Liver Outcome in Renal Transplant Recipients Who Acquired Hepatitis C Infection From an Infected Graft: Study Based on Liver Biopsy Findings

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Background. Long-term liver outcome in hepatitis C virus (HCV)-negative kidney recipients who acquired HCV infection from viremic donors is of intense interest in the transplant community. We evaluated the incidence of fibrosis in liver biopsy specimens of recipients who were transplanted with HCV-infected grafts. Methods. Patients were evaluated in the hepatology clinic, and 29 patients agreed to undergo liver biopsy. The liver histology was scored by the meta-analysis of histological data in viral hepatitis scoring system and was assessed by hepatopathologists. The fibrosis score was compared between patients who initiated direct-acting antiviral (DAA) within 6 wk (n = 6) and after 6 wk (n = 29). Results. Eighty-nine aviremic patients were transplanted with HCV-infected grafts between March 2018 and October 2019. All patients developed HCV infection and were treated with DAA treatment after kidney transplantation (median, 70 d; interquartile range, 55–85 d). All patients (n = 89) achieved sustained virologic response with DAA. The median follow-up time from kidney transplant to liver biopsy was 28 mo (interquartile range, 26–30 mo). Twenty-five patients (86%) had F0, and 4 patients (14%) had F1 fibrosis. No patient had advanced fibrosis (F3–F4). Grade 1 inflammation was present in 6 (21%) patients, whereas 26 (90%) patients had iron accumulation in the hepatocytes and reticuloendothelial cells. There was no difference in the fibrosis score between patients who received treatment within 6 wk versus after 6 wk (P = 0.55). Conclusions. Kidney transplantation of HCV-infected graft to HCV-negative recipients is safe and has no long-term liver-related complications with successful eradication of HCV. In our cohort, delayed treatment did not affect sustained virologic response or liver histology.

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before KT with an impressively low transmission rate.\textsuperscript{18,19} A study by Gupta et al\textsuperscript{19} reported ultrashort treatment with DAA therapy started within 6 h before KT followed by 3 daily doses after KT. Although this unique treatment approach has shown an impressively low HCV transmission rate of 7.5%, the failure to respond to first-line DAA therapy, the potential for development of resistant mutations, and possible long-term liver-related complications are concerning with these treatment strategies. Both preemptive and early posttransplant initiation of DAA appear to decrease the risk of degree and duration of acute HCV viremia after HCV + KT.\textsuperscript{11} Thus, DAAs should be started as early as possible to prevent complications because of prolonged posttransplantation HCV viremia. Also, it is unknown what degree and/or duration of acute HCV viremia after HCV + KT is safe without any effect on long-term liver outcomes, mainly fibrosis and inflammation.\textsuperscript{11} We evaluated the incidence of fibrosis in liver biopsy specimens of recipients who were transplanted with HCV-infected grafts in a single-center observational study. Our hypothesis was there was no difference regarding liver fibrosis between those recipients who received early versus late DAA.

**MATERIALS AND METHODS**

**Cohort Definition and Data Source**

Ninety-eight aviremic patients were transplanted with HCV nucleic acid testing (NAT)-positive and/or antibody-positive kidney between March 2018 and October 2019 at our center (Figure 1). Nine recipients were excluded from this cohort because they received HCV NAT-negative, antibody-positive donor kidneys. Our final cohort consisted of 89 patients who received HCV NAT-positive, antibody-positive/ negative (HCV-infected) donor kidneys. All patients were evaluated in the hepatology clinic, and 29 patients (33%) agreed to undergo liver biopsy (Figure 1).

The data were extracted from hospital electronic medical records, our local transplant database, and the United Network for Organ Sharing system. All study data were collected, managed, and stored in the Research Electronic Data Capture tool hosted by the University of Tennessee Health Science Center.

**Donor Acceptance, Recipient Selection, Screening, Treatment Protocol**

The detailed explanation of donor acceptance, recipient selection, screening, and treatment protocol is outlined in detail in our previous articles.\textsuperscript{12,13} Our transplant center accepted HCV NAT-positive and/or HCV antibody-positive donors who had a donor biopsy showing <10% glomerular sclerosis. These organs to recipients who previously agreed to accept HCV-infected donor kidneys for transplantation. Our exclusion criteria were the recipient with a history of severe liver disease or HIV infection. Written informed consent explaining HCV transmission rate, potential complications of hepatitis C, and our treatment plan was obtained from all recipients who agreed to receive HCV-infected donor kidneys. All patients were counseled again by transplant nephrologists, transplant surgeons, and transplant coordinators when at notification for organ availability and immediately before surgery.

