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Advances in IgAN Care From Kidney Week

Announcer:
Welcome to CME on ReachMD. This activity, titled “Advances in IgAN Care From Kidney Week” is provided by Medtelligence.

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Dr. Latus:
We have heard a lot of interesting and exciting clinical trial results in nephrology here at ASN Kidney Week. Today, we will review the results of some of the recent IgAN studies and discuss how the application can improve outcomes for our patients. Throughout this conversation, we will also be considering the anticipated updates to the KDIGO Clinical Guidelines.

This is CME on ReachMD, and I'm Dr. Jörg Latus.

Dr. Tang:
And I'm Dr. Sydney Tang. Jörg, there's been a lot of emerging new data at the Kidney Week, but our focus today is on IgA nephropathy, IgAN. I understand you have some recent data and relevant results to share with us.

Dr. Latus:
So I'm going to focus on sparsentan, because sparsentan was really recently approved in Germany. And the first poster I was visiting at the ASN was the PROTECT open-label extension phase. In the open-label extension phase, the patients were treated with sparsentan and an SGLT2 inhibitor therapy was added, and there was a significant reduction in proteinuria and preserved kidney function. So the PROTECT study was without SGLT2, so there was always a big discussion whether there is additional effects with sparsentan.

And the next was the SPARTACUS real-world data. And patients were treated with a RAS inhibition and SGLT2 inhibitor on stable treatment, and sparsentan was added, and there was again a significant reduction in proteinuria and a preserved eGFR.

And then a very, very interesting session at the ASN was the data with the SPARTAN trial. Only 12 patients, but it was the first study showing that the inflammatory markers in the urine went down. And I think that's very important to see that sparsentan is more than a hemodynamic treatment. It's, of course, an anti-inflammatory treatment.

Nevertheless, one more poster. It was my poster, and the data were accepted and presented in the *Clinical Kidney Journal*. It was the first real evidence of the treatment with sparsentan in SGLT2 patients. So 23 patients were treated with SGLT2 and on stable RAS treatment and then were switched from a RAS to sparsentan, and we could show a 60% reduction add on to the SGLT2 therapy in our patients. So I believe that's a very good thing for the patients to decrease proteinuria and the risk of kidney failure.

Dr. Tang:
That's very nice real-world data.

Dr. Latus:
Yeah. So the question is, do you have any additional comments to the studies at the ASN?

Dr. Tang:
Well, I think these studies have shown the effect of sparsentan or the endothelin type A receptor antagonist on reducing proteinuria in patients with IgA nephropathy. And I think concomitant sparsentan and the use of the SGLT2 inhibitor in adults with IgA nephropathy in the ongoing phase 2 SPARTACUS trial will be a good one to look at, because I think at the KDIGO recently updated draft guideline, sparsentan was included as one of the treatment for reducing IgAN-induced nephron loss.

And the next study I wanted to mention, of course, is on the use of atrasentan, the AFFINITY and the ALIGN trial. They were just looking at single agent, so atrasentan in combination with an angiotensin-II receptor. And once again, I think also showing very impressive anti-proteinuric effects. And I think we will probably see full approval once the 2-year eGFR slope data become available, and I think that will be also good news for our patients.

So atrasentan is a single endothelin type A receptor antagonist. And I think if we use atrasentan, we would also need to add an ARB, angiotensin receptor blocker, so that would be two medications.

Sparsentan, on the other hand, is a dual endothelin and an angiotensin receptor antagonist, so it is a single pill that the patient can take without the need to take an additional pill to reduce or to block the angiotensin receptor.

The other therapy that is coming along – two of them actually; one of course is the BAFF/APRIL inhibition, and the other one is complement inhibition. Well, both of these have not yet been included in the updated KDIGO guideline, because we need the trial data. We need high-level RCT evidence before these can be incorporated into the guideline.

But I think there are initial results showing that BAFF/APRIL inhibition can also, like Nefecon, reduce Gd-IgA1, reduce proteinuria, and even stabilize kidney function or eGFR in the long run. So I think it is a promising agent.

Complement inhibition, of course, is also a very important aspect because we know that IgAN, the pathogenesis, is actually involving alternative pathway and maybe also lectin pathway activation. So I think complement inhibition definitely will be coming along as an important adjunctive therapy for patients with IgAN. And once again, complement inhibition, for example, factor B inhibition with iptacopan or there are now other agents under trial inhibiting the C5 or C3, these agents can actually deal with the inflammatory portion of IgAN and therefore to reduce the tubular interstitial inflammation in IgA nephropathy.

Dr. Latus:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Jörg Latus,

and here with me is Dr. Sydney Tang. We're discussing the recent clinical trials from Kidney Week and their impact on advances in IgAN care.

Sydney, what do you think of the new draft of the guidelines? How do you think the updates will impact how you treat your patients in terms of progression and risk of proteinuria?

Dr. Tang:
Well, I think there are several aspects in the new guideline that we need to take note of. I think number one is the treatment goal, because we know that patients with IgAN, they would deteriorate with time. And most of the patients, if their eGFR attrition rate is more than 1 mL/min/year, then most of these relatively young patients within their expected life span would actually reach kidney failure. So I think one of the goals of the new guideline is to reduce eGFR loss to less than 1 mL/min/year for the rest of the patient's life.

