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Hepatitis C Positive Donor Liver Transplantation for Hepatitis C Seronegative Recipients

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Abstract

Background: The opioid crisis has led to an increase in hepatitis C virus positive donors in the past decade. Whereas historically hepatitis C seropositive organs were routinely discarded, the advent of direct-acting antiviral agents has notably expanded the utilization of organs from donors with hepatitis C. There has been growing experience with liver transplantation from hepatitis C seropositive donors to hepatitis C seropositive recipients. However, data remain limited on liver transplantation from hepatitis C seropositive or hepatitis C ribonucleic acid positive donors to hepatitis C seronegative recipients.

Methods: We performed a retrospective study of 26 hepatitis C seronegative recipients who received hepatitis C seropositive donor livers followed by preemptive antiviral therapy with direct-acting antiviral treatment at the Johns Hopkins Hospital Comprehensive Transplant Center from January 1, 2017 to August 31, 2019.

Results: Twenty-five of the 26 recipients are alive with proper graft function; 20 of them received livers from hepatitis C nucleic acid testing positive donors. All 12 recipients who completed their direct-acting antiviral courses and have reached sufficient follow-up for sustained virologic response have achieved sustained virologic response. Nine of our recipients have either completed direct-acting antiviral treatment without sufficient follow-up time for sustained virologic response or are undergoing direct-acting antiviral treatment. One patient is awaiting

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antiviral treatment initiation pending insurance approval. Of note, 11 of 12 patients with sustained virologic response, received a hepatitis C nucleic acid testing positive donor liver.

Conclusion: Hepatitis C seronegative patients who receive a hepatitis C seropositive or hepatitis C nucleic acid testing positive liver allograft can enjoy good short-term outcomes with hepatitis C cure following direct-acting antiviral treatment.

Keywords

hepatitis C virus positive donor liver; hepatitis C virus negative recipient; liver transplantation; direct acting antiviral; preemptive antiviral therapy

Introduction

Liver transplantation (LT) is the only curative and lifesaving treatment for end-stage liver disease and acute liver failure. The median wait time in the United States for an LT is 11.3 months; accordingly, waitlist mortality remains considerably high.[1] The recent decline in wait times was in large part related to the increase of deceased-donor livers, which coincided with the opioid crisis and deaths from narcotic overdose.[1]

Amidst this opioid epidemic, there has been a rise in the number of increased-risk donors due to intravenous drug abuse.[2] Increased-risk donors have a higher than average risk of transmitting human immunodeficiency virus, hepatitis B virus, or hepatitis C virus (HCV) infection to their organ recipients due to behavioral factors, but they do not necessarily affect the quality of the organ or graft survival.[3,4] At times, donor risk index can be lower in increased-risk liver donors than in standard donors.[5] Since the approval and the remarkable clinical success of anti-HCV direct-acting antiviral (DAA) medications, the nationwide acceptance of potentially HCV positive liver allografts has increased.[6,7]

Between 1995 and 2016, 4.1% of deceased donors in the United States were HCV seropositive (HCV Ab+) (Box 1).[8] Prior to the introduction of DAAs, livers from HCV Ab+ donors were discarded at a higher rate than livers from HCV seronegative (HCV Ab−) donors, leading to the loss of precious transplant resources.[9] While HCV Ab+ recipients of HCV Ab+ livers have demonstrated acceptable patient and graft survivals up to 5 years post-transplant, outcomes data for transplantation of HCV Ab+ livers to HCV Ab− recipients remain scarce.[10,11] HCV Ab+ donors can be further classified by the detectability of HCV ribonucleic acid (RNA) through serum nucleic acid amplification testing: i.e., HCV nucleic acid testing (NAT) positive (HCV NAT+) or HCV NAT negative (HCV NAT−). HCV NAT+ donor livers universally transmit HCV infection to their recipients; in contrast, HCV Ab +/NAT− donor livers result in HCV transmission up to 16% of the time.[12] The aim of the present study was to describe our institutional experience with 27 HCV Ab− patients who received HCV Ab+ donor livers.

Materials and Methods

We performed a retrospective study of 268 adult liver transplant recipients at the Johns Hopkins Hospital Comprehensive Transplant Center (CTC) from January 1, 2017 to August

31, 2019. The electronic medical record was reviewed for recipient data: age at transplant, sex, race, etiology of liver failure, blood type, DAA regimen selected, date of DAA initiation, date of liver transplant, HCV antibody status prior to transplant, HCV RNA viral load, liver-associated enzyme (LAE), biologic model of end-stage liver disease (MELD) score at transplant, and donor liver biopsy pathology. We obtained donor information from DonorNet, including age, sex, race, HCV antibody status, HCV NAT, and Public Health Services (PHS) increased risk status.

