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Highlights from PHA's 2024 International PH Conference and Scientific Sessions

Program Description

The mission of *Advances in Pulmonary Hypertension* is to serve as the premiere forum for state-of-the-art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension (PH). The 2018 Nice revision of the World Symposium on Pulmonary Hypertension (Simmonneu G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1). DOI:10.1183/13993003.01913-2018) serves as a guide to categories of PH addressed in *Advances in Pulmonary Hypertension*. While focusing on Group 1 PH (PAH: pulmonary arterial hypertension), the other categories (Group 2, PH due to left heart disease; Group 3, PH due to lung diseases and/or hypoxia; Group 4, PH due to pulmonary artery obstructions; Group 5, PH with unclear and/or multifactorial mechanisms) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

Objectives

- Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of PH.
- Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

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Advances in Pulmonary Hypertension is directed to cardiologists, pulmonologists, rheumatologists, pediatricians, internists, and other health care professionals involved in the treatment of patients with PH.

Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned pulmonary hypertension (PH) experts with oversight by PHA's Scientific Leadership Council. The mission of *Advances in PH* is to assist physicians in their clinical decision-making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in peer-reviewed publications. Each article is reviewed and approved by members of the Editorial Board.

While most articles are invited by the Editorial Board, the following submissions will be considered for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
- Letters to the Editor
- Clinical case studies

Submitted manuscripts are reviewed by the Editorial Board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision-making.

***Advances in Pulmonary Hypertension*'s Web Platform**

Advances in Pulmonary Hypertension is available at www.AdvancesinPH.org. This site offers enhanced capabilities including a dedicated DOI and cross-referencing potential, as well as other features valuable to practitioners, researchers, and educators. Registration is recommended to access all site features and benefits.

In August 2024, members of the Pulmonary Hypertension Association (PHA) gathered in Indianapolis for the 2024 International PH Conference and Scientific Sessions. This event brought together patients, caregivers, and medical professionals for a series of presentations dedicated to advancing our understanding and treatment of pulmonary hypertension along the theme "United Toward a Cure." The varied program included a comprehensive overview of the latest advances in pulmonary hypertension research, from novel therapeutic strategies to emerging diagnostic tools, and important discussions of ongoing challenges in patient care and research.

In this special issue of *Advances in Pulmonary Hypertension,* we have curated a selection of manuscripts from members of the Scientific Sessions Planning Subcommittee that reflect the breadth of research and patient care developments presented in the Scientific Sessions.

One of the highlights was a session showcasing recent updates from the 7th World Symposium on Pulmonary Hypertension. Here, we include a roundtable discussion of the key topics presented and the impact of these updates on clinical practice, from the perspective of committee members practicing in different clinical and research disciplines.

We also include a discussion of patient care and quality of life, led by Dr Scott Visovatti, highlighting the importance of the patient experience in both clinical care and clinical trials.

Dr Yuri Matsurov presents an overview of the research presented in the Scientific Sessions regarding pulmonary hypertension associated with parenchymal lung disease, emphasizing how the unique disease and clinical phenotypes impact the approach to patient care.

Dr Sandeep Sahay highlights discussions from the Scientific Sessions focused on the future of clinical research, including use of real-world evidence, clinical trial design, and how we define response to therapy. He reviews how the definition of disease modification impacts the approach to clinical research and regulatory approval of medications.

The early career physicians came together at Conference this year for events fostering community and mentorship. Dr Jacqueline DesJardin calls attention to the many opportunities for early faculty within PHA discussed by this group, including participating in research using the PHA Registry (PHAR), which celebrated its 10th anniversary this year.

Lastly, we are pleased to present the collection of abstracts submitted for presentation at Conference that showcase the remarkable work being done in the PHA community.

I would like to express my sincere gratitude to all the Scientific Sessions subcommittee members, speakers, sponsors, and volunteers who contributed to making this conference a success. I hope you enjoy reading this issue and find it as inspiring and thought-provoking as the conference itself.

Rachel K. Hopper, MD
Chair, Scientific Sessions Subcommittee

My friend and medical school classmate Atul Gawande once wrote, "Human beings are social creatures. We are social not just in the trivial sense that we like company, and not just in the obvious sense that we each depend on others. We are social in a more elemental way: simply to exist as a normal human being requires interaction with other people."[1] This applies to the growth and development of physicians as clinicians, researchers, and medical educators. Medical conferences remain an essential component of this process, as during this time important clinical trial data is presented, controversies in practice are reviewed and debated, and most importantly of all, side conversations and meetings occur that often lead to lifelong collaborations and practice-changing research. There is simply no substitute for this in-person exchange of ideas.

The recent COVID-19 pandemic challenged the execution of large medical conferences, and many initially pivoted to video-based or hybrid models.[2] Most physicians, myself included, welcomed the return of face-to-face meetings over the last few years. This issue of *Advances in Pulmonary Hypertension* is devoted to proceedings from one of these in-person conferences, the 2024 International PH Conference and Scientific Sessions. In this issue, Dr Hopper, the Scientific Sessions Chair, has provided a wonderful sample from the meeting for those who could not attend and a good refresher for those who attended. We learn how the development of newer classes of therapy in pulmonary arterial hypertension is changing the therapeutic approach to one of being proactive rather than reactive, how parenchymal lung-related pulmonary hypertension has gone from a black box to a hotbed of clinical research, ways to positively influence the early career development of our specialists, as well as a sampling of the depth and breadth of current research in our field. There is also a nice discussion about the patient perspectives of participating in clinical trials.

The past few months have witnessed new challenges, among them social and financial, that have led many institutions to restrict travel to national meetings. We can hope that this response is only brief and that common sense eventually prevails, as the exchange of ideas fostered by such conferences remains irreplaceable.

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PH ROUNDTABLE

A Roundtable Discussion Addressing Patient-Centered Care and Quality of Life in Patients With Pulmonary Arterial Hypertension

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This session highlighted creative, multidisciplinary approaches to improving quality of life in patients with pulmonary arterial hypertension. Tiffani Brown shared her journey, from initial diagnosis to the present day, with the following panel of pulmonary hypertension experts: Cheryl Carmin, PhD; Emily Fedewa, NP, MSN; Jennica Johns, MD; Debbie Kittel, BSN, RN, CCRN; Laura Mudd, PharmD, BCCCP; Kristen-Allyson Ramones, MD, MBS; Allyson Rupp, MSW, LCSW, ACM-SW; and Scott Visovatti, MD.

The Initial Diagnosis: *"Everything Has Changed."*

Dr Visovatti (cardiologist): Tiffani, first of all, thank you so much for sharing your story. Could you give us an idea of what life was like before your diagnosis and how things changed leading up to it?

Ms Brown: I was living a normal life. I had started having symptoms about 3 to 4 years beforehand and was treated for asthma. The inhalers never helped, but they kept treating me for years. My symptoms started progressively getting worse in 2019, and it was in 2020 that I finally got my diagnosis. I went in for what I thought was just going to be another appointment with another doctor ordering more tests. So I thought this day was going to be just like any other. The doctor looked at me and told me that I had pulmonary arterial hypertension and that I was lucky to be alive. He told me he would be admitting me to start treatment. I was in denial. I had never heard of this disease, and so I didn't believe the diagnosis. I spent the weekend googling, which is the worst thing you can do. When it was time to be admitted to start treatment, I refused to go into the hospital. It took multiple phone calls with Debbie, my PH nurse, to get me to agree to come in for treatment because Google had me convinced that I was just going to die, so I didn't understand the point of treatment. So googling is definitely the worst thing I could've done because here I am, 4 years into treatment, and I'm still alive.

Ms Rupp (social worker): So many things to adjust to. Those of us who treat patients can't imagine what all of those things are. Dr Carmin devotes her time to this, so tell us a little bit about the kind of things people are adjusting to at this phase.

Dr Carmin (psychologist): What Tiffani described is typical: the deer in the headlights look: "Oh my God, what's going on? I'm dying." We really do try to dispel that. Everybody's reaction is different. Some people are anxious; some people are depressed. Most people are overwhelmed by worry. We acknowledge that feeling overwhelmed is absolutely appropriate for this situation, especially early on in this process. We also try to find out how resilient each person is by learning how they have coped with life events in the past. We help people to not focus on the "I can't." We focus on "I'm going to need to do this differently." The other piece is pointing out that this is not a hopeless situation and that you've got a team. That medical team is part of your journey; you're not doing this alone.

Initial Treatment Considerations: *"I am so overwhelmed."*

Dr Visovatti: Tiffani, you were in the clinic one day and admitted to the hospital soon after that. You're getting bits and pieces of information from your inpatient team, your outpatient team, and from the Internet. Must have felt like you were hit by a tidal wave in so many different ways. Were folks listening to you, or were you just being talked at.

Ms Brown: In my opinion, I was being talked at. I had shut down, so there was really no talking to me. I didn't feel like anyone could get through to me. I had to now grieve the life I thought I was going to live. It was the death of a life that I thought I would live.

Dr Visovatti: Debbie, you are often the point person for our patients once they are admitted. Well-meaning people are providing a lot of information. How do you ease people into having to make decisions?

Ms Kittel (nurse program manager): As overwhelming as it is for her, it's just as overwhelming for me. I know how much information you need to get to the patient so that they understand their disease, understand their options, and it's difficult when they're thrown into this. The whole world has changed, and you have to break it down in little pieces and parts. It's really a team approach, and the leader of the team is the patient; she has to be the one to say what she is willing to do. Are you willing to do IV therapy, are you willing to do SQ therapy, or is that just not an option for you? And then we have to do a social assessment as well. Are they good patients to put on parenteral therapies? Socially, do they have a clean place

to mix their medicine? Do they have a mixing buddy? Do they have help? What is their support system? We involve palliative medicine early on to help us with side effect management. We involve our psychologist to help with some of the emotional support. There's so much information to get to patients, and you only have so much time, so it helps to ease them into this process. One of the things that we do with some patients who need parenteral therapy is to have the specialty pharmacy nurse go to their home to teach them the pumps and get some of the teaching done at home, before the admission. This is not always possible, but that would be the ideal scenario.

Starting Medications: *"The medications are as bad as the disease."*

Ms Rupp: So what treatment plan did you and your team choose, Tiffani?

Ms Brown: Starting out, I was on subcutaneous Remodulin once I left the hospital. I was not ready for that. Now, looking back, I wish we had the ability to have another patient come into the room and talk to me to prepare me for what's about to come because, even though we have our doctors and our nurses telling us what to expect, we need that other patient telling us what's to come. They could have prepared me for the site pain that I was about to endure, and I was on subcutaneous for about 2.5 years before I just couldn't do the site pain anymore. So I am a year and a half into intravenous, and I say all the time I wish I would've done IV from the start because my quality of life on IV is so much better.

Ms Rupp: Laura, how do you think about treatment plans to help with side effects?

Dr Mudd (pharmacist): We really try to take a proactive approach to side effect management. In that initial period, we typically up-titrate much more quickly than we do in the outpatient setting. We like to schedule side effect management, and we find that this can help avoid those unmanageable, severe side effects during the initial up-titration period. At our facility, we typically utilize scheduled acetaminophen and scheduled prochlorperazine. We find the combination is really helpful for headaches as well as nausea and vomiting. To avoid delays, we also enter orders for as-needed medications to help with refractory nausea, vomiting, or diarrhea. There's a lot of education on medication side effect management that is needed. We definitely don't want patients to be surprised by them, and we want them to have open communication with us about how they're feeling. Even if there's a slight change in a side effect, we can sometimes get ahead of it and make a change that might help avoid a really severe side effect. We have a standard up-titration protocol as well as a goal dose that we're trying to get to before discharge, but I think it's so important to make sure patients never feel that they have failed if they can't get to this dose right away. We know that patients respond to these medications differently, and so we really want the patient to be the leader and go at their own pace. So we can definitely make modifications to that titration plan. Also, sometimes our patients just need a titration vacation, as we call it. They just need a day to kind of reset and see where they are with side effects. We can then go back and see if we're able to continue with up-titration. Occasionally, a patient has severe, uncontrolled side effects, or comorbid conditions that limit our usual strategies. In these situations, we're very fortunate to have our palliative medicine colleagues, so I'll turn it over to Dr Johns.

Dr Johns (pulmonologist, palliative medicine specialist): When I meet a patient for the first time, I introduce myself and ask about their understanding of palliative medicine. It's like what Tiffani was saying: They're googling things, and then they see palliative, and they say, "Oh my goodness, I am dying." I spend a lot of time explaining what palliative really is. Sometimes I'll show a big circle and say this is palliative medicine; this is all the things that we can do. Then I'll show a tiny circle inside the big circle and explain that this is end-of-life care and hospice. Modern palliative medicine is really meeting patients early in their disease process to manage their symptoms. In PH, we're really trying to manage symptoms aggressively so they can optimize maximal therapeutic interventions for that patient. I also follow them in the clinic to help optimize outpatient symptoms, like diarrhea. Ideally, I prescribe medications that address more than one symptom at the same time. The other part of what we do is help them navigate all the things that they're going through.

Settling In: *"How do I get my life back?"*

Dr Visovatti: Tiffani, I hope that the benefits of you medications have outweighed the side effects.

Ms Brown: Yes. About a year into treatment, I was finally feeling well enough to get up and do things again, but with that came a whole new routine, and I had to figure out how to go about my daily life outside of the house. I needed to make sure I had the alarm set and that I was taking everything I was going to need with me. I had to pack that extra bag of supplies and the extra pump. You really have to plan ahead. You couldn't do anything just on a whim anymore. So you have to find your new routine, find your new normal. You also have to remember that, even though you're feeling good, it doesn't mean that your body can keep up with everything your mind wants to do. Sometimes you wake up the next day not feeling so great because you overdid it on your good day. So it's about learning how to take your good days and not overdo it so the next day can be a good day as well. Also, learning how to navigate the site pain was a big one for me because I was on subcutaneous. When I was hanging out with friends, I had to think, "Okay, where am I at with my site?" Do I need to take all the ice packs and all the creams? Can I be out of the house for an hour or two and be okay with my site? Once you've gotten your routine down, it does make life a lot easier.

Dr Visovatti: Tiffani, were you on supplemental oxygen at some point in your journey?

Ms Brown: No, I got very lucky.

Dr Visovatti: We are so grateful that our delivery systems are getting easier and easier for patients in many ways. They are becoming less visible to the outside world. Emily, I wonder if we could ask you for your thoughts about Tiffani's situation up until now and discuss the concept of an "invisible disease."

Ms Fedewa (nurse practitioner): Yes, certainly. I think it's really important to recognize that pulmonary hypertension is often an invisible disease which, honestly, can be a double-edge sword. Patients receive this diagnosis, go home, and they look often like they did prior to the diagnosis, but they're likely not feeling their best physically or emotionally. They have this new full-time job that is managing their pulmonary hypertension. They are coordinating with specialty pharmacies; they're staying on top of refills (often from 2 to 3 or more pharmacies); they're contacting pharmacies when their medications aren't delivered; they're contacting their PH clinic when they have trouble contacting the pharmacies. I mean, the list goes on, and these are not one-and-done tasks, right? These are ongoing for life: taking medication 2 to 4 times a day, planning those medications around meals, planning to take their medications and their supplies anytime they leave their house, coordinating oxygen deliveries, making sure they have enough oxygen when they leave the house. We have patients that require 10 to 15 tanks just to attend a medical visit. Doing all of these things and processing all of these things when a patient still looks how they looked prior to their diagnosis can make it really hard to communicate this experience to their friends and families. Of course, not all patients go through this, and for those that do, there's an opportunity for education, but education takes time. So I think it's really important to recognize the challenge of having this invisible diagnosis, and on the other side, once somebody is wearing oxygen or sometimes parenteral therapy, that previously invisible disease is now visible, and that can bring into play a whole host of other psychosocial considerations. This can be especially hard for younger people in school and people in their 20s that are trying to go out. I think it's really important that we, as providers, recognize the complexities and challenges and that we acknowledge these things (out loud) to a patient. I think this acknowledgment goes a long way towards validating their experience.

Ms Kittel: I remember a time when Tiffani would never use a scooter in the grocery store. Now, in order to be able to do everything else she wants to do in a day's time, she'll use one of those little motorized carts to get through the grocery store.

Dr Carmin: I encourage patients to bring partners, support people, with them to their doctor's appointment because it is an invisible illness. It's important that people who are close to you understand what your needs are or what the course of the disease is. This is important information for them.

Dr Johns: I've had a patient ask me to tell their significant other that they can't do things because it's hard for them to tell their significant other themselves.

Ms Brown: Sometimes we can tell people, but they don't always hear it. We can say it over and over and over again, but they don't hear us.

Dr Visovatti: Kristen, you had your own personal journey with PAH. You were in the prime of life when you were diagnosed: You were accepted into medical school; you were thinking about your career, thinking about starting a family. Could you give us your perspective on how you struggled with life as you had envisioned it and then the life you were suddenly handed?

Dr Ramones (pediatric pulmonary fellow, patient): I was in the hospital, and my doctor was so good. She explained what pulmonary hypertension is, what the management would be, what the prognosis was. The sentence that really stuck with me and probably will sit with me for the rest of my life were the words, "You can never get pregnant," and that really just broke me. I just felt like my life was taken away at that moment. I got discharged, and I went to my bridal shower the next day. It was hard to adjust to that new life. Even now, I'm dealing with it. Although I have a lung transplant, I'm on immunosuppressants that are teratogenic. So PH has a lasting effect, even though I don't have PH anymore.

Dr Visovatti: You are devoting your life to pediatric pulmonary hypertension. We talked a lot about how adults have felt and what Tiffani has gone through. Could you give us an idea about how things are different for kids?

Dr Ramones: In pediatric PH, we focus on the challenges for patients in school and also caregivers' support. One of the most challenging things is how patients miss school because of so many appointments and hospitalizations. They're unable to participate in gym class, or they have to carry an oxygen tank when they're on the playground. We even start seeing them dissociate from other kids because other kids just don't understand what they're going through. As pediatricians first and foremost, we really want to protect the overall development of the child. We now have multidisciplinary clinics where patients see pediatric pulmonology, pediatric cardiology, social work, and nutrition. This really cuts down on the number of appointments that patients have to make. I think connecting families is really helpful, too, because you just don't see kids with PH that often. So they see someone like them, which helps a lot. Caregiver support is important in pediatrics because most of our patients can't take care of themselves. So relying on parents, guardians, caregivers and really focusing on their support is important. I went to a conference a couple of months ago, when they mentioned the concept of the forgotten patient. They were basically saying that the caregiver goes along the journey as the forgotten patient. When the patient has good days, the caregiver has good days. When the patient has a bad day, the caregiver has a bad day.

Giving Back: *"How can I help others?"*

Ms Rupp: We all talk so readily, whole-heartedly, and passionately about support; it looks different for everyone. Everybody's support network is certainly important. Tiffani and Debbie are a prime example of how to make a good support network. Would you share with us about how support groups, peer support, and the support of your team has been really integral to your path?

Ms Brown: There was a pivotal point for me. I was just in a really bad place. I was in the hospital. I just had a heart catheterization, and Debbie walks into the room and says, "I want to talk to you about starting a support group, and I want you to co-lead it with me." I said, "Let's do it." It was like music to my ears because I had been thinking that I wished I had a support group to go to. I wished I could talk to other patients who understood PH. So we started. Our first meeting came around, and we were both so nervous and excited. It was a wonderful first meeting. The patients were just as excited as we were. We had a great turnout, and to this day, we still have an amazing group.

Ms Rupp: Can I ask: Reliving your PAH experience can be negative, right? It can be very traumatic to have to go through it again. How does it feel to share that on a regular basis in the support group?

Ms Brown: I feel like it helped heal a part of me that I didn't know needed healing. Your initial diagnosis is so raw and full of so many emotions, but you just get through it, and you keep going. Then you meet another patient who's going through it, and you're like, "Let me hold your hand. Let's get through this." As you're helping them or guiding them, it's healing a part of you that you didn't know was damaged. So the support group has just helped me immensely in a lot of different ways.

Ms Kittel: I learned from patients just how much misinformation you find on social media. I wanted a more supportive place for patients. During the first couple years, we did a lot of lectures or talks about pulmonary hypertension. Now I feel like our support group has shifted to not just learning about PH but also about supporting each other. For example, Tiffani was going through a really bad time. We had a support group meeting that week, and I secretly pulled everybody aside and asked if they would please write a little note of encouragement for Tiffani.

We put them into a "jar full of support" and gave it to her. She sat in bed and just cried and cried as she read through every note that everybody sent. We've given out multiple jars of support to different patients who are struggling. Our biggest event of the year is a low sodium Thanksgiving dinner. Tiffani and I cook Thanksgiving dinner for all the families in our support group.

Ms Rupp: I love what you've done with your group. We want to make sure that people are supported and informed, so we've put together a list of resources that people can explore further. We list things you can do as a community to rally people around pulmonary hypertension awareness, diagnosis, management, and support.

REGULAR ARTICLE

Pulmonary Hypertension Associated With Parenchymal Lung Disease

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Pulmonary hypertension (PH) is a frequent occurrence in interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD) and combined pulmonary fibrosis and emphysema and can be associated with higher morbidity and mortality than pulmonary arterial hypertension. Historically, PH therapy has not been shown to improve outcomes in patients who have PH associated with parenchymal lung disease until more recent approval of inhaled treprostinil in PH-ILD. Unfortunately, this success has not been replicated in PH-COPD. More careful selection of patients who have a predominantly pulmonary vascular phenotype in treatment with PH therapy may be beneficial, and novel trial design may be helpful to determine subgroups within this blanket category who may benefit. Finally, it is critical to approach patients with PH and parenchymal lung disease in a comprehensive fashion, addressing all aspects of medical, psychological, and socioeconomic challenges faced by patients and their caregivers.

