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Longer-Term Clinical Outcomes From the THINKER and EXPANDER Trials of Transplantation of HCV-RNA+ Donor Kidneys Into Hepatitis C Virus-Negative Recipients

Vishnu Potluri[1,15], Fizza Naqvi[2,15], David S. Goldberg[3], Mital Shah[4], Alexandre Loupy[5], Peter Abt[6], Emily Blumberg[7], Jennifer Trofe-Clark[1,8], Roy Bloom[1], Deirdre Sawinski[9], Michael Chattergoon[2], Dorry L. Segev[10], Nichole. Bair-Marcantoni[11], Christine M. Durand[2], Rajender Reddy[12], Matthew Levine[6], Nicholas Brown[13], Shristi Mapchan[1], Olivier Aubert[5], Niraj Desai[11,15] and Peter P. Reese[1,5,14,15]

[1]Renal-Electrolyte and Hypertension Division, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [2]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [3]Division of Digestive Health and Liver Diseases, Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida, USA; [4]Division of Nephrology, Department of Medicine, Robert Wood Johnson University, New Brunswick, New Jersey, USA; [5]Université de Paris, INSERM, Paris Translational Research Center for Organ Transplantation, Paris, France; [6]Department of Surgery, Transplant Division, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [7]Division of Infectious Disease, Department of Internal Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [8]Department of Pharmacy Services, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA; [9]Department of Medicine, Weill Cornell Medical College, New York, New York, USA; [10]Department of Surgery, New York University, New York, New York, USA; [11]Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [12]Division of Gastroenterology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [13]Department of Pathology & Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; and [14]Department of Biostatistics, Epidemiology and Bioinformatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence: Peter P. Reese, Center for Clinical Epidemiology and Biostatistics, 917 Blockley Hall, 423 Guardian Drive, Philadelphia, Pennsylvania 19104, USA. E-mail: Peter.Reese@pennmedicine.upenn.edu

[15]VP, FN, ND, and PPR contributed equally.

Received 6 February 2023; revised 6 April 2023; accepted 24 April 2023; published online 29 April 2023

Kidney Int Rep (2023) **8,** 1460–1463; https://doi.org/10.1016/j.ekir.2023.04.018
KEYWORDS: hepatitis C virus; kidney transplantation; organ donors

Long waiting times for kidney transplantation and the major health burdens of dialysis have generated interest in transplanting kidneys from donors with bloodborne viral infections. Until 2015, most kidneys from deceased donors with hepatitis C virus infection (HCV) were discarded or not procured because of the toxicity of interferon-based HCV treatment in recipients.[1] The development of direct-acting antiviral (DAA) therapy and high HCV cure rates in the general population generated new optimism that organs from HCV-RNA+ donors could be safely transplanted. THINKER (Transplanting Hepatitis C Kidneys into Negative Kidney Recipients) and EXPANDER (Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV-negative Recipients) were the first trials to report outcomes for HCV-RNA+ donor kidneys transplanted into recipients without HCV infection, followed by DAA therapy. Both trials reported 100% HCV cure rates and good allograft function through 12 months.[2-4] These encouraging early results, as well as the growing number of HCV-RNA+ organ donors who have died as a result of the opioid epidemic, motivated wider use of HCV-RNA+ donor organs.[5]

Nevertheless, questions remain about whether donor HCV infection is associated with worse longer-term allograft function or carries immunologic consequences, including elevated rejection risk. No detailed clinical data have been published describing outcomes beyond 1 year posttransplant. Given this knowledge gap, we obtained data for THINKER and EXPANDER

participants collected during usual care until 3 years posttransplant. Our aim was to report allograft survival and function as well as immunologic complications, including rejection and development of *de novo* donor specific antibodies (DSA). We also examined estimated glomerular filtration rate (eGFR) trajectories versus matched comparators and estimated future allograft survival using the integrative Box (iBox) scoring system.[6]

