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Experts on the Ground: Data Updates on Emerging Therapies for IgAN

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**Dr. Lafayette:**
Hello, this is Richard Lafayette. I'm a Professor of Medicine at Stanford University Medical Center. And I'm here at Kidney Week in Philadelphia. And it's been a really exciting time. We have some really wonderful new additions to our knowledge about IgA nephropathy, a field that's really being transformed very, very rapidly. And I have the pleasure to review four abstracts with you that I think are notable, and again, add to our understanding of the disease and perhaps into our treatment options. So, we can talk about some of these abstracts.

The first one is sort of easy to talk about. I presented this as an oral presentation, and it's about EGFR decline in patients with IgA nephropathy who are treated with Nefecon versus placebo. And this is referring to results from the 2-year NefIgArd phase 3 trial. And what was very exciting here is we had already talked about the results which are published, and this was a 2-year prospective, randomized controlled study of Nefecon in patients with biopsy-proven IgA nephropathy. And the results had shown that patients who are treated with Nefecon enjoyed a significant reduction in proteinuria, out in 9 months. And that's why the FDA approved the drug for use for patients at high risk for progression.

But the 2-year results of the study added an ongoing control of proteinuria, also demonstrated a clinically and statistically significant reduction of progression of loss of GFR with roughly a half the loss in patients treated with Nefecon as compared to those patients who are treated only with standard of care, blood pressure control, and maximally tolerated RAS inhibitors. What this abstract added was an analysis of patients who experienced a 30% reduction of GFR or had loss a kidney function needing dialysis or transplant. And the study concluded a pretty substantial reduction again by about a half for the number of patients who had a reduction of GFR by 30%. And not only was the number of patients who had this marker of bad outcome reduced, but also it took much longer to get to that 30% reduction in patients treated with Nefecon.

So, this just adds to the evidence that Nefecon treatment in patients with biopsy-proven IgA nephropathy can result in proteinuria reduction, stabilization of GFR, but also a first surrogate markers of progression, less loss of 30% of kidney function, again, suggesting that Nefecon may be a disease-modifying medication.

So, I think great excitement to have new medications that we can use for patients with IgA nephropathy. And that sort of comes together with further abstracts, one presented today by Laura Keuanga at Saturday at the meetings about concomitant use of sparsentan and sodium-glucose cotransporter inhibitors in IgA nephropathy patients in the PROTECT study. And I think this is really important because when we have our patients with IgA nephropathy at risk for progression, we really want to maximize their, I guess we call this conservative care, their blood pressure control, their antiproteinuric therapy, and there's great excitement about the SGLT2 inhibitors in patients with reduced GFR with significant proteinuria. So, within the sparsentan study, again, a double-blind placebo-controlled study of sparsentan versus maximal RAS inhibitor full-dose irbesartan, they've shown a very nice antiproteinuric effect and stabilization of GFR as well. And in this report, they were able to find us subgroup of patients who were co-treated with SGLT2 inhibitors as well.

And this is very exciting because this may mimic some of the treatment patterns that we're going to see over these next few years. And

basically, this subgroup amounted to 20 patients; not a large number, but very telling, in that the patients tolerated sparsentan very well. Again, there was no significant hyperkalemia, no significant hypotension, no side effects for the patients. But very, very rarely, in a couple of the patients, there was some headache, some transient hyperkalemia, and some hypotension. But the patients were able to enjoy a reduction of proteinuria and stay in the study. And so, the data were really consistent with additive benefit of sparsentan, even in patients who are already SGLT2 inhibitor treated, and demonstrates that this combination therapy is likely to be well tolerated in most of the patients, 90% of the patients in this little subgroup tolerated the treatment well and experienced benefit.

So, it's very exciting and interesting to think how that could reflect on your practice to have these two FDA approved drugs that at least in this initial experience, look to be effective together and to be well tolerated. And I think that sort of ushers in the idea that we may be looking to treat our patients with multiple modalities as time goes forward. So again, very telling, and very helpful information.

