the defects outlined previously, loss of β-catenin activity results in a failure to maintain ureteric tip identity and impaired branching morphogenesis, perhaps related to premature differentiation of collecting duct cells.9,10 β-Catenin activity is also crucial in nephron progenitors, where it seems necessary and sufficient for the inductive pathways mediated by Wnt4 and Wnt9b signaling.13 Taken together, canonical Wnt signaling has distinct functions in at least two different renal lineages and at different developmental time points during renal development.

To summarize, Bridgewater et al.11 propose a novel model in which stabilization of β-catenin in ureteric cells leads to inhibition of ureteric branching, an ectopic pool of nephron progenitor cells mediated by Tgfβ2, and inhibition of nephrogenesis mediated by Dkk1. These findings have significant implications for defining the pathogenesis of human renal dysplasia of multiple etiologies and mouse models of renal dysplasia, which are known to overexpress β-catenin.14,15 Increased canonical Wnt signaling may represent a common pathway that is triggered by a primary insult in renal dysplasia and subsequently serves to propagate aberrant renal development. This report lays the basis for future experiments to define the common molecular pathways involved in the pathogenesis of renal dysplasia and provide insights that may lead to the development of innovative molecular tools to predict outcomes or guide interventions in children with renal failure.

DISCLOSURES

None.

REFERENCES


See related article, “β-Catenin Causes Renal Dysplasia via Upregulation of Tgfβ2 and Dkk1,” on pages 718–731.

Endothelin Antagonist as Add-on Treatment for Proteinuria in Diabetic Nephropathy: Is There Light at the End of the Tunnel?

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After the seminal discovery by Yanagisawa et al.1 of the endothelial cell–derived vasopressor endothelin-1 (ET) and eventually the identification of two other isoforms, inhibitors of the ET receptors (ETA, ETB1, and ETB2) were high on the list of therapeutic drugs for the pharmaceutical industry. The first clinical trials with ET receptor inhibitors, however, were fraught with adverse effects and somewhat disillusioning. The main reason for concern was their tendency to produce fluid retention and edema, which overshadowed their indubitable positive effects.

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A crucial issue in the discussion of adverse effects is receptor selectivity: ETs in the collecting duct promote sodium excretion through their complex inhibitory effects on epithelial sodium channels along the aldosterone-sensitive nephron, and ET$_A$ receptor–null mice retain sodium and water. Inhibition of ET$_B$ receptors, therefore, may be responsible for fluid overload in clinical trials with the dual ET antagonist bosentan and the more ET$_A$–selective antagonist darusentan. In the kidney, ET$_A$ receptors induce stronger afferent than efferent vasoconstriction, thereby reducing GFR, and they also promote renal growth in the tubular system. Experimental data suggest antifibrotic as well as antiproteinuric effects of ET$_B$ blockade, the latter of which is supported by clinical trials in diabetic nephropathy. Uncertainty persists, however, as to whether all clinically available ET antagonists inhibit ET$_B$ receptors at higher dosages and which dosage of the corresponding ET antagonist can be regarded as selective.

After the initial enthusiasm was dampened, interest in ET receptor blockade recently resurfaced because of the encouraging results of studies on BP (darusentan) and in diabetic nephropathy (avosentan). Unfortunately, another study of this substance had to be stopped prematurely in patients with more advanced diabetic nephropathy and proteinuria because of prohibitive adverse effects, specifically a nonsignificant trend for higher mortality and significant sequelae caused by fluid retention—obviously again the result of relative nonspecific receptor effects at high dosages of avosentan.

Fortunately, interest in this group of therapeutics continues because the current mainstay in the treatment of proteinuric nephropathy, renin-angiotensin system (RAS) blockade, although undoubtedly effective, does not completely resolve the problems of proteinuria and progression; in many patients, either lowering of proteinuria is incomplete or a secondary increase in proteinuria (escape) occurs. Furthermore, in more advanced stages of chronic kidney disease (CKD), RAS blockade fails to abrogate completely progressive loss of GFR. Because of incomplete efficacy of RAS blockade, there is great interest in ancillary add-on treatments, such as mineralocorticoid receptor blockers, renin blockade, vitamin D receptor activators, and ET receptor blockers, to achieve greater reduction of proteinuria and progressive loss of GFR.

