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Addressing the Burden of PH-ILD: Early Recognition, Evidence-Based Management, and Care Coordination

Announcer:
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Dr. Nathan:
Hello, everyone, and welcome to this talk. We're going to be talking about addressing the burden of PH-ILD, early recognition, evidence-based management, and care coordination. And this talk is brought to you by the ATS in conjunction with the France Foundation. I'm Dr. Steven Nathan. I'm the Medical Director of the Advanced Lung Disease and Lung Transplant Program at Inova Fairfax Hospital in Falls Church, Virginia, and I'm joined today by my colleague, Dr. Sandeep Sahay.

Dr. Sahay:
Hello, everyone. I'm Sandeep Sahay. I'm a pulmonologist at Houston Methodist Hospital, Houston, Texas. I lead the PH program here, and I'm excited to be here with my friend and colleague Dr. Nathan for this program.

Today, our learning objectives will be to summarize the increasing clinical burden of PH in ILD and associated disease progression, including decreased functional capacity, impaired patient health-related quality of life, and increased mortality. We will also try to identify approaches for improving the early diagnosis of PH and ILD, including proactive screening and symptom assessment and differentiation. Lastly, we will also evaluate the latest clinical data and practice guidelines to support evidence-based decision-making in the treatment of PH-ILD.

So, roadmap for today is the increased clinical burden for PH-ILD. We will learn the impact on functional capacity, quality of life, and mortality. Then we will talk about early diagnosis of PH-ILD and the importance of proactive screening. Then we will discuss the clinical data and practice guidelines for evidence-based treatment approaches in PH-ILD. And then, lastly, we will have question and answer and recap and post-test evaluation. Keep an eye out for the brain icon, which identifies the content related to the pre- and post-test questions.

So let's start with the patient's journey. Meet our patient Javier, who is a 50-year-old Hispanic male presented with chronic cough and worsening dyspnea. We performed a high-resolution CT scan on him and demonstrated the evidence of interstitial lung disease, which was categorized as intermediate UIP pattern. He has no history of chest pain, palpitations, or syncope. Is it too early to suspect pulmonary hypertension in this gentleman? Or do we need to do further screening or further evaluation, and why it is important to evaluate pulmonary hypertension in this gentleman?

So we will start with some background review of literature on this topic. With the increased clinical burden of pulmonary hypertension and ILD, we'll focus on the impact on functional capacity, quality of life, and mortality.

Dr. Nathan:
Before we talk more about PH complicating ILD, specifically precapillary pulmonary hypertension, and the definition has changed over

time. If one goes back to pre-2018 and the Fifth World Symposium on Pulmonary Hypertension, we used to define it by a mean pulmonary artery pressure of 25 mm or more, accompanied by a PVR, pulmonary vascular resistance, of 3 or more Wood units, and in association with a wedge pressure of less than or equal to 15 mmHg to rule out the presence of group 2 pulmonary hypertension, any element of heart failure.

The wedge pressure has been about the only thing that hasn't changed because the Sixth World Symposium then lowered the threshold of the mean pulmonary artery pressure from greater than or equal to 25 to greater than 20 mmHg, with the PVR remaining the same.

That was in effect until the more recent Seventh World Symposium, where the PVR was also changed to greater than 2 Wood units. So the current definition of precapillary pulmonary hypertension includes an MPAP, mean pulmonary artery pressure, of 20 mm or more, a PVR of greater than 2 Wood units and a wedge pressure of less than or equal to 15 mmHg.

If one looks at the prevalence of pulmonary hypertension associated with interstitial lung disease, it really depends when in the disease course one looks for it. If you look at patients early on who have mild to moderate interstitial lung disease, then it's estimated at around 8 to 15% By the time patients require transplant, it's closer to 29 to 46%, and by the time they actually transplanted, it's as high as 86%. Now, I have to caveat this by saying that all of this data is based on IPF, but it probably is applicable to other forms of fibrosing interstitial lung disease. In addition, this data comes from our older definition of pulmonary hypertension with a mean pulmonary artery pressure of 25 or more.

Dr. Sahay:
So, based on what we learned so far, it appears that PH prevalence, the correct option is option A: PH prevalence rises from 10 to 15% at diagnosis to 85% at lung transplantation. And my friend Dr. Nathan already explained it.

Dr. Nathan?

