IgA Nephropathy: A Disease in Search of a Large-Scale Clinical Trial to Reliably Inform Practice

Related Article, p. 26

Due to its frequency, IgA nephropathy has attracted significant scientific interest. Research has mainly covered the natural history of disease, predictive factors, and pathogenesis.[1-5] Although IgA nephropathy was first identified as the pathological correlate of "benign recurrent hematuria," it is now recognized that it is not benign, with about 15% to 40% of patients developing kidney failure within 20 years of kidney biopsy.[1,6]

Identification of effective treatments for IgA nephropathy has posed challenges for the renal community, and randomized trials like the one described by Lv et al[7] in this issue of the *American Journal of Kidney Diseases* are welcome additions to a sparse evidence base.[8-10]

Lv et al provide the results of a trial of the combined effects of the glucocorticosteroid prednisone and the angiotensin-converting enzyme (ACE) inhibitor cilazapril versus an ACE inhibitor alone in patients with IgA nephropathy. A total of 63 patients (33 to combination therapy and 30 to ACE inhibitor alone) were randomized in the study. Key results were that the risk of a 50% increase of serum creatinine (what they referred to as kidney "death") was significantly lower with combination therapy than with ACE inhibition alone (1 out of 33 events in the combination group versus 7 out of 30 in the ACE inhibitor alone group; relative risk [RR], 0.13; 95% confidence interval [CI], 0.02 to 0.99). At 24 months from trial initiation, kidney survival was 96.6% in the combination therapy group versus 75.7% in the ACE inhibition alone group. Those in the combination therapy group also had a more rapid and stable reduction in proteinuria than those in the ACE inhibition alone group.[7] The authors suggested that the addition of glucocorticosteroids to ACE inhibitors provided additional benefit compared to ACE inhibition alone, although they pointed out that their study was a pilot only and a much larger study needs to be conducted.

Strengths of the trial include random allocation of patients and the reporting of results in the public domain. In this way, more information is provided to guide practice than routine clinical care, which would involve nonrandom and variable administration of corticosteroids to people with IgA nephropathy and no systematic collection and reporting of outcome data. The trial, however, has a number of limitations related to design and reporting that are common to many trials in kidney disease, which adds substantial uncertainty to what appear to be very favorable results.[11]

Of particular concern is the small sample size. Calculations about how many patients are needed for a randomized trial to be able to detect a difference across 2 interventions, if it exists, are based on precise criteria, which must be respected to be sure that the findings reflect an underlying truth. Lv et al planned to randomize 134 patients with biopsy-proven IgA nephropathy to combination therapy versus ACE inhibition alone, which, they report, would give the trial 80% power to detect a 20% reduction in the primary outcome of kidney death over a follow up of 5 years. The basis of many of the key assumptions underlying their sample size estimation is unclear. The authors report that they used control and event rates from previous trials of corticosteroids in IgA nephropathy but refer to the GISEN (Gruppo Italiano di Studi Epidemiologici in Nefrologia) and the REIN (Ramipril Efficacy in Nephropathy) studies of ramipril versus placebo in patients with chronic nephropathies.[12,13] Even using the incidence of doubling of creatinine (about 13%) provided in GISEN (while only incidence of end-stage renal disease of about 15% was provided in REIN), we estimate a trial of around 400 patients would be needed. If one uses control event rate data from existing systematic reviews of immunosuppressive interventions in patients with IgA nephropa-

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0272-6386/08/5301-0002$36.00/0
doi:10.1053/j.ajkd.2008.10.035

thy, assuming a 30% event rate in the untreated arm and about a 15% to 20% risk reduction in the treatment arm, one would need at least 600 patients (300 in each arm) to prove their hypothesis.[8] This makes the early termination of the trial even more surprising, especially when the stopping rules were not given, and it would be unlikely that the nephrology community would regard the results of this trial sufficiently convincing to change policy and practice. A detailed discussion of the perils of early termination of randomized trials is beyond the scope of this paper but has been provided elsewhere.[14]

There are also other aspects of this trial which make the validity of the results uncertain, including unclear allocation concealment; no blinding of participants, investigators, and outcome assessors; no measurement of compliance; no details about regulatory or ethics clearance; and no information about the existence and procedures of the data and safety monitoring committee.

