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Proteinuria First: Managing What Matters in FSGS

Announcer:
Welcome to KDIGO Conversations in Nephrology. This episode titled, “Proteinuria First: Managing What Matters in FSGS ” is provided by KDIGO and supported by Travere. Here’s your host, Dr. Kirk Campbell.

Dr. Campbell:
Hello and welcome to KDIGO Conversations in Nephrology. I'm Dr. Kirk Campbell, chief of the Renal Division at the University of Pennsylvania. Joining me today to discuss managing proteinuria in FSGS is our distinguished guest, Dr. Laura Mariani. Dr. Mariani is an associate professor and associate chair of medicine for clinical research at the University of Michigan. She's an expert in glomerular disease and has a primary research interest in developing and applying statistical methods for clinical outcomes definition and prediction of kidney disease progression.

Dr. Mariani, welcome to the podcast.

Dr. Mariani:
Thanks so much for having me. It's really nice to be here.

Dr. Campbell:
So let's begin our discussion with our first question. Why is proteinuria reduction central to the management of FSGS?

Dr. Mariani:
That's a great question. So obviously, Kirk, you know that FSGS is really a pattern of injury, and we know that it results from really multiple underlying biological processes. But I think really whether that is a circulating factor or a genetic variant or any of the other many secondary causes of FSGS, like viruses or toxins, fundamentally FSGS really is a disease of unhealthy podocytes. And when you have those unhealthy podocytes and you lose them, the biomarker we observe is proteinuria.

So I'll say all the different causes of FSGS really share that proteinuria as a marker of podocyte dysfunction is really central to the underlying biology, and so that makes proteinuria really useful. So clinically, obviously it's noninvasive, it's pretty easy to track over time within a patient, and so it makes a really good biomarker for managing the severity of the disease.

And obviously we've known for a long, long time how important proteinuria is. So there's lots of epidemiology data from many studies over long periods of time that show that patients who have high levels of proteinuria, those are the ones we really worry about. Those are the patients that are going to eventually lose their kidneys to kidney failure. And vice versa, those that get really low or even normal levels of proteinuria can do really, really well. So I think it's those combinations of things that make proteinuria so important for FSGS.

Dr. Campbell:
Yeah. So you're a leader of the PARASOL project that was really defined to develop acceptable endpoints for FSGS drug approval. Can you tell us more about that initiative?

Dr. Mariani:

Of course. So this is such an amazing time for glomerular disease in general. We've made so many incredible discoveries around the biology the biology of our different glomerular diseases.

But of course, to translate that novel understanding into new therapies, one of the steps in the middle there is clinical trials. And so for rare disease, like FSGS or really any number of our glomerular diseases, it's really important to know that the outcome we measure in a clinical trial is really reflecting what we want to know. And that's that how confident are we that a new therapy is going to prevent those long-term outcomes of kidney failure?

And so IgA is a perfect example of this where there was discovery in biology, new therapeutics were developed based on that, and then new clinical trial endpoints needed to be developed such that those new therapies could really be tested effectively.

And that's, I think, really why we see now just a wealth of new therapies in IgA nephropathy. I mean, who would have really thought that our problem in IgA nephropathy was going to be that we have too many new drugs? Okay, so I think that sort of model from IgA is really, I think, important for all of our rare diseases.

And for FSGS in particular, I would say that the issue of clinical trial endpoints was really highlighted by the results of the trial of sparsentan in a broad population of patients with FSGS. And you may remember that when those trial results came out, essentially what they showed was that as compared to irbesartan, there was a greater reduction in proteinuria, but GFR slopes were not statistically different between the 2 groups.

And I remember when that trial got reported out that probably myself and many other people were wondering, gosh, what does this really mean? Does this new medicine protect our patients or not when we see this improvement in proteinuria but really no difference in GFR? So what does that mean?

So really, kind of as a result of that, I think it made many people question what's the best way to design trials in FSGS. And so it's actually NephCure, the patient advocacy group, and the International Society of Glomerular Disease who reached out and brought together a group of researchers to try to gather sufficient data to really answer this question, which was do short-term changes in proteinuria and GFR, how well do they predict someone's subsequent risk of developing kidney failure?

And so that's how I got involved. That's when I got involved in the PARASOL project. And unlike IgA, where a lot of the surrogate outcome work was done using previously completed clinical trials, in FSGS that wasn't available. Really the bulk of what we had was observational data.

And so the group that were working on PARASOL, we essentially went out and asked people all over the world to share their data. So we went group to group to group and said, who has data on the shelf that can help us answer this question? And importantly, we wanted individual patient-level data. We wanted long follow-up so we could see who ended up reaching kidney failure and who didn't. And we wanted all the important subgroups. We wanted children, adults. We wanted people with low GFR, normal GFR, high proteinuria, low proteinuria.

And I would say it was an incredible story for nephrology in general about how willing people were to share data. And I think it was the urgency around better trial design for this disease that really doesn't have good therapies. But I think it was also the partnership of the patient advocacy group, our professional societies, including ASN and NKF, as well as having the FDA as a co-sponsor of this study. They also wanted really good data to help them make decisions about trials in FSGS.

So that's really the process and the rationale behind the project.

Dr. Campbell:
Yeah, certainly a great example of the whole field coming together for a worthy cause and really accomplished in record time.

If you're just tuning in, you're listening to the KDIGO podcast on Proteinuria First: Managing What Matters in FSGS. I'm Dr. Kirk Campbell, and I'm speaking with Dr. Laura Mariani.

So what were the conclusions and outcomes of the PARASOL project?

