Early change in proteinuria as a surrogate endpoint in studies of IgA nephropathy: An updated patient-level meta-analysis and discussion of appropriate methodology

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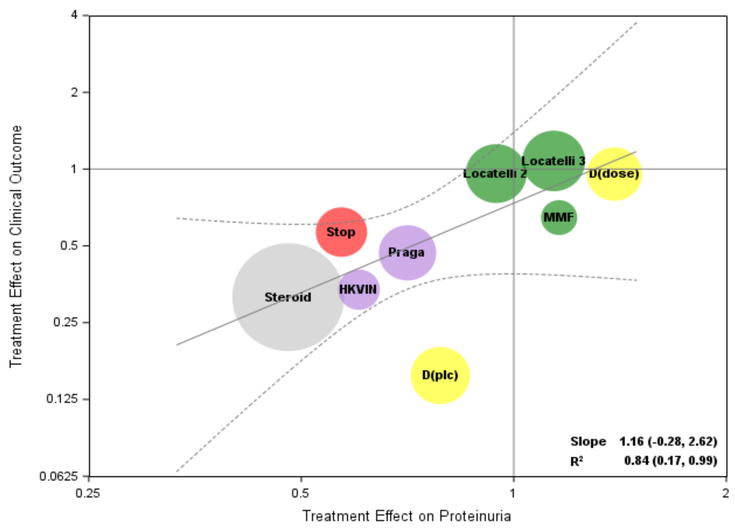
Introduction

- Immunoglobulin A nephropathy (IgAN) is the most common primary cause of glomerulonephritis worldwide, with an incidence of 2.5 cases per 100,000 people per year.[1]
- Due to the progression of IgAN to kidney failure generally taking many years and the rarity of the condition, it is not practical to conduct large-scale phase 3 randomized controlled trials (RCTs) to evaluate whether a new therapy improves kidney survival outcomes.
- Therefore, surrogate endpoints are necessary when assessing novel treatment options in RCTs to allow new, effective treatments to be identified in a timely manner such that they can be provided to patients with a significant unmet clinical need.
- On the basis of published meta-analyses of RCTs in IgAN, showing the association between treatment effects on 9-month change in proteinuria and treatment effects on the composite clinical outcome of doubling of serum creatinine, kidney failure or death (Inker *et al*. 2016; Thompson *et al*. 2019, Figure 1), the FDA and EMA have approved a number of treatments based on analysis of 9-month change in proteinuria.[2,3]
- The present research aimed to update the earlier meta-analyses with additional patient-level data in order to further assess the validity of early change in proteinuria as a surrogate endpoint in IgAN trials and to provide guidance on how these results should be interpreted.

Figure 1: Association between early change in proteinuria and the composite clinical endpoint: As presented by Thompson *et al*. 2019



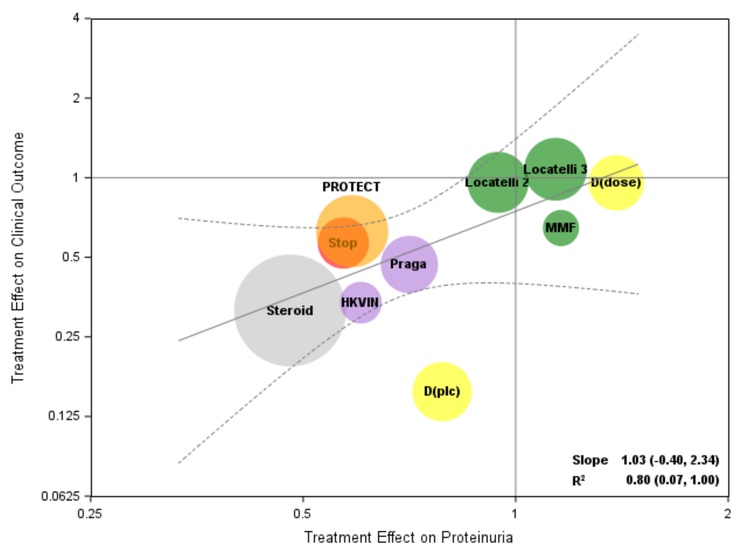
Methods

- The updated meta-analysis was conducted in line with the previously published meta-analyses, with the addition of patient-level data taken from the PROTECT Double-Blind RCT.[2,3,4,5]
- Early change in proteinuria was defined as change from baseline at a median of 9 months (ranging from 5 to 12 months) and the composite clinical endpoint was defined as the composite of doubling of serum creatinine level, kidney failure (eGFR <15 mL/min/1.73 m^2 or kidney replacement therapy) or death.
- The association of treatment effects was ascertained using individual patient data from all studies via a Bayesian mixed-effect regression model as developed and employed in both the previous 2016 and 2019 meta-analyses, to relate treatment effects on the composite clinical endpoint to treatment effects on early change in proteinuria with study as the unit of analysis.[6]

