O1 DIAGNOSTIC VALUE AND CONFOUNDING FACTORS OF URINARY BIOMARKERS IN THE NON-INVASIVE SCREENING OF RENAL ALLOGRAFT INFLAMMATION

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Introduction: The diagnostic value of urinary biomarkers has already been demonstrated in the acute rejection (AR) of renal allograft, but confounding factors (like BK virus (BKV) reactivation) which may interfere with their interpretation, have been poorly evaluated. Our goal was to evaluate the respective impact of urinary tract infection (UTI), BKV reactivation and acute rejection on these biomarkers to optimize a noninvasive strategy of AR assessment.
Method: In this retrospective single center study, a total of 391 urine samples collected at time of graft biopsy and BKV blood nucleic acid testing were included. Urinary concentrations of BK viruria, CXCL9 and CXCL10 proteins and CD3ε, CXCL9, CXCL10, granzyme B, perforin mRNAs were quantified.
Results: Our results confirmed the impact of UTI and BKV reactivation on urinary chemokine protein levels. To determine the impact of different stages of BKV reactivation, 262 samples are evaluated (after samples exclusion with AR or UTI): 84 viruria, 26 viremia without proven BKV nephritis (BKVN) and 20 BKVN. While viruria had limited impact, concentrations of mRNAs and protein biomarkers were significantly increased and similar in viremic patients and patients with BKVN. In a multivariate analysis, after elimination of UTI and BK viremia, a 3-parameter diagnostic model (urinary proteins CXCL9 and CXCL10 and serum DSA status) diagnosed acute rejection with an area under the curve of 0.81 ($p = 9.93E-13$). Restricted to unstable patients at the time of indication biopsy ($n = 168$), the rejection prediction was even more robust with an AUC of 0.85 ($p = 5.09E-12$).
Conclusion: BK viremia with BKVN or not and UTI are two status to determine before urinary CXCL9 and CXCL10 use in AR diagnosis.

O2 VALUE OF DONOR-SPECIFIC-ANTIBODIES CHARACTERISTICS AT TIME OF KIDNEY ALLOGRAFT BIOPSY

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This study aimed to investigate for serum IgG donor-specific-antibodies, whether the mean fluorescence intensity with or without serum ethylenediamine tetraacetic acid treatment, the ability to bind C1q or C3d, and/or the intra-graft detection, showed clinical utility at time of transplant biopsy. Seventy-seven kidney transplant recipients with an allograft biopsy for cause and serum donor specific antibodies were included. Median time between transplantation and biopsy was 25 months (range: 0.5–251), and median follow-up was 24 months (range 0–125). Antibody-mediated rejection was proven in 40% of biopsy specimens. Sensitivity and specificity of C1q, C3d and gDSA assays for predicting antibody-mediated rejection were 68% and 61%, 52% and 70%, 64.5% and 56.5%, respectively. In univariate analysis, donor-specific-antibodies mean fluorescence intensity, C3d positivity and intra-graft detection were associated with death-censored graft loss. In multivariate models, factors associated with death-censored graft loss were glomerular filtration rate, interstitial fibrosis/tubular atrophy score, and C4d positivity. In conclusion, at time of an allograft biopsy for cause, glomerular filtration rate and histopathologic criteria are the best prognosis factors for subsequent kidney allograft loss. Our findings weaken the rationale for implementing C1q, C3d or gDSA assays at the time of the biopsy because they do not independently predict antibody-mediated rejection and graft loss.

O3 FP7 BIOMARGIN: SMALL SETS OF URINARY CELL mRNAs LEADING TO A PARTITION TREE ON KIDNEY ALLOGRAFT LESIONS

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Background: FP7 Biomargin aimed at detecting and validating biomarkers of kidney graft lesions. In this study, we investigated the diagnostic potential of messenger RNAs (mRNAs) in urine samples.
Methods/Materials: Urine samples were collected at the time of protocol or for-cause biopsies in 4 European clinical centers. Patients were retrospectively selected after centralized histological reading of their biopsy by expert pathologists, and classified into 4 groups (normal, ABMR, TCMR or IF/TA). Absolute quantification of mRNAs was performed on urine cell pellets by qPCR. A statistical pipeline including 2 uni- and 5 multivariate analyses was applied to identify which biomarker candidates were associated with one of the 4 groups. Multivariate models were built to define parsimonious subsets of mRNAs that collectively were highly associated with graft lesions.
Results: A total of 24 mRNAs was quantified on 238 urine cell pellets from the case-control study, which included 73 Normal, 34 TCMR, 71 IF/TA and 60 ABMR samples. A set of 4 mRNAs differentiates patients with a biopsy showing acute rejection (AMBR or TCMR) from a normal biopsy (mean AUC = 0.73). Another set of 3 mRNAs discriminates the patients with a biopsy showing acute rejection from IFTA (mean AUC = 0.72). Finally, among the rejection group, a 4 gene signature enables to distinguish ABMR from TCMR (mean AUC = 0.77).
Conclusion: We identified small subsets of urine mRNAs, which enable a multistep approach to discriminate patients into 4 clinically relevant situations. These non-invasive molecular signatures could advise clinicians on the indication of performing a biopsy. The diagnostic performance of our mRNA signatures is currently been investigated in a trans-sectional set of urine samples, obtained at the time of 458 consecutive biopsies. Their predictive performance will then be assessed in a prospective Cohort Study.

O4 FP7 BIOMARGIN SHOWS THAT A SMALL SET OF BLOOD MICRO-RNAS IS ASSOCIATED WITH ACUTE KIDNEY ALLOGRAFTS REJECTION

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Background: FP7 Biomargin aimed at detecting and validating biomarkers of kidney graft lesions. In this study, we investigated the diagnostic potential of microRNAs (miRNAs) in whole blood samples.