SUPPLEMENTAL TOC

Methods for updated metaanalysis of the effect of treatment on proteinuria reduction and preservation of GFR from randomized controlled trials in IgAN

The trial level analysis methodology has been previously described (Inker 2016) and the same approach was used when updating the analysis to include results from the Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) and Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN) trials. A trial level meta-analysis for the assessment of potential surrogacy requires two steps: first, the estimation of the treatment effects within each study and, second, a Bayesian meta-regression of treatment effects across studies, with study as the unit of analysis.

For the first step of estimation of the treatment effects within each study, for trials included in the original publication, we had access to the first individual patient level data. We applied linear and Cox regression analyses in each study to estimate the treatment effects (and associated standard errors) on the 9 month change in proteinuria (expressed as the log transformed ratio of follow-up vs. baseline geometric mean proteinuria (GMR) between treatment groups) and on the clinical endpoint (expressed as log transformed hazard ratios). We obtained estimates of the correlation between the treatment effects on the clinical and surrogate outcome within each study by performing bootstrap resampling with 2000 repetitions for each study. . In order to assure convergence of the Cox models for each bootstrap sample, we pooled studies of the same intervention that had fewer than 10 clinical events. In sensitivity analyses, we evaluated the impact on the final results by setting a fixed correlation of 0.25 if the trial/grouping had less than ten events or if the bootstrapped correlation was less than 0.25; and similar conclusions were reached. For the two additional trials added to the current analysis, TESTING and STOP-IgAN, we did not have access to the individual patient data. The authors provided estimated treatment effects on the 9 month change in proteinuria and clinical endpoint. Given the results from our sensitivity analyses we had performed for the original publication, we set the correlation in both trials to be 0.25.

For the second step, TESTING and STOP-IgAN were then added to the dataset used in the original 2016 analysis. We then performed the Bayesian mixed effect regression model using the original X studies together with the two new ones. The Bayesian analysis describes the association of the treatment effects on the change in proteinuria to the treatment effects on the clinical endpoint and provides a slope and 95% credible interval. A slope greater than zero would indicate that treatment effects on early change in proteinuria are associated with treatment effects on the clinical endpoint and support the surrogacy hypothesis.