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Association of Treatment Effects on Early Change in Urine Protein and Treatment Effects on GFR Slope in IgA Nephropathy: An Individual Participant Meta-analysis

Lesley A. Inker, Hiddo J.L. Heerspink, Hocine Tighiouart, Juhi Chaudhari, Shiyuan Miao, Ulysses Diva, Alex Mercer, Gerald B. Appel, James V. Donadio, Jürgen Floege, Philip K.T. Li, Bart D. Maes, Francesco Locatelli, Manuel Praga, Francesco P. Schena, Andrew S. Levey, and Tom Greene

Rationale & Objective: An early change in proteinuria is considered a reasonably likely surrogate end point in immunoglobulin A nephropathy (IgAN) and can be used as a basis for accelerated approval of therapies, with verification in a postmarketing confirmatory trial. Glomerular filtration rate (GFR) slope is a recently validated surrogate end point for chronic kidney disease progression and may be considered as the end point used for verification. We undertook a meta-analysis of clinical trials in IgAN to compare treatment effects on change in proteinuria versus change in estimated GFR (eGFR) slope.

Study Design: Individual patient-level meta-analysis.

Setting & Study Populations: Individual data of 1,037 patients from 12 randomized trials.

Selection Criteria for Studies: Randomized trials of IgAN with proteinuria measurements at baseline and 6 (range, 2.5-14) months and at least a further 1 year of follow-up for the clinical outcome.

Analytical Approach: For each trial, we estimated the treatment effects on proteinuria and on the eGFR slope, computed as the total slope starting at baseline or the chronic slope starting 3 months after randomization. We used a Bayesian mixed-effects analysis to relate the treatment effects on proteinuria to effects on GFR slope across these studies and developed a prediction model for the treatment effect on the GFR slope based on the effect on proteinuria.

Results: Across all studies, treatment effects on proteinuria accurately predicted treatment effects on the total slope at 3 years (median R^2 = 0.88; 95% Bayesian credible interval [BCI], 0.06-1) and on the chronic slope (R^2 = 0.98; 95% BCI, 0.29-1). For future trials, an observed treatment effect of approximately 30% reduction in proteinuria would confer probabilities of at least 90% for nonzero treatment benefits on the total and chronic slopes of eGFR. We obtained similar results for proteinuria at 9 and 12 months and total slope at 2 years.

Limitations: Study population restricted to 12 trials of small sample size, leading to wide BCIs. There was heterogeneity among trials with respect to study design and interventions.

Conclusions: These results provide new evidence supporting that early reduction in proteinuria can be used as a surrogate end point for studies of chronic kidney disease progression in IgAN.

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Correspondence to L.A. Inker (linker@tuftsmedicalcenter.org)

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IgA nephropathy (IgAN) is rare, but is the most common cause of glomerulonephritis and has few proven therapies. Trials early in the disease course are challenging to undertake because of the low event rates of clinical end points, generally defined as kidney failure (receipt of kidney replacement therapy or glomerular filtration rate [GFR] <15 mL/min/1.73 m^2) or doubling of serum creatinine level. In many chronic kidney diseases (CKDs), a large decrease in GFR, assessed as a doubling of serum creatinine level from baseline, and more recently as a 30%-40% decrease in GFR, has often been used as a surrogate end point for kidney failure in randomized clinical trials (RCTs) of patients with low GFRs or rapidly progressive disease.[1-3] In a rare disease such as IgAN, these end points may not be feasible because of the long duration of the disease, leading to large expense and complexity of trials that would be required to detect treatment effects on a large decrease in GFR. In addition, the goal of most therapeutic strategies is to treat the disease early, before the development of irreversible changes. These issues have likely contributed to the paucity of therapies. Recent evidence supports early change in urine protein level as a reasonably likely surrogate in IgAN.[4,5]

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In the United States, reasonably likely surrogate end points can be used as a basis for accelerated approval of therapies intended to treat serious or life-threating conditions such as IgAN.[6,7] The clinical benefit of products approved under this program would need to be verified in a postmarketing confirmatory trial.[8] Recent empirical data demonstrated the validity of GFR slope as a surrogate end point for clinical benefit in general CKD progression studies.[9-13] For IgAN, the slope of GFR decrease would be a more viable end point for verification in postmarketing confirmatory trials given the low likelihood of sufficient clinical events. Here we report an individual patient-level

PLAIN-LANGUAGE SUMMARY

Drug regulatory agencies allow changes in urine protein level to be used as end points for trials in immunoglobulin A nephropathy as part of accelerated approval of treatments as long as there is confirmation of the treatment benefit in postmarketing trials following approval. We performed an individual-patient meta-analysis including data from 1,037 patients across 12 trials to assess how treatment effects on the change in proteinuria predicts the treatment effects on the change in estimated glomerular filtration rate (GFR), a surrogate outcome that has recently been validated. We found that treatment effects on urine protein accurately predicted treatment effects on the total GFR slope at 3 years and on chronic GFR slope. These results provide new evidence supporting that a change in proteinuria can be used as a surrogate end point in treatment trials of progression of immunoglobulin A nephropathy.

meta-analysis of a pooled dataset of 1,037 individuals from 12 RCTs in IgAN to evaluate the association of treatment effects on early change in urine protein level compared with treatment effects on GFR slope. These data would be valuable for the design of confirmatory trials.