Before transplantation, patients who were willing to accept HCV Ab+ donor organs initially provided consent to their primary hepatologist. If offered an HCV Ab+ organ, patients then additionally consented to the operating surgeon. The Johns Hopkins clinical consent form for HCV Ab+ LT delineated the risks and benefits of receiving an HCV Ab+ liver. Specifically, the form detailed the efficacy of DAAs, their potential side effects, and the expectation that treatment will be started within 3 months of LT. Our approach to HCV treatment was preemptive antiviral therapy with DAA, defined as DAA initiated in the early post-LT period prior to clinical evidence of HCV. The specific DAA selected was based on the HCV treatment guidelines published by the American Association for the Study of Liver Disease. We did not communicate with insurance companies prior to transplant, but insurance companies have not denied coverage in our experience. All transplants were performed with the knowledge of our CTC administrator. In the event the patient's insurance does not cover DAA, we verbally informed our patients that our CTC would cover the cost of the medications. We informed patients of a small possibility that DAA would not lead to HCV cure. We stated that the alternative would be to remain on the transplant waitlist with a potentially longer wait time and that there is a risk of death on the waitlist.

The Johns Hopkins Institutional Review Board approved the present study protocol (IRB00201219).

Results

During the study period, there were 191 liver recipients who were HCV Ab− pre-transplant; 26 (13.6%) received an HCV Ab+ donor organ. There were also 77 recipients who had pre-transplant HCV Ab+; among them, 33 (42.9%) received an HCV Ab+ liver.

The present analysis focused on the 26 HCV Ab− recipients who received an HCV Ab+ donor liver. Their median biologic MELD was 21.5 prior to transplant; the median allocation MELD was 29.5. Table 1 provides the baseline characteristics for each recipient in our cohort.

The liver donors in our cohort were all HCV Ab+. Importantly, 20 of the 26 donors were HCV NAT+ before graft harvest. PHS increased risk status was elevated in 19 out of 26 donors. Table 2 summarizes the donor demographic data and liver biopsy pathologies. For clarity, we have numbered the donors to correspond to their respective recipients.

All but one of our HCV Ab− recipients are still alive. Recipient #21, the most critically ill patient in our cohort, had a biologic MELD score of 40 prior to transplant and was listed as status 1A. The indication for liver transplantation was Wilson disease with fulminant liver

failure. The post-transplant course was complicated by ischemic bowel, multiorgan failure, and acute respiratory distress syndrome. Unfortunately, the recipient succumbed to these complications within a week after transplant. The corresponding donor was HCV Ab+/NAT −, but we did not measure a post-transplant HCV viral load before the recipient's death.

The 20 HCV Ab− recipients of HCV NAT+ donor liver all acquired active HCV infection post-LT. In contrast, only 2 out of 5 HCV Ab− recipients of HCV Ab+/NAT− donor liver acquired active HCV infection. We planned for all recipients who developed active HCV infection to receive a treatment course of DAAs to be initiated after HCV RNA became detectable in the recipient's blood. To date, 12 of the 22 recipients who developed active HCV infection post-LT is in SVR12, another 3 completed DAA course awaiting sufficient follow-up to SVR12, 5 are still undergoing DAA treatment, and 1 is awaiting insurance approval for DAA. The number of days from LT to the initiation of DAAs ranged from 9 to 74 (median of 37). The most common reason for the lag period was the insurance approval process. For recipients #5 and #22, our CTC paid for the initial portion of their DAA course while we awaited insurance approval because liver biopsy findings could not exclude HCV as a cause of LAE elevations. Recipient #6 suffered massive blood loss during transplant that required delayed closure of the abdomen and bile duct reconstruction, which led to prolonged intubation, subglottic stenosis, and subsequent dysphagia. There was a 56-day gap until DAA initiation because of the lack of a liquid or crushed formulation of DAA amenable to nasogastric tube administration.

