Endothelin Receptor Antagonists in Proteinuric Renal Disease: Every Rose Has Its Thorn

Eberhard Ritz* and René Wenzel†
*Department of Internal Medicine, Division of Nephrology, Ruperto Carola University, Heidelberg, Germany; and †Department of Internal Medicine, Division of Nephrology, Zell am See, Austria


When Yanagisawa et al. first identified endothelin (ET), a novel polypeptide vasoconstrictor for which numerous other functions were identified later, there was early widespread enthusiasm and great expectation for therapeutic opportunities. ET-1 is the most powerful vasoconstrictor in this peptide family; the ET system is complex with a converting enzyme and two receptors, ET\textsubscript{A}-R and ET\textsubscript{B}-R. The receptors offer an opportunity for selective blockade. ET\textsubscript{A}-R primarily mediates vasoconstriction and plays a role in the genesis of hypertension, states of endothelial dysfunction, insulin resistance, inflammation, and fibrosis. From a renal perspective, it is important to note that both ET\textsubscript{A}-R and ET\textsubscript{B}-R are found in the kidney, ET\textsubscript{A}-R in vessels and ET\textsubscript{B}-R mainly in the medulla but also in glomeruli. Of note, collecting duct ET\textsubscript{B}-R null mice develop elevated BP, pointing to a potential causal role in the genesis of hypertension. It was immediately perceived that such a multifunctional system might provide promising therapeutic targets, but early enthusiasm waned when renin-angiotensin system (RAS) blockade stole the show. But the slogan “they never come back” apparently is not true for drugs.

Today it is clear that RAS blockade with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in renal patients does not consistently reduce proteinuria, which is not only a powerful predictor but also a promoter of renal progression; this is true for the dosages recommended for hyper tension control and even for supramaximal dosages. This shortcoming has triggered a search for novel interventions in addition to RAS blockade, such as mineralocorticoid receptor blockade, renin inhibitors, and active vitamin D.

In this context, the property of ET-R antagonists to lower proteinuria and BP when added to RAS blockade is of great interest. ET-R antagonists also have beneficial effects on the cardio renal syndrome, at least in experimental animals. In a nondiabetic model of renal ablation, the combination of RAS blockade and an ET\textsubscript{A}-R antagonist had BP-independent additive effects on indices of glomerulosclerosis and tubulointerstitial and vascular damage. In an experimental model of diabetic nephropathy, administration of avosentan (predominantly ET\textsubscript{A}-R–specific antagonist) in addition to lisinopril caused impressive benefit, including regression of lesions. These findings fully justify the notion that ET-R blockers hold much promise for the management of diabetic nephropathy. On top of these favorable renal effects also comes recent evidence for powerful lowering of BP: Successful intervention with the ET\textsubscript{A}-R blocker darusentan was reported in patients with resistant hypertension.

In a recent issue of JASN, Mann et al. report A Randomised, Double Blind, Placebo Controlled, Parallel Group Study to Assess the Effect of the Endothelin Receptor Antagonist Avosentan on Time to Doubling of Serum Creatinine, End Stage Renal Disease or Death in Patients With Type 2 Diabetes Mellitus and Diabetic Nephropathy (ASCEND) of patients with type 2 diabetes, proteinuria, and advanced CKD (mean eGFR approximately 30 ml/min). Patients received avosentan in a dosage of 25 or 50 mg/d on top of either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for a duration of 6 months. The good news is the albumin/creatinine ratio is significantly lowered by 44.3 and 49.3%, respectively, in both avosentan groups versus 9.7% in the placebo group. This result confirms the finding of Wenzel et al., including the flat dose response curve. Although there was a borderline trend for less doubling of serum creatinine, the decrease in eGFR was more marked with avosentan. Of note, more patients who were on avosentan than on placebo achieved target BP. The authors provide arguments that the antiproteinuric effect is not explained by changes in eGFR or BP—but there is a price to pay. The bad news is that serious safety concerns prompted premature termination of the study. The investigators observed threatening signs of fluid overload and redistribution. Weight gain from fluid overload was observed in the past in patients who had hypertension without renal disease and were treated with darusentan and in patients who had proteinuria and diabetes with less advanced CKD. The adverse effects in the study by Mann et al. seem more severe and beyond past observations: Congestive heart failure was approximately three times more frequent (but it is admittedly difficult to distin-
guish from marked fluid retention) and acute pulmonary edema was two times more frequent in the avosentan-treated patients.

Disquieting as well is that death occurred in 4.6 and 3.6% of patients who were on avosentan versus 2.6% in the placebo group, although this difference was not statistically significant. Of note, approximately 45% of patients were taking dihydropyridine calcium channel blockers and 10% glitazones, which by themselves promote fluid retention; but this alone certainly does not explain differences between the groups. Avosentan is known to increase body weight and proximal tubular Na⁺ reabsorption, especially at dosages of ≥10 mg/d.¹⁹ Because the selectivity of avosentan for ET₄-Rs is weak, this may be due to a partial blockade of tubular ET₂-Rs, which are known to influence Na⁺ excretion.

Where does study by Mann et al.²⁰ leave us today with respect to the use of ET₄-R blockers in CKD? Does this new observation preclude the use of ET₄-R blockers in patients with proteinuria and diabetic (or nondiabetic) renal disease irrespective of GFR? Would lower dosages of comparable efficacy be devoid of these adverse effects? If not, then what precautions must be taken when ET₄-R blockers are added to RAS blockade to reduce proteinuria?

One has some déja vu when reading article by Mann et al.¹⁸ documenting weight gain and excess frequency of pulmonary edema. This constellation is reminiscent of past studies with glitazones.²⁰ We can learn from what cardiologists found out about using glitazones. Glitazones are possibly a perfect analgesic of edema. This constellation is reminiscent of past studies with ET₄-R blockers in CKD. Does this new observation preclude the use of ET₄-R blockers in patients with proteinuria and diabetic (or nondiabetic) renal disease irrespective of GFR? Would lower dosages of comparable efficacy be devoid of these adverse effects? If not, then what precautions must be taken when ET₄-R blockers are added to RAS blockade to reduce proteinuria?

We suspect that lower dosages of ET₄-R blockers may be associated with fewer adverse effects, and hopefully those dosages will be clinically effective.¹⁷ Before making any sweeping suggestions, however, it is absolutely necessary to have more information on the long-term safety of avosentan in the 5- to 10-mg/d dosage range. Sodium retention per se should not be an absolute contraindication to their use: Insulin sometimes causes a weight gain of 5 kg and no one frets: It is the cost–benefit ratio that is decisive.

Finally, there is no question that the high incidence of adverse outcomes in patients with stages 3 to 4 CKD observed in the study by Mann et al.¹⁸ is a clear contraindication to the use of ET₄-R blockers in advanced CKD. Should we continue to use ET₄-R blockers in all proteinuric kidney disease? Presumably, yes, particularly in earlier stages of diabetic (and possibly nondiabetic) nephropathy in view of the aforementioned impressive experimental²¹ and clinical²² findings, but watch out for clear contraindications (stages 3 and 4 CKD and preexisting heart disease), and monitor patients carefully.

DISCLOSURES
None.

REFERENCES


