PAH Clinical Research Highlights CHEST 2024

Dr. Jean Elwing:

Welcome everyone. Thank you so much for joining us. We're going to be talking today about pulmonary arterial hypertension research highlights from CHEST 2024, and my name is Dr. Jean Elwing, and I'm a professor of medicine and the Director of the Pulmonary Hypertension Program at the University of Cincinnati. This is a CME-approved program. I do have some disclosures that are listed here, and we do want to thank our sponsors, both Merck and Mallinckrodt Pharmaceuticals for making this possible.

So let's begin with talking about pulmonary arterial hypertension. What is it? It is a rare condition. As its name implies, it's associated with high blood pressure in the pulmonary arteries. Symptoms include shortness of breath or dyspnea during exercise, syncope, fainting spells, swelling, lower extremity edema, chest pain and palpitations or racing pulse. Some cases of PAH are associated with underlying genetic abnormalities in the BMPR2 gene. That's the most common genetic abnormality, and that is autosomal dominant.

Diagnosis is made by a hemodynamic assessment with right heart catheterization, but depends on symptoms, clinical evaluation, and additional testing to really hone in on the diagnosis and the right treatment. There are numerous treatments available for pulmonary arterial hypertension, and they include phosphodiesterase inhibitors, endothelin receptor antagonists, prostacyclin pathway agents, including infusions, inhaled therapies and oral therapies, activin signaling inhibitors, and a combination of those. We use those medications in addition to other therapies for general care, like anticoagulation in certain circumstances, diuretics, oxygen, and maintain patient's health with things like vaccinations.

Since this is a rare condition, it sometimes gets overlooked and we want to bring our thoughts about CHEST 2024 to you so you can get the highlights from this program. So what is CHEST? CHEST is the meeting from the American College of CHEST physicians, and we have it annually. In 2024, it was held in October in Boston, Massachusetts. It's one of the largest gatherings of clinicians and researchers focused on pulmonary medicine. The abstracts from this program are published annually in a supplement issue of CHEST magazine.

We're going to talk about selected clinical trials presented at CHEST 2024. So I want you to take a second and think about how do you as a busy person in this very busy world stay updated on latest clinical trial data, and what strategies do you use to effectively synthesize and apply that information to your clinical practice? Well, I think one thing is to go to meetings, listen to experts speak on topics, see the abstracts, listen to the presentations, and then try to apply that to what you're doing at home. But we can't be everywhere all the time. So that's why this may be helpful to you to go through the different presentations and the research projects that were presented at CHEST.

One study I think was very important to discuss, and I learned a great deal from this abstract, was the outcomes from the long-term safety and efficacy from the BREEZE study. As you may recall, the BREEZE study looked at patients with pulmonary arterial hypertension who were receiving inhaled trepostinil nebulized, and transitioning them to inhaled trepostinil with a dry powder inhaler. They were given an option to then transition to an extension phase, and this study reported out the results of that extension phase. Of the 51 patients who enrolled in BREEZE, 49 of them opted for that extension phase, and during the time of enrollment, they were able to titrate up on the dose of their inhaled trepostinil, and they found that their inhaled trepostinil with dry powder inhaler was well tolerated with no new unexpected serious adverse events, and they had improvement in their six-minute walk distance during that time, and had very high level of satisfaction with their dry powder inhaler. So something important to know for our patients transitioning to dry powder inhaler and staying on that long term.

Another thing I think we really need to spend some time thinking about and talking about is real world data and real world evidence, and how we can use that information in our patient care. So Dr. Safdar and colleagues looked at a very difficult situation of hypotensive patients with pulmonary arterial hypertension or hospitalized, and they need to increase their pulmonary hypertension medications. We know that PAH is a progressive disease and it results in right heart failure, and with right heart failure, develop low blood pressure occasionally.

So they looked at a retrospective analysis of 433 Group-1 PAH patients from 2005 to 2022, and 57 of them were given, treated with midodrine to augment blood pressure to allow up-titration of their pulmonary hypertension medications. They were compared to a controlled group of 57 PAH patients who did not require midodrine, and they found that those patients who received midodrine were more likely to up-titrate their prostacyclin therapies. They were able to increase their selexipag, their epoprostenol, and their trepostinil more frequently than those who were not exposed to midodrine. They tolerated it hemodynamically and did not have any significant bradycardia associated with the use of this medication, increasing our awareness that possibly this might be a medication we could add to our critically ill, oftentimes hypotensive patients with pulmonary arterial hypertension, to allow us to go up on the medications that may improve their pulmonary vascular resistance and their pulmonary hypertension.