Dr. Nathan:
If one looks at the distribution of mean pulmonary artery pressures in patients with IPF, one can see that most of these patients are centered around 20 to 25, 25 to 30. From one study, 19% of the population with IPF had mean pulmonary artery pressures greater than or equal to 25 mmHg, while 30% of the population had a mean pulmonary artery pressure of between 20 and 25. In another study, 32% of patients with IPF had a mean pulmonary artery pressure of more than 25 mmHg.

If one looks at the impact of the presence of pulmonary hypertension in interstitial lung disease, it has a significant impact on patients' functional ability and exercisability. It's been shown, for example, that patients who do 6-minute walks and have pulmonary hypertension, walk significantly less and they desaturate more. So this is actually a very important point in terms of one of the clues to the presence of pulmonary hypertension. We should do 6-minute walks in our ILD patients. The more oxygen they need, the more they desaturate, and the shorter the distance, the more likely it is that they will have underlying pulmonary hypertension.

In terms of the economic burden of PH-ILD, patients who have interstitial lung disease complicated by pulmonary hypertension are more likely to be hospitalized. From one particular study, the rate of hospitalization for those without pulmonary hypertension was just under 30%, while if they had pulmonary hypertension, it was just under 60%. So that's a twofold increased risk of hospitalization.

Similarly, for ICU use, the number of patients who required ICU care if they didn't have pulmonary hypertension was 6.6%, and if they did have pulmonary hypertension, it was 17.2% So that's almost a threefold increased likelihood of needing ICU care if you have PH-ILD versus ILD alone.

There is an association between pulmonary hypertension and acute exacerbations of the interstitial lung disease. This is interesting because the same has been shown in other parenchymal lung diseases such as cystic fibrosis as well as COPD. Acute exacerbations are associated with very high mortality, and certainly patients who have PH just by virtue of the PH are at higher risk of mortality. And if they have an acute exacerbation, then their mortality risk is even further increased.

If one looks at the survival of patients with group 3 pulmonary hypertension, and PH-ILD resides under group 3 pulmonary hypertension, it carries a worse prognosis than any of the other groups, including group 1 PAH, group 4 pulmonary hypertension, group 5 pulmonary hypertension, and group 2 pulmonary hypertension as well. If one looks at the different causes of group 3 pulmonary hypertension, then it's the fibrotic disorders, IPF being the prototypical disease, that carry the worst prognosis. It's been estimated, for example, that if one looks at the median survival of these patients, it's around 18 months. The 3-year survival is around 30% once you have pulmonary hypertension or complicating fibrosing interstitial lung disease.

There was a study from the Spanish PH registry looking at various grades of pulmonary hypertension, and what was very interesting about the study is that no matter if patients had borderline pulmonary hypertension, mild to moderate pulmonary hypertension, or severe pulmonary hypertension, their outcomes looked very much the same. Specifically, if one looks at the median survival, once again, it's

around 15 months. And I think a concept that needs to be disassociated is the notion of mild pulmonary hypertension is equivalent to mild disease because mild pulmonary hypertension carries the same poorer prognostic ramifications as severe pulmonary hypertension. Even mild pulmonary hypertension in the context of ILD should be called severe disease because it carries a very poor prognosis.

This has been verified in a number of other studies, including studies out of Japan. There was a article in *Thorax* in 2024 looking at different cut points in the mean pulmonary artery pressure associated with different cut points in the PVR. What they showed in this study in particular was that the PVR was associated with survival, whereas the MPAP by itself was not necessarily associated with survival.

I think the most important point, if one thinks about the vasculature and all these different hemodynamic thresholds, is that it's a continuum. The higher the pressures, the higher the PVR, the greater the likelihood that patients are going to have downstream morbidity and mortality consequences from this.

Dr. Sahay:
So let's move on to the next topic, which is early diagnosis of pulmonary hypertension in interstitial lung disease and the importance of proactive screening.

Let's go back to our case, our patient Javier, who was a 50-year-old Hispanic male who initially presented with chronic cough and worsening dyspnea, no history of chest pain, palpitations, or syncope. We did a CT scan, which showed evidence of indeterminate UIP pattern ILD. We performed a VATS biopsy, which, based on the multidisciplinary team meeting, the consensus was a diagnosis of cellular and fibrosing NSIP, which is non-specific interstitial pneumonia with the components of organizing pneumonia and features of respiratory bronchiolitis. He had mild rash on face and neck and mechanic's hand. And an auto antibody testing panel showed ANA positive at 1:80, and also PL7 antibody was positive. He used home oxygen at 2 L at rest and 6 L on exertion.

I'll pass it on to Dr. Nathan.

