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Link Between Parenchymal Lung Disease and PH

Announcer:
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Dr. Saggar:
So I'm just going to take 20 minutes to talk about the link. There's so much I would love to talk about here, and I'm sorry if it doesn't cover everything you want, but we just have to kind of get through some basic things here. But I would have you think about the case that Houda just present it in the setting of, if you didn't know what that CAT scan showed and you saw the hemodynamics and the symptoms, etc, you would probably be offering or considering PH-directed therapy. And the question is, you know, what is it about having lung disease that gives us pause? And should we be pausing at all? And when should we pause? And when should we not pause? That's really the key question in front of us.

So just to make sure everyone knows what we're talking about here, we're talking about Group 3 PH, there at the top with the arrow, we're talking about PH associated with enough lung disease that you're going to get worried that the lungs are playing a role as well. And by that, I mean that in most PAH studies that have been done to date, mild lung disease has been included, mild fibrosis was always included as part of the inclusion criteria. So the idea that any fibrosis was never included in our standard Group 1 PH studies is just simply not true. So we're really talking about moderate to severe fibrosis, and how do we really define that, you know, or emphysema for that matter, or CPFE? That's kind of what we'll talk - get a little bit into.

So these are discussion points. You know, a little bit about a background of PH complicating COPD and pulmonary fibrosis, and really how should we target Group 3 PH? A little look at the vascular pathology, some gas exchange stuff, looking at circulatory limitation. That's really what you're interested in, right? You're really interested in treating the patients who are circulatorily limited, not ventilatorily limited. And a clinical phenotype perhaps will suggest one for where PAH targeted therapy may work in patients who - and I'm going to focus more on pulmonary fibrosis, and I'll tell you why in the next slide.

It's because COPD and pulmonary hypertension is a very interesting - and I would say, if you're looking at pure COPD, not CPFE, combined pulmonary fibrosis and emphysema, COPD and the PH associated with that is very slow to evolve, and rarely is severe. So the slow natural history of this, I have had the references there for you, but you can see it moves very, very slowly over a 5- or 7-year period in its natural history. And if you look at the National Emphysema Treatment Trial, there was very only mild to moderate PH and severe COPD; these are people who had FEV1's of less than 35%. And in fact, only 5% of that cohort actually had mean PA pressures of 35 or higher. So severe pulmonary hypertension in the setting of severe emphysema is uncommon. And that's, I think, the main point. So I'm going to leave COPD out of this for a moment and also leave CPFE out of this, because I think the heterogeneity there is complicated and just now being unraveled.

So just kind of go into interstitial lung disease, which is no - which is also extremely heterogeneous. I think, probably more so perhaps, than COPD as we know it today. So the etiology of interstitial lung disease or pulmonary fibrosis, it's natural history for each one, the risk

for pulmonary hypertension in each of those categories, and the subsequent natural history of that PH are all completely different for each of the type of interstitial lung diseases that we're talking about. You guys have probably seen this picture before, diffuse parenchymal lung disease. Again, we determine this by multidisciplinary discussion, right? You have a pulmonologist, a pathologist, a radiologist at a lot of the academic institutions. You have the known causes there on your left, right? Collagen vascular diseases, drugs like amiodarone, you have the interstitial - the idiopathic interstitial pneumonia is where IPF is the most common in the middle there. You have granulomatous lung diseases, such as sarcoidosis. And you have other sort of rare forms like LAM and eosinophilic granuloma. So the biggest one we're seeing is IPF, and then you have all the other idiopathic interstitial pneumonias. But complicating all this is you have interstitial pneumonia with autoimmune features, right? So this is now a defined entity. This is the idea of people who have ILD who don't have an overt rheumatologic disease, but they have features of autoimmune disease. So this is characterized now and there's criteria for this. You also have the concept that most of the time collagen vascular diseases have been excluded in the PAH studies that we've done except for the more recent INCREASE study, and also sarcoidosis is excluded. And on top of all that, you have CPFE. So you have fibrosis and, you know, you have some form of emphysema, all different kinds, paraseptal, central lobular, mild, moderate, severe, complicating all the interstitial lung diseases that we see. So very heterogeneous and difficult to sort of quantify.

