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Almost Like Being There: Updates in IgA Nephropathy From Kidney Week

Announcer:
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Dr. Trachtman:
Here at ASN [American Society of Nephrology] Kidney Week we've seen a lot of very interesting and exciting clinical trial results in nephrology. Let's take a deep dive into the IgA [immunoglobulin A] nephropathy studies, their design, their results, and their application in clinical practice to improve outcomes for your patients.

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

Dr. Heerspink:
And I'm Dr. Hiddo Heerspink.

Dr. Trachtman:
To start things off, Hiddo, what's the latest in glomerular disease research, specifically in IgA nephropathy, here at Kidney Week?

Dr. Heerspink:
We have seen 2 major outcome studies in patients with IgA nephropathy, the PROTECT study and the NefIgArd study. And I want to start with these 2 studies.

The PROTECT study looked at the dual RAS [renin-angiotensin system] inhibitor, angiotensin-1 receptor inhibitor, endothelin receptor antagonist sparsentan in patients with biopsy-proven IgA nephropathy. The study involved adult participants with a GFR [glomerular filtration rate] greater than 30 mL/minute and proteinuria more than 1 g/day. The study evaluated the effect of sparsentan at the dose of 400 mg up-titrated from 200 mg to 400 mg versus an active control, namely irbesartan, 300 mg/day. And the reason that the study used an active control was because sparsentan targets both the AT1 receptor and the endothelin receptor. The follow-up of the study was 2 years, and the primary outcome was proteinuria change at 9 months and then the change in GFR at 2 years.

The other study I want to talk about is the NefIgArd study. The NefIgArd study evaluated the effect of budesonide. We know that gut mucosal immune system is implicated in the pathogenesis of IgA nephropathy, and more specifically, mucosal-derived galactose-deficient IgA1 is a major contributor in the pathogenesis of primary IgA nephropathy. Budesonide targets galactose-deficient IgA in the gut and could thereby reduce proteinuria and CKD progression. So the study involved adult participants with a proteinuria level of more than 1 g/day and a GFR between 35 and 90 mL/minute. All these patients were using an ACE [angiotensin-converting enzyme] inhibitor or angiotensin receptor blocker, so we are looking at the effect of add-on therapy on top of maximal RAS inhibition.

And in this trial, patients were treated once daily with 60 mg budesonide for a follow-up of 9 months, after which, the medication was stopped, and patients were followed for another 15 months. So the total duration of follow-up was 24 months.

Dr. Trachtman:
I think that they're both very, very important because they're going to increase the number of options that are available to clinicians in the treatment of patients. And I think that opens the possibility of trying to individualize the therapy by having these options of an immunosuppressive and a non-immunosuppressive agent that can be used depending upon the patient profile.

With that in mind, Hiddo, are there any other clinical trials that we should be aware of, anything in investigation currently?

Dr. Heerspink:
There are many, many clinical trials ongoing with new drugs that target different mechanisms in the pathogenesis of IgA nephropathy. At the ASN, and as published at the same time in *The New England Journal of Medicine*, we've seen the results of a new phase 2 study, the ENVISION trial, with a so-called APRIL inhibitor sibeprenlimab. This is a monoclonal antibody and targets, actually, the cause of IgA nephropathy. And we've seen marked effects on proteinuria in this study. And since proteinuria is such an important risk marker of disease progression, I have high hopes that this APRIL inhibitor will lead to a slowing of decline in kidney function, eGFR [estimated GFR] over the long term.

And we have heard positive interim data from both the ALIGN study and APPLAUSE study. ALIGN evaluates the effects of the endothelin receptor antagonist atrasentan in IgA nephropathy, and the primary endpoint, proteinuria reduction at 9 months, was met. The APPLAUSE study evaluates the complement inhibitor iptacopan and also reported that the primary 9-month proteinuria endpoint was met. And then subsequently, we have other trials ongoing, like the ORIGIN trial that assess the effect of a dual inhibitor of APRIL and BLyS, atacicept. And the BEYOND trial also evaluates the effect of an APRIL inhibitor, namely zigakibart.

Dr. Trachtman:
Thanks so much, Hiddo. I think we both agree these are exciting times in nephrology.

Dr. Heerspink:
I would fully agree. Of course, we should realize that proteinuria is the surrogate, and that's why all the trials also use GFR slope as the coprimary/secondary endpoint to confirm that the proteinuria effect will translate into a benefit on kidney function decline.

Dr. Trachtman:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Howard Trachtman, and here with me today is Dr. Hiddo Heerspink. We're discussing the latest clinical trial results in IgA nephropathy from Kidney Week.

Can you summarize the key results from these IgA nephropathy clinical trials?