Supplementary Tables S1 and S2 provide trial inclusion/exclusion criteria. Details about methods are provided in Supplementary Methods S1–S4 and Supplementary References. The baseline characteristics of trial participants as well as data about HCV genotype are presented in Table 1. Data from 45 participants (10 in EXPANDER and 35 in THINKER) were analyzed. The median age at transplantation was 63 (interquartile range [IQR] 54–66) years, 12 (27%) were female, and 15 (33%) identified as Black race. Diabetes or hypertension was the primary cause of end-stage kidney disease for 23 (51%) recipients. The median days to transplantation from waitlisting was 360 (IQR 184–521). All participants received rabbit antithymocyte globulin for induction.

Table 1. Demographic and clinical characteristics of recipients of kidneys from HCV-RNA+ deceased donors in the THINKER and EXPANDER trials

Characteristics	THINKER ($N = 35$)	EXPANDER ($N = 10$)
Age in years at transplant, median (IQR)	60 (53–65)	71 (65–72)
Female (%)	10 (29)	2 (20)
Race (%)		
White	18 (51)	8 (80)
Black	14 (40)	1 (10)
Other	3 (9)	1 (10)
Cause of ESKD (%)		
Diabetes/hypertension	20 (57)	3 (30)
Congenital and cystic disease	6 (17)	2 (20)
FSGS and GN	2 (6)	1 (10)
IgA nephropathy	4 (11)	1 (10)
Other	3 (9)	3 (30)
Pre-emptive transplant (%)	3 (6)	2 (20)
Months on waitlist before study, median (IQR)	10.9 (3.6–14.1)	4.2 (0.9–18.3)
Months on waitlist from HCV NAT activation, median (IQR)	1.1 (0.4–3.2)	1.0 (0.7–2.0)
HCV genotype (%)		
1a	30 (86)	4 (40)
1b	4 (11)	0 (0)
2	0 (0)	1 (10)
3	0 (0)	1 (10)
4	1 (3)	0 (0)
Not performed/unable to determine	0 (0)	4 (40)

ESKD, end-stage kidney disease; EXPANDER, Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV-negative Recipients; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; HCV, hepatitis C virus infection; IQR, interquartile range; NAT, nucleic acid amplification testing; THINKER, Transplanting Hepatitis C Kidneys into Negative Kidney Recipients.

Twelve (27%) recipients had delayed graft function. The most recent median eGFR with 3 years of follow-up was 65.8 ml/min per 1.73 m^2 (IQR 56–81.5). At the end of follow-up, 36 patients had a median urine protein-creatinine ratio of 0.13 (IQR 0.1–0.2) g/g, and 8 patients had proteinuria evaluated by dipstick measurement (7 with no protein, and 1 with trace protein).

As shown in Supplementary Table S3, 8 (18%) recipients underwent a kidney biopsy, 7 enrolled in THINKER and 1 in EXPANDER. One THINKER recipient with a pretransplant diagnosis of IgA nephropathy had a biopsy showing focal segmental glomerulosclerosis at 8 months posttransplant and was treated with losartan for subnephrotic range proteinuria. At 3 years following transplant, this recipient had excellent graft function with a creatinine of 0.97 mg/dl (eGFR >80 ml/min) and proteinuria was below 300 mg. Another THINKER recipient experienced Banff 1a acute cellular rejection at 13 months, treated with intravenous corticosteroids. No other THINKER or EXPANDER patient had biopsy-proven rejection, and none had BK virus nephropathy on biopsy.

In THINKER, recipients were evaluated for DSA a median of 6 times (IQR 6–9), whereas in EXPANDER, recipients were evaluated for DSA a median of 2 times (IQR 1 – 2). Six patients (13%) developed any *de novo* DSA, among whom 3 developed class 2 only, 2 developed class 1 only, and 1 developed both class 1 and class 2 DSA. Taking the highest recorded mean fluorescent index for each individual patient, we calculated the median highest DSA. The median class 1 DSA was 2204 mean fluorescent index, and the median class 2 DSA was 2777 mean fluorescent index.

