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Treating FSGS: From Steroids to Dual Endothelin Angiotensin Receptor Antagonists and What Comes Next

Announcer:
Welcome to KDIGO Conversations in Nephrology. This episode titled, “Treating FSGS: From Steroids to dual endothelin angiotensin receptor antagonists and What Comes Next,” 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 proteinuric FSGS is our distinguished guest, Dr. Jai Radhakrishnan. Dr. Radhakrishnan is professor of medicine and the clinical director of the Division of Nephrology at Columbia University. He's a world-renowned expert in glomerular disease.

Dr. Radhakrishnan, welcome to the podcast.

Dr. Radhakrishnan:
Thanks so much, Kirk. Really glad to be here.

Proteinuria management in FSGS is something I deal with every single day, and honestly, the landscape has shifted quite a bit in recent years, so I'm really looking forward to digging into this with you.

Dr. Campbell:
Excellent. So when you see a patient with suspected primary FSGS and significant proteinuria, what is your standard approach to treatment? And where do you see it falling short?

Dr. Radhakrishnan:
Great question. So I will start with 2 parallel tracks. First of all is supportive care, because it helps nearly everyone optimize blood pressure, manage edema, and use RAS inhibition to reduce proteinuria.

One should also remember FSGS is firmly within the CKM syndrome, which is recently recognized. It's a cardiovascular kidney metabolic syndrome. So cardiovascular risk reduction is also very important.

And second, of course, is to decide whether immunosuppression is appropriate for this given patient. And this truly hinges on whether we believe this is primary FSGS, which is immunologically mediated, or some other form of FSGS, and this can be difficult.

And you asked me where this falls short? Where this falls short is that FSGS is truly a heterogeneous disease. Some patients relapse, some become steroid dependent, and many experience treatment toxicity without durable remission.

So even when proteinuria improves, progression can still occur. And FSGS is a situation where misclassification is real. Secondary and genetic forms can be labeled as primary, leading to immunosuppression that does not really help the patient and, in fact, can harm them from toxicity.

Dr. Campbell:
So let's stay on that diagnostic problem. In practical terms, what are the biggest classification traps that lead to the wrong therapy? And what quick checks can help you avoid them?

Dr. Radhakrishnan:
A major trap here is that we are treating sometimes the biopsy pattern of the disease. So FSGS is a histological pattern, and it can reflect any kind of podocyte injury. It could be a primary podocytopathy. It could be a genetic disease. It could be an adaptation to nephron loss or obesity. We see this in drug-related podocyte injury. We can have viral-associated disease and many more.

And really the point to ask is, what is it that is driving podocyte loss? So a quick check includes a careful history for secondary drivers, the tempo of the disease, the degree of nephrotic syndrome, and the family history. Now, we must know that genetic testing is becoming more accessible nowadays and should be utilized if there's any suspicion of an underlying genetic etiology.

And of course, since it's a very heterogeneous disease, we should be honest about uncertainty. If the phenotype is not classic for primary FSGS, I lower my threshold to emphasize supportive care. And then one should consider referral to a center with expertise in glomerular disease, rather than reflexively escalating immunosuppression in these patients.

Dr. Campbell:
So that sets up an interest in treatments that target podocyte injury without assuming an immune-mediated mechanism. Agents that target endothelin-1 like sparsentan are often described as podocyte-focused therapy. What is its mechanism in plain language? And what did the phase 2 DUET data show?

Dr. Radhakrishnan:
So sparsentan is a single molecule, and that blocks 2 pathways concurrently, the endothelin A receptor as well as the angiotensin II type 1 receptor. So conceptually, it is a dual endothelin and angiotensin blockade, which is aimed at reducing proteinuria and alleviating podocyte stress.

In the DUET study, the key headline was proteinuria. Over an 8-week double-blind period, sparsentan produced a significantly greater reduction in proteinuria than irbesartan. That was an important proof of concept that dual-pathway blockade could be more antiproteinuric than ARB alone in this population. And further, the open-label extension provided longer-term safety and durability signals. This matters in a chronic disease where we are not treating for 8 weeks but for years.

Dr. Campbell:
So the phase 3 DUPLEX trial is where many clinicians focus. What did that show? And how should we interpret the proteinuria results alongside the eGFR findings?

Dr. Radhakrishnan:
DUPLEX compared sparsentan to irbesartan and showed high rates of partial remission of proteinuria with sparsentan at the 36-week time frame, and that difference was sustained over longer follow-up. However, the eGFR slope outcome did not show a statistically significant difference between the groups over the reported follow-up, and this is a key nuance.

