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Can We Do Better in IgAN?

Announcer:
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Dr. Barratt:
Immunoglobulin A nephropathy, or IgAN, is the most common form of glomerulonephritis and a primary cause of kidney failure. But despite the risk of advanced kidney disease, we have few therapeutic options. So what are the limitations of current therapies? And how can we do better for our patients with IgA nephropathy?

This is CME on ReachMD, and I'm Dr. Jonathan Barratt.

Dr. Bruchfeld:
And I'm Dr. Annette Bruchfeld.

Dr. Barratt:
So welcome, Annette. I'm really looking forward to our discussion. And I want to kick things off by asking you if you can tell us about the current standard of care in IgA nephropathy. And what are the limitations of current therapies in your practice?

Dr. Bruchfeld:
Thank you for this question. So I would like to just point out to the audience that IgA nephropathy is a heterogenous disease, and we see a pattern of injury and clinical correlates that vary, and they can vary in an individual patient over time or patients can be still maintaining these various states for a long time, also, and that you have to take into consideration. And so the more important things are the clinical factors for CKD [chronic kidney disease] progression, and the most important ones are proteinuria during follow-up and medial arterial pressure during follow-up, and then there are, of course, chronic histological damage.

So it has been studied for quite some time already, looking at the proteinuria as a prognostic factor, that remission of proteinuria improves prognosis in IgA nephropathy. And if you have a very low proteinuria level, less than 0.5, you will have a better prognosis as compared to worsened proteinuria, and the nephrotic-range function proteinuria gives a really bad kidney survival already over 15 years.

We all start after biopsy with supportive care. We treat the blood pressure, we prefer to use ACE [angiotensin-converting enzyme] inhibitors and angiotensin receptor blockers because they have their own anti-proteinuric effect, and we also discuss a lifestyle management, patients to stop smoking and lose weight and think about what they eat, and also we have to take care of the cardiovascular risk in the individual patient. But even with the supportive care, if proteinuria still is at a level of 0.75 to 1 g per day, the patient has a high risk of progressive loss of kidney function and may be considered for a glucocorticoid therapy or, if it's possible, the opportunity to take part in therapeutic clinical trials, which are many today. But the clinical benefit of glucocorticoids in IgA nephropathy is not well established and should be given with extreme caution, especially in high-risk groups, in patients who have eGFR of less than 30, latent infection, severe osteoporosis and so forth.

The 10-year follow-up of this STOP-IgA nephropathy study showed that there was actually no additional benefit of this immunosuppressive treatment on top of supportive care measures. So right now the updated KDIGO [Kidney Disease: Improving Global Outcomes] guidelines from 2021 put a lot of emphasis on this maximal supportive care and in select cases use glucocorticoids, and this should be also discussed with the patients because the side effect profile is not negligible with glucocorticoids.

Dr. Barratt:
Thanks, Annette. When we remember that most of the patients we diagnose are in their 30s, and so 20 years may seem a long time, but it means they're only in their 50s when potentially they might be developing kidney failure, and so we need to be thinking much longer term about lifetime risk of kidney failure and accepting that the therapies we have at the moment, quite frankly, don't cut the mustard. They are not going to prevent the majority of our patients from ending up on dialysis, and we desperately need new approaches, which we're going to talk about in a little while.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Jonathan Barratt, and here with me today is Dr. Annette Bruchfeld. We're discussing how we can do better for our patients with IgA nephropathy.

Dr. Bruchfeld:
Thank you. So, Jonathan, now that we have an understanding of the limitations and unmet needs of the current treatments, can you tell our listeners about the determinants of disease progression? And what do we need to keep in mind about the mechanism of action of dual-acting receptor antagonists?

Dr. Barratt:
So I think when we think about the predictors of future kidney failure within IgA nephropathy, we have invested a lot of time and effort globally in trying to understand this. So this work has been a collaboration from nephrologists and researchers across the globe using patient populations from East and Southeast Asia, Europe, and the Americas, and this work has culminated in the generation of the International IgA Nephropathy Risk Prediction Tool. And this has identified very clearly factors that determine or influence outcome that are independent of one another. And so when we look at those factors, we have some straightforward things such as age, we have kidney function at the time that you want to prognosticate from, we have the degree of proteinuria, and as you very nicely discussed, the more proteinuria you have, the worse the outcome in IgA nephropathy. And the better we can reduce proteinuria, the better the improved outcome. But actually the kidney biopsy features are also important in determining risk of progression in using the MEST-C Oxford score, and those are fed into the risk prediction tool, along with the medications that are being taken at the time that you want to prognosticate.

So here, we're talking about RAS [renin-angiotensin system] inhibitors and immunosuppression. And so in my clinical practice, I use this all the time when I make a diagnosis of IgA nephropathy. I use this to help inform the patient about what's likely to happen to them in the short term, and here we're talking 5 years or up to 7 years, and help guide decisions about the risk-to-benefit of certain treatment approaches.