Dr. Nathan:
Thank you, Sandeep. So the problem with PH complicating interstitial lung disease is it kind of lurks in the background, and one thing that's common to both interstitial lung disease and pulmonary hypertension is they share common symptomatology, mostly shortness of breath. And so when patients with ILD have shortness of breath and it becomes progressive, how does one know when the progression of the shortness of breath is due to progression of the underlying interstitial lung disease versus the development of intercurrent pulmonary hypertension?

So there are ways at getting at this in terms of screening for pulmonary hypertension in patients with interstitial lung disease, and I'll go through the clues to the presence of pulmonary hypertension in a sequential fashion. So obviously, a history and physical exam are foremost and most important. If patients are getting more short of breath, certainly if they have any dizziness or syncope, that's usually late pulmonary hypertension. That would be very unusual in the context of interstitial lung disease. Signs and symptoms of right heart failure can be very subtle in the context of mild PH. One thing I always listen for is an increased P2 heart sound. One shouldn't wait for leg swelling, peripheral edema, jugular venous distension. This is usually going to be more moderate to severe pulmonary hypertension. So patients might not have any physical signs of underlying pulmonary hypertension.

But there's a lot of testing we get in our daily routine management of patients with interstitial lung disease that can provide clues to the presence of pulmonary hypertension. We get PFTs in our patients. Now, there's a very poor correlation between FVC and pulmonary hypertension, but there is a correlation with the DL, the DLCO, and pulmonary hypertension. So, the lower the DL, the more likely it is that the patients might have pulmonary hypertension. There have been various cut points that have been proposed. A DL less than 40%, for example, but certainly you can have pulmonary hypertension even with DLs greater than 40%. We oftentimes will look at the FPC to DLCO percent ratio. Once again, this is a continuum, but a cut point that has been touted in the literature is a ratio greater than 1.6. So, just to give an example, if someone has an FPC of 80% of predicted and a DLC of 40% of predicted, that would give one a ratio of 2, and that's the situation where I'd be suspicious that there's pulmonary vascular involvement.

We get 6-minute walk tests in all of our patients with interstitial lung disease. I alluded to this earlier, but there are a lot of clues that can emanate from the 6-minute walk test. The more oxygen they need, the more they desaturate, the more short of breath they become, the shorter the distance, all are clues to the presence of underlying pulmonary hypertension. And then one thing we also measure is pulse rate recovery. The lower the pulse rate recovery during rest after the 6-minute walk, the more likely it is that there's pulmonary hypertension.

We get CT scans in all of our patients to assess the parenchyma, but I don't only look at the parenchyma for UIP versus probable UIP versus indeterminate; I always look at the mediastinum and look at that pulmonary artery segment. If the pulmonary artery segment at its

bifurcation is greater in its diameter than the ascending aorta, then that's also a clue and might be one of our best non-invasive clues to the presence of pulmonary hypertension.

Of course, then we have our biomarkers in the BMP and NT-proBNP, but these are also relatively insensitive. There was a paper looking at this where the sensitivity of the NT-proBNP for underlying pulmonary hypertension in interstitial lung disease was only around 30%.

When we get all these tests, we develop an index of suspicion as to whether or not patients might have pulmonary hypertension or not, and the next step and probably best screening tool is echo. We'll get an echo, and then we'll further risk stratify the patients as high likelihood, intermediate, or low likelihood of pulmonary hypertension, and then a decision has to be made as to whether or not to proceed with the right heart catheterization.

Dr. Sahay:
So, with what we learned so far, and with the literature review which Dr. Nathan went over and he shared his expertise, it appears that proceeding to the right heart catheterization to evaluate for pulmonary hypertension is the right answer. Option number B. Although in the case I presented and the data which Dr. Nathan discussed that our patient had some of the markers to indicate towards the probability of pulmonary hypertension, but at the same time we know the echocardiography is not a very good screening tool in the setting of interstitial lung disease. So proceeding with the right heart cath in a patient with intermediate to high-risk probability for pulmonary hypertension appears a right option.

Dr. Nathan, do you have any other comments on this?

Dr. Nathan:
Yeah, I think that's a good point that you made there, Sandeep. Even though many folks regard echo as our best screening tool, it does have its flaws with regards to interstitial lung disease in particular. And I think we get echoes, and it's a good screening tool. But the biggest danger of echo is that it can mislead you away from getting a right heart cat. So the point that you made, I think, is well worth reiterating. If your clinical index or suspicion is high enough, it almost doesn't matter what the echo shows, one should still proceed with the right heart cath.