INTRODUCTION

Pulmonary hypertension (PH) is a frequent occurrence in interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD), and combined pulmonary fibrosis and emphysema (CPFE). Although precise estimates are difficult, among patients undergoing lung transplant evaluation for idiopathic pulmonary fibrosis, approximately 46% of patients are found to have PH, and the incidence ranges from around 10% to 15% in patients with ILD associated with systemic sclerosis and 20%–25% in patients with ILD associated with mixed connective tissue disease (CTD).[1–3] In patients with COPD, the prevalence of PH is around 30%–40%, with around 5%–7% of patients experiencing severe disease.[4,5] Furthermore, patients with CPFE likely have a higher incidence and more severe pulmonary vascular disease than those who have emphysema or pulmonary fibrosis alone.[6]

Patients with coexisting lung disease and PH have a prognosis which is markedly worse than that of patients with pulmonary arterial hypertension (PAH). As an example, in 1 registry, patients with World Symposium on Pulmonary Hypertension Group 3 PH had a 5-year survival of under 40%, while patients with PAH had an overall 5-year survival of just over 60%.[7] Significant differences in survival have been found between patients who have PH associated with emphysema, CPFE, non-IPF ILD, and IPF.[7] The combination of these conditions significantly impacts patients' quality of life, frequency and duration of hospitalizations, and health care costs.[8]

DIAGNOSTIC CHALLENGES IN PH ASSOCIATED WITH CHRONIC LUNG DISEASE

Apart from systemic sclerosis,[2] no well validated screening algorithms exist for PH in patients with ILD, COPD, or CPFE. Patients who have CTD or other ILD are often evaluated for PH when they have low diffusing capacity, particularly out of proportion to extent of restrictive lung disease, when they have an elevated pulmonary artery (PA) size or PA : aorta ratio on computed tomography scanning, when they have serologic positivity known to be strongly associated with PH, or when they have cardiopulmonary symptoms out of proportion to or not consistent with the known manifestations of their CTD or other ILD.[9–11] A similar approach, focused on signs and symptoms out of proportion or inconsistent as well as elevation in B-type natriuretic peptide, is used to trigger echocardiographic screening for PH in patients with COPD and CPFE.[12]

Screening for PH by transthoracic echocardiography is limited in its accuracy of detection and estimation of PA pressure, particularly in patients with parenchymal lung disease.[13] Thus, right heart catheterization (RHC) remains the best tool for diagnosis of PH this population, but patient selection for RHC remains inconsistent outside of populations undergoing transplant workup or clinical trial consideration, and PH in ILD and COPD likely remains underdiagnosed. The RHC hemodynamic thresholds of mean PA pressure >20 mmHg, PA occlusion pressure ≤15 mmHg, and pulmonary vascular resistance (PVR) ≥3 Wood units are identical in World Symposium on Pulmonary Hypertension Group 1 and Group 3 PH, and classification

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is dependent on the assessor's attribution of pulmonary vascular disease to parenchymal lung disease or to another underlying cause.[14]

EVOLVING UNDERSTANDING OF PH ASSOCIATED WITH CHRONIC LUNG DISEASE

The traditional understanding of PH development in chronic parenchymal lung disease has rested on the combination of diffuse hypoxic vasoconstriction and architectural distortion of lung parenchyma leading to a rise in PA pressure and PVR. Increasingly, however, the relationship has been recognized between parenchymal changes and pulmonary vasculopathy as significantly more complex (Figure 1). For example, endothelin-1, a known culprit in PAH, is overproduced in IPF and may drive progressive pulmonary fibrosis independently of pulmonary vasculopathy,[15] which was the basis for several trials of endothelin receptor antagonists (ERAs) in ILD, discussed below. Furthermore, genetic predisposition through BMPR2 mutation, inflammation and oxidative stress from underlying lung disease, or from the underlying CTD, when present, may increase patients' predisposition to ILD and PH.[16] Similar pathways of proinflammatory cascade leading to endothelial dysfunction may also contribute to the development of PH associated with COPD.[17] The parallels in the pathogenesis of PH with ILD and COPD are reflected in histopathologic similarity of vascular remodeling between these patients' and that of patients with PAH.[14]

Importantly, it is well established that the severity of ILD does not correlate with development of PH; it has been demonstrated that reduction in forced vital capacity, extent of radiographic fibrosis, and elevation in mean PA pressure are unrelated in IPF and CTD-ILD.[1,18–20] This is important for several reasons. First, it means that clinicians should consider evaluation for PH in all patients with ILD, not just those with advanced disease. Second, it highlights the possibility of predominantly vascular and predominantly parenchymal disease phenotypes, which can suggest the utility of using PAH therapies in patients with ILD.

Guideline and expert opinions on this topic have largely left treatment decisions for patients who have severe PH with significant parenchymal changes up to clinicians and individualize care.[21] Among patients who develop significant pulmonary vascular disease in the context of parenchymal lung disease, symptom burden and mortality are largely driven by consequences of PH, such as right heart failure; this raises the question of whether screening for PH and treating earlier, rather than waiting for disease progression, can improve patient outcomes.

CLINICAL TRIALS IN PH ASSOCIATED WITH ILD

Multiple negative randomized controlled trials (RCTs) of ERAs as well as sildenafil alone or combined with antifibrotic therapy in patients with IPF have been done. Authors of these studies generally either excluded or were agnostic to the presence of PH and were designed to be ILD trials. Investigators of 2 of the trials published subset analyses of patients with PH and ILD—a subgroup of patients with mild (mean PA pressure [mPAP] = 30 mmHg, PVR = 3.9 Wood units) Group 3 PH in ARTEMIS-IPF (n = 68)[22] and a subset of patients with right ventricular dysfunction in STEP-IPF (n = 119).[23] No obvious difference was found for outcomes in the ARTEMIS subgroup, and the STEP-IPF subgroup

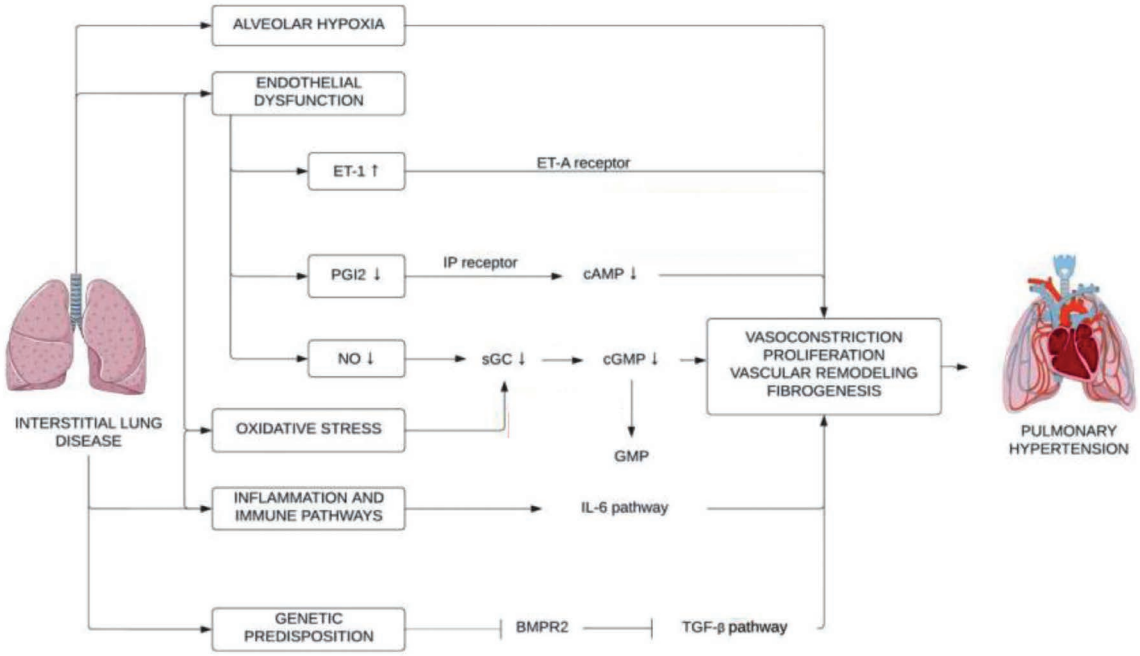

Figure 1: Proposed pathophysiologic mechanisms in the development of pulmonary hypertension (PH) and interstitial lung disease (ILD). Adapted from Dhont et al.[16] Reproduced under Creative Commons Attribution Noncommercial License 4.0.

with RV dysfunction had a lower reduction in 6-minute walk distance (6MWD) and improvement in quality of life on sildenafil.

Authors of several prospective, open-label, registry, and retrospective series have suggested a benefit to treatment of patients with PH-ILD with systemic pulmonary vasodilators, including phosphodiesterase 5 inhibitors, ERAs, and systemic prostacyclins. The benefit seen in these studies seemed to be most prominent among patients with severe PH (mPAP > 35 mmHg), who respond to therapy early and robustly, and those who had CTD-ILD (particularly systemic sclerosis).[24–26] Authors of an early single open-label study[27] of patients with ILD and PH assigned to intravenous (IV) epoprostenol or sildenafil 50 mg suggested a slight increase in V/Q mismatch with aggressive uptitration of IV epoprostenol (no V/Q change with sildenafil), which was not associated with adverse events and has not been reproduced since. None of the authors of subsequent trials of pulmonary vasodilators in ILD without PH, published prospective case series—including 1 of IV treprostinil in severe ILD with PH awaiting lung transplant[28]—or registry or retrospective series suggested worsening hypoxemia with systemic pulmonary vasodilators.

Investigators of 3 RCTs specifically evaluated patients with PH and ILD. In BPHIT (n = 60), no difference was found in PVR index reduction among patients with moderate PH receiving bosentan as compared with placebo.[29] RISE-IIP (n = 229) was stopped early due to safety concerns (in part related to adverse events in patients with CPFE and significant emphysema) in patients receiving riociguat, and investigators found no difference in 6MWD at 26 weeks as compared with placebo.[30]

Most recently, in the INCREASE trial (n = 326), a significant improvement of 31 m was demonstrated with inhaled treprostinil over placebo in patients with ILD (a mix of IPF, CTD-ILD, and others) and PH (mPAP = 37 mmHg, PVR = 6.2 Wood units),[31] even among patients with less severe hemodynamics.[32] A secondary endpoint was lower clinical worsening in the treprostinil arm, and authors of a subsequent post hoc analysis have suggested a reduction in disease progression events and a survival benefit to inhaled treprostinil.[33,34] It should be noted that the benefit was greatest at a dose of ≥9 inhalations 4 times daily. However, enthusiasm has been tempered somewhat by a fairly high discontinuation rate (almost 10% stopped treprostinil due to intolerance in the study, and most experts' real-world experience has suggested much higher discontinuation rates), lack of independent adjudication of clinical worsening events, and the use of a nebulized treprostinil device, rather than the more commonly prescribed dry powder inhaler used today. In fact, in some large-volume centers, patients with PH-ILD are started on nebulized treprostinil, rather than dry powder inhaler, due in part to a lower rate of discontinuation.[35] Nonetheless, inhaled treprostinil represents an exciting potential treatment in a disease with few other options. In the long-term extension study of INCREASE, continued inhaled treprostinil was associated with ongoing improvement in 6MWD and reduced risk of exacerbation as compared with placebo.[36]

Consideration of inhaled treprostinil has a class IIb, level B recommendation for PH-ILD, and phosphodiesterase 5 inhibitors have a Class IIb, level C recommendation for ILD associated with severe PH in the 2022 European Society of Cardiology/European Respiratory Society guidelines.[37] Inhaled treprostinil is the only currently Food and Drug Administration–approved therapy for PH associated with ILD (see Table 1).

CLINICAL TRIALS IN PH ASSOCIATED WITH COPD

Authors of several small RCTs have evaluated systemic pulmonary vasodilators, mainly sildenafil and bosentan, in patients with COPD and PH. These have had mixed results. Authors of 2 trials of sildenafil 20 mg 3 times daily and 1 trial of bosentan in patients with COPD and PH by either echocardiogram (PA systolic pressure

Table 1. Randomized Controlled Trials of PH Associated With ILD

Trial	Study population	Intervention	PH diagnosis and characteristics	Primary outcome
ARTEMIS-PH[22]	Subset of ARTEMIS-IPF (14% of cohort)	Ambrisentan	RHC: mPAP 30 mmHg	No obvious difference (underpowered)
STEP-IPF subgroup[23]	Subset of STEP-IPF (66% of cohort)	Sildenafil	Right ventricular systolic dysfunction	Smaller drop in 6MWD on sildenafil; improvement in QoL
BPHIT[29]	IIP + PH	Bosentan	RHC: mPAP 37 mmHg	No difference in PVR index reduction >20% between groups
RISE-IIP[30]	IIP + PH	Riociguat	RHC: mPAP 33 mmHg	No difference in 6MWD; stopped early due to increased harm with riociguat
INCREASE[31]	ILD + PH	Inhaled treprostinil	RHC: mPAP 37 mmHg	31.1 m improvement in 6MWD over placebo

Abbreviations: 6MWD indicates 6-minute walk distance; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; mPAP, mean PA pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; QoL, quality of life; RHC, right heart catheterization.

>40 mmHg) or RHC suggested improvements in 6MWD, quality of life, and PVR[38–40]; however, authors of other trials have had contradicting results.[41,42] Authors of only 1 study[43] of bosentan in COPD associated with PH suggested worsening hypoxemia with no similar signal in any other trial.

Most recently, a larger RCT of inhaled treprostinil in PH associated with COPD (PERFECT) was stopped early after an interim analysis suggested a higher rate of serious adverse events in the treprostinil group.[44] In this trial, investigators attempted to enrich for a pulmonary vascular phenotype (mPAP ~ 44 mmHg and PVR = 7–8 Wood units in all groups) and failed to demonstrate improvement in the primary endpoint of 6MWD, although its early termination meant that the trial was underpowered for this conclusion. Although it is not entirely clear what contributed to this safety signal, it is possible that the inclusion of a significant number of patients with marked reduction in low diffusing capacity (≤25%), who are already at increased risk of morbidity and mortality, contributed to the number of deaths seen in the study. In PERFECT, CPFE was excluded, and so it was mainly a trial of emphysema-PH; in the INCREASE trial, patients with CPFE had a much less robust response to inhaled treprostinil than patients with PH and IIP and CTD-ILD, which may have been due to the extent of emphysematous parenchymal change.

NONPHARMACOLOGIC TREATMENT CONSIDERATIONS IN PH ASSOCIATED WITH PARENCHYMAL LUNG DISEASE

Patients with PH and parenchymal lung disease benefit from expert, multidisciplinary evaluation. This team should ideally be led by a PH specialist who understands the nuances of pulmonary vascular disease in chronic lung disease and often requires collaboration with other specialists, such as rheumatologists and supportive care medicine specialists, to ensure that all aspects of disease are being treated. Patients should be referred early for lung transplant evaluation since delays in referral can mean that patients are too frail, malnourished, or deconditioned to tolerate lung transplant.[45] Early referral can allow for optimization of nutrition, esophageal reflux (if present), obstructive sleep apnea, atherosclerotic disease, and PH among patients with COPD and ILD.[45] In general, most patients with severe or progressive COPD or ILD with PH and age less than 75 years merit lung transplant evaluation, but it should be noted that, historically, older patients have had worse outcomes than younger patients.[46]

It is important to remember that patients with COPD or ILD and PH have multiple comorbid diseases which can significantly affect their trajectory and quality of life. Patients with progressive pulmonary fibrosis should be treated with antifibrotic therapy early, with more supportive data for nintedanib than pirfenidone in reducing the rate of forced vital capacity decline in patients with non-IPF fibrotic ILD.[47] Patients with ILD responsive to immunosuppression should be treated accordingly, sometimes in combination with antifibrotic therapy. Patients who have COPD should be treated with appropriate guideline-directed inhaler therapy, consideration of chronic azithromycin or roflumilast and, more recently, ensifentrine.[48,49]

Patients with PH and ILD or COPD who have resting or exertional hypoxemia should be treated with supplemental oxygen with a goal SpO2 of ≥90%, although the best data for this are in patients with COPD. Patients with nocturnal hypoxemia should be started on supplemental oxygen.[50] Nocturnal noninvasive positive pressure ventilation is indicated for patients with sleep-disordered breathing, common in patients with ILD and COPD,[51] and patients who have chronic hypercapnia (although, again, this is largely extrapolated from patients with COPD).[50,52]

Pulmonary rehabilitation should be considered for all patients, as it may improve exertional tolerance and reduce frailty in patients with PH and ILD and COPD.[50,53–55] Patients who cannot undergo a formal pulmonary rehabilitation program for logistical or financial reasons should be encouraged to engage in regular exercise, while avoiding exertion to the point of chest pain, syncope, or lightheadedness.[50] Patients should be counseled on low-salt diets, appropriately treated with diuretics, and treated for gastroesophageal reflux disease, as appropriate. Finally, all patients who continue to smoke should be counseled on tobacco cessation and appropriate vaccination[50] against influenza, COVID-19,[56] pneumococcus, and respiratory syncytial virus since infection with these pathogens can contribute to exacerbations of underlying parenchymal lung disease and accordingly accelerate decline in lung function.

Most patients with PH of all types experience significant symptom and treatment burden. Quality of life may be worse in patients with PH associated with parenchymal lung disease than in patients with PAH, despite more favorable hemodynamics.[57] Also, an extraordinary physical and psychological burden exists for patients' caregivers. These translate directly to enormous impacts on day-to-day life, mental health of patients and caregivers, and financial challenges faced by patients and their loved ones.[58] Early referral to palliative or supportive care and support groups should be considered, even among patients who are potential transplant candidates, as well as timely and thoughtful discussions about end of life.[59] Supportive care referrals should not be seen as "giving up hope" or focusing on the end of life, as is commonly felt by PH physicians[60] but, on the contrary, helping patients to live their lives as fully as they can. Unfortunately, even among PH centers of excellence, only 5.8% of patients are referred to palliative care, and 43% of these referrals are made at the last visit prior to death.[61] A summary of overall management in PH associated with ILD and COPD is provided in Figure 2.

FUTURE DIRECTIONS

Future trial designers may need to focus on the extent of severity of parenchymal

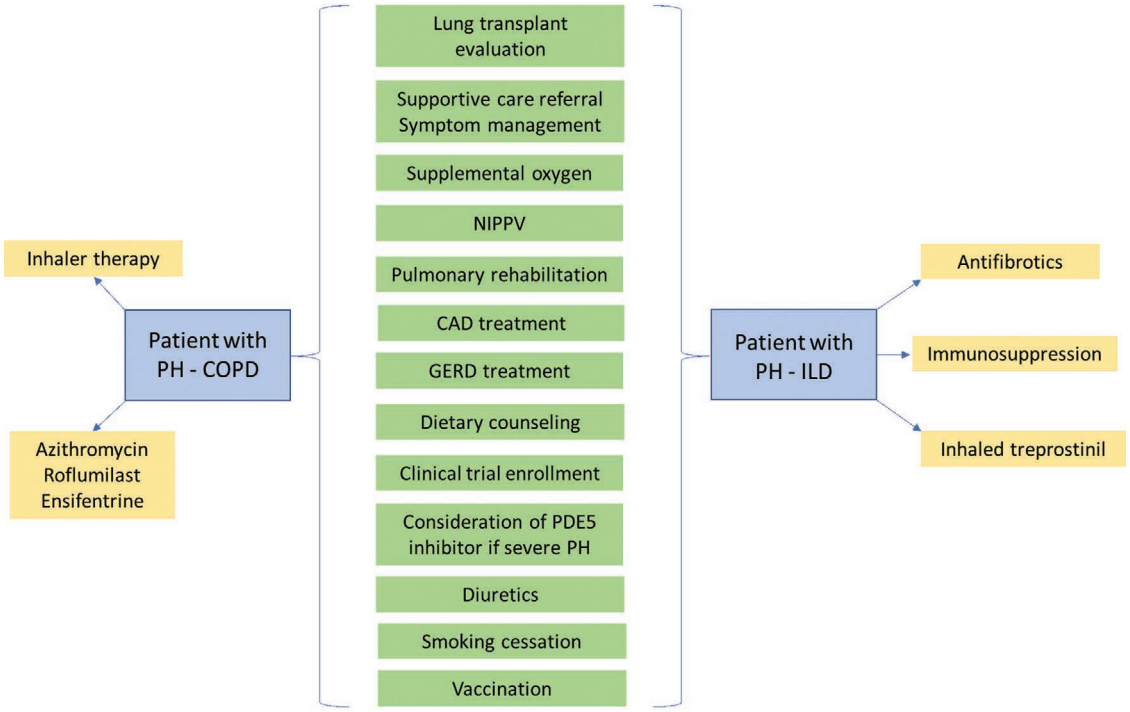

Figure 2: Overall approach to management of patients with pulmonary hypertension (PH) and interstitial lung disease (ILD) or chronic obstructive pulmonary disease (COPD). Abbreviations: NIPPV, noninvasive positive pressure ventilation; CAD, coronary artery disease; GERD, gastroesophageal reflux disease; PDE5, phosphodiesterase 5.

and vascular disease, the specific subtype of parenchymal disease (particularly with differences in patients who have CPFE), and severity of hemodynamics. Furthermore, novel trial design, such as adaptive and event-driven trials and master protocols to optimize efficiency in drug development, may allow for more robust recruitment.[62] Finally, use of trial endpoints past the traditional 6MWD may allow for exploration of more clinically relevant, patient-oriented outcomes.[62]

CONCLUSIONS

Despite recent advances, PH associated with COPD and ILD remains a disease with very high morbidity and mortality and few good treatment options. Although a treatment option now exists for PH-ILD, many patients will be unable to tolerate it, and for many patients, it may not be adequate. Management of these complex patients should be done while keeping in mind the other aspects of their disease. High-quality data are desperately needed in particular phenotypes of patients who suffer from PH associated with COPD or ILD.

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REGULAR ARTICLE

Defining Disease Modification in Pulmonary Arterial Hypertension

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With the advent of novel therapeutic agents for pulmonary arterial hypertension (PAH), the debate surrounding disease modification has gained attention. While distinguishing therapies with disease-modifying potential is of interest to patients, clinicians, and industry partners, the ultimate authority for such designations rests with regulatory agencies like the U.S. Food and Drug Administration and European Medical Agency. In this review, we explore the challenges in defining and establishing a therapy as disease-modifying in PAH. Additionally, we examine whether this distinction truly matters from the perspectives of both patients and clinicians.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a relentlessly progressive disease marked by increasing resistance of the pulmonary vasculature.[1] The increasing resistance leads to uncoupling of the pulmonary vasculature from the right ventricle (RV), gradual reduction in the RV cardiac output (CO), and end-organ failure of the right heart and death.[1] The mechanisms leading to the development of increasing resistance in the pulmonary vasculature are multifactorial and have led to the development of therapies that target mainly vasoconstriction.[1] Further investigation has led to the identification of other pathways that are involved in a more fundamental manner in the pathogenesis of PAH. One such signaling mechanism is the activin pathway, which was found to be closely tied to proliferative effects within the pulmonary vasculature and ultimately laid the groundwork for the development of the activin receptor antagonist sotatercept.[2] By opposing the activin 2a receptor, sotatercept acts to balances 2 opposing mechanisms, the proproliferative transforming growth factor-beta (TGF-beta) pathway and its antiproliferative counterpart, the bone morphogenic protein receptor-2 (BMPR-2) pathway.[2] This was subsequently tested in PAH patients, with both trials meeting their primary endpoints of a robust drop in pulmonary vascular resistance (PVR) in the Phase 2 trial[3] as well as a significant increase in 6-minute walk distance (6MWD) in the Phase 3 trial.[4] The identification of a therapy that appears to target more fundamental pathways of disease has spurred a growing interest in the concept of disease modification and disease-modifying therapies (DMTs). While the exercise of defining what a DMT is (and perhaps just as importantly, what it is not) retains great value, its translation to trials and clinical medicine is still fraught with challenges. These challenges range across the spectrum of health care, encompassing trial design that must be able to demonstrate disease modification, interactions with industry and regulatory bodies, and most importantly, the patients seeking to understand the mechanisms of their therapies. The benefits of this exercise are far reaching, spurring us to the development of new treatment paradigms for PAH.