All 25 surviving recipients still enjoy normal graft functions after a median follow-up time of 8 months as of September 2019. Six of the recipients required liver biopsy post-LT. The biopsy of recipient #1 indicated mild acute cellular rejection (ACR), and his LAEs normalized after increasing the dose of corticosteroids. Recipient #3 had a liver biopsy for refractory ascites and biopsy showed nodular regenerative hyperplasia, which was also present on explant of pre-transplant liver; no predisposing factor was identified for nodular regenerative hyperplasia. Recipient #5 had a gradual uptrend of LAEs up to 3 to 5 times the upper limit of normal (ULN) in the 4 weeks between the LT and a liver biopsy that showed mild ACR with concurrent HCV infection. We increased the steroid dose and started DAA immediately after the biopsy. The recipient's aspartate transaminase (AST) and alanine transaminase (ALT) continued to rise to a peak of 8 times the ULN at 8 weeks after DAA initiation, but a repeat biopsy 3 weeks after the first biopsy showed interval improvement. The LAEs normalized over the subsequent 12 weeks. Recipient #5 did eventually have another repeat biopsy 42 weeks after transplant for persistent alkaline phosphatase up to 6 times the ULN; biopsy result was consistent with mild to moderate ACR, and LAEs normalized with a steroid pulse and taper. Recipient #6 had cholestatic elevations; liver biopsy was consistent with mild to moderate ACR without features of HCV activity. The abnormal LAEs normalized after high dose corticosteroids. Recipient #6 subsequently had a repeat biopsy 38 weeks after transplant for LAE elevations and was found to have mild ACR; we increased steroid dose and started mycophenolate mofetil, and LAEs normalized within one week. Recipient #9 had a liver biopsy in the setting of persistent hepatic encephalopathy with elevated ammonia, but biopsy was not consistent with graft dysfunction and she improved clinically after withdrawal of narcotics. Recipient #22 had an initial decrease of LAEs post-LT, but LAEs rapidly rose during the subsequent hospital-acquired

pneumonia. Liver biopsy showed changes consistent with mild ACR, but it could not exclude concurrent HCV infection. We initiated both DAA and high dose corticosteroids immediately after biopsy, and LAEs normalized within 2 weeks. Table 3 presents additional details on these liver biopsies.

The viral loads for all recipients started on DAA decreased rapidly from their baseline pre-DAA viral load. Figure 1 depicts each recipient's viral load as a function of time for the first 90 days post-DAA, highlighting the rapid response of every surviving recipient's viral load after DAA initiation. SVR12 was achieved in 12 out of 12 patients who completed DAA with sufficient follow-up; eleven of these patients received an HCV NAT+ liver. Nine patients either have completed DAA course or are still on DAA treatment, but their viral loads are all undetectable. Although protease inhibitors are not recommended for use for Child-Pugh B, glecaprevir/pibrentasvir was used for recipients #5 and #6 who both reached Child-Pugh B at one point during their treatment course. We did not use protease inhibitor containing therapy on any patient with Child-Pugh C classification, for which protease inhibitors would be contraindicated. In general, the selection of DAA regimen used was per HCV treatment guidelines published by the American Association for the Study of Liver Disease (AASLD) and this was also explicitly stated in our consent form. One exception was for recipient #22 who received a total 24-week course of therapy with 8 days of sofosbuvir/velpatasvir followed by ledipasvir/sofosbuvir, which was due to insurance company preference for a 24-week course of treatment. The initial choice of sofosbuvir/velpatasvir was per our transplant team prior to genotyping results and our CTC paid for the medication prior to insurance approval. The DAA regimen selected, the timing of initiation relative to transplant, and the current HCV treatment status for each recipient are summarized in Table 4.

To summarize, all except one patient in our series currently possess functioning liver grafts. All 12 recipients who completed their DAA courses and have reached sufficient follow-up for SVR12 have achieved SVR12. Nine of our recipients have either completed DAA treatment without sufficient follow-up time for SVR12 or are undergoing DAA treatment. One patient is awaiting DAA initiation pending insurance approval. Of note, 11 out of our 12 patients in SVR12 received an HCV NAT+ donor liver and have normal graft function.

Discussion

Our results are consistent with a prior case series of 10 HCV NAT− LT recipients of HCV NAT+ donors, with all of the patients achieving SVR12 post-LT. However, 7 out of 10 recipients in the prior series were HCV Ab+ before transplant whereas all recipients in our case series were HCV Ab−.[13] More recently, Luckett et al. described 55 LT recipients of HCV Ab+ donor livers of whom 49 recipients were HCV Ab−.[14] None of the donors were HCV NAT+, which differed notably from our present series.