Methods

Study Selection and Study Populations

We identified studies through systematic searches of the medical literature on Ovid MedLine published from January 1, 1979, to December 15, 2016, as previously described[10,14] (Item S1; Tables S1 and S2; Figs S1 and S2). Twelve studies were included that investigated 4 intervention types: renin angiotensin system blockade, fish oil, steroids, or other immunosuppressive agents (Table S3).[15-28] Participants provided informed consent at 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 level from baseline to 6 (range, 2.5-14), 9 (2.5-14), and 12 (2.5-19) months, taking the value closest to the target month. For the primary analysis, we used change at 6 months to be consistent with the recent publication evaluating associations between treatment effects on changes in urine protein and those on the clinical end point.[14] Urine protein level was recorded in units of g/d and was log-transformed because of skewness of the data.

GFR Slope

GFR was estimated using the CKD Epidemiology Collaboration (CKD-EPI) 2009 creatinine equation.[29] Creatinine was standardized to isotope-dilution mass spectroscopy–traceable reference methods using direct comparison or was reduced by 5%.[10] As we have previously described, we used a simplified linear mixed-effects model based on a single slope starting at 3 months after randomization adjusted for baseline GFR, with the model accounting for various sources of variation in GFR slopes between and within participants and treatment arms.[10,30] The slope was estimated for all participants in each study. For studies with greater than 15 dialysis or death events, we used a shared parameter model to account for informative censoring due to dialysis or death.[16-18,22] Under this model, the differences between the randomized groups in the mean intercepts at 3 months' follow-up, the mean slopes after 3 months, and the estimated mean changes from baseline to 1, 2, or 3 years' follow-up factored by the follow-up duration represented the treatment effects on the acute, chronic, and total slopes, respectively. To recreate a more realistic trial scenario, in sensitivity analysis, we also present the results for the chronic slope computed over a 2-year period, which we defined as the last visit by 27 months (referred to as 2-year chronic slope).

Analyses

Objective

Our first goal was to evaluate the association of the treatment effects on the change in urine protein level with treatment effects on GFR slope. Our second goal was to use these results to describe the probabilities of treatment benefit on GFR slope associated with varying treatment effects on urine protein for application to future studies. Item S1 includes a more detailed description of the methods.

Trial-Level Analysis

The trial-level analysis requires 2 steps: intention-to-treat estimation of the treatment effects on both end points within each RCT, followed by a meta-regression to relate the treatment effects on the 2 end points of interest across RCTs.[2,5,10,31] In the first step, treatment effects on change in urine protein level were estimated by performing analyses of covariance within each study, with log urine protein level change as the end point, adjusting for treatment and log baseline urine protein level. Treatment effects on urine protein level were expressed as geometric mean ratios. Treatment effects on GFR slope were estimated using a shared parametric mixed-effects model as described earlier and were expressed as mean differences in the GFR slopes between the treatment and control groups, in units of mL/min/1.73 m^2 per year.

In the second step, a Bayesian mixed-effects meta-regression related the estimated treatment effects on one end point to the estimated treatment effects on the second end point with study as the unit of analysis (details in Item S1). The model relates the treatment effects on the 2 end points after accounting for random errors in the estimated effects in each RCT. The meta-regression

Table 1. Patient Characteristics by Study for Analysis of Change in Urine Protein Level at 6 Months

Study	Intervention	N	Age, y	Female Sex	eGFR	UP, g/d	Follow-Up, mo
Donadio 1999	Fish oil	91	38.8 ± 13.4	23 (25.3%)	65.8 ± 21.7	1.9 [1.2-3.4]	37.1 [26.4-44.9]
Donadio 2001	Fish oil	66	46.4 ± 13.4	10 (15.2%)	41.8 ± 14.1	1.6 [0.7-2.6]	28.2 [25.1-38.5]
Praga 2003	RASB	44	31.6 ± 11.5	17 (38.6%)	98.1 ± 26.5	1.7 [1.1-2.4]	76.0 [61.0-129.5]
HKVIN	RASB	107	40.1 ± 9.1	77 (72.0%)	75.6 ± 29.1	1.6 [1.1-2.6]	34.9 [34.8-35.1]
Maes	IS	34	44.8 ± 11.3	10 (29.4%)	62.2 ± 18.9	1.0 [0.6-2.7]	45.0 [33.0-45.0]
Appel	IS	20	37.6 ± 13.3	2 (10.0%)	47.4 ± 29.2	2.3 [1.6-3.0]	25.8 [15.1-28.8]
Pozzi 2004	Steroid	83	38.6 ± 11.7	25 (30.1%)	87.2 ± 21.6	1.9 [1.4-2.4]	102.0 [66.0-126.0]
Pozzi 2010	IS	190	39.3 ± 12.7	55 (28.9%)	74.0 ± 25.0	2.0 [1.5-2.7]	72.7 [52.6-90.3]
Pozzi 2013	IS	44	42.1 ± 11.6	8 (18.2%)	27.9 ± 7.1	2.5 [1.5-3.9]	50.3 [35.2-62.9]
Katafuchi	Steroid	74	36.2 ± 11.4	44 (59.5%)	98.5 ± 21.8	1.3 [0.9-2.6]	78.0 [60.0-90.0]
Schena	Steroid	95	33.7 ± 11.1	29 (30.5%)	91.3 ± 23.7	1.6 [1.3-2.5]	66.0 [42.0-78.0]
STOP-IgAN	IS	142	44.5 ± 12.3	32 (22.5%)	59.5 ± 27.3	1.6 [1.1-2.1]	37.6 [37.2-38.0]
Overall	—	990	39.7 ± 12.5	332 (33.5%)	71.9 ± 29.8	1.8 [1.2-2.6]	42.6 [34.9-78.0]

