Treatment of Chronic Proteinuric Kidney Disease
What Next?
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The vascular endothelium synthesizes and releases a range of vasodilators and vasoconstrictors that have key roles in the local regulation of vascular tone. Among those, endothelin (ET) was identified in 1988 by Yanagisawa et al, as one of the most potent vasoconstrictors known, and so far, the landmark discovery of ET has led to >22,000 publications. These have revealed that ET exerts its activity by binding to 2 types of receptors, namely, ETA and ETB, with the ETA mediating the majority of the deleterious effects of ET in the kidney, including vasoconstriction, cell proliferation, and fibrosis. ET is an important physiological regulator of blood pressure through its effects on blood vessels, heart, and kidneys, and the ET system can be overactive in disorders, eg, hypertension, heart failure, and renal disease. Such observations have created much interest among researchers and have prompted pharmaceutical companies to set up high-throughput screens to search for antagonists of ET receptors.

The initial observation in 1993 of a renoprotective effect of a selective ETA receptor antagonist in rats with renal mass reduction was further confirmed by a large body of publications that consistently documented the involvement of ET in the process of progressive renal injury in experimental models of nondiabetic and diabetic proteinuric nephropathies. Animal data also suggested that concomitant blockade of the renin-angiotensin system (RAS) and the ET system displayed more renoprotective effects than blockade of either system alone, a synergism based on the interaction of angiotensin II (Ang II) and ET at the molecular level. Results in experimental animals led to great hope that such an approach could ameliorate the treatment of progressive renal diseases in humans. When control of blood pressure and proteinuria cannot be achieved by angiotensin-converting enzyme (ACE) inhibitors (ACEis) and/or Ang II receptor antagonists (ARBs), patients theoretically can benefit from combining one of these drugs with an ET receptor antagonist. However, there have actually been relatively few studies in humans so far.

The interesting article by Dhaun et al. in the present issue of Hypertension suggests the ETA receptor antagonist as a candidate drug in a multiphasiological strategy to promote renoprotection. They found in an acute study that administration of ETA receptor antagonist BQ123, on top of maximally tolerated treatment with ACEis or ARBs, further reduced blood pressure and proteinuria and increased renal blood flow in patients with stable proteinuric nondiabetic chronic kidney disease. Arterial hypertension is a major determinant of renal disease progression, and lowering the blood pressure has become the main strategy for nephroprotection in patients with chronic kidney disease. In addition to arterial hypertension, increased urinary protein excretion is another important factor associated with the tendency of renal function to decline over time with heavy proteinuria (>3 g per 24 hours) invariably predicting the progression to end stage kidney disease and cardiovascular events.

Proteinuria does not simply reflect glomerular injury, but it is itself harmful. The injury of the tubular epithelium and the protein overload of proximal tubular cells as a consequence of the increased glomerular permeability of proteins in the setting of glomerular disease activate intracellular signals that cause increased production of vasoactive, inflammatory mediators and growth factors, including ET-1. These substances are released into the interstitium and promote the local recruitment of inflammatory cells, in turn stimulated to release cytokines/chemokines and growth factors and to produce extracellular matrix collagen and fibronectin that are responsible for interstitial fibrosis.

Studies in patients with chronic kidney disease have shown that, other than their effect on blood pressure, Ang II blockers (by their unique capacity to lower proteinuria and its deleterious consequences) effectively limited the rate of progression of renal disease to end stage kidney disease and reduced cardiovascular risk. In this context, the study by Dhaun et al. found that BQ123, a peptidic ETA receptor antagonist, administered intravenously on top of ACEis or ARBs, reduced proteinuria by 30%. Should studies with the available orally active ETA receptor antagonists after a prolonged treatment period confirm this trend, these results would have major clinical relevance. The effect of BQ123 was related to baseline proteinuria with subjects with a higher level of baseline proteinuria achieving greater reductions in line with previous reports.

One limitation of the present study is the heterogeneity of patients, as well as therapeutic regimens. Subjects with IgA nephropathy, membranous glomerulopathy, and focal segmental glomerulosclerosis were considered. Although patients with IgA nephropathy have been shown to have a high rate of proteinuria remission and a remarkably good long-
term outcome with conservative treatment alone, those with focal segmental glomerulosclerosis may have a more severe disease with heavy proteinuria, and, despite intensified treatments with Ang II blockers, they remain at very high risk of poor renal outcome. Along this line, it would have been important to know the type of focal segmental glomerulosclerosis, whether it was idiopathic or secondary, and to separately analyze individual data from this group of patients for which no valuable treatments are available to date.

