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Building a Patient Profile for Complement Inhibition in IgAN

Announcer:
Welcome to KDIGO Conversations in Nephrology. This episode titled, “Building a Patient Profile for Complement Inhibition in IgAN” 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 from the Division of Nephrology at The Ohio State University Wexner Medical Center. Joining me today to discuss the use of complement inhibitors in IgA nephropathy is our distinguished guest, Dr. Andrew Bomback. Dr. Bomback is associate professor of medicine and co-director of the Glomerular Kidney Disease Center at Columbia University. His clinical and research interests include exploring novel therapies for glomerular diseases.

Dr. Bomback, welcome to the podcast.

Dr. Bomback:
Thanks very much for having me, Brad.

Dr. Rovin:
All right, so let's get right into it. First question is really a little bit about what you all do at Columbia. You and your colleagues have demonstrated genetic associations implicating the complement system in the pathogenesis of IgA nephropathy.

While we don't use genetics clinically yet for IgA nephropathy, do you anticipate that genotyping IgA patients may become relevant in the future, especially with anti-complement therapies?

Dr. Bomback:
That is a really important question, and I do want to sort of make a distinguishing comment on the complement genes that have been identified by my colleagues at Columbia who have done large genome-wide association studies in IgA nephropathy.

Those aren't necessarily the kind of complement genes that might show up on a commercial genetics panel. That being said, we still do the commercial genetics panel on pretty much every IgA nephropathy patient because we're also seeing some non-complement genes that you would pick up on those panels. For example, collagen defects show up in a proportion of IgA patients.

And every once in a while, you'll get an IgA patient that does have the kind of targeted complement gene variants that you'd see in a commercial panel, and that might certainly tip you towards thinking that this IgA nephropathy is part of a complement-mediated disease spectrum.

So in general, it's an evolving field, and as these commercial panels expand and move beyond just 75 genes to maybe a more comprehensive whole genome or whole exome approach, that will become a more routine part of how you're choosing between all these IgA therapies that are coming out.

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So I think I gave a very long answer to saying we do it. We're not quite using it to guide therapies yet, but I think it's reasonable to expect that in the future it will as these panels become more expansive.

Dr. Rovin:
I think we can both say that, A, we're pleased that many of these drugs are doing good things for our patients. Proteinuria comes down, GFR seems to stabilize or slow the decline of GFR. But choosing between these drugs and the many drugs we now have, at least in the United States, is really quite difficult, so we're going to be looking for an edge, I think, going forward to see how best to individualize therapy.

Dr. Bomback:
Yeah, absolutely. What we need now are the studies to help us choose between these drugs.

Very deep type of phenotyping, which I think is sort of the next thing that's needed, is to expand our phenotype of IgA to something more expansive that really gets us into the pathogenesis of the disease.

Dr. Rovin:
Do you think at all for the future that serum complement levels might become relevant? The way we use them now, we just usually get C3 and C4 as complement profiles in most of our diseases.

Can we incorporate them into deciding how to use a complement inhibitor?

Dr. Bomback:
So traditionally, most people who are getting worked up for glomerulonephritides will get C3 and C4 levels as part of their initial lab screening, and IgA nephropathy has always been a normal complementemic glomerulonephritis for the majority of the patients.

There's a very small subgroup of IgA nephropathy that's hypocomplementemic. They tend to have a much more rapidly progressive form of the disease and do much worse than the average IgA nephropathy patient. But so I think those cases are sort of a very unique subset of IgA nephropathy where just C3 and C4 staining is going to give you an idea of prognostication.

And to be honest, those patients, when they go to biopsy, very often have crescentic IgA, where their disease is so aggressive that you're consuming complement at a rate, and you really can't replete it fast enough, and that's why they're hypocomplementemic. Whereas most IgA, it's a slower, more gradual progressive form of the disease, and even though you are consuming complement on a regular basis, it's slow enough that we're able to generate enough complement that we never actually detect hypocomplementemia with our traditional assays.

