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# Strategies to Implement Risk Stratification in the PH Clinic

**Announcer:**
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**Dr. McLaughlin:**
Welcome. We've had some very exciting advances in the next-generation treatments for patients with pulmonary hypertension, but what are the implications for your everyday clinical practice? Today, we're taking a look at the standard of care in PH and how to incorporate some of these newer therapies.

This is CME on ReachMD, and I'm Dr. Vallerie McLaughlin.

**Dr. Preston:**
And I'm Dr. Ioana Preston.

**Dr. McLaughlin:**
Ioana, let's start talking first about the A DUE study which looked at a combination tablet that has both macitentan and tadalafil in it. So we all know that both of these agents have been FDA-approved for use in patients with pulmonary arterial hypertension. And we know that the first step in treating most of our patients who have low- or intermediate-risk status is a combination of ERA and PDE5. This was established in the AMBITION trial, which looked at ambrisentan versus tadalafil versus both together. But the ERS/ESC guidelines also give a high rating to macitentan and tadalafil based on a number of studies, including the OPTIMA study and including the very impressive hemodynamic and hall walk improvements with this combination in patients in the TRITON study. So in TRITON, there were patients on macitentan/tadalafil/placebo or macitentan/tadalafil/selexipag, and about a 50% reduction in PVR and a 50-meter improvement in hall walk.

So the A DUE study looked at a fixed-dose combination tablet, so one tablet that has 10 mg of macitentan and 40 mg of tadalafil, and compared the changes in PVR [pulmonary vascular resistance] with macitentan or tadalafil alone and, again, demonstrated a very robust improvement in PVR with the combination tablet. And so the FDA has approved this combination for use in our patients.

And so let's talk about how this agent fits into clinical practice. Ioana, how are you using it in your practice?

**Dr. Preston:**
Vallerie, I think we've all known, and A DUE study proved again, that the combination of tadalafil and macitentan are very powerful treatments for patients with PAH. But think about it, for this combination, if you take the pills separately, the patient has to take 3 pills a day. And if you add other therapies for PAH that the patients may be on, maybe they're on inhaled therapy, maybe they're on infusions, and even if they're not, many of them are on diuretics, many are on supplemental oxygen. Maybe have some comorbidities that require other medications. So improving adherence by combining these 2 medications that we know act synergistically makes the most common sense.

**Dr. McLaughlin:**

Yeah, I think that's a great point. It improves pill burden and adherence. I would say it also reduces the copays. You have a copay now for just 1 tablet instead of 2 different prescriptions. So that might save some patients money.

I think that in my practice, though Ioana, I've been thinking about this, and oftentimes when I start a treatment-naïve patient on up-front combination therapy, I tend to spread it out a little bit to just manage or at least understand if they're having side effects, which pill it's from.

**Dr. Preston:**
Yes, I think it's a very good point. Another approach would be to start one monotherapy to make sure they tolerate and then move, as a next step, very quickly to the combined pill, and that's how we can stagger the side effects.

**Dr. McLaughlin:**
Ioana, that was a really great summary. And I think both, our patients and our community are really excited to have this combination pill that may improve adherence and compliance and reduce costs with less copay. So we're excited to have that.

There's another new, exciting option that we have, and that is sotatercept. And, Ioana, maybe you could just start out by summarizing the STELLAR trial for us.

**Dr. Preston:**
Sotatercept is an activin signaling inhibitor that blocks the pro-proliferative effects of activins and rebalance the activin effects against the BMPR2, or bone morphogenetic protein receptor II pathway. It was studied extensively in preclinical trials, as well as in a phase 2 clinical trial, PULSAR. And all these, up front, all these studies showed positive effects. So in order to really ascertain whether sotatercept works in PAH, it was studied in a phase 3, multicenter, placebo-controlled clinical trial called STELLAR.

In STELLAR, patients with PAH who were symptomatic and were on background therapies were randomized to either sotatercept, an injection subcutaneously every 3 weeks, or placebo, similar injection. And the study included patients who were typically on 2 or 3 background PAH therapies. So those are long-term patients who were still symptomatic, in whom the treatments available at that time were not able to control the disease enough. Patients were randomized, and the primary endpoint was a 6-minute walk distance at 24 weeks. There were several secondary endpoints that we can discuss a little bit afterwards, but the main endpoint, the 6-minute walk distance, showed a significant improvement by an average of 40 meters in the sotatercept arm compared to placebo.

What do you think, is 40 meters, on average, a clinically significant improvement, Val?

