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Treatment Revolution in IgA Nephropathy

Announcer:
Welcome to KDIGO Conversations in Nephrology. This episode titled, “Treatment Revolution in IgA Nephropathy,” is provided by KDIGO and supported by Travere. Here’s your host, Dr. Dana Rizk."

Dr. Rizk:
Hello. Welcome to KDIGO Conversations in Nephrology. I am Dr. Dana Rizk. I am a 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 trials research for the School of Medicine. Joining me to discuss the latest updates in IgAN treatment is Dr. Shikha Wadhwani. Dr. Wadhwani is an associate professor of medicine at the University of Texas Medical Branch and her clinical and research interest center around glomerular diseases. Dr. Wadhwani, welcome to the podcast.

Dr. Wadhwani:
Thank you, so happy to be here.

Dr. Rizk:
It's a pleasure having you. So today we're gonna discuss the treatment revolution that we're witnessing in IgA Nephropathy and understanding how the IgA Nephropathy pathophysiology contributed to this revolution. So let me start by asking you, how has the IgAN treatment paradigm changed since the KDIGO 2021 guidelines were published?

Dr. Wadhwani:
Yeah, so it's kind of incredible. You know, so much has changed in just four years, and I think prior to this not much movement had happened in this field. And now we're at a place where there's really been like a seismic shift in the treatment paradigm. Really based on our improved understanding of the disease, the risks associated with the disease, and as we're all excited about, new available treatment options. So, you know, for decades the focus has really been on the effects of the disease, which we really collectively called supportive care. And we would only resort to immunosuppressive therapies such as corticosteroids in those patients who did not have a proteinuric response to those supportive measures and remained at what we called high risk. In the past, we thought that threshold was greater than a gram per day of proteinuria. But as you know, the 2021 CKD GO guidelines were an update to the 2012 guidelines, and so much has changed in this field since 2021, that there has been a need for a major update given the trial successes, which really led to the availability of therapies that now target not only the consequences of nephron loss, but also the drivers of the disease.

Dr. Rizk:
Absolutely. And it sounds like these updates may start coming more frequently which is wonderful. So how did understanding the pathophysiology of IgA Nephropathy contribute to this therapeutic revolution?

Dr. Wadhwani:
You know, I think that's a really important piece of this. Really, I think better understanding the disease pathogenesis, reframed how we think about our therapies, and moved us from kind of, a generic way of treating everyone the same, to really being able to target specific hits in the four hit hypothesis of IgA Nephropathy, which we're all becoming much more familiar with. So, when we think about a genetically susceptible individual, it's really felt that IgA Nephropathy is initiated by increased production of Pathogenic Galactose-

deficient IgA1 in response to some sort of environmental or infectious trigger, and we collectively named that HIT 1. And then that antigenic, Gd-IgA1 is then recognized by anti-Gd-IgA1 auto antibodies. And that piece of it is called HIT 2. And then the Gd-IgA1 and the autoantibodies combined to form immune complexes, which we call HIT 3. And those immune complexes go and deposit specifically in the mesangium of the glomerulus which is that fourth HIT. And that's when we get the glomerular inflammation, complement activation, and subsequent damage to, our glomerular capillaries, which leads to the hematuria and proteinuria that we can detect in clinic and, you know, sets off our protocol for evaluating that patient, getting a kidney biopsy, et cetera. So I think now that we are able to think about this disease from this sort of four HIT hypothesis, we are able to then say, you know what? We, we don't just need to address one part of this hypothesis. We can really look at targeting specific HITs. We can look to maybe combining therapies and trying to target multiple HITs so that we can hopefully have greater success. And I think that's what we're seeing with the, the recent clinical trials.

Dr. Rizk:
That sounds great. So if you're just tuning in, you're listening to the KDIGO Podcast on treatment revolution in IgA Nephropathy. I am Dr. Dana Rizk, and I'm speaking with Dr. Shikha Wadhwani. So Shikha with the larger armamentarium of available therapies that you just alluded to, what are some of the factors to consider when selecting specific agents?

Dr. Wadhwani:
Yeah, this is a great question and it's one that many of us in this space are really fielding regularly. I think that just like with any other condition, we have to weigh risks versus benefits and actively engage our patients in these decisions. So I think that's the number one thing. So there's no one size fits all therapy plan, especially when it comes to treating a disease with not only heterogeneity in terms of the presentation of the disease, but also in terms of disease course and prognosis.

So we now have the luxury of having observational registry data from multiple large international cohorts, which all point to the fact that IgAN patients have a very high lifetime risk of kidney failure, even at proteinuria levels that were traditionally thought to be safe or low enough. And we know from these studies as well as our recent, you know, randomized controlled clinical trials that patients who were treated with RAS inhibition alone actually have significant eGFR decline even just in nine months, which is at the time of interim analysis for phase three trials currently. So we've learned that in order to truly avoid kidney failure in the lifetime of our patients, our patients need to be able to reduce the rate of kidney function loss to around, one ml per minute per year, GFR which is essentially that of the normal population after the age of 40.

So to me, anyone who presents with proteinuria over 0.5 grams per gram needs a kidney biopsy to, first of all, definitively diagnose IgA Nephropathy and then initiate treatment. So I think the paradigm is really shifting to thinking about simultaneously addressing consequences of nephron loss and drivers of disease simultaneously. And so that means that we're sort of automatically considering a multi targeted therapy regimen. And just like with other autoimmune diseases we treat, I think we're really shifting our concept of what is standard of care.

