Transcript Details

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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The Endothelin System and IgAN: Emerging Evidence

Announcer:
Welcome to ReachMD. This medical industry feature, titled “The Endothelin System and IgAN: Emerging Evidence” is sponsored by Novartis Pharmaceuticals Corporation. Here’s your guest, Dr Donald Kohan.

Dr. Kohan:
Hello, my name is Doctor Donald Kohan and I am a nephrologist at University of Utah Health in Salt Lake City. In this video, we will discuss the role of the endothelin system in kidney health and in IGA nephropathy. Endothelin one, or ET 1, is a highly stable peptide produced by multiple cell types with effects on various biological systems. There are two endothelin receptors, ETA and ETB. These receptors mediate a wide range of complementary or opposing actions. Through its autocrine and parocrine actions, ET1 regulates multiple renal physiological functions and is particularly important in maintaining fluid and electrolyte homeostasis and blood pressure. Renal injury is associated with increased formation of renal ET1 and subsequent overactivation of the ETA receptor, leading to downstream pathogenic signaling. ETA overactivation in the kidney can induce vasoconstriction, endothelial cell injury and glycocalyx degradation, potocyte cytoskeletal disruption, slit diaphragm dysfunction, inflammation, apoptosis and fibrosis. Tubulo interstitial fibrosis, mesandial cell proliferation contraction and extracellular matrix accumulation, and inflammatory cell production of pro inflammatory cytokines and chemokines.

Many pathophysiological effects of ET 1 result from direct action on kidney cells and do not depend on hemodynamic effects. ET1, proteinuria and angiotensin 2 can act in a positive feedback loop that may contribute to renal injury, inflammation and disease progression. IGA nephropathy is an autoimmune glomerulonephritis with a heterogeneous clinical presentation and variable disease progression. The multi hit mechanism of disease in IGA nephropathy encompasses several key steps in the disease pathogenesis.

The first three steps lead up to formation of galactose deficient IGA, one containing immune complexes, while the deposition of these immune complexes in the kidney in the fourth step involves renal injury processes. Endothelin system activation is involved in HIT 4 and plays an important role in the pathogenesis and progression of IGA nephropathy. All ETA receptor mediated pathophysiological processes previously mentioned applied to IGA nephropathy following immune complex deposition in the mesangium. Activation of the endothelin system promotes mesangial cell injury, Inflammation, podocyte dysfunction, proteinuria, vascular injury and dysfunction, and fibrosis.

In several studies, activation of the ETA receptor has been shown to contribute to IGA nephropathy progression and markers of endothelin system activity are elevated in patients with this disease. Patients with IGA nephropathy and higher degrees of proteinuria show an increase in glomerular and tubular interstitial ET1 staining. Patients with IGA nephropathy had more intense and diffuse tubular epithelial ETA receptor staining compared to controls. Elevated total kidney ET1 mRNA expression was associated with risk of progression in patients with IGA nephropathy 12 months following kidney biopsy. Since ET1 induced ETA activation may contribute to disease progression, the potential effects of ETA receptor in IGA nephropathy continue to be investigated. Multiple treatment approaches targeting the drivers of the multi hit mechanism of disease may provide a way to tailor therapy for patients with IGA nephropathy. Thank you for your time and interest in watching this video.

Announcer:
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