Dr. Mariani:
Yes, exactly. So we had in the end—actually and even now we still have people willing to share data. So now we have over 3,000 patients initially where we shared data, but about 1,600 of them had enough long-term data with frequent measurements of GFR and UPCR such that we could do the analysis that we had planned. And so we had about 1,600 patients who had proteinuria more than a gram and a half and still had a GFR greater than 30. Those are the patients that I worry about in my clinic, obviously.

And what we found was really fascinating. So I would have to say first we looked at GFR, and we found that GFR slope over 2 years, it definitely does predict your risk of kidney failure, but there was a lot of noise. And I think for clinicians that take care of these patients, I think in some ways it was maybe a little surprising but also makes some amount of sense in that there's a lot of noise in GFR, especially when people have normal-range kidney function. So you can imagine how variable GFR between a GFR of 120 and 90 and 80 and then back to 110 in an individual patient. And so sometimes it's hard to be confident what the actual slope is and whether that's actually going to predict kidney failure over that 2 years. And so we found it was especially problematic in patients with really high levels of proteinuria, pediatric patients, and those with normal GFR.

And so as a result, when we saw that information, we could do some back calculations using that observed data and found that if you're going to take 2 groups of patients with FSGS and you're going to try to detect a difference in slope, let's say of 1 or 2 mL/min/year, you need a very, very large sample size. In fact, if you took the noisiest group, all-comer population, you might need a sample size that's as big as 800 or 900 people per arm. And so that's why it's going to be really hard to detect small differences in slope.

By contrast, we looked at change in proteinuria over 2 years and subsequent risk of kidney failure, and we looked at it in the way of what proportion of patients reached certain proteinuria thresholds. So did they get down to less than 1 or 0.7 or 0.5 or 0.3? And the association between reaching that threshold and subsequent risk of kidney failure is very, very strong. So for example, if you took the people who reached a proteinuria less than 0.7 compared to those who didn't, the hazard ratio of subsequent risk of kidney failure was 0.15—really, really low. And that association was true across all of our subgroups. And we actually independently validated it in the UK database called RaDaR.

And when I think about it biologically, why might that be, I think we know there's so many things that can affect GFR and make it fluctuate, make it hard to interpret, whereas proteinuria, the link between proteinuria and risk of kidney failure in FSGS is just much tighter. And so that's why sample sizes to detect a difference in proteinuria could be a lot smaller. So more in the range of like 120-150 per arm as opposed to 800.

I'll give one big caveat. We only had observational data to work with. So the usual surrogate outcome work that you would like to do, you'd like to use trial data where you can really estimate treatment effect on the surrogate and treatment effect on kidney failure. That data didn't exist in FSGS, but that's okay. Sometimes we have to work with what we have, and that's why we're looking for those really, really strong associations. A hazard ratio of 0.8 really wasn't going to do it. We really needed much, much stronger associations to feel confident that it was really capturing what we would want it to capture.

Dr. Campbell:
So, Dr. Mariani, based on the PARASOL findings, how should clinicians and patients use proteinuria as an endpoint in managing FSGS?

Dr. Mariani:
Yeah, this is a great question. Obviously, the analysis that you do in a trial, you're really looking at outcomes in a group and comparing different groups, and that's pretty different actually from managing a patient sitting in front of you in the clinic. So in a lot of ways, I think, probably this doesn't change too much about probably how all of us were taking care of our patients, that we don't look at just one moment in time; we do look over time. We look at proteinuria, we look at GFR, but we look at many other things in terms of medication tolerance and things like that.

But I will say this work really did make me a lot more confident that paying attention to proteinuria really is important, that in this population, that the lower your proteinuria is, on average, your risk of kidney failure goes down. And so I do think proteinuria is one of the key things that we were looking at before PARASOL, but I think even more so afterwards made me feel more confident that proteinuria is something we should try to reduce in our patients with this disease.

Dr. Campbell:
So this has been a tremendous initiative. What's next for PARASOL?

Dr. Mariani:
Yeah. So like I said, I think a successful clinical trial and a trial that makes sense and is well designed and fits our clinical practice is such a key step to getting new discovery into new therapeutics for our patients. And there are so many of our rare diseases that really don't have enough therapies.

And so sort of building on the success of this and the community and all the infrastructure that was built for PARASOL around data sharing, which was no small feat, there's enthusiasm to actually take this model to other glomerular diseases. So PARASOL, again, led by the International Society of Glomerular Disease, partnered with NephCure and our other organizations, is going to take a look at surrogate outcomes in APOL1-related kidney disease and also in membranous nephropathy. And the thought is that just by actually gathering the data from diverse data sources, I think it'll help all of us really interpret the results that are coming out of these trials and make us confident that if we want to try new therapies, we really know what that might mean for our patients.

Dr. Campbell:
So before we close, are there any final messages you'd like to leave with our listeners?

Dr. Mariani:
I guess I would just say, number one, I think the PARASOL initiative is really something the whole nephrology community should be proud of. I'm just so impressed with people's willingness to share data, to work collaboratively, to try to answer key questions. I think that was really a wonderful part of that.

And I hope that for many of our glomerular diseases now, that if we are able to design really good clinical trials and understand what the results mean, that we're going to have many new therapies for FSGS and hopefully other kidney diseases where right now—and probably all of us would agree—we sure would like some other options in how to treat these patients.

Dr. Campbell:
Definitely the case. So I'd like to thank my guest, Dr. Laura Mariani, for joining me. It was great having you on the podcast.

Dr. Mariani:
Great. Thanks for having me.

Dr. Campbell:
I'm Dr. Kirk Campbell. To access this and other episodes in our series, visit kdigo.org/podcast. Thanks for listening.