Dr. Heerspink:
The PROTECT study involved 404 participants, and adherence to the medication during the 2 years of follow-up was excellent.

Interestingly, in this trial, sparsentan compared to irbesartan reduced at 9-months proteinuria by 40%. And this effect was sustained all the way up to 2 years of treatment, at which point the proteinuria difference between sparsentan and irbesartan was 42%. The chronic slope in eGFR, which is basically the decline in eGFR from the first on-treatment visit after randomization until the last on-treatment visit, was 2.7 mL decline/year in the sparsentan group versus 3.8 mL/minute/year in the irbesartan group, cross forming to a difference between the 2 groups of 1.1 mL/minute/year, which was statistically significant with a *P* value of 0.037.

We can also evaluate the total GFR slope, which is the GFR decline calculated from the randomization visit until the end of treatment. And this was declined in the sparsentan group of 2.9 mL/minute/year versus 3.9 mL in the irbesartan group, leading to a difference of 1.0 mL/minute, which just was not statistically significant with a *P* value of 0.058.

The reason why we typically focus on the chronic slope is that we know that these endothelin receptor combination with AT1 receptor antagonists have acute effects on GFR, and these acute effects are reversible as soon as we stop the treatment. And in clinical practice, we seem to slow the progressive loss of kidney function, which is typically reflected by the chronic slope and not by this initial acute effect. So that's why we all consider that these are positive results of this trial with a chronic slope reduction of 1.1 mL/min/1.73 m^2/year.

In the PROTECT trial there were also fewer patients who initiated immunosuppressive medication in the sparsentan group compared to the irbesartan group during follow-up.

Interestingly, the clinical endpoint, which was a combination of a 40% GFR decline in end-stage kidney disease or mortality, occurred less frequently in the sparsentan group compared to the irbesartan group. And this is consistent with the slower decline in kidney function because that should translate into less clinical endpoints, which occurred during the trial.

As would be expected, if you look at the safety, we see a modest increase in edema, and that is probably because the endothelin

receptor antagonist component of the molecule causes a modest fluid retention. Hypotension was another adverse event that occurred slightly more frequently with sparsentan.

So in conclusion, we have a drug that causes a significant reduction in proteinuria compared to active control. It's important to mention that this was an active-controlled trial with irbesartan 300 mg, the maximal blood pressure-lowering dose, in all patients. And the drug slows the chronic rate of kidney function decline.

Now looking at NefIgArd, 364 participants, budesonide reduced proteinuria at 9 months by 27%, and the maximum reduction in proteinuria was seen at 12 months, at which time it was about 35%. And then after 12 months, when the study medication was stopped – remember these patients were treated for 9 months – we saw a gradual increase in proteinuria up to 2 years, and at 2 years the reduction was again at 27%. But during that year, again, patients were not treated with budesonide.

The GFR endpoint in the NefIgArd study was the time-weighted average change in GFR over 2 years, and in the placebo group it was, over those 2 years, 7.5 mL/minute, and in the budesonide group it was 2.5 mL/minute. So there was also a difference in the weight of eGFR decline.

With respect to safety, edema also occurred more frequently with budesonide compared to placebo treatment, 17% of patients in the budesonide group versus 4% of patients in the placebo group. Hypertension occurred more frequently, 12% versus 3% in the placebo group. But these AEs, adverse events, were generally mild. HBA1c levels remained unaffected with budesonide.

So we have 2 trials that reduce proteinuria and slow the kidney function decline, and thus we hope that these results will now be translated into clinical practice.

What are the implications, actually, for pediatric patients?

Dr. Trachtman:
With regard to the use of these agents in pediatrics, I'm encouraged by the fact that sponsors are recognizing that the clinical implications of these primary glomerular diseases is just the same whether you're an adult or a child with these diseases.

Well, this has certainly been a fascinating conversation, Hiddo, but before we wrap up, what's your one take-home message for our audience?

Dr. Heerspink:
This was a very exciting and motivating Kidney Week with many new therapies for patients with IgA nephropathy in the pipeline. And I'm sure that we will hear much more in the near future about the efficacy and safety of these new therapies.

Dr. Trachtman:
I'm encouraged at the convergence between the basic science research and drug development, and I would also encourage the community and all of the stakeholders, patients, their nephrologists, industry sponsors, and the regulators to join forces to make sure that we can accelerate the design and implementation of clinical trials to determine what agents are optimal for each individual child and adult with IgA nephropathy.

I want to thank our audience for listening in and thank you, Dr. Hiddo Heerspink, a tremendous authority in this area, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Heerspink:
Thank you very much, Howard Trachtman.

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