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Updates on Pulmonary Hypertension Clinical Trials

Announcer:
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Dr. McLaughlin:
Welcome to CME on ReachMD. I'm Dr. Vallerie McLaughlin, and today I'm reviewing the latest pulmonary hypertension clinical trials and what their data means for your practice.

So there are a lot of different trials going on, and I want to just mention some of the trials that are looking at older pathways but newer delivery systems or newer doses because this is very important research that is trying to get to a drug that's either more efficacious or more safe or better tolerated for a patient. So there are some inhaled SGC formulations being studied. There's a higher dose of macitentan, which is approved at a 10-mg dose, being studied at a dose of 75 mg. Inhaled treprostinil has been very successful not just for PAH, but also PH associated with interstitial lung disease. And so there's newer formulations of that being studied by various companies, and then there's also another prostacyclin receptor agonist, ralinepag, being studied in an endpoint-driven trial.

Let's move on to some of the other new pathways. It's very exciting to have new pathways in PAH. And so we know that this is such a complicated disease and we're only targeting 3 or 4 pathways right now. But there're many other dysfunctional pathways going on in pulmonary hypertension. And we're learning more and more about these different pathways and starting to have the translational research that we might exploit some of the other abnormalities, the inflammation, the mitochondrial abnormalities. We're really looking at starting to exploit some of those in our therapies.

One that we've recently learned about is sotatercept, which is an activin signaling inhibitor and this is a new pathway. It's just become FDA-approved and the goal here is to try to rebalance the growth that is out of balance with the reduction in BMPR2 signaling and really the overaction of the activin pathway and help balance that anti-proliferative with the pro-proliferative states.

And this has been studied in a large pivotal clinical trial, the STELLAR trial, looking at sotatercept on top of current therapies in patients with pulmonary arterial hypertension. The primary endpoint of 6-minute hall walk improved by about 40 m, and there was an improvement in 8 of 9 of the secondary endpoints including the very important time to clinical worsening and even including some of the quality of life questionnaires, which is really important to patients.

And we've also learned a great more information about hemodynamics, about RV function from the right heart cath and echo substudies, so a drop in mean pulmonary pressure of about 14 mmHg and an improvement in RV function on echocardiogram.

So like I said, this has recently become FDA-approved, but it is actually still in research in other patient populations. I think one thing that's really interesting about the sotatercept development program is that it's looking at the breadth of PH. So STELLAR, what led to the FDA approval, what I just reviewed, was pretty much prevalent patients with functional class II and III symptoms, the majority of patients that we see today. Those patients had disease, on average, 8 or 9 years, so it was a prevalent population, functional class II and III.

But there are 2 other randomized-controlled studies going on with sotatercept. One of them is HYPERION, which is to look at sotatercept in patients with newly diagnosed or recently diagnosed pulmonary hypertension that remain high risk despite stable, double background therapy, or it could be triple. So these are patients that are diagnosed within the past year, who have been treated with other agents, but who have not gotten to our goals in terms of risk assessment. So it's looking at adding sotatercept earlier in the course of disease and looking at outcome, looking at time to clinical worsening.

ZENITH is on the other end of the spectrum. ZENITH is a study looking at patients who still are at high risk despite multiple background therapies. These are generally the patients who are too sick to get enrolled in any other clinical trial. These are patients who are on their way to lung transplantation. So it's the other end of the spectrum, and that also is looking at the addition of sotatercept or a placebo on top of all of the other background therapy that they're on, looking at a first event of all-cause death, lung transplantation, or PAH-related hospitalization.

So even though sotatercept is recently become FDA-approved, there's still a lot of research going on to help learn how it could be effective in this wide array of patients from the prevalent and STELLAR, but also the newly or recently diagnosed with still intermediate or high-risk PAH, and the end-stage patients who are at high risk despite multiple other therapies.

For those of you just tuning in, you're listening to CME on ReachMD. I'm Dr. Vallerie McLaughlin, and I'm reviewing the latest pulmonary hypertension clinical trials and the relevance of their data.

Now, we're very excited about sotatercept and it's been proven efficacious, but we are always looking for additional therapies and choice is good and other therapies that work in the same way could have different side effect profiles. And so there's another agent that's being developed that is also an activin signaling inhibitor that is slightly modified from sotatercept. And again, its goal is to rebalance that pro-proliferative and anti-proliferative BMPR2 activin scale.