Values for categorical variables are given as number (percentage); values for continuous variables as mean ± standard deviation or median [interquartile range].
Abbreviations: eGFR, estimated glomerular filtration rate; IS, immunosuppression; RASB, renin angiotensin system blockade; UP, urine protein.

supports strong association between the 2 end points if: 1) the slope of the meta-regression line is statistically significant as defined by Bayesian credible intervals (BCIs) that do not cross 0, with a large magnitude; 2) the intercept is close to 0, implying absence of an average effect on the GFR slope when the treatment does not affect urine protein; 3) the R^2 is high, so treatment effects on urine protein level account for most of the variation in treatment effects on the GFR slope; and 4) the root mean square error is low, assuring low variation in the GFR slope given a fixed treatment effect on urine protein level. We also used separate random-effects meta-analyses to summarize the distributions of the treatment effects on each end point across the 12 RCTs.

Predicting Clinical Benefit in Future Trials

From the trial-level meta-regression, we computed 95% and 80% Bayesian credible prediction intervals and estimated the probabilities of treatment benefit on GFR slope (defined by a difference in slope >0) for an infinite-sized, modest-sized, or small RCT. Under the meta-regression model for an infinite-sized RCT, a treatment effect has a 95% or 80% probability of falling within the prediction interval, a 2.5% and 10% probability of exceeding the upper limit, and a 2.5% and 10% probability or falling below the lower limit, respectively. A modest-sized RCT was defined as having a sample size of 250 (SE, 0.09), and a small RCT was defined as having a sample size of 100 (SE, 0.15), assuming an SD of 0.75 for change in log urine protein level. We computed the threshold associated with the smallest observed treatment effect on a change in urine protein level that provides positive predictive values of 97.5%, 95%, and 90% for treatment benefit on the GFR slope.

Analyses were performed using SAS version 9.4M6 (SAS Institute) and R 4.0.1 (R Project for Statistical Computing).[32]

Results

Table 1 and Tables S4 and S5 summarize aggregate characteristics of the included studies. Of the 12 studies, 2 tested renin angiotensin system blockade,[15,16] 3 tested steroids,[23-27] 2 tested fish oil,[17,18] 2 tested mycophenolate mofetil,[19,20] and 2 others tested azathioprine.[21,22] STOP-IgAN contained 2 interventions, each at different levels of GFR. At higher GFR, the intervention was steroids, whereas at lower levels of GFR, the intervention was cyclophosphamide followed by azathioprine as well as steroids. Across the trials, the mean age of the study participants ranged from 32 to 46 years, and the proportion of women ranged from 10% (2 of 20) to 72% (77 of 107). Average baseline estimated GFR and urine protein level were 71 ± 30 (SD) mL/min/1.73 m^2 and 1.8 (IQR, 1.2-2.6) g/d, respectively, in the pooled dataset.

Over a period of 6 (IQR, 5.9-6.9) months, the overall mean percentage changes in urine protein in the control and treatment arms were −35% (IQR, −57% to 18%) and −53% (IQR, −68% to −9%), respectively, resulting in a treatment effect corresponding to a geometric mean ratio of 0.75 (95% CI, 0.61-0.94), which corresponds approximately to a 25% (95% CI, 6%-39%) relative reduction in urine protein level due to the treatment (Fig 1, left panel; Table S6). Similar results were seen with the 9- or 12-month change in urine protein level (Fig S3; Table S6).

For most studies, the mean total GFR slopes at 1, 2, and 3 years and chronic GFR slope were less steep (ie, less negative) in the treatment arm compared with the control arm (Figs S4 and S5; Tables S7 and S8). The pooled mean total slopes at 3 years were −3.51 (SE, 0.83) mL/min/1.73 m^2 per year in the control arm and −1.91 (SE, 0.54) mL/min/1.73 m^2 per year in the treatment arm. The mean treatment effect on the total slope at 3 years (1.39 [95% CI, −0.21 to 2.99] mL/min/1.73 m^2 per year) was stronger than the mean treatment effect on the chronic

