Transcript Details

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Experts on the Ground: New Data and Practical Clinical Integration of Therapies Approved for IgAN

Announcer Open:
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Dr. Canetta:
Hi, this is Pietro Canetta. I'm an Associate Professor of Medicine at Columbia University in New York City. I'm a nephrologist, and I'm here at ASN Kidney Week in Philadelphia. I wanted to talk about a few of the interesting abstracts in IgA nephropathy that I've seen or I'm excited to see at this year's Kidney Week. There's been a lot going on in IgA nephropathy, posters, oral abstracts, presentations at the late-breaking clinical trials. So, there's really way more to talk about than I would have time for.

I'll highlight a couple of abstracts that I was looking forward to seeing. So, one is a poster being presented tomorrow, first author's Obrisca, and it's titled: An Open-Label Trial Evaluating the Safety and Efficacy of Budesonide in patients with IgA Nephropathy at High Risk of Progression. Why am I interested in this? This is a group from Romania that is looking at a form of budesonide that is not the marketed form of targeted release budesonide that's FDA approved for IgA nephropathy in the United States. And so, one of the questions that I get all the time when I give talks on IgA nephropathy, and I talk about the target release, budesonide, which is marketed as Tarpeyo in the U.S., and I literally came from a talk where I got this question is, can I use regular budesonide, the type that's been around for years that is used by patients with ulcerative colitis or Crohn's disease? Can I use that instead and get the same effects? And we have no idea. We don't have any such study of the drug in IgA nephropathy patients, and it's clearly not FDA approved, the regular budesonide is not FDA approved.

So, this group from Romania has actually published already some retrospective data on their use of conventional budesonide in patients with IgA nephropathy. And in this abstract, they're going to present their results from the treatment of 32 patients with IgA nephropathy with budesonide. And at least from the abstract, they've shown that proteinuria did decrease over 3 years in patients treated. And I'm looking forward to seeing this abstract because it'll give me something to answer all those patients like one who literally came up to me after my last talk and said, 'I have IgA nephropathy; I live in a country where we don't have access to

Targeted-release budesonide, what can you tell me?' And since we've had so little to talk about this far, this is going to be an interesting piece of evidence. I don't expect that we'll ever see a study randomizing the branded Tarpeyo, and comparing that to the conventional budesonide. No expectation for that to happen.

But I think for patients, particularly outside of the U.S., who don't have access to Tarpeyo, or Kinpeygo as it's called in Europe, patients who come from countries where the health system perhaps can't afford it, patients who now have those questions, this is going to be an interesting abstract to look at.

So, that's one. Another abstract that I'm interested in is going to be presented again tomorrow, Saturday, first author is Lieberman and it's an oral abstract at one of the glomerular sessions. It's Preliminary Findings from the Phase 2 EPPIK Study of Sparsentan in Pediatric Patients with Selected Proteinuric Glomerular Diseases. There has been a lot of interest and a lot of discussion about sparsentan. Sparsentan is a novel dual endothelin and angiotensin receptor blocker. It is FDA approved as of now. It has an accelerated approval for the treatment of IgA nephropathy in the United States, with an ongoing clinical trial in IgA nephropathy, and ongoing clinical trials in

FSGS, as well.

Both of the sparsentan randomized controlled trials in IgA nephropathy called the PROTECT study, and the study for FSGS were presented today at the late-breaking clinical trials. They both have publications now; PROTECT in *The Lancet* and DUPLEX FSGS study in the *New England Journal of Medicine*, both of them published just today.

So, needless to say, there's a lot of interest in this drug, sparsentan, and more broadly in this class of drugs called endothelial antagonists because they've been of interest in CKD for a long time, going back to the SONAR study that looked at atrasentan, another endothelial antagonist in diabetic CKD. And that drug, atrasentan, is still being investigated for IgA nephropathy in an ongoing phase 3 clinical trial. There's now other endothelin antagonists, zibotentan, which had a large study in CKD, just published, just presented today and just published today. So, lots of activity with endothelin.

Well, sparsentan is interesting, because it's the only one that actually currently has an FDA approval for IgA nephropathy. And so, it is available and currently being marketed. And the approval is for adults. And what I'm interested in seeing in this abstract is two things.

One is that in this study, they're looking at the use of sparsentan for a basket of different glomerular diseases, not just IgA nephropathy for which it's approved, but also FSGS and minimal change disease. And so, this is interesting because it highlights the potential for this drug to be used as a general type of protective drug for, whether you want to call it CKD or proteinuric CKD or glomerular disease, number one.

And then number two, the current FDA approval for sparsentan is in adults. Well, our colleagues in pediatrics have patients too, and they have human kidneys, even though they're smaller. And so, I think it's quite interesting to see if some of the benefits that we see in adults might be seen in children as well.

