Dr. Lerma serves as a member of Bayer's RENOVATE Steering Committee. In that role, he is involved in an initiative that aims to better understand and communicate the CKD and type 2 diabetes disease state, as well as provide and develop educational materials that can be used by clinicians. He is also a member of the Bayer Speakers' Bureau. Dr. Lim reports no conflicts of interest.

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# New Studies in the Pipeline with Endothelin Inhibitors

By Marina Lopez-Martinez and María José Soler

Endothelin-1 (ET-1) plays a role in chronic kidney disease (CKD) progression (1). In the kidney, ET-1 binding of the endothelin A (ETA) receptor drives afferent arteriole vasoconstriction, cell proliferation, podocyte and glycocalyx damage, matrix accumulation, and proinflammatory effects, whereas binding of the endothelin B (ETB) receptor produces vasodilation, antifibrotic effects, and decreased sodium reabsorption and natriuresis (1, 2). Although renin-angiotensin-aldosterone system (RAAS) inhibition has proven a reduction of albuminuria and a proportional effect on kidney protection (3, 4), residual albuminuria still implies a significant risk of CKD progression (5). Therefore, other therapies, such as endothelin receptor antagonists (ERAs), are currently being evaluated as promising treatments for different proteinuric nephropathies (1, 2).

The first phase 3 clinical trial of ERAs was the ASCEND study (A Study of Cardiovascular Events in Diabetes) (6), published in 2009. It compared, in 1392 patients with diabetic kidney disease, avosentan (ETA:ETB receptor blockade ≈ 50–300:1) with placebo in addition to continued angiotensin-converting enzyme inhibition (ACEi) and/or angiotensin receptor blockade (ARB) (Table 1). In patients who were treated with avosentan 25 mg/day, 50 mg/day, and placebo, the median reduction of the albumin-to-creatinine ratio (ACR) was 44.3%, 49.3%, and 9.7%, respectively ($p < 0.0001$). However, the trial was ended prematurely because of an excess of cardiovascular events with avosentan associated with fluid retention, which may be in part explained by the antinatriuretic effect secondary to the ETB receptor blockade (6). Since then, all future clinical trials have been designed to reduce cardiovascular events, by excluding patients with brain natriuretic peptide (BNP) ≥ 200 pg/mL or with a history of heart failure.

Sitaxsentan (ETA:ETB receptor blockade ≈ 6000:1), at a dose of 100 mg daily, was studied in nondiabetic CKD patients (7). This ERA (Effects of Sitaxsentan on Proteinuria, 24-Hour Blood Pressure, and Arterial Stiffness in CKD Subjects [FCRD01]) was withdrawn due to two cases of fatal hepatic failure in 2010. The SONAR study (Study of Diabetic Nephropathy with Atrasentan) (8) included, after an enrichment period (excluding patients who did not have albuminuria reduction and/or edema), 2648 patients with diabetes who received either 0.75 mg of atrasentan (ETA:ETB receptor ≈ 1200:1) or placebo, on top of RAAS inhibition, during a median follow-up of 2.2 years. The primary outcome was the efficacy of atrasentan in delaying progression of CKD (composite endpoint): patients treated with atrasentan had a significantly lower risk of doubling serum creatinine or end stage kidney disease (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.49–0.88, $p = 0.0047$) compared with placebo. Adjudicated hospital admission for heart failure occurred in 3.5% of patients in the atrasentan group compared with 2.6% in the placebo group (HR 1.33, 95% CI 0.85–2.07, $p = 0.65$). This study was performed in a selected diabetic kidney disease group of patients without heart failure and normal BNP.

As additive effects on proteinuria were observed with ERA and ACEi/ARB, sparsentan, a molecule with a dual-acting angiotensin type 1 receptor blocker and highly selective ETA receptor antagonist (negligible ETB receptor blockade) has been recently evaluated in other proteinuric kidney diseases. DUET (Dual Endothelin Receptor and Angiotensin Receptor Blocker, in Patients with Focal Segmental