For the next abstract, it sort of just looks very much larger, and sort of uses a title that a lot of us are discussing, which is From Famine to Feast in IgA Nephropathy, and talking about new treatments, present new opportunities for our patients. And this was presented as a poster at ASN by Chris Dudzenski and his coworkers. And again, this basically talks about this transition that we're really enjoying now, that over just last few years, we've gone from the opportunity to only diagnose our patients, support them with RAS inhibitors, think about clinical trials, and then move on to consider whether the steroids, or too risky or immunosuppressive therapy is too risky, or whether we can try to treat the patients with corticosteroids, potentially leading to complications.

And what this abstract really looks at is an interview of reviewing charts, talking to nephrologists, and finding out that indeed in the United States, in an experience of about nearly 1,400 patient charts that were reviewed, that indeed nephrologists are becoming aware of new therapies like targeted budesonide or Nefecon, sparsentan, utilizing SGLT2 inhibitors, and that they are at least considering and starting to use these medications, and that many physicians do consider this a significant advance in their ability to treat the patients, that despite that, at the time of this data evaluation, 2/3 of nephrologists still think there is a high unmet need for further IgA nephropathy treatments. And they're again excited about the ongoing pipeline that seems to be emerging from present phase 2 and phase 3 studies.

So, here again, looking to the community of nephrologists, saying that they're getting insights and understanding that there are new ways to treat our patients, that SGLT2 inhibitor utilization is definitely increasing, that there's awareness of other new drugs, and that physicians are excited, but think there's more to do. And again, I certainly can agree with that mindset.

So, to move in a slightly different direction, for the final abstract that we can discuss, is again, there's lots of excitement about understanding the pathophysiology of IgA nephropathy better, to lead to better therapies. And in this abstract presentation by Eric Olson and their colleagues, what they did is they really are trying to look at serum and urinary noninvasive biomarkers to understand the disease better. And in this report, they really focused on endothelin and looking at protein signatures in patients with IgA nephropathy to see whether or not you could see signals that relate to endothelin activity by using atlases and databases, and looking at patient results from serum and urine, and looking at biobanks, and then looking at the protein distribution and see if that aligns to a pattern of endothelin activation.

And so, this was taken in patients, not only with IgA nephropathy, but in other diseases, and then taking this down into animal models and trying to again see, do we know the patterns for endothelin activity, and then if we treat those patients with an endothelin blocker, can we actually see that that noninvasive pattern can reflect resolution of endothelin activation, and perhaps, overactivity.

So, in the end, what they looked at is serum and urine samples from patients. They had about 100 serum samples. They also had patient-matched kidney biopsies for each of their samples. And then they analyzed the proteomics and mRNA expression for these patients. And they were able to find a very vast array of proteins in patients, over 150 serum and urine proteins that correlated with atrasentan response, and with improvements in proteinuria. And to find that these protein responses were, as was hoped, to be evidence of identifying endothelin, ended up addressing the endothelin and resolving endothelin. So, again, just a little bit more scientific, to say that, again, there is a signature and blood and urine and kidney of endothelin increased activity, that there may be biomarkers that can be followed. And again, in this population there were, that reflect that if you use endothelin antagonist, that those get resolved. And so, for in this case, atrasentan therapy, there may be other biomarkers that we can monitor to see if those drugs are effective at resolving endothelin hyperactivity. And ultimately, we'll find out if that's a surrogate of improved patient outcomes, such as GFR loss and ultimately dialysis and transplant. So, again, very exciting because it's a major, major goal to replace some of our surrogate endpoints such as proteinuria, even short-term GFR change with better biomarkers. And perhaps this is just a glimpse of us being well on our way.

So again, I tried just review four representative abstracts from Philadelphia here at the ASN Kidney Week, just to point out that this is a tremendously exciting time for IgA nephropathy, that these abstracts range from telling us, first, that there are new treatments that we have for our patients that can really move the paradigm forward and improve outcomes, including the approved drugs of sparsentan, of Tarpeyo, and of SGLT2 inhibitors, that there's early glimpses that we may be able to use some of these medications together safely and

ever more effectively, and that we still have great hope that there's further scientific exploration of the pathophysiology that will let us guide our therapy and monitor it in the appropriate patients so that we can really have personalized care.

So, thank you for joining me. I hope you find this of interest. Have a wonderful day. Thank you.

**Announcer Close:**
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