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Management of patients with APOL1 Kidney Disease

Announcer:
Welcome to KDIGO Conversations in Nephrology. This episode titled, “Management of patients with APOL1 Kidney Disease,” is provided by KDIGO and supported by Vertex. Here’s your host, Dr. Kirk Campbell.

Dr. Campbell:
Hello and welcome to KDIGO Conversations in Nephrology. I'm Dr. Kirk Campbell, the Chief of Renal at the University of Pennsylvania. Thank you for joining me in discussing the management of patients with a one kidney disease. With Dr. Barry Freedman. Dr. Freedman is a John H. Felts Professor and Chief of the Section of Nephrology at Wake Forest University School of Medicine. His clinical and research interests include APOL1- Mediated Kidney Disease, and he serves as the PI on the NIH APOL1 Long-Term Kidney Transplantation Outcomes Network or APOLLO Consortium. He's also the US Lead Physician on the AstraZeneca APPRECIATE trial. Dr. Freedman, welcome to the podcast.

Dr. Freedman:
Kirk, it's great to join you. Thanks for having me. And it was a pleasure working with you in 2023 at the KDIGO Controversies Conference on APOL1.

Dr. Campbell:
Absolutely. A lot happening in this space. So let's begin our discussion to talk about the evaluation and prognostication of CKD and the progression towards end stage kidney disease. Right. What are some of the factors that patients and providers need to consider as they try to provide some risk assessment for patients progressing towards end stage kidney disease?

Dr. Freedman:
Thanks, Kirk. Great lead off. And you know, as nephrologists, as primary care physicians, we often look at three things. We look at kidney function or estimated glomerular filtration rate, we look at the degree of proteinuria or albuminuria, often we look at co-variants, like blood pressure control, hypertension control. And the good news is that lots of things in APOL1 mediated kidney disease look the same as patients who have other forms of kidney disease. I think key prognostic factors are kidney function at baseline. And obviously anybody who presents with advanced CKD is certainly going to be at higher risk for progression, whether it's APOL1 mediated kidney disease or not. Same for proteinuria. You know, the APOL1 kidney disease spectrum includes a wide range of histologic lesions, all caused by an underlying same genetic defect to risk variants in the APOL1 one gene. And some patients present with collapsing glomerulopathy, that's due to APOL1 in patients with HIV infection, COVID after interferon administration, and they often have very heavy proteinuria and the fastest rates of progression. We see patients with FSGS, you know, in African Americans, 70% of FSGS is attributable to APOL1. And some patients present with Nephrotic syndrome, very heavy proteinuria, way more than three and a half or four grams a day. They have rapid progression as well. Some patients present with FSGS and sub nephrotic proteinuria, one and a half or two grams a day. We think their rate of progression's a little slower. And then we have this big category we call solidified Glomerulosclerosis. These are patients who have low levels of urinary protein, often microalbuminuria or sometimes normal levels. Chronic kidney disease with a low GFR and high blood pressure, and that's been mislabeled, hypertensive nephropathy. I call it hypertension attributed nephropathy with very low levels of proteinuria, and they seem to have the slowest rates of progression. So, proteinuria albuminuria are key factors, but the final concept is blood pressure control. And, especially in those patients with low levels of proteinuria or FSGS, you know, historically nephrologists have told these patients, listen, we've got these very special medicines that

protect the kidney. ACE inhibitors, ARBs, we can talk more about them later, but if I can get your blood pressure down with these drugs, I think I'm really going to be helping you with slow progression of kidney disease. And I think the data strongly suggest that's not the case. Studies like AASK, the African-American Study of Kidney Disease and Hypertension funded by NIH, showed that really strict blood pressure lowering with high dose ACE inhibition did not halt the progression of kidney disease and APOL1 was a better predictor. And finally, we've learned from studies like SPRINT, which looked at optimal systolic blood pressure control, that getting the systolic blood pressure to less than 120 was better than lowering it to below 140 in non-diabetic patients. And a lot of those patients in SPRINT had up to a gram of proteinuria per day. Well, lowering the blood pressure is very important to prolong life and prevent cardiovascular disease, but the protection to the kidney was not as robust. So I think blood pressure control, it's important we do it, but I think if we're doing it solely for kidney protection, it's not the answer. And we need better therapies.

