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Emerging Novel PH Therapies: Will They Impact Treatment Strategies?

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Dr. Rajagopal:
Hello, everyone. Thanks for joining us today for this roundtable discussion on emerging therapies in PAH. My name is Sudarshan Rajagopal, and I'm at Duke University. I'm joined today by Dr. Oksana Shlobin Inova Fairfax Hospital, and Dr. Rajan Saagar from UCLA.

So, as we're all aware, there are a lot of exciting new potential therapies for the treatment of PAH. These include drugs like sotatercept, new inhaled formulations of drugs, and new oral formulations of drugs, and then just drugs targeting new pathways. So Oksana, we have a lot of options for treating our patients with PAH, but there's still some unmet needs here. So what do you think sort of the next step is in gaining better control of the disease?

Dr. Shlobin:
So as you said, there are a lot of unmet needs. Most of our patients still do not get to low-risk status. And so, we do need more therapies. We need therapies that provide more vascular remodeling, that improve right ventricular function, and ultimately lead to improved survival in those patients.

Sotatercept data is very exciting. It's a totally different pathway for this medication, not a pulmonary vasodilator, and really offers patients, I think, hope for the future, that there is going to be vascular remodeling in the lungs, which results in decrease in pulmonary vascular resistance, and ultimately, improvement in RV function. And maybe in the future, either with that medication or combination of other anti-proliferative drugs, pulmonary vasodilators will not be a main stamp of therapy. So definitely a lot of great developments. And I think the pulmonary hypertension

community is really looking forward to more results to come from other drugs with anti-proliferative potential.

Dr. Rajagopal:
You brought up a lot of great points there, Oksana. So, Rajan, how do you foresee drugs like this being incorporated in our current therapeutic strategies? We've been talking about upfront triple combination therapy for some patients, where do you see these drugs being used?

Dr. Saggar:
That's a great question. I think Oksana brought up some good points. I think we're at a point in the PAH world of therapeutics where we're sort of at a crossroads in some ways, because we have, as Oksana mentioned, this brand-new pathway with sotatercept. And as you mentioned, some of the inhaled therapies like imatinib, we have the serotonin antagonist data that should be unveiled soon. And we're sort of, you know, assuming these drugs all come to an FDA approval, how they actually sort of fit in with the existing regimen that we have, you know, with the two oral drugs, and the prostacyclin and prostanoid pathways, remains to be seen.

And I think one of the questions that we all wonder is, right, what's the best combination of medications up front? So right now, we're so

used to our sort of ambition approach where we have two oral drugs up front, is that going to be shaken up? Or are we first going to shake up sort of what we do, we add on, you know, to the three drugs that we have available? And I think the future of all this is in flux.

Personally, I think that a drug like sotatercept, which has a lot of human data; this is not the first time it's been studied in humans, and imatinib, which we know have the 2011, you know, large paper, the IMPRES data, which was oral imatinib, but now we have the inhaled version; these two drugs have quite a track record now, and have been looked at, I think, pretty elegantly and with good results in patients who have very advanced disease despite being on three drugs. So, they're offering a lot to the table on top of maximal therapy, so it's going to be fun to watch.

Dr. Rajagopal:
Highlighting that point of inhale therapy directly targeting the lungs, Oksana, as a pulmonologist, you've been using drugs like that for a while. Me, as a cardiologist, I'm not as used to doing that. So could you give us some insights onto sort of these approaches of directly targeting the lung with these therapies? Do you think there - what are the benefits? What are the drawbacks? And what have you seen in your practice?

Dr. Shlobin:
From that whole bucket of the drugs that are currently available, we have inhaled treprostinil. Obviously, that prostanoid pathway that we use in Group 1 pulmonary arterial hypertension, and more recently in patients with interstitial lung disease induced pulmonary hypertension. The drive to deliver a drug, not systemically but directly into pulmonary circulation, I think always comes with several reasons. One of them is you want to put more drug into pulmonary circulation. So, really directed therapy.

The other one is to minimize systemic side effects. And we all use a lot of, let's say, intravenous and subcutaneous treprostinil, an effective drug, but both mode of delivery and the side effects can be difficult for patients to deal with and bothersome. So, therefore, inhaled treprostinil came to market from oral imatinib to inhaled imatinib, there is also a story, one of the reasons that oral imatinib did not come to market was gastrointestinal side effects, it was very difficult to tolerate. So, again, the hope is that you can deliver a sufficient concentration of the drug into the lungs to minimize those systemic side effects.

Inhaled seralutinib is also another drug, another tyrosine kinase inhibitor. In the world of pulmonary hypertension due to interstitial lung disease, inhaled nitric oxide was developed using the same sort of thought. If you look at the data of inhaled treprostinil, the drug is well tolerated. It doesn't appear to probably have the same

benefit as intravenous or subcutaneous drug. It will be very interesting to see whether that drug with anti-proliferative properties versus just vasodilative properties can deliver more. So whether the effects on pulmonary vascular resistance actually is as good as, let's say, with oral formulation of oral imatinib.

Dr. Rajagopal:
And then Rajan, to close, you know, we always talk about getting our patients to low-risk status. That's sort of the main goal of our therapies. Do you think we're going to be able to do this with all these new therapies? Or is there always going to be a group of patients who don't see that benefit? Or just there's something different about them?

Dr. Saggar:
Yeah, I think we were all sort of shocked or sort of, you know, surprised, perhaps by looking at the data of what happens to patients when we start treating them, our incident cases that go through therapy. You know, it turns out that, you know, there's a few manuscripts looking at this, and, you know, maybe over 50% of patients actually are not able to achieve low-risk status, let's say, with upfront combination therapy. And while I think that was - to me, that was a little surprising, I didn't expect to see that number that high, but it's a gross reality. And I think, the survival, that we were hoping to sort of improve over time with the therapies we have, it's not very clear that we've, you know, made a dent in that necessarily. And so this clearly is still a very mortal disease, with median survivals, on depending on who you read, you know, 7 to 9 years on the best of therapies. And with that in mind, you know, we have a lot of work to do, I think. So I do think it's feasible to get people to low-risk status.

Now with the, with the group of drugs in front of us, the question is, how do we actually put those to work? And what do we start? How do we use these drugs to the best - you know, in the best manner, to get the best results? The best results would be to achieve low-risk status in the majority of patients, and ideally, to improve survival. So I do think it's – I think it's exciting times because we have a lot of drugs in the pipeline and a lot of the drugs that are even already available. And as you know, we still struggle with prostacyclin pathways. Should, you know - should we bring it in earlier? Or should we bring it - should we use it as a third-line agent? You know, when exactly do we do this? We know what to do for intermediate high-risk and high-risk, but maybe we should be introducing the prostacyclin earlier as the French have suggested. So, yeah, there's a lot to discuss.

Dr. Rajagopal:

Thank you for this discussion. I learned a lot here today. And thank you for joining us.

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