Results

- The updated meta-analysis including data from PROTECT DB (Figure 2) resulted in an overall slope of 1.03 (95% Bayesian credible interval [CI] −0.40 to 2.34) with an R^2 of 0.80 (95% Bayesian CI 0.07 to 1.00).

Figure 2: Association between change in early proteinuria and the composite clinical endpoint: Updated analysis



- This result is slightly attenuated relative to that attained by Thompson *et al*. 2019, but nonetheless continues to support treatment effects on early change in proteinuria as a reliable surrogate for treatments effects on clinical outcomes in RCTs in IgAN (Table 1).
- Across Inker *et al.*, Thompson *et al*. and the updated analysis, R^2 values ranged from 0.80 to 0.91, showing a strong association of treatment effects on early change in proteinuria and treatment effects on clinical outcomes.

Table 1: Summary of the findings of the three individual patient-level meta-analyses

Individual patient-level meta-analysis	Slope (95% Bayesian credible interval)	R^2 (95% Bayesian credible interval)
Inker *et al*. 2016 [2]	2.15 (0.10 to 4.32)	0.91 (0.47 to 1.00)
Thompson *et al*. 2019 [3]	1.16 (−0.28 to 2.62)	0.84 (0.17 to 0.99)
Present analysis	1.03 (−0.40 to 2.34)	0.80 (0.07 to 1.00)

Table 2: Treatment effect on proteinuria versus treatment effect on the clinical outcome

Proteinuria treatment effect	Clinical outcome treatment effect	Clinical outcome 95% credible interval
−50%	−63.3%	−79.2% to −35.2%
−45%	−59.6%	−74.8% to −35.1%
−40%	−55.8%	−70.5% to −33.7%
−35%	−52.0%	−66.7% to −30.8%
−30%	−48.2%	−63.8% to −25.9%
−25%	−44.2%	−61.9% to −19.0%
−20%	−40.6%	−60.7% to −10.2%
−15%	−36.8%	−60.2% to 0.3%
−10%	−33.0%	−60.0% to 12.3%

Interpretation of results

- Care needs to be taken not to fall into simplistic interpretation based solely on p-values as, by its very nature, any given meta-analysis is not powered in any conventional sense and thus p >0.05 does not mean there is no association and, equally, p <0.05 does not mean there is some association of clinical relevance.
- The correct interpretation of the meta-analysis, in line with FDA input, is shown in Table 2, where the estimated treatment effect for the clinical outcome with its 95% CI are provided for a given treatment effect on proteinuria (relative reduction between treatments based on changes from baseline).
- A treatment effect on proteinuria of at least −15.1% is required to result in an estimated treatment effect on the clinical outcome with an upper 95% CI below 0%.
- Thus, the smallest effect required on proteinuria to have a high probability of conversion to a treatment effect on the clinical outcome is approximately −15.1%.
- Of more interest and reassurance might be a proteinuria treatment effect of at least −30%, as this results in an estimated treatment effect on clinical outcomes with upper 95% CI of −25.9%.
- Therefore, a −30% treatment effect on proteinuria will provide at least a 25.9% reduction in the risk of the clinical outcome with 97.5% probability.

Discussion

- This updated individual patient-level meta-analysis, including data from the PROTECT DB RCT, confirms the findings of previous analyses by Inker *et al.* and Thompson *et al*. corroborating the use of early change in proteinuria as a valid surrogate endpoint for treatment effects on long-term renal outcomes in IgAN studies.
- Interventions that reduce proteinuria in a short-term trial are likely to improve kidney outcomes over the long term.
- It is crucial that analyses such as this are conducted using patient-level data as when only aggregate data are used the vital within-study correlation of errors is unknown and has to be assumed and, as such, equivalent analyses conducted using aggregate data should be interpreted with caution.[7]
- It was possible to include PROTECT DB in the updated analysis as the authors had access to the patient-level data, but additional trials in IgAN have been conducted and the authors would welcome collaboration with the other study groups to incorporate additional patient-level data.

References

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