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Emerging Therapeutics: The Potential of Targeting the Serotonin Pathway in PAH

Announcer:
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Dr. Rajagopal:
So hello, my name is Sudarshan Rajagopal, and I'm Co-Director of the Pulmonary Vascular Disease Center at Duke University School of Medicine. Today, I'm going to be talking to you about the potential of targeting the serotonin pathway in PAH.

So first, let's go over the science behind the current PAH clinical trials. We know there are a number of pathways that are dysregulated in pulmonary arterial hypertension. These include, moving from left to right, the nitric oxide pathway, which we target with PDE5 inhibitors and soluble guanylate cyclase stimulators, prostacyclin pathway, which we target with prostacyclins and prostanoids. Then other pathways which we currently don't have drugs for, like the PDGF receptor and serotonin receptors. And then what I've highlighted in red, where we have the serotonin pathway, and how this can be targeted through inhibition of tryptophan hydroxylase. And then lastly, on the right, we see the pathways that are mutated in pulmonary hypertension, which are the BMPR2 pathway.

So drugs that target serotonin are associated with PAH. And in the 2022 ESC/ERS guidelines, there are a number of drugs that have been definitely associated with PAH. These drugs that target the serotonin pathway are a aminorex, benfluorex, dexfenfluramine, and fenfluramine, or fen-phen for short. And we know that patients who were exposed to these drugs were at a much higher risk for the development of pulmonary arterial hypertension.

How does this happen? So what's the role of serotonin in PAH? So serotonin is a small molecule, which I'll go over shortly, but it is actually generated with stimulus such as hypoxia, or in pulmonary arterial hypertension, you can increase the levels of serotonin in the bloodstream. And serotonin is brought into cells through a serotonin transporter, SERT. And serotonin also acts through a number of receptors, which are highlighted on the left, the 5-HT21B and 5-HT2A receptors. And when serotonin acts through those receptors, they promote changes in smooth muscle cells, promoting contraction and proliferation of smooth muscle cells. And serotonin that enters the smooth muscle cell through SERT also can have direct effects through serotonylation. And these can also work through other signaling pathways such as BMPR2, to lead to abnormal pulmonary vascular remodeling in PAH.

How is serotonin synthesized? And it's through the pathway shown here on the left. So there is an enzyme called tryptophan hydroxylase, which takes tryptophan, which is an amino acid in all of our bodies, and converts it to 5-hydroxy tryptophan. This is then decarboxylated by aromatic amino acid decarboxylase to end up with serotonin, on the bottom left. Now the rate-limiting step in the synthesis is the enzyme tryptophan hydroxylase. And there are two forms, a peripheral form and a central form. And this is highlighted on the right. So the peripheral form is tryptophan hydroxylase 1, or TPH1, and that converts tryptophan to serotonin and leads to its peripheral effects where it causes – it can cause a lot of vasodilation. But then in the brain and central nervous system, we have TPH2, which controls its central effects where it affects mood and a lot of other effects.

So how about decreasing serotonin levels by targeting TPH1 through a TPH1 inhibitor? So this is the effect of such an inhibitor called rodatristat ethyl in rodent pulmonary arterial hypertension models. So on the left, we have the monocrotaline model, and on the right, we

have a SUGEN-Hypoxia model. Both of these models are well-described, well-validated models of pulmonary hypertension in rodents. And when you treat with this tryptophan hydroxylase in one inhibitor, you decrease pulmonary vascular remodeling and the severity of pulmonary arterial hypertension.

This has led to the current ELEVATE 2 trial of rodatristat ethyl. This is a phase 2B clinical trial of this drug in patients with pulmonary arterial hypertension. The arms include a placebo group of rodatristat of 300 mg twice a day and at 600 mg twice a day. The primary outcome measure is going to be a percent change from baseline and PVR at 24 weeks, with a secondary outcome measure of improvement in functional class, 6-minute walk distance, and NT-proBNP. The estimated enrollment is 90 subjects with primary completion expected in 2023. So hopefully we'll have the results of this study soon, as there are currently no drugs that are FDA approved to target the serotonin pathway.

So the take-home points. There are a number of new pathways that are targeted by novel PAH therapies; many of these are in clinical trials at this time. The serotonin pathway has been clinically validated as contributing to the development of PAH, the strategy of TPH1 inhibition has shown benefit in rodent models of PAH. And this approach is currently being tested in the ELEVATE 2 phase 2B clinical trial of rodatristat ethyl in PAH.

Thank you for joining me today.

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