We must note at the outset of our discussion that, while the term *disease modification* has been variously used in the literature as a general catch-all phrase for any molecule that could potentially target original pathophysiologic pathways, the use of the DMT designation for specific medications is generally avoided since none of our current therapies have been approved as disease-modifying agents by regulatory authorities.

DEFINITIONS AND IMPLICATIONS

The definition of DMT found its origins in the annals of neurological disease, eventually spreading to multiple other specialties. Whether in clinical practice or by Food and Drug Administration (FDA) guidelines, a common theme to many of these definitions is the focus on a drug that acts directly on the underlying pathophysiologic mechanisms, fundamentally altering disease course and resulting in improved clinical outcomes. We will discuss these commonalities, their variants, and the resulting implications of their use within the context of PAH.

The indication for disease modification originated with interferon-beta (IFN-B) in 1993, which was labeled as a DMT for relapsing-remitting multiple sclerosis (MS).[5] Investigators of an earlier trial had shown that IFN-B was able to decrease relapses; however, it was not until the pivotal Multiple

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Sclerosis Collaborative Research Group Phase 3 trial in 1996 that researchers demonstrated that IFN-B could alter disease course by decreasing patient disability over time.[6] The FDA continued to furnish more direction on attainment of the disease-modification designation in guidance documents published in 1999 and then 2013.[7] The DMT definition would be further bolstered by the advent of rheumatologic disease-modifying agents (DMARDs), ultimately followed by multiple other chronic diseases including systemic sclerosis, Alzheimer's, epilepsy, MS, Parkinson's disease, chronic obstructive pulmonary disease, and emphysema (see Table 1).[8] A review of these demonstrates the breadth of varying definitions, with some focusing on prevention of end-organ failure and others on prevention of disease relapse.[8] The majority, however, focus on the alteration of disease course by targeting underlying disease mechanisms.[8]

While this emphasis on alteration of disease course is readily acknowledged, 2 other key concepts have been variably described in DMT, which the PAH community will need to define for itself: that of durability of effect and end-organ dysfunction.

First, disease modification is intrinsically durable. How *durability* is defined varies across disease state. Mounting evidence has clearly demonstrated that early initiation of therapy alters the course of a disease and its progression in MS.[9] Certain other realms argue that the definition should be taken even farther—that is, because it alters fundamental mechanisms of disease, the drug should be able to induce beneficial effects within the molecular milieu that persist after the drug has been cleared.[8]

Second, and perhaps more controversially, the PAH community must determine whether to include prevention of end-organ failure in our definition of disease modification. In the case of PAH, the most obvious candidate for end-organ failure is the RV. Acknowledging that sotatercept has not been granted the FDA designation of DMT, let us consider it as a corollary for a DMT for the moment, given its effects on fundamental signaling pathways. In this context, we must allow that the relationship of sotatercept to the RV has yet to be fully elucidated. Use of sotatercept did not increase CO in the STELLAR[4] and PULSAR[3] trials, while it did improve multiple other echocardiographic parameters of RV function in a post hoc analysis of STELLAR.[10] By this standard, would sotatercept fail the definition of disease modification in this hypothetical context? We would argue that, while CO did not increase during the trials, it did not decrease, which has been demonstrated to occur in untreated placebo populations linked to trials of similar length. It can be argued that prevention of end-organ failure does not necessitate increase in but rather maintenance of CO, which occurred in the STELLAR[4] and PULSAR[3] trials, and thus, a delay in end-organ failure can be presumed.

Considering these variable descriptions, we propose the following definition of DMT in PAH: It must be able to alter an underlying common pathophysiologic pathway in Group 1 PAH, improving clinical outcomes and delaying end-organ failure in such a fundamental physiological way as to demonstrate durable benefit beyond drug discontinuation and clearance.[11]

Having defined DMT, we must note that there are multiple other characteristics of therapy that this definition excludes; we will discuss the implications these have within the PAH realm. First, disease modification does not imply disease reversal. Disease modification is not equivalent to cure. This would necessitate the identification of a fundamental cause of PAH that is yet unrecognized. We know that PAH is the culmination of multiple processes—genetic, epigenetic, and environmental—which result in disordered regulation. From a genetic perspective, for example, we know that while BMPR-2 mutations are the major cause of heritable PAH, the overall penetrance of the mutation is only 20%.[12] This suggests a strong role for nongenetic factors.[12] Further, we know that many patients with PAH who do not code for the mutation nevertheless have disordered BMP signaling—what we have not identified is the cause of this disruption, in the absence of genetic mutations.[12] Additionally, this represents only 1 of multiple disordered pathways.[12] The concept of disease reversal is further hindered by the advanced state at which PAH presents. The pulmonary vasculature is extremely generous compared with the systemic circulation, with about 10 times the density of the other arterial vasculature.[12] The resultant high compliance and redundancy is adaptive; however, this also means that, by the time the disease is reflected in the proximal vasculature on screening echocardiography, approximately 50%–60% of the vasculature has been destroyed.[12] Reversal in this case would necessitate reformation of a large amount of obliterated, fibrotic pulmonary vasculature to such a degree that the distal pulmonary arterioles would achieve significant recanalization and functionality.

Second, disease modification does not signal a particular level of drug efficacy. It is well established in the rheumatologic world that DMTs have differing potencies, and multiple meta-analyses have been done attempting to quantify comparative efficacy among the various agents.[13] Further, drugs may have variable responses based on yet unrecognized phenotypes. The discussion invites further investigation into subgroups that are nonresponders and superresponders to DMT, using biomarkers, proteomics, and immunologic phenotyping, with the goal of one day being able to predict individual response to therapies. Until then, our ability to identify a patient who would experience particular benefit from DMT is limited.

Third, the designation of disease modification should not apply to all medications that have secondary, less potent effects within a similar biologic pathway. These secondary benefits have been demonstrated in both the phosphodiesterase-5 (PDE-5) inhibitors and the endothelin receptor antagonists (ERAs). For instance, the PDE-5 inhibitor sildenafil, in addition to its vasodilatory effects via the cyclic guanosine monophosphate pathway, has been demonstrated to potentiate BMPR signaling in human pulmonary arterial smooth muscle cells and monocrotaline

Table 1. Prior Definitions of Disease-Modifying Therapy by Disease State

	Definitions
Rheumatologic disease	
Rheumatoid arthritis	"A DMARD is defined as a medicine that interferes with signs and symptoms of rheumatoid arthritis, improves physical function, and inhibits progression of joint damage"[8] EULAR: "The concept of 'disease modification' comprises a combination of relief of signs and symptoms; improvement or normalization of physical function, quality of life and social and work capacity; and most characteristically the inhibition of occurrence of progression of structural damage to cartilage and bone"[8] ACR: "Agents that apparently alter the course and progression of rheumatoid arthritis, as opposed to more rapidly acting substances that suppress inflammation and decrease pain, but do not prevent cartilage or bone erosion or progressive disability"[8]
Multiple sclerosis	"Ideal DMT should halt the progression of the disease and hopefully induce remission, and preferably also reverse some of the major organ complications. . . It is reasonable to expect a DMT to stabilize organ function without any further worsening of other domains"[8]
Neurologic disease	
General neurodegenerative diseases	"A disease-modifying therapy is an intervention that produces an enduring change in the trajectory of clinical decline of a neurodegenerative disorder by impacting the disease processes leading to nerve cell death"[8] EMA: "For regulatory purposes, a disease modifying effect will be considered when a pharmacologic treatment delays the underlying pathological or pathophysiological disease processes and when this is accompanied by improvement in clinical signs and symptoms of the dementing condition"[8]
Alzheimer's disease	"Disease modification can be defined as treatments or interventions that affect the underlying pathophysiology of the disease and have a beneficial outcome on the course of Alzheimer's disease"[8] "A disease-modifying therapy is as an intervention that produces an enduring change in the clinical progression of Alzheimer's disease by interfering in the underlying pathophysiological mechanisms of the disease process that lead to cell death"[8] EMA: "A medicinal product can be considered to be disease modifying when the pharmacologic treatment delays the underlying pathological or pathophysiological disease processes. This can be demonstrated by results that show slowing in the rate of decline of clinical signs and symptoms and when these results are linked to a significant effect on adequately validated biomarkers. Such biomarkers should reflect key pathophysiological aspects of the underlying disease process based on a plausible disease model. The choice of biomarker as well as the type of analysis is left open, although more weight will be given to those biomarkers showing not only target engagement, but also an effect on the downstream disease mechanisms"[8] FDA: "Permanently altering the course of Alzheimer's disease through a direct effect on the underlying disease pathophysiology; the effect persists in the absence of continued exposure to the drug"[8] PMDA: "Medical agents that delay neurodegeneration and neuronal cell death by acting on the pathological mechanism of Alzheimer's disease and, as a result, inhibit the progression of clinical symptoms"[8]
Epilepsy	"According to the definition of epileptogenesis, 'disease modification' refers to every clinically relevant therapeutic outcome which does not necessarily prevent epilepsy onset but significantly improves the disease course by reducing seizure burden and/or decreases concomitant comorbidities"[8]
Multiple sclerosis	Disease-modifying therapies are "drugs targeted to prevent relapses of the disease, and consequently, progression of disability"[8]
Parkinson's disease	"A disease-modifying therapy. . . slows or stops disease progression"[8]
Pulmonary disease	
COPD	"An improvement in, or stabilization of, structural or functional parameters as a result of reduction in the rate of progression of these parameters which occurs whilst an intervention is applied and may persist even if the intervention is withdrawn"[8]
Emphysema	"Disease modification is a sustained improvement in disease state following therapeutic intervention that persists when therapy is discontinued"[8]

Abbreviations: ACR indicates American College or Radiology; COPD, chronic obstructive pulmonary disease; DMARD, rheumatologic disease modifying agents; DMT, disease-modifying therapy; EMA, European Medicine Agency; EULAR, European Alliance of Associations for Rheumatology; FDA, Food and Drug Administration; PMDA, Pharmaceuticals and Medical Devices Agency.

rats.[14] Endothelin-1, in addition to being a potent vasoconstrictor, has a much less potent effect on mitogens that contribute to vascular overproliferation via the rapidly accelerated fibrosarcoma/mitogen-activated protein kinase pathway.[15] Based on these findings, we can reasonably hypothesize that ERAs would exert a weak and indirect antiproliferative effect.[16]

REGULATORY AND CLINICAL CHALLENGES

While the delineation of definitions is helpful in theory, multiple challenges arise to its use. From a regulatory standpoint, the main challenges center on how to demonstrate durability in clinical trials and how to address barriers to FDA approval; within clinical practice, the challenge is to identify the best phenotypes for therapy and the ideal timing of treatment initiation and withdrawal. Finally, the most important challenge is to responsibly communicate the DMT label and incorporate the perspective of our patients.

The most conspicuous difficulty is that of demonstrating durability of benefit in clinical trials. Two study designs that can demonstrate persistence and thus disease-modifying effect include delayed-start and drug discontinuation studies.[11,17] The delayed-start trial design involves 2 study groups, an early and a delayed-start group, who are followed for clinical worsening from the baseline study visit through 2 phases.[17] In Phase 1, the early group is started on therapy, while the delayed group is treated as the placebo; in Phase 2, the placebo group is then also initiated on therapy.[17] Once on the same therapy, the 2 populations are expected to demonstrate a constant rate of clinical worsening over time, with the difference between the 2 groups presumed to be due to disease-modifying effect (Figure 1).[17] The main challenges of these trials involve discerning the best length of time for each phase. Phase 1 requires a duration that is long enough before the delayed group is started, to demonstrate benefit to the first group.[17] Likewise, Phase 2 must be able to avoid an early conclusion that could miss a potential intersection of the slopes.[17] Thus, the delayed-start design exposes the trialist to all the costs and risks of a study that will be at least twice as long as single-phase trials. The second type of trial, the drug discontinuation design, follows the slope of clinical worsening after withdrawal of a treatment.[11] This design introduces multiple inherent difficulties. The first is the obvious safety issues from withdrawal of treatment in a disease characterized by persistent progression (Figure 2). Strict monitoring guidelines for disease worsening would be required.[18] The second would be defining how late in the disease stage one could withdraw and still see results—ie, how far into the disease state will we able to attain enough of a slope differential to demonstrate durable effect? In such a scenario, the ability of a DMT to not only prevent forward progression but to also demonstrate resounding ability to reverse prior processes could help bolster the results of such a trial. Encouragingly, both experimental and genetic studies of a sotatercept analog demonstrate not only prevention of progression but also potential reversal of inflammatory processes and normalization of pulmonary vasculature.[19]

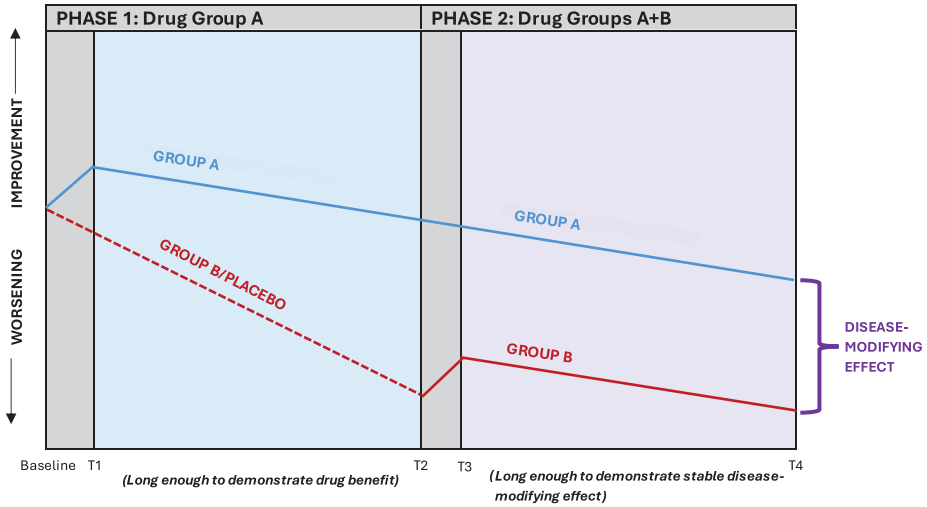

Figure 1: The delayed-start trial. Two groups are started at baseline: Group A (the early-initiation group) and Group B (the placebo/delayed-start group). In Phase 1, Group A is started on therapy. Group B, the delayed start group, is monitored as the placebo group. When sufficient time to allow demonstration of efficacy (and even worsening) in Group A has passed, Phase 2 begins, and Group B is then started on therapy. The difference between the 2 stable rates of worsening is the disease-modifying effect.[17]

Aside from adequate trial design, the issue of FDA approval as a DMT remains. Use of previously accepted trial frameworks does not automatically guarantee FDA designation. As an example, the TRAILBLAZER-ALZ2 was one of the most recent trials in which investigators used a drug withdrawal design in pursuit of DMT designation for its molecule to treat Alzheimer's.[20] Even with a strongly positive endpoint, the FDA delayed approval to convene a panel of experts to discuss the validity of the novel trial design and its results.[20] Only after delays and panel approbation of the study did the FDA move forward with approval[21]—and despite the promising findings of persistence of disease effect demonstrated by drug withdrawal, the disease-modification designation was not given to this therapy.[22] This may be a reflection of the FDA's evolving attitude toward the use of the DMT label. After its initial approval of IFN-B, the FDA continued to provide guidance on DMT designation for the next 20 years.[7] In a 2018 FDA industry guidance document, however, the DMT terminology was removed, and the emphasis was instead placed on a drug's potential to have "persistent effect on disease course."[7] This has led many to conjecture that the FDA was moving away from the DMT designation altogether.[7]

Within clinical practice, several seminal questions persist in the use of DMT. The first is to identify which patients could most likely benefit from DMT. While on first blush this would

appear simple based on previously recognized Group 1 PAH phenotypes, further examination reveals increasing complexity. Subgroups of PAH can be quite heterogeneous, not only in terms of clinical disease but also in terms of molecular pathway modulation. Further, the crosstalk between the 2 of these can be quite variable. This is supported by findings that delineate distinct immune phenotypes in PAH via proteomic analysis, which exist independent of classical Group 1 subtypes.[23] The development of cytological profiles that define immunologic profiles is encouraging and will be part of a broad phenotyping panel that would stratify potential for treatment response.

The next challenge is to identify the ideal time to start DMT along the pathophysiologic continuum. It stands to reason that a DMT should be started early in the course of disease, as pathways are beginning to undergo dysregulation, a phenomenon that has been demonstrated in rheumatology. Indeed, trials in MS and autoimmune disease have consistently shown that earlier initiation of DMT tends to change the course of disease.[9,24] In the HYPERION trial, the use of sotatercept is being examined within the first year of diagnosis, and investigators will hopefully provide further instruction on its use early in the disease course.[25] However, as previously demonstrated, even at the time of diagnosis, the disease has far progressed.[12] It has been shown that patients have a 40% risk of hospitalization within the first year of diagnosis, with hospitalization carrying increasing risks of mortality.[26] Indeed, this almost begs the question of whether there is a point of no return in fundamental disease mechanisms, beyond which disease-modifying pathways can demonstrate lasting benefit and withdrawal would be unwise. In Huntington's disease, this is being defined in terms of genetic mutation rates,[27] while in rheumatoid arthritis, it is defined by functional disability.[28] PAH has yet to assign a descriptor of this point.

The final challenge of disease modification is to responsibly involve the patient perspective. Any use of the term DMT must consider the perceptions of patients who will be interacting with the medication. Certainly, pitfalls to its use exist—as in the case of MS before it, the advent of sotatercept was greeted with much enthusiasm, with some media sources going so far as to proclaim its ability to "stop PAH."[29] Therefore, any discussion using the term must responsibly begin with the absolute distinction between *disease modification* and *cure*—in our speech, writing, and pictorial representation.[11]

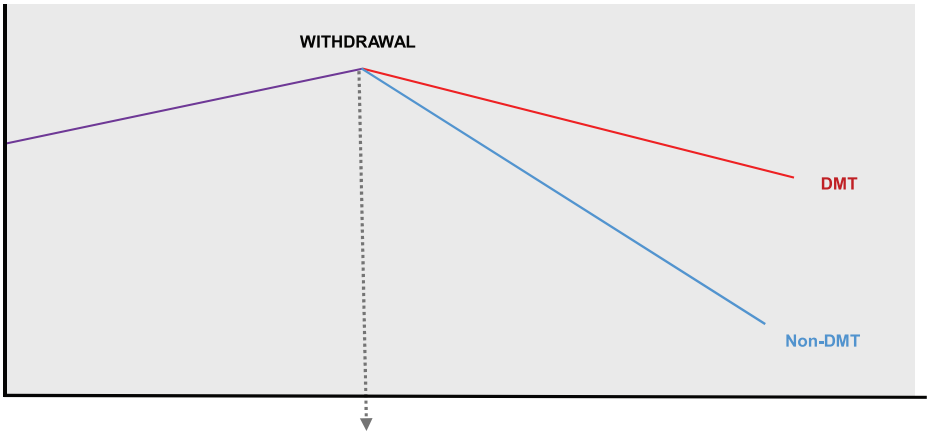

Figure 2: The drug withdrawal trial. Patients are treated with usual therapies, and at a prespecified point, the drug is withdrawn. The rates of clinical worsening are compared between the disease-modifying therapy (DMT) and non-DMT groups.[18]

BENEFITS AND FUTURE DIRECTIONS

Given all the challenges inherent to the use of the DMT designation, the most pressing question is: What is the benefit?

Certainly, the most self-evident benefit of working out the DMT designation is its use within our treatment algorithm. Barring heavy side-effect burdens, one can argue that the ability to modify a course of disease mandates that all patients should have access as early as possible to DMTs. However, this could introduce further issues for all drugs in the same class. Future trials are inevitably affected by the treatment landscape of a recent approval of a DMT.[5] Trial participants would have to balance the risks of forgoing an approved therapy with the potential benefits of a new one.[5] This involves attempting to balance many factors that, in the wake of a newly approved therapy, are often unknown; moreover, not only is the benefit of the trial drug unknown, but the potential risks of the approved therapy outside of the trial in real-world use have also yet to be elucidated.[5] Both noninferiority and superiority trial designs are often introduced at this point as possible alternatives.[5]

Another benefit of the DMT designation is its focus on outcomes that are most important to patients. As previously shown, the Multiple Sclerosis Collaborative Research Group was able to change the focus from disease outcome to the more patient-centered outcome of disability.[6] An FDA report entitled "Voice of the Patient" held specifically for patients with PAH is particularly enlightening on the patient view of current therapies, in which patients described ideal therapies as those that are "less invasive, have fewer side effects, and address the pervasive symptoms of PAH," especially those that are "easier to administer," with "more convenient dosing schedules."[30] The urgency was clearly directed on ease of use and patient quality of life.[30] Taken together, we can presume that the advent of disease modification can only be beneficial to patients if it introduces therapies that balance efficacy with ease of use and improved quality of life.[30] This is in line with the FDA patient-focused outcomes that encourage outcomes assessment based not only on survival but also on how the patient feels and functions.[31]

The final benefit lies in the way in which it forces us to challenge our own current paradigms of therapy. We readily acknowledge that our treatment goals

at this time cannot involve a cure, and thus, our current methodology involves treatment to low risk of progression. This relies upon the tools we have available to profile our patients, which admittedly are not individualized and reliant upon retrospectively derived registry data. The next wave of treatment goals should incorporate a panel of biomarkers, hemodynamics, risk assessment tools, and a focus on patient feeling, function, and survival.[18] Instead of the focus on low risk, the paradigm is instead shifting toward a broader goal of treatment remission that incorporates all these factors.[18]

CONCLUSION

With the increasing focus on fundamental pathways in PAH, we have entered a new realm of therapeutics, one in which we stand at the threshold of being able to not only treat but also fundamentally alter the course of PAH. It is incumbent on our specialty to define DMT for itself, in such a way that we can accurately communicate its promise (and challenges) within clinical trial development and clinical practice to regulators and, most importantly, to those to whom it most affects, our patients.