We compared the eGFR trajectories for recipients of HCV-RNA+ kidneys and highly similar recipients of HCV-seronegative donor kidneys. The characteristics of matched pairs are presented in Supplementary Table S4. The eGFR trajectories and measurements are shown in Supplementary Figure S1 and Supplementary Table S5. Trial participants had numerically higher median eGFR at 36 months (65.8 ml/min per 1.73 m^2 [IQR 56–81.5]) compared to recipients of kidneys matched on the same allocation kidney donor profile index (61.8 ml/min per 1.73 m^2 [IQR 49.3–79.3]), whereas recipients of kidneys matched on an "optimal kidney donor risk index" (kidney donor risk index recalculated as if participants were HCV-negative) had an eGFR of 67.4 ml/min per 1.73 m^2 (IQR 55.4–80.7). In general, however, recipients of HCV-RNA+ kidneys and the 2 comparator groups had excellent allograft function and differences between groups were not clinically meaningful.

Unfortunately, 1 recipient in THINKER died because of pancreatic adenocarcinoma, which was

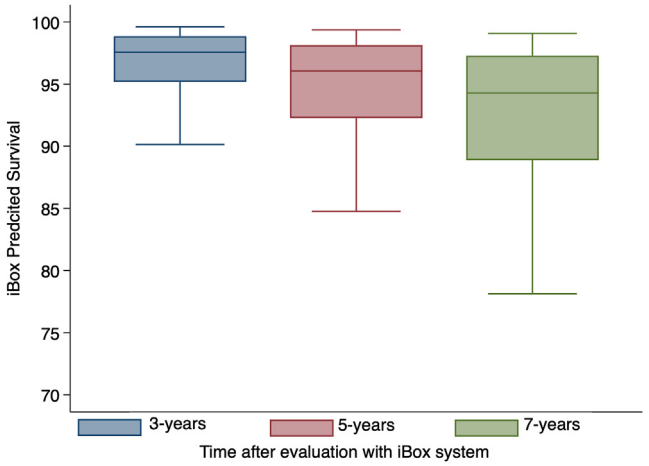

Figure 1. iBox scores predict excellent allograft survival for recipients in the THINKER-EXPANDER trials* (*Assessed using data from 3 years posttransplantation). iBOX, Integrative Box.

unrelated to HCV-viremia or its treatment. In Figure 1, we show predictions of future allograft survival using the iBox scoring system, using data from 3 years post-transplant among the surviving patients. The median allograft survival predicted by the iBox was 97.6% (IQR 95.2–98.9) at 6 years post-transplant (i.e., at 3 years post-assessment), 96.1% (IQR 92.3–98.1) at 8 years post-transplant, and 94.3% (IQR 88.9–97.3) at 10 years post-transplant.

Follow-up data from the EXPANDER and THINKER trials demonstrate that carefully selected kidneys from HCV-RNA+ donors provided excellent allograft function up to 3 years. Furthermore, eGFR trajectories and the iBox suggest that this excellent allograft function will continue well into the future. Allograft rejection and death were rare. Thirteen percent of recipients developed DSA. Taken together, these longer-term data should generate greater confidence among patients and transplant clinicians that they can manage complications of transplantation using HCV-RNA+ kidneys.

The longer-term function of THINKER and EXPANDER organs suggest that serious virally-mediated kidney injury is not common among deceased donors with HCV infection. In the pre-DAA era, registry data studies showed that recipients of HCV-seropositive kidneys had worse allograft survival and, in some cases, higher mortality.[7,8] These concerning outcomes were attributed to morbidity from uncontrolled HCV infection and serious toxicities, including rejection, from interferon treatment. However, in the DAA era, these fears about HCV-related kidney injury may have less relevance.[9] First, many donors with HCV infection die from opioid overdose, are generally young, and may only have HCV infection for a short period. Second, because many of these donors are young, the allografts may function well even if some have a degree of HCV injury. Lastly, the ability to rapidly eradicate HCV with DAAs may limit viral injury post-transplant.

