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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Essential Biomarkers for Assessing and Treating IgA Nephropathy

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is sponsored by Vera Therapeutics. Here's your host, Dr. Gates Colbert.

Dr. Colbert:
Welcome to *Clinician's Roundtable* on ReachMD. I'm Dr. Gates Colbert, and joining me to discuss the essential markers for evaluating IgA nephropathy activity and progression is Dr. Abdallah Geara. He's an Associate Professor of Clinical Medicine, Clinical Director of the Glomerular Diseases Program, and the Director of Onconephrology at Penn Medicine in Philadelphia. Dr. Geara, thanks for being here today.

Dr. Geara:
Thank you, Gates. Looking forward to our discussion.

Dr. Colbert:
So Dr. Geara, let's start with the big picture. When assessing IgA nephropathy disease status, why is it so important to think about the interplay between hematuria, proteinuria, and estimated glomerular filtration rate, or eGFR?

Dr. Geara:
So when we establish diagnosis of IgA nephropathy, the first step is to prognosticate in order to see what will be the clinical course of these patients. As we know, IgA nephropathy is a disease that has a very long clinical course. Usually, the onset is early—in their 20s and 30s most of the patients are diagnosed—and it does have a disease course that can go over a decade.

So in order for us to prognosticate what's going to happen with these patients down the line, we utilize demography, we utilize clinical markers, and we also utilize histologic markers. And this is where the importance of eGFR, proteinuria, and hematuria comes in.

So in terms of the role of eGFR, it does tell us the amount of chronic kidney disease that's been established and the fact that the patient does have a chronic kidney disease secondary to IgA nephropathy. It's a marker that this patient has a progressive disease and the IgA nephropathy is going into a progressive course.

When it comes to proteinuria, we know that proteinuria is an important biomarker. We used to think that a target of proteinuria less than one gram would be a very good target to slow the progression. We have more recent data that actually show that any level of proteinuria could be associated with some progression.

When it comes to hematuria, the data is not very clear there. So we have data that suggests that the combination of hematuria and proteinuria is bad. As far as having hematuria alone for prognostication, the value of hematuria alone for prognostication is not very clear.

I think in order to put all these biomarkers into the same context, it's important to correlate these biomarkers with the findings on the kidney biopsy. I think a patient with even low levels of hematuria but with a kidney biopsy that's concerning, even with low eGFR but a kidney biopsy that's already showing some chronic changes, that will be a quite significant finding. And we can utilize these clinical biomarkers in order to assess the prognosis and also to assess response to therapy down the line.

Dr. Colbert:
And with all that being said, I'd like to zero in on each of these three markers. Starting with hematuria, it was historically seen as benign

unless it was paired with proteinuria or an eGFR drop. But what do emerging data now suggest about persisting or fluctuating levels of hematuria?

Dr. Geara:
So hematuria is a tricky biomarker. I think eGFR, chronic kidney disease, and proteinuria have better data and well-established data consistently across all populations when it comes to biomarkers and prognostication biomarkers. When it comes to hematuria, the data is a little bit inconsistent. So when we look at the bedside, we have patients who have this fluctuation of the hematuria, and then depending on the therapy—so the way they respond to therapy—the hematuria would disappear, and then the hematuria would recur when the disease comes back. In these patients, hematuria can be utilized as a reliable marker of quote-unquote inflammation in the kidney that will require additional and maybe immunosuppressive therapy.

Some other patients will have microscopic hematuria that's synpharyngitic or coincides with maybe a viral illness, like ENT or GI viral illness. So as far as utilizing hematuria, I think hematuria should be taken into consideration when you are treating these patients. Unfortunately, we cannot utilize it as the only biomarker for disease response. I think the data on hematuria is better in some other nephritic syndromes, like, for example, ANCA-associated vasculitis.

Dr. Colbert:
And when it comes to proteinuria, how should clinicians weigh the consistency of proteinuria control versus the size of the initial drop?

