Transcript Details
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Where Do Complement Inhibitors Fit in the IgAN Therapeutic Toolbox?

Announcer:
Welcome to KDIGO Conversations in Nephrology. This episode titled, “Where do complement inhibitors fit in the IgAN therapeutic tool box?” is provided by KDIGO and supported by Alexion. Here’s your host, Dr. Brad Rovin.

Dr. Rovin:
Hello, everyone, and welcome to the KDIGO Conversations in Nephrology. I'm Dr. Brad Rovin. I'm at The Ohio State University Wexner Medical Center, Division of Nephrology. And joining me today to discuss the use of complement inhibitors in IgA nephropathy is our distinguished guest, Dr. Sayna Norouzi. Dr. Norouzi is associate professor of medicine at Loma Linda University in California and the director of the Glomerular Diseases Clinic. Her clinical and research interests include the study of genetic and rare kidney diseases.

Dr. Norouzi, welcome to the podcast.

Dr. Norouzi:
Thank you so much, Dr. Rovin. It's a pleasure to be here, and thank you for the kind intro.

Dr. Rovin:
So listen, I know you have some news about where we can contact you after December 1st. So why don't you tell our listeners how they can get ahold of you if they want to ask questions?

Dr. Norouzi:
Sure, of course. I'm actually moving to UC Irvine and I'm going to be the director of GN and PKD clinics there, and I'm really excited. And, of course, you can find me in Irvine in Orange County after December 1st.

Dr. Rovin:
Okay, perfect. So let's start our discussion, and let's say, in terms of IgA nephropathy, we all subscribe, at least presently, to the 4-hit hypothesis of IgAN pathogenesis. Where do you put complement inhibition in that pathway as being effective, and what are your expectations for what it will do in IgA nephropathy?

Dr. Norouzi:
This is a fantastic question. Our understanding of IgAN is evolving, and the 4-hit hypothesis might evolve in the future as well. But so far, with the understanding that we have, complement inhibitors are probably going to work on Hit 4, and Hit 4 is the time that we have this mesangial deposition of immune complexes, that they lead to inflammation and scarring.

Dr. Rovin:
And you said this right at the beginning, of course, you said inflammation. When I think about complement activation, I think about inflammation. Is your expectation, and I know we don't have good data on this, but is your expectation that using a complement inhibitor in IgAN is actually going to reduce glomerular or intrarenal inflammation?

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Dr. Norouzi:
This is, again, the hypothesis that we have, hopefully we're going to see less inflammation and less fibrosis over time in patients who receive complement inhibitors.

Do I need more data to prove what I'm saying right now? Yes, of course.

Dr. Rovin:
All right, let's move on to our next question. This is another tough question. Given all of the available drugs in the United States, now I'm talking just the United States right now because we are very fortunate to have all of the new novel therapies available to us, when would you choose to start treatment of an IgAN patient with a complement inhibitor, how you do it in clinic?

Dr. Norouzi:
Yeah. This is a really good question. We do have the eGFR data and proteinuria data on iptacopan from the APPLAUSE trial. The analyzed eGFR slope was 3.1 per year versus 6.12 in placebo group, so the difference was about 3. And the composite endpoint for them was 21.4% in iptacopan versus 33.5% in placebo. Both of them were statistically significant, and they can make a difference in clinic.

We do have experience with ravulizumab in the past, and they released some high-level results couple of months ago about meeting their endpoints at week 34, which I'm sure that we're going to see more data soon as the clinical trial is ongoing.

When you talk about using complement inhibitors, I know that now we know more data about the eGFR data for B-cell medications, APRIL, and APRIL/BAFF inhibitors, and I'm sure your question is kind of leaning towards that now you know the data, how are you going to find indication for other medications?

And we have nonresponders, hyporesponders, and super-responders in every clinical trial that I really want to see the data, this kind of detailed data from every clinical trial. There are different combinations of patients that they might benefit from different medications. So it's really personalized at this point depending on their biopsy findings, what treatments they failed in the past, their clinical symptoms, how fast their eGFR is dropping, how biopsy is—we don't make decisions based on the biopsy findings, but the biopsy tells us how much inflammation you have and how much scarring you have and does affect how we think about the disease. I think anyone who says no, they are making a mistake because that's the reason that we do the biopsy. If it's not changing the way that we are thinking and how we are deciding about the treatment, then are we just doing the biopsy to know about the disease? For a patient who has a lot of scarring, the decision is different than a patient who has minimal scarring and a lot of inflammation on the biopsy.