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REGULAR ARTICLE

Getting Started Early in Your Pulmonary Hypertension Career

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The Pulmonary Hypertension Association (PHA) biennial conference welcomed more than 1000 health care providers, patients, families, and industry partners to Indianapolis this August, and there was much to celebrate this year. Among other notable accomplishments in advocacy, patient care, and promotion of research, the PHA is commemorating 10 years of both accredited care centers (PHCC) and the association's national registry (PHAR). In 2024, PHA has accrued 92 accredited programs, and PHAR has enrolled over 3000 patients from which 18 publications have been generated. The scope and growth of PHCC and PHAR is remarkable, but what is most important is sustainability. The PHA recognizes this and has made a major commitment to investing in the future. PHA understands the need to foster the next generation of pulmonary hypertension (PH) clinicians and researchers who will carry on the organization's missions for years to come. Along every step of its growth, PHA has supported the development of early-career and trainee members by providing research opportunities, mentorship, and leadership roles.

Through its dynamic mission, PHA offers many opportunities for early-career members to serve our community via membership and leadership positions in committees and working groups. These roles provide meaningful opportunities for young clinicians and researchers to contribute to the development of programs aimed at improving the experiences of patients, caregivers, clinicians, and researchers. These working groups and committees are responsible for organizing much of PHA's educational content, ranging from live events allowing clinicians and patients to interact and exchange ideas to recorded educational videos by experts in the field. Early-career members often participate in these events, allowing them to connect with the community, elevate their own professional visibility, and accumulate public speaking experience. To further this mission, PHA held its first early-career member reception on the first evening of this year's international conference. At this event, young clinicians and researchers met to connect and develop community, spend time with old friends and formed new relationships, and learned from each other. This event also allowed PHA leadership to meet the next generation of our community. We look forward to future events and the evolution of PHA's early-career development programs.

In addition to formal programs, the PHAR represents a unique and highly effective career development mechanism for early-career members of PHA. We know this from personal experience. I wrote my first PHAR protocol as an Internal Medicine intern during a time when I had little research experience, no formal training, and a lot of uncertainty about where my career would lead. I discovered an international community of thoughtful clinicians and researchers who were excited to welcome a very junior investigator among their ranks. This early experience working with PHAR clearly shaped my professional trajectory, and 6 years later, I am more committed than ever to dedicating my career to the care of patients with PH. My early-career coauthors Jasleen Mihas and Navneet Singh also had similar experiences with PHAR during their early training.

Our experiences were not in isolation: We'll let the stats speak for themselves. Of the 18 PHAR manuscripts published to date, all but 1 had a lead author who was either a trainee or early-career professional (<10 years from training). This includes an astonishing 10/18 articles (56%) led by students or trainees and 7/18 (39%) led by early-career professionals. Of the total 90 individual authors who have contributed to PHAR publications, over half (47/90, 52%) were either trainees or early-career professionals at the time their article was published. These authors included medical students, graduate students, residents, fellows, and postdoctoral scholars who

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not only participated in research using PHAR data but led major projects and produced high-impact publications. In this respect, PHAR truly stands alone, as few other multicenter registries can claim similar involvement of junior investigators. PHAR is, therefore, an investment not only in patients but also in building the next generation's PH workforce.

Practically, how has PHAR accomplished its impressive track record? Primarily by 2 mechanisms: (1) lowering the barrier to entry for trainees and early-career members and (2) providing an abundance of mentorship and support. PHAR research proposals are no more than 2–4 pages and can be submitted by a broad array of individuals including members of a PHCC director's team or representatives of PHA such as allied health professionals and patients. Trainee and early-career members receive inherent mentorship because they submit proposals alongside a more senior PHAR principal investigator. All PHAR investigators can participate in and comment on pending PHAR proposals, and so lead authors receive feedback from experts across the nation. This exchange allows for the opportunity for junior authors to collaborate with senior PH providers across the country. Protocol reviews are conducted primarily to ensure scientific integrity, data availability, and no overlap with prior proposals, with a goal of providing authors feedback to strengthen their projects and lead to successful publication. Most protocols (88%) are ultimately approved, and most denied proposals are rejected due to overlap with other preexisting protocols. Once a PHAR protocol is approved and a data use agreement is in place, the investigator is granted access to the PHAR database and, sometimes, additional statistical support from the coordinating center if requested in the original proposal. This system encourages inclusion by trainees and early-career professionals by creating a culture in which the goal is junior author participation and success, with senior investigators providing the necessary feedback and mentorship along the way.

We are grateful to have had the opportunity to have access to this powerful resource during the course of our training. We urge trainees and early-career investigators to review the registry data fields, current approved proposals, and pose novel questions using the PHAR that will enhance the real-world knowledge of pulmonary arterial hypertension, chronic thromboembolic PH, and PH due to interstitial lung disease and form the basis of further investigation in this field. The PHA and PHAR have unequivocally helped launch our research careers in PH, and we know it can do the same for you.

Roundtable Discussion: Highlights From the Seventh World Symposium on Pulmonary Hypertension

Rachel Hopper, MD, Sandeep Sahay, MD, MSc, Scott Visovatti, MD, and Lori Reed, MSN, APRN, FNP-C met to discuss the Proceedings of the Seventh World Symposium on Pulmonary Hypertension, which were recently published in the *European Respiratory Journal* (Humbert et al. *Eur Respir J*. 2024;64(4):2401222). The key takeaway from this discussion was to highlight the inclusion of a fourth pathway drug (activin signaling inhibitor) in the treatment algorithm. The panelists also explored the implications of the changes in the classification of Group 3 PH, the importance of phenotyping patients and the potential for a "zone of uncertainty" in the classification of patients. Lastly, they discussed the implementation of genetic testing recommendations, the continuum approach to patient treatment, and the complexities of diagnosing and treating PH, particularly in relation to chronic thromboembolic disease.

Dr Hopper: I'm curious, for all of you who take care of adults, what you think were the biggest changes and most impactful recommendations from the World Symposium that were shared at conference this year.

Dr Sahay: For me, the biggest takeaway was the inclusion of the new pathway drug, which is an activin signaling inhibitor, in the treatment algorithm. I think this World Symposium document highlights where we can use it in the treatment algorithm. The other change, big change, was to suggest not high risk and high-risk categories at baseline. Probably an attempt to simplify it. But it also had a box created along with it which had a lot of information to be paid attention to when you're performing risk stratification in PH patients. So I think this was a little different approach. But I guess the biggest takeaway for me still is the introduction of the fourth pathway drug in the treatment algorithm.

Lori Reed: Yeah, I'll kind of copy you in that it gave us some guidelines in adding in this new fourth-line treatment, which is helpful. We weren't part of the study, but we're definitely using enough of it in the right population, and so to have that to guide us is helpful. It also gives me a little bit of a pause to see where they place it. You know, that's kind of interesting because, in our practice, the 3 foundational pathways we're very familiar with, and we're pretty heavy handed with our parenteral prostacyclins in the patients that really need it. And so to see this newer activin signaling inhibitor placed potentially prior to that is very interesting. One thing that they really stressed in the World Symposium that I think is valuable is patient-centered care, the patient's perspective, the patient's experience, and making sure that that's wrapped in, in every step of their PH journey, and so having them part of the symposium and part of every journey of it, I think, was one of their key points, and they made that clear, and I appreciated that.

Dr Sahay: She's absolutely right. This World Symposium probably was the first one to start with the Patient Perspective Task Force to highlight how central patients' viewpoint or opinions or expectations are in the management of PH, so I think that was a very nice and a very welcoming move. We have patients that presented and also participated as authors in these documents. I think that's unique. Thanks, Lori, for bringing that up.

Dr Visovatti: The European guidelines had prepared us for the idea of comorbidities. Instead of thinking about clear-cut Group 1 PAH versus Group 2 PH versus Group 3 PH, we need to consider the possibility that Group 1 PAH may coexists with some degree of parenchymal lung disease or left heart disease. This brings up many of the challenges we face in our daily clinical PH practice. Is what appears to be a comorbidity actually the primary driver of the disease? Do we need to modify how we treat patients who appear have Group 1 PAH but also have COPD? It's important to think about patients' comorbidities as being on a continuum; this was really well presented at World Symposium.

Dr Hopper: That's a great point. I'm curious: in your practice, how much impact did the change of the structure of Group 3 diagnoses going sort of from a physiologic diagnosis to more of a clinical diagnosis, what impact do you think that will have on the care of patients with Group 3 PH, or even patients with Group 1 who also may have lung disease?

Dr Visovatti: That's a great question for the entire group. I think this is one of the most important questions to answer in all of PH, and it takes a multidisciplinary care team to answer it. I'm a cardiologist, so I really depend upon the expertise of the pulmonologists at our institution to help figure out if a patient has Group 1 PAH with some lung disease versus Group 3 PH. I think the Seventh World Symposium emphasized the importance of a multidisciplinary approach to help figure out PH diagnosis and treatment.

Lori Reed: I work in pulmonary. I also treat all advanced lung disease including interstitial lung disease. Also, we get our COPD patients, and from my perspective, this currently won't change much of what I do, but I think it's setting us up to help with phenotyping in the future

and research designs and trials, so that we can start to build on what is going to be most successful for the patients with this phenotype or that phenotype. I think they're setting us up for what we need to do next.

Dr Sahay: Yeah, I think it's just the evolution of what we used to call just Group 3 pulmonary hypertension. Now we have different phenotypes, and we actually have successful treatment for one of the groups. I think this really highlights that Group 3 PH is not just the same disease in all. Going to what Lori just mentioned, about the importance to phenotyping them, and then selecting treatment, in Group 1, we have different types of PH—idiopathic, heritable, calcium channel, connective tissue disease, etc, but our treatments work on all of them, but Group 3 PH is way more heterogenous. You cannot treat them in the same way as you do it for Group 1 PH. Initially, we used to think of only Group 3 or PH due to diffuse parenchymal lung disease. Now you have PH-ILD, COPD-PH, combined pulmonary fibrosis, and emphysema, a lung phenotype PH which is still not very clearly defined, so within each group, there is evolution of the classification. The difference between Group 3 and 1 PH is that, in most of the Group 1 PH, drugs work for most of that group's subtypes of PH. But we have not achieved that level of success in Group 3 PH as yet. But the first thing is to identify that these are different entities, and hopefully, by the next World Symposium, we might have more successful therapies which may be working for all subtypes of Group 3, but we don't know yet. But I think it's really important to categorize patients correctly.

Dr Hopper: And another discussion that I found really fascinating was in regard to Group 2 and the importance of the wedge pressure in hemodynamics. Seems like there were some strong opinions expressed by people in the audience, as well as the speakers, in terms of the appropriate wedge cutoff and some of the pitfalls of obtaining an accurate wedge. You know, as a pediatrician, the cutoff of 15 has always seemed wildly high to me. A wedge pressure of 15 is almost never normal in a child. I thought the discussion was interesting, and I'm curious if you think that sort of "zone of uncertainty" that was described may make that idea of overlap and recognizing that diagnostic heterogeneity will be improved with recognition that there is a zone. It's not necessarily an absolute cutoff of 15. There may be some wiggle room, either due to the patient's intrinsic, clinical state, or unfortunately, the errors in measurement that can happen.

Dr Sahay: I think that goes back to the original question of phenotyping these patients. We all know that, in the REVEAL registry, when it first started, it had wedge up to 18. They actually published separately the outcomes in patients between the wedge pressures of 16 to 18 and 12 to 15. It did show that higher the wedge at follow-up in these patients did not carry much worse outcome. It's important. As far as the hemodynamic definition is concerned, I personally feel that staying at 15 is reasonable, but I agree that wedge pressure of 12 is normal. With that, I have a question for you, Rachel. What about the classification in pediatric PH which they propose? What are your thoughts on that?

Dr Hopper: The Pediatric Task Force recommended continuing the definition of pediatric PH with an indexed PVR of >3, which I think is reasonable because we do index for body surface area. For me, I think the interesting thing was thinking about treatment algorithms in pediatrics because this was the first time where they really separated out congenital heart disease with open shunts versus other PAH, and a bit of discussion about our kids with developmental lung diseases, but I think we're again recognizing the idea of different phenotypes in pediatrics that may need a different approach to therapy. That said, we don't have enough data in children to make evidence-based recommendations. And yet the Task Force recommended upfront dual therapy in children extrapolating from adult data. They mirrored the adult recommendations, which was interesting. And I think many of us who care for kids with PH have adopted that approach over the years after the AMBITION trial. I thought it was interesting that they did incorporate that this year as the concrete recommendation. And like always, it highlights that we have to do better in terms of getting data on kids and how these medications are used in children.

Dr Visovatti: As we discuss the hemodynamic criteria for PH and the need to more deeply phenotype children and adults with PH, we should emphasize the need for accurate hemodynamic assessments. Also, as a long-time believer of exercise PH and the value of provocative testing, I was excited to see that the Proceedings include some great discussion about pre- and postcapillary exercise PH, which are now defined by pressure versus cardiac output relationships. I'm excited that the global PH community recognizes the importance of gathering accurate hemodynamic information to facilitate deeper phenotyping of PH. This is really what's going to take us to that next level in terms of enrolling appropriate patients in clinical trials. How do we include the right patients? What inclusion and exclusion criteria should we use?

Dr Hopper: That's a great point, Scott. One of the other task forces that wasn't explicitly presented, but was reviewed in the guidelines, was the Genetics Task Force. Along the lines of phenotyping, there's been a big interest in the genetic phenotyping of our patients to understand that better. The recommendation of the Task Force was that all Group 1 PH patients should be tested, and children with Group 3 developmental lung disease PH should have genetic testing done, which I think in a perfect world would be amazing, but there are a number of challenges in terms of having adequate genetic counseling support and getting genetic testing paid for. So I'm curious to hear from the adult providers. We have some workarounds in pediatrics, but do you think that will be something that you can and will implement in your practice, or do you perceive

challenges with implementing that piece of the recommendations?

Dr Sahay: No, I think, personally speaking, I am always looking forward to recommendations from genetic testing in PH because we do it routinely in our clinical practice. I really liked the table in the Genetics Task Force manuscript, then if the target gene testing is negative, then how you move on to do the whole exome sequencing. I think that's a very nice recommendation and just highlights the importance of performing genetic testing in PH care. I think genetic testing is an issue, not just with the cost but also an awareness among the clinicians. So the more we put it in the guidelines and recommendations like World Symposium, the more it will be acknowledged and people will be aware of doing it.

Lori Reed: We probably don't test enough in our center, but we don't have a lot of access to genetic testing and counselors, and our patients can't afford the extra costs of travel, so it would be a pretty big hurdle for us to even get a portion of our patients in with a genetic counselor at all. But I do agree, too, the more we use it, the more we recommend it, the more we keep it top of mind and push insurance companies and centers to hire more people and cover the costs that we'll get there.

Dr Hopper: Yeah, and we hope recommendations will help with that to give us evidence to go back to insurance companies and say, "Look, it's recommended."

Dr Visovatti: I'll add the importance of not only performing the genetic testing but sharing the information on a global scale. How often do we get a variant of unknown significance, and we don't know what to do with it? We need to share data in order to advance research efforts in this area. It's critical.

Dr Hopper: Good point. Absolutely.

Dr Visovatti: I also appreciate the emphasis on wearables. How often do our patients say, "My Apple Watch showed this today; what does it mean?" This is a hot topic.

Dr Hopper: Yeah, I think that's really exciting. There are even some studies of wearables in children as young as 1 year old, which is great, and as you mentioned, it's really exciting when we think about trials to have endpoints that are really meaningful to our patients. It'll be nice to see that included going forward and to see how that evolves.

Dr Visovatti: How does that work in a baby?

Dr Hopper: There are different types of actigraphy devices. This is a little bit tangential, but we can look at different parameters in terms of movement and heart rate variability. And these can actually be used in pretty young kids. Obviously, it's not a step count. That's not as useful in younger kids. But there are some indices that are useful.

Dr Sahay: The other important thing in this World Symposium was the Imaging Task Force. I guess this was the first time they had a task force to really talk about how imaging can improve diagnosis management. They discussed functional respiratory imaging. They also talked about standardization of cardiac MRI parameters. We have seen a lot of literature about MRI, and things have shown different findings depending on the data from different centers. It is more like a call to action that we should standardize the imaging parameters across the globe and see how we can best utilize those.

Dr Visovatti: Also, the emphasis on leveraging advanced imaging techniques when it comes to risk stratification. We intuitively know that we have to figure out how to include aspects of RV function in our risk stratification at baseline and frequent reassessments.

Dr Sahay: Was there anything groundbreaking in CTEPH? I guess we can say that, for CTEPH, instead of thinking that patient just needs surgery or is nonsurgical, it is more like a continuum approach. Now you may have a patient who will need surgery and may very well need BPA to complement to achieve full benefit. The RACE trial findings were discussed where they used a PVR of 4. It's just to highlight that, for a particular patient, you may utilize all the options: surgery followed by BPA, maybe medical therapy also.

Dr Hopper: I remember going to conferences in years past, and there were debates. It was surgery versus catheter-based, and it was one or the other. It's a great point to highlight now. I think there's a recognition of being able to incorporate different treatments, but I have to defer to you all because we don't see much of this in my world.

Dr Sahay: Right? And the one other point which we did not talk about when we were talking about Group 3 specifically was the PVR cutoff because abnormal with the new hemodynamic definition is at 2; however, INCREASE trial results included patients above 3 WU, and the World Symposium document said above 4. There was no clear recommendation between 2 to 3. It's up to the clinician to see how they want to approach between that range.

Dr Visovatti: Yes, that brings up the concept of "early PH." We need more clinical trials to help us figure out how, or whether, to treat patients with a PVR between 2 and 3.

Dr Sahay: I guess before this World Symposium and before the success of INCREASE trial, the European data showed that with a PVR of 5 WU have treatment benefit in this group. Then they talked about the post hoc analysis of the INCREASE data where they saw that forest plot with cutoff of 4 WU and more benefit in patients with PVR > 4 UW versus those with <4 WU. But I was thinking when the inclusion criteria of the INCREASE trial was mean PAP > 25 with PVR of 3 and above, then why are we making recommendations based on the post hoc analysis and not just what the inclusion criteria of the INCREASE trial was. I was just a little confused why we relied so much on the post hoc analysis data to make that

recommendation because it would have cleaned up this confusion between the PVR of 2 to 4 WU. Hopefully, we have more data to support it after the next World Symposium.

Dr Visovatti: Sandeep, I wanted to circle back to your very important point about CTEPH. If we use our new hemodynamic definition of precapillary pulmonary hypertension, then a large portion of the group of patients that we used to call "chronic thromboembolic disease" has now been reclassified as CTEPH. But should we really consider sending a patient with a PVR between 2 and 3 for endarterectomy? I think not. Also, patients with a mean PA pressure <25 mmHg were not included in the CHEST-1 trial, so we shouldn't be treating them with riociguat. These issues emphasize the need for more research in CTEPH. I think invasive cardiopulmonary exercise testing can help us figure out who really needs to be treated for CTEPH and in what way.

Dr Sahay: To me the answer lies in what your patient is telling you. If you have a patient with a PVR of 2.5 and you are seeing there is a lesion and the patient is saying that they're symptomatic and not able to do day-to-day activities, that's a situation where you need to do something. Now there could be another scenario where a patient was getting testing done for something else and you incidentally found CTEPH, but the patients says they feel fine and have no problems. The right heart looks fine, and well, that's a case you may do something or not do even if you identified it. In CTED patients, there is not very strong evidence that this really progresses to CTEPH. Then it's a big question if the patient is feeling fine: Should I do anything, or should I just observe the patient? That's a million-dollar question I guess we don't have the answer to right now.

Dr Hopper: Your comment takes it full circle to what we started with: Lori brought up the Patient Task Force, and I think keeping in mind that patient perspective is so important to incorporate into the clinical algorithms because, as you say, the hemodynamics are guidelines, but they're clearly not the whole story, and the patient perspective is so important in making decisions about treatment plans.

Lori Reed: What I was going to add a little bit to each one of these classifications is it's all coming back down to us better understanding the phenotype, better involving the patient, and understanding that this is complex, no matter which category they fall into. Remember to fall back onto your risk stratification that does include the patient's perspective and their functional class as well as the hemodynamics and everything else. Bringing it back together, treating the patient, meeting them where they are, and having our data and science helps support the group in which direction to go. And as Sandeep was talking about, you get a patient that you're unsure if it is something or if you need to do anything about it. I think the World Symposium is starting to help guide us with that, so that might be an opportunity to get the MRI or the CT scan and see the early changes, the early detection, and maybe get ahead on some of those patients where you think this was incidental.

Dr Hopper: That's a good point and a good way to wrap up here, incorporating all of that together. You tied it up nicely, Lori.

Conference Abstracts

A GLOBAL ASSESSMENT OF ACCESS TO CARE FOR PATIENTS WITH PULMONARY HYPERTENSION

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Category: Clinical Science
Subcategory: Health Disparities/Social Determinants of Health

Background: Pulmonary hypertension (PH) remains a serious disease with poor outcomes. The Pulmonary Vascular Research Institute (PVRI) Innovative Drug Development Initiative (IDDI) Access to Care Taskforce was charged with exploring how to improve global access to care for PH diagnosis, management, and treatment by considering knowledge gaps and contextual differences within and between countries or regions.
Methods: A 36-question English-language survey focusing on access-to-care aspects was developed and disseminated to PVRI members, the PH Association, and other PH providers around the world with instructions for each specialty center to submit 1 survey. Data were analyzed using descriptive statistics.
Results: A total of 123 surveys were completed. Surveys were returned from Asia (37), USA or Canada (28), Europe (27), Latin America (22), Africa (7), and Oceana (2). Centers predominately treated adults only (53.3%) or a combination of adults and pediatric patients (42.6%). Most centers had a PH patient census >50 (75.4%) and a referral region or area of coverage >100 square km or >40 square miles (73.3%). Diagnosis of PH was made predominantly by multidisciplinary teams (57.4%) versus individual clinicians (42.6%). Most centers had access to electrocardiograms (EKG; 98.4%), echocardiography (97.6%), 6-minute walk test (6MWT; 95.1%), B-type natriuretic peptide (BNP)/N-terminal pro-brain natriuretic peptide (NT-proBNP; 95.1%), right heart catheterization (RHC; 93.5%), computed tomography (CT; 91.1%), and V/Q scan (69.1%). PH genetic testing was found in <50% of centers (43.4%). Limitations to diagnose PH included insufficient financial resources (37.4%), staff (32.5%), time (24.4%), and expertise (13.8%). No limitations in diagnosis were seen in 24.4% of centers. Delayed referral to a PH specific center was also mentioned but not quantified in the survey. Centers had medians of 10, 2.5, and 2 patients under their care for Group 1, 2, and 3 PH, respectively. For Group 4, patient volume was mostly <10 (33.9%) or >20 (46.3%). Most patients were diagnosed as Functional Class (FC) II (median 35%) or FC III (median 40%) and were white (median 65%). All races were treated at varying percentages with ranges from 0% to 100% based on the individual centers (Asian [median 10%], Black [median 5%], and Hispanic [median 5%]). Most centers used phosphodiesterase-5 inhibitors (98.4%) and endothelin receptor antagonists (88.6%). Parenteral prostacyclin was used in 63.4% of centers, with most having 1–5 active patients on parenteral therapy (42%). Thirty percent of parenteral therapy–using centers had >20 active patients on treatment. Other common therapies used included selexipag (74.8%), inhaled prostanoids (66.7%), riociguat (65.9%), and oral treprostinil (30.9%). Health insurance coverage ranged from 0% to 100% among centers. Most had >75% of patients with insurance (57%) followed by 0%–25% (29.8%).
Conclusion: The global survey showed that most responding centers, who had large referral geographies and patient numbers, had limitations to diagnosing PH, although access to diagnostic tools seemed to be present. Patients continue to be mostly diagnosed as FC II/III, like previously published data. Strategies for earlier referral and diagnosis would likely benefit the entire PH community along with general practitioners.