So the practical interpretation is not that proteinuria does not matter in this study, but rather FSGS trials are hard. The biology is mixed. There is variable chronicity at enrollment, and the relatively short windows to detect differences in kidney function decline may not sort of lead to a meaningful change in the eGFR slope. Proteinuria reduction remains clinically meaningful, but regulators and clinicians also want confidence that this translates to longer-term preservation of kidney function.

Dr. Campbell:
If you're just tuning in, you're listening to the KDIGO podcast on treating FSGS, from steroids to dual endothelin angiotensin receptor antagonists, and what comes next. I'm Dr. Kirk Campbell, and I'm speaking with Dr. Jai Radhakrishnan.

So let's make this practical. Can you propose a simplified clinical algorithm for providers managing FSGS today, including where sparsentan might fit and what a clinical checklist could be for safety monitoring?

Dr. Radhakrishnan:
Great question. Here's a step-by-step suggested approach that I use in the clinic. So I first look at the risk and the phenotype. I confirm, as far as possible, is this primary versus a secondary or a genetic FSGS, and I stratify by the level of proteinuria, the eGFR trajectory, and whether there are high-risk clinical features. I always begin with supportive care. I optimize blood pressure and volume management, and I maximize antiproteinuric therapy with a clear monitoring cadence.

SGLT2 inhibitors are somewhat controversial in FSGS. In a secondary analysis of the EMPA-CKD trial, kidney disease progression was not reduced by empa in this population.

Cardiovascular risk, again, should be looked at very, very carefully, including targeting your lipids and blood pressure management.

When it comes to immunosuppression, I reserve steroids or CNI, calcineurin inhibitors, for cases who have a high likelihood of benefit. And this is informed by chronicity, comorbidities, and also my diagnostic confidence in whether this is primary or it's not.

So when I look at podocyte-targeted options, I consider very early on in the process non-immunosuppressive therapy when appropriate, for example sparsentan, which has recently been FDA-approved for this indication.

I discontinue other RAS blockers. I monitor for hypotension or edema, and I perform baseline and every-3-month liver function tests with pregnancy contraindication counseling based on the REMS program.

I reassess and then I escalate. I track proteinuria, I track the eGFR trends, and then I may trigger referrals or enroll patients in a clinical trial if there's persistent nephrotic range proteinuria, whether there's a rapid decline in kidney function and I'm not sure of the diagnosis, and especially when I suspect a secondary or genetic disease.

Dr. Campbell:
So there are a number of novel agents currently in development being evaluated in clinical trials. Can you comment on some of these?

Dr. Radhakrishnan:
We are very fortunate to be in a time where there's a lot of activity in the research space for FSGS. So beyond sparsentan, FSGS therapy is now shifting towards precision and pathway targeting.

So I'll give you some examples of specific targeted therapies that are being actively investigated. So the AMPLITUDE trial is evaluating inaxaplin, which is an APOL1-directed agent.

There's a TRPC6 channel blocker called apecotrep. There is also growing interest in anti-nephrin antibodies, especially in the post-transplant recurring disease as a model for biomarker-guided immunomodulation.

Another pathway is the CCR2 modulation with repagermanium also being tested in a phase 3 trial.

And trials are becoming more efficient through deeper phenotyping and biological enrichment. For example, Sanofi has a phase 2a result umbrella trial which is looking at primary FSGS and primary minimal change disease, and they are concurrently investigating 3 medications with 3 different pathways, frexalimab, brivekimig, and rilzabrutinib versus placebo.

Another endothelin receptor antagonist called atrasentan is being investigated in a basket trial for FSGS and other glomerular disease, and this is called the AFFINITY trial.

There's also movement in the genetic FSGS space. We mentioned inaxaplin for APOL1, but in Alport syndrome, which by the way is the most common genetic form of FSGS in adults, one FXR is being investigated. It's a farnesoid X receptor antagonist. And then there's BAY 3401016, which targets Semaphorin 3A.

Dr. Campbell:
Certainly an exciting time in the field. Before we close, are there any final messages you'd like to leave with our listeners?

Dr. Radhakrishnan:
Yes. The treatment paradigm in FSGS is now moving from broad empiric approaches with nonspecific agents like corticosteroids toward more precise, biology-driven strategy that pairs optimized supportive care with targeted therapies and biomarker-informed immunomodulation. The near-term priority is to identify the right patient for the right pathway, track proteinuria and eGFR rigorously, and use smarter trial designs to translate early response signals into durable kidney protection.

Dr. Campbell:
I'd like to thank my guest, Dr. Jai Radhakrishnan, for joining me. It was great having you on the podcast.

Dr. Radhakrishnan:
It's my pleasure, Kirk, and happy to be on the show.

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