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Risk and How Risk Directs Treatment: Challenges and Barriers to Risk Stratification

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

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Dr. Preston:
Today, I'm looking into the future of pulmonary hypertension management to give you an overview of the next generation of treatments and mechanisms.

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

We've known for the past 10 years that PAH is a complex disease and no one single treatment cures the disease or is sufficient to control it. In 2015, the AMBITION trial showed that up-front combination therapy with a PDE5 inhibitor and an endothelin receptor antagonist favor better outcomes compared to any monotherapy alone. So we've learned that combination therapy, multiple treatments, are required to treat patients with PAH.

And further research and expert opinion summarized the current recommendations that were published in 2022 that guide the clinician of how to treat patients with PAH. This algorithm summarizes that patients who have PAH, if they're a low or intermediate risk, they should be studied on up-front combination therapy with 2 oral medications, whereas those in high-risk category, meaning high risk of death at 1 year, they require triple combination therapy. So you see the treatment algorithm is complex and patients end up on multiple therapies.

This is a summary of the FDA-approved current therapies for PAH in the United States and includes endothelin receptor antagonists, nitric oxide pathway stimulators, prostanoids or prostacyclin analogs, prostacyclin receptor agonists, and lastly, activin signaling inhibitors that are newly approved drugs.

So combining all these treatments lets patients with PAH be burdened by their medication therapy. The targeted therapies may include at least 2 oral therapies, but also sometimes additional inhaled, parenteral, or subcutaneous treatments. And then you can add adjunctive therapy, such as diuretics, anticoagulants; some use oxygen. And the comorbid conditions may require also medications on top of that.

So there are very significant barriers to medication adherence. And to help patients to be compliant and adherent to the multiple treatments that we recommend, we have to recognize specific barriers that are depicted in this slide.

So that leads me to the development of a program geared at easing this burden for patients with PAH. This is a very new trial that was published this year. It's called A DUE, which in Italian means 2. And it was a multicenter, randomized, controlled, double-blind, phase 3, adaptive study that looked at combining in 1 pill, 2 types of drugs: macitentan, which is an ERA, and tadalafil, which is a PDE5 inhibitor. So patients, instead of taking 3 pills once a day, they end up taking 1 pill. And this is a very interesting designed study where patients were randomly assigned to either monotherapy with macitentan, monotherapy with tadalafil, or combination therapy with this one pill.

The primary endpoint was change in pulmonary vascular resistance at week 16. And if you see the measurement, the improvement in PVR with the combination therapy in purple bar was much better than with only macitentan. And then on the other slide, you can see very similar results of the combination therapy versus monotherapy with tadalafil.

Looking at the secondary endpoints, the trend and the significance of the combination therapy was similar with the PVR, with the hemodynamics, where 6-minute walk distance improved more in the arm that was assigned to the combination therapy. And that holds our understanding for the past 10 years that double oral combination therapy works better than each drug alone.

There are safety and tolerability measures that did not raise any new suspicions or worries in the combination therapy.

So summarizing the results of the A DUE trial, the combination therapy of macitentan and tadalafil in 1 pill favored better hemodynamics and exercise improvements and was well tolerated. And as a result of this study, the FDA approved this combination therapy in 1 pill. The other important factor in this is financial, so patients will not have 2 copays, but only 1 copay by using the combination pill instead of the 2 drugs separately.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Ioana Preston, and I'm reviewing the next generation of treatment for patients with pulmonary arterial hypertension.

So let's move on to the newer pathways. And I would like to speak now about the BMP activin pathway, which is abnormal in pulmonary arterial hypertension and in pulmonary vessels in patients with PAH. Sotatercept is an activin signaling inhibitor. Activin stimulates proliferation, and BMP pathway inhibits proliferation. And BMP pathway is deficient in PAH. Sotatercept binds to activin, it traps it, and it decreases its activity, with the aim to rebalance this abnormality in the proliferation pathway and anti-proliferation pathway.

Sotatercept has been studied in a phase 2 trial called PULSAR that was highly positive, and the latest phase 3 trial was called STELLAR. STELLAR was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial that enrolled patients with PAH in functional class II or III who were still symptomatic and had certain baseline characteristics, that are shown in this slide. They were randomized to either a placebo or sotatercept, a subcutaneous injection every 3 weeks. The double-blind period lasted 24 weeks. And the primary endpoint was 6-minute walk distance change at 24 weeks compared to baseline.

There was a double-blind extension until all the patients finished the treatment, after which everyone was rolled over into an open-label trial, which is called SOTERIA.

These are patients' characteristics. These are patients with long-standing pulmonary arterial hypertension with different etiologies and forms of PAH shown in this table and who were heavily treated mostly with double and also triple therapy. In fact, 61% were already on a triple therapy, and then 39%, almost 40% were already on prostacyclin. So these were heavily treated, still had significant hemodynamic and systemic impairment.

Let's look at the results of the primary endpoint, change from baseline in 6-minute walk distance at week 24. From 2 statistical analyses, we found that patients who were assigned to the sotatercept arm improved their walk distance by an average of 40 meters compared to placebo patients who stayed the same. Forty meters is a clinically significant improvement in PAH patients. We know that the minimum clinically significant difference is around 33 meters from prior studies.

It is not only the primary endpoint that improved, but 8 of the 9 secondary endpoints also achieved statistical significance, and that included the multicomponent improvement, pulmonary vascular resistance, NT-proBNP, functional class. But I think 2 aspects are very important: the time to clinical worsening or all-cause death improved by 84%, and 2 of the quality of life questionnaires, the physical impact and the cardiopulmonary scores, improved significantly with sotatercept.

The overall summary of safety is shown here. Patients who were assigned to sotatercept had a higher tendency to bleed. Most bleeds were deemed as non- significant, non-severe, and there were episodes of epistaxis. There was noted a decrease in platelets into the moderate range, a mild increase in hemoglobin that could be managed by decreasing or withholding the dose, and also a new AE of note was telangiectasia that seemed to occur after many more months of treatment.

So sotatercept has been approved by the FDA recently, and we will learn more about its long-term effects, both in clinical practice as well as in the long-term clinical trial called SOTERIA.

So in summary, the treatment of pulmonary arterial hypertension has been seeing significant paradigm shifts and improvements, as well as increasing complexity. Now we have approved improved treatment regimens to lessen the physiological and financial burden of patients. They improve adherence by the approval of the 1 pill that includes macitentan and tadalafil. And then lastly, the new effective therapies in the form of an activin signaling inhibitor, sotatercept, which will add to the existing armamentarium that we have available

now.

Thank you for joining me today. I hope you found this information useful for your practice.

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