Use of Hepatitis C Virus Antibody-Positive Donor Livers in Hepatitis C Nonviremic Liver Transplant Recipients

Keith Luckett, MD, FACP, Tiffany E Kaiser, PharmD, Khurram Bari, MD, Kamran Safdar, MD, Michael R Schoech, MD, Senu Apewokin, MD, Tayyab S Diwan, MD, FACS, Madison C Cuffy, MD, FACS, Nadeem Anwar, MD, Shimul A Shah, MD, MHCM, FACS

BACKGROUND: Given the shortage of available liver grafts, transplantation (LTx) of hepatitis C virus antibody-positive, nucleic acid test-negative (HCV Ab+/NAT-) livers into nonviremic HCV recipients can expand the donor pool. Having previously described the sentinel experience of HCV Ab+/NAT- allografts in nonviremic recipients, we report the growth and extended follow-up of this program for 55 patients compared with recipients of Public Health Services (PHS) increased-risk donor HCV Ab-/NAT- allografts.

STUDY DESIGN: A prospective review of all HCV nonviremic LTx patients receiving HCV Ab+/NAT- organs between March 2016 and August 2018 was performed. All HCV Ab+/NAT- organ recipients underwent HCV testing at 3 months and 1-year post-LTx to determine HCV transmission.

RESULTS: Fifty-five HCV nonviremic candidates received HCV Ab+/NAT- organs; 64% male, median age 59 years (range 36 to 69 years) and median Model for End-Stage Liver Disease score of 22.5. Two recipients were excluded due to death before HCV testing. The HCV disease transmission occurred in 5 recipients (9%). Of these, 4 (80%) underwent anti-HCV treatment with eradication of virus. No patient found to be negative at 3 months seroconverted at 1-year follow-up. No patients who received PHS increased-risk donor HCV Ab-/NAT- organs had viremia develop (0 of 57) and there was no difference in graft and renal function, complications, or survival between HCV Ab+/NAT- recipients and PHS increased-risk donor HCV Ab-/NAT- recipients.

CONCLUSIONS: We report the largest experience with LTx from HCV Ab+/NAT- donors into 55 seronegative recipients with a HCV transmission rate of 9% with no late conversions at 1 year and no difference in function or graft loss compared with PHS increased-risk donor HCV Ab-/NAT- recipients. Due to availability of safe and effective HCV therapies, the use of such organs should be strongly considered to increase the donor organ pool. (J Am Coll Surg 2019;228:560−569. © 2018 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Suitable organs for transplantation remain in short supply. In 2017, there were 8,082 liver transplantations performed, leaving more than 13,000 patients on the waiting list.[1] In the US, the heroin epidemic has increased the availability of procurable organs, albeit with some increased risk. This has presented an opportunity to expand life-saving transplantation through the use of organs that might have otherwise been discarded. Previously, we described the sentinel experience with 25 patients, using hepatitis C virus antibody positive, nucleic acid testing negative (HCV Ab+/NAT-) donor organs in hepatitis C nonviremic recipients.[2] This particular serology, HCV Ab+/NAT-, could be found in individuals infected with HCV previously who cleared their infection spontaneously (15% to 25% of all HCV cases),[3-5] or could be the result of either a false-positive antibody testing (specificity 92% to 100%) or false-negative

Disclosure Information: Nothing to disclose.

Presented at the Southern Surgical Association 130th Annual Meeting, Palm Beach, FL, December 2018.

Received December 10, 2018; Accepted December 10, 2018.

From the Department of Medicine and Surgery, University of Cincinnati School of Medicine, Cincinnati, OH.

Correspondence address: Shimul A Shah, MD, MHCM, FACS, Department of Surgery, University of Cincinnati School of Medicine, 231 Albert Sabin Way, ML 0558, MSB 1555, Cincinnati, OH 45267-0558. email: Shimul.shah@uc.edu

https://doi.org/10.1016/j.jamcollsurg.2018.12.004
ISSN 1072-7515/18

Abbreviations and Acronyms

Ab = antibody
HCV = hepatitis C virus
IRD = increased risk donor
IVDU = intravenous drug use
NAT = nucleic acid testing
OCI = occult hepatitis C infection
PCR = polymerase chain reaction
PHS = Public Health Services
SVR = sustained virologic response

