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

Challenges of Implementing Evidence-Based Guidance for IgA Nephropathy

Dr. Rizk:
Hello and welcome to KDIGO Conversations in Nephrology. I am Dr. Dana Rizk. I'm professor of medicine in the Division of Nephrology at the University of Alabama at Birmingham, where I also serve as the associate dean for Clinical Trial Research in the School of Medicine.

Joining me today to discuss the challenges of implementing evidence-based guidance for IgA nephropathy is our distinguished guest, Dr. Suneel Udani. Dr. Udani is a consulting physician at Nephrology Associates of North Illinois, also known as NANI and medical director of NANI Research. His clinical and research interests include glomerular diseases and cardiorenal syndrome.

Dr. Udani, welcome to the podcast.

Dr. Udani:
Dr. Rizk, thank you so much for inviting me and having this conversation.

Dr. Rizk:
Great. So, Suneel, I know, of course, you are aware of the updated KDIGO guidelines, and so my first question to you today is what are the most significant challenges to adopting these guidelines in your practice?

Dr. Udani:
As you well know and has been outlined, this is a rapidly evolving time in IgA nephropathy, and the guidelines that have just been updated are quite recent and we know there's definitely always a lag between them being published and then global awareness, especially in the community nephrology space.

So I think the first step is awareness and awareness of the specific changes that have been highlighted. The first being the proteinuria threshold and that's really a much lower proteinuria threshold than we are previously used to or previously had been targeting has been outlined, the guidelines really getting proteinuria down to as low as possible. If you can get under 0.5 g/g ideal, but really as low as possible as opposed to simply being okay with the UPCR of 1 g or slightly below.

And the second thing I think is a key thing that'll be a new change in the guidelines is the idea of simultaneous therapy, of multiple targets of treating renal protection with our conventional agents such as RAAS inhibitors, SGLT2 inhibitors, as well as endothelin receptor antagonists, while also treating the immune and inflammatory nature of IgA nephropathy. This is a very different concept than was previously outlined, and I think disseminating this information is going to be the first key. It's also a shift in the paradigm, and nephrologists are not used to and no one is comfortable with implementing multiple therapies at once. There are certain disease states where we've done this, lupus nephritis perhaps, and certainly in the transplant arena we've done this, but not for IgA. IgA, it's been trying to find a single therapy that has been effective or a single therapy that's been helpful. We know that's, you know, with the advent of multiple new therapies available, demonstrating reduction in proteinuria, preservation of renal function, and knowing the natural course of this disease being quite severe for young people in terms of an expectation that they'll progress to end stage kidney disease. We know that this sort of multi-targeted or simultaneous approach in treating the whole aspects of IgA nephropathy become key. So I think

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it's definitely a hill that nephrologists have to sort of climb in terms of their understanding, their adoption, integrating that into their—not only their cognitive approach to IgA nephropathy but their day-to-day therapeutic interventions.

Dr. Rizk:
Yeah, absolutely. And you mentioned changing the therapeutic goal of proteinuria. As you mentioned, the bar is much higher and we try to target lower and lower levels of proteinuria. And I think the guidelines also for the first time kind of recommend performing a kidney biopsy to diagnose the disease once you see a proteinuria of 0.5 g/day, which was not really spelled out in the previous guidelines. So again, increasing, hopefully, detection of the disease at an earlier stage.

Dr. Udani:
I think we've been so complacent with our approach because we thought there was nothing to do, or at least the things that were available, ie, glucocorticoids or conventional immunosuppression like cyclophosphamide, that from the previous guidelines really highlighted that we should move away from those because of the toxicity. And so there was—I think that people were, exactly to your point, that people would, you know, 0.8 g/g or right around 1 that had microscopic hematuria. They said, yeah, we think it's IgA nephropathy. We're not going to do anything differently. We're going to treat with RAAS inhibition, etc. And so we didn't make a definitive diagnosis, but I think, you know, I'm hoping that it's not just IgA that changes with this, but really a global direction of really defining kidney diagnoses more precisely so that we really can, then, provide the specific recommendations for patients that help them.

Dr. Rizk:
Yeah, I couldn't agree more. So there have been a flurry of new clinical trials and new therapies as we just mentioned. What are the key learning points that we can take away from the clinical trials in IgA nephropathy, their design, the outcomes? And conversely, what key knowledge gaps have been also highlighted in adopting the new classes of therapy?

Dr. Udani:
Yeah, it's such a great time in terms of the evolution of trials and therapy, and I think, naturally, one of the key steps—and as you were, I'm sure, involved with this idea of looking at proteinuria reduction as a surrogate outcome for kidney protection and the idea of the FDA adopting that through the partnership between KHI and industry and ASN and the FDA, that allowing for an accelerated pathway of approval. And then, of course, then waiting for the 2-year data to get confirmation. And what we've seen really so far to date is that that is translated over each time. The proteinuria reduction that's been achieved has also translated into preserved kidney function. So it's reassuring to see that surrogate outcome that has been sort of accepted is demonstrating a better validity.

