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LETTER TO THE EDITOR

Repeat kidney transplant recipients with active rejection have elevated donor-derived cell-free DNA

In 2015, 13% of recipients of kidney transplants in the United States were recipients of repeat transplants for prior allograft failure.[1] Compared to single kidney transplant recipients (SKTRs), these repeat kidney transplant recipients (RKTRs) have inferior graft survival and a higher risk of rejection.[1,2] Despite these risks, transplant patients benefit from a repeat transplant compared to dialysis support.[3] The use of noninvasive biomarkers of allograft injury may optimize the care of RKTRs.

Donor-derived cell-free DNA (dd-cfDNA) has established utility in diagnosing the probability of active rejection in SKTRs,[4] but its value in RKTRs remains undetermined. In this study, we evaluated the dd-cfDNA in patients with more than one kidney transplant. We compared the levels of dd-cfDNA in 12 RKTRs to levels in 202 SKTRs. These cohorts were drawn from the Circulating Donor-Derived Cell-Free DNA in Blood for Diagnosing Acute Rejection in Kidney Transplant Recipients (DART) study (ClinicalTrials.gov Identifier: NCT02424227),[4] where surveillance for rejection began less than 2 months posttransplant and there was no clinically indicated biopsy at the first visit and no rejection while on the study. Of the 12 RKTRs, 11 patients had 2 and one patient had 3 kidney allografts in situ. Median dd-cfDNA in the RKTR surveillance cohort (n = 12) (0.29%) was higher than in the SKTR surveillance cohort (0.19 %, $P < .001$) (Figure 1A). However, both were significantly lower than the established 1% dd-cfDNA rejection threshold.[4]

We also examined dd-cfDNA levels in all 11 RKTR patients (9 patients with 2, one patient with 3, and one patient with 4 kidney allografts in situ) at the time of a clinically indicated biopsy of their current allograft. We compared the dd-cfDNA levels in the subset of 5 RKTRs with no rejection findings to the 6 RKTRs with biopsy diagnosis of rejection (2 RKTRs with T cell–mediated rejection and 4 with antibody-mediated rejection). dd-cfDNA in RKTRs with rejection was higher (median 1.36%) than in RKTRs without rejection (median 0.41%, $P = .009$) (Figure 1B). The dd-cfDNA levels in RKTRs with rejection are similar (median 1.36%) to the levels in SKTR with rejection[4] (n = 27, median 1.62%, $P = .85$).

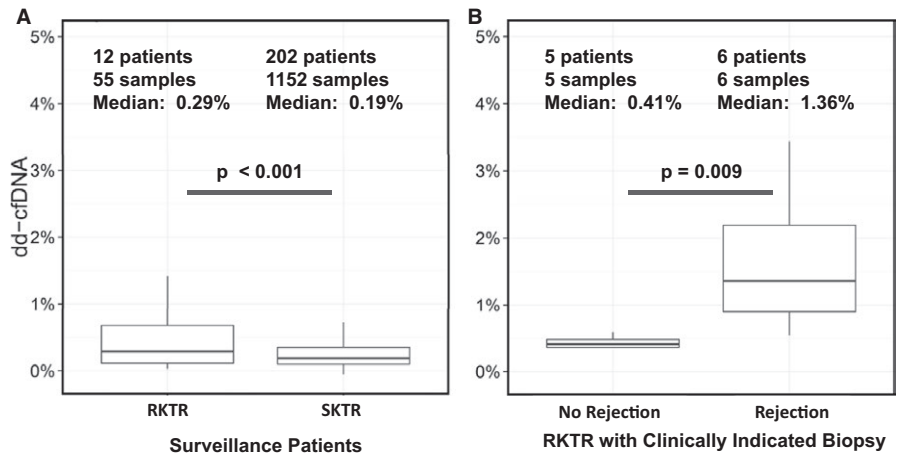

FIGURE 1 Donor-derived cell-free DNA measured in kidney transplant recipients. (A) Percent of dd-cfDNA in recipients with repeat transplants (RKTRs) is significantly higher than in recipients with single kidney transplant (SKTRs). (B) In RKTRs, at the time of clinically indicated biopsies, dd-cfDNA is significantly higher in patients with biopsy-proven rejection than in patients without rejection. The 6 rejection cases (and respective dd-cfDNA) are one acute Banff 1A T cell–mediated rejection (TCMR, 0.94%); one Banff IB TCMR (0.88%); one acute/active antibody-mediated rejection (ABMR, 0.54%), and 3 chronic, active ABMR (1.78%, 2.33%, and 3.44%). The biopsy findings in the 5 nonrejection graft dysfunction episodes consisted of acute tubular injury (ATI) and grade I interstitial fibrosis/tubular atrophy (IF/TA) (0.12%); glomerulonephritis, ATI, and grade I IF/TA (0.36%); BK polyomavirus, ATI, and grade I IF/TA (0.41%); glomerulonephritis and grade I IF/TA (0.48%); and one had no major findings (0.59%). The TCMR median (0.91%) was not significantly higher than the 5 nonrejection median (0.41%) ($P = .095$), whereas the ABMR median (2.06%) was significantly elevated ($P = .032$) in this small sample

The AlloSure method used in this study to determine the dd-cfDNA level does not require genotyping of the donor(s) and does not distinguish which allograft(s) may contribute to the total dd-cfDNA measured.[5] However, our results demonstrate higher "combined" dd-cfDNA levels in RKTRs at the time of surveillance testing than the levels observed in SKTRs. Of practical consequence, these "combined" dd-cfDNA levels in RKTRs at the time of surveillance testing are significantly below the dd-cfDNA levels seen in RKTRs at the time of rejection. Although patients with rejection have significantly higher levels of dd-cfDNA compared to those without rejection, the small number of cases precludes defining test sensitivity or specificity. Moreover, ongoing inflammation in prior allograft(s) could be a confounding feature and limit test utility. Our findings warrant further study and highlight the potential utility of dd-cfDNA monitoring regardless of prior kidney transplantation.

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AUTHOR CONTRIBUTIONS

DJH, MG, and JPY participated in research design; SGM, JHC, TA, JSB, DJH, MG, JPY, and RBM participated in the writing of the paper; SGM, JHC, TA, JSB, RBM, DJH, MG, and JPY participated in carrying out the research; and DJH participated in data analysis.

DISCLOSURE

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ORCID

Tarek Alhamad https://orcid.org/0000-0003-4289-0817
Roslyn B. Mannon https://orcid.org/0000-0003-1776-3680

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Shikha G. Mehta[1]
Jae H. Chang[2]
Tarek Alhamad[3]
Jonathan S. Bromberg[4]
David J. Hiller[5]
Marica Grskovic[5]
James P. Yee[5]
Roslyn B. Mannon[1]

[1]*Division of Nephrology, Department of Medicine, University of Alabama School of Medicine, Birmingham, Alabama*
[2]*Columbia University Medical Center, New York, New York*
[3]*Washington University, St. Louis, Missouri*
[4]*Division of Nephrology, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland*
[5]*CareDx, Brisbane, California*

Correspondence
Roslyn B. Mannon
Email: rmannon@uabmc.edu

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