NAT testing (sensitivity 98% to 99%).[6-8] Previously, all HCV Ab+ donor organs would have been considered for transplantation into HCV-seropositive recipients only, given concerns for transmission of the virus.[9] With the advent of NAT testing in donors, as well as the surge in effective and nontoxic treatments for HCV, the use of these organs in HCV nonviremic patients has been considered. Little literature existed about the risk of transmission of HCV from HCV Ab+/NAT- donors, as most of these organs historically went to HCV-seropositive recipients. Direct experience was limited to case reports[10,11] until our earlier study of 25 HCV Ab+/NAT- liver donors to nonviremic recipients revealed that the risk of transmission of HCV was approximately 16%.[2] We now report the clinical outcomes and incidence of transmission from our expanded pool of 55 HCV Ab+/NAT- allografts transplanted into HCV nonviremic recipients with extended follow-up. We also compared the clinical outcomes from this group to 57 HCV Ab-/NAT- patients transplanted within the study period.

METHODS

Study population

In 2015, the University of Cincinnati Medical Center began offering HCV nonviremic liver transplantation candidates the option of receiving an organ from HCV Ab+/NAT- donors as a way to decrease waiting times on the transplant list, as described previously.[2] Nonviremic status of recipients was defined as either HCV antibody-negative or, in the case of HCV antibody-positive candidates, an undetectable NAT test within 6 months before transplantation. Patients were informed that the risk of HCV transmission was unknown, but could be as high as 16%, based on previous data.[2] Notably, the majority of HCV Ab+/NAT- donors meet Public Health Services (PHS) increased-risk criteria for infection transmission and can potentially fall within the "eclipse period" of HCV reinfection, during which viremia might not be detectable by current assays. Earlier studies suggest a 0.32% risk of HCV infection transmission within the eclipse period,[12] however, recent guidelines from the Disease Transmission Advisory Committee of Organ Procurement and Transplantation Network suggest that the risk of HCV transmission could be as high as 3% from donors with immediate needle exposure.[13] We also considered the conceptual risk of HCV transmission from occult hepatitis C infection (OCI), in which residual HCV RNA is present in liver tissue or peripheral blood mononuclear cells after self- or treatment-induced clearance of viremia.[14-16] Informed consent was obtained in the office setting, and transplant candidate profiles were updated to reflect their eligibility for HCV Ab+/NAT- organs.

Donor selection

Donor status was defined based on the results of a single serum anti-HCV antibody test and single serum HCV RNA determination by NAT, as provided in DonorNet. Testing was performed at the respective organ procurement organizations. Enzyme-linked immunosorbent assay HCV antibody testing (Ortho HCV, version 3.0; Ortho Clinical Diagnostics) was used for all donors, and the methodology for HCV NAT testing varied.[17-19] Donor liver biopsies were performed at the discretion of the transplantation surgeon. No donor organs were obtained from executed prisoners or other institutionalized persons.

Follow-up and outcomes measures

All patients received standard immunosuppression post transplantation, which consisted of tacrolimus, mycophenolate mofetil, and corticosteroids, as per institutional protocol. Patients with renal insufficiency or who were on hemodialysis in the perioperative period received anti-thymocyte globulin (rabbit) to suppress CD3 count to $<25/mm^3$ until delayed introduction of tacrolimus by postoperative day 7. Tacrolimus trough targets were reduced in those recipients that received anti-thymocyte globulin (rabbit). Tacrolimus trough-level targets varied according to elapsed time post transplantation and were maintained between 10 and 12 ng/mL, 8 and 10 ng/mL, and 3 and 8 ng/mL during month 1, months 2 to 6, and 6 months and after, respectively. In addition to standard post-transplantation management, all patients underwent HCV nucleic acid testing[17,18] 3 months after transplantation, or sooner if indicated by a rise in liver chemistries. The 3-month time point was selected because, as per our institutional protocol, post-transplantation HCV patients are considered for antiviral treatment at 3 months after transplantation when systemic steroids have been tapered off. Although asymptomatic viremia with normal liver chemistries can develop early on, it would be highly unlikely for the recipients to develop clinically significant liver

injury, mainly fibrosing cholestatic hepatitis C, with normal liver chemistries. Patients in whom HCV viremia developed were screened for any behavioral risk factors or healthcare exposure for HCV infection. Antiviral therapy was initiated unless contraindicated. The selection of antiviral therapy was based on provider preference and payer discretion. Data were collected prospectively through November 2018 on consecutive liver transplant recipients that received liver grafts from HCV Ab+/NAT- donors between March 2016 and August 2018.

