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Original Investigation

Early Change in Urine Protein as a Surrogate End Point in Studies of IgA Nephropathy: An Individual-Patient Meta-analysis

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Background: The role of change in proteinuria as a surrogate end point for randomized trials in immunoglobulin A nephropathy (IgAN) has previously not been thoroughly evaluated.

Study Design: Individual patient–level meta-analysis.

Setting & Population: Individual-patient data for 830 patients from 11 randomized trials evaluating 4 intervention types (renin-angiotensin system [RAS] blockade, fish oil, immunosuppression, and steroids) examining associations between changes in urine protein and clinical end points at the individual and trial levels.

Selection Criteria for Studies: Randomized controlled trials of IgAN with measurements of proteinuria at baseline and a median of 9 (range, 5-12) months follow-up, with at least 1 further year of follow-up for the clinical outcome.

Predictor: 9-month change in proteinuria.

Outcome: Doubling of serum creatinine level, end-stage renal disease, or death.

Results: Early decline in proteinuria at 9 months was associated with lower risk for the clinical outcome (HR per 50% reduction in proteinuria, 0.40; 95% CI, 0.32-0.48) and was consistent across studies. Proportions of treatment effect on the clinical outcome explained by early decline in proteinuria were estimated at 11% (95% CI, −19% to 41%) for RAS blockade and 29% (95% CI, 6% to 53%) for steroid therapy. The direction of the pooled treatment effect on early change in proteinuria was in accord with the direction of the treatment effect on the clinical outcome for steroids and RAS blockade. Trial-level analyses estimated that the slope for the regression line for the association of treatment effects on the clinical end points and for the treatment effect on proteinuria was 2.15 (95% Bayesian credible interval, 0.10-4.32).

Limitations: Study population restricted to 11 trials, all having fewer than 200 patients each with a limited number of clinical events.

Conclusions: Results of this analysis offer novel evidence supporting the use of an early reduction in proteinuria as a surrogate end point for clinical end points in IgAN in selected settings.

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INDEX WORDS: Proteinuria; urine protein; surrogate endpoint; IgA nephropathy (IgAN); end-stage renal disease (ESRD); prognostic marker; clinical end point; disease progression; kidney disease; glomerulonephritis; meta-analysis.

Immunoglobulin A nephropathy (IgAN) is a common cause of glomerulonephritis. It can have a highly heterogeneous course; some patients have hematuria with minimal progression, others have slowly progressive decline in glomerular filtration rate (GFR) culminating in kidney failure years later, and rarely, fast progression to kidney failure. For patients with progressive disease, treatments are thought to be

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most effective early in the disease course. In many chronic kidney diseases (CKDs), a large decline in GFR, assessed as doubling of serum creatinine level from baseline and more recently 30% or 40% decline in GFR, has often been used as a surrogate end point for kidney failure in randomized clinical trials of patients with low GFRs or rapidly progressive disease.[1,2] However, for the majority of patients with IgAN with progressive disease, these end points are not feasible because of the long duration of the disease, leading to expense and complexity of trials that would be required to detect a large decline in GFR. These issues have likely contributed to the paucity of therapies to treat IgAN.

For many diseases, use of surrogates has helped accelerate the development and evaluation of new therapies.[3] Critical to the correct assessment of surrogacy is the use of appropriate methods to evaluate patient data across multiple trials to avoid approval of ineffective or harmful therapies.[4,5] Two recent individual patient–level meta-analyses provided empirical evidence for the use of change in proteinuria as a surrogate outcome for disease progression across many causes of CKDs.[6,7] One criticism of these analyses was that they grouped together different causes of kidney disease, and the role of proteinuria in the cause and progression of the disease may differ among causes.[8] If so, the performance of proteinuria as a surrogate would differ, in which case pooling across studies may have masked true associations between change in proteinuria and clinical end points in a particular disease. We report an individual patient–level meta-analysis of a pooled data set of 830 individuals from 11 randomized controlled trials of 4 intervention types in IgAN to evaluate an early change in proteinuria as a surrogate end point for progression of this specific cause of kidney disease.

