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Real-World IgAN: A Case-Based Approach to Maximizing Kidney Preservation

Announcer:
Welcome to CE on ReachMD. This activity, titled “Real-World IgAN: A Case-Based Approach to Maximizing Kidney Preservation” is provided by Medtelligence.

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Dr. De Vriese:
It's a very exciting time in the treatment of IgAN. Several new therapies are now at hand, many others are in the pipeline. So join us in this case-based discussion where we will talk about real-world strategies to manage IgAN.

This is CE on ReachMD, and I'm Dr. An De Vriese.

Dr. Wong:
I'm Dr. Muh Geot Wong from Concord Hospital from Sydney, Australia.

Dr. De Vriese:
One of the major changes, as far as I'm concerned, in the new KDIGO guidelines, when you compare them with the 2021 guideline, is that the proteinuria target to define a patient as being at risk for progressive kidney function loss has been lowered to 0.5 g per 24 hours, from the original 0.75-1 g per 24 hours, thus acknowledging that proteinuria is not just a symptom but a very powerful driver of adverse kidney outcomes.

And in addition, rather than a stepwise treatment approach, more aggressive combination therapy from the beginning is now advised with the aim to bring proteinuria down as low as possible.

Now while I obviously completely agree with this, I have a concern that the KDIGO guidelines remain very proteinuria-centric. The focus lies on proteinuria alone, and we know that proteinuria alone does not allow you to decide whether the risk of progressive kidney function loss is either the result of chronic kidney damage with incomplete repair of the glomerular filtration barrier or, on the other hand, whether there is active glomerular inflammation, or perhaps a combination of both.

So I would argue that when the kidney biopsy was performed relatively recently, you can calculate the MEST-C score and it can help you to appreciate whether indeed there is evidence of proliferative disease or, on the other hand, primarily chronic damage. You can also look at the presence of microscopic hematuria, and if you see that there's persistent microscopic hematuria, it can help you because it points out that there is active glomerular inflammation.

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Dr. Wong:
I think it is important for us to congratulate all the efforts of the various collaborative clinicians globally to collect individual patient-level data and working together with the regulatory authorities, and that has gained acceptance of proteinuria reduction at 9 months as a surrogate marker for heart-kidney endpoints. And you must admit that this has really shaped the current clinical trial designs in IgA nephropathy and accelerated approval for several emerging therapies for IgA nephropathy and that there's more to come.

And another thing to consider about some of these agents, like sparsentan and SGLT2 inhibitors, it may be the additive or pure trophic effect of additional effects of these drugs are beyond its hemodynamic effects, including podocyte preservations, reduction of mesangial proliferations and other tubular protections such as anti-inflammatory, antifibrotic property, that may have contributed to the anti-additive, antiproteinuric, and nephron protections effect.

Dr. De Vriese:
Thank you, Muh Geot. So, now that we have reviewed the new KDIGO guidelines, let's see how current treatment paradigms may apply in a real patient case.

Muh Geot, you have a case to share with us.

Dr. Wong:
Yes, I do. And I'd also like your input as well, and I'd like to share a 34-years-young little lady of Indian origins who presented initially a couple of years ago with relapsed IgA nephropathy, whom I saw. And she was diagnosed several years ago, brought with biopsy-confirmed IgA nephropathy around 8 years ago.

Her initial presentation was hematuria, edema with preserved kidney functions, and a proteinuria of about 2.5 g per day. This was measured by 24 hours. And she responded initially with the standard treatments; was given some RAAS inhibitions and had a biopsy that confirmed the biopsy. And the clinicians abroad had made a decision to give her a course of oral prednisone, where she responded very well, and she remained in remissions until about 2023 with the baseline proteinuria around 300 mg/day.

When she first referred to me, she was noticed to have frothy urines, and following an episode of flu, a 24-hour urine showed proteinuria of 2 g/day, despite her being on telmisartan 80 mg daily. And also, she had at that time – still had preserved kidney function. She doesn't have edema, but she had 3+ of proteinuria and her blood pressure was actually quite well controlled and she had a BMI of 28.

So a repeat kidney biopsy shows with MEST-C score of M1, E0, S0, T0, and C0. I've decided to give her a 3-month course of SGLT2 inhibitors, which is dapagliflozin, and her proteinuria remains elevated in the urine, PCR of 100 mg/mmol.

So, An, I'd like to know what your approach is to this lady.

Dr. De Vriese:
Yes. This case is a perfect example to illustrate what contemporary foundational therapy in IgAN could look like.

So we know that subgroup analyses from the EPI-CKD and the EMPACT kidney trials revealed that SGLT2 inhibition reduces albuminuria, reduces kidney disease progression also in patients with IgAN. So, therefore, SGLT2 inhibition is now part of the standard of care for patients with IgAN, along with RAASi.

But the PROTECT trial, which you mentioned, the randomized, controlled trial that compared sparsentan with irbesartan, did not allow SGLT2 inhibition. So, until recently, we had no formal data on the additional effect of sparsentan on top of SGLT2 inhibition.