So, that study is going to be presented as an oral abstract. Oral abstracts tend to have a lot of data available. What we know from what's been published just in the information with the abstract itself is that this was a study of treating patients with either FSGS or minimal change disease, podocytopathies, or IgA nephropathy, or IgA vasculitis, or Alport syndrome. And so, those are two different groups, all pediatric, all under the age of 18, treated for 108 weeks with sparsentan, which is similar to what was done in the PROTECT study and DUPLEX study. And with a 4-week safety follow-up as well. And, so, the data that's been shown is that the proteinuria decreased over the first 12 weeks, which is what we're seeing in PROTECT and DUPLEX as well, fairly substantially 26 to 52%, and 35% overall in these groups, the drug appears to have been well tolerated.

And I'm looking forward to seeing the details of that. I'm not a pediatric nephrologist. But I think that this is going to be revealing it will be helpful for our pediatric colleagues, number one, in helping them to potentially have information on a future therapy that may or may not be eventually approved for their patient group, it's currently not. But I think it'll also give us some insights into the differences of the drug used in these different types of CKD, or these different types of glomerular diseases. And help us get a sense of how much of the effect of the drug is a class effect that might be generally valuable, versus whether there's any disease-specific effects or even age-specific effects. So, I'm excited to see that.

A third abstract, which is a poster that was presented earlier today, titled Further Insights in Iptacopan Mode of Action in IgA Nephropathy Through Protein Profiling. So, I stopped by this poster earlier today. And I think this is such an important line of investigation. So, iptacopan is a complement blocker, a factor D inhibitor, that is currently being developed by Novartis for the treatment of IgA nephropathy. It's in an ongoing phase 3 clinical trial, randomized controlled trial, one that my group and my institution is enrolling patients into in part dissipating in. And what this poster was showing was data from earlier phase 2 study of the same drug in the same type of patients with IgA nephropathy and proteinuria. And what the authors did is they took bio samples from those patients in order to examine the effect of drug treatment, iptacopan treatment on plasma proteins. And so, they used a SomaScan technology, which is a proteomics platform, to look at different protein expression in patients being treated with the drug versus those being treated with placebo.

Now, I don't want to go into great detail about the findings, because I think those are interesting, but I'm not a basic scientist. And most of the nephrologists I work with are not basic scientists. Why I think this is so important is that they did find proteins that had increased expression in kidneys from IgA patients, IgA nephropathy patients, and differentially in the setting of iptacopan use.

And I think if you come away with anything from this Kidney Week about IgA nephropathy is that the big message that you'll come away with is that there is a lot of science going on and clinical trial work going on to develop drugs, different types of drugs for this disease. And we are already in a situation where we have two FDA approved drugs. As of today, there's large phase 3 randomized controlled trials showing additional, very, very suggestive data from other drugs, sibeprenlimab, which was just published in the *New England Journal of Medicine*, for example. And so, we're entering a world where we're going to have a lot of different choices of drug treatments for IgA nephropathy.

And the key question that's going to come up and that is already coming up is how do you choose? How do you decide? How do you match the right patient to the right drug? And vice versa? And I think right now, we don't have the biomarkers yet to tell us that somebody with IgA nephropathy is going to be more likely to respond to a complement drug, a particular complement drug, or an endothelial drug, or an APRIL or BAFF inhibitor, or whatever other type of immunosuppressant or non-immunosuppressant drug that is being developed. And so, it's going to be a real challenge for clinicians.

And so, I think data like the data was presented on the poster today is really critical, as these drugs are being developed to try to understand what is going on physiologically, what's going on in the kidney itself, both prior to and in response to these drugs. And does that help us recognize and correlate which patients are going to be more likely to respond? Is there a protein signature? Is there a complement signature, you know, related to complement D blocker, for example, that is going to help us understand which patients are going to respond to these drugs? What our expectation is going to be for proteinuria changes with these drugs? What our expectation might be for inflammatory markers? And we're in a world where we've been able to bring these drugs to market based on proteinuria.

But proteinuria is really a very, very rough, biomarker, very undefined biomarker that encompasses many different types of pathogenic mechanisms that generate kidney injury and proteinuria. And we need to have more specific insight into pathomechanisms in order to best understand how to use the variety of drugs going forward.

So, I'm grateful that the authors did this type of work. I enjoyed looking at it this morning. And I enjoy – I look forward to hopefully seeing more such studies associated with many of these clinical trials that are coming up, if not, this year's Kidney Week, then at future Kidney Weeks to come.

And I'll end there. Thank you very much for your attention. I hope that if you've had a chance to be here, that you're enjoying Kidney Week and learning as much as am.

Announcer Close:
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