Statistical analyses

SPSS software, version 22 (IBM Corp) was used to generate descriptive statistics for clinical parameters. Mann-Whitney U test was used to analyze the ordinal variables. Chi-square and Fisher's exact tests were used to analyze categorical variables.

RESULTS

During the 29.5-month study period from March 2016 to August 2018, fifty-five liver transplantations were performed giving HCV Ab+/NAT- organs to HCV nonviremic recipients, including 6 simultaneous liver/kidney transplantations. Two patients did not survive to 90 days and so did not have testing performed per the protocol, and were excluded from analysis for HCV viremia. Mean age of liver recipients was 59.3 years (range 31 to 69 years) and the mean Model for End-Stage Liver Disease (MELD) score at transplantation was 22.5. Six (10.9%) of the transplant recipients were HCV Ab+, but all were NAT- at the time of transplantation. Mean age for donors was 42.6 years and 43 (78%) were classified as PHS increased-risk donors (IRDs); 42 had a reported history of IV drug use (IVDU). Eighteen (33%) donors had a positive hepatitis B core antibody. Additional clinical characteristics of the

Table 1. Recipient Characteristics after Liver Transplantation According to Donor Type: Comparison of Hepatitis C Virus Antibody-Positive/Nucleic Acid Testing-Negative Donor to Public Health Service Increased-Risk Hepatitis C Virus Antibody-Negative/Nucleic Acid Testing-Negative Donor Livers

Characteristic	Recipient who received HCV Ab+/NAT- donor liver (n = 55)	Recipient who received a PHS increased-risk HCV Ab-/NAT- donor liver (n = 57)	p Value
Age of recipient, y, mean (range)	59.3 (31–69)	53.5 (26–70)	0.006
Sex, male, n (%)	35 (64)	37 (65)	1
Caucasian race, n (%)	50 (91)	52 (91)	1
MELD score at time of transplantation, mean (range)	22.5 (10–39)	26.1 (15–40)	0.002
Cause of liver disease, n (%)			NA
Non-alcoholic steatohepatitis	23 (42)	15 (26)	
Alcohol	12 (22)	16 (28)	
Primary sclerosing cholangitis	6 (11)	2 (4)	
HCV	5 (9)	8 (14)	
Cryptogenic	3 (5)	0 (0)	
α-1-Antitrypsin deficiency	2 (4)	2 (4)	
Hepatitis B virus	0 (0)	3 (5)	
Primary biliary cirrhosis	0 (0)	2 (4)	
Other*	4 (7)	8 (14)	
Pretransplantation HCV Ab+, n (%)	6 (11)	8 (14)	0.78
Retransplantation, n (%)	4 (7)	5 (9)	1
Simultaneous liver/kidney transplantation, n (%)	6 (11)	3 (5)	0.32
Anti-thymocyte globulin (rabbit) received, n (%)	19 (35)	13 (23)	0.21
Cytomegalovirus immunoglobulin G, n (%)			NA
High	20 (36)	14 (25)	
Intermediate	30 (55)	31 (54)	
Low	5 (9)	12 (21)	
Developed post-transplantation HCV viremia, n/N (%)	5/53 (9)	0/54 (0)	0.03
Length of post-transplantation follow up, d, mean	481	497	0.77

*Other includes: autoimmune hepatitis, hepatitis B virus, hemochromatosis, sarcoidosis, alligiles, biliary atresia, cholangiocarcinoma, cryptogenic, hemochromatosis, hepatic adenomatosis, and polycystic liver disease.

Ab, antibody; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; NA, not applicable; NAT, nucleic acid testing; PHS, Public Health System.

HCV Ab+/NAT- recipients and their donors can be found in Tables 1 and 2.

In the HCV Ab+/NAT- group, 53 patients had an HCV polymerase chain reaction (PCR) at 3 months, and 5 (9.4%) were found to be positive. There was no biopsy-proven rejection in this group. The mean aspartate aminotransferase, alanine aminotransferase, bilirubin, and creatinine at 3 months and 1 year are summarized in Table 3. This group had 12 biliary complications, including 4 bile leaks and 8 biliary strictures. Eight (14.5%) graft losses occurred, and 7 (12.7%) recipients died. Two of these deaths were before the 90-day point, at which repeat HCV testing routinely occurred. Causes of death in these 2 patients were primary liver graft nonfunction and sepsis. A postmortem was not performed on either, but liver biopsies performed during their hospital stays demonstrated no changes consistent with HCV.

