Transcript Details
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How I Treat IgA Nephropathy: Lessons From the Case Files

Announcer:
Welcome to *KDIGO Conversations in Nephrology*. This episode titled, "How I Treat IgA Nephropathy: Lessons from the Case Files," 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'm Dr. Dana Rizk. I'm 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 today to discuss IgA nephropathy treatment are 2 distinguished guests, Dr. Andrew Lazar and Dr. Gaia Coppock. Dr. Coppock is an assistant professor at the University of Pennsylvania School of Medicine, where she runs the Glomerular Disease Clinical Trials Group, and her clinical and research interests include immunomodulation in glomerular diseases. Dr. Lazar is the clinical trial director at the University Hospitals of Cleveland, and his clinical and research interests include glomerular diseases, genetics in kidney diseases, and the development of an implantable dialysis device.

Dr. Coppock and Dr. Lazar, welcome to the podcast.

Dr. Coppock:
Thank you. It's so great to be here.

Dr. Lazar:
I really appreciate you having me. Thank you.

Dr. Rizk:
Pleasure. So we have a nice conversation ahead of us in light of the updated KDIGO guidelines. And as a reminder for perhaps our listeners over the past 2 sessions, we reviewed some of the data behind the new KDIGO guidelines that were recently published and the IgA nephropathy pathophysiology. So today we're hoping to illustrate how we would apply these new guidelines to cases that we see in our daily practices.

So I'm going to just share with you a couple of cases and see how you would manage, again, in light of these new guidelines. So let's start with a newly diagnosed case. This is a 19-year-old Caucasian man with a history of depression, chronic constipation complicated by hemorrhoids but no history of inflammatory bowel diseases, who presents with gross hematuria around May of 2025 after having a sore throat. At the time of presentation, his creatinine was around 0.9 mg/dL, and his prior known baseline was about 0.7, and he was found to have quite a bit of hematuria with more than a hundred red blood cells per high power field and quite a bit of proteinuria with about 2.3 g/g on a UPCR. So evidently, he was referred for a kidney biopsy that confirmed the diagnosis of IgA nephropathy, and his MEST score that was provided by the pathologist was M1, E1, S1, T0, and C1.

So, Gaia, let me start with you. How would you approach the management in this patient?

Dr. Coppock:

So, you know, I think that this is a great example, maybe a classic example of why we need to address both immunologic and non-immunologic aspects of disease in our patients with IgA nephropathy. This one, I think, has a lot of features that would make us concerned for immune activation, including his young age, his hematuria, the higher-grade proteinuria, and then, of course, the inflammatory changes on his MEST-C score, the M1, E1, and C1. And so I think this is a very good example of somebody who I would, quite early, try to put on a HIT1-targeting drug as well as HIT4-targeting agents.

In terms of what to choose for him for the HIT1 approach, right now we're still—we're choosing oftentimes between systemic steroids and targeted-release budesonide. This is a young person who has relatively well-preserved kidney function and is a new diagnosis, and so just kind of to minimize toxicity and hopefully achieve good outcomes for him, I think that targeted-release budesonide would be a good choice. With the systemic steroids, oftentimes it comes with the prophylaxis and other pills. And so especially for a young person, I think that that can be a little bit more of an overwhelming choice. And then I like the data for targeted-release budesonide efficacy. So that would probably what I would choose for his HIT1 drugs.

Dr. Rizk:
That sounds great. Yeah. And I guess if one doesn't have access to targeted-release budesonide, a systemic steroid at a low dose, based on the testing, trial would be another option for sure.

So, Andy, besides the immunologic management of this patient, would you consider any CKD management? And if so, what would you start with?

Dr. Lazar:
I certainly would. I have a 19-year-old, so I'm a little bit afraid that I'm going to bombard this young person with a lot of drugs. So I know that we have to be a little bit careful or we'll probably affect adherence. But I tell patients that I'm really as much their cardiologist as I am just about anything else. Any CKD patient, including IgA nephropathy patients, they are at greater cardiovascular risk. Certainly, the worse their CKD is, we know that they really have a shorter lifespan.