Dr. Sandeep Sahay:
Okay, so with that, we're back to our patient, Javier. So let's take a look at the PFD. We have a FVC of 2.44, which is 48% of predicted FEV1 of 2.07, 51% of predicted, and FEV1 by FVC ratio is well preserved at 85. The DLCO, however, is 11.29, which is 38% predicted. So if we go back to what Steve showed earlier, that clearly this gentleman's DLCO is below that absolute cutoff of 40, and probably increasing probability of pulmonary hypertension.

So we collected more information on our gentleman. He performed a walk test and he walked to 74 meters, which is not great. Before starting the walk, his saturation was 98%, but he dropped down to 79%. So you can see that profound desaturation on exertion. And as Dr. Nathan highlighted, the rest pulse was 96, the max pulse 130, and pulse rate recovery of 24, which is actually delayed. So and then, but also another interesting thing here is if we look at the NT-proBNP, it's 51, which is well within the normal range. So we'll be discussing a little bit more about it. But definitely on the walk test, there were some indicators.

I'll pass it on to Dr. Nathan again to continue with his journey on further testing.

Dr. Nathan:
So another important point that I made earlier is looking at that pulmonary artery segment in relation to the aorta, and if it's bigger than the aorta, then one should be suspicious of underlying pulmonary hypertension.

The CT of interstitial lung disease, and this is Javier's CT by description, shows subpleural reticulation that can be seen throughout the lungs. Really, there's also diffuse fibrotic changes and traction bronchiectasis at the bases within the areas of fibrosis. There does appear to be a rim of subpleural sparing. So, this would look like an NSRP type pattern because of that rim of subpleural sparing, it was called, if I recall correctly, indeterminate or probable UIP pattern. I can see how this can be called a probable UIP pattern as well because of the reticulation and attraction bronchiectasis. But we know what he had because he ultimately underwent a VATS biopsy. In his particular case, his pulmonary artery was significantly larger than his ascending aorta.

And I'll hand it back to Sandeep to summarize what we have so far.

Dr. Sahay:
Thank you, Steve. So let's go back and put all together for our patient. So he was a 50-year-old Hispanic male with chronic cough, with worsening dyspnea, and again, he did not have any history of chest pain, palpitations, or syncope. We did a CAT scan on him, which showed ILD pattern, ILD with indeterminate UIP pattern. We also had the biopsy results on him, and in our multidisciplinary discussion,

we found cellular and fibrosing NSIP organizing pneumonia and respiratory bronchiolitis. Then we have a mild rash on clinical examination. The gentleman had mild rash on face and neck and mechanic's hand. ANA was 1:280. PL7 antibody was positive. Home oxygen was at 2 L and 6 L at exertion. And so, putting everything together, we made a diagnosis of dermatomyositis in him.

Okay, so based on the information we learned in this gentleman, I actually, my personal opinion is that I have a pretty high suspicion for pulmonary hypertension in this gentleman. I mean, not because I'm a PH doctor, but I do feel that there are a lot of pointers here in his history. I'll ask Dr. Nathan also to weigh in his opinion on what he thinks.

Dr. Nathan:
Now, Sandeep, I do agree with you. I was impressed by the size of his pulmonary artery segment, number one, and then he had profound desaturation on his walk test and got significantly short of breath. I found that quite impressive as well. His DL was just a little bit below 40, but I think there was enough information there to cause a high index of suspicion.

I just want to make another point around this particular case because it can happen quite often that patients can have connective tissue diseases that just manifest later on. At the time he had the surgical lung biopsy, you can understand that he hadn't manifest yet the mechanic's hand or the positive autoimmune screen. So his diagnosis evolved over time, in case folks are wondering why someone with dermatomyositis underwent a lung biopsy, so that's the reason for this in terms of his sequential progression.

Dr. Sahay:
And to that, I just wanted to add that we also noticed that his NT-proBNP was normal, but as you can see, the clinical evaluation dilated pulmonary artery, profound desaturation, lower DLCO, these are sufficient enough indicators, as pointed by Dr. Nathan, for proceeding with a right heart catheterization in this gentleman. So our answer to that is obtain an echocardiogram and a right heart cath, option E.