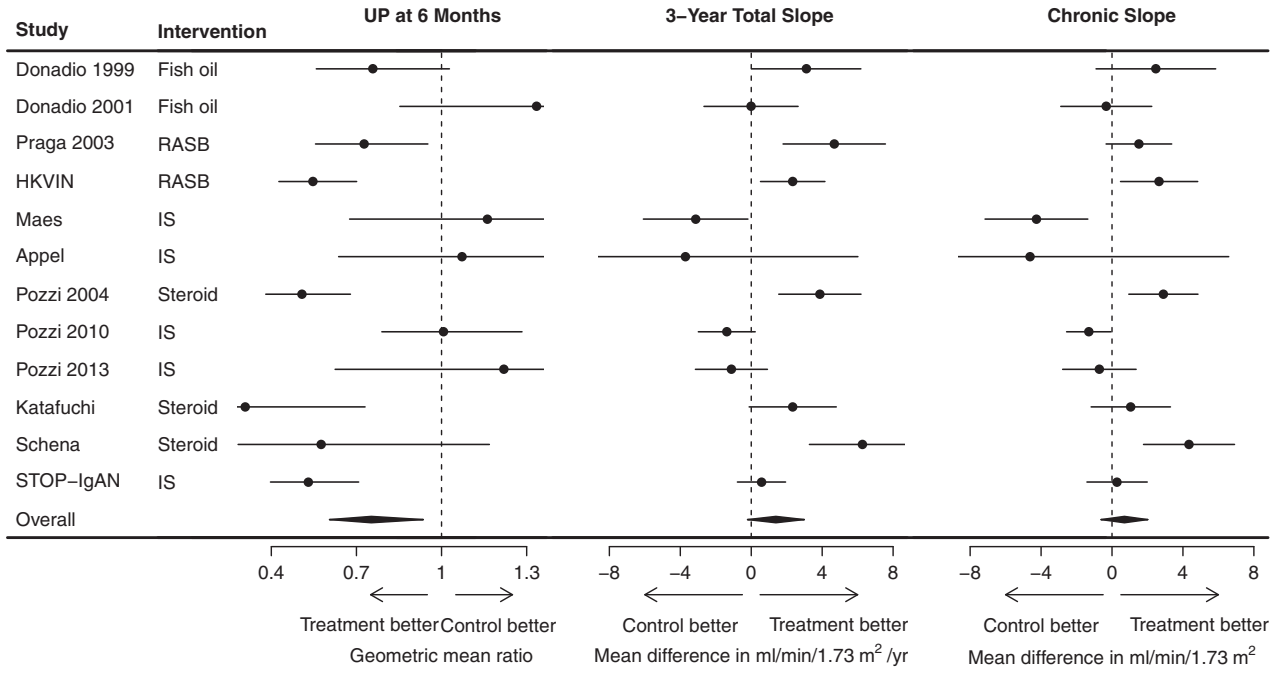

Figure 1. Treatment effect on change in urine protein level at 6 months, on 3-year total GFR slope, and on chronic slope. Treatment effects on urine protein level are expressed as geometric mean ratios and were estimated by performing analyses of covariance within each study. Treatment effects on slope are presented as the difference in GFR between treatment and control arms in mL/min/1.73 m² per year and were estimated using a shared-parameter mixed-effects model. The circles represent the estimated treatment effects and the horizontal lines the 95% CIs. Abbreviation: UP, urine protein (measured in g/d).

slope (0.70 [95% CI, −0.62 to 2.02] mL/min/1.73 m^2 per year), with variation by study (Fig 1).

There appeared to be strong agreement between the treatment effects on the change in urine protein level and the treatment effects on total slope at 3 years (Fig 2; Fig S6; Table S9). For change in urine protein level at 6 months, the slope of the meta-regression line was −7.18 (95% BCI, −13.03 to −1.80). A slope of −7.18 would imply that each additional 10% reduction in geometric mean urine protein level by the treatment is associated with an additional 0.72-mL/min/1.73 m^2 per year reduction in mean slope by the treatment. The intercept of the regression line was −0.93 (95% BCI, −3.06 to 1.27), indicating that there is no evidence that treatments with no effect on the change in urine protein level at 6 months have a nonzero average effect on the total slope at 3 years. The median posterior estimate for R^2 was 0.88 (95% BCI, 0.06-1.00; 80% BCI, 0.30-1.00). Results were similar for total slope at 2 years (R^2 of 0.86; 95% BCI, 0.03-1.0; 80% BCI, 0.24-1.0). Higher R^2 values were estimated for the chronic slope (R^2 of 0.98; 95% BCI, 0.29-1.00; 80% BCI, 0.68-1). For total slope at 1 year, there was a nonsignificant association between the 2 treatment effects (Fig S6; Table S9). Results were similar for chronic slope estimate over the entire study duration and over 2 years (Fig S7; Table S9). Results were similar for changes in urine protein levels at 9 and 12 months (Figs S6 and S7; Tables S9 and S10).

For future trials, an observed treatment effect of a 30% reduction in urine protein level at 6 months confers probabilities of approximately 90% for nonzero treatment benefit on total GFR slope at 3 and 2 years and on the chronic GFR slope (Table 2; Table S10). Predicted treatment effects on GFR slope are stronger at higher magnitudes of treatment effect on urine protein level (Fig 3; Table 2; Fig S8; Tables S10 and S11). For example, for future modest-sized trials, the model predicts that a treatment effect of change in urine protein level of 30% would predict a treatment effect on total GFR slope at 3 years of 1.62 (95% BCI, −1.59 to 4.91; 80% BCI, −0.06 to 3.48), whereas a treatment effect of 40% would predict a treatment effect of 2.73 (95% BCI, −0.63 to 6.15; 80% BCI, 0.94 to 4.79; Table 2; Table S10). Similar results were observed for changes in urine protein level at 9 and 12 months (Fig S8; Tables S10 and S11).

Discussion

Valid surrogate end points may improve the efficiency of clinical trials, particularly for clinical trials of CKD in which progression to clinical end points can be slow. For studies of IgAN, use of surrogate end points also allows for evaluation of interventions early in the disease course, before kidney scarring and irreversible changes, when interventions might have additional value. There is a sound