But I think what you're implying, and I hope I'm getting this right, is that we need better complement assays than just C3 and C4. And there are people who are using these kinds of expanded complement assays and complement panels in other kidney diseases like C3 glomerulopathy, where we don't just stop at C3 and C4.

You know, we'll get an AH50. We'll get a CH50. A lot of us will send our samples to labs that can give us readouts on Bb, factor B breakdown products, for example, and look at membrane attack complex level. So there's better complement testing that surely can be done than just C3 and C4, and I do think it may be beneficial in the IgA patient if you're trying to figure out how much is complement contributing to the pathogenesis in this patient.

Dr. Rovin:
So looking at complement activation products in the urine, that seems like potentially a fertile field for complement biomarkers for IgA nephropathy as well.

Dr. Bomback:
The one that I've seen the most used is C5b through 9, and that's the one I'm a little bit less inclined to put a lot of stock in. I think if we could get other urinary complement biomarkers beyond C5b through 9, that would make it more useful.

Dr. Rovin:

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Say you're using a urine C5b through 9 and a complement drug, this could be a way of showing that you're effective with your complement drug.

You would expect, if you're hitting the alternative pathway or the terminal pathway, which are our 2 complement drugs that are relevant to IgA nephropathy right now, you would see this decline in the urine.

Dr. Bomback:
Absolutely. The option of doing a noninvasive biomarker to read out just how well we've established control of complement, that would be a huge boon.

Dr. Rovin:
Do you consider the presence or absence of complement in the kidney biopsy when you make a decision to incorporate a complement inhibitor in the management of IgAN?

Dr. Bomback:
I absolutely do. If a pathologist who sees a lot of renal biopsies tells me, "This is more C3 than we typically see in an IgA nephropathy patient," that, to me, is going to really shift the way I think about treating this disease and think about getting a complement targeting drug on board as part of the regimen.

Dr. Rovin:
For our audience, if you're just tuning in, you're listening to the KDIGO podcast on building a patient profile for complement inhibition in IgA nephropathy. I'm Dr. Brad Rovin, and I'm speaking with Dr. Andy Bomback.

So Andy, let's get back to the biopsy a little bit. How do you characterize inflammation in an IgA nephropathy kidney biopsy? Do any of those features, other than the presence of complement on immunofluorescence, help you in deciding to incorporate or how to incorporate complement drugs?

Dr. Bomback:
If I see anybody with endocapillary proliferation on light microscopy, you almost have to find a reason, in my book, not to use immunomodulatory drug.

So that will always tilt me towards thinking about immunomodulation and as part of the treatment regimen. But whether there's anything on light that would tilt me towards using complement targeting therapy, not really. I mean, I guess you could say if there's a significant amount of neutrophils, and then I'm thinking, "Well, there must be some degree of C5a or C3a really being involved in recruiting this inflammatory response," that might tilt me.

But I still sort of make my complement-based decisions, if I'm using the biopsy as a guide, on the immunofluorescence. I also should say that I do think complement is very heavily involved in the inflammation we're seeing on light, and I, in theory, I think it would be perfectly reasonable to combine a complement targeting drug with another immunomodulatory drug in IgA nephropathy, whether it's one of the newer B-cell agents or an older agent like targeted-release formulation of budesonide.

I think they can work very synergistically. But I can also picture somebody from a payer right now listening to me and saying, "Hold on, Sparky. We're not giving you both of those drugs at the same time, especially without data to back that up." But I do think, in theory, combining a complement inhibitor with another immunomodulatory drug, that if you think of that multi-hit model of IgA nephropathy that's working at a much earlier stage of the multi-hit model, makes sense to me.

But I, again, I know there's a lot of logistic reasons why that's more theory than practice.