So another real world trial that I would like to mention is a look at the tolerability of inhaled trepostinil in our PAH patients. We know that PAH patients tolerate our medications fairly well, but do have adverse effects of certain therapies. With inhaled trepostinil, patients may have increased cough or they may have increased shortness of breath occasionally. So this was a look at real world data to identify factors that influence the tolerability of inhaled trepostinil in pulmonary arterial hypertension and pulmonary hypertension related to interstitial lung disease.

They looked retrospectively at 43 patients, about half PAH and half PH-ILD, and they found a few signals. They found that those patients that had lower tolerance oftentimes had increased obstructive changes on their pulmonary function, lower cardiac output and cardiac index as well as lower TAPSE scores, so the sicker hemodynamic patient as well as the patient who had a spirometry profile of obstructive lung disease. So something to think about when you're choosing therapy in patients with PH and PH-ILD, and trying to anticipate potential intolerances.

Another study that I thought was very intriguing, thought-provoking and makes me think that this needs to be studied further, was the one looking at the impact of SGLT2 inhibitors on mortality in pulmonary arterial hypertension. We know these drugs reduce mortality in patients with left heart disease with reduced ejection fraction and preserved ejection fraction, but we don't know how it impacts our PAH patients. This retrospective look evaluated the association between the use of SGLT2 therapy and all-cause mortality in PAH. This looked at patients from 2013 to 2023, and found an improvement in overall mortality at one, three, and five years in the PAH patients, see group A here, in a statistically significant way. So very thought-provoking, and telling us that this may be something important that we study in the near future.

Another thing we can learn from real-world data and real-world evidence is how we are practicing and how maybe our practice patterns are affecting outcomes. This was looked at in terms of how we treat patients of different ethnicities differently. We know that Hispanic/Latino ethnic groups are underrepresented in pulmonary arterial hypertension studies and registries, and they took a look at the OPUS and ORPHEUS registries, which are looking at macitentan real-world data focused on the patients that were Latino or of Hispanic ethnicity and looked at outcomes. They found that patients that were of Hispanic ethnicity were younger at the diagnosis, more often affected by congenital heart disease, and

had similar overall outcomes to our patients that were non-Hispanic. Important to be aware that there are differences in the presentation, the timing, and to recognize that when we're evaluating patients.

Another important thing that was evaluated is how we're approaching patients of different race in terms of our PAH management. Again, we looked at individuals in the OPUS and ORPHEUS registries, with treatment with macitentan. There were more than 4,500 patients enrolled in these registries, and they compared the approach and management of Black African-American patients with white patients, and they found that Black African-American patients had more comorbidities and higher hospitalization rates, but overall treatment survival and outcomes were similar to the white patients who were included in those registries. Again, important to be aware that we are approaching different races possibly in different ways and that we have different comorbidity risks and hospitalization risks.

So we know that pulmonary hypertension has been looked at in many ways in many studies, and per current guidelines, it is recommended that all patients without significant comorbidities are treated with combination upfront dual therapy. That's in our current guidelines, our consensus statements, and that's what we're teaching. So the question was asked, what are we really doing in the real world? So this presentation looked at real-world treatment approaches to PAH, and they surveyed pulmonologists and cardiologists looking at more than 750 patients with PAH from 2023 to 2024, and found that nearly half of the patients reviewed were on monotherapy. So very far away from that goal of all patients without significant comorbidities being treated with dual combination therapy.

So who received monotherapy? Well, they were more likely to have low risk status and oftentimes more often treated in community or private practice settings. So what they concluded, despite guideline recommendations, many patients remain on monotherapy, particularly lower risk patients and those in certain circumstances and healthcare settings like private practice. So something I think all of us need to be aware of. We need to think about this every time we see a PAH patient. Are we following guidelines? Are we assessing patients, and are we treating them as aggressively as they deserve? So just a thought.

