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Future Directions in FSGS Care

Announcer:
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Dr. Tesar:
This is CE on ReachMD, and I'm Dr. Vladimir Tesar. And here with me today is Dr. Kenneth Lieberman.

Today, we are going to be discussing what's coming in FSGS and what may be on the horizon in managing our patients.

This is a very broad area which covers potential new therapies, for instance, SLIT2 antagonists, CCR2 inhibitors, AMPK activators, small-molecule inhibitors of APOL1 in patients with APOL1 mutation, TRPC5 inhibitors, nitro fatty acid, and Nrf2 activators, and others. But only dual endothelin and angiotensin-2 antagonist, sparsentan, is the drug which went through both phase 2 and phase 3 trials and may be soon available for the patients in the large parts of the world and is just under discussion for the approval by FDA.

So I would like to ask Dr. Lieberman, what is your take regarding what's on the horizon for FSGS care and treatment?

Dr. Lieberman:
Thank you very much. A pleasure to be with you this morning. I would like to start with what I think is an extremely important advance in this field, and that is finally organizing the heterogeneity of FSGS, which after all, was originally a histologic classification, and we've come to understand that there are many patient subsets, and the understanding of the patient subsets can lead us to more specific therapies for these groups.

And so a classification system has emerged. There is this first category of primary FSGS. This is the FSGS that's most common. And so there really has been a search for this putative circulating factor.

The largest group is probably this adaptive FSGS, and this is reduced kidney mass. This is where there is a mismatch between the amount of kidney that you have available and the patient's needs. So, for example, this is an explanation of the FSGS in patients who have had various degrees of nephrectomies or patients who are obese or patients with diabetic nephropathy. But patients in which there is the need for increased GFR to meet their metabolic needs and that's not necessarily there. So this type of FSGS would certainly not be expected to be responsive to any sort of immunosuppressive therapy.

Next, I would like to touch upon the genetic FSGS, which has been an extremely important subset that we've come to understand better and better as the years have progressed and learned of more genetic loci that are involved with this disease. In particular, you'll see this

table, this schema, separates out APOL1. Inflammatory-associated conditions have been noted, and infection-associated FSGS, and you see there HIV and CMV are mentioned. And there are some medications, some chemotherapeutic agents, which have also been noted to cause FSGS.

And so recognition of these groups has enabled us to fine-tune our diagnostic approach, as well as, we hope, as the future rolls on, our therapeutic approach.

So sparsentan in is a novel drug that has a dual action. It is an angiotensin receptor blocker and adds an endothelin receptor blocker functionality to the same molecule, and so you get this dual action, which in early studies, has shown an incremental benefit in proteinuria reduction over an ARB-alone control. Sparsentan has already been approved for proteinuria reduction in IgA nephropathy, and it is currently under review for approval by the FDA for the treatment of FSGS. A target date has been set in January for the FDA to issue its ruling, and so we may have our first FDA-approved specific therapy for FSGS.

Some of the subsets on the table that we just discussed have specifically been looked at for efficacy with the use of sparsentan. The overall population that was treated had all of these subsets in it. But in particular, there was a recent post hoc analysis that pulled out the patients in the original sparsentan trials who had genetic forms of FSGS, and it was very reassuring to see that sparsentan was as effective in the genetic forms of FSGS as it was in the overall population.

Further work is going to go into defining how sparsentan affects the long-term outcome of FSGS, and that's going to include patient-reported outcomes, as well.

Dr. Tesar:
Thank you very much for this comprehensive and very important overview. So if I understood well, sparsentan should also work in what was originally called secondary and is now called maladaptive FSGS. Am I correct?

Dr. Lieberman:
Yes, that is what we have seen so far, and I think that's where sparsentan is going to have its greatest application.

Dr. Tesar:
So thank you once again for the review, and it was really a nice discussion with you. And I would like to thank you once again for listening in.

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