Transplantation of organs from HCV NAT+ donors to HCV Ab− patients is not an entirely novel concept. Goldberg et al. evaluated kidney transplants from HCV NAT+ donors to 10 HCV Ab− recipients, and they treated recipients with DAA at the first elevated HCV RNA level in the Transplanting Hepatitis C Kidneys Into Negative Kidney Recipients (THINKER)

trial.[15] Our group also previously described 10 HCV Ab− recipients of HCV Ab+ donor kidneys who received DAA as pre- and post-transplant prophylaxis with treatment regimen modified according to genotype results.[16] All patients in the two abovementioned trials reached SVR12. Transplantation of heart and lungs from HCV NAT+ donors to HCV Ab− recipients have similarly been reported with acceptable short-term outcomes and HCV cure with DAA treatment.[17–20] Despite these reports, liver transplantation with an HCV Ab+ donor into an HCV Ab− recipient is fundamentally and conceptually different as HCV infects hepatocytes; thus, the liver is the largest reservoir of HCV in the body. Little is understood about the impact of immunosuppression in HCV NAT− transplant recipients receiving an HCV NAT+ liver and, by extension, a large HCV load. Acute HCV infections do not typically cause significant liver injury in the non-transplant setting. However, the clinical course of transmitting new HCV infection to liver transplant recipients on active immunosuppression has the potential to progress differently. Our series helps to address this knowledge gap since we administered standard immunosuppression regimens without dose reduction despite HCV infection.

Despite enthusiasm for using HCV Ab+ donors for LT, the long-term outcomes of donor-derived HCV infection in HCV Ab− patients are yet to be determined.[14] Some possible risks of donor-derived HCV infection include fibrosing cholestatic hepatitis and graft rejection following HCV cure.[21] Furthermore, our series observed a 16% rate of ACR (4 out of 25 surviving patients), albeit 2 out of 4 of these cases were complicated by concurrent post-transplant HCV infection. This raises the possibility that ACR may occur more rapidly for HCV Ab− patients who receive HCV NAT+ liver transplantation, since prior experience with immune-mediated graft dysfunction primarily occurs after completion of DAA treatment post-LT.[22] Transplant providers must weigh these possibilities against the mortality risk while on the waitlist. For instance, Croome et al. showed a 136% increase in mortality for waitlisted patients who declined an increased risk donor liver relative to those who accepted one.[5] A recent mathematical model using UNOS data also suggested improved life expectancy for patients with MELD 20+ should they be willing to accept HCV Ab+ organs.[23]

Our study demonstrates the paradigm shift brought by DAA agents with high rates of treatment response for donor-derived HCV infections. Nonetheless, until long-term data become available, we recommend reserving the transplantation of HCV NAT+ donor livers to HCV Ab− recipients for specific subsets of LT candidates. Patients who may benefit the most include those whose MELD scores underrepresent the clinical severity of disease (e.g., recurrent cholangitis episodes), as well as those in whom prolonged waiting risks eventual transplant ineligibility (e.g., progressing hepatopulmonary syndrome) or other calamities (e.g., acute liver failure).[24]

All patients in our series started DAA within 12 weeks of LT. Awaiting insurance approval was the most common source of the lag time between LT and DAA initiation. In one patient, an inability to swallow led to the delay in DAA initiation. Additional studies should focus on the optimal treatment regimen and timing, specifically whether prophylactic treatment at the time of liver transplant would promote even better outcomes. While the availability of pan-genotypic DAA improves the theoretical feasibility of prophylactic treatments,

administration through a nasogastric tube immediately post-transplant may encounter poor drug absorption. A recent study of the pan-genotypic DAA glecaprevir/pibrentasvir in healthy subjects showed variable drug plasma levels when the medication was crushed or ground, precluding it from reliable delivery through nasogastric tubes.[25] We did note that, in the Using Hepatitis C positive hearts for Negative Recipients (USHER) trial, Mclean et al. reported HCV cure in an undisclosed number of HCV Ab− orthotopic heart transplant recipients who received crushed elbasvir/grazoprevir through nasogastric tube administration.[26] However, elbasvir/grazoprevir is not pan-genotypic. Its role may be limited to treatments after the HCV genotype result is confirmed, when the immediate post-operative need for crushed administration has often resolved.

Given the rise of HCV Ab+ donors in the United States based on available national data, the addition of DAA agents to our therapeutic arsenal has allowed us to explore the utilization of these increased-risk organs.[27] The transplant community underwent a similar transformation for hepatitis B core antibody positive liver grafts in the past decade. Despite the initial uncertainty, literature now supports the routine use of hepatitis B core antibody positive livers for transplantation.[28,29] In time, we may also view HCV Ab+ liver grafts in the same light. In conclusion, our case series presented the successful transplant of HCV Ab+ livers in HCV Ab− recipients when HCV receives treatment after transplant. The practice should be considered after a careful risk and benefit discussion with the potential candidate. Further discussions at the national level are warranted to reach a consensus within the transplant community regarding the use of HCV Ab+ donor livers for HCV Ab− recipients.

