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One-Year estimated GFR Slope Independently Predicts Clinical Benefit in Immunoglobulin A Nephropathy

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Received 14 July 2022; revised 6 September 2022; accepted 19 September 2022; published online 29 September 2022

Kidney Int Rep (2022) **7,** 2730–2733; https://doi.org/10.1016/j.ekir.2022.09.017
KEYWORDS: eGFR; end-stage kidney disease; IgA nephropathy; proteinuria; surrogate endpoint; UPCR

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is a serious, progressive, immune complex–mediated kidney disease. Being a rare disease, a key challenge for the evaluation of potential new treatments for IgAN is that the progression to end-stage kidney disease typically evolves over many years. Therefore, there is interest in defining earlier surrogate endpoints to serve as reliable predictors of treatment effect on long-term IgAN kidney outcomes.

Key endpoints evaluated as potential early surrogates across chronic kidney diseases include proteinuria reduction and change in estimated glomerular filtration rate (eGFR). Persistent 24-hour proteinuria, expressed as protein excretion or urine protein-creatinine ratio, is widely accepted as a consistent risk factor for kidney disease progression.[1–4] IgAN progression results in renal function deterioration, typically measured by eGFR. A large eGFR decline, assessed as doubling of serum creatinine levels from baseline, and more recently as a 30% or 40% decline from baseline eGFR, has been used as a surrogate endpoint for kidney failure in randomized clinical trials, including patients with low eGFRs or relatively rapidly progressive disease.[5,6] Nevertheless, for IgAN patients, using these surrogate endpoints is challenging because of the long duration and rarity of the disease, which would require large, long, expensive, and complex trials to detect a sufficiently large eGFR decline.

In 2016, the Kidney Health Initiative initiated a project to identify endpoints that could be used as a basis for IgAN therapy approval;[2,4] in 2018, the National Kidney Foundation, US Food and Drug Administration, and European Medicines Agency cosponsored a workshop on changes in albuminuria or eGFR as candidate surrogate endpoints across chronic kidney disease.[7,8] Meta-analyses were performed supporting the relationship between proteinuria reduction[4] or eGFR slope[9] and validated clinical outcomes of kidney disease progression. Here, we report an IgAN-specific meta-analysis evaluating 1-year proteinuria reduction and 1-year eGFR slope as early surrogate endpoints for disease progression.

RESULTS

The pooled study population comprised 1299 patients from 13 IgAN trials,[4,S1–S3] including TESTING,[S2] 10-year follow-up from STOP-IgAN,[S3] and trials (individually or in groups) from meta-analyses performed for or as a result of the Kidney Health Initiative and National Kidney Foundation/US Food and Drug Administration/European Medicines Agency initiatives[4,S1] (Supplementary Methods). The study characteristics are reported in Supplementary Table S1. The composite clinical endpoint was time to >40% reduction in eGFR, end-stage kidney disease, or death due to kidney disease, for TESTING;[S2] time to >40% reduction in eGFR, end-stage kidney disease, or death, for STOP-IgAN;[S3] and time to doubling of serum creatinine, eGFR of <15 ml/min per 1.73 m^2, or end-stage kidney disease, for the remaining studies.[4,9,S1] These composite endpoints will herein be referred to as clinical outcome.

Random-effects Bayesian analyses showed strong statistically significant agreement between treatment