Dr. Campbell:
Yeah. Thank you so much. A great response. So we often rely on repurposed agents to treat patients with glomerular disease. Can you comment on some of the immunosuppressive approaches that we've taken to treating idiopathic glomerular disease?

Dr. Freedman:
Sure. And, and you know, this is like our typical to non-genetic forms of glomerular disease we often turn to immunosuppressing drugs, anti-inflammatory drugs, immune modulators like steroids, calcineurin inhibitors, cytotoxic agents, mycophenolate cytoxan. And you know, many patients with genetic forms of glomerulopathy will not respond to immune modulating drugs because they have genetic modifications causing disease more so than inflammation. Now, you know, we have data from Dr. Jeffrey Kopp, who's been a leader in APOL1 Kidney disease. And he published data from the FSGS Clinical Trials Consortium, and they had 94 patients with known APOL1 genotypes that were African American and had FSGS. Of those, 27 of them had an APOL1 high risk genotype, and the patients who had FSGS in that trial were randomized to Cyclosporine versus mycophenolate plus pulse Oral Dexamethasone. So they got steroid therapy, which we often use for FSGS and Nephrotic syndrome, and a choice between a calcineurin inhibitor and mycophenolate. And although the results of the study said the people with APOL1 high risk genotype did not have an outcome that much different from those without an APOL1 high risk genotype. Patients with the APOL1 high risk genotype had more severe glomerulosclerosis and far worse tubular interstitial fibrosis and tubular atrophy. And at the end of the day, these patients really didn't do that well overall in the whole consortium. This paper is published in JASN. And I can tell you I've spoken to Dr. Kopp after publication and it's clear to him that the patients with APOL1 high risk genotypes had poor outcomes. So I think the limited data we have, Kirk, suggests that APOL1 mediated kidney disease is an inherited nephropathy, doesn't respond to these standard immunomodulating agents. And they can be toxic calcineurin inhibitors causing, you know, kidney disease, more interstitial fibrosis, risk of infection, osteoporosis. So I think that there's not a role for these as the primary agents in APOL1 kidney disease.

Dr. Campbell:
Thanks. Certainly making the case for more targeted therapies that are based on precision approaches that would be again, potentially more effective, but also carry a better side effect profile. So if you're just tuning in, you're listening to the KDIGO podcast on the management of patients with APOL1 Kidney Disease. I'm Dr. Kirk Campbell, and I'm speaking with Dr. Barry Freedman. So, Dr. Freedman can you give us a bit of an overview on the interim results of some of the ongoing APOL1 kidney disease studies? There are numerous approaches that are currently in the clinical development phase, so it would be great for listeners to hear an update on what's happening in that sphere.

Dr. Freedman:
Great. Thank you. I appreciate the question. And I know you're actively involved in this field as well. So, the first class of agents that have been out there with, you know, successful results are the small molecule inhibitors. You know, there's a small molecule inhibitor made by Vertex called inaxaplin. There's another agent made by Maze Pharmaceuticals and the inaxaplin data are very striking. And Kirk, you are part of that group publishing in The New England Journal of Medicine. You know, inaxaplin is a small molecule inhibitor of APOL1 protein, so it allows the protein to be made, but inhibits its binding to receptors in the kidney and elsewhere that would cause toxic effects. And in the initial inaxaplin study from The New England Journal of Medicine took patients with biopsy proven FSGS and more than 700 milligrams of proteinuria per day. And just remember, these patients have scarring in their glomeruli on the biopsy. The striking results showed that in very short order, in just a few weeks, proteinuria started to fall dramatically. And you know, it's, although it was a small study with 16 total patients, the drop in proteinuria approached 50% in just a matter of weeks in all comers. So I was struck by the rapidity of effect. The data are very exciting. It was a short-term trial, so GFR was not an endpoint that was, you know, expected to change in a study like that, but. I thought that it would take a while for the glomeruli to repair, and we might be looking for months to see reductions in proteinuria. The fact that we saw it in just a few weeks shows there's ongoing damage to podocytes and cells in the