**Dr. McLaughlin:**
So I would say a couple things. So one, yes, 40 meters is clinically significant. We've done studies correlating quality of life and change in hall walk, and kind of the number that has risen is about 33 meters. Like, 33 meters means a difference in a patient's life. So I would say that is significant, particularly in this highly pretreated population.

I would also say, and I know you're going to get into this, the consistency across all of the endpoints. So the consistency in not just hall walk but hemodynamics and BNP and MCI and clinical worsening, you know, I think all of that leads to the conclusion that this is a highly efficacious therapy for our patients with PAH.

**Dr. Preston:**
Yes, I agree, Vallerie. And let's discuss the secondary endpoints, which I think they're not only statistically important, but clinically important. The multicomponent improvement was so much important and it was positive in the sotatercept arm compared to placebo. Hemodynamics, pulmonary vascular resistance, and very interestingly, a drop in mean pulmonary artery pressure to the magnitude that we have not seen in other clinical trials, again, in the active arm. Also, brain natriuretic peptide prohormone was significantly reduced, and actually very early in the trial, which was surprising, thinking that this is probably an anti-remodeling drug, how quickly it started working.

And lastly, I think, what was surprising in a positive way, was that 2 of the 3 components of the quality of life questionnaires showed significant improvements in the active arm.

**Dr. McLaughlin:**
Yeah. I mean, hitting 8 of 9 secondary endpoints is impressive.

But Ioana, a clinical trial is a clinical trial; tell me how you're going to use sotatercept in your everyday clinical practice?

**Dr. Preston:**
That's a very good point. This is a new drug. It has shown significant improvement in a large clinical trial with so many secondary

endpoints that were hit. It does have a safety profile that we should take into account, notably an increase in hemoglobin that can be managed with adjustments in the dose, a decrease in thrombocytes that has not been a major problem in the clinical trial, and also bleeding events that the majority were epistaxis. However, like any therapy, we have to take into account the pros and cons for each individual patient.

I think in the beginning, in my practice, I will focus on choosing the patient profile

that is similar to those patients who were enrolled in the STELLAR trial. And once I gain more experience and I better understand the long-term effects of the drug and learn how to manage the side effects, then I can expand it to maybe patients with other aspects and other comorbidities that have not been included in the STELLAR trial.

**Dr. McLaughlin:**
Yeah, I think that's a good point. I think that's our approach too. We're looking at clear Group 1 PAH so, you know, not a lot of comorbidities, not a lot of lung disease.

But I can't tell you how many patients have asked me, and I'm sure it's the same for you, Ioana, “Can you get me off my pump? Can you get me off my pump?” What's your response to those patients?

**Dr. Preston:**
So you know, both you and I have had a lot of experience in trying to wean patients from parenteral prostacyclins over the years to less invasive therapies. And I think what we've learned is, first of all, if the disease is not well controlled on the current therapy and the right ventricle is not in fantastic shape – you know me; I say a happy ventricle, a happy RV ventricle, right – then I'm very wary to wean patients off the prostacyclin, even after starting sotatercept.

However, there are reports in the long-term trial that patients have gone off the prostacyclin after a good trial of sotatercept and follow up closely and repeat right heart catheterization. So I would say in selected patients, we could consider.

**Dr. McLaughlin:**
Yeah. And I think those are going to be very carefully selected patients. So those are the patients who have maybe nearly normalized their hemodynamics on a prostacyclin and are doing very well and low risk and happy right ventricles. and even then, at least in my practice, we do it very slowly, very carefully. We repeat echoes frequently and walks. We repeat a right heart cath when they're at the tail end of the prostacyclin. And I think I just want to emphasize the importance of monitoring these patients. So because of some of the side effects that you mentioned, particularly the increase in hemoglobin and the reduction in platelet counts, we have to get a CBC prior to each of the first 5 doses. So we really want to make sure people use this drug safely.

So Ioana, maybe you want to sum up sotatercept for us?

**Dr. Preston:**
Yes. So it's a novel therapy, a novel mechanism. It seems to be very efficacious on top of the background therapies that we have already available. It seems to work at least in the medium term. We cannot say long term for now, but definitely medium term, it's efficacious. We have to monitor patients very closely at the initiation of the therapy, at least 5 doses, and then periodically thereafter, and be aware of the potential side effects. But this is a very exciting new therapy for our patients.

**Dr. McLaughlin:**
Ioana, I think that was a great summary. I'm equally excited.

Unfortunately, that's all the time we have for today. So I want to thank our audience for listening and thank Dr. Preston for joining me and sharing all of your valuable insight and expertise. It was really great to speak with you today.

**Dr. Preston:**
Likewise. Thank you, Vallerie.

**Announcer:**
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