What I think is clear from the available data is that blocking the angiotensin system is clearly beneficial in proteinuric kidney disease, and actually there's a large wealth of data from experimental models and from small clinical studies that blocking the endothelin system can equally be advantageous in patients with proteinuric kidney disease. We know that the endothelin system works synergistically with the renin-angiotensin system to drive those glomerular hemodynamic changes that cause harm in our patients. We know that the endothelin system is activated and can drive mesangial cell proliferation; it can drive fibrotic responses both within glomeruli but also the tubulointerstitium. And therefore, there's a very logical reason why we would want to synergize with blocking angiotensin signaling to blocking also endothelin signaling. And certainly the early data with endothelin receptor antagonists in humans has shown an anti-proteinuric effect, and we're starting to see data come through from large studies now, particularly the PROTECT study, which we'll come on and talk about, that is showing the true value of blocking the endothelin system on top of the renin-angiotensin system in IgA nephropathy. And I think this data is going to really spread out into other proteinuric kidney diseases, and perhaps we'll talk about that in a little while. But I think certainly from what we understand about the pathophysiology of IgA nephropathy, blocking both angiotensin signaling and endothelin signaling makes perfect sense in terms of making an effort to control those glomerular hemodynamic changes but also those downstream inflammatory and profibrotic signals that we know are characteristic of IgA nephropathy.

Dr. Bruchfeld:
So, Jonathan, can you now provide some perspective on ongoing trials and the potential changes we need to incorporate in our management of these patients with IgA nephropathy?

Dr. Barratt:
I think the 2 major trials that we have at the moment are the data from the NefIgArd study, which is being presented in terms of the early change in proteinuria we see with directing treatment specifically to the gut immune system and showing there that we can, by targeting the gut, reduce the amount of proteinuria in patients with IgA nephropathy. And in the last month, we now have data on endothelin receptor antagonism in IgA nephropathy, and we have the interim data, the 9-month data from the PROTECT study. And the PROTECT study recruited those patients that we know are at high risk of progression despite optimized supportive care for at least 3 months. The PROTECT study compared sparsentan, a dual endothelin angiotensin receptor antagonist (DEARA) which has high selectivity for the

endothelin type A receptor (ETAR) and the angiotensin II type 1 receptor (AT1R), with an active control, which was maximally tolerated irbesartan. And what was seen was that a dual endothelin angiotensin receptor antagonist resulted in a significant reduction in proteinuria at 9 months compared to the irbesartan. Now we don't have GFR [glomerular filtration rate] data yet, but all of the information we have in the published literature would suggest that that reduction in proteinuria that we see with endothelin receptor antagonism will translate to future kidney function protection. But of course, we need the data, the 2-year data from the PROTECT trial to really confirm that when we look at eGFR outcomes. And interestingly, sparsentan is being studied in another glomerular disease, in FSGS [focal segmental glomerulosclerosis] in the DUPLEX study. And the data from that study has been a little disappointing, but I think it's explainable. It's not that sparsentan didn't do what we would expect it to do; it's just the degree of proteinuria reduction that was seen with sparsentan did not generate a sufficiently large reduction in proteinuria over RAS inhibition to generate those kind of eGFR protection effects that we are seeing in IgA nephropathy. And I think that stems from the differences in the 2 underlying pathophysiologies, but what I think the DUPLEX data certainly shows us is that the amount of eGFR protection that was seen in that study is directly related to the amount of proteinuria reduction that was achieved.

So I think, in summary, I think the data we have available is incredibly positive, certainly in IgA nephropathy.

Well, this has certainly been a fascinating conversation. As always, I like talking kidney disease with you, Annette, and in particular IgA nephropathy, which is my favorite of all of the kidney diseases. But before we wrap up, Annette, what's your own take-home message for our audience on what we've been discussing today?

Dr. Bruchfeld:
So I would say that it's important to recognize the disease, early detection, because still we see it centers on biopsy patients. And you can't really say that the patient has IgA nephropathy without the biopsy, and you should treat the patients according to guidelines which will now be updated.

Dr. Barratt:
Thanks, Annette, I think IgA nephropathy is a rapidly evolving space at the moment, and for everyone listening, please, watch this space, keep up to date, keep looking out for initiatives like this to make sure that you're fully aware of all those new therapies that are coming and how we can use these in combination, how we choose the right patient so that we give the right drug to the right patient at the right time with the goal to preventing kidney failure in the lifetime of every patient with IgA nephropathy.

Dr. Barratt:
Unfortunately, that's all the time we have today, so I want to thank our audience for listening in, and thank you, Dr. Annette Bruchfeld, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Bruchfeld:
So I want to thank you, Jonathan, for this really interesting discussion and also for the audience for listening in. Thank you, and goodbye.

Announcer:
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