	HBsAg	Negative
Hematocrit	40.3%	Albumin	3.9 g/dL	Anti-HBs	Positive
Platelets	276,000/μL	T.CHO	235 mg/dL	Anti-HBc	Positive
PT	100%	TG	85 mg/dL	HBV DNA	Undetectable
PT-INR	0.95	BUN	11.3 mg/dL	Anti-HCV	Positive
AST	19 IU/L	Creatinine	0.76 mg/dL	HCV RNA	Undetectable

Table 2. *Cont.*

Item	Values	Item	Values	Item	Values
ALT	16 IU/L	CK	85 IU/L	Anti-HIV	Negative
LDH	181 IU/L	BS	92 mg/dL		
γ-GTP	43 IU/L	HbA1c	5.4%		
ALP	244 IU/L				

WBC, white blood cell count; RBC, red blood cell count; PT, prothrombin time; PT-INR, PT international normalized ratio; AST, aspartate aminotransferase; ALT, alanine transaminase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyltransferase; ALP, alkaline phosphatase; T. Bil, total bilirubin; D. Bil, direct bilirubin; TP, total protein; T.CHO, total cholesterol; TG, triglyceride; BUN, blood urea nitrogen; CK, creatine kinase; BS, blood sugar; HbA1c, hemoglobin A1c; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; HBsAg, hepatitis B virus (HBV) surface antigen; anti-HBs, anti-HBV surface antibody; anti-HBc, anti-HBV core antibody; anti-HCV, anti-hepatitis C virus (HCV) antibody; anti-HIV, anti-human immunodeficiency virus antibody.

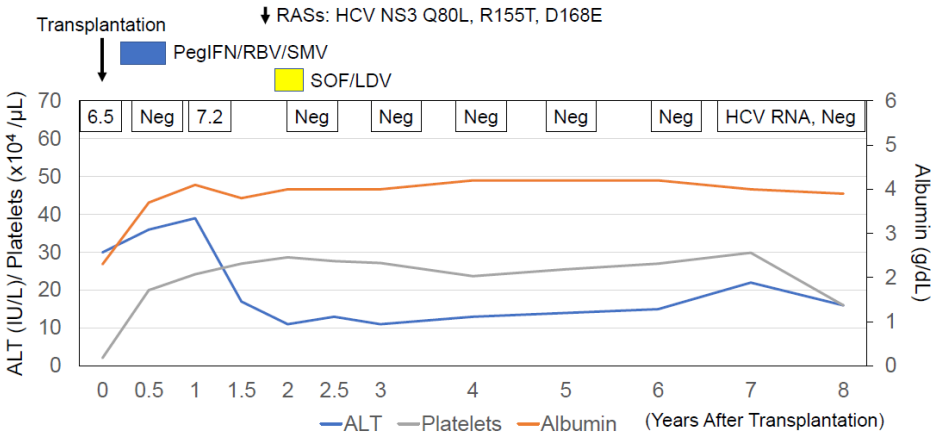

Figure 2. Clinical course of the patient. RASs, resistance-associated substitutions; Neg, undetectable HCV RNA; PegIFN, peginterferon α-2b; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; LDV, ledipasvir; ALT, alanine transaminase.

3. Discussion

In the present report, we present about 8.5 years of follow-up of a patient who had undergone LDLT for HCV infection and decompensated cirrhosis from an HLA-matched sibling donor, and no immunosuppressants after POD 7. Notably, we found that HCV easily re-infected the graft liver without immunosuppressants.

After LDLT from an HLA-matched sibling donor, it may be possible to stop the use of immunosuppressants. Table 3 shows seven reported cases with LDLT from HLA-matched sibling donors. It has been reported that careful attention should be paid to DSA-positive cases in liver transplantation from an identical twin without immunosuppression [4], although, in our patient, DSA had not been examined yet. A negative cross-match was observed in our patients, although a positive cross-match in liver transplantation is associated with worse outcomes [22].