Now moving on to some survey and registry data presentations. So when we think about pulmonary arterial hypertension patients, we talk about medications, initiation, timing, looking at risk status, and oftentimes we don't really focus as much attention as our patients would like us to on quality of life. So this is a study looking at symptom burden and health related quality of life in PAH. So we really thought this was an important thing to talk about and make everyone aware of. So the objective of this study was to explore symptom burden and quality of life in patients with PAH through self-reported data. We don't know how patients experience things day to day, so we really need to learn it from them.

So online survey data was conducted among 200 US PAH patients recruited through the Pulmonary Hypertension Association, and they found that patients are symptomatic and have impaired quality of life. Saw that 42% had bothersome tiredness and fatigue and 93% experienced some degree of symptoms in the seven days before completing the survey. So this just highlighted the impact of PAH on the everyday life of our patients, and making us more aware that we should ask about this, possibly use these quality of life tools in our everyday clinical care so we can track and hopefully target some of those symptoms to improve patients' daily life.

Another very important topic, and one related to quality of life also is one about transitioning medications and trying to find the medication that is most comfortable and most effective for our patients. In the SPHERE registry, looking at our patients on selexipag, they evaluated patients who were in that registry who previously were on other forms of prostacyclins. That registry spanned from 2016 to 2021, looking at more than 750 patients across the US. They found that patients who were previously on other forms of prostacyclins were able to transition safely to selexipag with an 89% 18 month survival rate with stable symptoms in more than 60% of them and improved in 21%, and only less than 10% having adverse events leading to discontinuation of selexipag, making us aware that our patients who

are on other forms of prostacyclins who may not be tolerating one or another symptom or side effect associated with that form of prostacyclin may be a candidate to transition to selexipag in selected patients.

So in addition to the things we talked about in terms of quality of life, we know patients come to us with other comorbidities, and we talk a lot about cardiac comorbidities, we talk about renal insufficiency. We probably do not talk enough about mental health comorbidities, and how this may impact patients' experience with pulmonary hypertension or may change how patients are treated. So they again looked at the SPHERE registry, that registry looking at patients exposed to selexipag, more than 750 across the US, and they looked at the differences in patients with reported mental health comorbidities and those without.

They found that a lower number of patients with mental health comorbidities did have exposure to that combination of endothelin receptor antagonists and PDE-5 therapy. But overall, in general, the approach to those patients was similar to those without mental health comorbidities. So something to be aware of that a large number of the patients we see and we care for, more than a third will have mental health comorbidities. These should not be ignored. Patients need support for these. But we can based on the SPHERE registry data, manage them in similar fashion as those without mental health comorbidities, but we need to be sensitive to specific needs of that patient population.

So let's move on to other comorbidities and some complicated case presentations that made us think about how we manage our patients, and step back for a second to make sure that we are doing everything we can to address patients' needs in the way that would best fit them. So something I want you to think about before we go on. What are the most common comorbidities observed in your PAH patients, and what strategies do you use to assess and address those issues effectively?

One study that I would like to mention, which was completed by my partner Dr. Arun Jose and a multicenter group was looking at cardiopulmonary hemodynamics and outcomes in pulmonary hypertension post-kidney transplant. The objective of this was to look at pulmonary hemodynamics and see what was associated with those adverse outcomes after kidney transplant. They looked at patients who had received an evaluation for kidney transplant and underwent transplant who had had a right heart catheterization within that one year prior to transplant.

They found that the vast majority of these patients had elevated pulmonary pressures with 79% them having mean pulmonary pressures greater than 20, so meeting that criteria for pulmonary hypertension. More than 20% of them had post-transplant mortality, a fourth had graft dysfunction, a third had major adverse cardiovascular events, and the major predictor of those adverse events was an elevated pulmonary pressure with a mean pressure of 30 or greater, another factor that was associated with worse outcomes with elevated cardiac output. The interesting thing was that echocardiogram and echocardiographic features were not able to predict outcomes. So really depending on that right heart catheterization and hemodynamic assessment to evaluate patients, and those parameters, that elevated pulmonary pressure and the elevated cardiac output were associated with worse outcomes.