Dr. Nathan:
While echo is a good screening tool in patients with interstitial lung disease for the presence of pulmonary hypertension, it can be inaccurate. It can both overestimate as well as underestimate what the true pressures are. So, from one study, it overestimated the RVSP in 48% of the cases, and it underestimated the RVSP in another 12% of cases, it was only accurate in about 40% of the cases. And when, from this particular study, accuracy was defined by MPA peak by a pressure that was either 10 mm above or below what the true pressure was. So, in other words, if the RVSP was 60, and the true right ventricular systolic pressure was 40, then that would be a difference of 20, and that would be inaccurate. If it was 60 versus 55, that's within the 10 mmHg threshold; that would have been regarded as accurate.

Dr. Sahay:
So let's go back to our case, Javier. We performed an echocardiography, and echo showed right atrium was mildly dilated, right ventricle was mildly dilated, RVSP of 64 mmHg, which is clearly abnormal. LA and LV were normal size. LVF was preserved, which is 51% and then there was a comment that ascending order is normal in size at 2.8 cm in diameter. And again my correct answer here is I still have a very high suspicion in this gentleman. Steve, did anything change for you, or you agree with that?

Dr. Nathan:
I agree with that. It's interesting because we both started out high. There should be another category saying super high, and it can't go any higher than high suspicion. So I do agree.

Dr. Sahay:
That's true. Okay, I'll pass it on to Dr. Nathan again to do some data review.

Dr. Nathan:
There's a interesting study that's ongoing, but there's a prelim analysis from the study. It's called the PHINDER study, and it's a play on words because it's spelled P-H, PHINDER. And the purpose of the study is to see how good non-invasive testing is in diagnosing or predicting the presence of pulmonary hypertension in patients with interstitial lung disease. Actually both Sandeep and myself are participating in the study, and there's been an interim prelim analysis of the study where we, as the investigators, we get all these tests, including the ones we spoke about: 6-minute walk, PFT, CT scan, echo, and then the principal investigators at each site is asked to categorize whether we think there's a low, medium, or high probability of pulmonary hypertension.

And what we've shown is that we, the so-called experts, are not very good at predicting pulmonary hypertension. For example, when we categorize patients as low index of suspicion, about 1/3 of those patients still have pulmonary hypertension. On the other end of the spectrum, when we categorize patients as having a high index of suspicion, about 1/3 do not have pulmonary hypertension. When we kind of equivocate and we say there's medium probability, then we're pretty good because 50% will have and 50% won't have pulmonary hypertension. It's the extremes, the high probability and the low probabilities, where we fall down a little bit and are not very good at

predicting the presence or absence of pulmonary hypertension.

Dr. Sahay:
Okay, that was a very interesting data from this study. Thank you, Steve.

So let's go back to our gentlemen. So we proceeded with performing the right heart cath, and I will read out the numbers to you. RV systolic pressure was 44, diastolic pressure of 1, systolic pulmonary artery pressure of 48, diastolic pulmonary artery pressure of 18 with a mean pulmonary artery pressure of 30, right atrial pressure of 3, pulmonary capillary wedge pressure or pulmonary arterial wedge pressure is 9. Cardiac output of 5.87 with the index of 2.77 with thermodilution technique and the PVR of 3.28.

So, for me in this situation, I would actually proceed with treating this patient. That's my option, but I will open this for discussion with Dr. Nathan. Dr. Nathan, how would you approach this patient?

Dr. Nathan:
Yes, I agree, Sandeep. I would certainly treat this patient, and I wouldn't wait and watch. We spoke about the dire prognosis of these patients with any level of pulmonary hypertension, and certainly wouldn't wait any time. And I'm not sure, and get another right heart cath. Of course, it always depends if the patient wants treatment, but it also depends on how we present the treatment option to the patient. And everyone I speak to, where I recommend therapy, pretty much all of them will agree to go on therapy.

So the key takeaways in terms of early diagnosis and proactive screening, is that non-invasive tools lack sufficiently accuracy to effectively rule in or rule out pulmonary hypertension. And while echo is a good screening tool, PH cannot necessarily be ruled in or ruled out by echo cardiogram. And beware the normal echo. If you have a high index of suspicion, and I would argue even a moderate index of suspicion, if the echo is read as normal, then one should still consider proceeding with the right heart cath. Given the poor prognosis and propensity for progression, the earlier the diagnosis of pulmonary hypertension, the better. And once again, right heart cath is always needed to diagnose any form of pulmonary hypertension.

Dr. Sahay:
Okay, thanks, Dr. Nathan. So let's move on to the next section, which is assessing the clinical data and practice guidelines for evidence-based treatment approaches in pulmonary hypertension and interstitial lung disease.