A MULTI-INSTITUTIONAL RESPONSE TO PROMOTING CAREGIVER EDUCATION IN PEDIATRIC PULMONARY HYPERTENSION: DEVELOPMENT OF THREE EDUCATIONAL BROCHURES

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Category: Clinical Science
Subcategory: Pediatrics

Background: As part of the Pediatric Pulmonary Hypertension Network (PPHNet), the Advanced Practice Provider and Nursing (APPN) Committee identified 2 main areas of focus for educational brochures to develop: subcutaneous (SQ) treprostinil management and World Health Organization (WHO) Group 3-associated pulmonary hypertension (PH).

For children diagnosed with severe PH, the use of continuous prostacyclin therapy is often used for aggressive pulmonary vasodilation. This therapy may be associated with changes to quality of life related to SQ site pain and management. A SQ treprostinil guide was created with experienced parent or patient input as a resource for new SQ parents or patients including pain and site management troubleshooting, practical advice from patients and parents, and basic medication information.

Patients with WHO Group 3-associated PH make up a large portion of pediatric PH patients. In the setting of this diagnosis, patient and caregiver educational materials, both printed and electronic, are limited. The APPN Committee identified 2 types of lung diseases that are often associated with PH to focus on: bronchopulmonary dysplasia (BPD) and congenital diaphragmatic hernia (CDH). Representatives from 6 PPHNet centers (6 total APPNs) volunteered to develop a caregiver educational flyer specific to BPD- and CDH-associated PH describing the definition, prevalence, risk factors, assessment or testing, treatment, and long-term follow-up to be used to help support caregiver education.

Methods: A review of the published literature available for all 3 topics—SQ treprostinil management, PH in BPD, and PH in CDH—was completed by members of the APPN Committee in the project. During monthly meetings, the educational brochures were outlined and edited to meet user readability, both in reading level (average ninth grade) and graphic layout. The content was derived from published literature and expert practice. See Figures 1–3.

Results: The APPN Committee produced three brochures that enable patients and families to have access to concise written educational documents. These documents are available in print, on the PPHNet website and have also been translated into Spanish and Arabic and will be reviewed at two-year intervals.

Conclusion: Using available literature and professional expertise from multi centers can produce well-written and visually pleasing educational brochures. These brochures fill a gap in written literature available to pediatric PH patients and caregivers.

"SQ" Prostacyclin Therapy

A guide for new medication starts

BY: ELISE WHALEN, NP, CLAIRE PARKER NP, ERIN ELY, RN, MELISSA MAGNESS, NP, & KATY TILLMAN, NP ON BEHALF OF PPHNET NURSING COMMITTEE

Pulmonary Hypertension: What is it?

An overview

Pulmonary hypertension (PH) is another name for high blood pressure in the lungs. It is a big word, but let's break it down. "Pulmonary" means lungs, and hypertension means "high blood pressure." The high blood pressure in the lungs occurs because the arteries narrow down causing higher blood pressures. This higher pressure in the lungs makes the right side of the heart work harder to push blood through the lungs. This extra work causes the heart to become less flexible and even get bigger over time.

SYMPTOMS

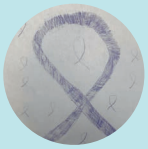
Symptoms may include being unable to perform exercise or do activities that are normal for age. Increased tiredness, shortness of breath, dizziness, upset stomach, decreased appetite, and swelling of the face hands, and feet are commonly seen.

TESTING

Your doctor may order an echocardiogram (ultrasound of the heart), chest x-ray, or MRI (pictures of the heart by a magnetic field and radio waves). They could order a cardiac catheterization. This procedure directly measures the pressures and flow in the heart.

Pulmonary Hypertension
An overview of the disease, symptoms, & testing

Treatment options



Pain Management Strategies

Frequently Asked Questions: Things I Wish I knew

Figure 1: SQ prostacyclin therapy: a guide for new medication starts.

Bronchopulmonary Dysplasia & Pulmonary Hypertension: A Guide for Patients & Families

By: Melissa Magness, NP, Anna Brown, NP, Elizabeth Colglazier, NP, Alicia Grenolds, NP, Emma Jackson, NP, & Elise Whalen, NP on behalf of the PPHNet APP and Nursing Committee

Did you know?

- Between 10-60% of children with BPD develop PH.
- Echocardiography screening for PH is recommended for all infants with moderate to severe BPD at 36 weeks

What is bronchopulmonary dysplasia (BPD)?

Bronchopulmonary dysplasia (BPD) is a condition of halted lung development that is primarily seen in children born prematurely (typically born < 30 weeks gestation and birthweight < 2 pounds). BPD can range from mild to severe and can improve as the child grows. Some patients with BPD may need long-term oxygen therapy and breathing help from machines like ventilators, even after they go home.

What is pulmonary hypertension (PH)?

Some children with moderate to severe BPD may be diagnosed with PH which is high blood pressure in the lungs. In BPD, PH is caused by small or abnormal development of blood vessels in the lungs. High blood pressure in the lungs can put extra stress on the right side of the heart, which can affect its ability to pump blood well.

RISK FACTORS DURING PREGNANCY

- Preeclampsia
- Fetal Growth Restriction
- Infection
- Oligohydramnios (low/absent amniotic fluid)
- Genetic Conditions

RISK FACTORS AFTER BIRTH

- Prolonged mechanical ventilation
- Infection
- Hypoxemia
- Presence of cardiac shunts (abnormal connections in the heart)
- Aspiration (accidental breathing in of fluid into lungs)

Figure 2: Bronchopulmonary dysplasia and pulmonary hypertension: a guide for patients and families.

Congenital Diaphragmatic Hernia & Pulmonary Hypertension: A Guide for Patients & Families

By: Melissa Magness NP, Anna Brown NP, Elizabeth Colglazier NP, Alicia Grenolds NP, Emma Jackson NP, and Elise Whalen NP on behalf of the PPHNet APP and Nursing Committee

Did you know?

- Most often CDH is on the left side
- CDH is one of the most common major congenital anomalies and affects about 1 in every 2,500-3,000 births
- There is a wide range of severity and outcomes for children with CDH and PH

What is CDH?

Congenital diaphragmatic hernia (CDH) is a condition that develops before birth. Children with CDH have a hole in their diaphragm, the wide, flat muscle that separates the chest from the abdominal cavity and is important for breathing. The hole in the diaphragm allows some of the contents of the abdomen, such as the stomach, part of the intestines, and liver, to move up into the chest. These abdominal organs occupy space in the chest and prevent the lungs from growing to a normal size before birth. Growth of both lungs can be affected, but the lung on the same side of the hole in the diaphragm is usually smaller. When the lung is smaller than it should be, it is called pulmonary (lung) hypoplasia.

What is Pulmonary Hypertension (PH)?

Children with CDH also have fewer and smaller blood vessels (arteries) in their lungs. This causes high blood pressure in the lungs, known as pulmonary hypertension (PH). PH can cause problems with blood entering the lungs, which makes oxygen levels in the blood lower. PH can also affect the ability of the right side of the heart (the right ventricle) to pump blood well. PH is very common in children with CDH, especially shortly after birth, and can be more severe in children with larger diaphragmatic hernias. PH most often occurs early but can also continue over time and need longer-term treatment.

Figure 3: Congenital diaphragmatic hernia and pulmonary hypertension: a guide for patients and families.

A PHASE 3, 2-PART, OPEN-LABEL, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF LIPOSOMAL TREPROSTINIL INHALATION SUSPENSION (L606) IN PARTICIPANTS WITH PULMONARY ARTERIAL HYPERTENSION AND PULMONARY HYPERTENSION IN INTERSTITIAL LUNG DISEASE

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Category: Clinical Science
Subcategory: Diseases and Conditions Associated With PH

Background: L606 is an investigational inhaled sustained-release treprostinil formulation with a liposomal matrix aimed at prolonging lung retention and maximizing efficacy while limiting toxicity. Delivered via a portable nebulizer, it requires twice-a-day dosing.
Methods: This Phase 3, open-label, multicenter trial targets patients ≥18 years transitioning from nebulized Tyvaso or Tyvaso DPI to L606 with pulmonary arterial hypertension (PAH) or pulmonary hypertension in interstitial lung disease (PH-ILD), or those naïve to prostacyclin on ≤2 oral therapies. Its primary objectives are to assess the safety and tolerability of L606, with primary safety measures being the incidence of adverse events (AEs) and serious adverse events (SAEs) over varying time frames.
Results: Of the initial 15 patients, all belonged to the transition PAH group. A total of 40% of these patients completed their 12-month follow-up visits. Additionally, 13% of the patients reached their 6-month visit milestone. Notably, 1 patient chose to discontinue the treatment due to experiencing mild AEs. Demographics: mostly female (73%), white (80%), non-Hispanic, average age 61. Baseline New York Heart Association (NYHA) Functional Class (FC) distribution was 40% FC III and 60% FC II, with 73.4% on triple combination background therapy. L606 was dosed up to 360 mcg BID. Of the patients, 60% experienced mild to moderate AEs, and 20% had treatment-related AEs like dyspnea, blurred vision, dizziness, feeling hot, dysphonia, rhinorrhea, or cough. Cough was the most noted AE, but no throat pain was reported. One unrelated SAE of acute kidney injury was recorded.
Conclusion: Patients transitioned from nebulized treprostinil to L606 without significant safety concerns, and L606 was well tolerated as an addition to oral therapy. One patient experienced treatment-emergent AEs typical of inhaled treprostinil; none were severe. The AE profile was mild to moderate, not hindering dose titration. Ongoing study progress will be crucial for understanding the long-term safety, tolerability, and dosing profile of L606.

QUALITATIVE INTERVIEW STUDY TO EVALUATE SINGLE-TABLET COMBINATION THERAPY WITHIN A PHASE 3 PULMONARY ARTERIAL HYPERTENSION CLINICAL TRIAL—INTERIM ANALYSIS

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Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Pulmonary arterial hypertension (PAH) is a rare, chronic disease that should be treated with double or triple therapy in most cases, requiring multiple tablets. A single-tablet combination therapy (STCT) of macitentan 10 mg and tadalafil 40 mg compared with equivalent monotherapies is being evaluated in a Phase 3 trial (A DUE, NCT03904693, AC-077A301): patients received 4 tablets during double-blind and 1 tablet (STCT) during open-label treatment. Interviews during the ongoing open-label extension are exploring patient and clinician experience with the STCT.
Methods: Qualitative, one-on-one, semistructured Web-assisted interviews are being conducted across multiple countries with A DUE trial participants and site investigators. Interim data on their experience of open-label versus double-blind treatment are presented from 4 US patients and 7 clinicians (4 US, 1 Poland, 1 Spain, and 1 South Africa).
Results: All participants provided positive feedback on the STCT and preferred the open-label STCT to the 4 tablets in the double-blind phase. Patients stated the STCT was convenient, aided adherence, and had a positive effect on their day-to-day lives. Patients discussed how taking more tablets made them feel more "sick" compared with STCT.

In comparison, the STCT improved their psychological well-being and reduced the stress of managing multiple tablets. Clinicians noted that the typically high pill burden in PAH causes their patients emotional distress, whereas patients had higher treatment satisfaction with the STCT. Clinicians predict the STCT will be well received in clinical practice and endorsed prescribing STCT for treatment-naïve patients.

Conclusion: Interim analysis suggests that the STCT was well received by patients and clinicians. The reduced pill burden minimized stress, simplified the treatment regimen, and facilitated adherence, which could improve patient outcomes and quality of life. Clinician endorsement of STCT for treatment-naïve patients increases the likelihood that these patients will receive guideline-recommended care.

QUALITATIVE STUDY EXPLORING RESILIENCE AMONG PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

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Category: Clinical Science
Subcategory: Quality of Life

Background: Patients with pulmonary arterial hypertension (PAH) have high rates of psychological comorbidities from stress and trauma of their disease. Resilience describes a person's ability to positively adapt to stress. Although minimal published research exists in PAH patients, evidence suggests resilience correlates with improved quality of life (QoL) in patients with chronic disease. Understanding differences in resilience among patients with PAH and identifying tailored interventions have implications for how we holistically care for PAH patients.
Methods: We performed a mixed-methods, prospective study to identify thematic areas of resilience in patients with PAH enrolled from the University of Colorado Health Pulmonary Vascular Disease Clinic. Participants completed the Connor-Davidson Resilience Scale (CD-RISC), then participated in in-depth, semistructured interviews. All data were recorded and transcribed and entered into ATLAS.ti23. We used an exploratory thematic content analysis approach. Coding and analysis were inductive and deductive, informed by Kumpfer's resilience framework.
Results: Enrolled participants (n = 20) had an average age of 56 ± 14 years, and 75% were female. Only half of patients tested highly resilient per predetermined cutoffs on the CD-RISC. Analysis revealed a resilience framework with 4 themes (Figure 1), which both aligned and diverged from the Kumpfer framework. The first theme focused on complicated environmental factors: disease effect on family and friends, medical team interactions, and the challenges of medical equipment. Second, PAH strongly influenced patients' sense of identity including struggles in productivity, parentage, survivorship, and internal or external locus of control. Third, coping strategies that patients engage in behavioral, emotional, and practices centered around meaning-making. Fourth, possible interventions included small group sessions, one-on-one support, and exercise. Highly resilient patients preferred one-on-one support, while less-resilient patients preferred small groups.
Conclusion: This resilience framework for patients with PAH can better characterize the disease experience and patients' adaptations and resilience. This understanding will inform development of effective interventions to improve resiliency and QoL for patients with PAH.

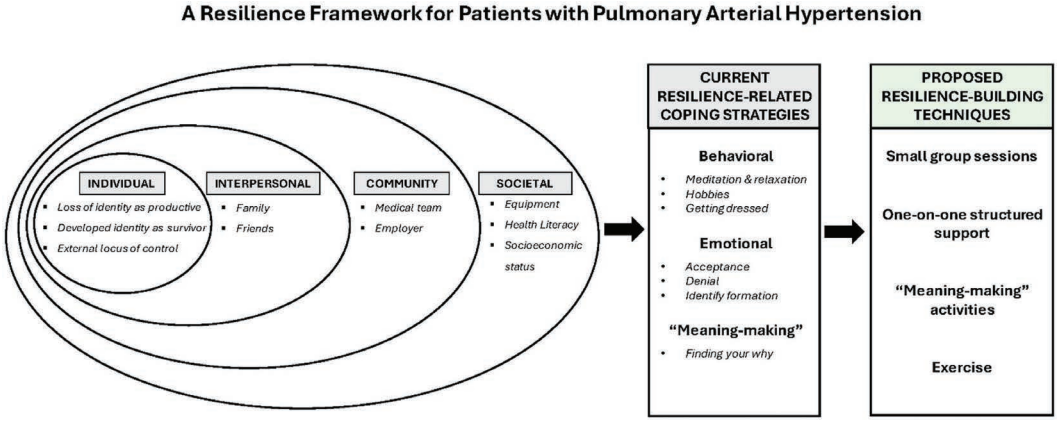

Figure 1: A resilience framework for patients with pulmonary arterial hypertension.

RETROSPECTIVE STUDY INVESTIGATING THE REAL-WORLD USE OF MONOTHERAPY IN PULMONARY ARTERIAL HYPERTENSION IN THE UNITED STATES

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Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Observational studies can provide descriptive data regarding real-world management of pulmonary arterial hypertension (PAH) patients. The current standard of care for PAH is considered upfront combination therapy for most patients. This analysis characterized real-world treatment patterns and investigated factors associated with and reasons for use of monotherapy based on a retrospective medical chart review.
Methods: An online questionnaire was fielded to PAH-treating physicians between December 2023 and February 2024. Respondents were required to have ≥5 years of experience in their specialty and be personally involved in the management and treatment of ≥10 PAH patients in the previous month, with ≥5 of those patients treated with PAH-specific drug therapy. Physicians provided deidentified medical record data for up to 7 of their most recent adult patients with PAH meeting the following criteria: diagnosed ≥1 year ago, World Health Organization (WHO) Functional Class (FC) II–IV, currently receiving PAH-specific therapy, primarily managed by the respondent for their PAH, and not currently participating in a clinical trial.
Results: Respondents (72 pulmonologists and 40 cardiologists from >80 institutions) provided medical chart data representing 768 patients for this study. The respondents were associated with Pulmonary Hypertension Association (PHA)–certified Centers of Comprehensive Care (CCCs, 45%), PHA-certified Regional Clinical Programs (17%), PAH centers without PHA certification (19%), or a non-PAH-focused institution (non-PAH center, 20%). Most patients were female (53%), with a mean age of 54 years, and were diagnosed with PAH between 1 and 3 years ago. Overall, 46% of the patients were currently receiving monotherapy, and 68% had cardiopulmonary comorbidities. Patient subgroups with high proportions of monotherapy included male patients (54%), those with Medicare-only (57%) or no insurance coverage (89%), ~1 year (55%) or ≥6 years since PAH diagnosis (58%), WHO FC II (52%), low risk status (81%), and treatment at a CCC (51%) or a non-PAH center (61%). The most frequently selected reasons for not prescribing combination therapy were patients "doing well on monotherapy" (57%), "the disease is not severe enough" (32%), and the "patient does not want additional therapy added" (22%). Of the patients considered to be "doing well on monotherapy," 12% were described by respondents to have a suboptimal status of either "stable but not satisfactory" or "unstable and deteriorating." Additionally, 25% of patients on monotherapy because they "did not want additional therapy" were also considered of suboptimal status.
Conclusion: This cohort demonstrates significant monotherapy use in an era with expanding evidence that combination therapy should be considered for most PAH patients. Real-world treatment patterns suggest that PAH treatment selection is complex and individualized, possibly following an escalate-as-needed approach based on physician perceptions of disease severity or patient stability or patient decisions. The drivers and barriers of patient choice in PAH treatment, particularly in the setting of unsatisfactory or declining PAH status, warrant further exploration in future research.

A SPOONFUL OF SUGAR? REIMAGINING THE ROLE OF THE INTEGRATED SPECIALTY PHARMACIST FOR MEDICATION MANAGEMENT IN PULMONARY ARTERIAL HYPERTENSION PATIENTS

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Category: Clinical Science
Subcategory: Specialty Pharmacy Involvement in PH Patient Care

Background: Patients with pulmonary arterial hypertension (PAH) are often on multiple medications. One of the major barriers to medication adherence in PAH patients is the significant adverse reaction profile associated with PAH therapies. An innovative pharmacist collaborative practice agreement (PCPA) will be implemented in the outpatient pulmonary hypertension (PH) clinic within the Medical University of South Carolina (MUSC) pulmonary vascular disease program. The PCPA is a pharmacist-driven management program to help patients manage adverse reactions including acute fluid and electrolyte management and electrolyte replacement. The PCPA will also assist patients with medication access, education, monitoring, and improve medication adherence in a longitudinal fashion.
Methods: The PCPA will allow the integrated specialty pharmacist (SP) in the PH clinic to provide medication education before initiation and during maintenance of drug therapy. The PCPA will help with periodic patient counseling for adverse reaction management, fluid and electrolyte management, and ordering appropriate laboratory tests for therapeutic monitoring. The SP will be able to interview patients in-person in clinic or virtually using a telemedicine platform to provide these services/interventions. Patients who fill PAH oral medications from MUSC Specialty Pharmacy will be included for data collection and analysis for this project.
Results: Outcomes include (1) time to medication delivery scheduled, (2) medication adherence, (3) the number of emergency department (ED) or hospital visits, and (4) change in PAH Self Report Functional Classification. We plan to collect data for these outcomes from other clinics and specialty pharmacies to evaluate the effect of our novel SP-driven PCPA on these outcomes.
Conclusion: PAH patients often have difficulties in accessing limited distribution PAH therapies and managing the adverse reactions related to their use. We hypothesize that the involvement of SPs in the PH clinic will improve patients' access to PAH medications and that the new PCPA will have a positive effect on patients' self-assessment of the disease state, PAH-related ED or hospital visits and medication adherence.

AGED LIKE PHINE WINE—AN UNMET NEED

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Category: Case Report
Subcategory: Diseases and Conditions Associated With PH

Background: World Health Organization (WHO) Group I pulmonary arterial hypertension (PAH) is a complex disease associated with a high mortality rate due to delayed diagnosis and treatment. The mean age in the Western world ranges from 45 to 65 years. PAH can be particularly unusual in the elderly. Additionally, PAH is known to be associated with poor outcomes, especially in emergent surgeries. Data pertaining to intraoperative or perioperative mortality in PAH are relatively scarce and can be considered an unmet need. Here, we present an unusual case of an octogenarian with high-risk WHO Group I PAH who underwent emergent abdominal surgery with a successful outcome.
Methods: Case Report: An 88-year-old female with a history of chronic WHO Group I PAH presented with the acute onset of nausea, vomiting, and abdominal pain for 5 days. PAH medications included long-standing subcutaneous treprostinil (80 ng/kg/min) and macitentan. The physical exam showed diffuse abdominal distension and tenderness. Lab results revealed an elevated B-type natriuretic peptide (BNP) of 183, and a contrast computed tomography (CT) of the abdomen and pelvis confirmed acute small bowel obstruction. Baseline O2 saturation was 85%–88%, the echocardiogram showed severe right heart dysfunction, and tricuspid

RIGHT HEART CATHETERIZATION

UNITS	2010	2014	2018	2021
MRAP (mmHg)	10	14	5	4
PAP (mmHg)	54/14	105/40	80/35	90/35
MPAP (mmHg)	35	62	50	53
PCWP (mmHg)	15	10	7	14
CO (L/min)	3.7	3.79	4.17	3.4
PVR (woods units)	---	13.7	10	11.4

Figure 1: Right heart catheterization hemodynamics.