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Abbreviations:

ACR	acute cellular rejection
ALT	alanine transaminase
Ab	antibody
AST	aspartate transaminase
CTC	Comprehensive Transplant Center
DAA	direct-acting antiviral
HCV	hepatitis C virus
LAE	liver-associated enzyme

LT	liver transplantation
MELD	model of end-stage liver disease
NAT	nucleic acid testing
PHS	Public Health Services
RNA	ribonucleic acid
SVR12	sustained virologic response at 12 weeks after treatment
ULN	upper limit of normal

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Box 1:

Terminology of Hepatitis C Virus (HCV) Infection Status used in this Manuscript

Term	Abbreviation	Definition
HCV seropositive	HCV Ab+	Detectable anti-HCV antibody in the serum. Can be either HCV Ab+/NAT+ or HCV Ab+/NAT−.
HCV seronegative	HCV Ab−	Undetectable anti-HCV antibody in the serum.
HCV NAT positive	HCV NAT+	Detectable HCV RNA through nucleic acid amplification test in the serum.
HCV NAT negative	HCV NAT−	Undetectable HCV RNA through nucleic acid amplification test in the serum.

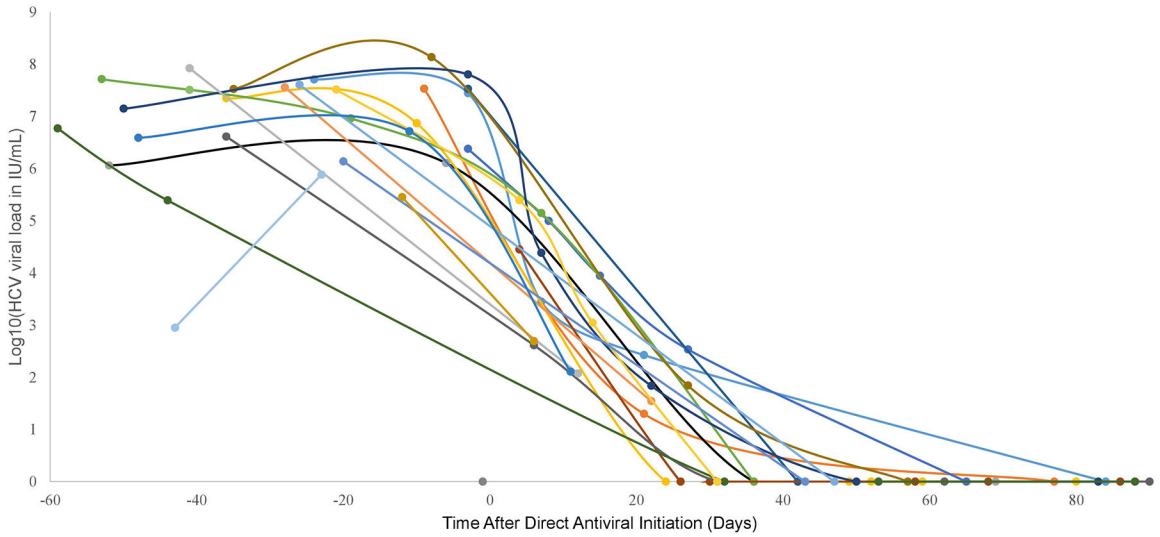

Figure 1: Viral Load for Each Patient Versus Time After Direct Antiviral Initiation

Only the first 90 days after initiation of antiviral therapy is shown for each patient. Each series of dots connected by lines represents the viral load trend for a given patient treated with DAA. The above graph contains the 21 patients treated with DAA; 4 patients were not infected post-transplant thus never started DAA and 1 patient died prior to DAA treatment. Abbreviations: hepatitis C virus (HCV), international units per milliliter (lll/mL), direct-acting antiviral (DAA)

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Table 1:

HCV Seronegative Liver Transplant Recipients of HCV Seropositive Livers between January 2014 and August 2019 at Johns Hopkins Hospital