So another study I'd like to mention is that looking at connective tissue disease in the treatment of PAH with a post hoc analysis of the TRIUMPH study. We know that patients with connective tissue disease associated pulmonary arterial hypertension have worse outcomes, and we approach them in a more aggressive way oftentimes so we can improve the overall outcome of that patient population. So how did they do in the TRIUMPH Study? So the objective of this post hoc analysis was to evaluate the efficacy and safety of inhaled trepostinil in patients with connective tissue disease associated PAH, as compared to those with non-connective tissue disease associated PAH. They found that in the TRIUMP study that inhaled trepostinil provided comparable improvements in walk distance and NT-proBNP as compared to the patients without connective tissue disease. So very encouraging that patients treated with inhaled

trepostinil in the TRIUMPH study had similar overall outcomes, whether they had connective tissue disease or not. You'll see that here, the connective disease PAH patients treated with inhaled trepostinil and the non-CDD PAH patients had improvement in walk distance and decrease in their NT-proBNP with similar adverse events.

Now going on to something I thought was an important thing to talk about because it's so very common in our patients and oftentimes not well recognized, and that's iron deficiency anemia. Iron deficiency anemia has long been associated with poor outcomes in patients. This study looked at patients with iron deficiency anemia, treating them either with oral or IV iron, and then assessing outcomes. It was a single-center retrospective study looking at 53 patients, 36 treated with oral iron and 17 IV iron, and they found that, as expected, serum iron improved, hemoglobin also improved. But what was very interesting was that patients had a decrease in the mean pulmonary pressure in a statistically significant way and improvement in their cardiac index. They also had improved six-minute walk distance, functional class, and improvement in their risk score. So something to take home with us to say, "Hey, this might be an important thing to look at in our patients, and address if it's positive, if we have abnormal iron levels and then follow our patients closely once we replace that iron."

One case report that we wanted to include was about drug interactions. Our patients obviously are not in a vacuum, we have multiple comorbidities, multiple other drugs that may be affecting the metabolism or the action or the side effects of our PAH therapies. One subgroup of PAH patients that have risk of drug-drug interactions that need to be respected are HIV PAH patients. A case presentation was given at CHEST on a 57-year-old male with HIV on antiretroviral therapy, initiated on dual upfront combination therapy with macitentan and riociguat.

In this individual they had a lot of side effects related to their PAH medications because of drug-drug interaction, and once that was transitioned to a different option in terms of the two medications used for that dual upfront combination therapy, the patient had improvement in their side effects, and of course they would have improvement then in their tolerance of medication long-term. Just making us more aware of the fact that we need to take a step back, look at what our patient needs in terms of all of the comorbidities and the medical therapies and make sure our PAH therapy fits as best as we can in line with the other therapies so we can have the least side effects, best efficacy of the drugs we choose.

Another interesting presentation and something we always talk about and encounter is outcomes with efficacy of parenteral vasodilators treating pulmonary hypertension, right heart failure when we have patients with advanced disease and we feel elevated wedge pressures likely related to that dilated, distended fluid and pressure overloaded right ventricul, and is it safe to proceed with prostacyclin therapy? So this was a look at five patients retrospectively with elevated wedge pressures in that 20 range, but significantly elevated pulmonary vascular resistance greater than 10, and if they could safely administer parenteral prostacyclins in that patient population.

They found that parenteral prostacyclin therapy improved right ventricular function in this patient population, reduced wedge as they treated that group of patients over time. We can see here the mean pulmonary pressures were elevated more than a mean of 50, pulmonary vascular resistance was significantly elevated above 11, cardiac index was low, TAPSE was reduced and echo estimated pulmonary pressures, RVSP, was elevated, and those patients, as I mentioned, had an average wedge at the time of diagnosis of 20. Over time, in this study, that patient population could be safely and effectively treated with parenteral prostacyclins.

Now changing gears a little bit to talking about how a new comorbidity may affect the outcomes of a PAH patient. Looking at the impact of having a diagnosis of PAH on outcomes in first myocardial infarction, looking at first ST elevation MI, non-ST elevation MI, and overall myocardial infarctions. This was to assess the impact of first event on PAH patients, looking retrospectively using the national

inpatient sample database from 2016 to 2020. They found that PAH was associated with higher mortality, longer hospital stays, greater cost, and increased need for interventions for that first myocardial infarction. We know that our patients with pulmonary arterial hypertension are more sensitive to any change in their status. Surgery, infection, hospitalization. This analysis also showed us that myocardial infarction had a greater impact on the PAH patient than that overall general patient without pulmonary arterial hypertension.

