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Navigating KDIGO Practice Guideline Recommendations to Maximize Proteinuria Reduction in Patients With IgAN

Announcer:
Welcome to CE on ReachMD. This activity, titled “Navigating KDIGO Practice Guideline Recommendations to Maximize Proteinuria Reduction in Patients With IgAN” is provided by Medtelligence.

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Dr. Cheung:
This is an exciting time in the treatment of IgA nephropathy. Join us as we explore real-world strategies for managing IgA nephropathy.

This is CE on ReachMD, and I'm Dr. Chee Kay Cheung.

Dr. Seikrit:
And I'm Dr. Claudia Seikrit.

So let's begin by reviewing the updated KDIGO guidelines and the rationale behind the changes and recommendations. So, Chee Kay?

Dr. Cheung:
So the new 2025 KDIGO guidelines for the management of IgA nephropathy and IgA vasculitis represented a real paradigm shift in the way we think and treat IgA nephropathy. I think one of the key factors was this recognition that IgA nephropathy carries a high lifetime risk of kidney failure, and that's because the disease is often diagnosed in younger adults and often at quite a late stage of their kidney disease as well. So there's an immediate need to try and preserve remaining nephrons to reduce the risk of kidney failure.

So the new guidelines have thought through a few new concepts. One concept is to try and diagnose our patients much earlier, and so it advocates for a threshold to do a kidney biopsy in patients with a proteinuria greater than 0.5 g/day. And this is because registry data from the UK RaDaR study, but also in many other registry studies, the German CKD cohorts, as you're well aware of, and also the Swedish Renal Registry, Chinese and US registries indicate that patients with lower levels of proteinuria are still at high risk of kidney failure.

There's also new treatment goals to aim for an eGFR loss of less than 1 mL/min for the rest of the patient's life in order to reduce the risk of kidney failure, and also aiming for much stricter proteinuria goals, less than 0.5 g/day and ideally less than 0.3 g/day, accepting that combination treatment may be needed to achieve this.

And the last concept is really thinking about parallel treatment strategies to tackle the immune drivers of nephron loss and also the

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downstream consequences of IgA-induced nephron loss as well. So thinking about more aggressive treatment up front, moving away from a stepwise treatment approach, which was the previous approach in the last guideline, and thinking about tackling the disease more aggressively from the beginning.

Dr. Seikrit:
And now we have more evidence leading to the change of these recommendations, and one of them is coming from the British RaDaR cohort, and there we could nicely see, as also in the other cohorts that have been mentioned by Chee Kay, that even if we had a proteinuria below 1 g/day, the patients had a high risk to achieve kidney failure during the next 6 to 10 years.

And so this is why the new KDIGO guidelines advocate to achieve a proteinuria of less than 0.5 g/day. And now this is the new goal, to achieve remission and not only to improve proteinuria and to slow down the disease until end-stage renal failure is reached.

And another interesting point is also hematuria. Well, the evidence for real recommendations for hematuria in IgA nephropathy treatments are missing, as hematuria has never been investigated in a uniform way. And hematuria can vary from day to day, and there are errors in sample assessment that can also interfere with the measurement of the blood cells in the urine. And so hematuria can be interesting to characterize active disease, but it might also be not only reflecting active disease but also chronic inflammatory activity.

Dr. Cheung:
At the moment the KDIGO guidelines state that proteinuria reduction is the only validated early biomarker for treatment response. I think I agree with you, there's still quite a lot of work to do to validate whether we can think about hematuria in the same way.

Dr. Seikrit:
Okay, so now that we know what the updated KDIGO guidelines are focused on, let's discuss the implications for clinical practice. So, Chee Kay, how do the IgAN disease mechanisms affect our approach?

Dr. Cheung:
So I think, Claudia, the new guidelines really emphasize these 2 causes for nephron loss in IgA nephropathy, the cause that is driven by an immune-mediated process where there are IgA immune complexes that deposit within the glomeruli and drive that process of inflammation and damage.

And then the second process is more the generic response. Once patients lose nephrons, there is a maladaptive hyperfiltration through remaining nephrons, increasing proteinuria, glomerular hypertension, and that itself can cause this vicious cycle of further nephron loss.

So 2 kind of arms of drivers of kidney damage in IgA nephropathy. We can think of it as being like an immune-mediated component and more of a more generic of the CKD component as well.

And as you know, there are several therapies being developed to tackle each of these. There are treatments that target pathogenic IgA immune complexes and that pathogenic galactose-deficient form of IgA. And those are treatments that are targeting, for example, gut mucosal B-cell priming with Nefecon or the B-cell-directed therapies, which are still in clinical trials. And there were also treatments that reduce the IgA-induced inflammation, for example, complement inhibition as well.

But I think what's also interesting is the other side, and we mustn't forget that other side once that IgA is deposited. And we know that once that happens, that there's upregulation of certain mediators within the glomeruli of angiotensin I and also of endothelin-1 as well. And these can signal through different receptors, the endothelin A receptor and the angiotensin I type 2 receptor as well. And signaling through both of these can drive kidney damage once that IgA is deposited.

We've had ways to block the AT(1) receptor using ACE inhibitors or angiotensin receptor blockers, but up to quite recently we haven't had safe ways to block endothelin signaling in IgA nephropathy. But sparsentan has now emerged to block both of these receptors. It has a dual effect, and we know that it can reduce hyperfiltration through glomeruli and have a beneficial hemodynamic effect as well.

