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

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When Yanagisawa *et al.*[1] first identified endothelin (ET), a novel polypeptide vasoconstrictor for which numerous other functions were identified later,[2] 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_A-R and ET_B-R. The receptors offer an opportunity for selective blockade. ET_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_A-R and ET_B-R are found in the kidney, ET_A-R in vessels and ET_B-R mainly in the medulla[3] but also in glomeruli.[4] Of note, collecting duct ET_B-R null mice develop elevated BP, pointing to a potential causal role in the genesis of hypertension.[5] 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 hypertension control and even for supramaximal dosages.[6] This shortcoming has triggered a search for novel interventions in addition to RAS blockade, such as mineralocorticoid receptor blockade,[7] renin inhibitors,[8] and active vitamin D.[9]

In this context, the property of ET-R antagonists to lower proteinuria and BP when added to RAS blockade is of great interest.[10,11] ET-R antagonists also have beneficial effects on the cardiorenal syndrome,[12] at least in experimental animals. In a nondiabetic model of renal ablation, the combination of RAS blockade and an ET_A-R antagonism had BP-independent additive effects on indices of glomerulosclerosis and tubulointerstitial and vascular damage.[13] In an experimental model of diabetic nephropathy, administration of avosentan (predominantly ET_A-R–specific antagonist) in addition to lisinopril caused impressive benefit, including regression of lesions.[14] These findings fully justify the notion that ET-R blockers hold much promise for the management of diabetic nephropathy.[15] On top of these favorable renal effects also comes recent evidence for powerful lowering of BP: Successful intervention with the ET_A-R blocker darusentan was reported in patients with resistant hypertension.[16]

In a recent issue of *JASN*[17] are results of a randomized, controlled trial of 12 weeks' duration of 286 patients with type 2 diabetes and early-stage chronic kidney disease (CKD; average estimated GFR [eGFR] 80 ml/min) using avosentan at dosages of 5, 10, 25, an 50 mg/d compared with placebo. Albuminuria decreased significantly by 28.7 to 44.8% on the various dosages of avosentan compared with 12% on placebo; the change was not explained by changes in creatinine clearance. The maximum effect was seen at a dosage of 10 mg/d. Peripheral edema was the main adverse effect, which was observed in 12% of patients, mainly at dosages >10 mg/d. Thus, avosentan looked promising indeed—but every rose has its thorn.

In this issue of *JASN*, Mann *et al.*[18] 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.*,[17] 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[16] and in patients who had proteinuria and diabetes with less advanced CKD.[17] 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-

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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^+ resorption, especially at dosages of >10 mg/d.[19] Because the selectivity of avosentan for ET_A-Rs is weak, this may be due to a partial blockade of tubular ET_B-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 ET_A-R blockers in CKD? Does this new observation preclude the use of ET_A-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 ET_A-R blockers are added to RAS blockade to reduce proteinuria?

One has some déjà 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 analogy to ET_A-R blockers, because the pathophysiology underlying their adverse effects is sodium retention, in the case of glitazones by stimulating sodium resorption along the collecting duct.[21] In taking a lesson from the glitazone story, it makes sense to monitor body weight, reduce sodium intake, possibly monitor sodium excretion, and intensify diuretic treatment as necessary. These steps are crucial when combining avosentan with RAS blockade.

We suspect that lower dosages of ET_A-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 ET_A-R blockers in advanced CKD. Should we continue to use ET_A-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 experimental[14] and clinical[17] findings, but watch out for clear contraindications (stages 3 and 4 CKD and preexisting heart disease), and monitor patients carefully.

DISCLOSURES

None.

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See related article, "Avosentan for Overt Diabetic Nephropathy," on pages 527–535.