Dr. Nathan:
There have been many small trials in PH-ILD looking at various medications, but very few randomized controlled studies looking at treating the pulmonary hypertension associated with interstitial lung disease. Inhaled iloprost has been trialed. This was the active study. It was a negative study. It was never actually published. It was just published as an abstract. Sildenafil had been tried in a number of different studies, some of these studies didn't have right heart cath proof of underlying pulmonary hypertension, and in the RCTs that have been done with sildenafil, it hasn't been shown to be of benefit. Bosentan is being trialed in a randomized controlled study of around 60 patients, and this was a decidedly negative study. Riociguat has been trialed in the RISE-IIP study, and not only was this a negative study, but it was actually a harmful study, with the study having been stopped early. Inhaled nitric oxides being trialed as well. This was not right heart cath-proven pulmonary hypertension, but the population was enriched for pulmonary hypertension, and this too was a negative study.

The only positive study to date, and the largest study to date in group 3 pulmonary hypertension, was the INCREASE study, which included 326 patients, and it was a positive study based on its change in the 6-minute walk distance at 16 weeks, as well as the number of secondary endpoints that were also positive as well. The study design was a typical randomized controlled study where patients were randomized to either inhaled treprostinil four times a day, or placebo given via nebulizer four times a day. The groups were equivalent in terms of their size, with 163 patients in each arm, and the goal was to get the patients up to 9 breaths four times a day with a maximum dose of 12 breasts four times a day. The primary endpoint was the 6-minute walk distance at week 16, and there were a number of secondary endpoints, including various looks at the 6-minute walk, the NT-proBNP, time to clinical worsening, as well as a number of exploratory endpoints.

If one assesses the baseline characteristics of the patients randomized into the increase study, the two groups were equivalent. The patients were generally in their mid 60s. There was more or less equivalence in terms of male to female breakdown, the etiology of the PH-ILD included what we know are causes of interstitial lung disease, including the idiopathic interstitial pneumonias, which was the largest group. This includes patients with IPF. We had patients with CPFE. We had patients with connective tissue disease, chronic hypersensitivity pneumonitis, and those were the majority of the patients. This was a sick group of patients, with about 70-73% of them being on supplemental oxygen, and there were some patients who came in on background anti-fibrotic therapy, and that that was mostly the patients with IPF, and there was equivalence between the two groups in the number of patients who came in on either pirfenidone or nintedanib, but about 73 to 82% of the patients were not on background anti-fibrotic therapy.

The study met its primary endpoint with a 31-meter placebo-corrected difference in the 6-minute walk at 16 weeks. Most of this was driven by improvement in the treatment arm, so we actually had patients with fibrotic ILD that we improved in terms of their functional ability by giving them the active drug, which was inhaled treprostinil. The study also met the most important secondary endpoint of time to clinical worsening. This was a composite endpoint constituted by either one of four events: hospitalization for cardiopulmonary reason, a decrease in the walk distance of 15% or more from baseline, all-cause mortality, or lung transplantation. The difference was that the folks who got inhaled treprostinil met this clinical worsening endpoint over the 16 weeks of the study, in 22.7 of the cases, while in placebo it was 33.1% who met this endpoint, and the P value was 0.04, which was statistically significant in favor of inhaled treprostinil. The hazard ratio was 0.61, which means or translates to a 39% relative reduction in the likelihood of having a clinical worsening event over the 16 weeks of the study.

Now, the study met its primary endpoint, its most important secondary endpoint. But then what was also gratifying to see was biomarker evidence of the clinical efficacy that was seen. So in the placebo arm, the NT-proBNP went up, while in the treatment arm, the NT-proBNP went down, and this infers that there was less right ventricular stress and strain, which translated to the clinical benefit as described.

There've been a number of post hoc analysis from the INCREASE study. At my last count, there were about 8 papers that have been published based on the INCREASE data set. One of them gets to the notion of whether or not we should be treating patients with mild PH-ILD. And when we say mild in the context of the study, it's patients with PVRs less than 4 Wood units. So this would be patients with a PVR of 3 or more Wood units, but less than 4. There was suggestion that maybe this group didn't have the same 6-minute walk benefit as patients with higher mean pulmonary artery pressures. But what was seen in this group was that they actually had a significant decrement in their NT-proBNP. And if one looks at the acute exacerbations in this group of patients and clinical worsening in this group of patients with PVRs less than 4, they did appear to have benefit. It didn't quite hit statistical significance, but the risk reduction was pretty profound, with a hazard ratio for acute exacerbations of 0.56 and a hazard ratio for a clinical worsening of 0.37, but because the numbers weren't that big in this particular subgroup, it didn't hit statistical significance.