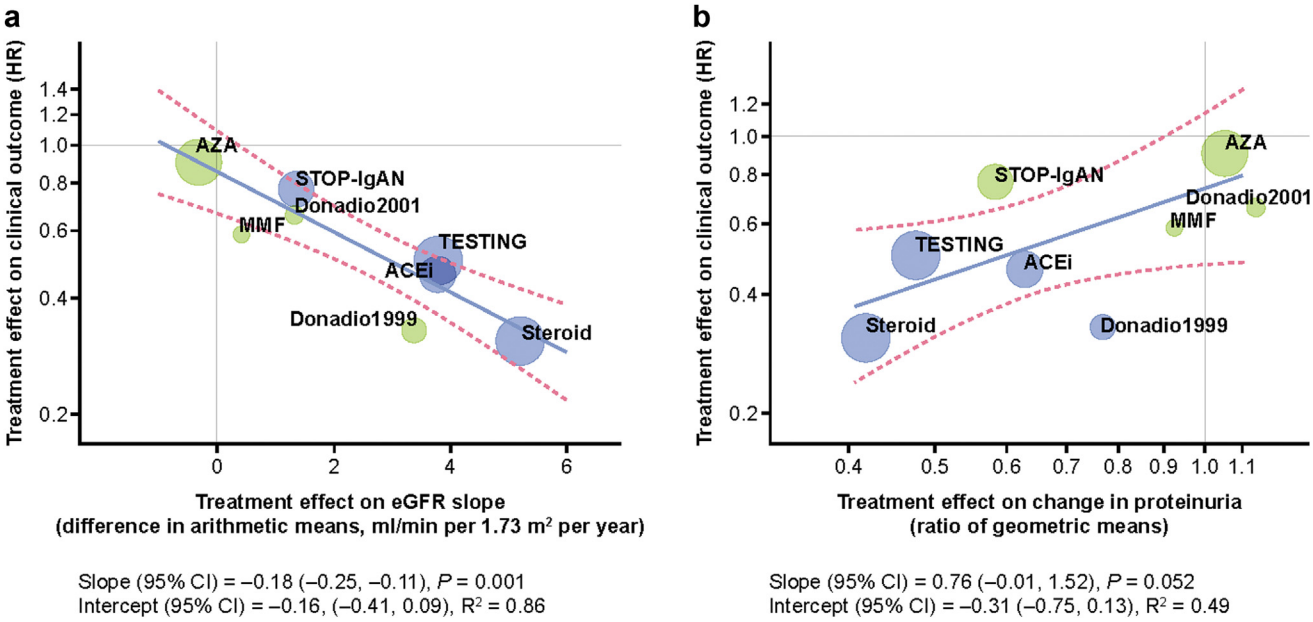

Figure 1. Trial-level assessment of the association between treatment effects on (a) 1-year eGFR slope or (b) 1-year proteinuria reduction with the treatment effects on clinical outcome. The vertical axes are the empirical Bayes estimates of treatment effects on the clinical outcome (HR) and the horizontal axes are the empirical Bayes estimates of treatment effects on the change in (a) 1-year eGFR slope (difference in arithmetic means, ml/min per 1.73 m^2 per year) or (b) 1-year proteinuria (ratio of geometric means). The circles represent the estimated treatment effects for each trial with the size of the circle proportional to the sample population. The blue line represents the regression through the studies, and the red lines indicate the confidence band. In Figure 1a, the trials with the 4 largest proteinuria treatment effects are colored in blue, and in Figure 1b the trials with the 4 largest eGFR treatment effects are colored in blue. ACEi, angiotensin-converting enzyme inhibitor; AZA, acetazolamide; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MMF, mycophenolate mofetil; STOP-IgAN, X-immunoglobulin A nephropathy.

effects on 1-year eGFR slope and treatment effects on the clinical outcome across individual studies (slope = −0.18, $P = 0.001$; $R^2 = 0.86$; Figure 1a). A less robust relationship was observed between treatment effects on 1-year proteinuria reduction and on clinical outcome (slope = 0.76, $P = 0.052$; $R^2 = 0.49$; Figure 1b). These data confirm previously published results.[4,9] Treatment effects for 1-year proteinuria reduction and eGFR slope are strongly correlated ($\rho = -0.81$; Supplementary Figure S1); while both endpoints have an association with the clinical outcome, they may not necessarily independently predict it.

To assess whether eGFR and proteinuria independently predict clinical outcome, multivariate analyses were performed using aggregate trial data. The relationship between 1-year eGFR slope and clinical outcome remained highly statistically significant after adjusting for treatment effects on proteinuria reduction ($P = 0.0057$; Figure 2a), indicating that treatment effect on 1-year eGFR slope is an independent predictor of clinical outcome. This suggests that, for studies showing similar treatment effects on proteinuria reduction but different effects on eGFR slope, the greater eGFR effect observed (blue in Figure 1a) would be predicted to have greater influence on the outcome. Nevertheless, the relationship between treatment effects on 1-year proteinuria reduction and clinical outcome, after adjusting for treatment effects on eGFR, is not statistically significant ($P = 0.1743$, Figure 2b). This suggests that for trials with similar effect on 1-year eGFR slope, the size of the 1-year proteinuria treatment effect would not be expected to have a bearing on the treatment effect for clinical outcome.