And so the mechanism of action is very similar but there are some slight changes in the molecule, and it may have a stronger component of activin binding. It may have more of an impact on inflammation fibrosis. This is all hypothetical. It may have a different side effect profile. It may not increase hemoglobin as much as sotatercept increases hemoglobin.

So there are some subtle differences between the agents. And it is being studied in a phase 2 trial, the TROPOS trial, which is looking at patients with group 1 PAH, stable but symptomatic, on background therapy. And those patients are being randomized to either placebo or 1 of 3 different doses of this investigational agent over a 24-week period and looking at a primary endpoint of pulmonary vascular resistance. what is the typical endpoint in a phase 2 clinical trial. And of course, there's an open-label extension looking at safety of this agent. And this trial is really just about enrolled, which means probably in the next 6 months, sometime early next year, we should have the results of that.

I want to move now to the tyrosine kinase inhibitors. Many of you remember, back in the day, looking at imatinib for pulmonary arterial hypertension. There were some trials that demonstrated an improvement in symptoms, but oral imatinib was not well tolerated. And tyrosine kinase inhibitors really could also impact, in a different way than the activin signaling inhibitors, impact the abnormal proliferation and accumulation of cells that occurs in the pulmonary vasculature. So this agent was developed as an inhaled agent so the thought was it's good, it actually works on the disease, but it wasn't tolerated orally. Can it be tolerated in an inhaled fashion? And that is what led to the IMPACT trial, which was a phase 2 trial looking at this drug in patients with pulmonary arterial hypertension. The primary endpoint was pulmonary vascular resistance at 24 weeks with a number of secondary endpoints. And, unfortunately, we now have the results of this trial, and it did not hit the primary endpoint of pulmonary vascular resistance and so, unfortunately, this drug is not going to be further developed for pulmonary hypertension.

There is, however, another drug in the tyrosine kinase inhibitor family that has some different characteristics, has some different effect on CSF1R, c-KIT, PDGFR signaling and that is a drug called seralutinib. And it may impact the underlying growth in a way that's a little different than some of the other tyrosine kinase inhibitors, and it's also given in an inhaled form. And this drug was studied in the phase 2 TORREY trial, which has been completed and was actually recently published.

TORREY was a phase 2, double-blind, placebo-controlled, multicenter trial looking at inhaled seralutinib on top of other background therapy in patients with PAH. The primary endpoint was change in PDR from baseline to week 24 with a number of other secondary endpoints.

And in this phase 2 trial, there was a statistically significant improvement in the primary endpoint of pulmonary vascular resistance at 24 weeks. There were also improvements in functional class. I think it's important to know that there was slight maldistribution of functional class in the placebo group and the seralutinib group, and the patients who had functional class III symptoms had an even more impressive improvement in the pulmonary vascular resistance.

So with this successful phase 2 trial, there is now a phase 3, randomized, double-blind, placebo-controlled trial going on. This is called PROSERA. It is looking at, again, patients with PAH, adult patients with functional class II and III symptoms, with a PVR greater than 400 and a 6-minute hall walk, 150 to 450. And randomizing those patients to either seralutinib or placebo and looking at a primary endpoint of change in 6-minute hall walk, so this is the phase 3 registration trial. It's also looking at a number of other secondary endpoints including the very important time to clinical worsening and multicomponent improvement endpoint, which looks at functional class, NT-proBNP, and hall walk, NT-proBNP, and REVEAL Lite score. So this is the phase 3 pivotal trial for seralutinib, which is ongoing.

So I think it's important to remember that we're so fortunate to have so many wonderful therapies for pulmonary arterial hypertension. We're certainly doing better than we've done a decade ago. But we still have so many patients who are not meeting low-risk status and so many patients who still have room to improve. We also have patients, even though they're doing well, that are inconvenienced by their therapy, by side effects, or by pumps, and so studying new ways of delivering some effective drugs is important. We're very fortunate to have a new agent, sotatercept, which has recently been FDA-approved, to be shown to be efficacious in PAH on the primary endpoint of walk and a number of other secondary endpoints. And it's really an exciting time of research.

That was a lot of data in just a few minutes. Thank you for tuning in.

Announcer:
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