Of the 5 patients in whom HCV viremia developed post transplantation, 1 died of non-HCV-related complications at day 253. There was no statistical difference in recipient age, MELD, biliary complications, graft loss, or mortality between the groups in which viremia developed and did not. One of the viremic patients had a history of treated HCV, but genetic analysis revealed that her post-transplantation strain, although the same genotype, was significantly different than her earlier strain, and most likely represented new infection as opposed to mutation and reactivation of her earlier virus. All 4 of the living viremic patients were treated with direct-acting antivirals and achieved sustained virologic response (SVR).

During the same study period, 57 HCV Ab-/NAT- PHS IRDs were used for liver transplantation in our center, including 3 simultaneous liver/kidney transplantations. Mean donor age was 37.5 years and 25 (44%) had a reported history of IVDU. Six (10%) donors were also hepatitis B core antibody-positive. Mean age of these liver recipients was 53.5 years (range 26 to 70 years) and the mean MELD score was 26.1. Eight (14.0%) of the transplant recipients were HCV Ab+, but all were NAT- at transplantation. Recipient HCV PCR at 3 months was performed in 94.7% (54 of 57) and none were found to be positive. Mean aspartate aminotransferase, alanine aminotransferase, bilirubin, and creatinine at 3 months and 1 year are summarized in Table 3. This group had 16 biliary complications, including 5 bile leaks and 11 biliary strictures. Seven (12.3%) graft losses occurred and 6 (10.9%) recipients died. Three of these deaths were before the 90-day point, at which repeat HCV testing routinely occurred. Causes of death were sepsis, likely pulmonary embolism and thrombosis leading to ischemia.

Table 2. Donor Characteristics

Characteristic	HCV Ab+/NAT- recipient (n = 55)	PHS increased-risk HCV Ab-/NAT- recipient (n = 57)	p Value
Age, y, mean (range)	42.6 (17–66)	37.5 (18–65)	0.04
Sex, male, n (%)	31 (56)	33 (58)	1
Caucasian race, n (%)	46 (84)	45 (79)	0.63
BMI, kg/m^2, mean (range)	28 (16–53)	28 (17–48)	1
PHS increased-risk criteria, n (%)	43 (78)	57 (100)	<0.0001
Reported history of IV drug use, n (%)	42 (76)	25 (44)	0.0005
Reported cause of death, n (%)			
Drug-related anoxia	33 (60)	25 (44)	0.09
Cardiovascular-related anoxia	8 (14)	9 (16)	1
Head trauma	8 (14)	13 (23)	0.33
CVA	5 (9)	9 (16)	0.39
Other	1 (2)	1 (2)	1
HCV NAT performed within eclipse period, n (%)	51 (93)	56 (98)	0.20
Days after admission HCV NAT performed, mean (range)	2 (0–11)	2 (0–13)	1
Hepatitis B core antibody-positive, n (%)	18 (33)	6 (10)	0.005
Hepatitis B NAT-positive, n (%)	2 (4)	2 (4)	1
Organ procurement organization, n (%)			
Local	6 (11)	26 (46)	<0.0001
Regional	27 (49)	28 (49)	1
National	22 (40)	3 (5)	<0.0001

Ab, antibody; HCV, hepatitis C virus; NAT, nucleic acid testing; PHS, Public Health System.