So very early on, out of the gate for this patient, while we're thinking about what can we do to low the chance, HIT1, HIT2, HIT3, HIT4, we've got to think about we've got to get blood pressure under control. We have data to show that these patients probably should be in the less than 130 range. And they often do have high blood pressure, so certainly we want them on RAAS inhibitors, but I think going to an endothelial antagonist early, certainly if I can use a drug, maybe one drug to improve adherence, or I can do RAAS inhibition and I can do endothelial antagonism, should be something that we should think about. We know when we add an endothelial antagonist, we usually drop by about another 5 systolic, so that's something I want to think about in addition to that RAAS inhibitor.

Thinking about the SGLT2 inhibitors. We have a lot of data now to show that we know they do lower proteinuria, and that's something I want to do as fast as possible. The less amount of time that we allow patients to be proteinuric—we don't want that proximal tubule to have all that protein that it can take up and all the inflammation and the tubulointerstitial fibrosis that may follow. So we know that SGLT2s are going to lower proteinuria. We know it looks like they probably save us eGFR, maybe on the order of about 1 mL/min/year. And when you look at trials like DAPA-CKD, where they had 270 such patients, IgA patients, we know that adding the SGLT2 for these patients, that it did lower cardiovascular events. You know, you looked at cardiovascular events, slash, and stage, and it lowered it about 70%.

So I think pretty much out of the gate, I've got to think about blood pressure, so I'm going to think about endothelial antagonism, the RAAS inhibitors, and I'm going to think about also LDL cholesterol. That's probably going to be next. And we have data also, IgAN patients, LDL greater than 100, are also at greater cardiovascular risk and maybe even renal worsening. But I'll be careful adding too many drugs too fast.

Dr. Rizk:
Yeah, I agree. Especially with a 19-year-old who was probably healthy a week earlier prior to his biopsy. So even though the guidelines do recommend potentially starting multiple agents at the same time, that doesn't mean we have to start them all on one single day. I totally agree with you. And you bring up and remind us again of the cardiovascular risk that's associated with kidney disease, even in these young individuals. So something to keep in mind and definitely look for hyperlipidemia. Vaping is a big deal. I don't know about you guys, but we see a lot of vaping now. So you ask about smoking, they say, no, I don't smoke. So you have to specifically ask about vaping, which is another risk factor.

So, Gaia, going back to you. This gentleman has a C1 lesion. And you kind of alluded to the fact that this is part of kind of your treatment choice and you look at the inflammatory lesions. Although of course the guidelines could not have any stand on the use of the MEST-C score for treatment choice, simply because the data's not there. All the trials did not take into account pathology findings. But I think in practice we do look at these lesions. So can you walk me a little bit through what are your thoughts, and how do you distinguish that from a crescentic disease?

Dr. Coppock:
Yeah, I mean, I think crescents and IgA nephropathy are the very murky space, because we see crescents in nephrology and it makes us quite alarmed. But of course, there is a distinction, particularly in these patients between an RPGN and less than 25% of glomeruli with crescents, which is the C1 lesion.

So with RPGN, they fall outside the KDIGO guidelines because they're not—well, they're addressed in the KDIGO guidelines, but they fall outside sort of these new recommendations for management because people with RPGN were excluded from clinical trials. And so we do tend to, and I tend to still treat them sort of with the classic steroids and cyclophosphamide based approach, more like a traditional RPGN management.