The patients were tested for HCV RNA and HCV genotype 3–8 wk after KT. All patients with detectable HCV RNA were started on a DAA regimen (glecaprevir/pibrentasvir, sofosbuvir/velpatasvir, or sofosbuvir/ledipasvir) for at least 12 wk by our transplant hepatologists. All DAA regimens were determined, and prescriptions were processed through a third-party payer. After treatment completion and sustained virologic response (SVR), patients were monitored every 6 mo in our hepatology clinic and were offered liver biopsy after 1 y of a KT.

**Induction and Maintenance Immunosuppression**

All KT recipients received rabbit antithymocyte globulin induction treatment with a cumulative dose of 4.5 mg/kg divided into 3 doses. All recipients were initiated on a triple immunosuppressive regimen consisting of tacrolimus, mycophenolic acid, and prednisone unless they had a contraindication and remained on a maintenance dose of prednisone, 5 mg daily as per our protocol.

**Outcome Assessment**

The primary outcome of this study was to evaluate the incidence of fibrosis in liver biopsy specimens of recipients who were transplanted with HCV-infected grafts. The liver biopsies 1-y post-KT were assessed by experienced hepatopathologists who were blinded to the clinical data. The meta-analysis of histological data in viral hepatitis scoring system was used to stage the fibrosis and grade the inflammation.\textsuperscript{20} Secondary outcomes were to measure the accuracy of noninvasive tests to assess the degree of fibrosis. Other secondary outcomes were liver-related complications; SVR at 12 wk (SVR12) after completion of treatment and the potential modification effect on liver outcomes based on time of DAA treatment initiation (comparing early < 6 wk versus late >6 wk initiation).

**Statistical Analysis**

Recipient and donor characteristics were reported as percentages for categorical variables and mean ± SD or median and interquartile range (IQR) for continuous variables.
Differences between groups were evaluated by using the Student t test for continuous variables and a chi-square test (or Fisher exact test) for categorical variables. To evaluate the predictive value of noninvasive test of fibrosis such as Transient Elastography (FibroScan), FibroTest-ActiTest (FIBRO) Panel, fibrosis-4, and Aspartate Aminotransferase to Platelet Ratio Index (APRI), receiver operating characteristics (ROCs) analysis was also performed and the area under the ROC curve was also calculated using liver biopsy as gold standard on those patients in which biopsy result was available. Reported P values were 2-sided and defined as statistically significant if <0.05 for all analyses. All statistical analysis was conducted using STATA/MP Version 15 (STATA Corporation, College Station, TX). The study was approved by the Institutional Review Board of the University of Tennessee Health Science Center (18-06409-XP).

RESULTS

Baseline Recipient and Donor Characteristics

Baseline characteristics of recipients and donors are shown in Table 1. The mean ± SD age of recipients was 57 ± 11 y, 28% were female, 7% and 90% of patients were White and African American, respectively. All patients (100%) had hypertension, 16 patients (55%) had diabetes, 20% had peripheral vascular disease, and 31% had coronary artery disease. The mean ± SD on dialysis before transplantation was 64 ± 40 mo.

The mean ± SD age of donors was 32 ± 5 y, 34% were female, and 90% and 0% of patients were White and African American, respectively (Table 1). All donors satisfied the criteria of US Public Health Services Augmented Risk Donor. Only 3 donors had hypertension, and 7% were donated after circulatory death donors. All donors were positive for HCV antibody and NAT testing.