Given the data on efficacy of combination therapy in IgA nephropathy are not definitive, it may be informative to quantify what, if any, new information this study provides. Figures 1 and 2 show the incremental information gained from this study compared with previous studies for the outcomes of doubling of serum creatinine (Fig 1) and values for proteinuria at study end (Fig 2). Previous studies had shown that glucocorticosteroids, compared to control treatments (placebo/no treatment/other) significantly reduced the risk of doubling of creatinine (6 trials, 341 patients; RR, 0.45 [95% CI, 0.29 to 0.69]). Addition of the data of Lv et al, which contributes 7.1% of the weight in the meta-analysis, did not change the findings significantly (7 trials, 431 patients; RR, 0.48 [95% CI, 0.32 to 0.72]; Fig 1). Although this summary treatment effect is highly statistically significant, the validity of this result remains very uncertain given the substantial methodological problems outlined above, which are common to all trials, resulting in implausibly large treatment effects.

Similarly, previous studies also found that glucocorticosteroids compared with control interventions are associated with a significantly lower proteinuria (g/24 h) at study end (5 trials, 244 patients; weighted mean difference, −0.58 [95% CI, −0.95 to −0.21]); addition of the study of Lv et al, which contributes 51.6% of the weight in the meta-analysis, does not significantly change the existing summary estimate of effect appreciably (6 trials, 307 patients; weighted mean difference, −0.56 [95% CI, −0.81 to 0.30]) and the uncertainty remains (Fig 2). In short, given the sample size of the trial, one could predict with

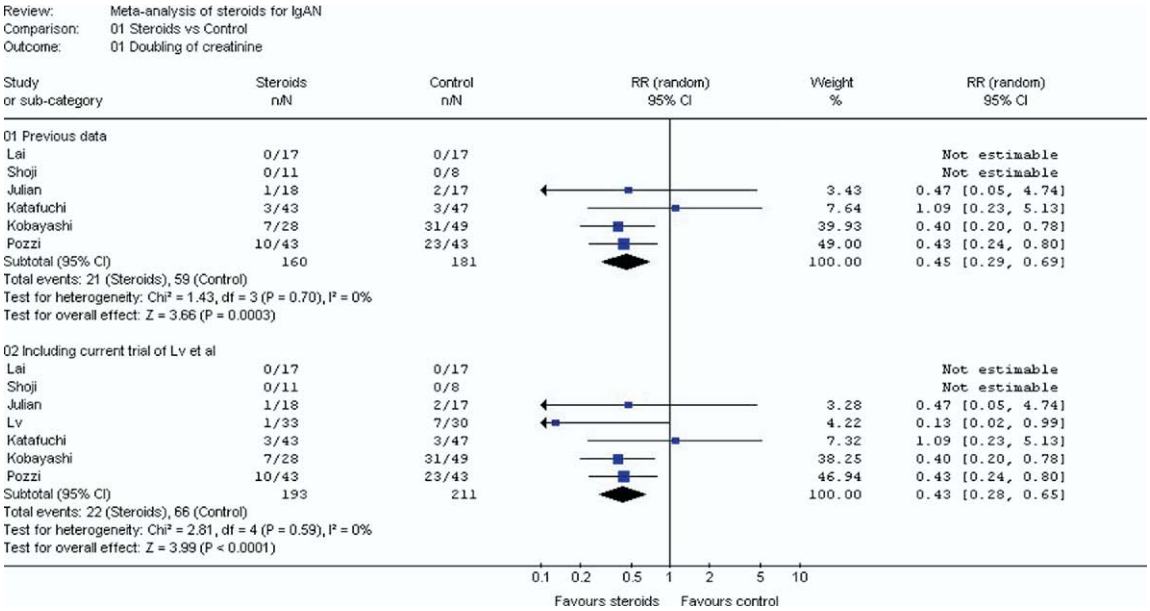

Figure 1. Effect of corticosteroids versus comparator treatments on doubling of creatinine in patients with IgA nephropathy.