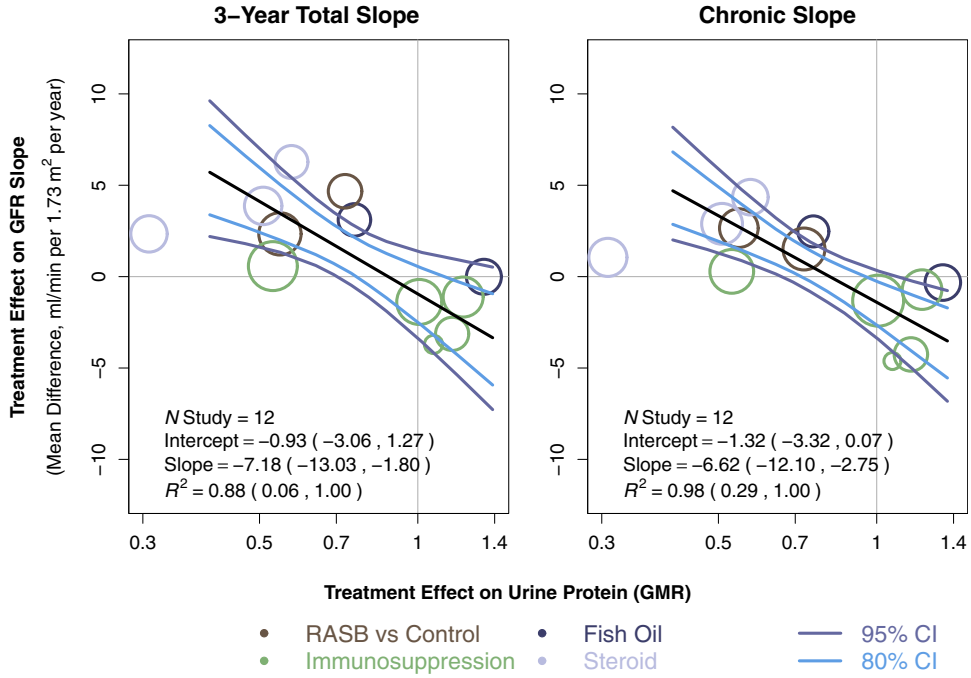

Figure 2. Trial-level associations between treatment effects on change in urine protein level and treatment effects on total GFR slope at 3 years and chronic slope for urine protein level at 6 months. Shown is the relationship between estimated treatment effects on the 3-year GFR slope on the vertical axis and estimated treatment effects on the change in urine protein level on the horizontal axis. Treatment effects on GFR slope are expressed as the mean difference in treatment and control arms and expressed in mL/min/1.73 m^2 per year. Treatment effects on urine protein are expressed as geometric mean ratios. Each circle is a separate intervention, with the size of the circle proportional to the number of events. The colors of the circles indicate intervention type. The black line is the line of regression through the studies. The dark blue lines represent the 95% confidence band, and the light blue lines represent the 80% confidence band computed from the model. Abbreviations: GMR, geometric mean ratio; RASB, renin angiotensin system blocker.

biological and empirical basis for the hypothesis that an early change in urine protein level is a valid surrogate end point for progression of IgAN. First, pathologic data show that the degree of urine protein correlates with greater evidence of disease.[33-35] Second, baseline levels of urine protein are prognostic for long-term disease progression,[36-43] and attenuation of urine protein levels after steroid therapy is associated with improved prognosis.[44,45] Third, we have previously provided trial-level analyses that demonstrate that early changes in urine protein level are a moderately strong surrogate relative to the clinical end point across a broad collection of kidney diseases, including IgAN.[5,14] A recent paper by the Kidney Health Initiative supports "the use of proteinuria reduction as a reasonably likely surrogate endpoint in future trials studying IgAN … when accompanied by verification of the clinical benefits in a postmarketing confirmatory trial."[8] Drug-development programs for treatments in IgAN using change in GFR are under way.[46-48] The present article provides evidence that is useful for the design of such studies in IgAN.

Using the trial-level approach, we found that, across 12 studies of multiple interventions, there is a positive relationship between the treatment effects on urine protein and on GFR slope. The BCIs did not cross 0. This suggests that observed treatment effects on the early changes in urine protein can inform investigators and sponsors of the longer-term treatment effects on GFR slope. The BCIs for the key parameters of our trial-level meta-regression analysis are wide. This uncertainty leads to uncertainty in the Bayesian credible prediction intervals for the treatment effects on slope that can be expected for different observed treatment effects on urine protein in future trials. For example, our model would predict that, even with a treatment effect of 0.8 (20% reduction) on the change in urine protein, the predicted treatment effect on GFR slope would have CIs that cross 0. These limitations in precision lead to the requirement for large thresholds for the treatment effects on the change in urine protein to demonstrate a high probability of benefit on GFR slope. The imprecision is the result of the limited number of studies, all with small samples sizes, rather than an inherent limitation of urine protein level as an end point in IgAN. Future analyses relating treatment effects on change in urine protein to treatment effects on GFR slope in the overall set of CKD studies are expected to achieve higher levels of precision.

Table 2. Application of Change in Urine Protein to Predict GFR Slope in New RCTs: Predicted Treatment Effect on Clinical End Point and Positive Predictive Values for 6-Month Sample

GFR Slope	Observed Treatment Effect on Change in UP	Infinite-Sized RCT		Modest-Sized RCT (N = 250)		Small-Sized RCT (N = 100)	
		MTE on GFR Slope[a]	PPV	MTE on GFR Slope[a]	PPV	MTE on GFR Slope[a]	PPV
Total slope over 3 years	0.5	4.10 (0.34 to 7.46)	0.98	4.07 (0.24 to 8.01)	0.98	4.01 (0.05 to 8.53)	0.98
	0.6	2.77 (−0.49 to 5.73)	0.96	2.73 (−0.63 to 6.15)	0.96	2.70 (−0.86 to 6.69)	0.94
	0.7	1.61 (−1.26 to 4.61)	0.92	1.62 (−1.59 to 4.91)	0.89	1.62 (−1.96 to 5.35)	0.85
	0.8	0.61 (−2.13 to 3.77)	0.75	0.66 (−2.51 to 4.00)	0.70	0.68 (−2.98 to 4.30)	0.67
	Threshold for treatment effect on UP to assure:						
	PPV ≥ 95%	0.64		0.62		0.58	
	PPV ≥ 90%	0.72		0.69		0.66	
Chronic slope	0.5	3.27 (1.08 to 5.83)	0.99	3.25 (0.91 to 6.36)	0.99	3.19 (0.56 to 6.96)	0.99
	0.6	2.06 (0.26 to 3.92)	0.98	2.04 (−0.01 to 4.56)	0.97	1.99 (−0.47 to 5.18)	0.95
	0.7	1.03 (−0.56 to 2.60)	0.94	1.03 (−1.03 to 3.16)	0.88	1.02 (−1.57 to 3.82)	0.81
	0.8	0.13 (−1.46 to 1.74)	0.58	0.16 (−2.05 to 2.18)	0.57	0.17 (−2.62 to 2.73)	0.56
	Threshold for treatment effect on UP to assure:						
	PPV ≥95%	0.69		0.64		0.60	
	PPV ≥90%	0.73		0.68		0.65	

