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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Management of PAH: Update on the Therapeutic Landscape

Announcer:
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Dr. Saggar:
I think we'll jump into the next talk. So this is just a quick update on sort of the therapeutic landscape and some of the new therapies that are out there.

So obviously, there's still a major survival disadvantage, despite all the therapies that we have today. You can see that the median survival looking at the REVEAL database, the U.S. based - the largest U.S.-based database, suggests that the median survival even on the best of therapies today is about 9 years. So we still have an unmet need.

So the current treatment targets we're all familiar with targeting the 3 pathways, endothelin, nitric oxide, and prostacyclin, but there are new developments of these well-established pathways. So there's looking at higher doses of macitentan, for instance, 75 mg instead of 10 mg, ralinepag which is sort of a new generation selexipag, if you will, changing the way we give treprostinil and the formulations, etc. And you may have heard that there's a dry powder inhaled vardenafil. So there's a lot of stuff going on in terms of the existing pathways and sort of modifying those in ways.

And then there's also the potential for new novel pathways in PAH. And these are all the areas where we might be able to consider additional therapies. So a lot of translational research going on to look at any one of these different areas, targeting any one of these different areas that affect the pulmonary vasculature.

So these are some of those. You can see in the at the top there, there's, you know, targets like looking specifically at BMPR-II, which is the biggest, the most well-known genetic modification that we see in PAH patients. And there's, you know, been some data looking at tacrolimus, for instance. There's a new drug called sotatercept, which we'll talk about a little bit. The old story of inhibiting PDGFR with imatinib, and there's a newer molecule known as seralutinib. So there's - I'll show you some of that data. There's a recent study that actually just recently read out as a failed trial but looking at antagonizing the serotonin pathway. So serotonin inhibition, we'll get into that a little bit. And then you can see there's multiple other pathways being targeted with different drugs or, in the past, inflammation and the metabolic pathways, looking at estrogen signaling which we do a lot here at UCLA, a lot of that research humoral, epigenetic, there's a VIP analog that's being looked at as well.

So I'll just touch base quickly about sotatercept, which is probably the biggest story in the last year with the article that came out early in 2023. So as I mentioned, bone morphogenic protein receptor-II and sort of the larger TGF beta superfamily, is really the signaling that we're targeting with this drug, sotatercept. And there's this homeostasis. There's a very nice picture of this in the *New England Journal* in the article that came out, looking at the fact that there's a bit imbalance between the pro-proliferative pathway and the anti-proliferative pathways, obviously favoring pro-proliferation. And sotatercept sort of comes in and rebalances this stuff by really focusing in on the activins and the growth-differentiating factors, and sort of, you know, rebalancing it so that there's more of an anti-proliferative

phenotype.

And as we know that up to 86%, I mentioned this earlier, familial PAH and 35% of idiopathic PAH actually show this defect, this genetic defect in the BMPR-II in terms of mutations. And PAH is associated with this dysregulation that occurs because of this genetic modification. And then we end up having this condition, and it turns out that sotatercept targets exactly this whole cascade.

So, sotatercept is the first in class, if you will. So another sort of pathway, if you will. It's a fusion protein. And as mentioned, we sort of rebalance into the, you know, promoting more of the anti-proliferative phenotype, and then hopefully, reversing some, I'd say, the characteristic remodeling that we see in PAH, although that remains to be seen.

There's been two studies, one was the phase 2 study called the PULSAR study, and the more recent one that you probably read in the *New England Journal*, and if you haven't, it's a very nice article. It's particularly with the pathway that's been worked out, looking at the phase 3 STELLAR study. And in the STELLAR study, the difference, they looked at 6-minute walk distance as the primary endpoint, and there was a difference of 40.8 meters in the 6-minute walk, which is statistically significant. But the really nice part of the study was, they had 9 secondary endpoints, which they looked at in terms of an hierarchical approach statistically, and the first 8 actually hit in terms of in favor of sotatercept. And they're all things that you would clinically find to be relevant, including the need for hospitalization, morbidity, as well as, you know, BNP levels, etc. So, interestingly enough, and this is important 40% of the patients in that study were on a prostacyclin infusion, and 60% were on triple therapy. So it wasn't, you know, these are patients that we treat on a daily basis.

So these are some of the studies that are currently ongoing. You can see SPECTRA was an older study. I won't get into that. STELLAR is completed. And then there's two other studies ongoing right now called ZENITH and HYPERION, looking at incident and prevalent cases using sotatercept.

So just switching gears to imatinib and seralutinib, so overexpression of PDGF and PDGFR and its receptor, it's been implicated in the development PAH for many, many years. And there's a whole pathway sort of outlined for how, you know, perhaps inhibiting PDGFR and PDGF in PAH patients may account for or may allow for reverse remodeling.

And so we're talking about tyrosine kinase inhibitors here, imatinib. It's an old story. There was an old study, older study, back in the late maybe 2009-2010. It was a phase 3 study called IMPRES looking at oral imatinib, which actually was put on top of patients who were pretty darn sick. It was actually a positive study, but it had serious side effects, specifically subdural hematoma increase in incidence, so Novartis actually put that program or stopped working on that program, so it never came to fruition. But now they're looking – there are studies looking at inhaling imatinib. And there's planned and actually ongoing phase 1, 2, and 3 studies looking at inhaled imatinib. So that's kind of cool.

