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AMKD Disease Burden and Management Strategies: The Need for Small Molecule Treatments

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.

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Dr. Kovesdy:
Hi. My name is Csaba Kovesdy. I am the Fred Hatch Professor of Medicine at the University of Tennessee Health Science Center in Memphis, Tennessee. I'll be speaking to you about the AMKD disease burden and management strategies: the need for small molecule treatments.

As we probably all know, chronic kidney disease is a very common condition in the general population with about 1 in 7 individuals suffering from it. CKD is especially common in African Americans, compared to the proportion of African Americans in the general population, which is at about 12%. Among patients with CKD, African Americans are represented at about 16%. And the preponderance of African American race is especially striking among patients on dialysis, as shown on the right lower side of this slide. For many years, this high risk of CKD and ESRD among African Americans was somewhat of a mystery. But in the last 10 to 20 years, we've learned that a mutation, the so-called APOL1 mutation, may be responsible for a good deal of this excess risk of CKD and end-stage kidney disease.

As shown in this left side, patients with two mutations of APOL1, the so-called G1 and G2 mutations, have a heightened risk of end-stage kidney disease as shown on the right side of the slide. We have learned now that APOL1-related mutations are responsible for a large proportion of the disease's seen in patients with CKD among African Americans. As you can see on the slide, conditions, such as interferon-associated FSGS and HIVAN, are largely accounted for by mutations in the APOL1 genes. Interestingly, some conditions such as diabetic kidney disease and IGA nephropathy seem not to be affected by the mutations.

APOL1 mutations, as shown on the left side of this slide, seem to have conferred a benefit in patients who were infected with trypanosoma infections. However, if two of these mutations are present, then affected patients will be affected by chronic kidney disease.

The mechanism of action is now fairly well described. And the mutations seem to be responsible for a gain of function, adverse effects that results in damage, especially in the podocytes. This table is somewhat busy, but it lists the various mechanisms of action, whereby APOL1 mutations can induce damage in the kidneys. These were mainly discovered in various animal models with a few human studies included.

So the big question for practitioners like myself, is what we can do to lower the risk of these patients, the risk of developing kidney disease, and if they already have kidney disease, the risk of progression towards end-stage kidney disease.

As you all know, RAAS inhibitors are standard of care for proteinuric kidney diseases. And on top of them, now we have SGLT2 inhibitors to combine with ACE inhibitors or ARBs. And these combinations are successful in lowering the risk of renal endpoints such

as end-stage kidney disease. These treatments are now effective in both diabetic and non-diabetic kidney diseases.

But as shown in this graph, despite the success of these agents such as SGLT2 inhibitors, they are not curative treatments, and patients treated with these agents still have a substantial residual risk of developing progressive kidney disease and end-stage kidney disease. So in terms of SGLT2 inhibitors, we also know now that they can be used not only for patients with diabetic and non-diabetic kidney disease, but also specifically in patients with FSGS.

As shown in this study, which is a post-hoc analysis of a clinical trial, patients with FSGS who were treated with dapagliflozin had a lower risk of progression over a follow-up of more than 2 years.

Obviously, the next question is then, can we somehow apply this knowledge about APOL1 mutations to improve the kidney outcomes in patients who are affected by high-risk mutations? Based on the extensive basic science data available now, the functionality of these mutations has been clarified, and subsequently various drugs are in development to alleviate the damage caused by the mutated cell structures such as the mitochondrion in this picture.

Specifically, in this picture, we are showing a drug called VX-147 which blocks the action of these mutated proteins, and is supposed to result in improved kidney outcomes. A phase 2 trial performed in 13 patients with this agent, VX-147, has shown that treated patients experienced a reduction of about 50% in albuminuria over 13 weeks. As we all know, albuminuria reduction is now an accepted surrogate outcome measure for longer-term kidney outcomes such as end-stage kidney disease. Hence, these results appear very promising for this drug, if shown effective in subsequent larger clinical trials.

And indeed, there are several trials now underway. One of them is a phase 2/3 adaptive study of this agent, VX-147, in adults who are affected with APOL1-mediated proteinuric kidney disease, and is testing efficacy and safety of the drug in preventing longer-term kidney outcomes.

A similar phase 1 study is testing another small molecule compound in healthy participants. Longer-term development obviously is expected. And then a separate drug, a janus kinase STAT inhibition is being tested in the so-called JUSTICE trial.

These studies offer hope that, given successful completion of phase 3 clinical trials at some point in the near future, we will have additional therapeutic means to positively affect the clinical outcomes, and specifically, kidney outcomes in patients affected by AMKD. Thank you for your attention and have a good day.

Announcer:
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