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**Table 1. Randomized clinical trials with endothelin receptor antagonists in patients with kidney disease**

| Study | Study type | Drug and effect | Disease | Number of subjects | Primary outcome (PO) |
|---|---|---|---|---|---|
| ASCEND | Phase 3 | Avosentan (ETA:ETB receptor blockade ≈ 50–300:1 ) | DKD | n = 1392 | PO: No significant differences in primary composite end point of doubling creatinine, end stage kidney disease, or death; SO: The median UACR significantly declined similarly by 40% to 50% in both avosentan groups ($p < 0.0001$). |
| FCRD01 | Phase 2 | Sitaxsentan (ETA:ETB receptor blockade ≈ 6000:1) | Proteinuric CKD (non-DKD) | n = 27 | Reduction of 24-h proteinuria and UPCR by 30% by study end ($p < 0.01$) |
| SONAR | Phase 3 | Atrasentan (ETA:ETB receptor blockade ≈ 1200:1) | DKD | n = 2648 | Lower risk of doubling of serum creatinine or end stage kidney disease (HR 0.65, 95% CI 0.49–0.88, $p = 0.0047$) |
| DUET | Phase 2 | Sparsentan (ETA receptor inhibitor + ARB) | Primary FSGS | n = 96 | Reduction in UPCR of 45%–47% (95% CI 52.7%–35.7%) and systolic BP of 7.2 mm Hg |
| DUPLEX | Phase 3 | Sparsentan (ETA receptor inhibitor + ARB) | Primary FSGS | n ≈ 300 | Ongoing: Slope of eGFR weeks 6–108, proportion of patients achieving UPCR ≤1.5 g/g, and a >40% reduction from baseline at week 36 |
| PROTECT | Phase 3 | Sparsentan (ETA receptor inhibitor + ARB) | IgA nephropathy | Estimated n = 380 | Ongoing: Change from baseline in the UPCR based on a 24-h urine sample at week 36 |
| ZENITH-CKD | Phase 2 | Zibotentan (ETA inhibitor) | Proteinuric CKD | Estimated n = 660 | Ongoing: Change in UACR and BP from baseline to week 12 |
| ZEBRA | Phase 2 | Zibotentan (ETA inhibitor) | Systemic sclerosis + CKD/ scleroderma renal crisis | n = 13 | PO: Unpublished; SO: 12% improvement of eGFR at 52 weeks ($p = 0.0082$) |

PO, primary outcome; ETA, endothelin A; ETB, endothelin B; DKD, diabetic kidney disease; SO, secondary outcome; UACR, urine albumin-to-creatinine ratio; CKD, chronic kidney disease; UPCR, urine protein creatinine ratio; HR, hazard ratio; CI, confidence interval; ARB, angiotensin receptor blockade; FSGS, focal segmental glomerulosclerosis; BP, blood pressure; eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A.

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Glomerulosclerosis [FSGS]: A Randomized, Double-blind, Active-Control, Dose-Escalation Study) (9), a phase 2 trial, studied the effect of 200 mg, 400 mg, and 800 mg daily in primary FSGS. All doses of sparsentan compared with 300 mg of irbesartan achieved greater reductions in the protein-to-creatinine ratio (45% vs. 19% with 200 mg; 47% vs. 19% with 400 mg and 800 mg). Blood pressure was also reduced in the sparsentan group, and estimated glomerular filtration rate (eGFR) was stable in both treatments. The incidence of adverse events was similar between groups. Moreover, a post hoc analysis (DUET-Open-Label Extension [OLE]) concluded that 40% of patients treated with sparsentan achieved complete remission of proteinuria (≤0.3 g/g) on at least one occasion (10).

DUPLEX (Study of Sparsentan in Patients with Primary FSGS) (11) is the phase 3 study that will evaluate the long-term antiproteinuric efficacy, nephroprotective potential, and safety profile of sparsentan compared with irbesartan in patients with primary FSGS. Also, in immunoglobulin A (IgA) nephropathy, which is the most prevalent primary glomerulonephritis worldwide, the potential benefit of 200–400 mg of sparsentan on kidney function will be evaluated by analyzing changes in proteinuria and eGFR as compared to 150–300 mg of irbesartan in the PROTECT study (A Study of the Effect and Safety of Sparsentan in the Treatment of Patients with IgA Nephropathy; ClinicalTrials.gov: NCT03762850).

