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Navigating Treatment Goals in IgAN: The Impact of ET-1 and Ang II

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

**Dr. Turck:**
This is *Clinician's Roundtable* on ReachMD, and I'm Dr. Charles Turck. Here with me today to discuss the roles of endothelin 1 and angiotensin 2 in the progression of IGA nephropathy, or IgAN for short, and how we can achieve and maintain our treatment goals are Drs. Jonathan Barratt and Shikha Wadhwani. In addition to being a Professor of Renal Medicine, Dr. Barratt leads the Renal Research Group within the College of Life Sciences at the University of Leicester in the United Kingdom. Dr. Barratt, welcome to the program.

**Dr. Barratt:**
Thank you. It's a pleasure to be here.

**Dr. Turck:**
And not only is Dr. Wadhwani an Associate Professor of Medicine in the Division of Nephrology and Hypertension at Northwestern University, but she's also the Founder and Director of the Northwestern Glomerular Disease Program. Dr. Wadhwani, it's great to have you with us as well.

**Dr. Wadhwani:**
Thank you so much. Glad to be here.

**Dr. Turck:**
So why don't we start with you, Dr. Barratt. Would you tell us a bit about how endothelin 1 and angiotensin 2 contribute to the pathogenesis of IgAN?

**Dr. Barratt:**
The fundamental, or initiating, injury in IgA nephropathy is the loss of nephrons due to deposition of immune complexes. But as that nephron loss increases, you then start to have those initially adaptive, but then become maladaptive, responses within the remaining glomeruli on nephrons. And that's really to try and replace the function that those lost nephrons would have delivered. And the principal biochemical drivers for those adaptive responses are an upregulation of angiotensin 2 and endothelin that work initially to promote blood flow through the remaining nephrons to increase and maintain our glomerular filtration rate, which in the short term is a positive thing. But as we lose more and more nephrons through those immune-mediated effects of immune complex deposition, the remaining nephrons have to work harder and harder. There's a stronger and stronger drive for angiotensin endothelin signaling.

And ultimately, that leads to maladaptive responses that promote injury to cells within the glomerulus, particularly podocytes, that promote segmental scarring within the glomerulus, and also, actually, these two biochemical mediators are involved in driving scarring itself in terms of the fibrotic response. And outside of the glomerulus and within the rest of the nephron, the proteinuria that's generated is impacting the tubular epithelium and driving tubular interstitial inflammation and fibrosis, and endothelin and angiotensin 2 have important roles in driving that profibrotic response within the rest of the kidney.

So they really are critical mediators of a lot of the damage that we see as we accumulate nephron loss due to the deposition of immune complexes in IgA nephropathy.

**Dr. Turck:**

So as a follow up to that, Dr. Barratt, what kind of impact could regulating these peptides have on disease progression?

**Dr. Barratt:**
Well, I think they can have a massive impact, and we've seen that in clinical studies. We've known for many, many years that blocking angiotensin signaling within the kidney has a positive effect. It reduces proteinuria, and it slows the rate of loss of kidney function. And we now, for the first time, have high-quality data from the PROTECT clinical trial that evaluated the addition of endothelin receptor antagonism on top of angiotensin receptor blockade. And what that showed was a significant additive effect on reducing proteinuria when you block the endothelin system on top of the renin angiotensin system, and that increased reduction in proteinuria translated to a slowing in the rate of loss of kidney function. So we have very clear evidence now in a very good quality Phase 3 clinical trial that combining renin angiotensin system blockade with endothelin receptor antagonism improves outcomes in patients with IgA nephropathy.

**Dr. Turck:**
So given the roles and impact of endothelin 1 and angiotensin 2, let's turn to you now, Dr. Wadhwani. What therapeutic goals should we be setting for our patients to help prevent disease progression?

**Dr. Wadhwani:**
Yeah. So I think first and foremost, we need to focus on things like blood pressure control, sodium or salt restriction, and lifestyle modification to ensure that we are decreasing cardiovascular risk. But then in terms of our specific therapeutic goals, and IgAN on top of that, we really need to focus on proteinuria reduction. And that's something we've known for quite a long time. I think in the past, we had data to show that if we reduced proteinuria to less than a gram per day, we likely would have a good long-term kidney prognosis. And I think some of the newer data from the UK Radar Registry, as well as data here in the United States and other places around the world, is showing us that getting to less than a gram per day probably isn't enough, and we're going to need to target lower proteinuria thresholds—whether that's less than half a gram per day, or ideally, trying to reduce the proteinuria to as low as possible.