kidney that a small molecule inhibitor like inaxaplin can treat and for stall the proteinuria. So, you know, inaxaplin now is in a phase three trial moving forward, and that data is very exciting. That's one approach, allowing the protein to be made but interfering with binding to receptors. Another approach is inhibiting the APOL1 messenger, or Messenger RNA, and there are anti-sense oligonucleotides that bind to APOL1 mRNA and lead to destruction that would reduce the production of APOL1 protein in the kidney, in the bloodstream, everywhere in the body. And there's a study underway by AstraZeneca called the APPRECIATE Study. It's a phase two trial looking at this, APOL1 anti-sense, oligonucleotide in 96 patients who have chronic kidney disease and proteinuria.They don't necessarily have to have a kidney biopsy to get in. And that was based on phase one data where escalating doses of the anti-sense oligonucleotide administered subcutaneously, reduced plasma APOL1 levels in a dose dependent and time dependent fashion. So that is a very exciting trial that I'm involved with as well. And then finally, there's a trial called the JUSTICE trial with baricitinib, which is an inhibitor of the JAK-STAT pathway. Inflammation upregulates the JAK-STAT pathway, that leads to increased production of APOL1 protein, baricitinib would inhibit the pathway and theoretically reduce the amount of protein made, and that is also under study. So I think we're an exciting era with drugs that have more specific effects than general immunomodulating drugs.

Dr. Campbell:
Thanks so much. Great to hear about all the developments in agents, right, that are specifically targeting APOL1 mediated injury pathways, but we use a lot of kidney protective agents, right? That might have generalized benefit on reducing proteinuria. Thinking about RAAS inhibitors, SGLT2 inhibitors, et cetera. Can you comment on any existing available data or your general thoughts and efficacy of some of these agents?

Dr. Freedman:
Yeah. And, you know, you and I spent a long time discussing this at the KDIGO controversies meeting, and as did the group, and one thing I think we can say unequivocally in 2025 is, you know, we need more data. We need more information. We need to see the effects of existing drugs that are thought to be renal protective for diabetic kidney disease, other forms of nephropathy. But, I think that results of studies like AASK and SPRINT suggest we have caution in using ACE inhibitors and ARBs, renin angiotensin system blockade, and expect that to halt or slow the progression of APOL1 mediated kidney disease. That doesn't mean we shouldn't use them. We should certainly use them. We need them to lower blood pressure. If they have effects on reducing proteinuria in an individual patient, that's a benefit. No argument. But I think we've seen from AASK where we knew the APOL1 genotypes after the study and in SPRINT where APOL1 genotyping was done that the drugs are not kidney protective, they're more cardiovascular protective. So I would use them as part of blood pressure lowering. And you know, the same thing for the mineralocorticoid receptor antagonists. You know, the newer ones, the non-steroidal, like finerenone or even drugs like spironolactone and eplerenone, the older steroidal variants, you know, we don't have any particular reason to suspect that they're going to have a special effect. But if you need them for other causes in a patient with APOL1 mediated kidney disease and they're tolerated well, you know, no hyperkalemia, gynecomastia, other problems. I think it's fine to use 'em. But it's important we use them as we test the newer molecules, the small molecule inhibitors, anti-sense oligonucleotide. Drugs like that, you know, the SGLT2 inhibitors and GLP1 receptor agonists are very exciting drugs. We, we just don't have enough data, but I think there are some anecdotal data that the SGLT2 inhibitors protect from several forms of non-diabetic kidney disease. And I'm sure that you and I both are awaiting data on SGLT2s in patients with APOL1 mediated kidney disease to learn if they will have any special renal protective effects. And then the, the last class I'll just throw out, 'cause I know it's under study in FSGS is sparsentan, you know, a dual inhibitor of angiotensin type one receptor, an endothelium type A receptor. In studies of FSGS with proteinuria, drug has been shown to reduce proteinuria somewhat. However, less of an effect on GFR. Not really slowing loss of GFR, but we think, you know, reducing proteinuria in and of itself is a good thing. The problem is there are not a lot of African American patients in the big sparsentan trial, which looked at sparsentan versus irbesartan in The New England Journal of Medicine in 2023. Of the 371 patients in that study, only 29 were black. So you know, we don't know the percentage of them with an APOL1 high risk genotype. And I would have to say that we just don't have enough data with sparsentan at this time. But again, another drug of interest.

