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Establishing Surrogate Kidney End Points for Lupus Nephritis Clinical Trials: Development and Validation of a Novel Approach to Predict Future Kidney Outcomes

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Abstract

Objective: End points currently used in lupus nephritis (LN) clinical trials lack uniformity and questionably reflect long-term kidney survival. This study was undertaken to identify short-term end points that predict long-term kidney outcomes for use in clinical trials.

Methods: A database of 944 patients with LN was assembled from 3 clinical trials and 12 longitudinal cohorts. Variables from the first 12 months of treatment after diagnosis of active LN (prediction period) were assessed as potential predictors of long-term outcomes in a 36-month follow-up period. The long-term outcomes examined were new or progressive chronic kidney disease (CKD), severe kidney injury (SKI), and the need for permanent renal replacement therapy (RRT). To predict the risk for each outcome, hazard index tools (HITs) were derived using multivariable analysis with Cox proportional hazards regression.

Results: Among 550 eligible subjects, 54 CKD, 55 SKI, and 22 RRT events occurred. Variables in the final CKD HIT were prediction-period CKD status, 12-month proteinuria, and 12-month serum creatinine level. The SKI HIT variables included prediction-period CKD status, International Society of Nephrology (ISN)/Renal Pathology Society (RPS) class, 12-month proteinuria, 12-month serum creatinine level, race, and an interaction between ISN/RPS class and 12-month proteinuria. The RRT HIT included age at diagnosis, 12-month proteinuria, and 12-month serum creatinine level. Each HIT validated well internally (c-indices 0.84-0.92) and in an independent LN cohort (c-indices 0.89-0.92).

Conclusion: HITs, derived from short-term kidney responses to treatment, correlate with long-term kidney outcomes, and now must be validated as surrogate end points for LN clinical trials.