DISCUSSION

These trial-level multivariate analyses show that an effect on 1-year eGFR slope is a major, independent predictor of treatment effect on long-term clinical outcomes in IgAN, supporting it as a surrogate endpoint. From a clinical perspective, this is not unexpected because lost renal function cannot be restored; indeed eGFR deterioration ultimately defines renal failure. Sustained effects on eGFR slope are a clear indicator of a disease-modifying treatment effect.

Although proteinuria reduction in IgAN is an important treatment goal,[1] our multivariate analyses did not find proteinuria reduction at 1 year (or earlier) to be an independent predictor of the clinical outcome, once the impact on 1-year eGFR was accounted for.

The impact on proteinuria reduction at 1 year or earlier may still provide an important indication of

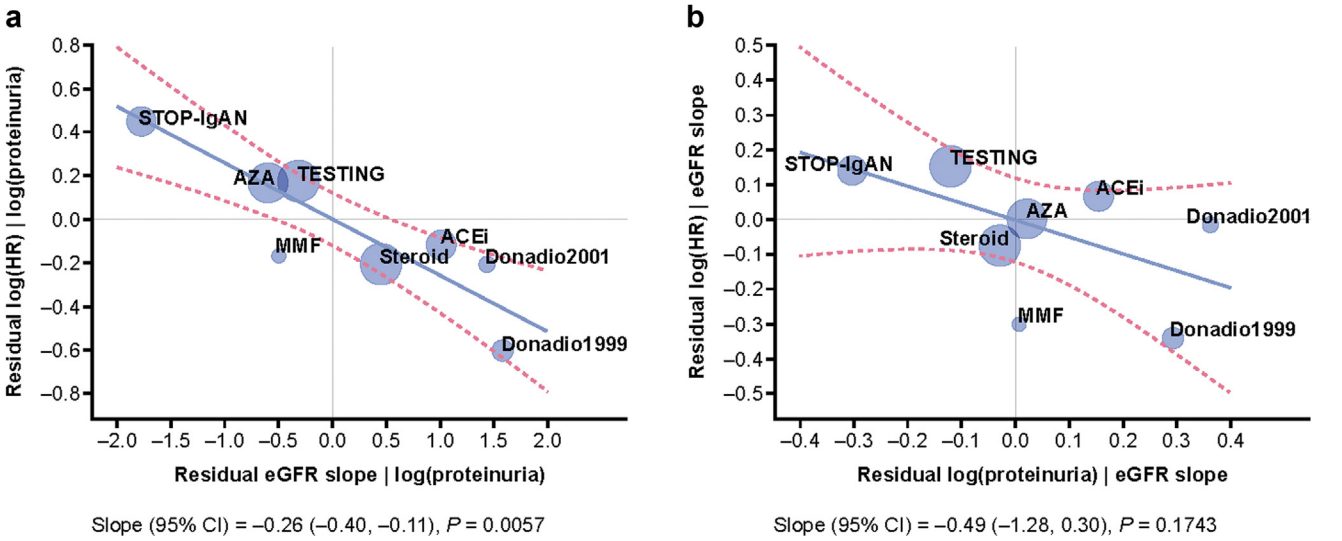

Figure 2. Added variable plots for (a) 1-year eGFR slope having adjusted for log(1-year proteinuria) and (b) log(1-year proteinuria) having adjusted for 1-year eGFR slope. (a) After adjusting for log(1-year proteinuria), the residuals from the fitted regression model of log(HR for the clinical outcome) are plotted against the residuals from eGFR slope. (b) After adjusting for eGFR slope, the residuals from the fitted regression model of log(HR for the clinical outcome) are plotted against the residuals from log(1-year proteinuria). Log(HR) adjusted for log(proteinuria) + eGFR indicates no evidence of an interaction between log(proteinuria) and eGFR ($P = 0.74$). Results were confirmed when using 6-month (a) proteinuria ($P = 0.006$) and (b) eGFR slope ($P = 0.173$). ACEi, angiotensin-converting enzyme inhibitor; AZA, acetazolamide; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MMF, mycophenolate mofetil; STOP-IgAN, X-immunoglobulin A nephropathy.

