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Exploring Developments in IgAN and FSGS

Announcer:
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Dr. Trachtman:
Immunoglobulin A nephropathy, or IgA nephropathy or IgAN, and focal segmental glomerulosclerosis, or FSGS, are 2 pivotal causes of end-stage renal disease, which we now call kidney failure. While the risk of progression to end-stage renal disease is high, the existing therapeutic options remain limited. Today, we're focusing on promising recent advances that can reshape the treatment landscape for our patients with IgA nephropathy and FSGS.

This is CME on ReachMD, and I'm Dr. Howard Trachtman.

Dr. Lafayette:
And I'm Dr. Richard Lafayette.

Dr. Trachtman:
Richard, since the clinical manifestations of IgA nephropathy can vary, we need to enhance screening and diagnosis for patients. Any ideas on how we could do this better?

Dr. Lafayette:
Yeah, that's a really important question. I think all care starts with identification. And in IgA nephropathy, we know that our patients come to us late with **reduced** kidney function, heavier levels of protein excretion than we would like, with sometimes years of being ignored for having blood in their urine. So there's got to be an opportunity to screen our pediatric and adult population better, maybe even with annual urinalysis. But clearly, when we find blood and protein in the urine, we need to go forward and diagnose our patients. I think a lot of primary care doctors and even nephrologists sometimes feel if you've got modest proteinuria and hematuria, relatively stable blood pressure and kidney function, that that's good enough. But now we know that these patients can really progress. And we have to get to our diagnosis, which in IgA nephropathy is a kidney biopsy. And then we can risk assess our patients. And these days, we are so lucky to have more and more therapies for our patients that we must identify them early and give them their best treatment options.

Isn't that also arising to be the same for FSGS?

Dr. Trachtman:
For sure. I think FSGS probably suffers from a very bad moniker. So therefore, the effort to identify the disease in the population is that much greater. We know that it can present either with asymptomatic proteinuria, as you well know, in both children and in adults, and overt nephrotic syndrome. The second category, they'll almost immediately come to medical attention, the children and the adults with asymptomatic proteinuria, they're the challenge.

With FSGS, we have the option for genetic screening. And therefore, as that becomes more accessible within the population, this may be another venue or approach for identifying patients with FSGS.

So, Richard, I think you have a case that can demonstrate a lot of these features that you think are important for case identification, management, and potentially future applications of new treatments.

Dr. Lafayette:
Yeah. I do think this case is a really good example, a 39-year-old gentleman who did have kidney biopsy and was diagnosed with IgA nephropathy. His prior physician had treated him with immunosuppressive therapies, but there were some side effects. And unfortunately, proteinuria stayed high; kidney function's low. Presently, he's on a good dose, maximally tolerated, ACE [angiotensin-converting-enzyme] inhibitor, but the blood pressure is at 132/80. But the kidney function, unfortunately, is already low at 35 mL/minute. The proteinuria is quite high at nearly 3 g/day. And a repeat biopsy demonstrated that the inflammation was really mild with an M0 E0 score. But there was some glomerular sclerosis with S1, and some interstitial fibrosis with T1. So we have to know how to handle these patients, because this patient's prognosis is particularly poor, and we had to discuss that. But luckily, there's some new findings that I can review to say that we can offer further therapy.

So perhaps you'd like me to go through some of the topline clinical data.

Dr. Trachtman:
Sure.

Dr. Lafayette:
I think it's very exciting because we just got to see the complete data from the PROTECT study. And as you know, that was a randomized controlled trial of sparsentan in adults who have biopsy-diagnosed IgA nephropathy, who have more than 30 mL/minute of kidney function, have been optimally treated with RAS [renin-angiotensin system] inhibition but still have more than 1 g of protein a day. And that randomized study was very nice because we already had seen that at 9 months, there was a substantial and meaningful reduction in proteinuria.

But now we've seen in the 2-year data that there was a clinically meaningful reduction of progression by GFR [glomerular filtration rate] slope. And furthermore, there are really, really meaningful findings, such that many patients had really substantial reductions of proteinuria, not just 50% reductions, but even complete normalization of their proteinuria. And that was associated with a really strong trend towards patients being spared from a 30% reduction in proteinuria or from going on to dialysis or needing a transplant. So that was a really key finding.

And this sort of follows other really positive findings in IgA nephropathy, including the NefIgArd study where a targeted budesonide called Nefecon, in another randomized controlled trial, was able to reduce proteinuria, was able to stabilize the GFR slope, and also reduce the number of patients who had 30% reduction in kidney function. So another kind of upstream treatment for our patients to try to reduce, perhaps, the galactose-deficient IgA and try to reduce side effects that we see in aggressive immunosuppression.

So we now have these 2 additional FDA-approved therapies for our patients that we potentially could offer patients. And we have SGLT2 [sodium-glucose cotransporter 2] inhibitors, sort of for any patient with chronic kidney disease and proteinuria. And even beyond that, we just heard of two phase 3 studies further suggesting that complement inhibition might be an avenue that we can take and that the endothelin antagonism story has further strength.

Dr. Trachtman:
IgA is the most common, so it's good that we can make progress on the one that's the most prevalent

Dr. Lafayette:
I agree. And I think some of the beauty of these findings is they really follow the pathogenesis –

Dr. Trachtman:
Yeah.