However, this is this population. We see these people with crescents, sometimes even with like minimal other inflammatory changes in IgA nephropathy. And I think the MEST group updated their scoring system in 2017 to try to address these patients specifically. But it's such a sort of sporadic finding that the data have been sort of a little bit hard to classify. And so, as you said, the MEST-C score is more about prognosis than it is about guiding management. But I certainly, with a C1 score, would not put them into an RPGN category, but my personal preference is to treat those people with immunosuppression. Whereas, in that higher grade, that RPGN category, more C2, I treat them more aggressively. Their prognosis tends to be poor regardless of treatment because it's a more inflammatory subgroup, but we try very hard to do everything we can to mitigate their disease.

Dr. Rizk:
Yeah, great point. And again, RPGN, just to remind the audience, is a clinical diagnosis, really. So you just have to look at this patient's trend in terms of rise in serum creatinine.

So, Andy, the KDIGO guidelines mentioned the goal of reducing galactose-deficient IgA1, that HIT1 that we've been talking about, and the circulating immune complexes. So how do you in your clinic, when you're seeing patients, how do you—operationally, how do you look at this at a time when we really don't have the biomarkers at our fingertips?

Dr. Lazar:
That's really a great question. I think the 3 of us and I know a lot of the audience are very excited about precision nephrology, that we're trying to head there. We don't want to put every single patient on all the agents that we have available to us. So we are, you know, I hope that we're nearing that time that we'll have biomarkers.

But looking at that table in the KDIGO guidelines where they really prioritized thinking about galactose-deficient IgA1 and circulating immune complex has made me really happy. Hopefully, in the not-so-distant future we'll be able to look at Gd-IgA1 and as probably a correlate to circulating immune complexes. So but the way that I prioritize it now or the way I really operationalize it is I want to think about prioritizing agents that I know do lower Gd-IgA1. They have legitimized it in the guideline. So we do know that TR budesonide does lower Gd-IgA1, maybe on the order of almost about 30%.

And we know that some of the B cell modulators that we will have soon are the other agents we know that do lower Gd-IgA1. And some of those, the anti-APRILs, as well as the Anti-BAFF, slash, APRILs I know have even looked—they have also measured circulating immune complexes, Gd-IgA1 and the accompanying IgG2 it. And so looking at being able to employ those drugs first are what I'll be looking forward to doing. I personally am also very excited about other biomarkers coming, looking at some of the soluble CD163 data that is a marker of the M2 macrophage activation, which looks like that's going to correlate maybe with the inflammation of IgA nephropathy. This is where I hope things are going, that we'll be able to look at these biomarkers and choose drugs and then see what happens to those biomarkers as we treat.

Dr. Rizk:

Yeah, I think people are working hard to get these biomarkers to clinical practice, and I would say to the audience to keep an eye out on some of the exploratory studies that come out of the large clinical trials because they will all be looking at different biomarkers to hopefully guide treatment choice in the future.

So if you're just tuning in, you're listening to the KDIGO podcast on How I Treat IgA Nephropathy: Lessons from the Case Files. I'm Dr. Dana Rizk, and it is my pleasure today to be speaking with Dr. Andrew Lazar and Dr. Gaia Coppock.

So let's move on to our second case. This is a little bit different in that this is a prevalent case that comes to your office. A 34-year-old Korean woman who has a history of obesity and uveitis. She has had episodes of syn-pharyngitic hematuria after strep infections as a child and ultimately underwent tonsillectomy. Since that time, she has not had any more recurrences of her gross heumaturia. She reports having had a biopsy as a child but does not have access to the biopsy report. She presents to your office, refers from her primary care physician with microscopic hematuria and proteinuria as well as mild CKD with a creatinine of 1.4 mg/dL. Her UPCR was 2 g/g and her urine analysis was remarkable for not only proteinuria but also hematuria with 5 to 10 red blood cells per high power field. She's already on the RAAs blockade for treatment of hypertension. So you send her to have a repeat kidney biopsy, and again, you confirm the diagnosis of IgA nephropathy. This time, in this case, the MEST-C score is M0, E0, S1, T0, and C0.

So, Andy, let me start with you. In clinic, do you calculate the patient risk of using the IgAN prediction tool at the time of a biopsy? And if you do, what you do with that information?