DSA to HLA have been associated with graft loss in hematopoietic progenitor cell transplantation [23]. The presence of mismatched antigens and epitopes might relate directly to the development of de novo DSA and rejection [24]. As seen in solid organ transplantation, the presence of DSA has been shown to be correlated with survival in recipients of hematopoietic stem cell transplants [25]. In general, development of anti-HLA antibodies may occur in certain patients receiving an HLA mismatched donor transplant. DSA-positive rate was significantly higher in the 90-day mortality group in LDLT. Post-operatively, the incidence of acute cellular rejection was higher in DSA-positive patients [26].

Antibody-mediated rejection (AMR) is relatively uncommon in ABO-compatible liver grafts, although antibody-mediated mechanisms may play a role in the differential pathogenesis of liver graft rejection [27]. Presence of DSA has been associated with inferior graft

outcomes among certain liver transplant recipients [27–29]. In ABO-compatible liver transplantation, humoral alloreactivity mediated by DSA appears to be frequently associated with cellular mechanisms of rejection, as well as playing a role in ductopenia development [28]. Immune-mediated graft injury or a manifestation of chronic antibody-mediated rejection are also involved in graft hepatitis and liver fibrosis [29].

Table 3. Seven reported cases with living-donor liver transplantation from human leukocyte antigen-matched sibling donors.

Case	Age (Years)/Gender	Disease(s) of Recipients	Graft	Immunosuppression (Duration)
1	49/Male	HCV cirrhosis	Right lateral sector from brother	mPSL (POD 0–30)
2	43/Female	HBV cirrhosis and HCC	Right lobe from brother	None
3	56/Female	Neuroendocrine tumor metastasis to the liver	Right lobe from sister	None
4	51/Male	HCV cirrhosis and HCC	Right lobe	None
5	38/Male	HCV cirrhosis	Right lobe	None
6	In his 40′s/Male	HCV cirrhosis	Left lobe from older brother	mPSL (POD 0–5)
7	57/Male	Acute liver failure	Right lobe from younger brother	FK/PSL (post operative 0–7 months)

Case	Rejection	Follow-Up Period (years)	Others: HCV GTs and Post-Transplantation Therapeusis	Reference
1	No	About 1	HCV GT1b; Mixed lymphocyte cultures, negative; Interferon α 2a plus ribavirin, SVR	[1]
2	No	About 1	Lamivudine along with monthly hepatitis B immune globulin infusions	[2]
3	No	About 0.5	Sandostatin (Novartis, Switzerland) and interferon	[2]
4	No	About 1.5	HCV GT1b; Interferon α plus ribavirin, SVR	[3]
5	No	About 0.5	HCV GT1b; Interferon α plus ribavirin	[3]
6	No	About 8.5	Mixed lymphocyte cultures, negative; simeprevir/peginterferon α/ribavirin; sofosbuvir /ledipasvir, SVR	Our case
7	No	About 0.5	DSA, positive (Class II ≥ 2000 MFI).	[4]

HCV, hepatitis C virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; mPSL, methylprednisolone; FK, tacrolimus; POD, post-operative day; GT, genotype; SVR, sustained virological response; DSA, donor-specific antibody.

The etiologies of liver diseases in recipients affect the prognosis of post-liver transplantation. Recurrent AIH frequently occurs following liver transplantation, and is a major cause of allograft dysfunction, reduced graft, patient survival, and need for re-transplantation [14]. The probability of recurrent AIH is 20%, 31%, 37%, and 49% at 5, 10, 15, and 20 years, respectively [14]. AIH is characterized by a loss of immunological tolerance to hepatocytes [30]. $CD4^{+}CD25^{high}$ $Foxp3^{+}$ regulatory T cells (Tregs) cellular therapy could restore immune self-tolerance in AIH as well as benefit post-liver transplant patients by preventing graft rejection [30,31].

Immunosuppression is a major factor responsible for the accelerated recurrence of HCV infection [32]. Development of HCV-related fibrosis is accelerated after liver transplantation, which is influenced by several factors related to the virus, donor, recipient, surgery, and immunosuppression [33]. SVR alone can attenuate liver fibrosis in patients re-infected with HCV.