Recipient number	Age† - years/sex	Etiology of cirrhosis	Race	Blood type	Biologic MELD at transplant	Allocation MELD at time of transplant (reason for exception points)
1	24/M	Chronic rejection≠	Caucasian	O+	15	28 (encephalopathy)
2	53/M	Alcohol	Caucasian	O+	17	17
3	60/M	Alcohol	Caucasian	O+	21	28 (hydrothorax)
4	59/M	Cryptogenic	Caucasian	O−	22	22
5	66/M	NASH	Caucasian	A−	17	17
6	53/M	Alcohol	Caucasian	O+	30	30
7	71/M	PBC	Caucasian	A+	19	19
8	60/F	HCC	Caucasian	A+	6	28 (HCC)
9	57/F	Alcohol	Caucasian	O+	17	25 (encephalopathy)
10	66/M	NASH	Caucasian	O+	30	30
11	44/M	Alcohol	Caucasian	O−	37	37
12	25/F	Dyskeratosis congenita	Caucasian	O+	7	29 (hepatopulmonary syndrome)
13	71/M	PBC	Hispanic	O+	25	25
14	60/M	NASH	Caucasian	O+	27	27
15	70/F	NASH	Caucasian	A+	33	33
16	57/M	NASH	Caucasian	O+	26	26
17	57/M	NASH	Caucasian	B+	19	19
18	55/M	A1AT deficiency	Caucasian	B+	11	11
19	56/M	NASH	Caucasian	O−	18	18
20	67/F	NASH	Caucasian	O+	29	29
21	21/F	Wilson disease	Black	O+	40	Status 1A
22	21/M	PSC	Caucasian	O+	27	27
23	54/M	Alcohol	Caucasian	O+	26	26
24	71/F	NASH	Caucasian	A+	31	31
25	28/M	Oxaluria	Caucasian	A+	20	30 (oxaluria)
26	65/M	HBV	Caucasian	A+	7	27 (HCC)

[†] Age at the time of transplantation

[‡] original indication for transplant was biliary atresia in 24 years prior to current transplant, with an episode of possible autoimmune hepatitis in 2015 (antinuclear antibody titer 1:160, anti-smooth muscle antibody titer 1:80, immunoglobulin G level normal) thought to be leading to graft failure, but explant pathology ultimately was most consistent with chronic rejection

Abbreviations: alpha-1-antitrypsin (A1AT), female (F), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatocellular carcinoma (HCC), male (M), model for end-stage liver disease (MELD), nonalcoholic steatohepatitis (NASH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC)

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Table 2:

HCV Seropositive Donors Corresponding to Recipients in Table 1

Donor number	Donor age/sex	Donor race	Donor blood type	Donor HCV NAT	PHS increased risk organ	Donor liver pathology			
						Inflammation	Fibrosis	Steatosis	Iron
1	37/M	Caucasian	O	positive	Yes	Mild, portal, chronic	None significant	None significant	None significant
2[†]	40/M	Caucasian	O	positive	Yes	N/A	N/A	N/A	N/A
3	57/F	Caucasian	O	positive	No	Mild, portal, chronic	None significant	Mild macrovesicular (<5%)	Patchy, mild, hepatocellular distribution
4	46/M	Latino	O	positive	Yes	None significant	None significant	None significant	None significant
5	42/F	Black	A	positive	Yes	Moderate, portal, chronic. Multiple portal non-caseating granulomata with giant cells.	Moderate, periportal	Moderate macrovesicular (40%)	Mild increase in reticuloendothelial cells and hepatocytes
6	57/M	Black	O	positive	No	Moderate, chronic, portal.	Moderate, portal	Large droplet macrovesicular (<5%), small droplet	Increased iron stores noted in reticuloendothelial cells
7	33/M	Caucasian	A	positive	Yes	Mild, portal, chronic	None significant	Large droplet (25%) and small droplet (30%) macrovesicular	Mild hepatocellular and reticuloendothelial stainable iron.
8	20/F	Caucasian	A	positive	Yes	Moderate, portal, chronic	Moderate, periportal	None significant	None significant
9	49/F	Hispanic	O	positive	Yes	Mild, portal, chronic	Mild, portal	Severe small droplet (90%), mild large droplet (<5%)	None significant
10	20/F	Caucasian	O	positive	Yes	N/A	N/A	N/A	N/A
11	22/M	Caucasian	O	positive	Yes	None significant	None significant	Small droplet macrovesicular (70%), minimal large droplet macrovesicular (<5%)	None significant
12	23/F	Caucasian	O	positive	Yes	Mild, portal, chronic	None significant	Small droplet macrovesicular (20%), minimal large droplet macrovesicular (<5%)	None significant
13	56/M	Hispanic	O	positive	No	Mild to moderate, portal, chronic	Minimal fibrosis	None significant	None significant
14	49/M	Caucasian	O	positive	Yes	Mild, portal, chronic	Mild, periportal	Small droplet microvesicular (5%)	None significant