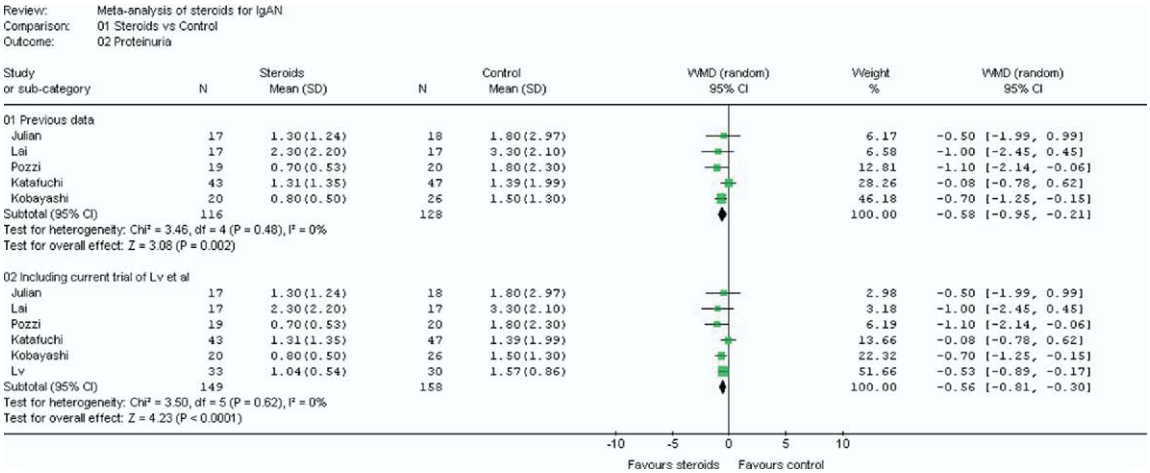

Figure 2. Effect of corticosteroids versus comparator treatments on proteinuria in patients with IgA nephropathy.

reasonable certainty that it would not make any appreciable difference to the known treatment effects of steroids for IgA nephropathy.

Proteinuria does deserve an additional comment. This outcome, used as a secondary endpoint in the trial and widely used as a valid proxy (surrogate) of more important hard clinical end points (such as kidney failure or doubling of serum creatinine) in nephrology, has recently come under question, and similarly has occurred for other.[15] Proteinuria was found to be an invalid surrogate of hard clinical end points in ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global End-point Trial) where combined inhibition of the renin-angiotensin system did reduce albuminuria and proteinuria more strongly than ACE inhibitor or angiotensin receptor blocker monotherapy, but the risk of doubling of creatinine or acute or chronic kidney failure was higher with combination therapy.[16]

This trial demonstrates again the importance of properly powered, designed, and reported clinical trials of existing immunosuppressive treatment options for IgA nephropathy. The pattern of small trials in nephrology must be reversed for the sake of our patient population. Examples exist of large multicenter collaborations to achieve the necessary sample size to test the efficacy of interventions for rare diseases.[17] This should be pursued also for IgA nephropathy and the other leading causes of kidney failure, or the epidemic will continue unabated.

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ACKNOWLEDGEMENTS

We acknowledge the contribution of Sharon Reid, School of Public Health, University of Sydney, who provided data on interventions for IgA nephropathy from an ongoing Cochrane systematic review.

Financial Disclosure: Dr Tognoni receives research support from Bayer, AstraZeneca, and Sigma Tau.

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