In the setting of liver transplantation, prevention of cytomegalovirus (CMV) infection and control of CMV replication by pre-existing natural adaptive immunity is minimally influenced by HLA-matching of the donor and recipient [34]. Host HLA class I and HLA class II determinants play a role in the lysis of Epstein–Barr virus-infected allogeneic host

cells by cytotoxic T cells [35]. Several HLA polymorphisms have been associated with HCV clearance or persistence [36–38]. The negative effects of HCV on antigen-presenting cell function could lead to reduced immunogenicity in vivo [39]. HCV plays an inhibitory role in cathepsin S-mediated MHC class II maturation, which may contribute to the weak immunogenicity of HCV antigens in patients with chronic HCV infection [40]. Interestingly, the present case also demonstrated that, without immunosuppression, HCV may easily re-infect the graft liver, although very rapid steroid withdrawal was performed.

The present case received a 12-week combination of peginterferon α-2b (50–90 μg weekly) and ribavirin (600 mg daily), followed by a 12-week combination of peginterferon α-2b, ribavirin, and simeprevir (100 mg daily) to combat HCV re-infection immediately after transplantation; however, HCV RNA relapsed after the stoppage of these combination therapies. The dose of interferon seemed less than the standard of care in the first anti-HCV therapy. We did not use a higher dose due to the adverse events of interferon. Although resistance-associated substitutions in the HCV NS3/4A region also appeared (Figure 2), SVR was achieved after the 12-week combination of sofosbuvir (400 mg daily) and ledipasvir (90 mg daily) at 2 years after liver transplantation, and his post-operative process is currently going well at about 8.5 years. Thus, interferon-free DAA treatment may be useful for the achievement of SVR. DAA should be started as soon as possible following liver transplantation in HCV-infected patients who receive the graft from an identical twin without immunosuppression.

When HCV was eradicated in these HBsAg-positive patients or patients with previous HBV infection (anti-HBc and/or anti-HBs-positive), it was shown that HBV reactivation or HBV DNA reappearance was observed in 41% or 0.9%, respectively [41]. In the present case, HBV DNA reappearance was not observed after the eradication of HCV RNA.

In general, minimal listing criteria for elective liver transplantation for HCV-related end stage liver diseases are similar to other causes of chronic liver failure. Although HCV causes cirrhosis, HCC and chronic liver failure, diuretic-resistant ascites or hydrothorax, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatopulmonary syndrome, intractable encephalopathy, and small HCC may occur before liver transplantation [42]. Li et al. favoured DAA therapy before liver transplant in patients with MELD scores < 18 and DAA therapy post-liver transplant in MELD scores > 20 [43]. HCV infection is a risk for intraoperative pulmonary embolism or intracardiac thrombus formation in patients with liver transplantation [44].

In transplant candidates with positive serum HCV RNA prior to transplant, recurrent HCV infection of the allograft occurs following liver transplantation [42]. Most patients will develop acute hepatitis C at 4–12 weeks post-transplant. A small number of patients (2–5%) develop severe cholestatic hepatitis, characterized by extremely high levels of HCV RNA, and severe cholestasis, often causing their death [42].

As recurrent HCV infection with accelerated progression to cirrhosis of the graft is a frequent cause of graft loss and the need for retransplantation, better pre- and/or post-transplant antiviral therapy is needed [45]. Improving the outcome of recurrent HCV infection may also be achieved by reducing overall immunosuppression [46].

Concerning the weaning of immunosuppression, a complete withdrawal of immunosuppression may be achieved in selected liver transplantation-recipients [47,48]. Although drug-induced suppression of the immune system is essential in preventing graft rejection, it has been well-established that it is also associated with oncogenesis [48]. Although the mechanism of graft acceptance in these patients is yet to be elucidated, we believe that no HLA-mismatch, DSA, and T cell-mediated rejection may be important for successful LDLT without immunosuppressants.

4. Conclusions

We reported on about 8.5 years of follow up in a patient who had undergone liver transplantation from an identical twin without immunosuppression. Although it is no doubt that direct viral inhibition should be started as soon as logistically possible following

transplant, we herein reinforce those results in living donors who have had minimal immunosuppression.

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