And I think this goes back to the question that was posed in the patient, Javier, that was presented. His PVR sat between 3 and 4, and both Sandeep and myself were in agreement that he should be treated early and not wait and watch, as was one of the answer options.

Dr. Sahay:
The answer is B. That is NT-proBNP significantly decreased compared with placebo. And I will pass on to Steve.

Dr. Nathan:
Even though inhaled treprostinil has been studied in randomized controlled study, the question comes up: What about other agents that are available for group 1 pulmonary arterial hypertension? Probably the most data resides with sildenafil and PDE5 inhibitors in particular. And there have been a number of studies that have looked retrospectively at outcomes, including survival, and there's a suggestion that sildenafil might improve survival. However, this is not definitive, as in order to make a definitive statement around this, one needs to see a randomized controlled study of sildenafil. But this hasn't been done or seen as yet.

But there have been suggestive studies from a number of different authors that suggest perhaps that sildenafil could be associated with improved outcomes. Certainly, the drugs that have been shown to be harmful in PH-ILD, the endothelin antagonists in particular, have been studied, bosentan and macitentan, which were studied for pulmonary fibrosis, as well as PH-ILD in the context of bosentan, and these were shown not to be helpful at all. Ambrisentan, on the other end, has also been studied for its fibrotic properties, and there was actually a suggestion of harm of ambrisentan in patients with IPF. In actual fact, the study got stopped early because of a suggestion of increased mortality and increased hospitalizations. Riociguat was studied in the RISE-IIP study, and this was definitively shown to be contraindicated because of the increased mortality in those patients who received riociguat in the context of this clinical trial.

Dr. Sahay:
Thank you, Steve. So let's go back to our patient, Javier, here. So quickly, I'll recap what we learned so far we know about our patient. So he was a 50-year-old male with worsening shortness of breath. CT showed indeterminate UIP pattern. With the biopsy, he had a fibrosing, NSIP with organizing pneumonia, and respiratory bronchiolitis. There was a mild rash on his face and neck, and also had mechanic's hand. Mildly positive ANA, PL7 antibody was positive, and we made a diagnosis of dermatomyositis. He was on home oxygen in 2 L at rest, 6 L on exercise. We performed a right heart cath, we found that his mean PAP was elevated at 30, PVR was 3.28. However, his NT-proBNP was normal, and on the walk distance, he profoundly desaturated. So now you can see that we have sort of gone over multiple different parameters to really make this diagnosis. And one more thing which is not mentioned on the slide, but he had a DLCO of 38% which was actually low with preserved FVC.

So, putting everything together, despite of him having normal NT-proBNP, and with the non-invasive testing, not so much of probability

for pulmonary hypertension, we proceeded with the right heart cath, and we made the diagnosis of pulmonary hypertension and likely the cause of his shortness of breath. So I think with Steve's presentation and the data we reviewed, it's pretty clear that we will proceed with treating this patient. So my answer here is option A. Yes.

Dr. Nathan:
And I remain the same also with you on A, Sandeep.

So how does one approach these patients in terms of a treatment algorithm? With the changing definition, there is no data as yet whether we should treat patients who have MPAPs between 20 and 24, or PVRs between 2 and 3, those studies remain to be done. But we do know, based on the INCREASE study, which included the old definition of pulmonary hypertension, in order to qualify to get into INCREASE, you had to have an MPAP of 25 or more and a PVR of greater than 3 units. So it's been definitively shown that inhaled treprostinil does work in these patients. So that's the only approved therapy and the treatment of choice. Now, inhaled treprostinil is not available in every country or everywhere, or some patients might be intolerant. In those situations, one can consider a trial of sildenafil, each patient being an N of 1 study by themselves.

Certainly, in the management algorithm, we should rule out contributory factors, comorbid conditions, uncorrected hypoxemia, sleep disordered breathing, and heart failure being amongst them.

I think always consider referral to either an ILD or PH program, and especially if they have more severe pulmonary hypertension, referral to a PH program I think is definitely worthwhile because there are some cases who have very severe pulmonary hypertension who behave more like a group 1 PAH phenotype, where consideration might be given to more advanced therapies, including parenteral prostanoids. And if the patient's a transplant candidate, potentially referral to a transplant center can happen concomitantly with trying to treat the patient's underlying pulmonary hypertension. The two are not necessarily mutually exclusive.