Hepatitis C Infection and Treatment-related Outcomes

The median (IQR) peak HCV RNA level before treatment initiation (log10) was 5.24 IU/mL (4.57–5.70 IU/mL). Genotype 1A was the most common genotype (62%) among the patients who acquired HCV after KT, followed by genotype 3 in 28% of our cohort. For all patients, DAA treatment was approved by a third-party payer. The median (IQR) time between KT and treatment initiation was 70 d (55–85 d). Most patients (80%) received glecaprevir/pibrentasvir, and 10% received sofosbuvir/velpatasvir. We used a sofosbuvir-based regimen in 3 (10%) patients as it was the preferred DAA by the third-party payer. All patients received 12 wk of treatment except for 3 patients who received 16 wk of treatment with DAA. Most recipients did not experience any major adverse events while on DAA. All recipients had undetectable HCV RNA levels at 12 wk after DAA treatment and achieved SVR12 (cure). The median (IQR) time between transplantation and SVR12 was 244 d (232–257 d) (Table 2).

Liver Outcomes

After SVR, all the patients were followed by a transplant hepatologist at 6-mo intervals. The median (IQR) follow-up time was 28 mo (26–30 mo). On liver biochemistry at the time of the last follow-up, the median (IQR) aspartate aminotransferase and alanine aminotransferase were 15 IU/mL (13–23 IU/mL) and 27 IU/mL (23–47 IU/mL), respectively.
All the patients have preserved synthetic liver function with median (IQR) total bilirubin, albumin, and international normalized ratio of 0.5 (0.3–0.6), 3.7 (3.6–3.8), and 1 (1–1.1), respectively. Of 89 total patients, 29 agreed to liver biopsy. All the liver biopsy specimens were at least 3 cm in length and contained a minimum of 9–11 portal tracts. Twenty-five patients (86%) had F0, and 4 patients (14%) had F1 fibrosis. No patient had advanced fibrosis (F3–F4). Mild steatosis (<5%) was seen in 8 (29%) of patients among 4 (50%) who had diabetes, and all had hypertension. Grade 1 inflammation was present in 6 (21%) patients, whereas no inflammation was present in the remaining 23 (79%) patients. Interestingly 26 (90%) patients had iron accumulation in the hepatocytes and reticuloendothelial cell (RE) (Tables 1 and 2). There was no difference in the fibrosis score between patients who received treatment within 6 wk versus after 6 wk ($P = 0.55$). No difference was observed in fibrosis scores between the patients before DAA treatment in patients with peak HCV polymerase chain reaction log (10) of >5 and <5 ($P = 0.55$). The ROC area under the curve (Figure 2; Table 3) was 0.81±0.08 for

### Table 2: HCV treatment and liver outcomes

| HCV treatment data | Outcome |
|--------------------|---------|
| HCV genotype       |         |
| 1a                 | 18 (62%)|
| 1B                 | 1 (3%)  |
| 2                  | 2 (7%)  |
| 3                  | 8 (28%) |
| Type of DAA and duration |         |
| Gileadlevir and pibrentasvir: 12 wk | 23 (80%)|
| Gileadlevir and pibrentasvir: 16 wk | 3 (10%) |
| Sofosbuvir and velpatasvir: 12 wk | 3 (10%) |
| Detectable HCV RNA level before treatment initiation | 29 (100%)|
| Peak HCV RNA level before treatment initiation, log10 IU/mL | 5.2 (4.5–5.7); 5.22 ± 1.04 |
| SVR12              | 29 (100%)|
| Time between transplantation and treatment initiation, d | 70 (55–85); 73.13 ± 45.03 |
| Time between transplantation and SVR12, d | 244 (232–257); 254.58 ± 47.43 |
| Follow-up since transplant, mo | 33 (27–35); 30.31 ± 5.82 |
| Liver outcomes     |         |
| Time between transplantation and liver biopsy, mo | 28 (26–30); 27 ± 4.63 |
| Laboratory characteristics at last follow-up |         |
| AST, median (IQR), U/L | *15 (13–23); 22.51 ± 16.39 |
| ALT, median (IQR), U/L | 27 (23–47); 35.03 ± 21.79 |
| Total bilirubin (mg/dL) | 0.5 (0.3–0.6); 0.51 ± 0.26 |
| Albumin (mg/dL) | 3.7 (3.6–3.8); 3.73 ± 0.24 |
| INR | *1 (1–1.1); 1.04 ± 0.24 |
| Liver biopsy       |         |
| Stage of fibrosis  |         |
| F0                 | 25 (86%)|
| F1                 | 4 (14%) |
| F2–F4              | 0 (0%)  |
| Steatosis          |         |
| No                 | 20 (69%)|
| Mild (5%)          | 8 (28%) |
| Moderate           | 1 (3%)  |
| Inflammation       |         |
| No                 | 23 (79%)|
| Mild               | 6 (21%) |
| Pattern of iron accumulation on liver biopsy |         |
| Location           |         |
| REs                | Grade   |
| 1                  | 1       |
| 2                  | 2       |
| 3                  | 3       |
| Hepatocellular, RE |         |
| 1                  | 9       |
| 2                  | 3       |
| 3                  | 7       |
| No                 | NA      |

