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Understanding the Recent Advances in IgAN

Announcer:
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Dr. Floege:
Immunoglobulin A nephropathy, or IgAN, is the leading primary cause of glomerular nephritis and is a significant contributor to kidney failure. While the risk of end-stage kidney disease looms large, the existing therapeutic options remain limited. Today we're exploring the promising recent advances that can reshape the landscape for our patients with IgAN.

This is CME on ReachMD, and I'm Dr. Jürgen Floege.

Dr. Barratt:
And I'm Dr. Jonathan Barratt.

Dr. Floege:
John, let's begin by considering how various emerging therapies are engineered to address distinct facets of IgAN.

Dr. Barratt:
I think we are at a very exciting time in the history of IgA nephropathy with the opportunity to target the different pathogenic pathways. I think we need to think about 4 aspirations. The first is to target those generic downstream responses to nephron loss and kidney injury. So glomerular hyperfiltration, the impact of proteinuria on the tubular interstitium. And here we've always had renin-angiotensin system [RAS] inhibitors, but we're now seeing exciting data for endothelin receptor antagonists. We've got the introduction of SGLT2 [sodium-glucose cotransporter-2] inhibitors. And in the future, we may well have mineralocorticoid receptor antagonists.

Dr. Floege:
Excellent, John. And I think another important aspect is that many patients first come to attention when they already have a lowish GFR [glomerular filtration rate]. And you know they already have interstitial fibrosis. And I believe it's really important to point out that many of these approaches like the RAS, like the endothelin system, like complement, are involved in tubular interstitial fibrosis, so you have a dual triple-action on the mechanisms that really drive renal failure.

So, John, and with these newfound insights into mechanisms and therapeutic targets of these emerging treatments, could you delve a little deeper into the latest trial findings?

Dr. Barratt:
There was some interesting data at the late-breaking clinical trials session on povetacicept and sibeprenlimab, 2 APRIL/BAFF-targeting therapies, B cell modulators, they showed very interesting data on suppression of the abnormal form of IgA, GDIgA1 [galactose-deficient IgA1]. That translated through to reductions in proteinuria and stabilization of GFR, although that data was far less mature on small numbers of patients.

We saw some phase 2 data on ravulizumab, which is a C5 biologic showing, again, a prompt impact on proteinuria.

But perhaps the highest and most impactful study we saw was the complete phase 3 results of sparsentan. That is the most mature dataset that was presented at the ASN [American Society of Nephrology], and we have the complete 2-year data now on that PROTECT trial. So talking about the PROTECT trial, what we saw here was in a population of patients we had – there were 404 patients studied. They were a typical high-risk IgA nephropathy population; they had high levels of proteinuria, they already had evidence of impaired kidney function, on average, there was a good racial and gender mix within the population, and quite honestly, they very much resemble the types of patients I see in my clinic.

It was an interesting trial design because it compared sparsentan against an active control arm, which was maximal dose of irbesartan and 95%+ of the patients in the active control arm were able to tolerate the maximal dose of irbesartan. And this is the only trial that has actually compared the investigational product against a formalized, protocolized, optimized supportive care arm. We saw a significant reduction in proteinuria that was sustained over the full 2 years of the study and that that translated through to clinically meaningful reductions in the rate of loss of kidney function.

The PROTECT study evaluated change or loss of kidney function in 2 different ways. It calculated the eGFR slope using mathematical formula to calculate the total slope and the chronic slope. And we need to just understand what that means. So total slope is using all the GFR data from randomization through to the end of the study at 2 years. Whereas chronic slope just uses the GFR data after the first 6 weeks following randomization through to the end of the study. And with a hemodynamically active drug like sparsentan, you do see an acute effect on change in GFR, and that's quite obvious in the trial data. And when you see that acute effect, it can influence the reliability of generating a mathematical slope from the data. And what we see in the data that was presented at the ASN is actually consistency that there's roughly a 1 mL/minute/1.73 m^2/year difference in both total and chronic slope between the active comparator arm, irbesartan, and sparsentan. So a consistent kidney function protection effect of sparsentan. But when the statistical analyses were done, the *P* value was less than 0.05 for sparsentan using chronic slope, but narrowly missed the statistical significance of *P* less than 0.05 for total slope. And that is disappointing, but actually can be explained by the way that we calculate slope, and that early change in GFR that you see with a hemodynamic drug. But I think in totality, when we look at the effect on GFR, we look at the endpoint on hard kidney endpoints, kidney failure, significant loss of kidney function, there is a highly consistent effect of sparsentan in reducing kidney endpoints in the PROTECT trial, which I think is really reassuring that this drug is protecting kidney function in patients with IgA nephropathy.

And what this trial shows us is that the addition of endothelin receptor antagonism on top of angiotensin receptor blockade improves glomerular hemodynamics, it reduces proteinuria, and protects against the loss of kidney function. I think this is particularly important because this is going to likely be one of those foundational therapies we will want to use in all our patients who have persistent proteinuria. Because we can see here that actually this will slow the rate of loss of kidney function. On average, the difference between the irbesartan and sparsentan arms was 1 mL/minute/1.73 m^2/year. And for a 30-year-old, that's a significant impact on delaying the time to dialysis.