Dr. Rovin:
Well, I think you've hit on something that's really relevant for all of us and the folks in the audience, which is it is a multi-hit hypothesis of how IgA is sort of affecting the kidney, how IgA nephropathy pathogenesis works, and the idea of combining drugs that hit different portions of that pathway makes wonderful sense. We need to show that, of course, and I think that's the next—a next frontier.

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Our last question for this episode, and this is going to draw a little bit on your overall background. I know you've been involved in studies of complement inhibition in C3G, obviously a very different disease. But what lessons might you think about from your experience with C3G and its treatment with complement inhibitors that we could bring over potentially to think about in IgA nephropathy?

Dr. Bomback:
Yeah, I think that's a really important point because one of the things we always talk about when we talk about developing drugs for rare diseases like C3G is that there are lessons learned that should be able to be transplanted over to more common diseases like IgA nephropathy. So the first thing I would say is, if you really think your patient needs a complement inhibitor, you don't need to lay initiation because of the vaccines.

You can start the patient on penicillin prophylaxis, and that's the way we start most of our patients on complement inhibitors. We start them on penicillin prophylaxis while we're updating their vaccines. It's very unusual that our patients are all up to date with their vaccines. Even if they've done their meningococcal vaccines, they're almost always past the point when they should have gotten a booster.

So the routine for us is to start people with penicillin prophylaxis while we update the vaccines. The second thing I would say is, this is a classic example of what we call that multidisciplinary approach. If you're a solo practitioner trying to do all this on your own, good luck. It really helps to have good ancillary staff in your own office, but also incorporate the primary care physician.

The vaccines and updating the vaccines is a not as easy a step as you would typically expect it to be for many of our patients. So coordinating with primary care and using your own PAs, nurse practitioners, MAs to really keep on the patients to make sure they're able to get all the vaccines they needed to take these drugs safely is crucial.

And then I think the biggest lesson we've learned, whether it's from studies or from real-world experience, that these drugs are safe when taken with the right precautions. So when using antibiotic prophylaxis when needed, when doing the vaccines, it is almost like a Halley's Comet type event now to get infections from encapsulated organisms.

You'll hear about one or two pneumococcal infections. I haven't heard of any real meningococcal infections with these newer complement agents, and that's a testament to the lessons that we've learned from prior studies where we did have more serious infections. We've learned how to give these drugs in what I think is a very safe manner.

So I think that's a key thing we can learn from the rare disease world and move it to the IgA world. And then, I think, the lessons that we might learn from the IgA world and bring it back to the rare disease world is I don't think we'll expect IgA patients to be on these complement targeted drugs for indefinite periods of time.

I think the typical IgA nephropathy patient is going to be treated with a complement targeting drug, is going to look at somewhere between a 1- to 2-year course of therapy and very unlikely to be extended beyond 2 years. And it'll be very interesting to learn from these IgA patients what is the complement system doing once the drug is stopped and whether we can take some of those lessons and bring it back to the rarer forms, like C3G and immune complex MPGN, to see can we learn from these IgA patients that they're able to potentially come off complement therapy, reset the complement system.

Dr. Rovin:
This was a great conversation, Andy. I really appreciate it. I think our audience will too. Before we close, any final message to leave the listeners with? Anything profound you want to say?

Dr. Bomback:
I will just say that it's a very exciting time to be treating IgA nephropathy. We have so many drugs, and yes, it is a challenge to have to choose between agent A versus B versus C versus D, but we and our patients are lucky that we have those options. So it's a very good testament to what the science has brought us to in terms of being able to help our patients.

Dr. Rovin:
Absolutely agree, and it's a very good time to be a GN physician, at least in the United States where we have access to these drugs.

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I want to thank my guest, Dr. Andrew Bomback, for joining me. Andy, it's been great to have you on the podcast. Thank you for these excellent insights and information.

I'm Brad Rovin. To access this and other episodes in our series, and there will be additional episodes discussing IgA nephropathy, visit KDIGO.org/podcast.

And thanks, everyone, for listening.

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