So the last thing I'd like to mention is something we've been working on, especially since the beginning of the pandemic. How do we help our assessment of patients through the patients' evaluation of how they're doing? This is looking at the Pulmonary Hypertension Functional Classification Self Report, the PH-FC-SR. Is it valid? Is it a helpful tool, and can we use it to complement our current care? This was a non-interventional observational study using the patient assessment and the clinician-reported data at the Cleveland Clinic and the Mayo Clinic to see how well these two evaluations correlated, and if this could be something useful for our patients.

It was found that the PH-FC-SR demonstrated strong constrict validity aligning closely with the functional class per the provider while offering unique insights into how the patient felt and their perspective of their PAH severity. So something we could easily add to our current evaluation to increase our understanding of how the patient feels they're doing, and also correlates well with how we assess patients when we evaluate our pulmonary hypertension patients in follow-up.

Now I'd like to leave you with some clinical pearls, and I hope that the studies and analyses we went through over the last 30 minutes are helpful in terms of your care of pulmonary hypertension and a better understanding of the complexities of this rare disease. So in summary, we talked about how inhaled trepostinil in the dry powder form can be safe and effective and tolerated long-term in our PAH patients. We also reviewed a study about midodrine, and that it was well tolerated and safe and could be used to facilitate PAH medication increases in hospitalized patients.

We talked about how there are certain patient populations that may have more difficulty with tolerating inhaled trepostinil, and that may include patients with obstructive changes on spirometry. We reviewed some data on SGLT2 therapy and its impact to reduce mortality in PAH patients in a real-world evidence study. We looked at race and ethnicity, and how it affected patient experience and treatment patterns in the Hispanic/Latino population and Black African-American patient, and we found that even though there are some differences in those populations in comorbidities, it seems that treatment safety and efficacy were similar. We talked about recent guidelines recommending upfront combination therapy for all of our patients with PAH. We found that based on real-world data, there's a significant number of our patients who are receiving monotherapy, and those patients oftentimes are of lower risk and in community-based practices.

We also talked about quality of life. Very important. And that our patients have significant impairment of their health-related quality of life, and frequently have symptoms that impact their daily functioning. We talked about things that look at how we're transitioning medications and the SPHERE study, and talked about how we could transition patients safely from other forms of prostacyclins to selexipag with stable or improve symptoms over an 18-month period. We talked about medical comorbidities but also mental health comorbidities, and we found that despite this frequent existence of mental health comorbidities in our PAH patients, they receive similar PAH-specific treatment and have similar outcomes.

We reviewed some of the high-risk subgroups of PAH, and we looked at connective tissue disease patients in a cohort from the TRIUMPH study and found that those patients with connective tissue disease had similar positive response to inhaled trepostinil as those without connective tissue disease in terms of their walk distance and their NT-proBNP. We talked about iron deficiency, very common

problem, and that we can replace iron with improvement in iron stores as well as anemia, but also a positive impact on cardiac indices and functional outcomes in our patients with PAH. We talked about comorbidities as I mentioned, but not only the existence of those comorbidities but the impact on our medication choices, and that we need to look at drug-drug interaction to ensure that we choose the best medications for the patient based on their other necessary therapies.

We talked about that high-risk patient who has severe right ventricular dilation, pressure and volume overload that has a elevated wedge, but still that very high pulmonary vascular resistance, and that they were able to be safely treated with parenteral prostacyclins, with improvement in that wedge pressure over time and improvement in the right ventricular function. We talked about the impact of new comorbidities like myocardial infarction on patients with pulmonary arterial hypertension, and that they had worse outcomes than those patients without PAH. We talked about a patient assessment of functionality, the PH-FC-SR, and that it could be used to complement our clinical assessment and the provider's assessment of functional class, and improve our patient-centered PH evaluation.

With that, I took you on a whirlwind tour of the research in pulmonary hypertension at CHEST 2024. I hope you enjoyed that review and I hope it prompted some thought and hopefully, some more interest in this rare lung disease. Thank you so much for joining me.