METHODS

Study Selection and Study Populations

We identified potential studies by a systematic search of the medical literature on Ovid MEDLINE published from January 1, 1979, to July 9, 2012 (see Fig S1 for flow chart and Table S1 for search terms, provided as online supplementary material). The key inclusion criterion was randomized controlled trial design of drug interventions in adults with IgAN (Table S2). In total, we were able to include 11 studies that investigated 4 intervention types (renin-angiotensin system [RAS] blockade, fish oil, steroids, or other immunosuppression agents; Fig S1). Risks of bias for each study were assessed using the risk-of-bias tool of the Cochrane collaboration[9] (Table S3). We defined the active treatment as the treatment hypothesized to produce the greater reduction in risk for the clinical end point. All participants gave informed consent as part of their inclusion in each study. This analysis was considered exempt from review by the Tufts Medical Center Institutional Review Board.

Early Change in Urine Protein

We defined change in urine protein excretion from baseline to a median of 9 (range, 5-12) months. Urine protein was expressed in units of grams per day and was log transformed due to skewedness of the data.

Clinical End Point

The clinical end point was defined as the composite of time to the first occurrence of doubling of serum creatinine level, end-stage renal disease, or death. If available, we used the study-defined censoring dates to define follow-up times.[10,11] As previously described, if study-defined censoring dates were not available, we approximated them as time from randomization to the final recorded visit date in the data provided plus 6 months plus the study-specific 90th percentile of the average interval between visits with serum creatinine measurements.[6,12-20] The purpose of adding 6 months to the estimated right censoring date is to retain a higher proportion of clinical outcome events that occurred following the patient's final study visit.

Analyses

As was previously used in Inker et al,[6] we performed 3 types of analyses that are widely used for validation of surrogate end points: (1) association between the clinical outcome and early change in proteinuria at the individual level,[21] (2) proportion of treatment effect on the clinical outcome explained by the early change in proteinuria (Prentice-Freedman criterion),[22,23] and (3) association between the treatment effect on the 9-month change in proteinuria and the treatment effect on the clinical end point.[24-27]

For all analyses, GFR was estimated using the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation.[28] We report results for each study, in the pooled data set and in subgroups based on intervention type, baseline urine protein excretion ($<$1, 1-2, and $>$2 g/d), estimated GFR (eGFR; $<$45, 45-90, and $>$90 mL/min/1.73 m^2), and blood pressure (systolic blood pressure $<$ 140 and diastolic blood pressure $<$ 90 mm Hg vs systolic blood pressure $\geq$140 or diastolic blood pressure $\geq$ 90 mm Hg). In a sensitivity analysis, we adjusted for follow-up blood pressure at the same time point as the second measurement of urine protein excretion in the subset of studies in which these measurements were available.

Individual-Level Association

Demonstration of a consistent patient-level association between a surrogate and the clinical outcome is widely regarded as necessary, although not sufficient, for establishing the validity of the surrogate end point in clinical trials.[4,29,30] We evaluated individual-level association by performing Cox regressions to relate the clinical outcome to early change in proteinuria, with results expressed as the hazard ratio (HR) associated with a halving of proteinuria. Our initial model was adjusted for treatment assignment, study, and baseline urine protein excretion, with the more fully adjusted models adjusted for additional baseline variables including age, sex, race, eGFR, and blood pressure. We obtained HRs and associated 95% confidence intervals (CIs) for the overall data set and for subgroups by repeating the Cox regression in the overall data set and in each of the subgroups pooled across each study, in which baseline hazards of Cox regressions were stratified by study.

Proportion of Treatment Effect Explained (Prentice-Freedman Criterion)

The proportion of the treatment effect on a clinical outcome "explained by the surrogate" (proportion of treatment effect) has been widely used as an index of the validity of surrogate end points.[22,23,31] When data permit, the proportion of treatment effect quantifies the magnitude of the attenuation of the treatment effect on the clinical outcome that results from statistically controlling for the surrogate.[24,32] We performed joint Cox regressions with baseline hazards stratified by study to estimate treatment effects on

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