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Urinary Clusterin as A Pharmacodynamic Response Biomarker for the Endothelin Receptor Antagonist Atrasentan

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Objectives : Endothelin-1 pathway activation in the kidney is associated with progressive kidney injury and GFR decline. The endothelin-1 receptor antagonist atrasentan reduces the risk of kidney failure in patients with type 2 diabetes and CKD. However, the individual patient's response varies. This study aimed to identify molecular biomarkers predictive of atrasentan response and its underlying molecular mechanisms.
Methods : SOMAscan was used to discover urinary biomarkers associated with atrasentan response in patients from the phase 3 SONAR clinical trial. Logistic regression was used to identify markers whose change from baseline to 6 weeks of treatment are predictive to response. ELISA was used to validate top candidate markers. Urinary biomarker concentration was normalized by urine creatinine. Transcriptomic data from atrasentan-treated BTBR ob/ob mice and human patients with type 2 diabtes and CKD were analyzed for mechanistic Insight. Candidate biomarker was validated in the remaining SONAR cohort using Cox proportional hazard regression model.
Results : Putative biomarkers predictive of atrasentan response were identified. Of these, urinary clusterin (uCLU) emerged as the top candidate and was further evaluated. Kidney transcriptomic data revealed that CLU is significantly correlated with an atrasentan reversible endothelin activation score (AR-EAS) generated using transcriptomic data from atrasentan treated BTBR ob/ob mice and cross-validated in patients with DKD. Higher uCLU at baseline is significantly associated with an increased risk of a composite endpoint of kidney failure or 57% eGFR decline [HR1.09 (1.03, 1.16; p=0.005)] in the SONAR clinical trial (N=3060). Atrasentan reduced uCLU during six weeks treatment by 42.6% and this early change in uCLU was independently associated with a lower risk of the composite kidney endpoint after adjustment for all covariates [HR 0.86 (0.78, 0.96); p=0.009]
Conclusions : This integrative study identified and validated uCLU as a promising pharmacodynamic biomarker for assessing treatment response to atrasentan. This calls for further clinical evaluation and implementation

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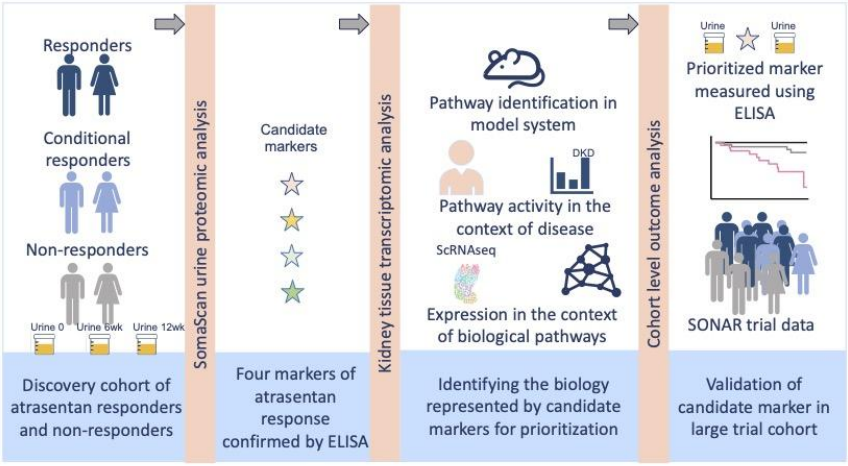

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