Treatment effect on change in UP is expressed as geometric mean ratio. This can be converted to percent reduction in UP by (1 – GMR) × 100. Treatment effect on GFR slope is expressed as mean difference between treatment arms. Prediction intervals are Bayesian credible intervals. PPV is defined as the probability that the treatment reduces the magnitude of the mean GFR slope by any amount greater than 0. The thresholds for the treatment effect on UP is the change in UP required to assure PPV for a GFR slope >0 of greater or equal to 95% (90%). A modest-sized RCT was defined as having a sample size of 250 (SE, 0.09), and a small RCT was defined as having a sample size of 100 (SE, 0.15), assuming SD of 0.75 for change in log UP level. Table S10 includes the 80% Bayesian credible intervals for the predicted treatment effect on the GFR slope along with the 95% credible intervals shown here. Table S11 includes the threshold for treatment effect on UP to assure PPV ≥97.5%, along with 95% and 90% shown here. Abbreviations: GFR, glomerular filtration rate; GMR, geometric mean ratio; MTE, median treatment effect; PPV, positive predictive value; RCT, randomized clinical trial; UP, urine protein.

[a]Values in parentheses are 95% prediction intervals.

Previously, we demonstrated that treatment effects on GFR slope have very strong associations with treatment effects on the clinical end point in 49 studies evaluating treatments for CKD progression, providing evidence for its validation.[10,11] These associations are substantially stronger than that observed between treatment effects on change in albuminuria and the clinical end point in CKD,[14] consistent with the biological nature of GFR decrease as an intermediate end point along the path to kidney failure. The US Food and Drug Administration has stated that they have "accepted GFR slope as an endpoint and basis for full approval of therapies for rare chronic kidney diseases," and the EMA stated that GFR slope "offers promising potential for a surrogate endpoint in the confirmatory phase of a specific clinical program."[13] This supplements the Food and Drug Administration's prior acceptance of confirmed 40% and 30% decrease in GFR as a basis for drug approval of therapies intended to treat common and rare CKDs, respectively.[12] Thus, the results presented here, together with our prior work evaluating treatment effects on urine protein and on GFR slope to clinical end points, suggest at least 2 potential uses for urine protein level as a surrogate end point in IgAN studies.[10] First, treatment effects on early change in urine protein can be used in early-phase studies for proof of concept or dose-finding, both of which may accommodate some degree of uncertainty. Second, change in urine protein level can be used for initial regulatory approval followed by a confirmatory trial that uses mean difference in GFR slope as the end point. This can be performed as 2 separate trials or as part of an adaptive clinical trial design. In such a design, the treatment effect on early change in proteinuria at an interim analysis can be used to estimate conditional power for treatment effects on GFR slope as an intermediate end point for the clinical end point. In this setting, treatment effects on change in urine protein and on GFR slope could also be used in combination to jointly predict treatment effect on the clinical end point should the patients be followed sufficiently. The ultimate decision as to how urine protein is integrated into a trial design or drug-development program rests with the sponsor and regulatory body and would be influenced by multiple factors, including but not limited to the intervention and population being studied. These data support these discussions.

Treatment effects on urine protein appeared to be more strongly associated with treatment effects on the chronic GFR slope than on the total slope. In general, variation between effects on the total and chronic GFR slopes likely reflects the presence of acute or immediate effects that differ from the longer-term effects. It is possible that a stronger

