More Work to Do on Renin-Angiotensin System Blockade

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Three articles in this month’s issue of CJASN are concerned with the use of renin-angiotensin system (RAS) blocking drugs to slow the progression of renal disease. Together they suggest that after two decades of productive research we are still a long way from knowing how best to prescribe these agents.

Kanno et al. (1) address the important question of whether the progression of renal disease can be slowed by adding an angiotensin receptor blocker (ARB) to an angiotensin-converting enzyme inhibitor (ACEi). They carried out an open-label, prospective trial over 3 yr in 90 subjects, mostly nondiabetic, who had baseline proteinuria >1 g/d and serum creatinine between 1.2 and 5.0 mg/dl while receiving either benazepril 2.5 to 10 mg daily or trandolapril 2 to 4 mg daily. Subjects were randomly assigned to receive added candesartan, 2 to 12 mg daily, or to continue on the ACEi without any ARB. Over 3 yr, the subjects receiving the ARB exhibited a larger reduction in proteinuria (1.78 g/d to 0.55 g/d as compared with 1.61 g/d to 1.21 g/d) and a lesser increase in serum creatinine. Doubling of the serum creatinine was observed in no patients receiving the ARB + ACEi as compared with seven patients receiving an ACEi alone. It should be emphasized, however, that the average ACEi dose was the same in the two groups and was considerably less than the maximum approved ACEi dose in the patients receiving benazepril. The findings of Kanno et al. thus strongly suggest that, at least up to some point, more RAS blockade is better than less RAS blockade, but they do not show that adding an ARB achieves benefit that could not be obtained by increasing the dose of ACEi.

The way we commonly consider the ACEi + ARB question has been strongly influenced by the history of drug development. Logically, the question should be expressed ACEi, ARB, or both. But the ACEi were discovered first, shown effective first, and have gone off patent first, which has lowered their cost. In uncomplicated patients, most physicians therefore use an ACEi first and then consider adding an ARB. It is harder to explain why we have only more recently addressed the question of adding a mineralocorticoid receptor antagonist. One reason may be that the side effects of spironolactone, which was for many years the only available mineralocorticoid antagonist, were considered to be unacceptable. Another may be that investigators considered spironolactone unlikely to be renoprotective as a single agent and then ignored the question of whether it would be useful in combination with other RAS blocking drugs. It should be noted that the assumption that mineralocorticoid antagonism cannot duplicate the effects of ACE inhibition or angiotensin receptor blockade has not been directly tested in human renal disease. But animal studies and theoretical considerations suggest that this assumption would prove correct. Aldosterone contributes to the progression of glomerular injury in the rat remnant kidney, but spironolactone cannot not replicate the protective effect of lisinopril and losartan in this model (2). Presumably this is because while an ACEi or ARB limits the activity of both angiotensin II and aldosterone, a mineralocorticoid receptor antagonist limits only the activity of aldosterone and leaves unchecked any reflex increase in the activity of angiotensin II.

The assumption that mineralocorticoid antagonists would be ineffective if used as the sole RAS blocking agents in human kidney disease, however, does not imply they can have no benefit when used in combination with an ACEi and/or ARB. As reviewed by Ponda and Hostetter (3), mineralocorticoid receptor antagonism could add to the protective effect of other RAS blocking agents either by limiting aldosterone-mediated distal nephron sodium reabsorption or by blocking various, imperfectly defined actions of aldosterone at the glomerulus and other sites. The evidence summarized by Ponda and Hostetter is amply sufficient to justify further research but not routine clinical use of mineralocorticoid receptor antagonists in patients with renal insufficiency. The most important practical question to be addressed is whether mineralocorticoid receptor antagonists have any advantage over diuretic agents, which tend to reduce rather than elevate the serum potassium. If they do not, the mineralocorticoid receptor antagonists will presumably continue to be used only in those rare patients who have renal insufficiency and a low potassium level.