Table 3. Recipient Outcomes after Liver Transplantation

Characteristic	Recipient of HCV Ab+/NAT- donor livers (n = 55)	Recipient of PHS increased-risk HCV Ab-/NAT- donor livers (n = 57)	p Value
Graft loss, n/N (%)			
3 mo	2/55 (3.6)	3/57 (5.3)	1
1 y	5/37 (13.5)	4/42 (9.5)	0.73
Overall	8/55 (14.5)	7/57 (12.3)	0.79
Mortality, n/N (%)			
3 mo	2/55 (3.6)	3/57 (5.3)	1
1 y	4/36 (11.1)	4/42 (9.5)	1
Overall	7/54 (13.0)	6/56 (10.7)	0.77
Mean aspartate aminotransferase, U/L (n)			
3 mo	22.6 (53)	24.2 (54)	0.72
1 y	25.3 (32)	26.3 (38)	0.82
Mean alanine aminotransferase, U/L (n)			
3 mo	22.1 (53)	30.3 (54)	0.16
1 y	27.1 (32)	30.2 (38)	0.58
Mean total bilirubin, mg/dL (n)			
3 mo	0.69 (53)	1.00 (54)	0.32
1 y	0.73 (32)	0.74 (38)	0.89
Mean creatinine, mg/dL (n)			
3 mo	1.26 (53)	1.24 (54)	0.84
1 y	1.12 (32)	1.26 (38)	0.17
Biliary complication, n (%)			
Bile leak	4 (7)	5 (9)	1
Biliary stricture	8 (15)	11 (19)	0.62
Total	12 (22)	16 (28)	0.67

Ab, antibody; HCV, hepatitis C virus; NAT, nucleic acid testing; PHS, Public Health System.

The two groups, HCV Ab+/NAT- and HCV Ab-/NAT-, were compared to ascertain whether any differences in demographics or outcomes would guide future use of these organs. In our cohort, the recipients of HCV Ab+/NAT- organs were significantly older, 59.3 vs 53.5 years ($p = 0.0062$) and had lower MELD scores, 22.5 vs 26.1 ($p = 0.0014$). Viremia developed in more patients in the HCV Ab+/NAT- group (5 vs 0; $p = 0.03$). There were statistically more donors in the HCV Ab+/NAT- group who had a reported history of IVDU, 76% vs 44% ($p = 0.0005$) and who were hepatitis B core antibody-positive, 33% vs 10% ($p = 0.0054$). Procurement location differed between the 2 groups, with more HCV Ab+/NAT- organs being procured from a national organization as opposed to a local one. Additional characteristics of the 2 donor groups and their recipients can be found in Tables 1 and 2.

DISCUSSION

A previous study by our group had demonstrated a risk of development of HCV viremia with the use of HCV Ab+/NAT- donor livers and had estimated that the risk can be as high as 16%.[2] This prolonged study served to continue to monitor the risk of development of HCV viremia through the use of these organs, as well as to look at both short- and long-term outcomes. Herein, we report a 9% risk of viremia with these organs, with longer follow-up and a larger sample size. As the prevention of hepatitis B virus, HCV, and HIV was the goal of the creation of the PHS IRD classification,[13] it seemed reasonable to use a PHS IRD HCV Ab-/NAT- cohort as a comparator group. Our findings that viremia continued to occur in the HCV Ab+/NAT- group, but that viremia was treatable with standard of care HCV direct-acting antivirals, and that 3-month and 1-year outcomes were no different in terms of liver enzymes, bilirubin, kidney function, graft loss, and mortality support the continued use of these organs.

Of first concern in the use of these organs was HCV transmission. At the forefront of everyone's mind is the concern for eclipse period infection in the donor. As 76% (42 of 55) of the HCV Ab+/NAT- donors had a reported history of IVDU, it stands to reason that some of these donors might have had HCV in the past (giving them a positive antibody), but cleared it spontaneously, as occurs in approximately 20% of cases.[3-5] If active

IVDU continued up to the point of hospitalization, it is plausible that these donors could have been acutely re-infected with HCV but remained in the nonviremic eclipse period. As the NAT was obtained during this eclipse period in 93% of donors, early infection could have been missed. The Disease Transmission Advisory Committee's PHS IRD guidance statement places the risk of eclipse period infection, even for the highest-risk active IDVU donors, at just 0.32%.[13] Having 5 episodes of viremia in a cohort of just 53 recipients differs significantly from this finding with 9% viremia rate ($p < 0.0001$). In addition, our study found a statistically significant increase in development of viremia in the HCV Ab+/NAT- cohort when compared with the PHS IRD HCV Ab-/NAT- group. In fact, in the PHS IRD group, no viremia occurred. Some differences did exist between the HCV Ab+/NAT- group and its comparator cohort, with the HCV Ab+/NAT- donors being older, more likely to have a history of IVDU and to be hepatitis B core antibody-positive. Even with significantly more IVDU in the HCV Ab+/NAT- group, it seems very unlikely that all the viremia could be attributed to that risk given the Disease Transmission Advisory Committee's statistics referenced here. False-negative NAT testing could also be a plausible explanation for HCV transmission in HCV Ab+ donors. Reported sensitivity of HCV NAT testing is 96% to 99%, with a negative predictive value of >99%.[6-8] We hypothesize that to have obtained 5 false-negative NAT tests in a cohort of just 55 patients is highly improbable.

