Donor-Derived Cell-Free DNA Identifies Antibody-Mediated Rejection With Graft Injury in DSA-Positive Kidney Transplant Recipients

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Background

Antibody mediated rejection (ABMR) is an important cause of acute and chronic allograft dysfunction and graft loss.1 Many transplant patients are monitored for donor-specific antibodies (DSA), which are a risk factor for ABMR.2 Pre-formed or de novo donor-specific antibodies (DSAs) may lead to ABMR, but are not diagnostic alone.2 Donor-derived cell-free DNA (dd-cfDNA) is a noninvasive test of allograft injury that may enable more frequent, quantitative, and safer assessment of allograft rejection and injury status. dd-cfDNA discriminates active rejection in kidney transplant patients indicated for biopsy,3 with a greater discrimination for ABMR as compared to T cell mediated rejection.

Objective

This study assesses the combined use of dd-cfDNA and DSAs to diagnose ABMR.

Methods

dd-cfDNA was assayed in 90 blood samples with paired clinically indicated biopsies from 87 kidney transplant patients (Figure 1). Patients were divided into those who had DSA (DSA+; n=33 samples) and those who did not (DSA−; n=57 samples). Prevalences of biopsy-based diagnosis of ABMR were computed. Samples were further divided into dd-cfDNA above 1% (dd-cfDNA+) and dd-cfDNA below 1% (dd-cfDNA−).

All patients were part of the DART study (a prospective, observational study at 14 centers) to assess the ability of dd-cfDNA to discriminate active rejection from no-rejection.4 These analyses are based on the subset of patients with a clinically-indicated biopsy. The ABMR were defined according to Banff 2013 and comprised allograft rejection and injury status (ABMR and DSA testing may improve the non-invasive diagnosis of active ABMR in kidney transplant patients. Further studies will be performed to continue to validate these results.

Conclusions

• Patients with dd-cfDNA+/DSA+ results have a high probability of active ABMR
• Patients with dd-cfDNA−/DSA− results are unlikely to have ABMR
• The combined use of dd-cfDNA and DSA testing may improve the non-invasive diagnosis of active ABMR in kidney transplant patients. Further studies will be performed to continue to validate these results.

Case Study: Despite DSA above 1000 MFI, there is no ABMR (or TCMR) by biopsy. Biopsy for rejection diagnosis may have been avoided based on dd-cfDNA result.

DART observational patient. Donor: 1.5y/o Caucasian male, KDP1 79%, CMV D+/R−. Recipient 47y/o African American male with ESRD due to hypertension. PRA 0%, induction with basiliximab at 20mg IV x 2 doses. CMV prophylaxis with valganciclovir 900mg/day. Maintenance IS: tacrolimus, MMF, prednisone.

Table I: The patient population is similar in the DSA+ and DSA− groups.

Table II: In DSA+ patients, the PPV is over 80% at a 1% threshold, and nearly 90% at 2.9% (median ABMR)

References


Figure 1: Patients and samples from DART used in the current analysis.

Figure 2: The median level of dd-cfDNA in samples from DSA+ patients with ABMR was significantly higher than the median level in DSA+ patients without ABMR.

References