So I do have patients on complement inhibitors in my clinic, and I have patients that are super-responders to complement inhibitors. And changing the treatment for someone who is responding really well to complement inhibitors because now we have data on other medications, I don't think it's absolutely necessary. Because if they're responding and you're controlling the disease and the patient is tolerating the medication, that's the optimal goal that you can achieve for any patients out there.

Dr. Rovin:
This nicely leads into my next question because you're using the complement inhibitors in your clinic, it sounds like, for particular patients.

Do you think you're going to use these long term? Or do you think you would use them until inflammation is controlled and then convert to something different? How would you think about that?

Dr. Norouzi:
This is a really interesting question. Having this hypothesis of doing a medication for inflammation, then switch to something. I know that we don't have the data on this yet, but I know it makes sense from the pathophysiology standpoint.

If you tell me that, are you going to go off after the inflammation first, and then you're going to use another medication to decrease the production of galactose-deficient IgA1? And the data on APRIL and APRIL/BAFF inhibitors are looking great. So from the hypothesis and pathophysiology of the disease, of course, it makes sense to me as well. Do we have data to prove this? We don't have it yet, and we might have it in the future too.

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For a patient who was really high risk, not responding to other medications or failing other medications, coming to my clinic, starting on complement inhibitors and responding really well, would I continue complement inhibitors for the duration of therapy? I will, because a patient is responding well, and they've exhausted other treatments as well. And other treatments, I may say, like maybe another line, maybe they've tried budesonide or another medication in the past. I'm not in a rush to change that medication just because I'm afraid of possible side effects of complement inhibitors because patient is responding well. And at some point when they are in remission, we're going to talk about stopping the medication.

If the patient is not responding well or the patient is really high risk for developing side effects from specific class of medications, I'm going to be more in a rush to adjust their medications as we get more data from other clinical trials. If they're responding to complement inhibitors and their eGFR is stable, I would continue the course of treatment.

But I understand the concept, and I would like to see study designs of going after the inflammation and switching to other medications to guide us and say that we do have some data, and it makes sense to switch you even though that you are stable, just because we want to minimize the possible side effects.

We don't have that such data, and my patients always come up with this question that, "You know, everything looks well, and I'm tolerating this medication really well, and my kidney function is stable, and I really don't want to switch to something else that I don't know how I'm going to respond to that medication."

And they are right, right? If something is going well, why try to switch to something else when there's not much data out there? In real life and with complicated patients, we're probably going to stick to the medication that is working for them instead of just chasing the pathophysiology of the disease.

Dr. Rovin:
Okay, so hold that thought. If you're just tuning in, you're listening to the KDIGO podcast on where do complement inhibitors fit in the IgAN therapeutic toolbox. And I'm Dr. Brad Rovin, and I'm speaking with Dr. Sayna Norouzi.

Sticking with the theme of if you have a patient with IgAN and you got a biopsy and it was inflammatory, let's say extensive endocapillary hypercellularity and some crescents, etc., how do you decide if inflammation's resolved? And particularly, do you repeat kidney biopsies in your patients with IgA nephropathy?

Dr. Norouzi:
Yes. I think kidney biopsy can guide us through the treatment, and there are so many clinical trials that are doing these biopsy studies on top of their trials as well, which is going to give us more information. I only do biopsies if I think that the biopsy is going to change my treatment course. So if my patient is responding to a treatment and proteinuria is going down, eGFR is stable, in the setting of IgA nephropathy, I do not actually repeat the biopsy unless they are part of a trial or something.

But for research purposes that makes sense. But if they are responding and they're doing well and tolerating the medication, the biopsy is something that I want to know, and I want to see the biopsy results, and it's interesting to me, but it's not going to change the treatment course for me. And I know what I'm going to do, the next step for my patients.

I've repeated biopsies for my IgAN patients, though, and most of the times I do that when they are flaring on top of the treatment, and it has happened before.

You see that proteinuria is going up or eGFR is dropping, and you become curious and say that, "Okay, let me repeat the biopsy and see what's going on at this point and how we should navigate your treatment." That biopsy, I guess, is really precious because it can help me to guide the treatment. And it's not just for research purposes at this point.

So I talk to my patients, and if they're open to that, I repeat the biopsy.

Dr. Rovin:
Let me push you a little bit. I think you said this, and I agree, and we say it in the KDIGO guidelines, which is, right now the biopsy

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shouldn't be used to guide our treatment because we don't have enough data, and I get that. And you said, which I also agree with, we do the biopsy for some reason, and we all probably use it a little bit to help guide the treatment.