Most chronic kidney disease patients need combination treatment with an ACEi and an ARB to minimize proteinuria and optimize renoprotection. In patients taking an ACE inhibitor, add-on ARB inhibits the activity of Ang II via ACE-independent pathways; on the other hand, in those on ARB therapy, an ACEi may limit the compensatory Ang II production sustained by Ang II type 1 receptor blockade. Combined treatment inhibits RAS more efficiently than each drug alone, which may explain the well-established superior antiproteinuric effect of dual compared with single-drug RAS blockade independent of blood pressure control. In the study by Dhaun et al, 12 of 22 patients received the ACEi and ARB combination, whereas the remaining 10 patients received ACEi alone. It would have been interesting to analyze differences in the response to treatment between the 2 groups and whether and at what extent the ET antagonist reduces proteinuria in patients with dual versus single RAS blockade. Should this evidence be available, ET antagonists could be considered drugs to be included in the remission clinic, the multimodal regimen titrated to urinary proteins, blood pressure, and lipids that has been shown to prevent functional loss in nondiabetic patients with otherwise rapidly progressing chronic nephropathies.

In approximately two thirds of type II diabetic patients with overt nephropathy, remission of proteinuria is not achieved by multimodal treatment, and renal and cardiovascular risks remain elevated. These patients are the ones who really need novel therapeutic interventions that would synergize with Ang II blockers.

Animal studies have suggested that ET antagonists may reduce the deleterious consequences of excessive ET produced by protein-overloaded proximal tubuli. This improved peritubular capillary architecture and renal interstitial blood perfusion. This, together with the effect of the ACEi to preserve the glomerular permselective properties of the glomerular barrier, renders the combination of the ET antagonist with ACEi very effective in protecting the kidney from progressive renal injury (Figure). Animal data on the beneficial concomitant blockade of the ET system and the RAS are now confirmed in humans, although in the present acute study.

An unprecedented finding described by Dhaun et al is the favorable effect on arterial stiffness, a key determinant of cardiovascular risk, of the ET antagonist, which induced a remarkable reduction in the pulse wave velocity that continued to fall even when blood pressure returned to baseline. Subgroup analysis of the data on arterial stiffness in patients with dual versus single RAS blockade could have strengthened the effect of the ET antagonist in the face of the maximum achievable RAS blockade. Dhaun et al claimed that reduction of proteinuria induced by the ET antagonist was independent from blood pressure control and chose to study in parallel nifedipine, which was selected as a drug that matches the antihypertensive profile of the ET antagonist with a similar effect on renal hemodynamics. However, it has been reported previously that dihydropyridine calcium channel blockers have an adverse effect on glomerular permeability. The selection of nifedipine here does not seem to be the appropriate control. Conversely, the effect of the ET antagonist on lowering proteinuria is likely attributable to renal

Figure. ACEi and ET receptor antagonist combination therapy protects the kidney from disease progression through diverse mechanisms acting synergistically.
hemodynamic changes consequent to the reduction of systemic hypertension and largely depends on the reduction of the filtration fraction. Inhibition of ET biological activity by means of the receptor antagonist could prevent the deleterious consequences of proteinuria on proximal tubuli and renal interstitium (Figure).

Overall, the study by Dhaun et al⁶ sets the stage for the completion of a future large, double-blind, controlled study in homogeneous populations of patients with chronic nephropathy of nondiabetic or diabetic origin with a residual proteinuria (1 g per 24 hours) despite maximal inhibition of the RAS with combined treatment with an ACEi and ARB. This study would help demonstrate whether an add-on ET antagonist offers advantages over combined therapy with a RAS inhibitor (including aldosterone antagonists and renin inhibitors) in reducing proteinuria in the short term with the ultimate goal to halt the progression of renal disease.

It would be crucial to know whether the presence of aldosterone escape could make a difference in the response to treatment. After an initial reduction, aldosterone plasma levels increase in a substantial proportion of patients on ACEi or ARB therapy, and this might explain the concomitant increase in proteinuria that can be observed in these patients after an initial decrease.¹² Hyperkalemia is likely one of the major determinants of sustained aldosterone production, but other factors may be involved, including a direct agonistic effect of ET on adrenal aldosterone synthesis.¹³ Whether ET blockade could be of value for patients with aldosterone escape during RAS inhibitor therapy merits further investigation.

Chronic kidney diseases are a worldwide threat to public health, and treatment of a relatively limited number of patients with renal replacement therapy represents a major societal commitment. After so many years from the observation of renoprotective properties of ET antagonists, it is now time to invest in chronic studies with rigorous design and appropriate sample size that will provide a convincing answer to the question of whether, on top of ACEi and/or ARB, ET antagonists are in fact capable of alleviating the burden of progressive renal diseases, particularly in type 2 diabetes mellitus with overt proteinuria, and reducing cardiovascular death.

Disclosures

None.

References

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*Hypertension.* 2009;54:29-31; originally published online June 8, 2009;
doi: 10.1161/HYPERTENSIONAHA.109.133579

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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