Would you tell us a little bit about the mechanism of action of sparsentan?

Dr. Wong:
Yes. And as you know, sparsentan is a DEARA, short form for dual endothelin receptor antagonists, and also an ARB, or angiotensin receptor antagonist. So it has a dual action, has very small molecules, and it binds with both the endothelin receptor as well as also the ARB. And it exerts a synergistic effect on the kidney cells. Particularly, it has been known for its protections for prototype integrity, mesangial proliferation, and also known to have some anti-inflammatory and antifibrotic properties.

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Dr. De Vriese:
At the recent EDTA, the SPARTACUS trial was presented. As you know, it was conducted in patients with IgAN that were stable on SGLT2 inhibition, and it showed that the addition of sparsentan resulted in a rapid, and a sustained reduction of albuminuria, with nearly one-third of the patients achieving an impressive UACR of less than 0.2 g/g.

There was also a real-world study of something like 20, 25 patients with IgAN that were already taking SGLT2 inhibition, and that were then treated additionally with sparsentan through the managed access program. And in these patients, sparsentan reduced UPCR with 62% after something like 14 weeks.

So if you put these things together, it looks like that the proteinuria-reducing potential of sparsentan on top of SGLT2 inhibition is impressive. So I would propose – and I would like to know if you agree with me – to add sparsentan in this patient.

Dr. Wong:
And I did actually put this lady on sparsentan.

And I guess a few points for consideration to be made when switching someone or in adding someone with addition a sparsentan or DEARA, the dual endothelin angiotensin receptor antagonists, is clearly it's a dual-action endothelin and ARB. She was on telmisartan, and the medications need to be withheld and replaced with sparsentan. Add on top of the SGLT2 inhibitors. And the other considerations that may be made is they sometimes do lower the blood pressure a little bit as per the trial in the PROTECT trial, and I think need to observe that. And a consideration sometime with hyperkalemia as well, but usually, I think one of the additive benefit of this synergistic effect of SGLT2 inhibitor in sparsentan is that one of them do lower potassium, and the other one perhaps increases potassium, and they have kind of bi-symbiotic activities that benefit.

But as I mentioned, these are high-risk patients and they're likely to progress if we do not intervene right now.

Dr. De Vriese:
For those just tuning in, you're listening to CE on ReachMD. I'm Dr. An De Vriese, and here with me is Dr. Muh Geot Wang. We're discussing a case-based approach to maximize kidney preservation in patients with IgAN.

I would like to come back to what you said about the PROTECT trial. Sparsentan, indeed, produced a rapid and meaningful reduction in proteinuria, something like 41% between-group comparison, and it was sustained over the course of 2 years. And what I found very important is that the differences in blood pressure between the sparsentan and irbesartan arms were minimal, suggesting that the proteinuria-lowering effect of sparsentan is at least partly independent from the blood pressure-lowering effect.

The difference in eGFR slope after 2 years was like, 1 mL/min/year, which may at first sight not look very impressive, but it means that the eGFR curves in both groups are separating over time.

So if we put everything together, the available evidence suggests that sparsentan has the potential to fundamentally alter the risk of kidney disease progression in IgAN.

Dr. Wong:
Yes, it is promising. And we do hope that you know the open-label extensions of the PROTECT trial will give us a little bit more information. Of course, all the patients will be on placebo, probably put on the active comparator arm will be to taking the sparsentan. It may not give us the exact information, but I think the long-term safety data will be useful.

Would you consider putting patients on sparsentan as a first line? Yes. Well, you have both the RAASi with sparsentan and then and the endothelin receptor antagonists. And I think sparsentan is now moving forward in the line of therapies and I think it could be used as a first therapy, yes.

Dr. De Vriese:
So before we wrap up, perhaps we can each offer a final take-home message? Muh Geot, what do you hope our listeners will leave with today?

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Dr. Wong:
Well, I think you agree with me that it is a golden era for therapy in IgA nephropathy. So identify the right patients with the right therapy for one or a right combined therapy should be how we should approach patients likely to be in the future, who are at high risk of progression over those IgA patients.

What's yours, then?

Dr. De Vriese:
Well, I think for the first time, we have the possibility to simultaneously treat the two fundamental drivers of kidney function decline in IgAN, where the first driver is obviously the IgAN-specific pathogenic pathway with the production of the galactose deficient IgA1-containing immune complexes that then subsequently deposit in the glomularae and activate proinflammatory, profibrotic pathways in the kidneys. And then, the second driver is shared with all forms of chronic kidney disease. The consequences of intragranular hypertension and the tubular interstitial response to persistent proteinuria.

So we are now, as you said, well equipped to target these fundamental drivers in IgAN.

That's all the time we have today. So, I want to thank our audience for listening in and thank you, Muh Geot, for joining me.

Dr. Wong:
Thank you very much. I really enjoyed what we did today, and thank you all.

Announcer:
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