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Understanding IgAN: More Than a Benign Disease

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

Dr. McDonough:
Although IgA nephropathy, or IgAN for short, was once thought to be relatively benign, it's now shown its true colors as a progressive high-risk disease. So what are we missing if we still view it through an outdated lens?

Welcome to *Clinician's Roundtable* on ReachMD. I'm Dr. Brian McDonough, and joining me to discuss our changing perceptions of IgAN and their impact on diagnosis and management is Dr. Suneel Udani. He is a nephrologist with Nephrology Associates of Northern Illinois, or NANI, located in Hinsdale, Illinois. Dr. Udani, thanks for being here today.

Dr. Udani:
Thanks so much, Dr. McDonough, for having me and inviting me to have this conversation with you.

Dr. McDonough:
Let's start with some context, Dr. Udani. Historically, how has IgAN been perceived by the medical community? And how have these ideas shifted over the past few decades?

Dr. Udani:
Through the course of the previous decades, we really looked at IgA nephropathy in sort of a binary lens. We would see these cases that were quite severe; they would have, oftentimes, large degrees of inflammatory changes in the kidney biopsy—oftentimes crescentic changes—and their renal function would deteriorate very quickly, more akin to what we refer to as the RPGN, or rapidly progressive glomerulonephritis. And then there was the other side that we thought was benign. They had microscopic hematuria. They would have subnephrotic range proteinuria. The renal function would oftentimes be very well preserved or not changing enough for us to notice. And we looked at this as a fairly—quote unquote—benign disease, and if you were to have a glomerulonephritis, that was the one you wouldn't want to have. But this has definitely changed. It's definitely changed with new data that's become available.

Dr. McDonough:
And expanding on that, what does recent data tell us about progression risk, even in patients who initially present with mild symptoms?

Dr. Udani:
It was a remarkable set of data released from the National Health Service called the RaDaR study, which is a cohort of many rare diseases including IgA nephropathy. And ultimately, this was the best snapshot of real-world experience with IgA nephropathy. And what it demonstrated is that this condition was not nearly as benign as we thought. Those individuals with fairly moderate degrees of proteinuria—even less than a gram, which we thought was the previous threshold for concern—progressed over time. And it wasn't again that rapid progression that we see with the RPGN, but it was a progression enough where many of them, depending on their age when they started, would end up on dialysis, requiring kidney transplantation. And with that data, we could also see that most of these patients are young and in their second, third, or maybe fourth decade of life when they're diagnosed. And so unfortunately, by the time their journey is complete, they have progressed through their native kidney function on dialysis, oftentimes even requiring multiple transplants.

The difficulty was, of course, that we didn't have this kind of dataset before, and also, because of its slower progression than what we

think about in the other glomerulonephritides, it was not enough for many nephrologists to perceive, and this span of change in function also may even go beyond any single nephrologist's career. And so we weren't there to really observe those changes in the way that they were happening. And it certainly gave us this false sense of security that this was a benign disease, which we now know it is not at all in many individuals, it will instead be quite life changing and devastating.

Dr. McDonough:
Now, if we zero in on proteinuria for a moment, what role does it play in predicting IgAN progression?

Dr. Udani:
Proteinuria has traditionally been the most important prognostication tool that we've had in IgA nephropathy in terms of looking at future kidney function. But there are some new data that has changed our perspective on the threshold of proteinuria at which we should be concerned. And, as I said before, we previously looked at proteinuria only greater than a gram per day, or UPCR greater than one gram/gram creatinine as concerning. And now we're seeing that at lower levels, 0.6 gram/gram, 0.5 gram/gram, those individuals still do progress.

The other thing I'd like to also add is that while proteinuria remains the most important prognostic tool, we are seeing emerging data on the role of persistent microscopic hematuria in that that, in itself, may also be a negative prognostic factor, in that the persistence of that hematuria is an indication of this ongoing kidney injury. So proteinuria still is the threshold and the most important factor, but we're seeing that it doesn't, by itself, explain the whole scenario in terms of the outlook for patients with IgA.