Dr. Geara:
So when it comes to proteinuria, we know that IgA nephropathy is a relapsing/remitting course in the majority of these patients. We know that the relapse can be triggered by a viral etiology, being ENT or GI in origin, or some other environmental triggers.

So that's why measuring proteinuria in a longitudinal way is very important. So in addition to the initial drop, I think this drop of proteinuria should be sustained. And the longer it is sustained, the better the prognosis for this patient.

Dr. Colbert:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Gates Colbert, and I'm speaking with Dr. Abdallah Geara about monitoring essential markers for IgA nephropathy.

So Dr. Geara, if we continue to look at these markers, eGFR is often labeled as a lagging indicator. But how can tracking it over time help guide earlier, more informed treatment decisions?

Dr. Geara:
When you are treating your patient with IgA nephropathy, you are introducing several tools to control the proteinuria for these patients. These tools will include ACE inhibitor, SGLT2, and some other medications like, for example, endothelin inhibitor, and so on.

All of these tools that are controlling the proteinuria at the same time, they do cause some fluctuation of the eGFR. And this could be one of the reasons why we look at the eGFR as a lagging tool. You cannot assess the eGFR slope over a short run, because you introduce all these hemodynamic medications that will affect your eGFR in a negative way. So it's better to look at the eGFR over two to three years' follow-up in order for us to assess the progression and to have a better estimation and a better assessment of efficacy of a therapy.

So in general, we look at the proteinuria as being the early biomarker, and we look at eGFR as more of a delayed or, like you said, lagging biomarker when it comes to progression.

Dr. Colbert:
Now, applying this knowledge in practice, what are some of the emerging strategies and agents that go beyond proteinuria reduction to preserve kidney function?

Dr. Geara:
I think this is an important point. When we look at the proteinuria reduction, and specifically with the newer agents where we have a lot of data that's emerging, we see that the proteinuria improvement has been around 30 or 40 percent across all of these agents.

But you see at the same time that the eGFR slope can be different depending on the agent. And this is where it is important to take the mechanism of action in order to evaluate the efficacy of this therapy. And I think that's where the guideline's moving; it's moving into a place where we are trying to address all the mechanisms of action that lead to the progression. And a combination therapy might be the future for the majority of patients with IgA nephropathy.

Dr. Colbert:

And just to bring this all together before we close, Dr. Geara, how can clinicians implement these management strategies to better preserve kidney function over the long term?

Dr. Geara:
So when treating IgA nephropathy, it is important to take into consideration it is a disease that has several decades of progression. So when we are trying to implement this therapy, we are trying to implement it in a timely fashion in order to control the disease early on and to have a continuous control of disease.

So if we look at, for example, targeted-release formation of budesonide, it is a medication that's currently being prescribed over a six- or nine-month treatment course. And this treatment course would be time limited. We've got to, at some point, utilize the other strategies, including RAS blockade, SGLT2, endothelin inhibitor, sparsentan, or atrasentan to control the complement activation at some point.

So it is important to have this continuous monitoring of these patients in order to detect any kind of relapse, specifically if we're using a steroid-based therapy, because we know that this steroid-based therapy has efficacy that's limited in time. And we see relapse afterward of the proteinuria and eGFR slope progression.

In addition to this continuous proteinuria control that will require maybe additional therapy, the pharmacologic or lifestyle adjustments need to be implemented in a continuous manner and monitored in a continuous manner. And adjustments need to be implemented as required.

Now, one last point. It is important to keep an open mind regarding clinical trials. I think clinical trials and the newer therapies that have been approved or even tested in these clinical trials can present additional therapeutic options for some of these patients.

Dr. Colbert:
With those closing thoughts in mind, I want to thank my guest, Dr. Abdallah Geara, for joining me to discuss how thorough evaluation of hematuria, proteinuria, and eGFR can help improve long-term outcomes for IgA nephropathy patients. Dr. Geara, it was great having you on our program.

Dr. Geara:
Thank you. It was a pleasure.

Announcer:
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