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The Rationale for Complement Inhibition in the Management of IgA Nephropathy

Announcer:

Welcome to KDIGO Conversations in Nephrology. This episode titled, "The rationale for complement inhibition in the management of IgA nephropathy." is provided by KDIGO and supported by Alexion. Here's your host, Dr. Brad Rovin.

Dr. Rovin:

Hello, and welcome to KDIGO Conversations in Nephrology. I'm Dr. Brad Rovin. I'm a nephrologist at Ohio State University Wexner Center in Columbus, Ohio. Today, joining me to discuss the use of complement inhibition in the management of IgA nephropathy is our distinguished guest, Dr. Dana Rizk. Dr. Rizk is a professor of medicine in the Division of Nephrology and associate dean for clinical trials at the University of Alabama in Birmingham. Her clinical and research interests obviously include IgA nephropathy. And, Dr. Rizk, please, welcome to the podcast, and happy you're here.

Dr. Rizk:

Thank you, Brad. It's a pleasure to be here, and thank you for joining us for the audience.

Dr. Rovin:

All right, let's start our discussion. So this is the first episode in our complement podcast on IgA nephropathy. So, Dana, could you summarize so the general audience gets the genetic data suggesting complement has a role in IgA nephropathy?

Dr. Rizk:

Yes. So there was a couple of GWAS studies. These are genome-wide association studies. That's what GWAS stands for. And essentially what they do in these very complicated studies, they take a very large population of patients with IgA nephropathy and compare them to people that do not have the disease and look for signals or differences in the genetic makeup of these 2 populations.

And what they had—again, this is effort driven by primarily Columbia University. In the first study and the second study they showed a number of genetic variants that cause susceptibility to the disease, and those revolve around gastrointestinal mucosal pathways, IgA production, but also the complement system, and in particular, complement factor H was confirmed as a major genome-wide significant susceptibility locus, suggesting that the complement pathway is an inherited contributor to IgA nephropathy.

And it's worth mentioning that this included patients of European and Asian descent.

Dr. Rovin:

So before we get to question 2, were you surprised when you saw these data? Because here, I obviously work with lupus a lot, and the complement system is very active in lupus, consuming complement, etc. We don't see this in general in the clinical care of our patients very often. So this sort of surprised me.

Dr. Rizk:

Well, I think part of the surprise is the fact that when we check complement levels in the blood for these patients, we typically don't see any variance in the values. We don't see low C3, low C4 like you would in a lupus patient. Having said that, we shouldn't be as surprised. If you biopsy a patient with IgA nephropathy, in about 90% of biopsy cases you do see C3 deposited in the tissue, again, suggesting that there is complement activation and it's pretty obvious. And we have a lot of data, even clinical data in humans that support the role of complement in IgA.

Dr. Rovin:

So all of us remember from medical school that complement as—painfully remember, I should say, complement has 3 activation pathways. Which pathways are activated in IgA nephropathy?

Dr. Rizk:

Yeah, so the 3 pathways you're referring to are the classical pathway, again, the one you alluded to and that's quite activated in lupus patients, for example. And there's a lectin pathway and an alternative complement pathway. And the alternative complement pathway is activated all the time. It just gets ramped up or amplified when there is a stimulus for it to do so. And it is particularly activated in patients who have IgA nephropathy. There's also a subset of patients that seem to have lectin pathway activation, and maybe we'll discuss some of that when we talk about the human data.

So these 2 pathways seem to play a role, primarily the alternative pathway of the complement system.

Dr. Rovin:

Okay. So let's really talk about some of the human data now because this is, as you said, we do see complement in various amounts, I would say, when we do the biopsies of these patients. Always a curiosity when we don't see it really being consumed in the periphery. And then you put the genetic data together and you start to form a picture.

What about the observational data in human IgA nephropathy? What puts this whole package together?

Dr. Rizk:

Yeah. So we talked about the genetic data. There's also serologic data that the complement system plays a role and is activated. As I mentioned, the levels are typically normal. However, the lower they are within the normal range, for example, C3, the more severe the disease seems to be. And if you start looking for other complement components, which unfortunately we don't routinely look for, such as C5b9, a marker of terminal complement pathway activation, you can see it increase. And as it increases, patients have worse kidney function.

We talked about the histologic findings. So C3 is present in more than 90% of cases, and usually without the presence of C1q, the other complement protein we test for or check for by immunofluorescence, suggesting or supporting the fact that the alternative pathway is activated, but the classical pathway is typically not.

You can stain for C4d, and when you do find C4d, again, patients likely have lectin pathway activation and tend to have a worse prognosis, worse finding, and sometimes even evidence of thrombotic microangiopathy, which is a rare finding in IgA nephropathy, but quite a severe one with a pretty bad prognosis.

And then you can look at the urine of patients with IgA nephropathy and find high levels of soluble C5b9. Again, this evidence of protein pathway activation. And the higher the level, the worse the prognosis. And again, it's associated with severe histological findings.

So we've talked about genetic evidence, serologic evidence, and histological evidence that the complement pathway plays a role in humans and is associated with severe disease.

Dr. Rovin:

And I want to emphasize a couple of things that you just brought up. One of the things that I think is really important for our audience is that C3 has an enormous range of normal. And it can be very confusing because we seldom have a complement level in a healthy person. Like, what is their good baseline? And I've always been concerned that even if the complement level is normal in a person who has an inflammatory disease, perhaps it's at the lower end of normal and it's important for that individual. So that sort of really emphasizes what you were getting at.

