Donor-Derived Cell-Free DNA is a Dynamic Biomarker of Active Rejection in Kidney Allografts

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Introduction

Donor-derived cell-free DNA (dd-cfDNA) has shown promise as a biomarker for identification of allograft rejection. In kidney transplantation, dd-cfDNA is higher at the time of Active Rejection as compared to No Rejection at the time of a renal biopsy performed for clinical suspicion of rejection (Bloom 2017). Here we report on the dynamic change of dd-cfDNA levels from the months prior to rejection, at the time of biopsy-proven rejection, and the months following. The impact of rejection treatment on dd-cfDNA levels is examined in rejection biopsy-proven or diagnosed without biopsy. All conditions are also analyzed for association with serum creatinine.

Methods

We measured dd-cfDNA in serial blood specimens from kidney recipients that had a clinically indicated biopsy. Plasma dd-cfDNA was collected from patients enrolled in the 14-center Circulating Donor-Derived Cell-free DNA in Blood for Diagnosing Acute Rejection in Kidney Transplant Recipients study (DART, Clinical Trials Identifier NCT02482487). dd-cfDNA was quantified in the CareDx laboratory using a clinical-grade targeted next generation sequencing method (AllSure, Grskovic 2016).

Two sets of analysis were performed. A group analysis examined dd-cfDNA levels before and after biopsy-proven rejection without restriction for serial samples within a given patient. Banff criteria for T-cell mediated rejection (TCMR) or antibody-mediated rejection (ABMR) were reported in 41 biopsies. Of these, 29 biopsies had a dd-cfDNA sample concurrent with biopsy, 5 patients with biopsy-proven rejection had 14 samples in the three months before biopsy, 25 patients with biopsy-proven rejection had 32 samples in the first month following biopsy, and 26 patients with biopsy-proven rejection had 33 samples in months 2 and 3 following biopsy. These results are compared to 104 patients with no-cause biopsies that lacked evidence of active rejection (no active rejection).

A paired analysis examined dd-cfDNA in response to rejection treatment. 131 patients received rejection treatment, of which 81 had a biopsy prior to treatment, and 30 of these had serial dd-cfDNA measurements within 1 month prior to treatment and another within 2 months after treatment.

Non-parametric methods were used for both group and paired analysis. Single asterisks mark P-values <0.05. Double asterisks mark P-values <0.01. A reference group of 350 samples from 53 transplant recipients with stable renal function was used as a control (Bromberg 2017), in which the median dd-cfDNA was 0.21%.

Results

Figure 1. Group analysis shows dd-cfDNA is higher at rejection than prior to active rejection. Serum creatinine does not differ.

Figure 2. Group analysis shows that dd-cfDNA is lower in the three months following active rejection.

Figure 3. Paired analysis demonstrates that dd-cfDNA is reduced by rejection treatment but serum creatinine does not change.

Conclusions

- dd-cfDNA is a dynamic biomarker that rises at the time of biopsy-defined rejection and is reduced following rejection.
- Serum creatinine does not display the same dynamic signal.
- Rejection treatment significantly decreases dd-cfDNA.
- Serum creatinine is not significantly changed following rejection treatment.
- Confirmed TCMR IB responds to rejection treatment with reduced dd-cfDNA. ABMR does not respond as well to treatment.
- As a dynamic biomarker, longitudinal surveillance with dd-cfDNA may be useful to detect and subsequently assess patient recovery from active rejection. Limited response in ABMR may reflect sub-optimal treatment.

References


Disclosures

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