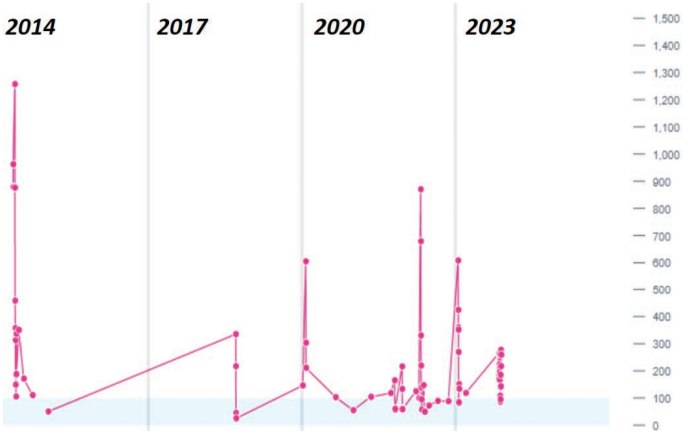

Figure 2: BNP trending–controlled BNP with occasional exacerbation.

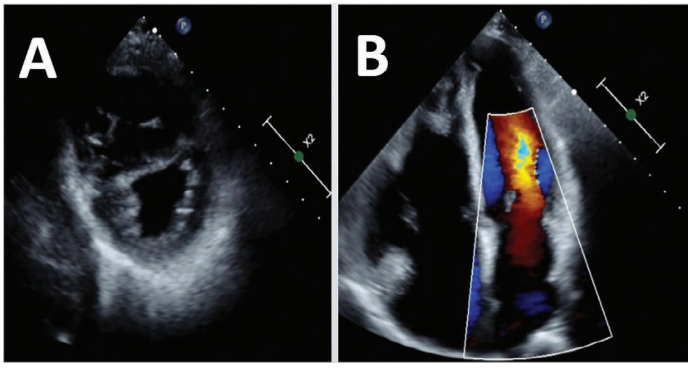

Figure 3: Baseline echocardiogram transthoracic. A, Abnormal septal motion. B, Moderately dilated left and right atria. Severely enlarged right ventricle with evidence of right ventricular pressure and volume overload.

annular plane systolic excursion (TAPSE) was measured at 2.1 cm. Surgical options were discussed, and conservative management was initiated due to severe PAH. However, the intestinal obstruction was refractory after 4 days of conservative measures with a nasogastric (NG) tube and bowel rest. After much deliberation, the patient underwent emergent exploratory laparotomy with adhesiolysis. Preoperative PAH-specific interventions included switching treprostinil to intravenous (IV), administering low-dose dobutamine, and cautiously providing IV fluids. The patient received general anesthesia, and surgical repair was successful. The patient passed flatus with the return of bowel function on postoperative day 1. Eventually, the patient was switched back to subcutaneous treprostinil and continued to make progress in recovery. See Figures 1–4.

Results: The mean age of PAH diagnosis in the Western world ranges from 45 to 65 years, particularly unusual in the elderly. Three classes of targeted therapies approved for Group I PH: (1) nitric oxide (NO) pathway mediators: phosphodiesterase type 5 (PDE5) inhibitors, guanylate cyclase stimulator; (2) endothelin receptor antagonists; and (3) prostacyclin pathway agonists: prostacyclins, prostaglandin I2 receptor agonists. Emergent surgery in patients with PAH carries significant perioperative risks, with a 30-day mortality rate ranging from 15% to 50%. Perioperative PAH therapies can be supplemented with inotropes (dobutamine, milrinone) to augment right ventricular (RV) myocardial contractility, but caution is required for systemic hypotension and arrhythmias.

Conclusion: Perioperative and intraoperative management require a multidisciplinary team approach for appropriate

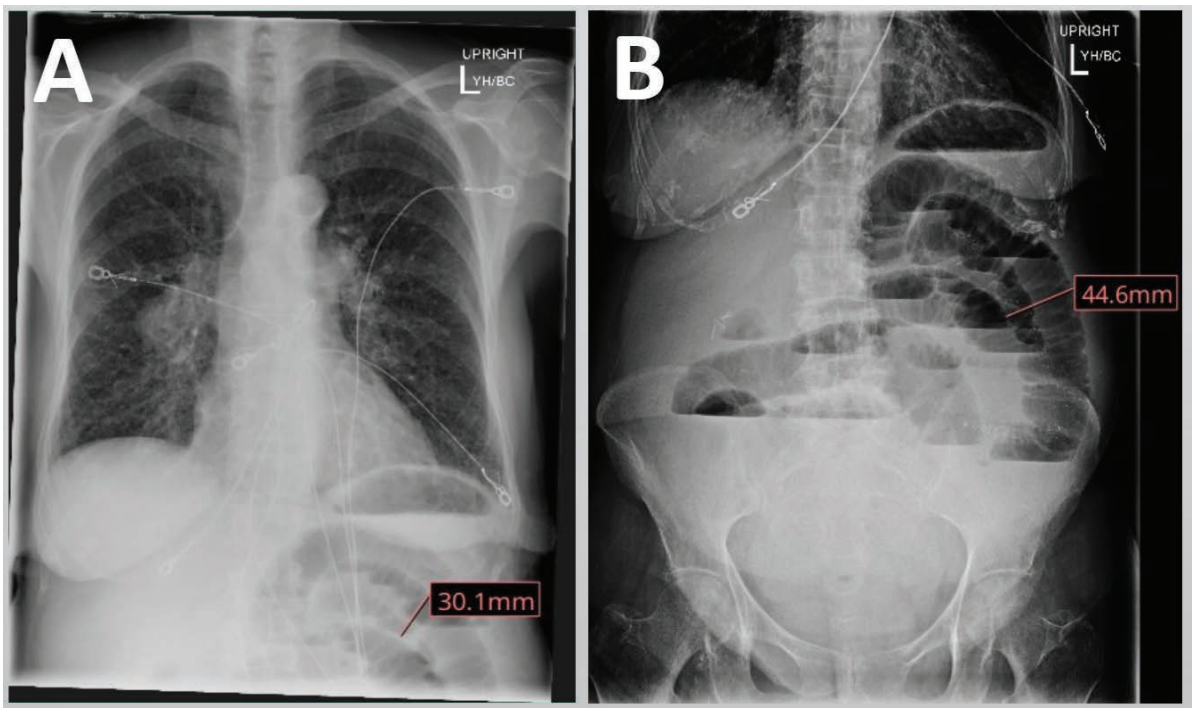

Figure 4: X-ray at Admission. A, XR chest—prominent perihilar marking, interstitial pattern of lung disease, gaseous distention of partial image. B, XR abdomen—small bowel obstruction with multiple air-fluid levels.

PAH management: optimize preload, reduce RV afterload, and ensure RV coronary perfusion. PAH remains a serious disease, but outcomes have improved with new knowledge and new therapies. Systematic understanding of PAH along with following current guidelines might help promote improve outcomes in PAH patients undergoing major surgeries.

ATYPICAL ALVEOLAR CAPILLARY DYSPLASIA AND MECHANICAL CIRCULATORY SUPPORT: A SURVIVAL STORY

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Category: Case Report
Subcategory: Pediatrics

Background: Alveolar capillary dysplasia is a developmental lung disorder associated with pulmonary hypertension (PH) and is typically fatal in infancy. Children who require mechanical circulatory support (MCS) for progressive PH rarely survive without a lung transplant. We present a patient case with likely atypical alveolar capillary dysplasia who required a prolonged MCS course. The patient is now thriving at home without having received a lung transplant.
Methods: A female infant born at 37 weeks had an echocardiogram completed day of life 2 due to failed congenital heart defect screen. This showed evidence of moderate right ventricular (RV) hypertension, an atrial septal defect (ASD) with left to right shunting, and low normal RV function. She was otherwise well and was discharged with no treatments but with cardiology follow-up.

Over the next 6 months, the patient's PH progressed with higher RV pressures and worsening RV dysfunction on serial echocardiograms. Initial PH workup was unrevealing with a negative genetic evaluation. She was initially started on sildenafil and oxygen but required escalation of therapy with the addition of bosentan. A hemodynamic catheterization was planned but deferred multiple times due to repeated viral infections requiring admissions.

At 8 months, the patient was admitted for bronchiolitis due to human metapneumovirus and adenovirus. One week into hospitalization, the patient had worsening desaturation with bradycardia, and inhaled nitric oxide was started. The following day, she had an acute hypoxemic event, likely PH crisis, resulting in intubation with brief peri-intubation arrest. Echocardiogram obtained the next day revealed suprasystemic RV pressure and moderately depressed RV function. Patient was started on remodulin and up-titrated to 80 ng/kg/min over the course of a week. On repeat echocardiogram, her RV function had normalized despite ongoing evidence of severe RV hypertension. The patient was extubated, but a second PH crisis resulted in reintubation. Remodulin was further increased to 100 ng/kg/min. Given concern for refractory PH despite aggressive triple PH therapy, the patient was electively placed on RV MCS for stabilization to allow for improved growth and development with the goal of lung transplantation. The cannulation strategy as described in Bigelow et al. (2023) was as follows: The pulmonary artery (PA) was the inflow (venous), and to the left atrium (LA) was the return (arterial) with a Quadrox iD pediatric oxygenator and a PediMag blood pump. Lung biopsy was obtained at the time of cannulation; results were consistent with a diffuse developmental lung disorder suggestive of atypical alveolar capillary dysplasia.

The day following cannulation, the patient was extubated to noninvasive ventilatory support (NIV). Remodulin was weaned off on day 25 of MCS. On day 42, hemodynamic heart catheterization on sildenafil monotherapy with MCS clamped was notable for the rapid development of suprasystemic pulmonary pressures and cardiogenic shock. Unfortunately, on day 82 of MCS, the patient was found to have a stroke with resultant aspirations of oral secretions, disqualifying her for lung transplantation.

Given concerns for inability to survive off MCS, withdrawal of life support was discussed. The decision was made by family to restart bosentan and remodulin and attempt to allow her to wean off MCS. Once on goal PH therapies, a step wise approach was used to gradually withdraw MCS, and she was decannulated on day 102. Twenty-four days after decannulation, at 13 months of age, the patient was discharged home on daytime nasal cannula, nocturnal NIV, nasogastric feeds, and triple PH therapy.

The patient is now 19 months of age at home, doing well, and making slow developmental progress. The patient remains on stable respiratory support and pulmonary vasodilator therapy.
Results: N/A.
Conclusion: Though the prognosis for children who require MCS for severe progressive PH is typically thought to be dismal without lung transplantation, our patient demonstrates that survival is possible.

BRANDED EPOPROSTENOL TRANSITIONS: SPECIALTY PHARMACY SUPPORT DURING TIMES OF DRUG SHORTAGE

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Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: The COVID-19 pandemic led to significant supply chain disruption. These disruptions have proven to especially affect the pharmaceutical industry. Increased medication backorders resulted in the need for specialty pharmacy agility to avoid gaps in care and maintain drug access, particularly for life-sustaining medications. On December 12, 2023, specialty pharmacies were notified of a branded epoprostenol (original approval in 1995) backorder requiring the need for patients to convert to an alternate prostanoid for the treatment of pulmonary arterial hypertension (PAH).
Methods: A retrospective review of the electronic medical records of patients active on the backordered branded epoprostenol therapy before December 12, 2023, was conducted. The review period began on June 1, 2023, and concluded on February 16, 2024. Patients were included in the sample if they were aged 18–89 and carried a diagnosis of World Health Organization (WHO) Group 1 PAH. Patients were required to be on therapy from the beginning of the review period to time of transition with no identified gaps in care. Exclusion criteria included patients who converted to another prostanoid, expired within the review period, or whose drug was covered by a payer with data-use restrictions. Patients verbalized understanding to clinical counseling provided by a PAH specialty-trained pharmacist before administration of an alternate prostanoid. Key counseling points included guidance on proper admixture technique, differences in vial appearance, and instructions on proper reconstitution for all patients transitioning to either thermostable epoprostenol (original approval in 2010) or infused treprostinil.
Results: Fifty-nine patients met criteria for review. Ninety-three percent (55/59) had a prescription for an alternative prostanoid therapy received by the specialty pharmacy within the review period. Thirty-nine (66% [39/59]) patients had a first shipment of alternate prostanoid delivered or scheduled in the review period. Thirty-six (92% [36/39]) patients transitioned to thermostable epoprostenol. Three (8% [3/39]) transitioned to infused treprostinil (2 intravenous [IV], 1 subcutaneous [SubQ]). All 39 patients received clinical counseling on transition before the first shipment by a PAH specialty-trained pharmacist. Thirty-two (89% [32/36]) patients converted to thermostable epoprostenol at an equivalent (1:1) dose: 2 patients (5.5% [2/36]) converted to a higher dose and 2 patients (5.5% [2/36]) transitioned to a lower dose. All 3 patients who transitioned to infused treprostinil achieved a maintenance dose of 10% or greater than their previous branded epoprostenol dose.
Conclusion: Specialty pharmacy support during a supply chain disruption resulted in conversions from a complex, life-sustaining prostanoid to an appropriate alternative with no gaps in care or undesired dose reductions. PAH specialty-trained clinicians worked collaboratively with prescribers, counseled patients, and provided clinical support to confirm appropriate mixing techniques and safety precautions were followed.

CARDIAC EFFORT IN PULMONARY HYPERTENSION–INTERSTITIAL LUNG DISEASE: A NEW AND PERSONALIZED CLINICAL TRIAL OUTCOME.

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Category: Clinical Science
Subcategory: Diseases and Conditions Associated With PH

Background: The 6-minute walk test (6MWT) is a simple, noninvasive, standardized exercise test that has been included as an endpoint in many pivotal pulmonary arterial hypertension (PAH) and pulmonary hypertension–interstitial lung disease (PH-ILD) trials. In pulmonary hypertension (PH), 6-minute walk distance (6MWD) is likely an indirect measure of right ventricular (RV) function and stroke volume. However, ordinary day-to-day variability, especially for walks >400 m, can make it difficult to detect improvement. This is because more variable 6MWD with longer walks approximate the minimal clinically important difference (~30 m).
Methods: By incorporating continuous heart rate (HR) monitoring during 6MWT, we found cardiac effort (number of heart beats used during 6MWT/6MWD, beats/min) enhances the information gleaned from 6MWT in PAH. Cardiac effort has less variability, tracks with treatment response (drop in HR with the same walk distance), and correlates better with stroke volume (cardiac magnetic resonance imaging [cMRI], right heart catheterization, and multigated acquisition [MUGA]) than 6MWD. Continuous HR monitoring during 6MWT also provides insight into HR variability (autonomic tone), peak HR, HR reserve, and HR recovery.

We believe cardiac effort is an innovative clinical trial endpoint that incorporates valuable dynamic physiologic data during the 6MWT in PH-ILD, a group we know very little about. Specifically, changes in HR during 6MWT will provide insight into stroke volume limitation (a higher HR for a given distance is more likely to be stroke volume limited), respiratory limitation (less dynamic HR changes for a given 6MWD), and treatment response. Cardiac effort in PH-ILD will be assessed during the open-label, prospective, multicenter study ASCENT, which aims at evaluating the safety and tolerability of dry-powder inhaled (DPI) treprostinil in patients with PH-ILD. Cardiac effort in PH-ILD will be measured with the Fourth Frontier HR monitor (reusable dry electrode electrocardiogram HR monitor that provides access to the raw data) during 6MWT. Electrocardiogram HR monitors have less data loss than photoplethysmography (wrist or pulse oximeter measurements), especially in the setting of skin thickening, poor perfusion, and/or narrowed pulse pressure (factors which afflict many of our patients). The accelerometer associated with the device also allows for 6MWD to be estimated. This can help verify 6MWD and ensure accurate measurements.
Results: N/A.
Conclusion: Cardiac effort is a novel noninvasive endpoint that has the potential to phenotype and characterize the physiologic limitations in PH-ILD at baseline and any improvement after adding inhaled treprostinil. Cardiac effort has less intrinsic variability than 6MWD (HR changes help mitigate changes in mood or effort), which makes it a more appealing endpoint. Cardiac effort also has the potential to help with treprostinil titration strategies, highlight need for more urgent transplant, and potentially improve patient care and outcomes.

CHARACTERIZING PULMONARY HYPERTENSION CARE IN RURAL APPALACHIA: RETROSPECTIVE ANALYSIS OF PATIENT DEMOGRAPHICS AND BARRIERS TO TREATMENT

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Category: Clinical Science
Subcategory: Health Disparities/Social Determinants of Health

Background: Pulmonary hypertension (PH) management in rural areas faces unique challenges due to limited health care resources. In this study, we aim to characterize the demographic profiles of PH patients and identify barriers to care within a large academic hospital in rural Appalachia. We present a detailed examination of patient demographics, lifestyle factors, and obstacles to health care access in this region.

Methods: This retrospective analysis included 163 patients diagnosed with PH according to the World Health Organization's classification, with an emphasis on pulmonary arterial hypertension (PAH, Group 1). Data on demographics, body mass index (BMI) classifications, geographical distance to the hospital, PH types and subtypes, social history, insurance status, engagement with patient assistance programs, and remote monitoring technologies were collected. Descriptive statistics were used for analysis. See Figure 1.
Results: We analyzed 163 patients, revealing a median age of 58 years with a female predominance (72.4%). Of these, 54% never smoked, 14.9% were current smokers, 3.6% reported illicit drug use, and 18.4% consumed alcohol. BMI classifications showed 55.8% under 30, 30.7% between 30 and 39, and 13.5% 40 or above. Notably, 66.6% lived >50 miles from the hospital, highlighting geographical barriers to care. Insurance analysis revealed that only 1.8% were inadequately insured. None were enrolled in remote monitoring programs, while 14.1% used patient assistance programs, indicating economic barriers to accessing PH medications. PH classification distribution: Group 1 (48.7%), Group 2 (10.4%), Group 3 (27.7%), Group 4 (11.5%), and Group 5 (1.7%), with 18.8% categorized as mixed PH.
Conclusion: In this study, we underscore the significant demographic, socioeconomic, and geographical factors affecting PH care in rural Appalachia. Over two-thirds of patients live >50 miles from the hospital, highlighting geographical distance as a significant care barrier. Notably, enrollment in patient assistance programs remains low, suggesting potential issues with accessibility, use, or awareness. These findings call for targeted interventions to enhance health care accessibility and patient outcomes, with further research needed on the effects of these barriers on treatment adherence and long-term health.

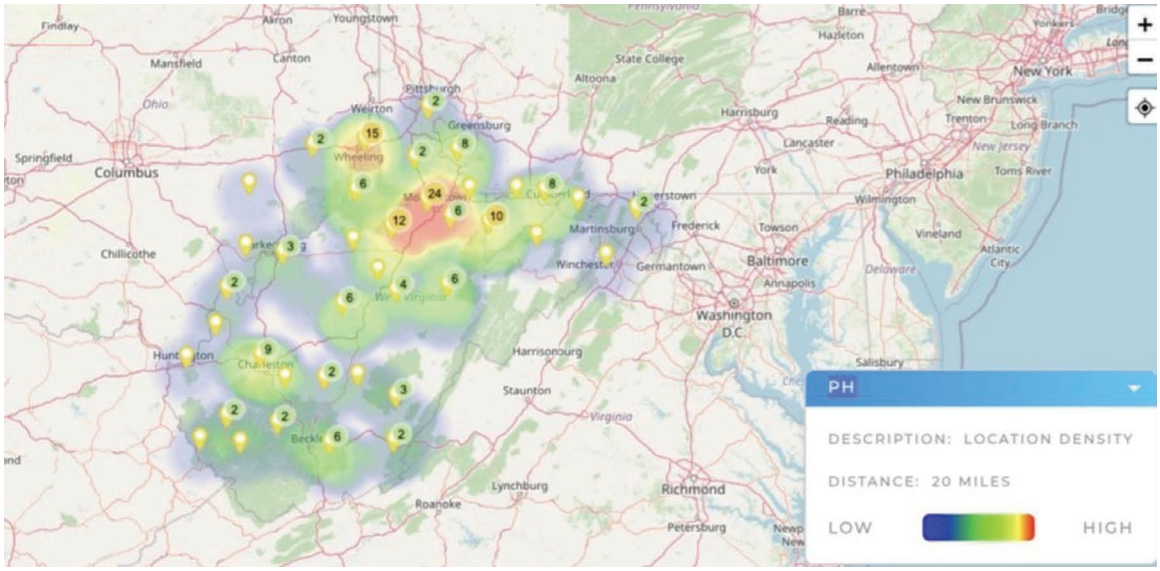

Figure 1: Geographical mapping of patients' distance from hospital.

CLINICAL PHARMACOKINETICS OF AN EXTENDED-RELEASE FORMULATION OF INHALED LIPOSOMAL TREPROSTINIL (L606) TO REDUCE DOSING FREQUENCY

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Category: Clinical Science
Subcategory: Diseases and Conditions Associated With PH

Background: Treprostinil is a prostacyclin analog used to treat pulmonary arterial hypertension (PAH) and pulmonary hypertension associated with interstitial lung disease (PH-ILD). Existing inhaled therapies, with immediate release formulations, require 4 times daily dosing due to short half-life, leading to exposure limited to waking hours. Inhaled liposomal treprostinil (L606) is a novel, extended-release formulation designed for sustained plasma levels, reducing dosing frequency and extending daily exposure. L606 aims to control treprostinil release in the lung, potentially reducing respiratory tract irritation.
Methods: In a comparative bioavailability study of healthy volunteers, we evaluated the pharmacokinetics of L606. Participants received L606 via a vibrating-mesh nebulizer or a Tyvaso comparator. Blood samples were collected over 24 hours for liquid chromatography with tandem mass spectrometry (LC-MS/MS) analysis, assessing systemic pharmacokinetics, total exposure, and dosing frequency.
Results: L606 and Tyvaso systemic exposures were compared at 51 and 54 µg, respectively. L606 achieved similar exposure to Tyvaso but with a lower peak plasma concentration. Its increased half-life and comparable plasma clearance rate suggest controlled release postdelivery. L606 maintains plasma concentrations for 12 hours, supporting a reduced dosing frequency to twice daily. When comparing equivalent daily doses, L606 provides sustained levels with similar total daily exposure and a reduced peak-to-trough ratio, ensuring continuous coverage throughout waking and sleeping hours.
Conclusion: The pharmacokinetics of L606 in healthy volunteers show sustained levels for 12 hours, supporting twice-daily administration and maintaining exposure during sleep. An ongoing open-label study is evaluating the safety of L606 in PAH and PH-ILD patients transitioning from Tyvaso or naïve to inhaled treprostinil in the US.