*Median (IQR); mean (SD); for continuous variables.

Data presented as n/N (%) or count (%) for categorical variables.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAA, direct-acting antiviral agent; HCV, hepatitis C virus; INR, international normalized ratio; IQR, interquartile range; NA, not available; RE, reticuloendothelial cell; SVR12, sustained virologic response at 12 wk.
FibroScan, 0.78 ± 0.09 for FIBRO panel, 0.75 ± 0.15 for FIB4, and 0.69 ± 0.18 for APRI, respectively. The sensitivity and specificity of FibroScan, FIBRO panel, APRI, and fibrosis-4 for detecting fibrosis for specific cutoff point are shown in Table 4.

**DISCUSSION**

The long-term liver outcomes in HCV-negative kidney recipients who acquired HCV infection from viremic donors are of intense interest in the transplant community. To the best of our knowledge, this is the first study evaluating long-term liver-related outcomes in patients who have received HCV-infected kidney grafts. This report is unique as 29 patients had liver histology >1 y after KT. During the early phase of using HCV-infected grafts in our center, many of our patients received HCV treatment after 6–9 wk because of delay in obtaining medications from third-party payors. In our initial report, 11 patients (11 of 53 [21%]) required an appeal after they were initially denied by the third-party payor.12,13 Because of the streamlining of the payor process and acceptance from third-party payors, now our patients are receiving treatment within 2–4 wk of renal transplant. However, this delay in initiating treatment during the early phase of implementation of this protocol provides an opportunity to study whether delaying HCV treatment had any impact on the liver outcomes in this patient population.

In our cohort, the median time between KT and liver biopsy was 28 mo (IQR, 26–30 mo). On liver biopsy, no patient had advanced fibrosis (stage 2–4), and only 4 patients (14%) had F1 fibrosis. The grade 1 inflammation was present in 6 (21%) patients. The long-term implication of this low-grade inflammation is still unknown. The median duration between KT and treatment initiation was 70 d, and all patients achieved SVR. Twenty-three patients (78%) had treatment initiation after 6 wk KT, whereas 6 (21%) received treatment within 6 wk of KT. We did not see any difference in the fibrosis scores between patients who received treatment within 6 wk versus after 6 wk of KT. Also, no difference was observed in fibrosis scores between the patients before DAA treatment in patients with peak HCV polymerase chain reaction log (10) of ≥5 and <5. In theory, pretransplant and early posttransplant initiation of DAA appear to decrease the risk of both degree and duration of acute HCV viremia after HCV + KT.

**FIGURE 2.** The ROC area under the curve for noninvasive test of fibrosis. APRI, Aspartate Aminotransferase to Platelet Ratio Index; FIB-4, fibrosis-4; FIBRO, FibroTest-ActiTest; FibroScan, transient elastography; ROC, receiver operating characteristic.

**TABLE 3.** Receiver operating characteristics analysis of noninvasive test of fibrosis using biopsy as a gold standard test

| Test          | Observation | ROC area | SE  | 95% confidence interval |
|---------------|-------------|----------|-----|-------------------------|
| FibroScan     | 29          | 0.81     | 0.08| 0.63-0.98               |
| FIBRO panel   | 29          | 0.78     | 0.09| 0.60-0.96               |
| FIB-4         | 29          | 0.75     | 0.15| 0.44-1.0                |
| APRI          | 29          | 0.69     | 0.18| 0.32-1.00               |

APRI, Aspartate Aminotransferase to Platelet Ratio Index; FIB-4, fibrosis-4; FIBRO, FibroTest-ActiTest; FibroScan, transient elastography; ROC, receiver operating characteristic.

