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The Promise of Sotatercept in PAH

Announcer:
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Dr. Preston:
Welcome to this microlearning episode. Today, I'm reviewing the latest evidence from the sotatercept trials and the implications for your clinical practice.

This is CME on ReachMD, and I'm Dr. Ioana Preston.

So let's talk a little bit about the pathophysiology of pulmonary hypertension. More than 20 years ago, we discovered that there is a abnormality in a gene called bone morphogenetic protein [BMP] receptor II that affects patients with pulmonary arterial hypertension. The BMPR2 is a molecule that acts on the pathway and decreases the vascular proliferation in the pulmonary arteries. So it was discovered that this molecule is deficient, either through a genetic deficiency or a functional deficiency.

Now this molecule is opposed by a pro-proliferative, pathway that is stimulated by a molecule called the activin. So activin pathway's pro-proliferative and the BMPR2 pathway, which is deficient in PAH, is anti-proliferative. So for the past 20 years, researchers tried to fix this abnormality to maybe enhance the BMP pathway which initially was tried, but it was unsuccessful. And then they started focusing on the activin pathway to see if they can decrease this activity to rebalance this pro- and anti-proliferative events.

So based on a lot of background research that happened in the preclinical area, there was a molecule called sotatercept that was designed, and it was discovered. And its role was to bind to the activin, kind of like a trap. So functioning as an activin signaling inhibitor, it will decrease the effects, the pro-proliferative effects of activin and rebalance the BMP activin pathways in the setting of low BMP function. So this molecule was studied in preclinical studies and in animal models, and it showed a very significant effect in alleviating experimental pulmonary hypertension.

The next step was to be moved into a human study. Sotatercept was studied in a phase 2, multicenter, placebo-controlled clinical trial called the PULSAR trial in patients with PAH. And it showed significant activity in decreasing several parameters that are associated with PAH. So the phase 2 trial was very positive.

So based on the phase 2 PULSAR trial that was positive, the next step was to study sotatercept in a phase 3 trial to really see if this molecule is effective in PAH. The phase 3 trial was called STELLAR trial. It was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial, and it evaluated sotatercept in patients with PAH group 1 who were symptomatic and who were already on background therapy. The primary endpoint was measured at week 24. And this slide summarizes the study design, which shows the inclusion criteria with adults with PAH group 1, functional class II or III, who had certain baseline hemodynamic impairments, a pulmonary vascular resistance of at least 400 dynes, an impaired walk test between 150 to 500 meters, and they were stable on background PAH therapies. These patients were randomized 1:1, and they received either sotatercept or placebo in a subcutaneous

injection every 3 weeks.

After the primary endpoint was measured at 24 weeks, patients entered the double extension phase that was also blinded until the end of the trial. You can see here the primary endpoint was changed from baseline at week 24 in 6-minute walk distance. But there are several hierarchically measured secondary endpoints that are summarized on the right side of the slide.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Ioana Preston. Today, I'm reviewing the evidence from sotatercept trials and the potential impact on your clinical practice.

Now what's very important in the study design is that patients were on background therapy, and they were maximally treated per the site and the country. So let's look at the patient characteristics that entered the trial. The majority were females, which is very expected in a disease with female predominance. Their age was around 48 years of age. There were functional class II or III, but as far as classification of group 1 PAH, the majority were idiopathic. A good proportion of them had heritable disease, but also a small proportion had connective tissue disease, drugs and toxins induced, and congenital shunts that were corrected.

Now very interesting are several aspects. The time from diagnosis, from the initial PAH diagnosis in these patients, was around 8 to 9 years. And then the other important aspect was that the background therapies consisted in the majority of patients having triple therapy already on board, with a good proportion of them having infusion therapy.

So let's look at the results of the primary endpoint, a change from baseline in 6-minute walk distance at week 24. In 2 different statistical analyses, 6-minute walk distance improved significantly in the treatment arm versus the placebo, which is the blue line. So if you look at the placebo arm, it stayed stable over 24 weeks. However, the active arm improved after 3 weeks and continued to improve further to week 24. And the average measurement improvement was around 40 meters, which I think, in my opinion, is not only statistically significant, but clinically significant.