So when I think about this, and I think there's a lot more that we need to learn about the new therapies and real world evidence is of course gonna be extremely helpful in addition to the trial data. But, you know, patients who have a very high degree of proteinuria have declining GFR. Or some people may think about, you know, an inflammatory phenotype on a kidney biopsy. Those may be patients that are more likely to be prescribed immunomodulatory therapies. But, in many ways, this is really a reactive rather than a proactive approach. And some people would argue that all IgA Nephropathy patients should be offered immunomodulatory therapy to really prevent disease progression and not just sort of cover up the problem that we've already discovered.

So, the choice between therapies that target the earlier HITs in IgAN pathogenesis is challenging. And part of that is because the patients enrolled in the recent trials are pretty similar. And also because the published analyses we have thus far has not shown that certain subgroups seem to respond while others do not. It's also important to note that patients in the recent trials were not enrolled at the time of biopsy, so it's really difficult to make any suggestions based on kidney biopsy findings in particular. And that's something that, you know, comes down to conversations between the nephrologist and the patient. But I, I really think that ultimately the decision of what therapies to start with will come down to what's accessible in that particular country or province, and whether the patient has any particular preferences regarding the mode of delivery, potential side effects et cetera.

Dr. Rizk:
So it goes back to the conversation, the one-on-one that you have with your patient when you see him or her in clinic. No question about that.

So what are the roles of the traditional therapies, the non-pharmaceutical lifestyle, non-systemic steroids therapies in the context of these new agents? So we've relied so far on lifestyle modification, RAS inhibition, as you mentioned, and then systemic steroids when needed. What, what are the role of these traditional therapies in this new world?

Dr. Wadhwani:
Yeah, so you know, I think when we have better and we know better, we should do better. So we of course always need to educate our patients on blood pressure control. You know, focusing on a healthy low sodium diet, weight loss as applicable. But I don't think we should be complacent, and I think we need to instead be willing to gain experience with new therapies. And as someone who, really focuses their career on clinical trials In my new role at my job, I also want to put a plug in for continuing to enroll patients in clinical trials so we can hopefully have even more treatments available for our patients in the future.

So, I'm not saying there's no role for traditional therapies but I think that we owe it to the many, many participants in clinical trials who got us to where we are today to really utilize the new drugs we have so desperately been hoping we could offer our patients. Finally. So, as you know, there was not a head-to-head trial comparing TRF budesonide to systemic corticosteroids. But, depending on, you know, where you are and whether the former is approved and accessible and affordable in that particular country or province, I do think that nephrologists may prefer the TRF budesonide due to perceived superior side effect profile and perhaps also beneficial local inflammatory effects. So I think there's definitely a movement in that direction, especially because we know. All the terrible side effects that come with systemic corticosteroids.

On the other hand, we also now have a, you know, a dual endothelial angiotensin receptor blocker, which is Sparsentan. And that was studied against an active comparator, Irbesartan, and there was a clear benefit on proteinuria EGFR with the Sparsentan which probably makes it, you know, a better choice in patients who have access to and can tolerate this new drug given it was compared directly to maximum dose RAS inhibition.

And then we, of course have SGLT2 inhibitors. We have two large scale trials that included a significant number of IgA Nephropathy patients, and they saw similar benefit over placebo in those patients with IgA Nephropathy just like they did in the rest of the cohort. So in patients who have IgA Nephropathy and decrease GFR at presentation, I do think that most of us would agree that there is definitely a role for SGLT2 and inhibitor therapy.

And then, you know, the story doesn't stop there. So we now have complement inhibitors, anti-APRIL or APRIL/BAFF therapies and plasma cell therapies that are all in phase three clinical trials. So we will definitely be keeping our KDIGO friends very busy updating the guidelines in the upcoming years because I think there's, there's a lot more to come.

Dr. Rizk:
Yeah, absolutely. And these are, you know, living, breathing documents that need to be updated as new data is generated. So before we close Shikha, are there any final messages you'd like to leave with our listeners?

Dr. Wadhwani:
Yeah, thanks. So I think, you know, as many of us say these days, we're truly in the midst of a revolution in IgAN and this is really due to decades of global research by groups like your own and as well the landmark success in the Kidney Health Initiative, which established endpoints for clinical trials and IgA Nephropathy.

So, there are, in my opinion, far too many people with this disease ending up needing dialysis or a kidney transplant. And we have to remember that these patients are typically diagnosed in their twenties and forties, which is very, very young. So in my mind, you know, my message is, let's seize the moment. Let's shorten the time to diagnosis, and then once we have a diagnosis, we really need to change our mindset to start with a multi targeted approach to this disease and eliminate any sort of therapeutic inertia we may have. And then above all, I think we need to continue to ensure we're engaging our patients in these discussions by educating them and really understanding their goals of care.

Dr. Rizk:
Thank you so much. Dr. Shikha Wadhwani. Thank you for joining me. It was great having you on the podcast.

Dr. Wadhwani:
Thank you so much, Dana. It was lovely to be here.

Dr. Rizk:
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, and until we meet next time.