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Are the current guidelines current?

Announcer:
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Dr. McLaughlin
Hello. I'm Dr. Vallerie McLaughlin from the University of Michigan and I'm here to talk about PAH management. Don't wait to escalate. We need to be aggressive with PAH management.

So we know that early aggressive treatment is important, and it really starts with timely referral. We would rather get patients early in the course of the disease than later in the course of the disease. So rapid referral to a PAH expert center for right heart catheterization is important, especially for patients with intermediate or high-risk findings on echocardiogram, if you have a suspicion of PAH, or if they have some factor which puts them at risk for PAH, like scleroderma or positive family history. And we want to be aggressive with early initiation of PAH medical therapy.

Now, we've learned from many, many trials that early therapy and combination therapy improves outcomes, including improvements in hemodynamics, slowing the progression of the disease, and improving quality of life and exercise capacity. So starting therapy early and reassessing with escalation of therapy as appropriate is important.

There are a number of medications that we have to treat PAH. Many have been around a long time, all of the prostacyclin pathway agents, analogs and agonists, as well as the endothelin receptor antagonists and PDE5 inhibitors. We have SGC stimulators as well, and more recently we had the first activin-signaling inhibitor approved. So we have more than a dozen therapies and we have 4 different classes that are often used in combination.

So we have guidelines on the management of PAH, which have most recently been updated at the 2022 ERS/ESC guidelines, and this is the treatment algorithm from those guidelines. Of course, making sure that you have the correct diagnosis and that the patient is being seen in an expert center. Some patients should have vasoreactivity testing, those with idiopathic drug- and toxin-induced and heritable disease might be candidates if they respond for calcium channel blockers. But the majority of patients then undergo risk stratification and treatment is based on their risk. There's certainly some patients who have high-risk features when we first meet them, advanced hemodynamics, right-heart failure, for example, and those patients get initial combination therapy that is often triple and includes a parenteral prostacyclin. But for the majority of patients, they're either at low risk or intermediate risk, we start with dual oral therapy with an ERA and PDE5. And that's just the first step. It's a really important step, but that's just the first step. I would say even the more important step is that subsequent follow-up, that reassessment of risk after 3 or 4 months of therapy.

And we used the 4-risk strata approach for that, and we then need to act on those results. If patients are still at intermediate-high or high risk with the first thing that you've done, you need to get more aggressive. For example, if you started with dual oral therapy, those patients should go to a parenteral prostacyclin. If they're still at intermediate or high despite a parenteral prostacyclin, then they might need to be evaluated for lung transplantation. On the other end, patients at low risk after that initial therapy have an excellent prognosis and you can continue therapy as it is. And those patients who fall into the intermediate-low risk category, perhaps they're not very high risk and we might need to go to a parental prostacyclin, but they still don't have as good of a prognosis as the low risk, and so we often add something else, like a prostacyclin receptor agonist or analog, or we can switch from a PDE5 inhibitor to an SGC.

And here's just the tables of evidence from the ERS/ESC guidelines that really highlight the best evidence for that initial combination therapy is with either ambrisentan and tadalafil or macitentan and tadalafil.

So let's go through some of those clinical trials, and it really all started with the AMBITION studies. So this is a number of years old, almost a decade old now, and back in those days, we were often starting with one therapy and then escalating if a patient didn't meet our treatment goals. And AMBITION said, wait a second, we have different ways of approaching this disease. We know these therapies are effective. We know combination therapy is used in many other disease states. And should this be the standard in patients with PAH as well? So the AMBITION trial looked at 500 newly diagnosed treatment-naïve patients and randomize them to receive combination therapy with ambrisentan and tadalafil, or monotherapy with either ambrisentan or tadalafil. And it looked at a composite primary endpoint of time to first event of clinical failure, defined as all-cause mortality, hospitalization, disease progression, or unsatisfactory long-term response.

And here are the curves from that primary endpoint demonstrating a significant benefit of 50% risk reduction in the endpoint of clinical failure in patients who received combination therapy with ambrisentan and tadalafil versus patients who received one or the other. So this really changed the treatment paradigm back nearly a decade ago.

Now there are a number of secondary endpoints that were also positive. There was an improvement of nearly 50 meters in the 6-minute hall walk in the patients receiving combination therapy versus 24 meters and the patients receiving monotherapy. There was a greater reduction in NT-proBNP, which we know is an important prognostic indicator, and the side effect profile was really quite similar and consistent with those individual therapies.

There was also the therapy with macitentan looking at that, often in addition to a PDE5 inhibitor in the SERAPHIN study, and that demonstrated a 45% risk reduction in a composite endpoint of morbidity and mortality.