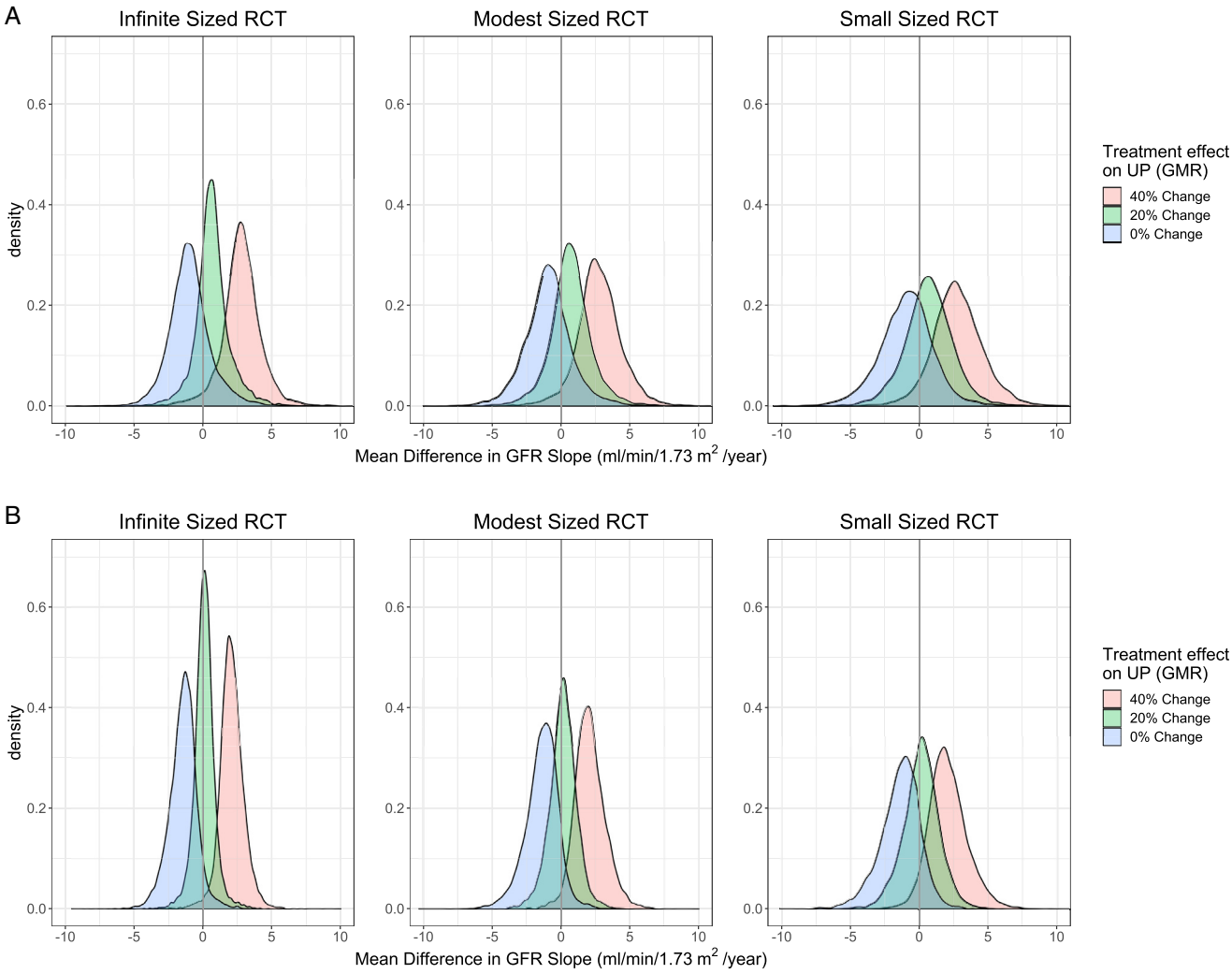

Figure 3. Posterior predictive probabilities of true treatment effect on (A) GFR slope at 3 years and (B) chronic slope given true treatment effect on change in urine protein level.

trial-level association would also be observed between treatment effects on urine protein and on the total slope in trials investigating treatments without an acute effect. We have previously shown that use of chronic GFR slope is one method to reduce the impact of the acute effect, and these results are consistent with that observation.[10,11] For future trials, the decision about the use of total versus chronic slope as the primary end point would rely on multiple considerations such as the drug's mechanism of action, knowledge about acute effects, and prior knowledge about the drug in similar or other populations. There has been reluctance to use the chronic slope as a sole primary end point because the chronic slope is computed from a postbaseline time point, after the GFR has already been modified by the treatment. In certain scenarios, this incurs a risk of bias due to attenuation of the acute effect or early discontinuation of the study medication.[49] Future work should guide us on how to minimize bias with end points that are designed to estimate and minimize the impact of the acute effect similarly to the chronic slope. Possibilities include employing off-treatment GFR measurements and application of different prerandomization baseline measurements for the treatment and control arms following introduction of the treatment in a run-in phase, as seen in the recent studies evaluating tolvaptan in polycystic kidney disease.[50] For some treatments, it may be appropriate to evaluate both slope end points as part of the totality of evidence in a drug-development program.

Strengths of the present analysis include a systematic literature search to include all available published English-language studies, uniform definitions of exposures and outcomes across studies, and a robust trial-level analysis. There are also limitations. First, because of the rarity of the disease, the analysis is underpowered to estimate the associations given the small number of studies, all of which had a small sample size. Second, our designation of the treatment arm in each trial as the group hypothesized to have the greater benefit was somewhat arbitrary. Because, in the studies that compared azathioprine and steroids versus steroids alone, the azathioprine/steroid group was

considered the active treatment group, and steroids are considered effective, this could have biased the results.[21,22] Third, we included only studies written in English that had sufficient data for our analyses and for which the investigators were able to share data. Fourth, the evaluation of urine protein level as a surrogate end point was limited to changes between approximately 6 and 12 months, and our findings may not extend to changes in urine protein level over longer (or shorter) time periods. However, our intention was to evaluate early changes in urine protein levels because, if trials are longer, GFR slope generally becomes more informative. Because the end point is defined by the change in urine protein level, all participants must have survived to have the second measurement. Finally, IgAN is heterogeneous and is treated with heterogeneous treatments, and these results apply to populations selected for inclusion and treatments evaluated in the present analysis.

Overall, the evidence presented here, when considered in conjunction with prior studies, supports the use of urine protein level as an initial surrogate end point followed by GFR slope for subsequent confirmatory studies and accumulation of safety data, or as parts of early-phase studies. This presents a pathway for drug development that could facilitate studies of new treatments for IgAN.