Dr. McDonough:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Brian McDonough, and I'm speaking with Dr. Suneel Udani about our evolving understanding of IgAN's effects on long-term kidney function.

So Dr. Udani, I'd like to talk now about how we can apply this knowledge into practice. What strategies do you recommend for early diagnosis and management of IgAN?

Dr. Udani:
I think that the early diagnosis is key in that there are many young individuals that have microscopic hematuria on a urine test. One, we don't do enough urine testing. But even in those that are tested, it's oftentimes attributed to something else like a urinary tract infection or some other less concerning etiology. And oftentimes they'll have some other clue—elevated blood pressure, maybe a protein in the urine. And I think expanding beyond the nephrology world, the primary care and even OB/GYN care providers may be identifying these individuals earlier on. They have microscopic hematuria. They may have some other change that suggests perhaps an element of renal dysfunction. So identifying those folks early on.

And then when they are referred to nephrology, the risk stratification and intervention could be occurring in a more, let's say, time-sensitive way. Now, what do I mean by that? Again, in the past, we thought these proteinuria thresholds of UPCR less than 1 gram/gram was safe, but now we recognize that's no longer the case. And so we would even defer a definitive diagnosis, meaning kidney biopsy, in individuals that had only a mild-to-moderate proteinuria, because we said, 'Okay, we're not going to do anything anyways. If they have IgA neuropathy, we're just going to be treating them the same way. We're going to keep their blood pressure control. We're going to talk about their diet, maybe put them on RAS inhibition.' But now we're saying, 'Okay, no, it is very important to actually give an explicit diagnosis,' because, A, the prognostication, but B, there are now disease-specific therapies that are emerging that will potentially have the role of really changing the future outlook for these individuals.

So both from a recognition standpoint, we should be expanding beyond nephrology and then also giving an earlier and more definitive diagnosis, followed by intervention from nephrologists.

Dr. McDonough:
And how can those strategies impact outcomes for our patients?

Dr. Udani:
Well, ultimately, what we hope to see and are seeing data already suggesting is that with if you're able to achieve lower degrees of proteinuria or resolution of hematuria with disease-specific interventions, kidney function is much better preserved. And ultimately, this is what our intention is, is to say, 'Okay, can we preserve eGFR? Can we preserve kidney function? Can this versus native kidney function last them as long as they need it to?' And if not, at least extend it to the point where they will only require one transplant in the course of their life? But ultimately, the goal would be identification, intervention, and then preserving kidney function for the outlook of that individual's life.

Dr. McDonough:

Before we wrap up, Dr. Udani, what key takeaways about diagnosing and managing IgAN would you like our audience to remember moving forward?

Dr. Udani:
There are a few things I'd like to highlight. One is again, to not overlook these cases of microscopic hematuria with some other changes like hypertension or some degree of proteinuria. Don't chalk them up to these benign etiologies that we have. Secondly, establish a definitive diagnosis as soon as it can be done appropriately and safely. And then, thirdly, do not be sort of reassured by these lower degrees of proteinuria, UPCRs of 0.6 gram/gram, or persistent microscopic hematuria even. Because what we know is that those individuals, while, again, may not have rapid progression in the course of a few months, over the course of their lifetime, will still progress. And so we identify and risk stratify them early on, then we can think about what tools we now have, which is a rapidly evolving and emerging area that we can then utilize to preserve this individual's kidney function and their overall health.

Dr. McDonough:
With those final thoughts in mind, I want to thank my guest, Dr. Suneel Udani, for joining me to discuss how IgAN's true progressive nature is reshaping its identification and management. Dr. Udani, it was great having you on the program.

Dr. Udani:
Dr. McDonough, thank you again for inviting me to speak with you. I thoroughly enjoyed it.

Announcer:
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