CORRECTING HIGH-OUTPUT HEART FAILURE VIA ARTERIOVENOUS FISTULA LIGATION IN A PATIENT WITH END-STAGE RENAL DISEASE: A CASE REPORT

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Category: Case Report
Subcategory: Diseases and Conditions Associated With PH

Background: Pulmonary hypertension (PH) occurs in 40% of patients with end-stage renal disease (ESRD) with arteriovenous fistulas (AVFs) and is associated with higher mortality and morbidity. The pathogenesis of PH in this group is not fully understood and is thought to be multifactorial with a suspected mechanism being high-output heart failure resulting in World Health Organization (WHO) Group 2 PH, with high cardiac output from AVF contributing to its progression. Additionally, patients with ESRD and AVFs are at increased risk for development of PH compared with patients receiving dialysis by alternative access.
Methods: We present an interesting case of a 67-year-old male with longstanding ESRD via a right upper extremity brachiocephalic AVG, chronic diastolic heart failure with preserved ejection fraction, moderate aortic stenosis, hypertension, hyperlipidemia, and mixed WHO group PH that presented with ongoing dyspnea despite continued up-titration of medical therapies.
Results: Transthoracic echocardiogram showed left ventricular ejection fraction 55% with moderately depressed right ventricular systolic function and elevated right-sided filling pressures. He endorsed ongoing dyspnea despite medical optimization and ongoing fluid removal via hemodialysis. Right heart catheterization was performed, showing moderate postcapillary hypertension with right atrial pressure (RAP) 8 mmHg, pulmonary artery systolic pressure (PASP)/pulmonary artery diastolic pressure (PADP; mean pulmonary artery pressure [mPAP]) 65/25 (40 mmHg), pulmonary capillary wedge pressure (PCWP) 23 mmHg, cardiac output (CO) 8.32 L/min, cardiac index (CI) 3.73 L/min, and pulmonary artery pulsatility index (PAPi) of 5. Additionally, AVF flow volumes were measured to be around 4000 mL/min on AVF duplex. Given high flows through AVF thought to be contributing to high-output heart failure, the patient subsequently underwent AVF ligation with flow reduction from 4822 to 2063 mL/min. After ligation of AVF, a tunneled dialysis catheter was placed to allow the patient to continue hemodialysis and volume removal. Repeat invasive hemodynamics were obtained during a state of suspected euvolemia where revealed central venous pressure (CVP) of 2 mmHg, CO 7.3 L/min, CI 3.2 L/min, systolic pulmonary artery pressure (sPAP)/diastolic pulmonary artery pressure (dPAP; mPAP) 34/10 (19 mmHg).
Conclusion: We present an interesting case of significant improvement and potential reversibility of PH in patients with high-output heat failure due to high-flow AVF. Heart failure and progressive PH are unintended consequences in patients with ESRD using an AVF. AVF ligation has been shown to improve both hemodynamics and symptoms in patients with high-output heart failure secondary to high-flow AVFs and should be considered in those patients with ESRD that present with ongoing symptoms that may be refractory to medical therapy.

CURRENT PATIENT PERSPECTIVES ON PALLIATIVE CARE IN PULMONARY ARTERIAL HYPERTENSION IN THE UNITED STATES

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Category: Clinical Science
Subcategory: Palliative Care

Background: Medicines are the primary treatment to ease symptoms, improve health-related quality of life (HRQOL), and delay disease progression for pulmonary arterial hypertension (PAH). However, palliative care (PC) can provide additional support for both patients and their caregivers. Despite the potential benefits, PC is an underused resource that can be helpful for patients with PAH. Barriers to PC include a lack of referral and a common misperception that PC is equivalent to end-of-life care.
Methods: An online survey was developed following an iterative process including review and input from clinicians and patients with PAH. The survey was completed by adult patients with self-reported PAH recruited via the Pulmonary Hypertension Association in the US. Patients' perspectives and experiences of PC as well as demographic and disease

information were collected via closed-ended and open-ended survey questions. Patients' functional class was self-reported via the Pulmonary Hypertension Functional Class Self-Report (PH-FC-SR), and their HRQOL was assessed using EmPHAsis-10 (E10). Quantitative data were analyzed descriptively; qualitative data were analyzed using a qualitative description approach.

Results: Two hundred patients from 42 states with self-reported PAH completed the online survey (173 female, 27 male; mean age = 58.5 years [range, 23–87]); 35.5% (n = 71) self-reported as having idiopathic PAH. Most patients self-reported as functional class II (n = 83; 41.5%) or class III (n = 71; 35.5%) on the PH-FC-SR. The mean E10 score was 27.1 (E10 scores range from 0 to 50; a higher score predicts worsening pulmonary hypertension [PH]–specific HRQOL). Twenty-seven patients (13.5%) had never heard of PC; 167 patients (83.5%) provided their own definition of PC (Table 1); 42 patients described PC as end-of-life care, followed by 24 patients who described PC as comfort care. Over 50% of patients associated PC with the following statements: the need for extra support (n = 111; 55.5%); that more support would result in improved well-being (n = 110; 55.0%); and that their PAH is a terminal, incurable disease (n = 107; 53.5%). Most patients (n = 171; 85.5%) had not discussed PC with their health care provider (HCP); 63.7% of the 171 patients (n =109) reported that "no one offered" to discuss PC services. However, most patients (n = 177; 88.5%) reported that they would be comfortable discussing PC with their HCP. PC discussions with HCPs engendered a range of emotions for patients; feeling anxious (n = 85; 42.5%) and hopeful (n = 61; 30.5%) were the most frequently reported emotional effects. Need for support (n = 78), specifically support for self-care, daily activities, and emotional or psychological well-being, was the most common reason that PAH patients believed someone would receive PC. Eleven of the 15 patients who received PC reported positive experiences including improved emotional or psychological well-being. *Supportive care* was the preferred term to describe PC by more than half of the survey sample.

Table 1. Patient Definitions of Palliative Care (n = 167)

Illustrative quote
"To me it means your care is mainly to keep you as comfortable as possible while knowing your health will not improve and your death will be if the next step" ~Female, 84 y old
"Palliative care provides hydration and medications to keep a person as pain free and calm as possible without extreme measures." ~Female, 74 y old
"providing comfort (physical, emotional, and medically) to a chronically ill patient toward the end of their life by recognizing their quality of life. Not utilizing often painful interventions that only prolong suffering without much hope of extending functional quality of life." ~Female, 66 y old
"Care designed to make you comfortable while allowing your disease to progress. Focus on comfort versus heroics." ~Male, 69 y old
"Special care to people with PAH such as nurses and doctors who help the patients. There is a PHA team that is on standby whenever I go to the emergency room that are trained to help patients with PHA." ~Male, 61 y old
"Palliative care is medical care for people living with a serious illness who may qualify to receive medical care for their symptoms and treatments for their chronic conditions and side effects." ~Female, 61 y old

Conclusion: Previous researchers have demonstrated that patients perceive PC as comparable with end-of-life care. The results from this survey suggest that patients' understanding of PC goes beyond this common misconception, demonstrating an awareness of the benefit of PC as a resource to help manage their PAH. Another important study finding indicated that, although most patients had not discussed PC with their HCP, many of these individuals would be receptive or comfortable discussing PC with their HCP if the opportunity arose. The survey results highlight the need for proactive engagement between patients and their HCPs to ensure that PC is optimally used to benefit patients' well-being and ability to manage their PAH.

DELPHI STUDY INVESTIGATING THE CLINICAL USE OF ORAL SELEXIPAG TO TREAT PULMONARY ARTERIAL HYPERTENSION

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Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Oral selexipag, a prostacyclin receptor agonist, has been shown in clinical trials to delay disease progression and reduce the risk of hospitalization in patients with pulmonary arterial hypertension (PAH). Despite the well-described clinical benefits, clinical use can sometimes be challenging due to issues related to the titration process and expected side effect (SE) management. The purpose of this study was to convene an expert panel to create a best-practices guideline to enhance patient care and assist with treatment management.
Methods: US health care professionals (n = 17, 11 physicians; 5 nurse practitioners; 1 registered nurse) participated in this modified Delphi panel. The study consisted of 2 online surveys and a consensus meeting, with consensus being defined as ≥80% of the panel agreeing using a 9-point Likert scale.
Results: Panelists prescribed selexipag in accordance with the Food and Drug Administration (FDA) label for dosing and titration. The panelists acknowledged considerations that would prompt faster or slower titration, including treatment tolerability or patient characteristics (e.g., age and comorbidities). Panelists agreed that an individual patient's maximum dose is identified by tolerability to SE. Prior receipt of parenteral prostacyclin therapy affected tolerability, and some panelists suggested higher selexipag doses in this group. Panelists identified SEs associated with oral selexipag, including headache and diarrhea as the most common and burdensome. Based on panelists' experience, duration of SEs is highly variable and patient specific, although they most frequently developed 3–4 weeks after the start of treatment. There was agreement that SEs often become more manageable over time. Panelists identified methods for managing each SE, agreeing that this should be proactive. Panelists highlighted the importance of communication with patients to set expectations, including the benefits of oral selexipag, expected SEs, and their management.
Conclusion: This panel provided expert opinion on the management of PAH and clinical use of oral selexipag. Insights are valuable for developing standardized clinical guidelines and best practices, highlighting the importance of understanding expected SEs for personalized treatment to accommodate patients' needs and improve their care.

DEVELOPMENT OF A COMPREHENSIVE PROGRAM FOR PULMONARY HYPERTENSION REGARDING END-OF-LIFE CARE

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Category: Basic Science
Subcategory: Psychosocial Considerations/Aspects of Care

Background: Patients with pulmonary arterial hypertension (PAH) have a complex disease process that is best addressed when advance care planning (ACP) is integrated into the management process earlier than the immediate end-of-life period. Management is also optimized when a tool assessing health-related quality of life (HRQoL) is used so patients can be referred to palliative or supportive care for appropriate symptom and disease effect management. This project assessed the feasibility of instituting HRQoL assessment with a patient-reported outcome measure and using this as a prompt to direct patients to an online ACP tool that can be shared with the PAH provider.
Methods: This project used the REVEAL 2.0 risk score calculator to identify participants who attended the clinic with the highest mortality risk and an active patient portal account. Those at high risk were asked to complete the Pulmonary Arterial Hypertension—Symptoms and Impact Questionnaire (PAH-SYMPACT). Patients with scores indicating significant effects were directed to the online ACP tool MyDirectives. These participants received messages from the patient portal with a presurvey and postsurvey to assess their experience.
Results: Ninety-one patients were appropriate for this quality improvement (QI) project. Due to a low rate of return of the presurveys and postsurveys, it was difficult to determine if the project changed the participants' perception of ACP or improved the clinic's care. Also, no difference was found between the prenumber and postnumber of ACP notes or frequency of documented advanced directives. The project showed that participants visited the MyDirectives Website when suggested and that most (88%) read at least 1 of the messages sent via the patient portal.
Conclusion: This pilot project showed that high-risk PAH patients with significant disease effects can successfully be identified and referred to online ACP tools via patient portal messaging. This project also showed that MyDirectives is an online tool that can assist with this goal. Methods to improve uptake and applicability in PAH need to be explored with further studies.

DRUG-ENCAPSULATING NANOPARTICLES WITH NONINVASIVE STIMULUS-INDUCED REMOTE DRUG RELEASE PROPERTIES FOR DEVELOPMENT OF A PRECISION DRUG DOSING AND MONITORING TECHNOLOGY

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Category: Basic Science
Subcategory: Therapeutic Strategies

Background: Estimates of the total costs associated with dosing failures approach $40 billion annually according to a 2017 World Health Organization (WHO) study. For pulmonary hypertension (PH) drugs, dosing errors can result in patient mortality. We developed a platform precision drug dosing and monitoring technology for use in improved PH drug dosing.

Prior work has demonstrated release of drug from tumor-targeting lipid nanoparticles (LNPs) with light illumination. This is typically achieved by incorporation of probe molecules that can absorb light and destabilize the LNP membrane, resulting in drug release. However, no authors to date have investigated the use of this phenomenon for systemic drug release nor whether probe illumination results in a detectable change in light absorption, which would enable monitoring of drug release.

Methods: In this study, we sought to establish scientific validation of our technology in vitro, using the anticancer agent doxorubicin (DOX) as a model drug. We chose DOX because it exhibits fluorescence self-quenching, where the local concentration of DOX is inversely proportional to its fluorescence emission, allowing quantification of entrapment (high concentration) and release (low concentration) from LNPs. We hypothesized that illumination of DOX-entrapping nanoparticles by focused light would (1) induce drug release proportionate to the illumination time and (2) that release would be correlated to the change in light absorption by those particles. See Figure 1.

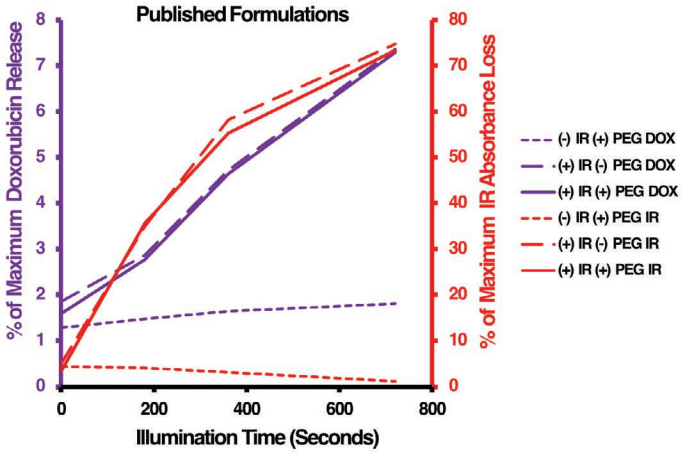

Figure 1: Proof of concept of a drug release and monitoring system using doxorubicin as a model drug. IR = light-reactive probe, PEG = polymer-lipid, DOX = doxorubicin.

Results: We formulated DOX-loaded LNPs with and without a light-sensitive probe based on published formulations and demonstrated probe-dependent drug release proportional to illumination time using DOX fluorescence emission measurements. Additionally, we established a proportionate decrease in the light probe absorbance as a function of illumination time. Critically, these 2 parameters of drug release and decrease in light-probe absorbance were correlated at each data point, serving as a proof of concept of Hikari's proposed technology. This study serves as a foundation for future applications of this platform, such as within a mock circulatory system consisting of flowing whole human blood.

Conclusion: In this proof-of-concept study, we demonstrate the feasibility of our technology. We are currently beginning studies on application of our technology to PH drugs. If successful, this precision dosing platform has the potential to drastically improve patient safety and patient quality of life by reducing dosing errors.

ECHOCARDIOGRAPHIC SCREENING FOR MILDLY ELEVATED PULMONARY ARTERY PRESSURE IN PATIENTS WITH SYSTEMIC SCLEROSIS: OBSERVATIONS FROM THE SEPVADIS TRIAL

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Category: Clinical Science
Subcategory: Diagnosis/Screening and Physiologic Studies

Background: With the updated hemodynamic definition of pulmonary hypertension (PH) including patients with a mean pulmonary artery pressure (mPAP) of 21–24 mmHg, it is not known what echocardiogram parameters can be used to screen patients for mildly elevated pulmonary pressures. This is particularly relevant for patients with systemic sclerosis (SSc) who undergo routine echocardiogram screening for early diagnosis of PH.

Methods: We used data from patients screened for the SEPVADIS trial, a randomized controlled trial of sildenafil for SSc patients with mPAP of 21–24 mmHg. All patients underwent diagnostic right heart catheterization (RHC) and were grouped by their mPAP as having (mPAP > 20 mmHg) or not having (mPAP ≤ 20 mmHg) PH. We performed receiver operating characteristic (ROC) curve analysis to describe the sensitivity and specificity of different tricuspid regurgitant jet velocities (TRJVs) for the diagnosis of PH. We then explored if right heart enlargement, defined as subjectively dilated right atrium or right ventricle, as well as N-terminal pro-brain natriuretic peptide (NTproBNP) could add to the diagnostic ability of TRJV for detection of SSc-PH.

Results: Thirty-three SSc patients were included (91% female, 63 ± 11 years old, 72% limited cutaneous disease), of whom 15 had a mPAP < 21 mmHg and 18 had a mPAP ≥ 21 mmHg. The median mPAP was 21 mmHg (range, 14–33 mmHg) with a pulmonary artery wedge pressure of 9 mmHg (interquartile range, 7–12) and pulmonary vascular resistance of 2.13 Wood units (1.64–3.2). TRJV had an area under the ROC curve of 0.66 (95% confidence interval [CI] = 0.46, 0.87) for detection of PH. A TRJV cutoff of ≥2.45 m/s yielded an 89% sensitivity and 42% specificity for PH, while a TRJV cutoff of ≥2.7 m/s had the highest combination of sensitivity (78%) and specificity (50%). Adding either right heart enlargement or NTproBNP to TRJV did not improve the test characteristics for detection of PH.

Conclusion: In SSc patients suspected to have mildly increased pulmonary artery pressures, TRJV had a modest ability to discriminate patients with a mPAP > 20 mmHg on RHC from those with normal mPAP. Larger sample sizes are needed to improve the discriminative ability of noninvasive testing to accurately predict the presence of mildly elevated pulmonary pressures in SSc patients.

EFFICACY OF ACTIVITY TRACKERS IN PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION

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Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Heart failure with preserved ejection fraction (HFpEF) remains a formidable challenge in modern health care. It encompasses over half of all patients with heart failure, and its incidence is growing when compared with heart failure with reduced ejection fraction. Despite significant therapeutic advancements, the disease continues to carry a substantial burden of morbidity and mortality. In addition to the pharmacologic therapies which have been proven beneficial in the treatment of HFpEF, management of comorbidities is imperative for optimal care of these patients. Lifestyle modification with physical activity and weight loss

can improve risk factors and functional outcomes in HFpEF. The 2022 American College of Cardiology (ACC)/American Heart Association (AHA) heart failure guidelines recommend physical activity because of replicated data demonstrating improved quality of life, functional status, and exercise performance. A sedentary lifestyle contributes to most risk factors associated with HFpEF. Despite the benefits of physical activity, challenges pertaining to accessibility, adherence, and motivation persist as substantial barriers to improving overall health. Wearable health technologies provide an opportunity to enhance healthy lifestyle behaviors through habit formation and goal adherence. Data in the general population have suggested that activity trackers can lead to increased daily step count and a decrease in body weight. In patients with heart failure, researchers have demonstrated that tailored, supervised, and progressive exercise programs result in improved physical function and prognostic benefit. However, these programs have strikingly low rates of enrollment and participation due to barriers including availability, travel, willingness to participate, and navigation of the medical system. Walking is recognized as an accessible, sustainable form of exercise which mitigates many of the obstacles patients face with a structured exercise program. Limited data exist regarding the effect of daily walking on functional status in heart failure patients. We sought to observe daily physical activity and determine whether using an activity tracker can enhance functional outcomes in HFpEF patients.

Methods: We performed a prospective analysis of 58 patients with HFpEF from 2021 to 2024 at a single academic medical center who used a Fitbit to record 1 year of daily step activity. The current results reflect the 35 patients who have completed a full year of data thus far. At a baseline visit, patients were provided with a wrist-worn Fitbit activity tracker to monitor their daily step count. Patients were instructed to wear the device for the entire day. The patients were evaluated in the ambulatory setting for the initial visit and subsequently at intervals of 3, 6, and 12 months to gather vitals, B-type natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), physical exam, and functional measurements, including the 6-minute walk test and Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12). Associations between variables were assessed with Pearson's *r* correlation using Stata 18.0. See Figure 1.

Results: In the cohort of 35 patients, the mean age was 67.3 ± 10.6 years with 74% of patients identifying as female. The average body mass index (BMI) was 35.8 ± 7.9 kg/m^2. Across each time interval, the mean number of steps per day was 4630 ± 3002 (1–3 months), 4679 ± 3122 (4–6 months), and 4630 ± 3286 (7–12 months). No statistically significant improvement was found in daily step count or 6-minute walk distance in the cohort. The daily step count was highly correlated with the 6-minute walk distance across all time points (1–3 months: r = 0.75, P = .001, 4–6 months: r = 0.68, P = .002, 7–12 months: r = 0.72, P = .001). The total KCCQ-12 questionnaire scores increased by 8.3 points from baseline to 12 months from 57.6 (95% confidence interval [CI] = 50.7, 64.5) to 65.9 (95% CI = 57.7, 74.2; P = .004). Among the subcategories of the questionnaire, we observed a positive correlation between physical limitation scores and daily step count (1–3 months: r = 0.45, P = .007, 4–6 months: r = 0.58, P = .002, 7–12 months: r = 0.59, P = .001). Of interest, 1 patient who was taking over 15 000 daily steps scored their physical limitation 10–20 points lower than those taking less than half the steps and had one of the lowest quality-of-life scores in the cohort, reflecting the subjective nature of heart failure symptoms.

Conclusion: Fitbit technology offers a convenient means to monitor real-time physical activity in patients with HFpEF. Using a Fitbit to record daily step activity enhances health-related quality of life in this population. In contrast with the improved average total KCCQ-12 score, we did not observe an increase in the 6-minute walk distance over the course of the year. Our findings establish the utility of daily step count as a valuable surrogate for 6-minute walk distance. These results highlight the need for further investigation into the role that wearable health devices play in improving physical activity and functional status in patients with HFpEF.

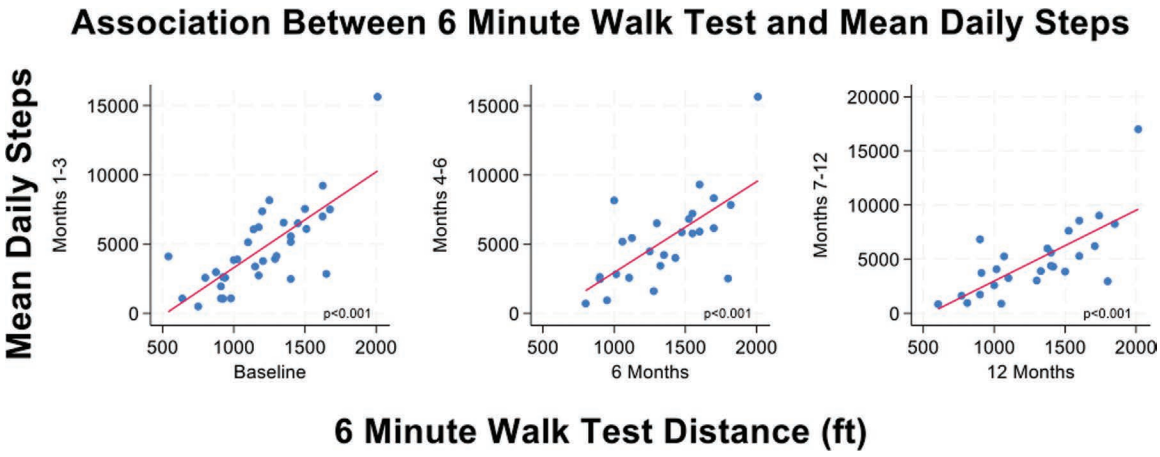

Figure 1: Association between 6-minute walk test and mean daily steps.