I think the other sort of stark reality that we've seen is what happens to folks in the control arms, in particular the degree of GFR loss. And I think it's, again, easy to overlook in these young folks with fairly well-preserved kidney function, oftentimes at diagnosis and even as we're seeing them. But they are, when we look, and it's certainly in the clinical trial setting, we can see they're losing 5 mL/min/year in the control arm, variable of course. It's been a harsh reminder of the natural history of this disease and why it's so important for us to act.

I think there's a couple other things that have been notable. I think it's been great that the more recent trials have allowed for SGLT2 inhibition in addition to RAAS therapy. So I think it's told us 2 things. One is that the use of SGLT2 inhibitors, while helpful, does not provide a treatment as an overall. People still need specific therapies for IgA nephropathy, but it hasn't attenuated the benefits either.

Also, it's been key that there's been a wide variation in terms of where people are in the disease state, where I think that the idea of complacency and saying, oh, this person had a biopsy 5 years ago. They have this much proteinuria. These are folks that are enrolled the trials and then they're still eligible for these new therapies that are becoming about.

There certainly are unanswered questions, though, as you alluded to. I think first is what happens when patients are freshly diagnosed? Really, these are patients that had an established diagnosis. Usually by the time they have a diagnosis they've had sort of established disease. They've run through at least supportive care. So what about patients that are newly diagnosed? What's the role of these therapies up front as opposed to going through our conventional markers of RAAS inhibition first and sort of watchful waiting? We have not had, at least to date, more information on which subtypes in terms of biopsy or histologic classifications, Oxford classifications, may respond to different therapies and really how long those therapies need to be maintained. The trials are all fairly similarly designed. They have 2-year trials. They have open-label extensions. And so we know at least that's how long people were in the trial and how long to be on therapy. But is there an endpoint? And I think we don't know yet. And naturally patients want to know. And I think that's—

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unfortunately we just have to be very honest and transparent. We don't know yet. Certainly we hope to know, but at least for now we'd say if this is helpful now and tolerable and safe, we should implement.

With the flurry of therapies, the other sort of a good problem to have is which therapy is best for each patient. I think especially with multiple pathways being looked at, we know that the supportive pathway of endothelin receptor antagonism and angiotensin receptor antagonism. But in terms of targeting the gut with enteric budesonide or targeting APRIL and BAFF or targeting complement, which of these pathways is going to be important for each patient? I think that's what's certainly the next question. And for clinicians, the hardest part is going to be saying, okay, well how long do I wait before potentially modifying therapy? How do I know they're responding? And what's the sort of the best response they're going to get? And I think, again, these are questions that we ultimately need to know.

Dr. Rizk:
You mentioned great points, Suneel, thank you for all that. And just to remind the audience that we are still writing this chapter, writing the story, right? I mean, it's been tremendous success so far and hopefully it will continue, but some of these questions will be answered hopefully with more science coming out.

Dr. Udani:
To your point, and I think that's what is also hard about adopting these in clinical practice, is this idea of the unknown. For clinicians doing things every day, we sort of have all these things. We relied on these sort of things that we we've been using for the last 30 years. And with all these unanswered questions, we have to be comfortable with that lack of knowledge and still think, hey, I got to do what's best for my patient, even though we don't have all the answers right now. Again, as long as we're looking at safety and all those things.

Dr. Rizk:
Yeah, absolutely. And again, have the confidence that these questions, you know, science is still trying to answer.

So if you're just tuning in, you're listening to the KDIGO Podcast on Challenges of Implementing Evidence-Based Guidance for IgA nephropathy. I'm Dr. Dana Rizk, and I have the pleasure of speaking today to Dr. Suneel Udani.

So, Suneel, with all the, again, exciting news but also challenges that we've been talking about, what in your mind are strategies to increase the implementation of these new guidelines?

Dr. Udani:
I think we can learn from some of the experience that we've had with evolution in renal therapeutics as of late, including the SGLT2 inhibitors in the sense of seeing how did adoption come about with those therapies. And I think that first is, of course, the distribution of knowledge. And I think that it's no longer the case where people are always reading journals, or if they are reading journals, it's no longer the case that everyone can go to scientific meetings. So we have to be innovative, and I think things like this where either podcasts or webinars that are asynchronous so people can listen in when they have the time. I think that's key.

I think that identifying the local people that are helpful, right? I mean, I think ultimately physicians want to do the right thing. But when it's a new therapy, there's natural anxiety about it. And so who do they trust locally? Because naturally there are guidelines and there are national speakers. But ultimately you want to have someone that it's local, you can be comfortable with. I think that's the key in terms of this idea of a hub-and-spoke model of expertise or identifying local centers of excellence or local experts that people feel comfortable with approaching.

And then for the people that are experts being open to and accessible to people to so that they can walk through cases and walk through concepts so that these things become less intimidating. The new therapies and things, and that can be, again, in a formal way, informal way.

I think that now we know that there's online forums. ASN Community has one. People have chat groups of their practice or the local communities that are key that can be accessed as ways to say, okay, yeah, I have this case. How would you approach this? What do you guys—can someone help me understand the new data on X therapy, etc.

So I think all of the above. We can't think of it as just saying put it out there and expect people to do it. We have to engage people where they are, and finding where they are is the key.