The other aspect is on proteinuria reduction. Once again, we see that patients with proteinuria at 0.5 g/g, which we previously may think to be relatively benign, is actually not benign because these patients can also progress rapidly to kidney failure. So the other goal of the new guideline is to reduce proteinuria as much as possible, to less than 0.5 g/g, preferably to less than 0.3 g/g, and ideally of course to 0, which may not be really achievable.

I think the other important aspect of the guideline is to treat patients with two targets. One is to reduce the pathogenetic source, which is the formation of Gd-IgA1 and Gd-IgA1-induced glomerular inflammation. The other target is to treat CKD. Because many patients, when they present to the clinic, they would have already developed a certain degree of CKD. They present with proteinuria, hematuria. We do a biopsy. We saw IgAN. And these patients have some degree of CKD due to preformed Gd-IgA1. So this is another target that we need to target. So now we have different types of therapy that can target the disease at source, which is Gd-IgA1 production. And then the other part is to manage CKD.

So just let me talk about the first part, which is to target Gd-IgA1 formation. I think the first drug that has been shown to really reduce Gd-IgA1 is targeted-release formulation of budesonide from the NefIgArd study, which uses Nefecon for 9 months to show a very impressive reduction of proteinuria and also stabilization of eGFR on a 2-year follow-up. And importantly, it reduced galactose-deficient

IgA1, Gd-IgA1, in these patients. So I think it is important to note that Nefecon can be given to patients for such purpose but note that the study design was for a 9-month course of Nefecon.

But I think in real-life practice, it is likely that many patients may require a repeat course of Nefecon or a lower-dose maintenance because proteinuria may not have dropped to less than 0.5 or less 0.3 g/g, so these patients may actually require a maintenance dose of Nefecon to deal with Gd-IgA1 formation and Gd-IgA1-induced glomerular inflammation.

Now, Nefecon has of course been fully approved by FDA for not only reduction of proteinuria, but also for stabilization of GFR. It is, of course, an immunosuppressive agent, although the side effect profile is very favorable because I think the systemic absorption is very limited.

Now, on the other hand, to deal with the CKD part or the Gd-IgA1-induced nephron loss portion of IgAN, there is a new compound in addition to RAS inhibition, SGLT2 inhibition, and also lifestyle modification. The new compound, of course, is, as you mentioned, is sparsentan, which is a DEARA, a dual angiotensin and also endothelin receptor antagonist. This is a non-immunosuppressive agent. It has also received full FDA approval for proteinuria reduction and also stabilization of eGFR in patients with IgAN. And I think sparsentan would be effective in reducing inflammation in the tubular interstitium caused by preformed Gd-IgA1.

And I think patients in the trial, in the PROTECT study, for example, have very favorable reduction of proteinuria and also stabilization of eGFR versus control or placebo.

Dr. Latus:
I was very happy to see the guideline because that means I'm not allowed to be satisfied with a proteinuria of 0.8 g like we did it in the past. So I believe we need more drugs to get the proteinuria to 0 and to preserve kidney function.

So now, because I'm treating a lot of patients and they sit in front of me in my office, and now I want to ask you, what would you recommend to me? There is a patient 40 years old. He has an eGFR of, let's say, 50 mL and biopsy-proven IgAN and now the proteinuria is 1.5 g. So I would be very happy to start with Nefecon and sparsentan at the same time point. Would you tell me that's a good idea or it's a bad idea?

Dr. Tang:
Well, I think from the available evidence and from the guideline, I think this is certainly a good approach. And should these drugs be readily available, the combination of Nefecon and sparsentan simultaneously for this young

patient with CKD with IgAN with proteinuria at 1.5 g/g, would certainly benefit this patient in terms of proteinuria reduction, in terms of reducing Gd-IgA1, and also in terms of stabilization of eGFR.

And I think the overall objective is to prevent disease progression, reduce eGFR loss to hopefully less than 1 mL/min/year. And these are the treatment goals. And I think this combination therapy would deal with reducing Gd-IgA1 formation and therefore reduce new or incident loss of kidney function due to Gd-IgA1. On the other hand, sparsentan would also deal with the effect caused by preformed Gd-IgA1 causing kidney inflammation. So I think both drugs will be complementary.

Dr. Latus:
Thank you. So, well, this has been certainly an= fascinating and necessary conversation. Before we wrap up, let's each provide a final take-home message for our audience. Sydney, what do you hope our listeners will leave with today?

Dr. Tang:
Well, I think it is important to realize that IgA nephropathy is not a benign disease. It affects many patients, and I think the rate of kidney failure is really a lot higher than we used to think. So I think we really have to focus on not just

optimize supportive care, which I think is important, but in addition, we need to think of some specific therapy that would deal with the disease at its source by, let's say, reducing Gd-IgA1, reducing intraglomerular inflammation, and also, at the same time, reduce Gd-IgA1-induced nephron loss.

Dr. Latus:
Yes, and I believe we should keep in mind that we have to lower proteinuria to 0, or, let's say, to 0.3 g/day. And therefore, I believe we need the multi-targeted therapy. And I'm very happy that we have the new drugs available.

Dr. Tang:
Excellent.

Dr. Latus:

That's all the time we have today. So I want to thank our audience for listening and thank you, Dr. Sydney Tang, for joining me and for sharing all of your valuable insights and expertise. It was great speaking with you today.

Dr. Tang:
Well, thank you very much, Jörg, for having me today and goodbye.

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