If you can predict the PH from the imaging here, you can imagine it looked like just the case that Houda presented, bad fibrosis, actually horrible fibrosis, actually, Houda's case had horrible fibrosis too. If you look at this, you know, CAT scan, you can't predict what the PA pressure is. And this person ended up having normal pulmonary pressures at the time of lung transplantation with an FVC of 37%. If you looked at Houda's case, and I asked you, 'Oh, what do you think this patient's PA pressures are?', I think you'd have a hard time sort of knowing what it was just looking at the imaging; the same way you'd have a hard time knowing if someone with bad fibrosis is on 2 liters of oxygen or 8 liters of oxygen just by looking at a CAT scan.

So here are some of the baseline factors that influence survival, the diffusing capacity, the saturation at rest and on exertion, as you might imagine, are factors that definitely contribute to our understanding of the survival of patients who have IPF. And we're focusing on IPF because that's where most of the data is.

So is PH a rational target for therapy in a setting of fibrosis? Well, there's no question that PH, as Rich brought up, Dr. Channick brought up earlier, you know, pulmonary hypertension, you know, with a PVR of, you know, greater than 2 may be associated with mortality, but whether it's the cause of mortality is a whole other, you know, discussion. So there's no question that pulmonary hypertension complicating any parenchymal lung disease, whether you're talking about sarcoid, any type of fibrosis, any type of emphysema, any lung disease you can think of, the correlate with PH is always going to have a worst survival, worse prognosis? But the question is, should we be targeting that for therapy? And you can see here we have right heart cath data, this is always in the setting of a lung transplant - possible, you know, a patient has been prepared for lung transplant; otherwise, we don't have homogenous right heart cath data in these patients, right? So there's no question that if you look at all this, the PH is a risk factor for death and mortality in patients with any type of fibrosis.

At the bottom there, you can see there's a lot of studies recently looking at cutoffs for pulmonary vascular resistance, not using mean PA pressure much anymore, but looking at PVR as a cutoff. So whether it's 6.23, or 6 Wood units or 8 Wood units, they're more recent papers with 5 Wood units, basically, when you get up to 5 to 8, you're talking about an increased risk of death, which is within that cohort of advanced pulmonary fibrosis cases.

And that's why pulmonary retention is considered a reason to transplant someone or certainly a reason to refer someone for transplant. So the current guidelines for lung transplant for IPF are like if you have histological or radiographic evidence of UIP, and one or more of the following: diffusing capacity that's less than 40%, 35%, somewhere in that area, a decline in FVC of 10% or more over a 6-month period, any type of pulmonary hypertension, and a saturation that's less than or equal to 88, basically exertional desaturation. And other types of pulmonary fibrosis in the guidelines share similar recommendations.

So just changing gears to the vascular pathology. So this is, just in a nutshell, you would think, and we know about PAH affecting small arterioles in fibrosis, whether you look at scleroderma, ILD, or whether you look at idiopathic pulmonary fibrosis, any form of fibrosis, and this is of course, mostly based on explanted lung tissue, the pathology is homogenous in the areas of dense fibrosis. So basically, you can't really see much in those areas in terms of what's veins, what's arteries, what's going on. But really where you see the differences is actually in the more preserved, architecturally preserved areas of lung, there's a pretty significant venopathy. And in many of those cases, there's capillary duplication or what we call, you know, PCH, a pulmonary capillary hemangiomatosis type of duplication of the endothelial cells. So you really see a pan-vasculopathy, the arteries, the veins, and the capillaries are affected. In this particular study, there was no association between venular occlusion and the mean PA pressure, but the point is, there's a pan-vasculopathy, which is very different from our Group 1 PAH patients, and gives people pause about treating these patients because they see it pathologically as a PVOD/PCH-like spectrum of disease.

So this pan-vasculopathy is similar to the what we see in scleroderma PAH without fibrosis. You actually often see a pan-vasculopathy in our scleroderma patients, you might be shocked to hear this, in patients who have PAH only, no ILD or minimal ILD. But it is readily distinguishable from Group 1 PAH. In the interest of time, I'll just move forward here.

