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Overview of the Latest Guidance in IgA Nephropathy Management

Announcer:
Welcome to KDIGO Conversations in Nephrology. This episode titled, “Overview of the Latest Guidance in IgA Nephropathy Management,” is provided by KDIGO and supported by Travere. Here’s your host, Dr. Dana Rizk.

Dr. Rizk:
Hello and welcome to KDIGO Conversations in nephrology. I am Dr. Dana Rizk. I'm 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 Trial Research in the School of Medicine. Joining me to discuss the latest guidance in IgA Nephropathy Management is Dr. Brad Rovin. Dr. Rovin is Professor of Medicine and the Lee Hebert Professor of Nephrology at the Ohio State University. He is an expert in glomerular diseases and co-chair of the KDIGO Glomerular Disease Guideline Working Group. Dr. Rovin, welcome to the podcast.

Dr. Rovin:
Thank you so much for having me. I'm very excited to be here today and to open up this series on IgA nephropathy.

Dr. Rizk:
Let's begin our discussion with why are we updating the KDIGO guidelines? And what have been the key developments in the IgA nephropathy space since the 2021 Glomerular Disease guidelines were published?

Dr. Rovin:
Sure. The reason we are updating the guidelines, and we'll almost certainly need to continue to update the guidelines on a very frequent basis, has been the explosion of new therapies that are being tested and in fact, some of which have been fully approved and some have accelerated approval. So, for the first time in my career as an nephrologist, we actually have targeted therapies for IgA nephropathy. And I think that this has created lots of opportunities for us, but it also has created a considerable amount of confusion in the community.

The therapies, as you well know, are quite varied in what they do and what parts of the presumptive pathogenesis of IgA nephropathy they act on. And they all have different, you know, strengths and weaknesses, and it's really going to be a learning experience of how to use these. The KDIGO guidelines were developed with this in mind and to provide some starting point, really. Not to tell people what to do for every individual patient, but to provide a starting point of how we would approach a patient, especially with the new therapies that are available.

Dr. Rizk:
Yeah, you make a great point. These are guidelines. They provide guidance, not edicts which is very important. So what are the key take home messages from this new guideline?

Dr. Rovin:
Yeah, so the updated guideline, in my opinion, has two really important messages for the community. One is that IgA nephropathy is not a benign disease. It's not a disease that we can watch and wait. There should be a sense of urgency when we see patients with IgA

nephropathy to protect the kidney and preserve renal parenchyma because by and large the patients with IG nephropathy present early in life and have a very long time horizon with which to unfortunately deal with this chronic disease.

The other big important issue is that we have changed our goals of therapy. We were very content in the past, and I was taught as, as were you when we were fellows, that if you got the proteinuria and IgA patient down below a gram, you were doing great and that patient would do really, really well. New data suggests that that may not be the case and certainly is not the case for not all patients, but a sizable minority. And I think we have to really, and we did, rethink what our, real goals are.

And then as we started to test the new therapies, we actually saw that not only were we reducing proteinuria, we were having a nice impact on GFR stability. And so we, we put forward a new goal for proteinuria, which I'm, I'm sure we'll discuss shortly. And then a new goal for what we really want to achieve in terms of GFR over time and decline of GFR over time. Unfortunately, I use the word decline because as we get older, we all have a decline in GFR, but we want that to be as, as small as possible to preserve kidney function for our lifetimes.

Dr. Rizk:
So to achieve all these goals or to start to implement any therapy, we have to identify patients with IgA nephropathy. So how did the guidelines approach the importance of biopsies? Did the threshold to perform biopsies change? Can you give us a little bit of information about that?

Dr. Rovin:
Yeah. So, we now know that you can have substantial histologic disease with pretty low levels of proteinuria. And so as the audience I'm sure realizes there is no specific biomarker for IgA nephropathy. You cannot diagnose IgA nephropathy. With a hundred percent certainty based on clinical information. You can have a pretty good guess, and that's okay. But the confirmation is with the biopsy. Someday that may be different. We may have specific markers that suggest like PLA2R perhaps for membranous suggest what the disease is. But right now we need the biopsy and we really recommend a kidney biopsy in patients who have, more than 500 milligrams of protein per day. And that's a little bit different than we did in the past. We sort of said, well, maybe a gram of protein a day, et cetera. But I think given the new information on the relationship of low levels of proteinuria with future kidney failure we want to really push to get the disease diagnosed early.