**TABLE 4.** Sensitivity and specificity of noninvasive test of fibrosis for detecting fibrosis using biopsy as a gold standard test

| Test          | Cutoff value | Sensitivity | Specificity |
|---------------|--------------|-------------|-------------|
| FibroScan (kPa)| ≥6           | 75%         | 80%         |
| FIBRO panel   | ≥0.27        | 75%         | 76.00%      |
| FIB-4         | ≥1.22        | 75%         | 84.00%      |
| APRI          | ≥0.4         | 50%         | 88.00%      |

APRI, Aspartate Aminotransferase to Platelet Ratio Index; FIB-4, fibrosis-4; FIBRO, FibroTest-ActiTest; FibroScan, transient elastography.
The DAAs should be initiated as early as possible to prevent complications related to prolonged posttransplantation HCV viremia.10 Although, the ideal strategy is to treat HCV as soon the patient becomes viremic. However, multipayer health systems in countries such as in the United States may delay initiation of DAA therapy until several weeks after KT. Hence, our finding of lack of any liver fibrosis in patients who received delayed treatment is comforting.

We also evaluated the predictive value of a noninvasive test of fibrosis using liver biopsy as the gold standard. The ROC area under the curve (Figure 2) was 0.81 ± 0.08 for FibroScan, 0.78 ± 0.09 for FIBRO panel, 0.75 ± 0.15 for FIB4, and 0.69 ± 0.18 for APRI, respectively. FibroScan appears to have the best sensitivity and specificity for detecting fibrosis in our cohort (Tables 3 and 4). We recommend doing a noninvasive test of fibrosis after 6- to 12-mo post-SVR for follow-up evaluation and considering liver biopsy if it shows advanced fibrosis (meta-analysis of histological data in viral hepatitis stage 3–4).

In our cohort, patients were treated with pan-genotypic regimens such as a combination of glecaprevir (300mg) and pibrentasvir (120mg) for 12–16wk or a combination of sofosbuvir (400mg) and velpatasvir (100mg) for 12wk that is similar to what is published in the literature.12,14–17,21 Recently, minimal inflammation. Because of the early initiation of cholestasis, periportal fibrosis, and neutrophil infiltrates with FCH include ballooning degeneration of hepatocytes, marked direct cytopathic effect of the virus in an immunocompromised patient.24 On liver histology, characteristic features of FCH are intrahepatic cholestasis, portal fibrosis, and neutrophil infiltrates with minimal inflammation.25 Because of the early initiation of HCV treatment and the availability of highly effective DAA therapies, the overall incidence of FCH remained very low.

In our study, a significant number of patients were found to have iron deposition in the liver biopsy. Iron overload is not uncommon in patients with end-stage renal disease because of hypoproliferative erythroid marrow function coupled with the need for frequent intravenous iron and red blood cell transfusions to manage symptomatic anemia. These can lead to iron deposition mainly into the RE with no organ dysfunction or failure. This secondary hemosiderosis can be complicated by concurrent hepatitis B or C infections and is likely responsible for iron deposition in liver parenchymal cells.24,29 In our study, 26 (90%) patients had iron accumulation in the hepatocytes cell and/or RE, most commonly in both hepatocytes cell and RE in 18 (66%) patients. Grade 3 iron accumulation was seen in 9 (31%) of patients. Long-term clinical significance of this iron overload is still unknown.

Despite being the first study to date describing the long-term liver outcomes in this patient population, the significant limitations of our study are the relatively small sample size, high refusal rate of biopsy, and no data of early inflammation of the liver. Finally, this was a single-center retrospective observational study; thus, generalizability is limited.

To our knowledge, this first study to date describing the long-term liver outcomes in HCV– recipients receiving kidneys from HCV-infected donors. This information is crucial when obtaining informed consent for HCV-negative patients considering undergoing transplantation with HCV-viremic kidneys.

CONCLUSIONS

Kidney grafts from viremic donors resulted in HCV infection in all recipients with no adverse events observed with use of DAA after KT. No patients had any significant fibrosis (stage 2–4) at a median duration of 28 mo after KT. Future studies are needed to define the long-term liver outcomes of kidney recipients with HCV-infected grafts.

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