And importantly, when we think about efficacy, we must always think about safety. And this drug was well tolerated. And there were no safety signals that concerned me in the data presented. And in particular, there were no safety signals around liver function, which has been a concern for this class of drug. But certainly, in the PROTECT trial, there was no signal of liver toxicity at all with sparsentan.

One of the commonly asked questions about sparsentan is what impact does it have on the blood pressure? And this was looked at very closely in the PROTECT trial. And there was very little change, certainly, in systolic blood pressure during the study, a very minor change was seen in a lowering of diastolic pressure, compared to the active control arm with irbesartan. These changes were modest and unlikely, in my view, to explain the very significant difference in proteinuria that was seen with this drug and the kidney function protection that we saw in terms of GFR slope. But I'd be interested in your thoughts on this, Jürgen.

Dr. Floege:
Yeah, John, I was going to ask you about this. I agree. The formal blood pressure measurements didn't show any real big difference. But the adverse events suggested a signal in that there was more dizziness, more hypotension being reported.

Dr. Barratt:
Actually, there was an opportunity in the trial to reduce the dose of sparsentan from 400 mg to 200 mg, although the vast majority of patients did tolerate the 400-mg dose. And I think, actually, when you look at treatment withdrawals, there was very few treatment withdrawals – 4 with the hypotension that was recorded. For me, I think, in the totality of the data, that minor change in recorded blood pressure during the study is not the reason we're seeing the kidney function protection.

So I think, Jürgen, this is an impactful study. It's one of the largest phase 3 clinical trials we've ever had in IgA nephropathy. It compared sparsentan against an active control arm in a typical high-risk IgA nephropathy population. And it showed that we can both achieve sustainable significant reductions in proteinuria and that that translates through to long-term kidney function protection, which is clinically meaningful.

Dr. Floege:
I fully agree. This trial certainly sets new standards, also in terms of ongoing trials.

For those just tuning in, you're listening to a CME on ReachMD. I'm Dr. Jürgen Floege, and here with me today is Dr. Jonathan Barratt. We're discussing recent advances in IgA and therapies.

The other trial that has recently been published is the NefIgArd trial where patients with some GFR impairment, modest proteinuria, so already on the way to kidney failure, had been treated with Nefecon – that's an encapsulated form of budesonide with preferential release in the terminal ileum – or a control, and all of them had been on maximum tolerated or allowed RAS blockade. And the treatment then lasted 9 months, 16 mg of Nefecon per day. And then the patients were left untreated for another 15 months. And what happened is that GFR initially increased slightly a few mLs, and this was probably a real increase because urinary creatinine excretion didn't change; so it was not muscle loss. And then it stabilized over the 9 months, whereas the control group lost significant GFR during that time. And then when you stop the treatment with Nefecon, GFR started to parallel that observed with the control arm for the next 15 months.

The other thing that happened is that proteinuria dropped sharply by about 50% and stayed low for 1 year, so 3 months longer after cessation of the active treatment, and then started to rise, again, suggesting that in the future we have to think about prolonged, different other treatment strategies with Nefecon. Even though it's a steroid, it has a very high first pass effect. And the cortisol suppression of 60 mg Nefecon corresponds to about 8 mg of prednisolone. So a reasonably safe dose. And in fact, mostly cosmetic and mild to moderate changes and adverse events were noted with Nefecon, whereas we didn't see an increase in infections, no diabetes increase, and no casualties, of course.

We have great new options coming to the clinic, and we will have to figure out how to use them best.

Dr. Barratt:
Clinicians are going to be faced with multiple therapies. So how can we actually use the data to optimize outcomes for our patients with IgA nephropathy?

Dr. Floege:
Well, very clearly, the mainstay still is a comprehensive supportive care regimen. And I think also in that respect, PROTECT has set a new standard. If you really optimize your ARB [angiotensin receptor blockers] or ACE [angiotensin-converting enzyme] inhibitor, you can do something. We will yet have to learn how the addition of an SGLT2 inhibitor modifies all this. But very clearly, I think most of us would agree that full RAS blockade and SGLT2 inhibition would be something to start right away, possibly then replacing an ARB with sparsentan in high-risk patients. And I've become more aggressive in terms of early therapy, arguing that a nephron lost is a nephron lost, and maybe we should rather step down treatment slowly, rather than slowly stepping up treatment and, in the course of doing so, losing nephrons.

Dr. Barratt:
Absolutely. And I think we are only going to be able to achieve that goal of no kidney failure in the lifetime of our patients if we cleverly use together these drugs in combination and we target those individual pathways using the drugs that are becoming available.

Dr. Floege:
Before we wrap up, John, what's your take-home message for our audience?

Dr. Barratt:
The challenge for us, but also for our younger colleagues, is how are we going to combine these treatments? For me, the ultimate goal is no patient with IgA nephropathy develops kidney failure in their lifetime. So we need to be innovative, we need to think about using these drugs in combination, we need to be finding the right drugs for the right patient at the right time in their disease.

Dr. Floege:
And keep watching for the latest KDIGO [Kidney Disease: Improving Global Outcomes] guideline update. John and I are heavily involved in this.

So that's all the time we have today. And I want to thank our audience for listening in and thank you, Dr. Jonathan Barratt, for joining me

and for sharing all your valuable insights. It's been great speaking to you today.

Dr. Barratt:
Yeah, it's been a real pleasure, Jürgen. As always, I've enjoyed discussing IgA nephropathy with you today.

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