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Reading the Warning Signs: Risk Stratification in IgAN

Announcer:
This is *On the Frontlines of IgA Nephropathy* on ReachMD. Your host today is Dr. Gates Colbert.

Dr. Colbert:
Welcome to *On the Frontlines of IgA Nephropathy* on ReachMD. I'm Dr. Gates Colbert, and joining me to discuss how risk stratification is evolving to better identify patients with progressive IgA nephropathy, or IgAN for short, is Dr. Dustin Le. He's an Assistant Professor of Medicine in the Division of Nephrology at Thomas Jefferson University in Philadelphia. Dr. Le, thanks for being here today.

Dr. Le:
Thank you so much for having me today, and I'm excited to talk about IgA nephropathy.

Dr. Colbert:
So to start, Dr. Le, when you're evaluating a patient with IgA nephropathy, how do you approach risk stratification at diagnosis and during follow-up?

Dr. Le:
Yeah, it’s a great question, and I think there are a couple components to this. So on one hand, especially practicing in an academic center, one thing I always have to remember is that for patients who are coming for either a new diagnosis of IgA nephropathy or a known diagnosis, for the patients who have a history of IgA nephropathy, sometimes the biopsy may not actually be recent.

That's actually something we see too in a lot of the clinical trials for IgA nephropathy, where patients could have had a kidney biopsy in the past 10 years. But at least for patients where I either had access to the biopsy or it's a new diagnosis of IgA nephropathy, looking at the kidney biopsy is one of the most important things we can look at.

And so there are criteria to look at on the kidney biopsy that we call the MEST-C criteria. And essentially, what we're looking for are markers of inflammation, which can sometimes help us see how active the IgA disease may be. And then we can also look at markers of chronic damage. That helps assess how much we think is reversible, how much may actually respond to treatment.

And then when you take these biopsy findings, we also have different risk calculators that can look at the long-term risk of having to be on dialysis. What I find is, when we use these prediction tools, it can be quite helpful for patients. So instead of saying, “You might be on dialysis at some point in your life,” we can say, "This is your risk," recognizing that for younger patients, their lifetime risk can be even higher.

And then outside of the biopsy findings, the ones that are most familiar to clinicians are looking at both the change in GFR over time and then looking at markers of proteinuria. So this would be your UACR or your UPCR. And then what makes intuitive sense is that the higher these numbers are, the higher the risk of progression. And then it helps to use these numbers with the patient to say, "If your proteinuria is very high or if your creatinine has been going down over the past year, these would all be signs that we'd have to talk more urgently about disease-modifying treatments and starting treatments in general for IgA nephropathy."

And then during follow-up, as we start these different treatments, we’d really be looking at the same thing. Instead of looking at biopsy findings, we'd be looking at what the change is in creatinine over time, which is part of the new IgA guidelines, and then looking at changes in proteinuria and hematuria and hopefully seeing improvements with those. And these would be something we'd monitor over the lifetime since IgA nephropathy is typically a disease of the lifetime and not, let's say, a short-term disease diagnosis.

Dr. Colbert:

Building on that, have you encountered patients whose disease activity isn't fully captured by routine monitoring? And if so, how do you evaluate those cases?

Dr. Le:
One thing I'd actually comment on and the way I think about it now is even just looking at the UACR, the UPCR change in creatinine, doesn't necessarily capture the patient's diagnosis of IgA nephropathy. Since these markers really evaluate overall kidney health, whenever I see changes in their proteinuria or hematuria, I need to think about whether this is in response to a recent change in their IgA therapy, whether that's initiation or discontinuation. Is this a response to other kidney therapies like ACEs and ARBs, SGLT2 inhibitors? Or is it just from other underlying risk factors? Maybe they have worsening hypertension, worsening diabetes. Maybe they've had a recent illness. So we have to keep all of these in mind whenever we're trying to interpret changes in proteinuria or hematuria over time.

And then really, the last resort we could always do if there's this question of, is the patient getting better? Are they not getting better? And more when I think about this, the other step you can always do is you can do another kidney biopsy in these patients.

A lot of times for me, though, I'm only going to consider doing a repeat biopsy if I'm wondering, is there a different process going on? A classic one for nephrology is maybe you have a patient with both IgA and diabetes. If the diabetes, potentially, is getting poorly controlled, and then their proteinuria and creatinine numbers are getting worse, the question would be, has the diabetes now led to a new pathology, something like FSGS? Or perhaps their IgA nephropathy is under worse control. And then getting a repeat biopsy would further motivate treatment for it and help you think about the risk-benefit of changing therapy.

Dr. Colbert:
For those just tuning in, you're listening to *On the Frontlines of IgA Nephropathy* on ReachMD. I'm Dr. Gates Colbert, and I'm speaking with Dr. Dustin Le about risk stratification and clinical decision-making in IgA nephropathy.

So, Dr. Le, I'd like to talk about galactose-deficient IgA1. Where do biomarkers like this fit into your approach to risk assessment? And what do you see as their current role in clinical practice?

Dr. Le:
So that's a great question and transition point into thinking about what the future of IgA treatment looks like. And I'll answer your second question first, about what I see the role of these IgA antibodies is right now in clinical practice. And at least for me, the easy answer is this is actually a test I can't order in my own academic practice. I'd say right now, it’s nothing we actively use in the day-to-day treatment of IgA nephropathy.

With that said, though, there are recent clinical trials now that have measured these antibodies following treatment initiation as well as after treatment discontinuation. And there's actually a lot of very promising data that seems to suggest that with these newer treatments that we have access to, they actually lower these galactose-deficient IgA antibody levels. And then we'll have to see how the data plays out over time.