So gas exchange, this is a complicated topic and really is fun to think about. But I'll leave you with some general principles. So if you look at patients who have pulmonary fibrosis, and then - this is permanent fibrosis, no pulmonary hypertension, okay, and compare them and just look at their - what they do at rest and what they do on exertion, right? Their gas exchange, and compare them to PAH patients, Group 1 PAH patients, right? Let's look at what these patients do at rest and on exertion. And again, without getting too much into the details, the point is that both of these conditions have fairly preserved V/Q spectrums. If you look at their ventilation perfusion, you know, distribution in terms of how abnormal it is, they're fairly preserved at rest. And during exercise, you can imagine the pulmonary fibrosis patient has a shift in the amount of diffusion abnormality. And the PAH patient has also a shift where you have more of a hypoxemia or a gas exchange issue really driven by the low mixed venous oxygen that comes around due to the relatively poor cardiac output, at least this is the theory. And that hypoxemia gets augmented for a given alveolar PAO2, (so P, big A, O2), which all which really augments the vulnerability of the oxygen exchange issue to diffusion. And this is work by Peter Wagner, and if you go back to sort of, you know, the physiology principles here. So you can imagine if you take a fibrosis patient and mix it with pulmonary hypertension, and you combine the two phenotypes, you're going to get a very perturbed situation, which is almost unpredictable, depending on where the fibrosis is and how it interacts with the pulmonary vascular changes. There's also some data showing that hypoxic vasoconstriction may be attenuated. In other words, it doesn't work in patients who have worsening PH with fibrosis. That's also interesting. And there's some great papers on this done back in the 70s, and 80s.

So one of the fears that we have is making people oxygenate worse, worsening their shunt, making them V/Q, making their V/Q spectrum bad, right? Worse. This has been what's been propagated in the literature. And it's really based on acute administration studies, looking at something called the multiple inert gas elimination technique. This is a technique that was used to sort of look at the V/Q spectrum, how the ventilation and perfusion match with each other. It's a study tool. It's not a - it's a research tool.

But the bottom line is the Germans, Dr. Ghofrani, published this article back in the early 2000s, looking at IPF patients and gave them epoprostenol, compared it to a single dose of sildenafil, and then compare that to inhaled nitric oxide. And this was all acute administration. So these were fibrosis patients who had significant pulmonary hypertension, and it was significant. And what they found was that there was an increased shunt when they gave epoprostenol; a very significant increase in shunt, about a 16% increase in the shunt fraction. Interestingly enough, this led to the concept of the possibility of hypoxemia; and in that case, we should really not be using parenteral prostacyclins in this population, hence the push to give inhaled prostacyclins, etc. But really, the theory was that, hey, you treating these patients and with any pH drug has the capacity to cause gas exchange abnormalities. That's where this came from. I just want to make sure you understand, in this acute administration study, they actually gave epo in very, very rapidly increasing doses; they started at 2 ng/kg per minute and went up every 15 minutes by 2. So it was a rapid up-titration to the point where they either had hypotension, thoracic oppression, nausea, vomiting, etc. So they went to symptom limitation. So that probably has something to do with the physiology they produced.

But what we've really seen in clinical trials, whether it's pulmonary fibrosis without PH where we're using a PH drug as an antifibrotic, or whether using - looking at pulmonary fibrosis with established pulmonary hypertension in general, and the paO2's, when they were checked, or the saturations of oxygen, are not affected or only marginally affected in the chronic administration of PH drugs in this group of patients. And that's the bottom line. We've actually never seen the hypoxemia that everyone's worried about in chronic administration studies. And there's a whole list of studies there you can see on the left, those include drugs like bosentan ambrisentan, macitentan, sildenafil, riociguat, treprostinil, they're all there. So all these studies, all these drugs have been looked at. Now, whether they work or not, that's a whole other story. The whole point is gas exchange is not clearly affected by these drugs.

So shifting gears to this concept of the Group 3 PH circulatory limitation, right, so if you have a patient who has fibrosis, COPD, some type of parenchymal lung disease, and they have really bad PH, you're asking yourself, is this patient limited by their ventilatory limitation or are they limited by their PH, i.e., circulatory limitation? And that's really the question that's in front of you. Right? So how do you tease that out? Well, this is, of course, this all goes back to CPET and cardiopulmonary exercise testing and understanding what these patients do on exertion, right? So in the clinic, we try to see if they're hypoxemic when they walk around, we try to see how symptomatic they are, we try to get a feel for what's going on. But the bottom line is you really want to figure out whether they're ventilatorily limited here, or whether they're circulatorily limited. And that's really the name of the game. And it's obviously easier said than done. But the point is there's some data on this.