Dr. Rizk:
Yeah, and biopsies add prognostic information as well. So there's always that. It's two for one, as I tell my patients. I'm sure you tell your patients in clinic as well.

Dr. Rovin:
Well, you know, and I think anyone in the audience who knows me, knows that I really believe in understanding what's going on at the tissue level. And I think we don't know how all the tissue findings correlate clinically over time. And I think this is really important for us to explore. And yes, I absolutely look at the biopsy with my pathologists after, you know, the, the tissues come out, I look at how much fibrosis there is in the tubular interstitium. I look at the number of glomeruli that are damaged. It helps me to explain to the patient what I think is going on and how I think their kidney will do.

And it also, and I know I'm not supposed to say that, and let me, let me preface this. This is my opinion. It's very clear in the guideline that at this point in our understanding of IgA, we do not have sufficient information on the biopsy to guide which therapy to choose. Having said that, when I look at a biopsy and if it's a very mild disease and not very inflammatory, I might go with therapy A and if it's really very inflammatory and very aggressive looking, I might go with therapy B. Now, again, that's a personal choice and we don't have the data to support that yet, but I do believe that we will have those data in the future, and so then the biopsy will become even more important in, in my opinion.

Dr. Rizk:
Absolutely. So if you're just tuning in, you're listening to the KDIGO Podcast on Overview of the Latest Guidance in IgA Nephropathy Management. I'm Dr. Dana Rizk, and I'm speaking with Dr. Brad Rovin. So Brad, the other thing that is recommended by the guideline is the use of the IgAN prediction tool. And can you tell us a little bit about the idea behind this guidance and any shortcomings from the prediction tool?

Dr. Rovin:

Yeah, so the prediction tool was, was quite a feat of mathematics and statistics and putting together large data sets. And the idea was, at the time of a kidney biopsy taking the information histologically as well as the clinical features of that particular patient like GFR, blood pressure control, medications they might be on ethnicity, et cetera. Could you then come up with a number that gives you the risk of having a 50% decline in GFR over five years or four years? You can pick the time in, in the calculator so that was the original calculator, and then it, it's really morphed a little bit. Now you can use biopsy findings within two years of, of putting the data into the calculator. They have a calculator for young people, for children, and, and so, the idea is to give you and the patient something to talk about in, in terms of prognosis that's a number.

Now what, what I do find a little bit, not a, a shortcoming, but you have to really think about this. You're talking about one point in time over a patient's entire lifetime, and you're talking about a prediction over the first five years, for example, after a biopsy. But the patient has to live with this disease for many, many years beyond that. And so what may sound like something reasonable, no deterioration or progression towards kidney disease is reasonable. Let, let me just reassure the audience that that's my belief. But if you said to somebody who's young and invincible that they have only an 8% chance of doubling their serum creatinine in five years, they may say, well, that's not very much. Playing the odds. So I think that could be a little bit misleading.

So I think it's really incumbent on the nephrologist discussing the results of these of this tool, of this percentage to say this is for the first five years. You know, if over 10 years, it's 16 or 20%, and then it's, you know, 30 some percent. That's really much more scary. And I would not like people to use this tool to say, oh, you got nothing to worry about. I use this tool to help me show the patient where their disease is currently at, where it could go, and what we might actually achieve by intervening right now. And my hope of course, is let's say a person has a 10% risk. I want that risk to be under 1%. I'd love that risk to be 0% if that's possible. So, I think you and I and the people who use this tool really need to explain it nicely to patients and well, so that they understand it. Because a single number taken out of context is almost meaningless and could potentially be harmful.

Dr. Rizk:
Yeah, absolutely. So it doesn't stop. The risk doesn't stop at five years. That's

Dr. Rovin:
No, it doesn't. It keeps going. Yeah.

Dr. Rizk:
For the time being. So, so Brad, we heard from at least comments after the draft was released for public review, that the treatment initiation threshold and goals may be too aggressive. So can you give reasons justifying this approach, given the guideline?

Dr. Rovin:
You know, when we were writing the guidelines and it was out for public review, the, the major paper that really pushed us to understand the real urgency. I think a lot of us, as nephrologists sort of knew in the back of our minds that this was not a benign disease and that you didn't need a whole lot of proteinuria and a lot of our patients were coming in already when we made the diagnosis, with impaired kidney function. And it was not a mild impairment. It was often a moderate impairment. The British data from the RaDaR study was really sort of the banner suggesting to us that patients with under one gram of proteinuria are between 500 milligrams and one gram, sort of that safe zone that we had assumed in the past. Really, those patients, about 30% of those progressed towards end stage renal disease. Over the following 10 years and even more scary to me or more, you know, raising our awareness is that patients under 500 milligrams also could progress about 20%. So I, I think that this is something that, you know, we sort of had a gestalt of, but there it was in black and white.