The hope, I think, from every nephrologist is that if these marker levels decrease over time, that'll indicate a good response for the patient. And then, where this will really impact care is, let's say we start trending these numbers over time with these newer treatments. And then if patients do not get better, are these patients who would need more aggressive therapy? Then would we be able to start them earlier in the disease course instead of having to wait longer and then not respond reactively to these biomarkers? These are all questions we'll have to get the answers to, but these are all questions already being investigated. And hopefully, we'll get answers to them over the next couple years.

I would suspect, just as the past couple years of IgA nephropathy have changed dramatically in terms of treatment and monitoring, we'll see even more changes in the next couple years as well.

Dr. Colbert:
Now, since the publication of the KDIGO 2025 guidelines, has anything changed in the way you approach biopsy decisions, monitoring strategies, or treatment escalation for patients with IgAN?

Dr. Le:
From the 10,000-foot view, the KDIGO 2025 guidance with IgA nephropathy has certainly changed a lot in terms of routine management and goals of treatment.

I would say the first point is, traditionally, for IgA nephropathy patients, we've said the goal was to get their proteinuria to be less than one gram. And so for this marker of kidney damage, we'd only target one gram, and we'd leave it there. With the recent guidelines,

though—and with recognizing all this recent data we've had over the past five to 10 years and even more recent than that, looking in terms of long-term outcomes for patients with IgA nephropathy—we know targeting their proteinuria to be less than 0.5 grams, and then in the best cases, less than 0.3 grams, will have better prognoses for all of these patients.

And then that leads to treatment. And I'd say the biggest thing with the recent KDIGO guidelines in terms of treatment paradigms is the new guidelines ask us to think about two different distinct simultaneous pathways for the treatment of IgA nephropathy. The first one targets the actual, we can say, pathology of IgA nephropathy. And so the way we tend to think about IgA nephropathy is, for whatever reason, the body will upregulate this galactose-deficient IgA that will then lead to immune complex formation, which will then lead to deposition in the kidney. And so we have recent treatments that have been FDA-approved, as well as multiple agents under investigation right now, which all target what I'll call this IgA pathway, with the hope of reducing the IgA pathology.

Dr. Colbert:
Dr. Le, before we wrap up, I have one final question for you. As risk stratification continues to evolve, what changes do you think are most likely to influence clinical practice over the next several years?

Dr. Le:
In terms of things that'll influence clinical practice over the next several years, I'd say there's kind of two different pathways. So one you mentioned is with risk stratification. And so with the advent of all these new therapies recently that have either been approved under FDA investigation and expedited or have released phase 1 and phase 2 data, a lot of these studies are also releasing treatment response data in terms of different biomarkers.

So really, one of the outstanding questions which we had touched on a little bit is, as we get more biomarker data, how can we use this data to help us inform and to think about what treatment should we start first? How long should patients be on treatment? When should they start a new treatment or restart the same treatment? And then, how do we think about these biomarkers in terms of context of treatment?

The example I can give, at least with the nephrology, is with the PLA2R receptor for membranous nephropathy. This biomarker is something that only came out in the past decade, and the whole treatment paradigm has shifted to if you see the biomarker and we can get it to an undetectable level, that means the patient has had a very good response with treatment and they don't need further doses.

And so the question is, can we have this same treatment paradigm on IgA nephropathy where patients can receive, let's say, drug A, and when it becomes undetectable, they could potentially stop getting further in treatment, and then hopefully decrease the risk of having different side effects from all these novel medications. Or perhaps, if the biomarker stays elevated, they need either a longer treatment or a different treatment.

And so that brings me to the second thought. What will change clinical practice the most over the next several years is the idea of what IgA treatment should we even be using. Just as an example, in the KDIGO guidelines that came out last year, one of the last sections talks about new therapies under development or evaluation in clinical trials, whether that's enrolling or currently monitoring. I was looking the other day at this point, actually; all nine of those drugs have now either released phase 2 or phase 3 studies, essentially all showing potential benefit in preventing long-term disease damage with IgA nephropathy. With these nine drugs, there are some overlap, but they also all have different mechanisms.

And so really, one of the challenging ideas that the KDIGO guidelines also mention is, how are we going to be able to identify which patients will benefit from which therapy? And again, how long do we use these therapies? When should we switch therapies?

Regardless, with these larger questions of different biomarkers and when and how to use these treatments, it's great that we're even in this place to begin with now. When I finished medical school—which was not that long ago—we really only had ACE/ARB therapy, maybe steroids. Then, during my time in fellowship and in the past couple years after finishing training, we now have guideline-recommended use of SGLT2 inhibitors. There are other therapies as well. And then all these immunomodulatory, immunosuppression therapies are all starting to come out now with more safety and efficacy data. And so I think this is all very exciting.

The last point we should mention as well is, with all these therapies and with all these larger outstanding questions about how we treat IgA nephropathy, I think one thing we'll have to think very hard about as nephrologists is at what point do we start referring all patients with IgA nephropathy to academic centers? Even within my own academic center, I'm not an IgA clinical trialist. We do have a couple in our division. And so at what point should we just be sending all of our newly diagnosed IgA patients to see them, to then give them access to these new therapies and these new clinical trials, so we can really start to address which therapies, when do we use them, how long do we use them, and how can we best prevent all these long-term complications of IgA nephropathy?

And so I think this is all a very exciting area, and we'll have to see what happens over the next couple of years.

Dr. Colbert:
Well, it seems like we certainly have a lot to look forward to. A big thanks to my guest, Dr. Dustin Le, for walking through how risk stratification is shaping the care of patients with IgA nephropathy. Dr. Le, it was great having you on the program.

Dr. Le:
Yeah. Thank you so much for having me today and talking about IgA nephropathy.

Announcer:
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