drug effectiveness. However, unless this also translates into an impact on the rate of eGFR loss, in certain populations it may not be sufficient evidence alone to reliably predict benefits on clinical outcome. Notably, several studies included active treatment for less than 1 year;[4,S1,S2] because of this somewhat limited treatment time, it is not possible to exclude an increase in proteinuria levels once treatment is stopped. In turn, one could speculate that that there may be a legacy effect on glomerular inflammation that persists beyond the reduction in proteinuria, causing an effect on eGFR. Recognizing that changes in urine protein-creatinine ratio are being evaluated at timepoints earlier than 12 months in a number of ongoing clinical trials,[S4–S7] we cannot comment on the validity of eGFR slope at time points earlier than 12 months.

Although random-effects trial–level analyses minimize the confounding risk inherent in assessing individual-level associations, we acknowledge the use of published aggregate data, which do not allow for patient-level correlation between endpoints. Individual patient data from each study are not publicly available; however, by using the confidence intervals for the published study-level data, the between-patient variability was deduced for each study, and individual patient datasets were sampled with the same mean, SD, and number of events as the corresponding endpoints in the published studies. Sensitivity analyses were performed using these sampled patient-level datasets for various patterns of subject-level correlation. The results fully support the conclusions from our primary analyses based on the published aggregate data (Supplementary Tables S2 and S3).

A separate concern is the impact that interventions have acutely on kidney function. Whether positive impact, as has been seen with corticosteroids; or negative impact, as seen with renin–angiotensin system inhibitors. For our analysis, total eGFR slope data for each trial come from a model that fits a separate acute and chronic phase.[S8] The frequent occurrence and uncertain implications of acute effects for chronic kidney disease therapies could limit the effectiveness of 1-year eGFR slope to predict outcomes. However, our data suggest that a 1-year time period is likely long enough to evaluate whether a positive impact on the eGFR slope will predict longer-term outcome, as several of the trials evaluated renin–angiotensin system inhibitors.[9] Utility of 1-year eGFR slope is also likely to depend on sufficient numbers of patients and significant disease progression. Application of these results to future trials with different characteristics to those included here must be undertaken with caution, particularly in trials with larger magnitudes of acute effect, or lower rates of eGFR decline.

Overall, our analyses support the use of 1-year eGFR slope as an important clinically relevant surrogate endpoint for confirmatory clinical trials in IgAN, which may allow early demonstration of a disease-

modifying treatment effect and consequent benefit that is independently predictive of the clinical outcome.

DISCLOSURE

RAL reports receiving personal fees and grants from Alexion, Aurinia, Calliditas, Omeros, Pfizer, Roche, Travere, and Vera, and being an advisory board member for Alkahest and Equillium. HNR's work is supported by the Gabor Zellerman Chair in Nephrology Research; HNR has acted as a consultant for Calliditas, Chinook, Novartis, Omeros, Pfizer, Roche, and Travere. AMS reports personal fees from Calliditas and has acted as a consultant for Athenex, BioSight, Carrick, Cogent, Confo, Cullinan, Deciphera, Dizal, GSK, Guard, Intellia, IO Biotech, iTeos, Jazz, Jounce, Keros, Mina, PsiOxus, Repare, RhoVac, and UroGen in therapeutic areas other than kidney disease. JB is a consultant to Calliditas and reports grants and personal fees from Calliditas outside the submitted work.

ACKNOWLEDGMENTS

This work was sponsored by Calliditas Therapeutics AB. Two medical writers, Fiona Wilson and Aarti Shah (Chameleon Communications), provided editorial assistance in the preparation of the manuscript, with funding from the sponsor.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary Results.

Supplementary References.

Figure S1. Correlation between log(1-year proteinuria ratio) and 1-year eGFR slope.

Table S1. Summary of study characteristics.

Table S2. Separate univariate sensitivity analysis of 1-year proteinuria reduction and eGFR slope with clinical outcome using sampled individual patient data.

Table S3. Multivariate sensitivity analysis of 1-year proteinuria reduction and eGFR slope with clinical outcome using sampled individual patient data.

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