Dr. Sahay:
So my answer here is option D with the PVR of 4 and above and mean PAP of 25 and above. Although I would say, this is sort of like an evolving area, but we have to talk about what the scientific evidence we have so far. So most of the studies which are conducted so far are done in patients where the inclusion criteria were mean PAP of 25 and above, so that clearly makes sense. I mean, of course, we have now ongoing trials and new data because we change the hemodynamic definition as Steve discussed earlier. So perhaps we could use it in sooner, depending on individualized approach. But for now, well, this is what the data shows. And the PVR cutoff of 4 is what was decided in the World Symposium on Pulmonary Hypertension, and also I think it was based on what the post hoc analysis from the INCREASE study. I may have different opinions on that part, but I will let Steve also contribute and share his insight what he wants to share.

Dr. Nathan:
Yeah, Sandeep, I agree. I think the INCREASE study included patients with PVRs greater than 3. That's not provided as an option here, but this patient certainly qualifies with a PVR greater than or equal to 4. And you know, there's some controversy with treating patients 3 to 4, but I think some of the evidence I presented with NT-proBNP, acute exacerbations, clinical worsening, it's pretty compelling that we should treat these patients who were included in the INCREASE study and who clearly had a benefit, even though it might not necessarily have manifest fully in the 6-minute walk. So I agree with you. Anyone who would have qualified for the INCREASE study should be considered a candidate for therapy.

Dr. Sahay:
I totally agree, and that's what I practice, and that's what I feel.

Okay, so my answer here from all these options was E, none of the above. I would have treated the patient already. However, if someone decides to wait and watch, I would suggest to have a very close follow-up in these patients, very low index of suspicion to repeat a right heart cath. I mean, I do not know if there is any strong data of whether 6 months or 1 year is a good timeline, but I would say it'll be clinically indicated. I'm doing a close follow-up. I see slight change, and I'll proceed with the right heart cath. That would be my approach.

I'll ask Steve to provide his experience insight into it as well.

Dr. Nathan:
Yeah, I agree with you. E to me is the right answer. I would have treated the patient as early as possible. And you're right, there's no guidance about when to repeat a right heart cath, and maybe we need some guidelines, Sandeep.

Dr. Sahay:
Probably.

Dr. Nathan:
Well, this is, you know, I'd mentioned initially that the prevalence at the time of diagnosis really varies from 8% up to 46%, and then 86% at the time of transplant. But what about the rate of progression once you do that first right heart cath? And there have been a number of studies that have looked at this. There was one Japanese study looking at patients with early IPF, where the rate of increment in the MPAP, of course, you needed two right heart caths to assess this, it was 1.8 mmHg per year. A more recent look at patients listed for transplant had a rate of increase of 3.8 mm per year. And then, as the patients get towards the end of their disease course, it seems like the PA pressures are at risk of almost going parabolic because there was one study that looked at the rate of increase, and it was 3.8 mmHg per month. So there is risk in these patients of progression, and getting a right heart cath is not a one and done. It doesn't mean that the PA pressures are going to stay static as the lung disease progresses.

So let's go back to Javier and just conclude the case. He is a gentleman who had ILD due to dermatomyositis, he had a confirmed diagnosis of precapillary pulmonary hypertension with his MPAP of 30, PVR of 3.28 Wood units. He was started on treatment with inhaled treprostinil. He started at 3 breaths four times a day, and this was titrated up to 9 breaths four times a day, and he had ongoing care in terms of optimizing his other aspects of disease as well as supplemental oxygen, and he did respond to therapy. Three months after being seen, he had an improvement in his walk test. He noted reduced dyspnea, reduced fatigue. His NT-proBNP came down, and he felt like he could do more in terms of his day-to-day activities. And importantly, he didn't require any hospital admissions or ER visits for worsening or acute exacerbations.

So, early evidence-based treatment can provide meaningful benefit even in mild to moderate PH-ILD. So, some of the key takeaways from this is that PH-ILD is underappreciated and underdiagnosed, it carries a dismal prognosis. Screening involves looking at routine ILD testing through a different lens. Spoke about the 6-minute walk and PFTs. Have a low threshold for right heart cath, especially since we have approved therapy now. Inhaled treprostinil is the only approved therapy for PH-ILD, and multimodality therapy for IPF and other ILDs, the era is now because we have the antifibrotics and if the patients develop pulmonary hypertension then we have inhaled treprostinil.

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