The current study has limitations. Patients and donors were carefully selected, and DAAs were started promptly and provided at no cost to the patient. It is possible that outcomes for contemporary recipients of HCV-RNA+ kidneys will not enjoy the same favorable outcomes, particularly if there is delay in starting the DAAs (e.g., because of insurance approval for the DAA) and/or if kidneys with more adverse attributes are accepted. Second, the trials were relatively small. Larger studies of long-term follow-up with comparators may be needed to estimate allograft survival and rates of rejection with precision. Third, neither center performed protocol biopsies. It is possible that subclinical rejection or HCV injury were not detected through routine clinical surveillance.

In conclusion, this study provides important evidence that HCV-RNA+ kidney transplants function well beyond 1 year, and that complications such as rejection and DSA did not occur at elevated rates. Finally, eGFR trajectories and iBox scores provide additional evidence that these transplants will continue to function well into the future.

DISCLOSURE

ND and CD have received investigator-initiated and collaborative grants from Merck and AbbVie to Johns Hopkins to support research on transplantation of HCV-infected organs into uninfected recipients followed by antiviral treatment. ND has been paid by Merck as a scientific advisor and speaker. CD also receives honoraria from Gilead for serving on a grant review committee. FN received a grant from CareDx. DS has received honoraria from Sanofi, Novartis, CSL Behring, Jazz pharmaceuticals, Veloxis, Mallinckrodt, CareDx, Transmedics, and Thermo Fisher Scientific.

NB served on the scientific advisory board for CareDx. AL is on the board of Cibiltech and OA is on the team at Cibiltech. EB received research support from Merck and Takeda, served as an advisor for Merck and Takeda, and is on the data safety monitoring board for Amplyx. DS served as an advisor for Veloxis, Natera, and CareDx. JT-C received research support from Veloxis to the University of Pennsylvania. RRreceived grant support (paid to the University of Pennsylvania) for the HCV-TARGET study. PR and DG received investigator-initiated and collaborative grants from Merck, Gilead, and AbbVie to the University of Pennsylvania to support research on transplantation of HCV-infected organs into uninfected recipients, followed by antiviral treatment. PR is an Associate Editor for the American *Journal of* Kidney

Disease. RB received research support from Veloxis, Natera, CareDx, and CSL Behring; served as an advisor for CareDx, Natera, and Paladin labs; served as a consultant for Veloxis; and has royalties from UpToDate. All other authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Some of the results of this manuscript were presented at the American Transplant Congress in May 2020. The authors thank Cibiltech for providing us with access to compute the iBox score.

This study was supported by NIH grant K24-AI146137 (to PR). VP was supported by a National Kidney Foundation Young Investigator Grant during this study period and is currently supported by NIH grant K08-DK127250. Both the THINKER and EXPANDER trials, which were conducted at the University of Pennsylvania and the Johns Hopkins University, respectively, were supported by investigator-initiated grants from Merck.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods S1. Methods section.

Supplementary Methods S2. Penn Transplant Institute protocols for assessment of donor specific antibody (THINKER trial).

Supplementary Methods S3. Johns Hopkins Comprehensive Transplant Center protocols for assessment of donor specific antibody (EXPANDER trial).

Supplementary Methods S4. Additional information about matching methodology.

Supplementary References.

Figure S1. Comparison of eGFR between recipients of HCV-RNA+ donor kidneys and matched comparators who received HCV-aviremic donor kidneys.

Table S1. Complete inclusion and exclusion criteria for participants and deceased donors in the THINKER trial (IRB #823833).

Table S2. Complete inclusion and exclusion criteria for participants and deceased donors in the EXPANDER trial (IRB #00089751).

Table S3. Results of kidney biopsies performed for patients transplanted in the THINKER and EXPANDER trials.

Table S4. Characteristics of matched pairs of recipients of HCV-RNA+ kidneys and HCV-negative kidneys.

Table S5. Number of matched pairs of recipients with eGFR available.

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