Dr. Campbell:
And of course there are several endothelial receptor antagonists currently being studied alone or in combination with SGLT2 inhibitors in Proteinuric CKD. And hopefully we can get some more information when subgroup analysis of those studies are performed. But, but thank you. On the topic of endpoints that's been again, a hot area of discussion where we need appropriate and feasible endpoints to be achievable during the course of a clinical trial to set the stage for drug approval and appropriate safety analysis. Can you comment on some of the ongoing initiatives right through the KHI and PARASOL that might have an impact on drug development in the APOL1 kidney disease space?

Dr. Freedman:

Yeah, absolutely. These are critical efforts to try and find the right endpoints in clinical trials that will allow speedier development of drugs, show success in a clinical trial and get these drugs to market to help our patients. So, you know, the PARASOL initiative, it's actually looking at change in proteinuria and change in EGFR as clinical trial endpoints in FSGS. It's jointly sponsored by the Kidney Health Initiative, National Kidney Foundation, NephCure, the USFDA, and the International Society of Glomerular Disease. And they're looking to use proteinuria as a clinical endpoint of treatment success in trials to speed you know, drug discovery. And the findings are that a drop in proteinuria, significant drop in proteinuria after 24 months, is significantly associated with a decreased risk of progression to end stage kidney disease. That's exciting data in FSGS. The initial cohort had more than 1600 children and adults with FSGS from around the world. And the validation cohort was a European data set of patients with FSGS, and it's striking that if you can show a marked reduction in proteinuria at 24 months, drugs look very renal protective. So,I think that that's a key endeavor. And you know, we also have data from studies like CRIC AASK and ARIC, that have published the risk for developing progressive kidney disease with APOL1 versus non APOL1 forms of nephropathy. And I think what they've shown is that if you can slow the slope of decline of EGFR by 30 to 40% at three years, that also translate to kidney protection down the line. So, you know, PARASOL looking at reduction in proteinuria at 24 months, other efforts to look at a change in the slope of GFR slowing it by 30 to 40% are nice endpoints that it validated as associated with risk for end stage kidney disease will allow us to get these drugs in the market and help our patients much more quickly.

Dr. Campbell:
Definitely. Very well said. So before we close Dr. Friedman, are there any final messages or thoughts you'd like to leave with our listeners?

Dr. Freedman:
Yeah, thank you. First of all, it's been a pleasure and Kirk, you're a true expert in the field. It's a joy to speak with you. The other big breakthrough you and I know is the development of ICD 10 codes APOL1 mediated kidney disease and family history of APOL1 mediated kidney disease that go into effect October 1st, 2025. So all these patients that we've been talking about with collapsing Glomerulopathy, FSGS, solidified glomerulosclerosis and low-level proteinuria that have historically been blamed on high blood pressure when high blood pressure's not the cause in African ancestry, patients with APOL1 high risk genotypes. We now have a chance to correct the epidemiology. Genotyping more widely is critical, so we get the diagnosis right. We inform patients of their risk, family members of these patients, and we allow these patients the opportunity to be enrolled in these clinical trials that are very exciting. So I'm really excited with the new ICD 10 codes, opening a new era in APOL1 mediated kidney disease.

Dr. Campbell:
Thank you. So, I want to thank my guest, Dr. Barry Freedman for joining me. It was great having you on the podcast.

Dr. Freedman:
Great, Kirk, thank you so much. It's been a pleasure.

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