Is Proteinuria Reduction by Angiotensin-Converting Enzyme Inhibition Enough to Prove Its Role in Renal Protection in IgA Nephropathy?

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IgA nephropathy (IgAN) is the most common biopsy-proven type of glomerulonephritis globally, including children (1). In the United States alone, it is estimated that as many as 30% of children with IgAN are likely to progress to ESRD (2). Most pediatric studies that deal with treatment, prognostic markers, and outcome indicators that are used in clinical trials in IgAN must rely on surrogate measures, such as changes in proteinuria, serum creatinine, or creatinine clearance, rather than renal survival because the disease has such a slow progression rate (3–6). The problem of establishing outcome targets within a reasonable trial time frame, especially ones that are valued by the clinician and not just of statistical importance, is illustrated in the study by Coppo *et al.* (7) in this issue. This randomized, controlled trial (RCT), conducted in 23 centers in five European countries over 6 yr, was designed to test the renal protective effect of the angiotensin-converting enzyme inhibitor (ACE-I) benazepril in 57 children and young adults with this disease. Coppo *et al.* tried to account for appropriate maintenance of equality of BP between the groups, an important potential confounder, based on pediatric standards by adjusting the limits according to patient height and gender. Although not statistically different, both the diastolic BP in children and the mean arterial pressure in adults was higher in the placebo group in the last 1 to 2 yr of the trial. Although this may have contributed to the differences that were found between the ACE-I–treated and placebo groups, its effect was likely to be small given that these differences were not seen during the first 3 yr of the trial. In support of their trial efforts to maintain BP control and its equality, we can only add limited RCT evidence has been devoted specifically to a target BP in IgAN that is necessary to preserve renal function. The best evidence is a recent 3-yr RCT of 49 patients with IgAN, in which an achieved mean BP of 129/70 stabilized GFR during the study, whereas patients with an achieved mean BP of 136/76 had an average decline in GFR of 13 ml/min during the same timeframe (8). Coppo's study means were within these boundaries. No RCT in children regarding effects of target differences in BP alone has been done.

The trial's primary end point, time to a 30% decrease from initial creatinine clearance value, was not significantly different between their ACE-I–treated and placebo groups even though the expected event rate of 3.3% in the placebo group and 0.83% in the active drug group was achieved. Part of the problem may lie in the marked difference between their estimated sample size ($n = 122$) and the number of patients who actually were randomly assigned ($n = 66$).

The significant differences between the ACE-I–treated and placebo patients in this RCT were limited to the secondary end points and largely involved changes in proteinuria. The level of evidence that supports the importance of outcome changes in proteinuria in IgAN therefore becomes critical in assessing the clinical value of the article by Coppo *et al.* These authors found that presenting proteinuria was not significant as an independent prognostic value in their trial when examined by multivariate survival analysis using a Cox regression model. This is not radically different from the literature. Although the severity of the presenting proteinuria in some early studies was found to correlate with outcome (9), more recently, especially in more mild cases, the presenting proteinuria has not been found to be a significant long-term predictor (10). More recently, approaches to predicting outcome have incorporated sequential information on proteinuria and BP. This type of algorithm, although not perfect, has significantly improved our capacity to predict the risk for progression and underlined the importance of change over time in these parameters on outcome (11–14). Certainly in other proteinuric glomerular diseases, the magnitude of the antiproteinuric effect of antihypertensive treatment has been shown to correlate closely and predict the renal protective benefits and, in addition, that the class of drug (*i.e.*, those that block the renin-angiotensin system) is also relevant. Data specific to IgAN dates back more than a decade, when it was shown that patients who had IgAN and were treated with an ACE-I had a significantly lower rate of annual loss of renal function than patients who were treated with alternative antihypertensive agents despite equivalent BP control (14). Recently, a predictive algorithm in adult patients with IgAN found that only lower BP and lower levels of proteinuria *measured over time* and not the values at presentation predicted outcome (12). An RCT of adult patients with IgAN recently confirmed an independent renal protective effect of ACE inhibition (enalapril) and confirmed by multivariate analysis the independent value of proteinuria reduction over the course of

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the trial (but not the presenting proteinuria) (15). The importance of renin-angiotensin-aldosterone system blockade on proteinuria, although not on GFR, is also supported by the results of a recent RCT in Asian patients with IgA using the angiotensin II receptor blocker valsartan (16).

These studies help place in context the importance of the trial of Coppo *et al.* Both of their secondary end points were positive. The first one was a composite of a 30% reduction from baseline in creatinine clearance and/or an increase in proteinuria to the nephrotic range (>3.5 g/d). A significant difference was found largely because a greater number reached this level of proteinuria in the placebo group ($n = 4$) *versus* in the ACE-I group ($n = 0$; $P = 0.034$). In addition, their other secondary end point, partial remission in proteinuria (<0.5 g/d), had a greater number (13 [40.6%] of 32) and was reached earlier (after 20 mo) compared with the placebo group (3 [8.9%] of 34; after 32 mo; $P = 0.0002$). In addition, complete remission of proteinuria (<0.16 g/d) occurred in four (12.5%) cases in the ACE-I group and in 0% in the placebo group.

Multivariate analysis showed that ACE-I treatment was an independent predictor of prognosis in their trial. The authors found no influence on the composite end point for gender, age, baseline creatinine clearance, systolic or diastolic BP, mean arterial pressure, or presenting proteinuria. Given the data discussed here, this is not a surprise and confirms earlier work by a number of adult studies in IgAN that it is the change, not the presenting BP or proteinuria, that is important in slowing progression of the disease.

This study by Coppo *et al.* is an important one and raises the level of evidence of the specific renal protective effect of ACE-I therapy in IgAN in this age group to a higher grade. It also raises some interesting questions about the mechanism of action of ACE inhibition in IgAN and what the proteinuria target level should be for clinicians, given the complete remission that was observed in some cases. Furthermore, given that the study population was largely children and young adults, it provides important support for the use of this agent in this particularly vulnerable age group whose whole life, both personal and professional, stretches before them.

Disclosures

None.

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See the related article, "IgACE: A Placebo-Controlled, Randomized Trial of Angiotensin-Converting Enzyme Inhibitors in Children and Young People with IgA Nephropathy and Moderate Proteinuria," on pages 1880–1888.