Dr. Lazar:
I like to use the IgAN prediction tool, and I try to get my fellows to use it also. I do it because I can start to better communicate with the patient regarding just how bad IgAN is. And I do it—this may sound funny, but I like to do it also to remind myself of how sick these people are. Because, you know, I trained during those years where we didn't think IgAN patients did that poorly, but we didn't realize that they're so young when we meet them. And you know what? Twenty years may seem like a long time, but it's not when you're 30 years old. And suddenly you're on dialysis or requiring transplant when you're only 50 years old.

So I think that I like to do that, I like to be able to take clinical and look at that biopsy, to use a validated tool that I could sit with the patient to say, you fall into this low, medium, or high risk. But what's funny is that a low risk of 15%, let's say, of a 50% drop in GFR or end-stage kidney disease at 5 or 7 years, it's still pretty darn high, you know? So I think it really instructs the patient. It reminds me that, wait a second, these patients really are ill. What I like to do is do it at the time of biopsy with the first tool that had been published, and then consider about 2 years later, I'll use the updated tool that was published maybe in 2022, that I can do the math when a biopsy was done up to 1 to 2 years prior. And I'll like to do the math up front, do the interventions we do, and then do the math using that updated tool 2 years out and see if we've moved that needle.

Dr. Rizk:
Hopefully the risk is reduced by then.

So you make a great point. The tool can predict up to 5 up to 7 years maybe, which in somebody's lifespan is not a long period of time, but it does really put in perspective sometimes how bad the prognosis is. I totally agree with you. So and then the older you get, the more you feel like, oh, you know, 40 years old, 50 years old is nothing. They still have a long time ahead of them.

So, Gaia, in this case does the patient's racial background, so the fact that she's Korean, change your approach to management? And if so, how?

Dr. Coppock:
Yeah. So the East Asian population, they tend to have had a little bit more success with different immunosuppression options looking back historically at data. And I think that has led to KDIGO including some alternative therapies for these populations, specifically CellCept or mycophenolate mofetil we can use in East Asian patients primarily. It's indicated in KDIGO; they referenced the Chinese population. Tonsillectomy, which this patient did have as a child, is also in the KDIGO guidelines for Japanese populations. And so although—I mean, that comes from the evidence, but sometimes I think in East Asian populations in general, I will sometimes try an alternative agent, even if they don't fit into the exact basket, just with the knowledge that those studies and in these various ethnic groups have shown some more efficacy than we've seen, like in some European studies, for example.

In terms of the newer agents, the targeted-release budesonide recruited very few Asians in their study, which is something to maybe consider when you're trying to think about how it may apply to our own patient populations. Systemic steroid trials actually tended to recruit larger numbers of Asian populations. And so I think that has been not necessarily a criticism, but it's always something that's looked at in clinical trials because we know this in our field, that with patients with IgA nephropathy, when you see a response to immunosuppression, as a reader, we always try to see is this skewed by a population that tends to respond better to immunosuppression, or does it have more of a global effect across different ethnic groups? And I think because this question comes up a lot, there's a big focus in the newer clinical trials that are being published to have a good representation across diverse populations so that they can try to answer more of these questions about applicability and which of our patients might have a better chance of response.

Dr. Rizk:
Yeah. And I think emerging data from these large clinical trials, at least the baseline characteristics that they're sharing publicly, does look like they've achieved that goal of having this global representation, which is wonderful.

So with that, I want to thank my guests, Dr. Andrew Lazar and Dr. Gaia Coppock, for joining me today. It was absolutely a great pleasure having you on the podcast.

Dr. Coppock:
Thank you so much. It's great.

Dr. Lazar:
Really appreciate you having me. Thank you.

Dr. Rizk:
Thank you both. I am Dr. Dana Rizk, and to access this and other episodes in our series, please visit kdigo.org/podcast. And thank you so much for listening.