Dr. Lafayette:
– which is a little better understood with perhaps, you know, some of the immunosuppression, trying to reduce galactose-deficient IgA and the anti-glycan antibodies, and then downstream therapies like endothelin blockade or complement blockade, trying to reduce the injury in the kidney and some of the inflammation. So it's certainly very exciting.

What's happening in the world of FSGS along those lines?

Dr. Trachtman:

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Howard Trachtman, and here today with me is Dr. Richard Lafayette. We're discussing recent advances in therapies for IgA nephropathy.

We know less about the pathogenesis of FSGS compared to IgA nephropathy. We're making tremendous progress, and I think we're learning that it's a very heterogeneous disorder. And you and I are both working with extraordinary colleagues that are doing the basic science, and I think the challenge really is to leverage that knowledge. We know that parallel with the PROTECT study, the DUPLEX study was completed. The findings were encouraging, not quite as robust. While we know that sparsentan had this strong antiproteinuric effect, translating that into a clinical effect on GFR remains open. I'm optimistic that maybe with continued treatment, that with a study with open-label extension, we'll be able to learn more about the impact of the reduction in proteinuria and preservation of kidney function and expanding our knowledge base to figure out potentially targeted populations that we can use these new therapies.

The DUPLEX trial was the largest trial that was done in FSGS, historically, and it was an extraordinary accomplishment. There are other trials that are ongoing; it's a harder road to follow. But one of the ones I would want to highlight is a trial of a TRPC6 inhibitor that's targeting a specific pathway within a podocyte.

Dr. Lafayette:
I think working on the characteristics of our patients and really targeting them as well, genetic versus autoimmune versus others, is going to be critical.

Dr. Trachtman:
So, Richard, your experience is crucial here. What insights can you share about translating the recent clinical trials into actionable approaches to optimize outcomes for the patients with IgA nephropathy?

Dr. Lafayette:
If we come back to the example, like our patient who has advancing chronic kidney disease, substantial proteinuria, and particularly in that case, maybe not really optimized blood pressure, we have to optimize the blood pressure, get the patient their best diet, make sure they're not doing anything that's ill advised. But now with this further tool kit, we really can expand their care. And, you know, dual endothelin angiotensin-2 blockade in that kind of setting with heavy proteinuria, advancing loss of kidney function, would be a very, very reasonable consideration, would perhaps improve the blood pressure a little bit, but would improve the proteinuria and slow the patient's progression. There'd be strong consideration for an SGLT2 inhibitor as well. And you'd look very carefully at the biopsy considering if there's ongoing IgA deposition. And if you think inflammation is still playing a role, utilizing a targeted budesonide, like Nefecon, could be reasonable.

It's going to be really, really important as we do post hoc analysis of these trials to try to learn if all IgA nephropathy patients should be treated the same or whether some of the anti-inflammatory immunosuppressive drugs versus those other mechanisms of actions like endothelin blockade, which may be hemodynamic and specific to some patterns of injury in the kidney, as well, based on preclinical studies, ought to be utilized. But luckily, we have things to offer. And we could probably already start improving the outcomes of our patients with less toxicity.

So another very important issue in the PROTECT trial is that the GFR slopes really did separate. The chronic slope was significantly less rapid in patients treated with sparsentan. And while the net difference amounted to just over 1 mL/minute/year, obviously, when we have young patients who have time to go to dialysis, at nearly 8 mL/minute, that extra 1 mL/minute builds up year after year after year, because we think this would be a consistent benefit. And therefore, it really can delay the time to dialysis in a very clinically meaningful way.

I think the blood pressure changes and GFR changes and proteinuria changes are not all codependent, and we'd love to hear what you think about that.

Dr. Trachtman:
I agree 100%. I know the drugs that have been tested, other than budesonide, they're hemodynamically active drugs; they're going to have acute changes in blood pressure, and presumably in intraglomerular hemodynamics as well. But I think one of the things that impresses me is that the blood pressure reduction occurs early and is relatively sustained. But the antiproteinuric effect, at least for sure within the context of FSGS, was progressive and accumulating over time, suggesting that there was something happening at the podocyte level or at the glomerular level that's sustained, that's reflecting a genuine improvement in overall kidney function over and above the blood pressure reduction.

Dr. Lafayette:
Yeah, agreed.

Dr. Trachtman:
I think the only thing I would add is I think you and I both know that we've lived through an era where we go to conferences and the slide we show, the clinical trials in nephrology are at the bottom of all the lists of subspecialties. And hopefully we can galvanize the community that we're doing better work, the science is advancing, and we can translate this into better therapeutics.

Dr. Lafayette:
I'm really glad you made it that we're not at the endpoint even in IgA nephropathy. We have more tools, but we need many more and we need to learn how to use them. And across glomerular disease, clinical trials are awesome and need to be supported.

Dr. Trachtman:
Hopefully this kind of conversation can be a paradigm for how people can work together from across the life span, because these diseases affect children, they affect adults, and there's an urgent need across the life span.

That's all the time we have today, so I want to thank our audience for listening in and thank you, Dr. Richard Lafayette, for joining me and for sharing all of your valuable insights and thoughts. It was great speaking with you today, and I hope you can continue your great work in this area.

Dr. Lafayette:
It was my great pleasure. And thank you very much, Howard. Pleasure spending time with you. And again, hopefully, together we can advance the field.

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