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Taking a Deep Dive into the Pathophysiology of IgA Nephropathy

Announcer:
Welcome to *Clinician's Roundtable* on ReachMD. On this episode, sponsored by Chinook, we'll hear from Dr. Jonathan Barratt, who's the Mayer Professor of Renal Medicine at the University of Leicester in the United Kingdom. Today, he'll discuss a key driver behind the pathophysiology of IgA nephropathy. Here's Dr. Barratt now.

Dr. Barratt:
So in IgA nephropathy, the fundamental abnormality is the deposition of IgA immune complexes within the mesangium of the glomeruli. And that deposition triggers a whole range of biochemical changes within the glomeruli driven by mesangial cell activation. And one of those changes is an upregulation of endothelin-1. And endothelin-1, rather like angiotensin II, drives a number of pathogenic changes within the glomeruli. It alters the glomerular blood flow causing glomerular hypotension. It interacts and promotes glomerulus scarring and fibrosis. And it also interacts with podocytes, promoting podocyte injury. So it does many other things alongside angiotensin II, but fundamentally, when IgA deposits occur in IgA nephropathy, they trigger upregulation of the endothelin cascade and activation of endothelin receptors, which derive progressive loss of kidney function through glomerulus scarring.

So as I mentioned, with the activation of mesangial cells, there is an upregulation of endothelin-1 alongside angiotensin II locally within the kidneys within the glomeruli. And this drives many of those processes that lead to worsening proteinuria and glomerular hypotension, podocyte injury and loss, mesangial cell activation, and ultimately, glomerular fibrosis with activation of fibrotic pathways, not only within the glomeruli but also within the tubular interstitium. And we know that endothelin-1 alongside angiotensin II works synergistically to cause these pathogenic changes.

So we know for many years of history and research that angiotensin II receptor antagonists and ACE inhibitors can be incredibly beneficial in proteinuria kidney disease. And we now know that the endothelin system parallels the renin-angiotensin system in many, many ways and is working synergistically with that system to promote glomerular injury and loss of kidney function. And so the real excitement is that we can potentially improve kidney outcomes by combining renin-angiotensin system inhibition with endothelin receptor antagonism.

And this new class of drugs that's been evaluated in kidney disease, particularly, IgA nephropathy and focal and segmental glomerulosclerosis, are looking at the ability to reduce proteinuria and protect the loss of kidney function. And certainly, the early data is looking incredibly promising that by blocking the endothelin receptor, we are working in addition to the renin-angiotensin system inhibitors to protect long-term kidney function.

Announcer:
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