The papers by Kanno et al. and Ponda and Hostetter both indicate that further trials are needed. The analysis of Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study data by Keane et al. (4) is intended to facilitate the design of such trials. RENAAL was a placebo-blinded trial of the effect of losartan on the progression of nephropathy in patients with type 2 diabetes. A total of 1513
subjects with nephropathy characterized by a baseline creatinine of 1.3 to 3.0 mg/dl and a urine albumin to creatinine ratio (UACR) of >0.3 g/g were followed for an average of 3 yr. ARB treatment was found to reduce by 25% the number of patients whose creatinine doubled and to reduce by 16% the number of patients reaching a composite endpoint comprised of doubling of the creatinine, ESRD, or death. In their analysis, Keane et al. show that regardless of treatment, the risk of progression to ESRD was highly dependent on baseline values for UACR, serum albumin, serum creatinine, and hematocrit (Hct). They reasonably suggest that the power of future trials to detect treatment effects could be enhanced by adjusting for these factors.

An obvious question raised by the analysis of Keane et al. is why the factors included in their formula for ESRD risk proved to be important. In accord with previous studies, the strongest single predictor of progression was UACR (5). This makes sense if we consider that the UACR reflects the severity of glomerular injury, and presume that function is lost faster when injury is more severe. It is not so clear why a low serum albumin was associated with a further increase in the risk for progression. It is tempting to speculate that including the serum albumin simply refined the assessment of glomerular injury, in that excretion of the same amount of albumin at a lower serum albumin reflects greater impairment of glomerular permselectivity. In this regard, it would be interesting to know if use of the fractional albumin clearance as an index of glomerular injury might predict progression better than the UACR, the serum albumin, or the serum creatinine alone. But it should be noted that a lower serum albumin may reflect other processes associated with renal disease progression, including vascular injury and inflammation. The inclusion of the serum creatinine in a formula predicting ESRD can be easily explained, in that patients who have already lost a large portion of their renal function will reach ESRD first if other things are equal. But previous work suggests that a high serum creatinine is associated not only with earlier arrival at ESRD but also with a more rapid rate of GFR decline, although the predictive power of the serum creatinine is much less than that of the UACR in this regard (5). Presumably, the addition of the Hct as a risk factor may refine the assessment of baseline renal function, in that among patients with the same serum creatinine, those with lower Hct values have likely sustained greater renal injury. The hypothesis that anemia, once established, further accelerates loss of renal function is being addressed by ongoing studies of erythropoietin use in patients with chronic kidney disease.

Keane et al. reasonably suggest that risk factors for progression be taken into account in the analysis of future trials. But although they have experienced the difficulty and borne the cost of including patients who progress slowly in a therapeutic trial, they resist the temptation to suggest that future trials should include only fast progressors. Theoretically, the power of a trial could be increased and its size and/or duration reduced by including only such patients. The problem is that there is more to be gained, in terms of extending the period before ESRD, when treatment is started early, and that we cannot be sure that treatments which slow the progression of early disease will still work in patients who have lost most of their renal function. In this regard, one conclusion of Keane et al. is susceptible to being misconstrued. They suggest that the UACR should be monitored in patient with diabetic nephropathy. Some physicians assume this implies that only patients with a high UACR, who are expected to progress rapidly, should receive aggressive treatment including high doses of RAS blocking agents. Given what we know at present, it seems equally likely that most patients with diabetic nephropathy should be treated aggressively, and that the benefit will be greatest when aggressive treatment is started early in the course of the disease. This may also be true of some other proteinuric renal diseases, but our knowledge outside of diabetic nephropathy is generally very limited.

A major unanswered question is how future trials will be supported. Treatment trials in renal disease are particularly difficult, in that our most important diseases progress slowly and for the most part without symptoms. Short-term trials using surrogate end points such proteinuria may provide clues as to which therapeutic regiments will be most effective. But long-term trials with large numbers of subjects will ultimately be required to demonstrate preservation of renal function. Some of the most valuable trials of RAS blocking drugs in renal disease have been sponsored by industry. But it seems unlikely that industry support will continue on the same scale as patent protection for RAS blocking drugs ends. It will thus presumably require public support of the type that demonstrated the renoprotective effect of ACEi in African Americans with hypertension to answer additional major questions concerning the use of RAS blocking agents in patients with renal disease (6).

References