And then since then, there's been a number of, of publications that have indicated that very low levels of proteinuria do incur a risk beyond that of no proteinuria in patients with IgA nephropathy.

And what is no proteinuria in patients with IgA nephropathy? Well, right now, even in the guidelines, we, we sort of define complete renal responses. Less than 300 milligrams of protein. And, and if you actually look at the data patients with 300 milligrams or less of proteinuria tended to have a fairly flat slope of decline of GFR, but that slope wasn't zero. As it turns out there, there was still some decline in GFR, and I think it might have been the Swiss study that looked at very low levels of albuminuria. And you could see that there, there was risk even up to 300 milligrams of, of proteinuria. Now, of course these are in particular populations, et cetera, et cetera, but when you take the bulk of the data together, there's studies to this effect from China studies to this effect from the United States,

from the UK and other places in Europe. You really get the picture that we overestimated, I believe, the amount of proteinuria that was quote “safe” in IgA nephropathy and, and so I do not think that our guidance is too aggressive. I think that our guidance is, is spot on.

I always try to think of, if I had a glomerular disease, what would I want done and I would want it treated. I don't want to play the odds. Now, you and I both know, we've seen patients certainly for many, many years who've remained stable with a low level of proteinuria. That's the other problem is we don't know in whom this is going to be important and, and who it isn't going to be important in without having sort of the backlog of time.

So, I think this indicates to me that we need to approach this disease like we approach other forms of glomerular disease. While it may not be as rapidly progressive as an ANCA vasculitis or anti GBM or lupus, it certainly is progressive and waiting and waiting is probably not the right approach. And so having a target starting early and then you know, sort of putting therapy on board at that point to try to stem the progression to me will preserve more nephron mass for the future.

So that's to me the biggest factor of pushing this agenda, if you will, forward to be diagnosing earlier, treating earlier biopsying earlier. So I do think it's justified and it is evidence based in my opinion.

Dr. Rizk:
Yeah, absolutely. And like you mentioned at the beginning of this podcast, this is a living, breathing document that you will update as new data becomes available, perhaps new biomarkers, better risk stratification. So, you know, you have to follow the science as you put these guidelines together. So before we close Dr. Rovin, are there any final messages you'd like to leave with our listeners?

Dr. Rovin:
I think what we did in the guidelines, and I think we did get quite a bit of feedback, negative and positive, when we did the public review, is we do push an algorithm that's a little bit different than people are used to. And that algorithm suggests that we look at this disease when we see the patient in terms of the damage that has been done because of the IgA nephropathy already. So, in other words, the CKD that exists. And at the same time consider the ongoing immunologic disease.

And so one of the prominent figures, which we, we really worked on hard because there was a lot of confusion with the draft guideline on the figure, and I think the new figure is very clear. We are suggesting that you look at the patient and you treat the chronic kidney disease, and of course, how do you treat chronic kidney disease? Lifestyle modification, dietary modification, excellent blood pressure control, RAAS inhibition, et cetera. And then you treat the immunologic disease, sort of what the basis of what is causing the I nephropathy. Because we do have therapies now that target the immunologic disease, and I'm sure you'll get into this in later series on the podcast as to specific therapies and what they do. But for the first time, I think we can do both, and I don't think there's any reason why we can't start with doing two things at once.

Now, there are arguments on either side. If you do sort of CKD therapy and you inhibit proteinuria, we're taking away our best biomarker of what the disease is doing. But like in lupus and other diseases, many of us are now saying before we consider a person free of disease or heavy hit remission, we like to maybe take away the hemodynamic drugs that are causing proteinuria to be low to see if the proteinuria is really resolved. So there's little tricks you can do as well. So I don't think any of this harms our ability to actually understand how the disease is going in a particular patient as long as you pay attention to what medications they're on.

Dr. Rizk:
I want to thank my guest, Dr. Brad Rovin for joining me. Brad, it was great having you on the podcast.

Dr. Rovin:
It is really been a pleasure, and this is a very exciting time for not only IgA nephropathy, but for many of our glomerular diseases. So the more we can do this sort of thing, the better I think for our community.

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