I think if we're all being honest with ourselves, we look at the biopsy and it helps us form an opinion about how we might approach a certain individual. But let me push a little bit. The biopsy may not help us at the beginning to guide treatment, but as you said, if the patient isn't doing well, okay, maybe I need the biopsy to change treatment. What if the patient's doing really well? Do you want to continue that treatment? Couldn't you use the biopsy to say, "Well, maybe I can back off a little bit"? That would be beneficial to a patient.

Dr. Norouzi:
Yeah, of course, but I don't need the biopsy necessarily because patient is doing well, and I have surrogate markers, right? So I have eGFR, and they're not perfect markers, but if eGFR is stabilized and then proteinuria is in remission, then I don't need a biopsy to stop the treatment. I just talk to the patient and say that, "Do you want to give it a try and make it easier and see how you're going to behave?"

From the human side of that, not just the science, is that I'm working on this patient-reported outcomes with IgAN Foundation for IgA nephropathy, and I'm interviewing a lot of patients across the country right now with caregivers. These biopsies and these things that we do, it's stressful for them.

And we're talking about long-term therapies for these patients, so we have to be careful how much we are putting this pressure on the patients as well. As much as I want to see the repeat biopsy, I'm not sure if they're doing well, I'm going to give them an easier prescription from now on anyways.

Dr. Rovin:
Let's finish up with the last question, which you sort of alluded to at the beginning. So complement inhibitors in IgA nephropathy slow the rate of decline of kidney function, but not really to a slope of zero or minus 1. And so you had sort of said something about combination therapy at the beginning.

So would you consider, to get the GFR down into the rate where the patient hopefully won't progress to end-stage kidney disease, would you combine complement inhibitors with other drugs and to try and slow GFR even further than what the trials have shown so far? And if you consider that, what combination do you feel comfortable using right now?

Again, I know we don't have data on all of this.

Dr. Norouzi:
We don't have data on combination therapy. Is this happening in the community too? It is. It is happening, and people are using medications off-label as a combination therapy.

Have I had patients on combination therapy? Yes, definitely. I've had patients on steroids already in the community or CellCept or delayed-release budesonide coming in, and all of a sudden, they are flaring. The question comes up of how you're going to do combination therapy, or you're just going to taper down the medication and start something else? And that's the time that you're usually going to have some overlap, and you're going to do combination therapy as well. And I have patients on combination therapy because of these reasons. When we talk about combination, the question is are you talking about combining 2 immunosuppressants or having, for example, sparsentan, atrasentan on top of immunosuppressants?

Dr. Rovin:
What I wanted you to sort of think about, would you put 2 immunosuppressants together, including a complement inhibitor plus something else? Or would you do something that's not necessarily an immunosuppressive?

Dr. Norouzi:
Right. I mean for immunosuppressants, it's specific situations that you really need to do that, and it's an extensive discussion with the patient as well. For combining atrasentan or sparsentan with a medication, for example, complement inhibitor, I have patients on combination therapy, and I know that we don't have data on that, but I always discuss the clinical trials results and I have many patients

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that they are on combination therapy in terms of atrasentan, sparsentan plus complement inhibitors, delayed-release budesonide or APRIL/APRIL-BAFF inhibitors.

Dr. Rovin:
And it sort of makes sense when you think about it because you're hitting different parts of the pathogenesis. So presumably you're not duplicating an effect; you're hopefully making an additive complementary effect.

Dr. Norouzi:
We always say that we don't have data on this, and one of my patients was really educated the other day. He told me something really interesting, that, "Do you have data on combining all of the medications that I'm taking at this point?"

And I said, "No," and so I don't think that you have data on combination therapy because he's right. In real life, patients take many medications and if you want to think about it that way, they are taking GLP-1 agonist, they are taking multiple medications for their blood pressure. They might have diabetes.

So yeah, we won't have data on is that safe to do all of these medications together. And yeah. And he said that, "This is a risk that I'm willing to take, and if it's going to stabilize my kidney function, just the rest of my medications." And he told me, "Doc, I don't think you'll ever have data on all of my combination of medications that I'm taking."

And he's right. So I think at some point it makes sense if we have enough data to at least discuss that with our patients and see if we can maximize the treatment.

Dr. Rovin:
Okay. So we're out of time. We're going to close. Sayna, any final messages for the audience?

Dr. Norouzi:
I had a really good time actually today on this episode. Thank you so much for having me.

Dr. Rovin:
Well, that's what we wanted, to educate our audience with our own experience. So I want to thank Dr. Norouzi for an excellent discussion and joining me today. It was great having you on the podcast. And I'm Dr. Brad Rovin. To access this podcast and other episodes in this series on IgA nephropathy, please visit the KDIGO.org/podcast website.

And thank you all for listening.

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