But then there's also a larger trial looking at macitentan and tadalafil in the context of the TRITON study. Now the TRITON study was designed to say, hey, if 2 therapies are good to start out with, are 3 better? And so the premise of this was to look at macitentan and tadalafil either with or without selexipag, and there was no difference in those 2 groups. But I really want to emphasize what we saw with the combination of macitentan and tadalafil. Over a 50% reduction in pulmonary vascular resistance and over a 50-meter improvement in 6-minute hall walk, so that's very similar to the AMBITION trial. And this has led to the evidence in the ERS/ESC guidelines citing the macitentan and tadalafil as an initial combination, as well.

Now more recently, this has been approved in a combination pill of macitentan 10 mg and tadalafil 40 mg that is now FDA-approved for the treatment of PAH. So this reduces the pill burden for patients, so instead of 3 pills a day, it's 1 pill a day, and it's also only 1 prescription as opposed to 2, so that could potentially impact cost; they have one less co-pay.

So we also have evidence on combination therapy used from the GRIPHON trial. This looked at selexipag in patients who were receiving therapy for pulmonary arterial hypertension. A large proportion of them were on background therapy with either 2 or 3 agents, a handful of patients that were naïve to therapy or on monotherapy, and there was a 40% reduction in the morbidity and mortality endpoint with the use of selexipag versus placebo in these patients. So again, showing that combination therapy yields better long-term results.

Now when we think about the treatment approach, early and aggressive therapy, I really want to highlight that. And this slide shows some data from the French registry when they looked at treatment approach. So the French registry is a very large registry, over 1000 incident PAH patients in this registry. And this slide looks at patients who are at high risk to start out, but even patients who are at intermediate risk to start out and looks at how they did subsequently in terms of mortality if they were treated with triple therapy, which is the red line, double therapy, which is the blue line, or monotherapy, which is the green line. And I really want to highlight, even in the intermediate-risk patients triple therapy conferred a much better prognosis. And so, again, aggressive therapy is important.

So the guidelines say for most patients to start with double combination therapy and, you know, that enough? Well, some patients respond very well, but others don't get as much better as we would like, and that's why that reassessment is really very important.

These are data from an Italian study where they looked at patients' risk score at diagnosis using the European approach on the left and the REVEAL 2.0 approach on the right. So either low, intermediate, high at baseline, and then the colors represent what their score was at the time of first follow-up around 4 months. And you can see that if you focus just on intermediate-risk patients at baseline, those who are intermediate risk at baseline, less than half of them get to low risk with initial double combination therapy. So it's great. We're getting half of those intermediate-risk patients to low risk and that's good; they have a good prognosis. But the point is, also, that half of those intermediate-risk patients are not getting to low risk and we need to do more. And you'll also see for those at high risk at baseline, none of the patients get to low risk on an approach of, generally, dual oral combination therapy.

And one of the things that can impact that likelihood is the change in pulmonary vascular resistance. So this shows the percent change in pulmonary vascular resistance for the group as a whole.

And if you look to see who gets to low risk on this slide, the people who get to low risk using the ERS/ESC score on the left and REVEAL score on the right, the people who get the low risk are in green. And that is plotted against their change in PVR. And so you can see that the people who get to low risk are those who have about a 50% reduction in their PVR. So I think that's really important evaluate as we do risk assessment. Are they getting to low risk? Is there a change in their hemodynamics?

And I want to make another important point about aggressive therapy. We have learned so much from clinical trials, and many clinical trials, the placebo patients are then offered open-label extension. And this was a large analysis of patients who were in these clinical trials, and it found that the patients who were randomized to placebo, they just really never caught up. So a delay in therapy is really not good for our patients.

So I really want to emphasize the importance of monitoring and close follow-up, and this is highlighted in the ERS/ESC guidelines, which call for early and regular follow-up after that initial diagnosis. A very formal assessment at 3 months with escalation if the patient is not meeting low risk. And it's important as part of our routine care for these patients to regularly reassess their risk, and we have a number of objective risk tools to do this, so it's part of what we do every single time we see a patient in clinic. Of course, we have to acknowledge some of the challenges of aggressive management.

All of these therapies have side effects and it's really complicated for many, many patients, especially when they're managing a lot of different medications. Sometimes we have to think about adherence, they're complex, and sometimes it's really hard to comply with these therapies. And of course, there are potential side effects of the delivery systems. And there's challenges with access. All of these therapies are expensive, sometimes patients have high co-pays, some patients just can't even get to specialists, so there are certainly challenges.

So I want to conclude by saying the importance of aggressive management of PAH. It's really crucial for improving the outcomes. We have so many combination therapy studies now demonstrating the improvement when we target multiple pathways. Of course, our greatest opportunity for improvement is by early diagnosis and early initiation of up-front combination therapy, but that's just the first step. We have to regularly risk assess our patients to determine if they're meeting our goals or if they're having disease progression and if they need more therapy. And of course, it's really an exciting time in PAH. While we have many FDA-approved therapies, we also have a lot of new therapies that are being studied. And so there's a lot of hope for even more effective therapies for PAH.

Thank you for joining me for this segment.

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