A final mechanism by which HCV transmission might have occurred is via OCI. The existence of OCI is hotly contested in the literature, with estimates of its prevalence ranging from 0% to 95%.[20,21] Patient population and testing methodology varied from study to study and the significance of finding HCV RNA in liver tissue samples is unclear, as relapse of viremia is uncommon (1% to 2%) after treatment.[14] However, spontaneous relapse in the absence of renewed risk factors is well documented in patients receiving immune suppression and/or chemotherapy.[22-25] Given that the rate of HCV RNA detection in liver tissue samples varied widely, it is unclear what predisposes to OCI vs full clearance of the virus. Existence of viral RNA has been demonstrated in liver transplant recipients with recurrent HCV, despite treatment and achieving SVR.[26] Therefore, OCI remains controversial but seems another plausible mechanism for transmission in this cohort, especially given the low likelihood of the mechanisms mentioned previously.

Until the advent of more widely used NAT testing in December 2014, these HCV-seropositive livers were primarily used in HCV viremic recipients only or were discarded.[27,28] Even more recently, the American Society of Transplantation issued guidelines encouraging the differentiation between viremic and nonviremic donors with positive HCV antibodies.[29] Despite suggesting that transmission risk is minimal from HCV Ab+/NAT- donors, the guidelines had few data on actual outcomes. The previous study by our group[2] demonstrated a 16% transmission rate in this population and additional follow-up has maintained that transmission does indeed occur, though suggests that it might be slightly less common, approximately 9%.

In addition, this is the first study to explore outcomes other than transmission in recipients of HCV Ab+/NAT- liver transplants. The case reports previously published alluded to good outcomes, but were insufficiently powered to draw any additional generalizable conclusions. Our study shows that when compared with other PHS IRD liver recipients, those receiving HCV Ab+/NAT- allografts had no difference in liver enzymes, bilirubin, creatinine, biliary complications, graft function, or death at 3 months or 1 year. Overall graft function and mortality were not different either. Although outcomes were not different between the groups, the difference in incidence of development of viremia is not trivial. Of the 5 recipients in whom viremia developed, 1 died of unrelated complications and the other 4 were treated with direct-acting antivirals. Insurance approval for treatment was obtained in all 4 and all have achieved SVR at this point.

Several limitations exist to our study. Tissue samples from the donor livers were not analyzed for HCV RNA at the time of transplantation, though it might be assumed that viral RNA would have been found in both OCI and eclipse period infection. In addition, repeat HCV NAT testing of the donors on the day of transplantation was not done routinely. Typically, HCV NAT testing was performed around day 2 of admission and procurement of the organs was often days later. The NAT testing closer to procurement might have helped to eliminate eclipse period infection as a possibility in some of the donors. Finally, as the study period was only about 2.5 years, longer-term outcomes are still not clearly generalizable. We will continue to follow this cohort of HCV Ab+/NAT- recipients over time to ensure they continue to do as well as their comparator cohort.

The waiting list for liver transplantation continues to outpace the availability of organs, resulting in a waiting list mortality of nearly 20%.[30] Even as the heroin epidemic has increased the number of available organs for transplantation, concern remains about the use of these increased-risk organs.[31] The routine acceptance of HCV Ab+/NAT- livers presents an opportunity to expand the donor pool and access to transplantation for those on the waiting list. Despite the risk of HCV transmission demonstrated in this study, the ever-expanding repertoire of direct-acting antivirals has eased the

management of HCV, even post transplantation, with similar rates of SVR compared with those treated pre-transplantation.[32-35]

CONCLUSIONS

Use of HCV Ab+/NAT- livers for transplantation presents an increased risk of HCV transmission of approximately 9% through as of yet unclear mechanisms. Post-transplantation HCV viremia is readily treatable and the use of these organs is not associated with worsened liver or kidney chemistries, or an increase in biliary complications, graft loss, or mortality compared with other PHS IRD donors. Use of HCV Ab+/NAT- organs should be routinely considered even in HCV nonviremic recipients.