The efficacy of the considerably more ET$_A$–specific receptor blocker atrasentan has been documented in patients with resistant hypertension. Atrasentan has also been studied in prostate cancer: Dosages of up to 95 mg/d produce astonishingly low rates of adverse effects. A new study with atrasentan by Kohan et al. in this issue of JASN also resuscitates interest in ET$_A$ receptor blockade. The encouraging results of this short-term pilot study specifically address its impact on renal parameters and potential adverse effects. The authors document substantial reduction of proteinuria in the short term, and it is plausible to extrapolate that in the long term this may attenuate progressive loss of GFR; it will require further long-term studies to determine whether such treatment actually translates into less loss in GFR.

Against the background of the previous study by Mann et al., it is important that the study by Kohan et al. also included patients with relatively advanced reduction of estimated GFR, roughly 50 ± 25 ml/min. In view of the dependence of adverse effects on dosage, as shown in past studies with avosentan, the dosage findings in this study are of particular importance: 0.75 mg/d provided an acceptable balance between efficacy and adverse effects. ET$_A$ receptor blockers are highly effective antihypertensive agents. With the effective dosage of 0.75 mg in this study, systolic office BP was lowered by 8.8 mmHg, a potential confounder. Statistical analysis showed, however, that BP lowering accounted for only 20% of the extensive antiproteinuric effect. Given that office BP is a relatively insensitive measure of 24-hour BP, this potentially confounding source should be more definitely assessed in future studies. Nevertheless, at a dosage of 0.75 mg/d, an impressive reduction of proteinuria by >40% was achieved in 50% of the patients.

In past studies, sodium retention was a major concern. Although atrasentan in this study had no significant effect on body weight, there was evidence of internal fluid shifts—that is, redistribution of fluid indicated by lowering of blood hemoglobin concentration. Peripheral edema also occurred at higher dosages to a similar extent (14% to 46%) compared with the studies with avosentan, in which edema occurred dosage-dependently in 9 to 26% of patients. In addition to the co-administration of (collecting duct–active?) diuretics after a weight-gain protocol, it would certainly be sensible also to advise patients to reduce sodium intake—advice that is inevitable for patients with proteinuric kidney disease in general and those on ET$_A$ receptor blockers specifically.

How about other adverse effects? Two cases of acute renal failure developed, presumably the result of aggressive diuretic treatment. In future studies, the right balance will have to be found between sodium restriction and aggressive diuretic treatment, which may have triggered acute renal failure.

Estimated GFR was not significantly changed in this study, but this does not definitely exclude changes in glomerular pressure. Data on filtration fraction and in animal experiments on glomerular capillary pressure would be highly desirable. In a study of uninephrectomized rats with streptozotocin-induced diabetes, co-administration of lisinopril and avosentan synergistically improved altered glomerular size selectivity and induced regression of glomerular lesions. Of further interest with respect to CKD progression, together they also ameliorated peritubular capillary architecture and reduced interstitial inflammation and fibrosis.

What are the differences between past trials with avosentan and this study? The authors come to the reasonable conclusion that the advantage of atrasentan is the higher selectivity for the ET$_A$ receptor, which may translate into reduced inhibition of ET$_B$ receptor–mediated sodium retention.

This short-term study in JASN leaves some important questions unanswered. First, long-term efficacy (escape?) and safety, particularly the issue of potential long-term elevation of liver enzymes, are important. Apart from the persistence of the effect, more detailed...
analysis of the effects on BP lowering (24-hour BP measurements) and its effect on cardiac performance, important because of the high prevalence of cardiac disease in CKD, is required.

Pharmacokinetic data on atrasentan show a half-life of 21 hours in patients without renal disease, but pharmacokinetics may be different in proteinuric nephropathy. The preliminary data show negative effects in patients with preexisting cardiac disease, and more data on the safety of atrasentan in patients with CKD and cardiac changes will be required. On the basis of the available information, one can already state specifically that major diastolic heart failure is a contraindication.

DISCLOSURES

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REFERENCES


Aspirin and Arteriovenous Graft Thrombosis in Hemodialysis: Just What the Doctor Ordered?

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The Center for Medicare and Medicaid Services’ (CMS) Fistula First initiative has changed dialysis practice. In 2003, more

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