And then there's a newer molecule called GB002, which is actually seralutinib, which is a small molecule inhibitor, also of PDGFR, which I can show you some data for in a second.

So this seralutinib is also a tyrosine kinase inhibitor. Remember, a lot of these tyrosine kinase inhibitors are sort of dirty in the concept that they block multiple tyrosine kinases. This one blocks PDGFR, CSF1, and c-KIT. So this is sort of a, you know, has its own profile, if you will, and it's also designed as an inhaled therapy for PAH. It's administered as a dry powder inhaler. And so, it's kind of cool. And you can see the device at the bottom there in the Panel B.

So the study that they just completed looking at seralutinib is this TORREY phase 2, called TORREY study. They randomized, double-blind, placebo-controlled study, and the primary endpoint of the study was changing PVR from baseline to week 24. And they did actually meet the primary endpoint. Sixty percent of the patients in this study were on triple background PAH therapy, and 45% were on parenteral prostacyclin. So in the overall population, the drug, seralutinib, actually reduced PVR statistically significantly and it seemed to be more beneficial in people who had Functional Class III symptoms as opposed to Functional Class II, not surprisingly. So the current status of this drug is that there is proof of concept and now there's a global registration phase 3 program that's in process using seralutinib.

What about serotonin antagonism? I sort of mentioned earlier that this drug is more recently - the study has actually stopped. But it's kind of an interesting story. And I know we don't have much time but the serotonin pathway has been a pathway of interest for many, many years. As we all know, serotonin is released by intestinal, you know, the enterochromaffin cells, 90% of what we see comes from that, the platelets as well as the brain, and it turns out the human pulmonary endothelial cells also express tyrosine, or tryptophan hydroxylase-1, and by using that enzyme, produce serotonin in the pulmonary endothelial cells, which has been seen in patients with PAH.

So, serotonin itself induces proliferation and vasoconstriction, and potentially leads to PAH. This is obviously the mechanism that they're trying to go after. So there is a drug that was studied in a study called the Altavant study, looking at a serotonin, you know, antagonizing

that pathway and it was a tryptophan hydroxylase inhibitor. This study was stopped, you can see here, pretty recently in June of 2023. But interestingly enough, it wasn't just stopped. - it was stopped but the reasons are interesting. It actually worsened PVR and the NT-proBNP levels in the wrong direction. And I think that's also something to be aware of.

Just switching gears to devices. So this company called Aria has a device that actually tries to work on, we're all used to sort of working on the pulmonary vascular resistance. This device is interested in looking at pulmonary artery compliance, and sort of modifying that and sort of changing how using a device and trying to get the pulmonary vasculature to act like the elastic system that it should be. And so, that's what it looks like. You can see there's a holding chamber at the top there, there's a balloon, the reservoir at the top I should say, which has a proprietary gas in there. And then there's a balloon at the end with this nitinol stent, which actually wedges into the pulmonary artery on one on and went into one of the main pulmonary arteries. And you can see it's being deployed just on this video here. It should be coming through pretty soon. There it is. Going into the left PA there. And then you can see that stent at the top. So it wedges in with that nitinol stent, and then there's a balloon just proximal to that. And then the reservoir has a proprietary gas. And as the heart pumps, systole and diastole, you're going to - the pump - the balloon will actually deflate, inflate and deflate. So there's no pump, there's no battery, it this is a self-working system, if you will.

So the mechanism here, as you can see here at the top, during systole, the pulmonary artery wants to expand, which is what it should do. During that time, the balloon and this device deflates, and the opposite end diastole. So it sort of mimics the elastic recoil. And the idea is that it actually drops the pulse pressure, the difference between the systolic and diastolic PA pressures, and it augments cardiac output, which is what they've seen.

So what they've done is they've done three studies looking at the acute changes for WHO Group 1, 2, and 3 patients. And you can see the changes here on the left in compliance on the left, at baseline versus being on the device acutely. These are people on the table when the device is acutely put in. And on the right, you can see the same thing with pulse pressure. Again, the difference between the systolic and diastolic pressure is falling with the device acutely and they saw synonymous or homogenous results across all three WHO groups.

So there's a study known as the ASPIRE study, which is an early feasibility study looking at using this device in all groups, Groups 1, 2, and 3, using this device in the ambulatory setting, so not just acutely, but actually chronically, waking them up after placement and then getting them and seeing how they do over time, not just acutely.

And just to finish things out, there's several interventional and surgical devices that we could talk about, which we don't have time to get into. There's a resurgence of actually creating a Potts shunt, not just surgically, but even percutaneously. But we're not going to get into that, but it's interesting. There's been a whole story of pulmonary artery denervation, much like we use to sort of ablate renal arteries for systemic hypertension, which never panned out, but you get the concept there. looking at right ventricular assist devices. There's the possibility of pacing the RV, and there's some nice data in the *Blue Journal* from Ryan Tedford's group looking at that. And then ECMO of course, is always playing a role, both venoarterial and now the whole V-PA approach with a single catheter.

So in conclusion, phase 3 trials for new approaches to target the well-established pathways are there. There's a whole number of novel PAH targets. We mentioned sotatercept and other pathways. There's a whole bunch of phase 2 and phase 3 studies going on. It's ripe. The whole field is ripe with a lot of interest and a lot of interesting things happening. And I think an important goal for us is to prioritize drug discovery and development in PAH.

So with that, I'll stop.

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