Sodium glucose co-transporter 2 inhibitors (SGLT2i) cause, through tubuloglomerular feedback, afferent arteriole vasoconstriction and have also proven kidney protection from CKD progression (12). Therefore, a potent antagonist of ETA with no effect on the ETB receptor (zibotentan) is being evaluated in ZENITH-CKD (Zibotentan and Dapagliflozin for the Treatment of CKD), a phase 2b study in patients with CKD and proteinuria (ClinicalTrials.gov: NCT04724837), as monotherapy and in addition to the SGLT2i, dapagliflozin. Zibotentan has already been studied in ZEBRA (Zibotentan Better Renal Scleroderma Outcome Study; ClinicalTrials.gov: NCT02047708), with positive results in the scleroderma renal crisis.

In conclusion, ERAs are a strategic therapy with promising effects on proteinuria and CKD progression. However, their incorporation into clinical practice has been delayed as a consequence of their adverse effects in terms of fluid retention. New molecules seem to achieve results with statistical power and safe results that will finally allow us to include them soon in day-to-day practice. In the near future, the treatment of patients with CKD is expected to mimic the sequential treatment offered currently for patients with heart failure. ■

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# How We Learn
## Principles and Perspectives in Nephrology

By Tiffany Truong, Matthew R. Sinclair, and Sam Kant

Medical education, like medicine itself, has evolved over time—from the days of professional guilds and apprenticeships to the establishment of structured postgraduate residency training to duty-hours' restrictions, changes in licensing exams, and the growth of innovative educational resources (1). As the design of medical training changes, so too does the type of physician it produces. After all, medical education is not simply the acquisition of knowledge or even of skills and experiences but a process of shaping and the metamorphosis of the learner.

In a field like medicine, interwoven as it is with the science and humanity of life, the training is not only transformative but also inherently lifelong. Learning—and teaching—becomes a skill in itself. *How we learn* in addition to *what we learn* is pivotal to the type of physician we become. How then do we learn best? If we are to shape our own transformation in the years of our formal training in nephrology, what constitutes a "good" education? And what currently is the landscape of this training in nephrology?

To answer these questions, we gathered a few perspectives from a group of nephrology fellows and attendings with backgrounds in medical education and surveyed the literature on frameworks of adult learning as it may apply to medical training.

In the 1960s, Malcolm Knowles described an early theory of adult education that he called "andragogy" (in contrast to "pedagogy" for education during childhood, although this is acknowledged to be a continuum) (2). The basic principles of andragogy are assumptions about how adults learn. Among these assumptions are that adults must want to learn, that they need to know the reason for learning something and its relevance, that they are more centered on problem solving and their experiences, and that they need to be self-motivated or responsible for the planning of their instruction (2).

What we heard from both nephrology fellows and attendings was strikingly consistent with these assertions. Foremost, a sense of purpose and relevance is important. Many reported that learning is most effective when the applicability is clear, citing a preference for teaching that focuses on clinical relevance, for example, with bedside teaching and case-based approaches. Clinical experiences and the application of physiologic principles in a clinical context are the core of medical training, and learning this explicitly provides direct applicability. In particular, Free Open Access Medical Education (FOAMed) has been cited as a valuable resource to meet the challenges to early engagement in nephrology, including the perception that it is very technical, making it difficult to appreciate clinical applications early on (3).

Yet, clinical context is not enough. We cannot encounter every clinical scenario either directly or through cases. In another model of education—Kolb's cycle of experiential learning—learning is a cycle of feeling (having experiences), watching (observing and reflecting), thinking (abstraction and generalization), and then doing (applying concepts in new situations) (2). Learners have different strengths in this cycle, for example, "activists" who feel and do, "theorists" who watch and think, or "pragmatists" who think and do (2). In medicine, "feeling" would equate to having a clinical experience, and "doing" would mean applying that experience to a new situation. The concrete steps of having an experience and being able to apply that experience are separated by the more abstract steps of reflection and abstraction, which also allow for generalization. For many fellows, effective learning is not only about gaining clinical experiences but also involves how best to reflect and process information outside of the clinical environment.

In this regard, educational resources in nephrology abound with options to engage learners of every kind, with many recommendations for textbooks, auditory or visual material such as podcasts and pathology videos, question sets, as well as virtual courses and simulations of clinical cases. Leticia Rolon, MD, a nephrology attending and educator at the University of California in San Francisco, states, "Different platforms have different strengths. For acid-base and electrolyte physiology, you can go back to basics and read Burton Rose. But you don't have to read it alone now—you