Non-Invasive Metabolite-Based Urine Signature Detects Over-Immunosuppression in Renal Transplant Recipients

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DETECTING OVERIMMUNOSUPPRESSION: THE MISSING GUIDE RAIL

Managing complications related to over-immunosuppression is a critical challenge in post-transplant care, with infections accounting for the second leading cause of death with functioning graft (DFWG) in renal transplant recipients (RTRs) within the first year1. At present, there are no clinically validated biomarkers to detect over-immunosuppression2. Polymyosin-associated nephropathy (PVAN) is the result of an opportunistic infection indicative of over-immunosuppression that occurs in 5-10% of RTRs, which can lead to graft dysfunction or loss3.

STUDY DESIGN

In a pilot study, we identified differential metabolites in the urine from RTRs with biopsy-confirmed PVAN from those with a stable graft and built a machine learning algorithm model to classify patients with high accuracy4. To expand upon these results, we examined metabolites from a larger cohort comprising 115 RTRs with longitudinal samples (N=371). Urine samples were collected from patients at >90 days, 1 year, and 2 years post-transplant in conjunction with a protocol biopsy. Samples were also collected during clinically indicated biopsies. Urine metabolites were extracted and analyzed via 1D "H and 2D 1H-13C Heteronuclear Spectrum Quantum Coherence (HSQC) NMR spectroscopy. As previously described5, spectra were processed using in-house processing and normalization tools and metabolite concentration peaks were assigned to metabolites based on chemical shift mapping to a library of known metabolites. Metabolite levels and correlation coefficients were correlated with pathology results from gold-standard biopsy.

OLARIS CEREBRO PLATFORM: METABOLOMICS & MACHINE LEARNING

We first assessed survival and graft retention in each RTR population using Kaplan-Meier analysis. RTRs who were stable at 90 days but later experienced PVAN (N=39) were a discrete population with significantly lower survival (log-rank p<0.001) and graft retention (p<0.027) than those who were stable and did not experience rejection or PVAN over 2 years post-transplant (N=47), those who were under-immunosuppressed (N=14), and those who experienced PVAN at 90 days (N=15). The data for the analysis was right-censored at the last known record date, October 10, 2021.

OLARIS CEREBRO PLATFORM: METABOLOMICS & MACHINE LEARNING

90-DAY BIOPSY-CONFIRMED PVAN, REJECTION, OR STABLE RTRS HAVE DISTINCT METABOLIC FINGERPRINTS

Using a Kruskal-Walls F(0.05) non-parametric one-way analysis of variance, we identify a biomarker-based myOLARIS-KTdx™ score that can monitor patient disease status with a high degree of accuracy. In a similar analysis, differential metabolites between patients with PVAN or stable grafts at >90 days (heat map) were used to generate a myOLARIS-KTdx™ Score with high accuracy and optimal NPV. This score has the potential to serve as a diagnostic tool to confidently rule out PVAN in RTRs with stable graft function as well as a diagnostic tool from rejection, providing critical information to clinicians to optimize immunosuppressive dosage to prevent infection as well as rejection. Future directions include extending these results to a larger, more diverse patient population as well as to additional infections and other complications of over-immunosuppression.

CONCLUSIONS & FUTURE DIRECTIONS

Summary data for all patient groups at 90 days are shown. Demographic, biochemical, clinical, and immunosuppression-related metadata, including immunosuppressants) used and PCR results for BKV (not shown), were not found to improve the metabolite-based analysis of kidney transplant patients.

REFERENCES ~ DISCLOSURES

4. Jasna Fejzo for assistance with processing urine samples using NMR.
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7. E.M. O’Day is an Advisory Committee member for Olaris, Inc. and serves as a consultant for UCB, HANSA, and sits on the advisory board of InnoPhase Therapeutics, Inc. L.O. Rodrigues are employees of Olaris, Inc. and have ownership and salary interest in the company.

Clinical Use Cases 90 Days Post-Transplant

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