But also by blocking the endothelin A receptor, sparsentan, and also more specific endothelin A receptor blockers like atrasentan, can also have beneficial intrarenal effects on, for example, mesangial cells, podocytes that express the ETA receptor, and infiltrating immune cells as well.

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Dr. Seikrit:
And what you just mentioned, that we have to treat both sides of IgA nephropathy, so the immunologic activity, because it is an immunologic disease, and also the CKD side, which both are very important columns of treatment. And I think we can't say it often enough that it's so important to consider both parts of the disease.

Dr. Cheung:
For those just tuning in, you're listening to CE on ReachMD. I'm Dr. Chee Kay Cheung, and here with me today is Dr. Claudia Seikrit. We're discussing real-world strategies for managing IgA nephropathy.

Dr. Seikrit:
And so what about biomarkers? Do you have some data, or do we know data about biomarkers that could help us to distinguish better immunologic activity from chronicity in IgA nephropathy?

Dr. Cheung:
I think that's one of the key questions, because, as we discussed before, proteinuria is the only validated biomarker currently for treatment response, but it doesn't distinguish between active and chronic disease. And hematuria also has that caveat as well.

So there are very interesting studies pointing to emerging biomarkers. These are not quite ready to make it into the guidelines yet, because I think these need further validation, but I think there are some interesting biomarkers coming through. One of the ones that is of major interest at the moment is soluble CD163. This has gained a lot of traction, both in other fields, for example in lupus nephritis, in ANCA-associated vasculitis.

And we've seen data from the TESTING study that demonstrated that patients treated with methylprednisolone compared to placebo experienced a greater fall in this biomarker, soluble CD163, which is a marker of activated macrophages within the kidney. And then with urinary soluble CD163, the patients who have the greatest reductions also had a reduction in risk of reaching the kidney failure endpoint in that study compared to those who were less responsive.

We've also generated some data from the SPARTAN study. So SPARTAN is a study that we're running in the UK in 5 different centers, and this is a mechanistic study that looked at sparsentan as the first-line therapy in patients with IgA nephropathy who had not previously had ACE or ARB. And what we did was give these patients sparsentan and do biomarker studies, but also pre- and post-treatment kidney biopsy.

And what we showed in this study is that on sparsentan, levels of urinary soluble CD163 fell by about 50% after around 24 weeks of treatment. And currently, we are studying this further by looking at the repeat kidney biopsies of this study to see if we can see any changes in macrophage infiltration.

Dr. Seikrit:
So this is remarkable data, especially as we think about sparsentan as an improvement of CKD treatment, but it seems to have more influence on inflammation in the kidney as maybe we thought in the beginning.

Dr. Cheung:
So, Claudia, when we're talking about these different therapies, how do you think treatments like sparsentan might fit into the treatment paradigm, for example, with SGLT2 inhibitors and others?

Dr. Seikrit:
Yeah, this is a great question, Chee Kay, because in fact, when the PROTECT trial was run and patients had been included, the proportion of patients having SGLT2 inhibitors while they were entering the PROTECT trial was low. And we don't have so many data yet to see if the simultaneous use of SGLT2 inhibitors with sparsentan is effective and safe.

And then we had, last year, nice data, from Joerg Latus' group, who published with Moritz Schanz together data from his cohort, where they treated patients with sparsentan during the managed-access program. And those patients were on SGLT2 inhibition. And what we can see from this data is that adding sparsentan to patients on a stable SGLT2 inhibition has an additive effect on the improvement of

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proteinuria. And there were no unexpected side effects. We could rather say that combining these 2 drugs is efficient and safe and more beneficial, even, for patients with IgA nephropathy. And importantly, as you mentioned before, they addressed also in part, in some of the patients, both treatment arms for IgA nephropathy, so immunologic activity and the chronic kidney disease.

Dr. Cheung:
Those are really interesting data, really nice real-world studies. And I think they also are backed up by the results from the phase 2 SPARTACUS study, which studied switching ACE or ARB across to sparsentan in combination with SGLT2 inhibitors as well, and showing that that change in ACE or ARB to sparsentan in combination with the SGLT2, that you can still achieve a significant reduction.

And before we wrap up, this has been a great conversation. Let's each offer a final take-home message. Claudia, what do you hope our listeners will leave with today?

Dr. Seikrit:
Well, I would say let's not only read in the KDIGO guidelines about remission in IgA nephropathy but really adopt it. The new trial data that we have substantially changed the treatment landscape, and we have now strategies that can enable us to avoid kidney failure. And these are truly promising new opportunities, and we should do everything to make the most of them. So our new goal should be remission wherever it is possible.

Dr. Cheung:
And I think we now have emerging tools in order to achieve that, which appear to be well tolerated and effective. So in order to change those poor long-term outcomes, which have unfortunately been suffered by our patients for such a long time, we do all need to think about utilizing all these tools for the best, optimum treatment for our patients.

And that's all the time we have for today. So I'd like to thank our audience for listening in, and thank you, Claudia, for joining me.

Dr. Seikrit:
Yes, thank you. Thank you and goodbye.

Announcer:
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