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Characterization of Early Hepatic Injury in HCV-Negative Recipients of HCV-Infected Kidneys

Rafal D. Mazur¹, Peter L. Abt, M.D.², Emily A. Blumberg, M.D.³, Roy D. Bloom, M.D.⁴, K. Rajender Reddy, M.D.¹, Peter P. Reese, M.D., M.S.C.E.^{4,5}, and David S. Goldberg, M.D., M.S.C.E.^{1,5}

¹Division of Gastroenterology, Department of Medicine, Perelman School of Medicine, Philadelphia, PA

²Department of Surgery, Perelman School of Medicine, Philadelphia, PA

³Division of Infectious Diseases, Department of Medicine, Perelman School of Medicine, Philadelphia, PA

⁴Renal-Electrolyte and Hypertension Division, Department of Medicine, Perelman School of Medicine, Philadelphia, PA

⁵Department of Biostatistics, Epidemiology and Bioinformatics, Perelman School of Medicine, Philadelphia, PA

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Dear editor,

Recent data demonstrate that transplanting kidneys from hepatitis C virus (HCV)-infected donors could increase the number of kidney transplants (KT) by 500-1,000 per year with durable cure rates and excellent 1-year renal function.¹ However, data on the risks of acute donor-derived HCV are limited, hampering our ability to inform patients and providers. We sought to examine data from a trial of transplanting HCV-negative patients with kidneys from HCV-infected donors (THINKER, NCT #02743897) to determine whether these recipients had a greater likelihood of having early alanine aminotransferase (ALT) elevations versus comparator recipients of kidneys from HCV-negative donors.

We reviewed data from the first 40 THINKER recipients transplanted at the University of Pennsylvania, and randomly selected 40 HCV-negative comparators who received a KT from an HCV-negative donor at the same center during the same period (6/1/2016-5/23/2018). A THINKER exclusion criterion was, “persistently elevated liver transaminases,” which we also required of comparators for this study. ALT, the most specific test to identify hepatic injury, was the measure of hepatic injury.² The primary outcome was

an incident abnormal ALT during the 4-week post-transplant period, using the most stringent gender-specific definition of the upper limit of normal (ULN) (≤ 30 IU/mL for males, and ≤ 19 IU/mL for females).² Secondary outcomes included: 1) gender-neutral ULN of ≤ 40 IU/mL (recommended by NIH-sponsored clinical trials³; 2) peak ALT as a categorical outcome (<2 times ULN, $2-3$ times ULN, and >3 times ULN) for consistency with clinical trials and cohort studies;⁴ and 3) continuous measure of peak ALT relative to pre-transplant baseline. ALT levels were compared using Fisher's exact test and Wilcoxon rank-sum tests. We performed multivariable linear regression (outcome: log-transformed peak ALT relative to baseline), adjusting for key covariates (age, race, gender, BMI, and diabetes). In an exploratory analysis, we assessed the correlation between peak 4-week ALT elevation among THINKER recipients based on their pre-transplant measure of liver stiffness (transient elastography using Fibroscan, with study inclusion criteria requiring a baseline stiffness <8.0 kPa). All patients received thymoglobulin induction therapy followed by steroids, tacrolimus, and mycophenolate mofetil. The IRB granted permission to use the data on comparators receiving an HCV-negative kidney, however the data were initially collected without IRB approval.

THINKER recipients were more likely to be Black (40% vs 24%, $p=0.04$), have diabetes (55% vs 27.5%, $p=0.01$), and have a higher BMI (median: 29.3 vs 26.9 kg/m², $p=0.04$). The group trends in peak ALT among THINKER recipients and comparators were not different. Among THINKER recipients, the peak ALT post-transplant was 121 (median: 31 IU/mL; IQR: 22-51), versus 417 IU/mL in comparators (median: 37 IU/mL; IQR: 25 - 58; $p=0.58$; Figure 1). No patients experienced hepatocellular dysfunction (hyperbilirubinemia or coagulopathy). The categorization of peak ALT among THINKER recipients and comparators was not significantly different ($p>0.2$ for all comparisons; Figure 2). In multivariable models, there was no significant difference in peak ALT relative to baseline for THINKER recipients ($p>0.5$). There was no correlation between baseline liver stiffness of THINKER subjects and peak ALT relative to baseline (Spearman correlation coefficient = -0.045). Notably, 39/40 THINKER recipients had undetectable HCV viral loads by day 28 post-KT.

These data suggest that HCV-negative patients who receive a KT from an HCV-infected donor and are treated very early post-transplant are not more likely to have early post-transplant hepatic injury than recipients of a kidney from an HCV-negative donor. Outside of transplantation, there are only limited reports on the risks of acute hepatic injury following HCV transmission because the time zero of infection is rarely known. Studies of intentional HCV transmission via organ transplantation therefore provide a unique opportunity to examine this, albeit in a selected population who received early HCV therapy.

There were limitations. First, the sample size was small, but nonetheless the largest of its kind. Second, all patients had normal baseline liver tests, whereas KT recipients may have baseline abnormal liver enzymes. Third, THINKER patients initiated HCV treatment on day 3, leading to rapid viral suppression within 4 weeks.¹ Thus, findings may not generalize to settings where treatment is delayed. Finally, all recipients received thymoglobulin induction which has been attributed to ALT elevations in bone marrow transplant recipients.⁵

The findings can facilitate counselling patients considering HCV-infected organs about the potential for hepatic injury in the setting of acute HCV infection, albeit in a carefully selected population of recipients who initiate treatment shortly after transplant, and advance the burgeoning field of donor-derived HCV transmission in transplantation. This investigation provides evidence for potential hepatic safety of intentional HCV transmission in transplantation with early antiviral treatment, but should be extrapolated with caution when treatment initiation is delayed.

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Abbreviations:

ALT	Alanine Aminotransferase
HCV	Hepatitis C Virus
ULN	Upper Limit Normal
IU	International Unit

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Figure 1: Distribution of peak ALT in the 4 weeks post-transplant for THINKER subjects and comparators*

i. Footnote: * 1 comparator had a peak ALT of 417 IU/mL attributed to a newly-started statin, but the patient received limited workup without hepatology consultation

Figure 2: Comparison of ALT levels during 4-week post-transplant period between THINKER subjects and comparator patients

a. Figure 2d: Correlation between baseline liver stiffness and peak ALT relative to baseline in the 4 weeks post-transplant for THINKER subjects