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Diving into the Dual Role of ET-1 & Ang II in IgAN

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is sponsored by Travere. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and joining me to shed light on the role of endothelin-1 and angiotensin II in the disease progression of IgA nephropathy, or IgAN for short, is Dr. Rajeev Raghavan. He's the Program Director for HCA Kingwood Internal Medicine, and he's a board-certified nephrologist and internal medicine physician with Kingwood Internal Medicine Specialists in Texas. Dr. Raghavan, welcome to the program.

Dr. Raghavan:
Hey, thank you, Dr. Turck. Happy to be here.

Dr. Turck:
Well to start us off, Dr. Raghavan, would you tell us about the key markers of disease progression that we should be aware of in IgAN?

Dr. Raghavan:
Yeah, absolutely. So IgA nephropathy is a very common disease. It's not common to the general population, but for us in nephrology, it's one of the more common types of diseases we see in the kidney. There are a few markers that we use to, one, diagnose and then, two, measure the clinical activity or prognosis for patients with IgA nephropathy. The first really is the urinalysis. And so we look at the urine for the presence of blood or protein. And that's kind of a rough marker of, one, whether the patient has something within the kidney that could be IgAN, but two, the presence of blood, and more importantly, the amount of protein that the patient has, tells us more or less how advanced the patient's diseases or how active their IgAN is within the kidney.

So in addition to the urinalysis, we do like to measure the amount of urine. That's called the UACR, or urine albumin to creatinine ratio. Number three would be a kidney biopsy. The kidney biopsy not only is, one, required for diagnosis, but also is a marker of prognosis as well. For a patient who has a lot of inflammation in the kidney, that shows up on the biopsy and will point us towards the type of treatment we employ for our patient.

Besides those two, the biopsy and the urinalysis, finally, we use the lab test, which is a serum creatinine. And the serum creatinine is just a marker of how well the kidney's working. And so the creatinine tells us that the patient is not doing as well. The higher creatinine may suggest they have more advanced disease or more active inflammation within the kidney.

Dr. Turck:
And so in the context of IgA nephropathy, what could you tell us about the biochemical pathways involving endothelin-1 and angiotensin II?

Dr. Raghavan:
The angiotensin II pathways has been around for a while. And medications that block that are called RAS inhibitors, which typically involve ACE inhibitors or angiotensin converting enzyme inhibitors, or ARBs, which are angiotensin receptor blockers. So these medications basically block angiotensin II, which is a very potent vasoconstrictor within the kidney, which basically means it constricts the blood vessels within the kidney that may affect the way the kidney handles things like protein. And so blocking that has certainly led to improvement in all our patients with kidney disease, for example, diabetic kidney disease and specifically with IgAN as well.

The endothelin pathway is a little bit of a newer pathway. It's been studied for 10 or more years, but there's finally some medications that

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are coming through the pipeline that now have been studied in patients with IgAN. And so blocking the endothelin pathway is another potential treatment arm that we have within our armamentarium.

Like angiotensin II, endothelin also is a very potent vasoconstrictor, but endothelin also is involved in the fibrosis, which is the scarring pathway. And so having overactivation of this endothelin peptide or endothelin protein can lead not only to constriction of the blood vessel, but also can lead to scarring with the kidney. And so it's been studied in a whole host of kidney diseases and has shown some promising results.

Dr. Turck:
And how do these two pathways work in tandem to drive disease progression in IgAN?

Dr. Raghavan:
So basically, both the pathways work with constriction of the blood vessels within the kidney. So imagine if you have a kidney, the glomerulus is the filtering part of the kidney. And so that's where essentially the glomerular capillaries are, where blood and protein are supposed to stay within the capillary and not leak out into the urine. And so if you have damage to the glomerular capillary, you have all this blood and proteins that are now leaking out into the urine, causing more damage as they move through the kidney. So the ability to regulate or block the amount of protein and blood that's being squeezed out through the glomerular capillary is really essential to the treatment of many kidney disorders, but specifically for IgA nephropathy. And so we know for the longest time that the RAS inhibitors, ACE inhibitors, and ARBs do this, and the new data is pointing towards endothelin pathway as another type of pathway that can be targeted and blocked to help slow the progression of disease by reducing the amount of protein and blood that's being spilled through there.

Dr. Turck:
For those just joining us, this is *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Rajeev Raghavan about how the biochemical pathways involving endothelin 1 and angiotensin II can lead to disease progression in IgA nephropathy, or IgAN.

So Dr. Raghavan, you touched on this a little bit before, but now that we have a better understanding of endothelin 1 and angiotensin II's respective roles in IgA nephropathy, how might that knowledge impact the treatment landscape?

Dr. Raghavan:
Yeah, I think it's really fantastic for our patients. For the longest time, we really only had the RAS inhibitors to treat our patients. And so now having one new medicine, and there's another one that recently was approved as well, so having a couple of new medicines is really remarkable for our patients because IgAN typically follows the rule of thirds. About a third of patients with IgA nephropathy end up having progression of kidney disease to the point of eventually needing dialysis or transplantation. So for our patients, having one more medicines to help slow the progression of disease, that we could monitor the UACR, or albumin to creatinine ratio, to make sure we're reducing the amount of protein that they're excreting in the urine, this is really, really huge for us, as nephrologists. And I can't begin to tell you how excited we are to finally have some medications to treat these patients.

Dr. Turck:
So if we're able to lower proteinuria and address other markers of disease progression with those treatment approaches, what kind of impact could that have on our patients?

Dr. Raghavan:
I think the biggest impact really is delaying the progression of disease for our patients. And so ultimately, for patients with any type of kidney disease, whether it's IgAN or even diabetic kidney disease, which is probably the most common type of kidney disease we see, lowering the amount of protein that's excreted really does affect the kidney filter a little bit better, it reduces the amount of scarring in the kidney, and ultimately, that really just slows the progression to dialysis or transplant, which of course, are really terrible for patients if they have to progress on to those stages. And so we really want to do the best we can. And so I think that's where having medications that target this endothelin receptor pathway is going to be really important for our patients.

Dr. Turck:
Now lastly, Dr. Raghavan, are there any final thoughts you'd like to share with our audience today?

Dr. Raghavan:
The first thing I would say is just the recognition of a disease like IgAN; it's probably not one you think about right off the bat if you're not a nephrologist. But definitely look at that urinalysis on your patients. If you're screening your patients with a urinalysis, and you find blood or protein, just keep in mind that this is a fairly common disease, and catching it early and sending the person to a nephrologist may actually make a big difference in the patient's life. So that's probably the last point that I want to leave with the audience.

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Dr. Turck:
Well with those key takeaways in mind, I want to thank my guest, Dr. Rajeev Raghavan, for joining me to discuss the biochemical pathways involving endothelin 1 and angiotensin II and how they can lead to disease progression in IgA nephropathy. Dr. Raghavan, it was great having you on the program.

Dr. Raghavan:
Thank you.

Announcer:
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