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Mechanisms Matter! Optimizing Proteinuria Reduction In IgAN

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Dr. Cheung:
This is CE with GLC, and I'm Dr. Chee Kay Cheung. Here with me today is Dr. Jörg Latus.

Jörg, we now have a number of emerging therapies for the treatment of IgA nephropathy. In this episode, we will focus on some of the mechanisms of action. Why don't you start?

Dr. Latus:
Thanks, Chee Kay, excellent question. And I believe when we talk about IgA nephropathy, one of the most important developments in IgA nephropathy is that we have now therapies targeting different aspects of the disease pathophysiology, making it essential to understand their distinct mechanisms of action.

When I was a young doctor, historically the blockade of the renin-angiotensin system has been the foundation of supportive care and was the only drug available. No SGLT2, no other drugs available.

More recently, sparsentan introduced a dual mechanism by combining endothelin type A receptor antagonism with angiotensin type II-1 receptor blockade. This dual action was designed to reduce both, on the one hand, the intraglomerular pressure and, of course, to reduce the profibrotic and proinflammatory effects mediated by endothelin, resulting in greater reduction in proteinuria and, of course, in a more preserved kidney function for our patients with IgA nephropathy.

Building on this concept, it's important to distinguish between endothelin receptor antagonists, or ERAs, and dual endothelin and angiotensin receptor antagonists, or DEARAs. ERAs selectively block the endothelin pathway, whereas the DEARAs simultaneously inhibit both the endothelin and angiotensin pathways within a single molecule.

Although both of them target endothelin signaling, the additional angiotensin receptor blockade is a defining feature of DEARAs and may provide complementary hemodynamic and, of course, a reducing of proinflammatory and kidney-protective effects.

Chee Kay, now that I have discussed this, what can you tell us about some of the other classes?

Dr. Cheung:

Thanks, Jörg. I think there are a number of very exciting emerging therapies coming for IgA nephropathy, and hopefully we will see approvals across some of these classes very soon.

We have drugs that can be broadly divided in targeting the IgA-mediated immune drivers of nephron loss in IgA nephropathy and also those more generic responses to IgA deposition.

So on the side that affects the immune-mediated nephron loss, we have B-cell modulators that could target APRIL or BAFF and APRIL, and these are cytokines. They're important in class switching of B cells to IgA-producing cells and the plasma cells that drive IgA production.

We have drugs that target CD38, which cause plasma cell depletion and depletion of plasmablasts as well, which are responsible for pathogenic IgA production.

We also have drugs that can target the complement pathway, which we know plays an important role in inflammation and fibrosis.

And then we have drugs that targets more of the responses to IgA deposition and generic drivers of nephron loss, and those include SGLT2 inhibitors that are widely used in IgA nephropathy with good evidence for their benefit.

And more recently, in addition to what you mentioned before, we now have evidence for use of nonsteroidal MRAs, for example, finerenone from the FINE-CKD study, and also probably other drugs involved in CKD management will be shown to be beneficial in the treatment of IgA nephropathy.

So I think that now concludes this session. I hope you've enjoyed our brief overview, and thanks for listening.

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