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Donor number	Donor age/sex	Donor race	Donor blood type	Donor HCV NAT	PHS increased risk organ	Donor liver pathology			
						Inflammation	Fibrosis	Steatosis	Iron
15	50/F	Black	A	positive	No	Mild, portal, chronic. Minimal interface activity.	None significant	None significant	None significant
16	28/M	Caucasian	O	positive	Yes	Mild, portal, chronic	Mild, periportal	Small droplet macrovesicular (10%)	None significant
17	32/F	Caucasian	B	positive	Yes	Mild, portal, chronic	None significant	Moderate small droplet macrovesicular (60%)	None significant
18	34/F	Caucasian	B	positive	Yes	Mild, portal, chronic	Mild to focal moderate periportal	Small droplet macrovesicular (80%)	None significant
19	60/M	Black	O	positive	Yes	Mild, chronic, portal	Moderate portal fibrosis. Rare bridging fibrosis.	Minimal (<5%)	None significant
20	30/M	Hispanic	O	positive	Yes	Mild, lobular and portal	None significant	None significant	N/A
21[≠]	55/F	Caucasian	O	negative	No	N/A	N/A	N/A	N/A
22	27/F	Caucasian	O	negative	Yes	Mild, portal, chronic	None significant	Severe, diffuse, small droplet (100%)	None significant
23	41/M	Caucasian	A	negative	Yes	None significant	Mild, pericellular	Mild	None significant
24	68/F	Caucasian	A	negative	No	Moderate lobular and mild portal, mixed acute and chronic	None significant	Large droplet (10%) and small droplet (10%) macrovesicular	None significant
25	22/M	Black	A	negative	Yes	Mild, portal, mixed acute and chronic	None significant	Small droplet macrovascular (60%)	Mild increase in hepatocytes and Kupffer cells
26	58/M	Caucasian	A	negative	No	None significant	None significant	None significant (<5%)	Mild, intrahepatocyte

[†]Donor liver was sampled but there was no liver tissue identified on pathology. The sample obtained only revealed fibroadipose tissue and peribiliary glands.

[≠]Recipient died a week after transplant and biopsy was not obtained intraoperatively during transplant.

Abbreviations: female (F), hepatitis C virus (HCV), male (M), not available (N/A), nucleic acid testing (NAT), Periodic Acid-Schiff/Diastase (PAS/D), Public Health Service (PHS)

Table 3:

Liver Transplant Recipients Requiring Liver Biopsy Post-transplant

Recipient number	Indication for liver biopsy	Time between transplant and biopsy - weeks	Liver biopsy pathology
1	LAE elevations	69	Bile duct injury, mild endothelitis, and moderate eosinophil-rich mixed portal inflammation with scattered lobular eosinophils noted. Findings were consistent with mild ACR, with possible superimposed drug reaction.
3	Ascites refractory to transjugular intrahepatic portosystemic shunt	43	Vascular abnormality characterized by focal sinusoidal dilatation and features suggestive of nodular regenerative hyperplasia. Mild portal chronic inflammation. Reticulin stain highlights focal vague nodularity. No bile duct injury or endothelitis. No significant steatosis or fibrosis or stainable iron.
5	LAE elevations	4	Focal endothelitis and bile duct injury associated with moderate chronic portal inflammation with rare eosinophils and lymphoid aggregates found. Findings were consistent with mild ACR and concurrent recurrent HCV.
		6	Scattered zone 3 hepatocyte necrosis. Bile duct injury with intraepithelial lymphocytes and scattered endothelitis. In keeping with moderate cellular rejection.
		7	Persistent cholestasis associated with focal hepatocyte injury noted, but interval improvement in endothelitis and inflammation. Findings were consistent with interval improvement in chronic HCV and resolving acute process.
		42	Bile duct injury with mild ductular reaction. Moderate portal inflammation, focal endothelitis, and mild lobular inflammation with spotty necrosis. Mild portal fibrosis with rare bridging fibrosis. No steatosis or stainable iron. Findings are consistent with mild to moderate acute cellular rejection. No features of chronic rejection.
6	LAE elevations	3	Moderate chronic portal inflammation with associated eosinophils, bile duct injury, and endothelitis noted. Mild lobular chronic inflammation noted. Findings were consistent with mild to moderate ACR, without strong evidence for HCV.
		38	Moderate mixed portal inflammation with focal bile duct injury and focal endothelitis. Mild chronic lobular inflammation. Focal bile ductular proliferation. Moderate periportal fibrosis. Mild increased iron storage in reticuloendothelial cells. No significant steatosis. The findings are consistent with mild acute cellular rejection. No strong features to suggest active hepatitis C infection.
	One-year post-transplant liver biopsy	52	Mild lobular inflammation (lymphocytes) and mild portal inflammation. Focal bile duct loss and mild macrovesicular steatosis (10%); no evidence of acute cellular rejection. No significant fibrosis and minimal stainable iron.
9	Hepatic encephalopathy with persistent ammonia elevation	35	Mild bile ductular reaction and minimal bile duct injury. Focal lobular inflammation with few apoptotic bodies. Mild portal chronic inflammation (lymphocytes, plasma cells, neutrophils). Mild to focally moderate portal fibrosis (trichrome and reticulin). Stainable iron in reticuloendothelial cells. No steatosis.
22	LAE elevations	2	Few endothelitis and mild bile duct injury noted. Mild chronic portal inflammation admixed with eosinophils and neutrophils with mild lobular inflammation and few apoptotic bodies observed. Findings were consistent with mild ACR, but HCV infection could not be excluded.