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And then ultimately, I think as we evolve, I think at some point we have to also have expectations to say, okay, this is the standard of care now that we approach this and give clinicians feedback.

And the last thing I'll say is what is more motivating than anything else is a motivated patient. And as we educate patients that there are better therapies available, when they go into the nephrologist's office and say, hey, I've read about this or I've heard about this, can you help me understand if this would be helpful for me? I think that always spurs people to learn and do more.

Dr. Rizk:
Yeah, keeping the patient central. Absolutely. There are patient advocacy groups and we're certainly making a lot of effort providing lay summaries of even scientific publications. So I think all that disseminates information both to physicians but also to patients.

So what are, in your mind, remaining research or evidence gaps that we need to fill in?

Dr. Udani:
I think there's always been subgroups in each of the trials that have not been included. IgA vasculitis has been one that has been excluded, really, from all the trials that I've observed. And so in adults particularly, there can be overlaps with conventional IgA nephropathy. So all these therapies would be implemented in their cases.

The pediatric population. I'm an adult nephrologist, so I can't say I see pediatrics, but I know that my pediatric colleagues, they need trials and data for their patients as well.

Or people that may have secondary forms of IgA and, again, which of these therapies that we see are safe and effective? We have designed these trials based on previous KDIGO guidelines, which was at 1 g/g UPCR as the threshold. What about lower degrees of proteinuria? If we get people down to 0.6 or 0.4, but they still have hematuria, they still have IgA nephropathy, do they also benefit? I think that, again, we don't know the answer to that question yet, but I have to believe that that is a critical thing for us to know so that we can really make sure that all patients have good options.

It's been great, it's been a lot of positivity in terms of the clinical trials and the evidence of proteinuria reduction and GFR preservation and many of them to date. But what we don't always have with those trials is the granularity of understanding who doesn't respond. And I think that's going to be a key thing to say, okay, well why does this person not respond to this therapy, but they respond to the other one? And kind of when, as a point of saying, are there markers that we can look at that say, okay, this person's having a response and this is helpful, beyond looking at just simply proteinuria, beyond looking at GFR even, and without repeating a biopsy, so noninvasive ways that we can perhaps look at response rates and then get a better idea of who doesn't respond.

Each of the trials have also included individuals with fairly significant kidney disease. Thresholds have been eGFRs of 30, but most of them had exploratory cohorts of 20 to 30. And so, again, is there truly a point no return? I think the previous KDIGO guidelines were very clear that there's a point no return and then to not institute immunosuppression in those folks. But again, that was when we're using therapies that had higher toxicity profiles. So with therapies that are safer, is there truly a point no return where they don't benefit at all? Or what is that incremental benefit and is it worthwhile? But with ultimately those folks progressing to end-stage kidney disease and needing transplant, then what happens to the post-transplant period? We know IgA comes back and the allografts either—at least histologically it comes back. But what about those folks that have more clinically relevant disease? Are these therapies safe to use with background immunosuppression already? Are they effective in the same pathways? I think those are interesting and naturally exciting questions as we learn more.

Dr. Rizk:
So what I heard you say, Suneel, is we're going to need more clinical trials, perhaps in some populations that we left out. We're going to need real-world data, and we're going to need to just answer these questions, as you alluded to, by a hodgepodge of sources to fill in all these gaps as we start applying the guidelines. So, great points. Thank you for sharing that.

So before we close, are there any final messages you'd like to leave with our listeners?

Dr. Udani:

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There are knowledge gaps, there are implementation challenges, but undoubtedly this is an exciting time for IgA nephropathy—the patients and the nephrology community and our clinicians. And we need to embrace the knowledge that we've learned. The success of these new therapies that have demonstrated efficacy, tolerability, safety, as well as a more sort of insightful paradigm in terms of approach to therapy. Simultaneously treating the kidney-specific targets in terms of things we've been doing supportively as well as novel pathways to do that. But also treating the immune-related kidney disease. I guess ultimately this is an autoimmune glomerulonephritis, and similar to other autoimmune glomerulonephritis, we need to find the effective ways to treat that immune concept.

It's remarkable to have been part of some of these trials and to see the patients that have been willing to be part of that. None of these straws can be that big, right? The IgA nephropathy is not a common disease, so every patient counts so much, and it's incredible that this many patients have stepped up to be part of this process. And we are incredibly grateful to them for doing this and helping us advance the science. As well as the whole research teams have been part of it. The PIs, the coordinators, the sponsors that have made a commitment to developing therapies that have been otherwise forgotten. So I'm very excited that this really has changed the game in our way we evaluate and treat IgA nephropathy, and now the key step is us doing the work to deliver these therapies to patients.

Dr. Rizk:
Suneel, I want to really thank you for joining me today. It was great having you on the podcast.

Dr. Udani:
Dr. Rizk, thank you so much for inviting me and the conversation. Always a pleasure to talk to you.

Dr. Rizk:
Absolutely. I am Dr. Dana Rizk, and to access this and other episodes in our series, please visit kdigo.org/podcast. Thank you so much for listening.

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