The circulatory limitation, which we see in idiopathic PAH is a feature of pulmonary hypertension complicating pulmonary fibrosis. But it's got to be enough pulmonary hypertension, right? It can't be just the mild stuff. Right? How much pulmonary hypertension do you need

before you are limited by the pulmonary hypertension, i.e., circulatory limitation, as opposed to the ventilatory limitation. And just to cut to the chase here at the bottom, you can see there that there's a strong correlation with ventilatory equivalent for CO2, right, at the anaerobic threshold. And then the people have tried to look at slope cutoffs for, you know, percent predicted, in terms of trying to understand how CPET sort of helps us determine if someone is circulatorily limited. The caveat to all this is that the people that have been studied with CPET to date who have parenchymal lung disease, or those who are not very hypoxic, because the people we've studied on the CPET machine are not the typical patients that we're seeing in real life, right? They tend to be on quite a bit of oxygen in real life. And to do a CPET, you have to do it essentially on room air, most of the time, but you can supplement some low level of oxygen, generally speaking, although apparently there are now, you know, there's hardware that we can use to actually provide people enough oxygen, or lots of oxygen let's say, and actually do a CPET. And we're just starting to get into that at UCLA. But there's a whole literature here we need to make for these patients who are actually, in real life, have significant pulmonary fibrosis and significant pulmonary hypertension because those are the people that actually tend to be very hypoxic and the ones we actually haven't even studied yet. So more to come on that.

So what can we learn from the Group 3 PH experience in the world today? Well, with age, these patients are generally in their 60s, okay? They're very hemodynamically perturbed, you can see their mean PA pressures, they're 41, 37, 47 etc. They look just like your typical PAH patient. Not as bad, but pretty much like 80% of the bad hemodynamics. They have forced vital capacity that's usually in the 60s. They have variable definitions, right? We haven't decided how to define the fibrosis yet. Should it be based on a PFT parameter? Should it be based on the CT scan? Should it be based on a combination thereof? Every registry has used a different approach. But what we do know for all these people is that the survival is awful. Whether you're looking at ILD all-comers, CTD, ILD, etc, you're talking about the worst survival out of all the WHO Group PH populations that we see; Group 3 has the worst survival.

And the last point I will get into here is the clinical phenotype. So what should we target? So who should we be treating? Again, this is a work in progress, you guys are aware of the INCREASE study, but we did a study here looking at parenteral treprostinil in patients who were being prepared for lung transplant. These patients had mean PA pressures greater than 35. They had pulmonary vascular resistances of greater than 3. Most of them were on the order of over 6 Wood units. And they had baseline RV dysfunction on their echocardiogram. This was a positive study in the sense that there was no worsening of hypoxemia, all of them improved significantly with their hemodynamics, and they all improved on the SF-36 on the physical component, they all improved RV function by echo which I'll show you in a second, they all improved 6-minute walk distance, and they all improved brain natriuretic peptides. So there was a homogenous response to this parenteral delivery of a prostacyclin.

So you guys may remember the sildenafil IPF study published in the *New England Journal* many years ago to look at sildenafil for IPF, and likely PH. They didn't actually cap those patients. They all had diffusing capacities that were low. They were proposed to likely have PH. It was a negative study. But what they found was that patients with RV - when they went back and looked at a post-hoc analysis, the patients with RV systolic dysfunction on the echo who got sildenafil had a preserved or a better 6-minute walk than those, and quality of life, than those compared to placebo. Okay? So that was a piece of information.

And then this is our study, the treprostinil study I just mentioned, this was blindly reviewed echocardiograms pre and post by Paul Forfia, who was at Temple at the time, and he looked at RV end diastolic areas, systolic eccentricity index, and TAPSE for all the echocardiograms for those 15 patients and there were statistically significant improvements in all those variables. So maybe RV dysfunction is important when we're considering - on an echo it may be important to who will respond to therapy and who won't.