Author Contributions

Study conception and design: Luckett, Kaiser, Bari, Safdar, Schoech, Diwan, Cuffy, Anwar, Shah
Acquisition of data: Luckett, Kaiser, Bari, Shah
Analysis and interpretation of data: Luckett, Kaiser, Bari, Apewokin, Shah
Drafting of manuscript: Luckett, Bari, Shah
Critical revision: Luckett, Kaiser, Bari, Apewokin, Diwan, Quillin, Shah

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Discussion

DR ANDREW M CAMERON (Baltimore, MD): In this presentation, the authors extend their study of hepatitis C virus (HCV) antibody-positive RNA-negative liver donor grafts into hepatitis C-negative recipients. They have previously reported on 25 such cases and saw a 16% hepatitis C transmission rate. Now their series is up to 55 recipients, and they have seen a 9% hepatitis C transmission, which is 5 recipients, all of whom turned positive by 3 months, and all of whom were subsequently cured with new antivirals, though 1 of these 5 patients did die before a year's time post-transplant.

It is an interesting series. The work is a consequence of both the opiate overdose epidemic in our country, which has led to more HCV-positive donors, and the advent of the direct-acting antivirals, which has resulted in most of our recipient candidates seeing treatment with few HCV-positive patients left on the list. Given that some centers are now using HCV RNA-positive grafts in the negative recipients, I think this series is certainly less controversial, but it is as important as it is valuable to get a number on the transmission rate in this scenario, which was previously thought to be zero.

For patients who do end up getting hepatitis C after these transplantations, is this virus from a peri-donation, needle-in-the-arm "eclipse" infection that our testing could not catch, or from reactivation of an occult infection remnant in the donor liver, or maybe even from the recipient's reactivation if he or she were antibody-positive RNA negative? It might matter if the genotypes between the donor and recipient differed and the donor strain was more difficult to treat.

In this scenario, who pays for the expensive hepatitis C medicines? I assume insurance covered the cost in your 5 patients who developed hepatitis C, but if so, did you clear that with the insurance companies before the transplant? Do you tell patients that they may have to cover the cost if the insurance company declines, or would your center cover those costs?

Lastly, how did you pick recipients for these offers, or is the whole list offered these grafts? It looks like the recipients for these grafts had lower Model for End Stage Liver Disease (MELD) scores—around 22—when compared with recipients who received antibody-negative grafts who were closer to a MELD score of 26. Your antibody-positive recipients were also older than the control group. Was any of this intentional? Should we consider offering our whole wait list HCV RNA-positive grafts? Interestingly, 33% of your HCV antibody-positive donors were also hepatitis B core positive, relegating these recipients to a lifetime of Entecavir. Twelve weeks of direct acting antivirals seems like less of a big deal, so maybe it is time to start using these donors for any recipient.

DR JOHN A GOSS (Houston, TX): The authors have a long-standing history of using the hepatitis C antibody-positive nucleic acid test (NAT)-negative allograft in an effort to expand the cadaveric donor pool. The authors' current and previous studies are important because the true potential of liver transplantation still has not been met or realized due to the ongoing liver allograft shortage, and it should be noted that this ongoing shortage results in an approximately 20% wait list every year.

Have you had any difficulty obtaining the hepatitis C antiviral medication? If so, does your transplant program have a backup plan? In the age of successful hepatitis C antiviral treatment, have you considered transplanting hepatitis C antibody-positive, NAT-positive liver allografts? It is interesting that a small number of both the hepatitis C antibody NAT-negative donors as well as your control, increased risk donors, were hepatitis B virus NAT positive. Could you please describe the post-transplant management of this group of recipients? Finally, 40% of the hepatitis C antibody-positive NAT-negative donors were allocated nationally. Could you discuss the cold ischemia time between the groups and any other possible outcome measures that could be an issue for one to consider?

DR RONALD W BUSUTTIL (Los Angeles, CA): Despite the major advances in the treatment of hepatitis C with direct antiviral agents, there continues to be a rise in the new cases of hepatitis C because of the opioid epidemic. Furthermore, the number of patients needing liver transplantation remains elevated, and it's still because of hepatitis C, despite the fact that we have these excellent antiviral agents to control the disease. To expand the donor pool, the authors used HCV antibody nucleic acid-negative grafts in non-HCV recipients, which has certainly been controversial, but new data are supporting the fact that this could possibly be used successfully.

Despite an inevitable viral load in these donors, 9% of the recipients became HCV positive, which is very problematic. How were