The other thing that I think is sort of interesting, I had the opportunity to work with one of my fellows, and we actually measured complement activation products in the urine because I was so curious about complement and IgA nephropathy. And just as you said, we found elevated levels of C5b through 9, the terminal path, and we also found levels of BA, which is a byproduct of alternative pathway activation in C5a. So I think that what you're saying really resonates, that even though this disease did not have sort of the complement coverage that we thought about when we think about lupus, there is a good rationale for targeting complement in IgA nephropathy.

Okay. If you all are just tuning in, you're listening to the KDIGO podcast on why use complement inhibitors for IgA nephropathy. I'm Dr. Brad Rovin, and my guest today is Dr. Dana Rizk.

Okay, back to you. Traditionally, Dana, and this is going to take a little bit of explanation, and you can put it in the context of the trials that I know about and you've worked on.

Traditionally, when we think about complement, it mediates inflammation. And is this the role of complement activation in IgA

nephropathy, or can it be mediating other deleterious effects in the kidney after it's activated in IgA nephropathy?

Dr. Rizk:

Yeah, that's a great question. So we've traditionally thought about immune complexes in the blood depositing in the mesangium then kind of triggering inflammation, and that's where the complement participates in this injury. And there is certainly data that patients who have high levels of complement deposition also have crescents and have active inflammatory lesions. So that is definitely true.

What we probably underestimate—or at least I speak for myself, I underestimated—is also the association of this complement activation with chronic damage, so fibrosis. So for example, when you see C5b-9 that deposits in mesangial cells, that leads to proliferation but ultimately fibrosis and extracellular matrix deposition and changes suggestive of chronicity.

There is data in animals that complement activation leads to tubular interstitial fibrosis, and the same process seems to happen in humans as well. So the thing that also indirectly, perhaps, highlighted that is when we analyzed the data of the iptacopan trial looking at alternative complement pathway inhibition in people who have IgA nephropathy, we expected that patients who had only inflammatory lesions on their biopsy would potentially benefit from complement inhibition, and that did not pan out. We saw improvement across all MEST-C scores, both those that reflect inflammation or inflammatory changes and those that reflect also fibrotic changes.

And the data from other studies are probably going to emerge, and we'll see if that pans out in other complement inhibitor trials. And it's, of course, with the caveat that these biopsies were not done at the time of study entry, but they were done within a short period of time before study entry.

So they were not too far remote from enrollment.

Dr. Rovin:

Yeah, I think that's really an important point that complement may be mediating things other than what we expect, and these may ultimately benefit patients with IgA nephropathy. I don't want to call them off-target effects. I just think they're effects of complement that we haven't really thought of or thought too much about in the past.

Okay. So, this is for you in particular and your colleagues at Alabama. You've suggested through some of your work that complement may increase the pathogenicity of galactose-deficient IgA1, which we think might be the antigen, if you will, in an immune complex in patients with IgA nephropathy.

Could you explain this idea to the audience and the results of your work so far, and that of your colleagues, as you investigate this process?

Dr. Rizk:

Yes. So to be maybe a little more specific, it increases the immunogenicity or the nephrogenic capacity of immune complexes. And so first of all, we and others, I mean, there's studies from our center as well as Mayo Clinic that looked at mass spectroscopy studies of immune complexes, and you can detect within circulating immune complexes complement fractions.

And these, again, reflect what we've just talked about: high C3 levels, rarely any C1q, and complement factor H and complement factor H-related proteins. So again, suggesting that there's alternative complement pathway activation and that these complement proteins travel within immune complexes. We've showed similar data as well.

And then when we put immune complexes in simple terms with mesangial cells, they can activate mesangial cells and lead them to proliferate. However, if we deplete the serum from C3, those immune complexes can no longer activate mesangial cells, suggesting that the complement protein might be necessary for this, like I said, nephritogenic effect of immune complexes.

And so we're trying to drill down on what fragment of C3 is important, and we will be sharing some data at the American Society of Nephrology coming up in a poster format, that the immune complexes require, in fact, activated C3 to have, again, this proliferative effect on mesangial cells and that the size of the immune complexes changes depending on what fragment of C3 is attached to these immune complexes, so the galactose-deficient IgA1 and the autoantibody. And that might be relevant because in another kind of vein or somewhat related disease of IgA vasculitis, the size of the immune complexes seems to correlate with which patients are going to develop, for example, nephritis.

The larger the immune complexes, the more likely a patient is to develop nephritis rather than having just IgA vasculitis. Again, raising the question whether the complement proteins attached to these immune complexes not only are important for their nephritogenic effect in IgA nephropathy, but maybe in the cousin disease, if you will, the IgA vasculitis that we're starting to scratch the surface on.

Dr. Rovin:

Well, that sounds like really interesting work and look forward to seeing this in a couple weeks at the ASN.

It's been a pleasure to have you on this broadcast. I think we've had a very good conversation. Is there anything before we close, any final message you want to leave the listeners with?

Dr. Rizk:

No, I would say this is, again, as you mentioned earlier, a part of the immune system we've kind of tried to forget after medical school, but it's coming back, and I think it behooves us to understand it better, and hopefully in the future we'll have better ways of assessing complement activation in clinic.

That's the biggest, I think, limitation is everything we talk about, most of the time we can't measure in the blood and we cannot see on routine histological assessment. So hopefully in the future that'll become more mainstream and we can understand the role of complement much better in IgA and other diseases.

Dr. Rovin:

Yeah, no, I think the idea of complement-related biomarkers is a hot area of research now to understand how to use these new medications that we'll talk about in the subsequent episodes of this series.

So I'd like to thank the audience for listening. It's been a pleasure to be here and stay tuned for our other episodes.

Dr. Rizk:

Thank you very much for having me.