I'm not going to spend too much time on the inhaled treprostinil study, but this is now an FDA approved medication. It's the only FDA approved medication for Group 3 PH. And I'm going to step aside here. The one thing about the study which you have to remember is that it included patients who had connective tissue disease with ILD. Before that, no one had ever included this group of patients in the fibrosis population that was being studied. It was a quarter of the cohort, and they had a very brilliant response. So it was IPF that had a nice response. It was CTD, connective tissue disease, most of which are systemic sclerosis and ILD that had a nice response. The last group was CPFE, combined pulmonary fibrosis and emphysema, they had more of a modest response.

In the interest of time, I'll tell you that we've also looked at inhaled nitric oxide, looking at it ambulatory in an outpatient setting in IPF and echocardiographic PH. Again, we're running out of time, but I'll just tell you here that this study, the phase 3 study, just read out recently for ambulatory inhaled nitric oxide in pulmonary fibrosis with presumed PH based on probability on echocardiography. This was a negative phase 3 study was just read out in the third quarter of 2023. Okay, so that's important to realize. And it's also important to realize that sildenafil has been looked at either as monotherapy in addition to antifibrotic therapy, for fibrosis and PH, all these trials have been negative.

I'll leave you with this. So if you can think about the competing risks for morbidity and mortality. And you can see here on the left of your screen, right, ILD is the primary determinant of outcomes at the top there, right, so you can see over time on the X axis. And then you

can see at some point someone develops PH. And then at some point, maybe PH, you know, becomes the primary determinant of the outcome. You can see on the Y axis, there's decreasing FVC, diffusing capacity, 6-minute walk distance, hypoxemia. On the axis on the right, you can see there's increasing mean PA pressure, increasing PVR, decreasing RV function. And you can see that when you - there's also with ILD, we have these unanticipated insults, right. We have people who acutely exacerbate, the natural history is, you know, variable, there's infections, there's comorbidities, there's age, and that can take a patient out, right? My point here was that when you design a clinical trial - when you design a clinical trial here, what you want is you want your clinical course to be very stable, right? If you introduce a PH drug here, you don't want the clinical course of the patient to be one of a temporal decline in their pulmonary fibrosis. Otherwise, you'd be competing with the underlying condition that they have. You want a stable pulmonary fibrosis, you know, course. And you see that particularly in CTD-ILD. CTD-ILD tends to be a very much more stable course, long-term prognosis is much better than IPF. So in general, when we study fibrosis, and we were trying to teach - to use a PH to treat the PH that they develop, in clinical trials, we really want to use a pulmonary fibrosis phenotype, which is much more stable and much more predictable. And that's why I think CTD-ILD lends itself to that.

So with that, I'm going to stop and just go through conclusions. It's difficult to clinically predict PH complicating pulmonary fibrosis, there's a ton of heterogeneity in the types of fibrosis we see and how they act naturally and how they interact with PH. The pathology is very different from Group 1 PAH. And while there may be V/Q mismatch acutely, when we administer drugs like parenteral prostacyclin, hypoxemia and chronic administration in PH-targeted therapies and pulmonary fibrosis is not a thing. It's not predictable hypoxemia.

Inhaled treprostinil is the only FDA approved medication for Group 3 PH. The appropriate phenotype to treat, in my opinion, and likely respond to PH-targeted therapy is one that's circulatorily limited, and may include advanced pulmonary hemodynamics, echocardiographic evidence for RV dysfunction, and a baseline CPET if we can get to understanding these people a little bit better when they're hypoxemic. Similar to what we see in Group 1 PAH. We've looked at this with parenteral treprostinil and had some nice responses, both in regular all-comers with fibrosis as well as scleroderma, systemic sclerosis associated pulmonary fibrosis.

The future clinical trial design should include the advanced PH phenotype, measures of RV dysfunction, I think we have to focus more on echo pre and post since we do it all the time, and we shouldn't really have a stable pulmonary fibrosis phenotype that we study. We should generally avoid PH therapy in older patients with IPF and what a lot of whom have mild what we call reactive PH. They don't have RV dysfunction, they're not circulatorily limited. Failures in future clinical studies in pulmonary fibrosis with PH should really be due to the fact that we're using the wrong drug and should stop the - and should not be due to improper or inadequate clinical design.

So with that, I'll stop.

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