**Dr. Turck:**
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Drs. Jonathan Barratt and Shikha Wadhwani about the importance of achieving and maintaining treatment goals in the management of IgA nephropathy, or IgAN.

Now to help ensure that our patients reach and stay at their goals, Dr. Wadhwani, how should we approach monitoring them?

**Dr. Wadhwani:**
I think that this really starts with, from the get-go, having an important conversation with your patient, setting expectations, and educating them. I think we need to emphasize that this is a chronic disease and they're going to need to stay on top of monitoring their proteinuria, their kidney function, electrolytes, etc., for the rest of their lives. And I think this can be challenging for a lot of our patients because they don't come to us with symptoms that are directly related to their IgA nephropathy. So a minority of patients actually see blood in the urine. Most of them only see it when we detect it under a microscope with examination of the urine. And a lot of patients don't have pain or other systemic symptoms of their disease. And so I think it's really important from the outset to help patients understand what's important and what we need to focus on. And in terms of what that monitoring entails, it's going to involve at least, at minimum, urine and blood work every few months, if not more frequently. For a lot of my patients, I monitor their blood work and urine monthly, and this can certainly depend on where they are in the course of their disease. But I think having patients recognize that is important.

The other thing that I would say is important is actively engaging our patients in the discussion of what our targets are. So if patients know that we're really focusing on complete remission of proteinuria or trying to get proteinuria as low as possible and the fact that we're trying to keep their kidney function from further declining, they can also play an active role in that discussion and feel as though they are part of the treatment or management plan and not just sort of bystanders.

**Dr. Turck:**
Coming back to you, Dr. Barratt, and staying on the topic of patient communication for a moment, looking specifically at patient education, are there any specific approaches, tools, or resources that you use when speaking with patients?

**Dr. Barratt:**
In terms of educating our patients, I'm a very strong advocate for IgA nephropathy patients being involved with the IgA Nephropathy Foundation, which is a mainly US-based organization but wants to have a global reach, and they've got some great resources on their website for patients. And in the UK, we have a whole series of educational videos and podcasts on a YouTube channel that we set up from my own renal unit. So we do try and ensure that patients get access to information.

I was only talking to a patient today who the first piece of advice his nephrologist gave him when he got the diagnosis was “do not Google IgA nephropathy” because you will find terrible stories, there will be lots of misinformation, and you will end up not knowing what is right and what is wrong. And that is very true, I think. I don't know whether Shikha has the same experience in her US patients. But we need some trusted resources to direct our patients to because if we don't give them those, they will go looking themselves and then we will end up in a worse situation. So to cut a long answer short, we need to provide the information for our patients, and if not, we need to peer review any information that we are going to direct our patients to because if we have a fully engaged patient, we know they will do better.

**Dr. Turck:**
Well, we've certainly covered a lot today, but before we close, Dr. Wadhwani, would you share some key takeaways from our discussion?

**Dr. Wadhwani:**
Sure. You know, I think that we both have touched on the fact that it's really critical for our patients and our colleagues to recognize that this is a chronic disease. More than half of patients by the time they present actually already are at CKD Stage 3 or worse in the United States. And I think that recognizing and tapping the conversations with our patients about the fact that this can progress to kidney failure, regardless of the fact that you may be young and you may feel well now. This is why we need to work as a team and we need to ensure that we are addressing every aspect of this disease that we can now so that we can hopefully prevent, or at least delay, kidney failure in the future.

I think the other thing that I would try to make sure that we take-away is that we're learning more about IgA nephropathy, as Dr. Barratt shared, as time has gone on. We understand more about the pathogenesis, and we understand more about the key mediators, especially when it comes to kidney injury and how endothelin and angiotensin really work together to propagate further injury once those immune complexes have deposited in the kidney mesangium. And targeting both of them is really going to be critical in trying to prevent that further kidney injury and, hopefully, kidney failure down the road.

**Dr. Turck:**
Well, with those key takeaways in mind, I want to thank my guests, Drs. Jonathan Barratt and Shikha Wadhwani, for joining me to share their insights into the optimal management of IgA nephropathy. Dr. Barratt, Dr. Wadhwani, it was great speaking with you both today.

**Dr. Barratt:**
Thank you. It was a pleasure.

**Dr. Wadhwani:**
Thank you so much. It was really great.

**Announcer:**
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