The Effect of Rejection Therapy, Histological Lesions and Molecular Assessment on dd-cfDNA in Kidney Transplant Recipients

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Background: Donor-derived cell-free DNA (dd-cfDNA) is a promising non-invasive biomarker of kidney allograft rejection.

Objectives: We aimed to investigate the utility of quantifying dd-cfDNA in monitoring the effect of treatment of rejection.

Methods: In prospective study, 37 patients with rejection in case-biopsies (median 85 days after transplantation, min 6 days, max 30 years) were enrolled between March 2022 and August 2023. In 29 biopsies the Molecular Microscope Diagnostic (MMDx) results were available as well. dd-cfDNA was quantifiedby the Prospera™ test (Natera Inc., Austin, Texas) at biopsy and at week 1, 2 and 3 after biopsy to monitor the effect of treatment. Out of 37 cases, 14 exhibited TCMR (11 acute TCMR, 3 chronic TCMR), 17 had ABMR (9 active ABMR, 8 chronic active ABMR), 3 had borderline changes, 2 molecular ABMR by MMDX and 1 showed mixed rejection. MMDx showed ABMR in 14, TCMR in 6, mixed rejection in 3 and no rejection in 6 biopsies.

Results: dd-cf DNA correlated with eGFR (r =-0.27, p=0.0009). At the time of biopsy, the dd-cf DNA correlated with Banff histological lesions (glomerulitis (g), r=0.61, p=0.001; transplant glomerulopathy (cg), r=0.48, p=0.01 and peritubular capillaritis (ptc), r=0.43, p<0.003). In MMDx cohort, dd-cf DNA correlated with molecular g (r=0.52, p=0.004), cg (r=0.6, p<0.001) and ptc scores (r=0.6, p<0.001). Patients with (n=14) /without DSA (n=23) at biopsy had similar dd-cf DNA levels. C-statistics found dd-cfDNA at biopsy to discriminate histological g ≥1 and ptc ≥1 with AUC 0.84 (95% CI 0.70–0.97, p=0.001, optimal cut-off=0.97%) and 0.73 (95% CI 0.56–0.90, p=0.02, optimal cut-off=1.37%) respectively. dd-cfDNA levels decreased significantly after rejection therapy at 1, 2, and 3 weeks in both TCMR (p = 0.049, p = 0.14, and p = 0.0024, respectively) and ABMR (p = 0.087, p = 0.3, and p = 0.052, respectively) groups (Figure 1). Anti-rejection therapy treatment resulted in a normalization of dd-cfDNA (< 1%) in 13/14 (93%) TCMR while in 8/14 (57%) ABMR cases. The decrease of dd-cf DNA at 1, 2, and 3 weeks after therapy was observed also in molecularly confirmed (MMDx) TCMR (p = 0.039, p = 0.077, and p = 0.0079, respectively) and ABMR (p = 0.048, p = 0.5, and p = 0.054, respectively).

Conclusion: Dynamic monitoring of dd-cfDNA levels provides valuable insights into the progression and treatment response of TCMR and ABMR in kidney transplant recipients.

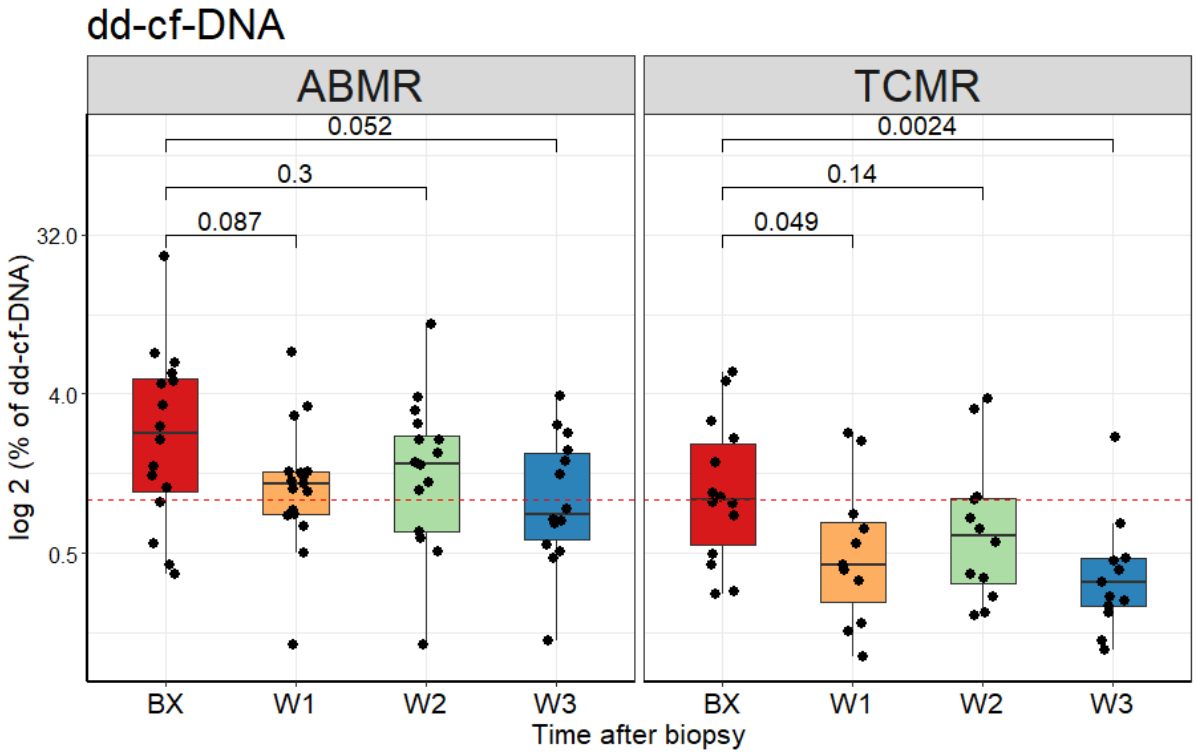

Figure 1. The effect of treatment on the level of dd-cf DNA (in %) at week 1,2 and 3 after indication biopsy (BX) with ABMR and TCMR. ABMR, antibody-mediated rejection. TCMR, T-cell mediated rejection.