Abbreviations: acute cellular rejection (ACR), hepatitis C virus (HCV), liver-associated enzyme (LAE)

Table 4:

Pre-transplant HCV Viral Loads of Liver Transplant Recipients and Current Treatment Status

Recipient number	Post-transplant HCV genotype	Time between transplant and DAA initiation - days	DAA selected (duration of treatment)	Viral load before DAA initiation -IU/mL (days before DAA initiation)	Current treatment status
1	1A	25	Ledipasvir/sofosbuvir (12 weeks)	28,200,000 (3)	SVR12
2	3A	12	Glecaprevir/pibrentasvir (12 weeks)	34,400,000 (9)	SVR12
3	2B	54	Glecaprevir/pibrentasvir (12 weeks)	1,290,000 (6)	SVR12
4	1A	39	Glecaprevir/pibrentasvir (12 weeks)	7,440,000 (10)	SVR12
5	1B	30	Glecaprevir/pibrentasvir (12 weeks)	2,410,000 (3)	SVR12
6	1A	56	Glecaprevir/pibrentasvir (12 weeks)	9,250,000 (19)	SVR12
7	1A	9	Glecaprevir/pibrentasvir (12 weeks)	33,900,000 (3)	SVR12
8	3A	17	Glecaprevir/pibrentasvir (12 weeks)	829 (12)	SVR12
9	3A	49	Glecaprevir/pibrentasvir (12 weeks)	4,140,000 (36)	SVR12
10	3A	37	Glecaprevir/pibrentasvir (12 weeks)	138,000,000 (8)	SVR12
11	3A	52	Glecaprevir/pibrentasvir (12 weeks)	64,300,000 (3)	SVR12
12	3A	74	Glecaprevir/pibrentasvir (12 weeks)	248,000 (44)	completed DAA
13	1A	28	Glecaprevir/pibrentasvir (12 weeks)	40,700,000 (26)	completed DAA
14	1A	31	Glecaprevir/pibrentasvir (12 weeks)	36,500,000 (28)	completed DAA
15	1A	44	Glecaprevir/pibrentasvir (12 weeks)	84,400,000 (41)	DAA ongoing
16	1A	24	Glecaprevir/pibrentasvir (12 weeks)	33,100,000 (21)	DAA ongoing
17	2B	22	Glecaprevir/pibrentasvir (12 weeks)	1,380,000 (20)	DAA ongoing
18	3A	46	Glecaprevir/pibrentasvir (12 weeks)	32,500,000 (41)	DAA ongoing
19	1A	54	Glecaprevir/pibrentasvir (12 weeks)	5,230,000 (11)	DAA ongoing
20	1B	DAA not initiated	DAA not initiated	DAA not initiated	DAA not initiated[†]
21	N/A	DAA not initiated	DAA not initiated	DAA not initiated	Deceased[‡]
22	1A	13	Sofosbuvir/velpatasvir (8 days) then ledipasvir/sofosbuvir (23 weeks)[§]	287,000 (12)	SVR12
23	N/A	DAA not initiated	DAA not initiated	DAA not initiated	Not infected, VL undetectable at 37 weeks after liver transplant

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Recipient number	Post-transplant HCV genotype	Time between transplant and DAA initiation - days	DAA selected (duration of treatment)	Viral load before DAA initiation -IU/mL (days before DAA initiation)	Current treatment status
24	N/A	DAA not initiated	N/A	DAA not initiated	Not infected, VL undetectable at 4 weeks after liver transplant
25	2B	55	Glecaprevir/pibrentasvir (12 weeks)	769,000 (23)	DAA ongoing
26	N/A	DAA not initiated	NA	DAA not initiated	Not infected, VL undetectable at 4 weeks after liver transplant

[†]Currently pending insurance approval for DAA.

[‡]recipient #1 died of bowel ischemia and subsequent multi-organ failure within a week of liver transplant

[§]sofosbuvir/velpatasvir was used as a pan-genotypic agent prior to the genotyping result, then transitioned to ledipasvir/sofosbuvir after insurance approval. Insurance approved a total 24-week treatment course which we delivered.

Abbreviations: direct antiviral agent (DAA), hepatitis C virus (HCV), international units per milliliter (IU/mL), not available (N/A), sustained virologic response at 12 weeks after treatment (SVR12), viral load (VL)