Supplementary Material

Supplementary File (PDF)

Figure S1: Flow chart of study identification process.

Figure S2: Assessment of bias in each study.

Figure S3: Treatment effect on change in urine protein at 6, 9, and 12 months.

Figure S4: Treatment effect on total slope at 1, 2, or 3 years.

Figure S5: Treatment effect on chronic slope computed overall and at 2 years.

Figure S6: Trial-level association of urine protein with total GFR slope at 1, 2, and 3 years.

Figure S7: Trial-level association of urine protein with overall chronic slope and 2-year chronic slope.

Figure S8: Posterior predictive probabilities for true treatment effects on total GFR slope at 1 and 2 years and 2-year chronic slope.

Item S1: Protocol.

Item S2: Study funding sources.

Item S3: Abbreviations, units, and terms.

Table S1: Search terms for systematic review.

Table S2: Inclusion criteria for studies in systematic review.

Table S3: Study characteristics and inclusion criteria.

Table S4: Patient characteristics, by study, for analysis of change in urine protein.

Table S5: Follow-up time, mean number of GFR assessments, and average maximum estimated GFR visit time.

Table S6: Change in urine protein by treatment arm and treatment effect, at 6, 9, and 12 months.

Table S7: Total GFR slope by treatment arm and treatment effect at 1, 2, and 3 years.

Table S8: Chronic GFR slope by treatment arm and treatment effect.

Table S9: Trial-level associations between treatment effect on change in urine protein and treatment effect on GFR slope.

Table S10: Predicted GFR slope for future trials.

Table S11: Threshold for treatment effect on urine protein change to assure positive predictive values above range of target.

Article Information

Authors' Full Names and Academic Degrees: Lesley A. Inker, MD, MS, Hiddo J.L. Heerspink, PharmD, Hocine Tighiouart, MS, Juhi Chaudhari, MPH, Shiyuan Miao, MS, Ulysses Diva, PhD, Alex Mercer, PhD, Gerald B. Appel, MD, James V. Donadio, MD, Jürgen Floege, MD, Philip K.T. Li, MD, Bart D. Maes, MD, PhD, Francesco Locatelli, MD, Manuel Praga, MD, PhD, Francesco P. Schena, MD, Andrew S. Levey, MD, and Tom Greene, PhD.

Authors' Affiliations: Division of Nephrology, Tufts Medical Center, Boston, MA (LAI, JC, SM, ASL), Institute for Clinical Research and Health Policy Studies (HT), Tufts Medical Center, Boston, MA; Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands (HJLH); Tufts Clinical and Translational Science Institute, Tufts University, Boston, MA (HT); Biometrics, Travere Therapeutics Inc, San Diego, CA (UD); Clinical Drug Development, JAMCO Pharma Consulting AB, Stockholm, Sweden (AM); Division of Nephrology, Columbia University Medical Center and the New York Presbyterian Hospital, New York, NY (GBA); Emeritus Staff, Mayo Clinic, Rochester, MN (JVD); Division of Nephrology and Immunology, RWTH Aachen University, Aachen, Germany (JF); Division of Nephrology, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong (PKTL); Department of Nephrology, AZ Delta, Roeselare, Belgium (BDM); Department of Nephrology and Dialysis, Alessandro Manzoni Hospital, Lecco (FL); Renal, Dialysis and Transplant Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari (FPS), Italy; Instituto de Investigación Hospital Universitario 12 de Octubre, i+12, Complutense University, Madrid, Spain (MP); and Departments of Population Health Sciences and Internal Medicine, University of Utah, Salt Lake City, UT (TG).

Address for Correspondence: Lesley A. Inker, MD, MS, Division of Nephrology, Tufts Medical Center, Boston, MA 02111. Email: linker@tuftsmedicalcenter.org

Authors' Contributions: Research idea and study design: LAI, TG, HJLH, ASL, AM, UD; data acquisition: LAI, GBA, JVD, JF, PKTL, BDM, FL, MP, FPS, ASL; data analysis/interpretation: LAI, HT, TG, HJLH, UD, AM, JC, SM; statistical analysis: LAI, HT, TG. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Treatment Effects on Early Change in Urine Protein and Treatment Effects on GFR slope in IgAN: An Individual Participant Meta-analysis

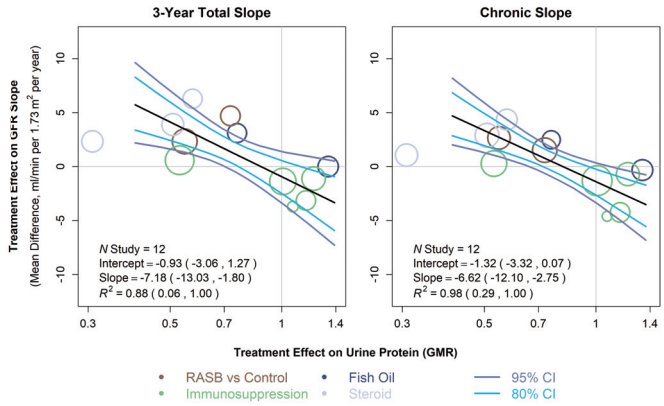
Study design

Treatment effects on GFR slope – – Difference in GFR slope in randomized groups

vs

Treatment effects on change in urine protein – – Difference in change in urine protein in randomized groups

Results



CONCLUSION: The results present a pathway for drug development that could facilitate studies for new treatments for IgAN.

Lesley A. Inker, Hiddo Lambers-Heerspink, Hocine Tighiouart, et al (2021)
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