Let's look at the secondary endpoints. So of the 9 secondary endpoints, we can go over each one, because they're all parameters very important clinically to understand the severity of the disease. So the multicomponent improvement was significantly better with the treatment, but also pulmonary vascular resistance, NT-proBNP, functional class, time to clinical worsening or all-cause death, the French risk score; they were all significantly improved.

And also, lastly, what I think is important for the clinician and the patient, 2 of the 3 quality of life questionnaires improved significantly in the treatment arm, and that included the physical impact and the cardiopulmonary impact of PAH-SYMPACT score, which is a PAH-designed quality of life scoring system. So across the board, out of 9 secondary endpoints, 8 achieved statistical significance.

But if we look further, beyond the primary results of the STELLAR trial, and we look at the most recently published post hoc analyses, we can look at the echo parameters that show how the right ventricle functions, which is a measure of how long the patient will survive. So if you look at this post hoc analysis, a couple of the important parameters are TAPSE [tricuspid annular plane systolic excursion]. TAPSE, divided by the systolic PA [pulmonary artery] pressure estimation ratio, the tricuspid regurgitant jet, and the peak tricuspid regurgitant velocity. So I'm giving you an example here of the TAPSE divided by sPAP [systolic pulmonary artery pressure], which is one of the parameters that we take into consideration when we evaluate patients with PAH. The placebo group had no change in this parameter, but then the treatment group improved significantly.

And on the right-hand side, you can see the other parameters that improved, such as TRG [tricuspid regurgitant gradient], the peak regurgitant velocity, the systolic PA pressure estimation, and also the right atrial pressure estimation, which I think is another important parameter to assess the severity of the disease and the risk of death.

The other post hoc analyses also looked at the hemodynamic parameter changes during the STELLAR trial, and it showed significant improvement in PVR, mean PAP, and mean right atrial pressure. And then on the right-hand side, you can also see effects on the systemic vasculature that are probably indirect positive effects. What's also interesting is the wedge pressure did not change, which shows a lowering of the left ventricular work and volume, which I think it's an important parameter.

And lastly, 2 of the very important parameters that we don't necessarily measure in clinical practice, but I think these 2 measures, PA compliance and RV [right ventricle] work, are very crucial to better understand how is the right ventricle coping with the increased workload against an increased pulmonary vascular resistance. So PA compliance and right ventricular work both improved significantly in the sotatercept arm. And then on the right-hand side, you can also see other parameters, such as PA elastance and RV power, as well, as SvO_2.

So we have to talk also about the safety of the drug. Is this drug safe to be used in our patients? So this is a summary of the safety profile, measured during the STELLAR trial, where we could see a slight increase in bleeding events, which were mostly epistaxis and

were mostly not severe. There was an increase in hemoglobin that could be counteracted by decreasing the dose or temporary dose holds. Also mild to moderate thrombocytopenia, also not associated with very severe events. A slight increase in blood pressure and events of telangiectasias that have occurred in more patients in the sotatercept arm versus the placebo.

In conclusion, if we look at a new therapy that is emerging that has been recently approved by the FDA for patients with PAH as an activin signaling inhibitor, sotatercept can be considered in patients in PAH group 1 who are symptomatic, who you don't think that on background therapy are well controlled. And then we can talk a little bit later of how you decide if they're under good control or not. Make sure that they're not pregnant and that their platelets are over 50,000. You start at 0.3 mg/kg subcutaneously. You monitor hemoglobin and hematocrit and platelets before each dose for at least 5 doses and periodically thereafter. And then after the first dose, if the drug is tolerated, you increase it to 0.7 mg/kg sub-q every 3 weeks, with monitor of the functional class, risk score, so its effects, but also tolerability events.

With that, my time is up. Thank you for joining me today.

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