ELEVATED RIGHT VENTRICULAR SYSTOLIC PRESSURE IS AN INDEPENDENT PREDICTOR OF MORTALITY IN PEDIATRIC PULMONARY VEIN STENOSIS

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Category: Clinical Science
Subcategory: Pediatrics

Background: Pulmonary vein stenosis (PVS) in children is associated with poor prognosis. However, the risk factors for mortality remain uncertain.
Methods: In this retrospective, single-center study, we identified children with primary and secondary PVS through a cardiac catheterization database. Kaplan-Meier analysis, log-rank tests and Cox regression analysis were performed to assess outcome and identify significant predictors of mortality. See Figure 1 and Tables 1–3.
Results: Among 56 children with PVS (33 males, 59%), 20 (36%) died at a median age of 10 months (interquartile range [IQR], 4–24). All patients underwent cardiac catheterization, with 45 (80%) undergoing at least 1 interventional procedure. Causes of death included multiorgan failure (35%), progressive respiratory failure (20%), and sudden cardiac death (15%). Prematurity, chronic lung disease, a genetic syndrome, or the number of affected pulmonary veins did not significantly correlate with mortality. However, right ventricular systolic pressure (RVSP) between half and full systemic, and RVSP greater than systemic pressure was associated with mortality (heart rate [HR] = 4.8, 95% confidence interval [CI] = 1.7, 13.0, $P = .002$, and HR = 9.2, 95% CI = 2.6, 32.8, $P < .001$, respectively). The final predictive model for mortality included only RVSP between half and full systemic (HR = 4.6, $P = .004$) and diminished right ventricular (RV) systolic function (HR = 5.5, $P = .030$).
Conclusion: With this report, we are the first to indicate that RVSP and RV dysfunction are significant independent predictors of mortality in children with PVS. A greater understanding of mortality in this population is necessary, particularly in those with RVSP less than half systemic.

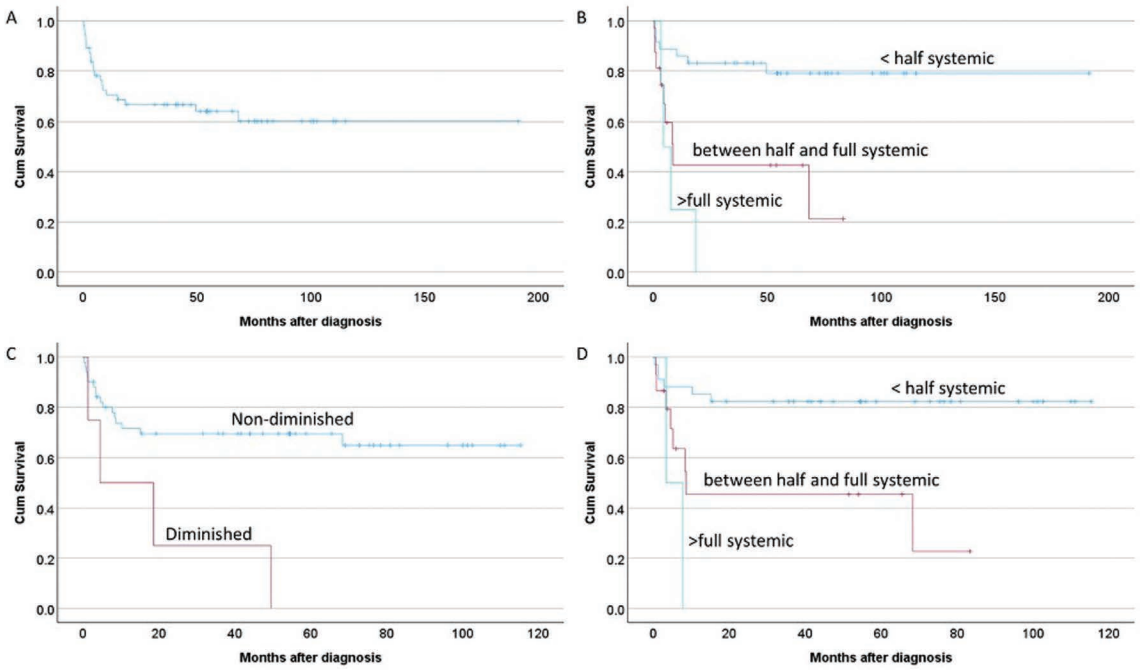

Figure 1: Kaplan-Meier curve with log rank test. A, Overall survival, B, subgroup analysis with RVSP at last catheterization, C, subgroup analysis with RV systolic function (nondiminished; normal or mildly diminished; moderately or severely diminished function), and D, subgroup analysis with RVSP at last catheterization among patients with nondiminished RV systolic function.

Table 1. Comparison of Demographic Parameters Between Patients Who Have Died and Those Who Are Surviving

	All (n=56)	Death (n=20)	Alive (n=36)	p value
Male gender	33 (59)	11 (55)	22 (61)	0.656
Gestation	37 (29-38)	37 (35-39)	36 (29-38)	0.376
Prematurity (<37 weeks)	26 (46)	6 (30)	20 (56)	0.066
Genetic syndrome	17 (30)	7 (32)	11 (31)	0.965
Heterotaxy syndrome	1 (2)	1 (5)	0 (0)	0.176
Scimitar syndrome	6 (11)	3 (15)	3 (8)	0.440
Chronic lung disease	30 (54)	11 (55)	19 (53)	0.873
Primary cardiac diagnosis				
Pulmonary vein stenosis	32 (57)	9 (45)	23 (64)	0.171
Other CHD	24 (43)	13 (55)	13 (36)	
including TAPVR	5 (9)	2 (10)	3 (8)	0.834
including PAPVR	8 (14)	3 (15)	5 (14)	0.909
Etiology				
Primary	39 (70)	13 (65)	26 (72)	0.573
Post-surgery	17 (30)	7 (35)	10 (28)	
Number of pulmonary vein inovlved				
Single	**24 (43)**	**5 (25)**	**19 (53)**	**0.044**
Multiple	**32 (57)**	**15 (75)**	**17 (47)**	
Unilateral	15 (27)	7 (35)	8 (22)	0.982
Bilateral	17 (30)	8 (40)	9 (25)	
Post-transplant PVS	7 (13)	3 (15)	4 (11)	0.673
Age at death (mo)	10 (4-24)	10 (4-24)	NA	NA

CHD; congenital heart disease, PAPVR; partial anomalous pulmonary venous return, PVS; pulmonary venous stenosis, TAPVR; total anomalous pulmonary venous return

Table 2. Comparison of Catheterization Data Between Patients Who Have Died and Those Who Are Surviving

Catheterization	All (n=56)	Death (n=20)	Alive (n=36)	p value
Median age at first catheterization (mo)	6 (4-12)	5 (2-12)	7 (5-14)	0.166
Median age at last catheterization (mo)	**35 (8-66)**	**8 (4-21)**	**51 (12-73)**	**<0.001**
Number of catheterizations underwent prior to date/death	**4 (2-6)**	**2 (1-4)**	**5 (2-8)**	**0.034**
Number of interventional catheterizations prior to date/death				
None	11 (20)	6 (30)	5 (14)	
One	17 (30)	7 (35)	10 (28)	NA
Two	8 (14)	3 (15)	5 (14)	
More than two	20 (36)	4 (20)	16 (44)	
Number of patients who had at least one stent placement	33 (59)	10 (50)	23 (64)	0.311
Number of patients who had at least one balloon dilation	41 (73)	14 (70)	27 (75)	0.686
Rate of catheterization (per year)	**3 (2-11)**	**10 (6-24)**	**2 (1-5)**	**0.002**
RV/systemic systolic pressure ratio at first catheterization (%)	53 (43-78)	67 (44-82)	48 (43-74)	0.110
RV/systemic systolic pressure ratio at last catheterization (%)	**45 (37-64)**	**64 (46-87)**	**44 (37-58)**	**<0.001**
RVSP at last catheterization				
<half systemic	**36 (64)**	**7 (35)**	**29 (81)**	
Between half and full systemic	**16 (29)**	**9 (45)**	**7 (19)**	**<0.001**
>full systemic	**4 (7)**	**4 (20)**	**0 (0)**	
Number of patients who lost 1 or more pulmonary veins	12 (21)	5 (25)	7 (19)	0.666
Interval between last catheterization and death (days)	NA	25 (8-82)	NA	NA

RV; right ventricle, RVSP; right ventricular systolic pressure

Table 3. Univariable and Multivariable Cox Regression Analysis to Identify Significant Parameters to Predict Mortality

	Univariable analysis		Multivariable analysis	
Predictors	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
RV/systemic systolic pressure ratio at first catheterization	**7.997 (1.292-49.497)**	**0.025**		
RVSP between half and full systemic at first catheterization¶	2.123 (0.546-8.262)	0.278		
RVSP > full systemic at first catheterization¶	**31.539 (5.261-189.084)**	**<0.001**		
RV/systemic systolic pressure ratio at last catheterization	**5.921 (2.117-16.563)**	**<0.001**		
RVSP between half and full systemic at last catheterization¶	**4.751 (1.743-12.953)**	**0.002**	**4.551 (1.641-12.618)**	**0.004**
RVSP > full systemic at last catheterization¶	**9.186 (2.574-32.791)**	**<0.001**		
Moderately or severely diminished RV systolic function*	**4.141 (1.370-12.520)**	**0.012**	**5.507 (1.185-25.601)**	**0.030**
Multivessel PVS	2.470 (0.897-6.803)	0.080		
At least one stent placement	0.584 (0.243-1.405)	0.230		
Gender	1.118 (0.462-2.701)	0.805		
Gestation	1.086 (0.979-1.205)	0.119		
Prematurity (<37 weeks)	0.464 (0.178-1.211)	0.117		
Genetic syndrome	0.892 (0.342-2.327)	0.815		
Heterotaxy syndrome	2.347 (0.313-17.626)	0.407		
Scimitar syndrome	1.806 (0.527-6.187)	0.346		
Chronic lung disease	0.987 (0.406-2.370)	0.966		

¶Compared with RVSP < half systemic. *Based on the echocardiogram closest to the last catheterization. RV; right ventricle, RVSP; right ventricular systolic pressure

EXPERT CONSENSUS ON PATIENT ENGAGEMENT STRATEGIES AND SHARED DECISION-MAKING TO IMPROVE PATIENT OUTCOMES IN PULMONARY ARTERIAL HYPERTENSION

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Subcategory: Psychosocial Considerations/Aspects of Care

Background: Pulmonary arterial hypertension (PAH) is a progressive disease which requires close monitoring to prevent disease worsening and patient deterioration.[1] Current approaches have demonstrated that empowering patients leads to greater engagement with care.[2] However, guidance is lacking, and strategies are needed to improve patient engagement and promote shared decision-making (SDM) with the goal of maintaining a low-risk status and improving patient adherence to therapy.[2–7]
Methods: United States (US)-based physicians (n = 5) and advanced practice providers (APPs; n = 8) who are directly responsible for treating or managing patients with PAH were recruited to a double-blinded modified Delphi panel (2 survey rounds and a virtual consensus meeting). Consensus was defined as ≥80% of panelists rating their agreement or disagreement using a 9-point Likert scale.
Results: The panel achieved consensus in agreement that SDM leads to improved disease management in PAH and that an engaged patient participates in SDM by asking questions, giving feedback, and following up routinely. Factors that motivate engagement include social support, quality of life, and the severity of prognosis. Panelists agreed health care providers' behavior

or attitude toward patients also affects patient engagement. Side effects of medications, symptom severity, and financial burden were identified as factors that frustrated patients, and poor health literacy and financial burdens discourage engagement. The communication of the importance and implications of risk assessments and resources to address poor education or health literacy were identified as areas that require improvement. Providing patients with a clear action plan, involving their family and caregivers, and encouraging patients to research and understand PAH are important for encouraging SDM.
Conclusion: The panel of PAH experts achieved consensus in agreement on the importance of SDM and patient engagement in treating patients with PAH. The identified areas of improvement can be used to ensure more patients and caregivers are involved in the management of PAH to advocate for their goals and preferences.

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EXPERT CONSENSUS TO EXPLORE THE USE OF TELEHEALTH AND ASSOCIATED STRATEGIES TO IMPROVE ACCESS TO CARE FOR REMOTE AND UNDERSERVED PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

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Category: Clinical Science
Subcategory: Psychosocial Considerations/Aspects of Care

Background: Pulmonary arterial hypertension (PAH) is a progressive and fatal disease in which affected patients are susceptible to rapid deterioration. The COVID-19 pandemic was pivotal in the expansion of telehealth to allow for remote patient management and access to expert care. However, identification of optimal strategies is needed to improve telehealth and address barriers to its use.[1–3]
Methods: United States–based physicians (n = 11) and advanced practice providers (n = 6) with experience with telehealth in PAH were recruited to a double-blinded modified Delphi panel (2 survey rounds and a virtual consensus meeting). Consensus was defined as ≥80% of panelists rating their agreement or disagreement using a 9-point Likert scale.

Results: Consensus in agreement was achieved that the definition of telehealth is the use of virtual or remote methodologies to interact with, monitor, and assess patients and deliver health care. Examples of telehealth interventions include patient questionnaires and remotely performed lab work. Patients with PAH may use telehealth for returning visits, diagnostic test follow-up, and medication management; telehealth is convenient, enables additional visits, and patient access to care. However, barriers to telehealth exist, such as socioeconomic status, patient digital literacy, visual and/or hearing impairments, developmental disabilities, geographical location, and reimbursement. Solutions to improve patient access to telehealth include health insurance reimbursements or financial support for health care professionals (HCPs) and improved connectivity infrastructure for patients.
Conclusion: Barriers to optimized use of telehealth that may affect the management of patients with PAH were identified, e.g., geographical location and reimbursement. These barriers and past clinical experiences can inform future PAH management and provide solutions to improve outreach and telehealth services for HCPs and patients. Improvements in telehealth practice may ensure that PAH progression is not exacerbated by insufficient care.

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EXPLORATORY EFFICACY ANALYSIS OF INSPIRE OPEN LABEL EXTENSION STUDY WITH INHALED TREPROSTINIL (YUTREPIA™)

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Category: Clinical Science
Subcategory: Diseases and Conditions Associated With PH

Background: The INSPIRE open-label extension (OLE), a 24-month analysis, examines the efficacy of Yutrepia™, a dry-powder treprostinil formulation. Using PRINT® technology, it creates uniformly sized and shaped particles, enhancing deep-lung drug delivery. INSPIRE, a Phase 3, multicenter trial, involves World Health Organization (WHO) Group I pulmonary arterial hypertension (PAH) patients in New York Heart Association (NYHA) Functional Classification (FC) II or III. Participants, previously on nebulized treprostinil and up to 2 oral PAH therapies, either transitioned to Yutrepia (Transition) or were prostacyclin-naïve and added Yutrepia to their regimen (Naïve). Those completing INSPIRE could join the OLE to assess the long-term effect of Yutrepia.
Methods: Of 121 INSPIRE participants, 92 (76%) entered the OLE, evenly split between Naïve and Transition groups. Most were female (84%) and in FC II (71%). Seventy-three percent of patients received dual oral background PAH therapies (endothelin receptor antagonist [ERA] plus phosphodiesterase type 5 inhibitor [PDE5i] or soluble guanylate cyclase [sGC]) at baseline. The OLE focused on collection of safety, tolerability, and exploratory outcomes like 6-minute walk distance (6MWD), NYHA FC, and N-terminal pro-brain natriuretic peptide (NT-proBNP), without data imputation (missing data attributed to the COVID-19 pandemic).
Results: After 24 months, median Yutrepia dosage was 132.5 mcg, with 33% exceeding doses ≥159 mcg. The highest dose recorded during this analysis was 238.5 mcg. Side effects mirrored those of inhaled prostanoid treatments. The majority maintained or improved NYHA FC over 2 years. 6MWD changes from baseline were stable (+8.4 m), with no apparent changes in NT-proBNP levels.
Conclusion: Long-term Yutrepia use showed tolerability and persistent benefit in PAH patients at 24 months. Approximately one-third of patients reached dosages over 159 mcg (≥18 breaths of nebulized treprostinil).

FROM BREATHS TO BEATS: PIONEERING PULMONARY ARTERIAL HYPERTENSION MONITORING WITH END-TIDAL CO_2

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Category: Clinical Science
Subcategory: Diagnosis/Screening and Physiologic Studies

Background: Driven by challenge in monitoring pulmonary arterial hypertension (PAH)—a complex, life-threatening condition—in our research, we aim at finding a surrogate for invasive right heart catheterization (RHC). Inspired by promising findings from our 2019 study, in which we revealed a significant correlation between end-tidal CO_2 ($ETCO_2$) levels and pulmonary vascular resistance (PVR), we aim to delve deeper. Our objective is twofold: to further validate $ETCO_2$ as a surrogate marker for RHC in monitoring PAH patients and to explore the potential variations in $ETCO_2$ across different subgroups of Group 1 PAH, hypothesizing that these differences could illuminate the severity of the disease among these subgroups. By potentially proving these hypotheses, we seek to pave the way for a revolutionary shift toward a noninvasive, more accessible method of managing PAH, offering a beacon of hope for patients and clinicians alike. This research not only promises to enhance our understanding of PAH but also to significantly ease the burden of disease monitoring, making our findings particularly relevant and of interest to health care professionals, researchers, and patients.

Methods: This was a prospective, single-center study in a cohort of 44 PAH patients undergoing standard RHC, where we measured $ETCO_2$ levels using a portable $ETCO_2$ monitor with a nasal cannula that was placed on the patient. The patient was instructed to breathe normally for 2 minutes to determine an average of the $ETCO_2$ before the RHC procedure. In addition to $ETCO_2$ levels, arterial and mixed venous blood gases and hemodynamic data from the RHC were recorded. The study protocol included obtaining informed consent for both study participation and the RHC procedure, ensuring ethical conduct and patient understanding. See Figure 1 and Table 1.

Results: Analysis from 44 patients highlighted a moderate negative correlation between PVR and $ETCO_2$ (TD-Dynes: $r = -0.38$, $P = .01$; Fick-Dynes: $r = -0.40$, $P < .01$; Table 2), indicating that lower $ETCO_2$ levels might indicate higher PVR values. This correlation was particularly pronounced in specific subgroups, such as Hispanic patients and those with portopulmonary etiology (TD-Dynes: $r = -0.67$, $P = .07$; Fick-Dynes: $r = -0.54$, $P = .17$) or receiving combined therapy (oral and intravenous [IV]; TD-Dynes: $r = -0.46$, $P = .13$; Fick-Dynes: $r = -0.62$, $P = .03$), suggesting ethnic and treatment-related differences in PAH management. A significant moderate correlation between arterial CO_2 pressure and $ETCO_2$ ($r = 0.40$, $P = .05$) was also observed, reinforcing the potential utility of $ETCO_2$ in PAH monitoring. The findings underline the potential of $ETCO_2$ as a noninvasive, cost-effective tool for monitoring PAH, especially valuable in certain patient demographics and treatment scenarios.

Conclusion: The study findings support $ETCO_2$ as a promising noninvasive surrogate for PVR in PAH, offering a less invasive, cost-effective monitoring tool. In this study, we underscore the importance of considering ethnic, etiological, and treatment-specific variations when interpreting $ETCO_2$ levels. The variability in correlations across etiologies and stronger associations in particular subgroups underscore the need for tailored interpretation of $ETCO_2$ levels. It calls for

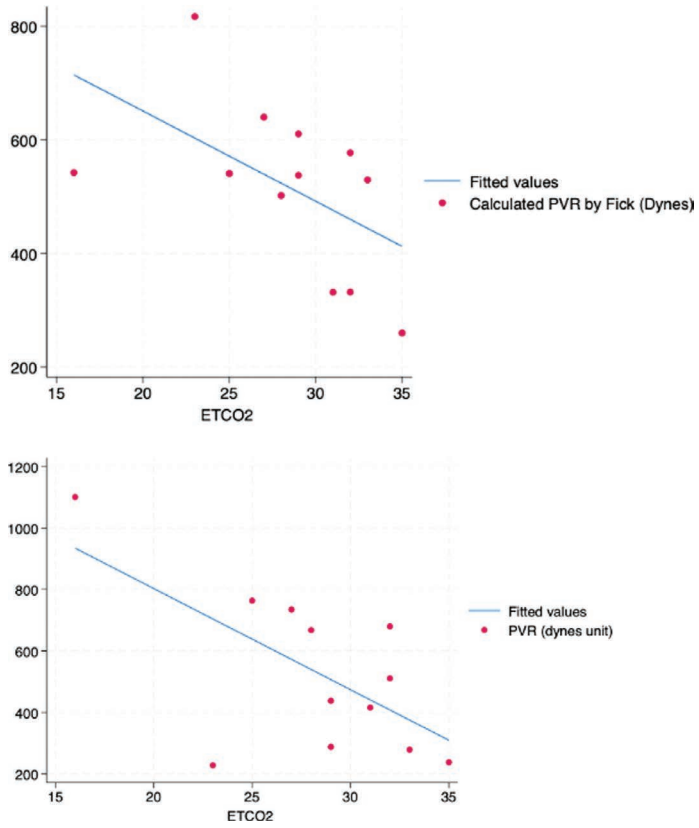

Figure 1: Scatter plot showing negative correlation of the PO+IV therapy groups calculated by Fick and thermodilution.

Table 1. Demographics and Clinical Characteristics of the Study Population (n = 44)

Variable[1]	Mean ± SD or Count (%)
Age	50.4 ± 12.5
Sex	
Male	19 (43.2)
Female	25 (56.8)
Body Mass Index	28.1 ± 5.7
PAH Etiology	
Idiopathic	6 (13.6)
HIV/HIV+Meth	4 (9.1)
HHT/PVOD	4 (9.1)
Meth+Diet Pills/Meth/Diet Pills	13 (29.6)
MCTD/Scleroderma/RA (Sjogren)	9 (20.5)
Portopulmonary	8 (18.2)
Ethnicity	
Not Hispanic/Latino	18 (40.9)
Hispanic/Latino	26 (59.1)
Race	
White	21 (47.7)
Other	23 (52.3)

Table 2. Correlation Between PVR and CO_2 Measurements Overall and Stratified on Sex, Race, and Ethnicity

Correlations	N	Spearman's r	p-value
Overall			
$ETCO_2$ and PVR (TD-Dynes)	43	-0.38	0.01
$ETCO_2$ and PVR (Fick-Dynes)	44	-0.40	<0.01
According to Ethnicity			
Hispanic			
ETCO2 AND PVR (TD-Dynes)	26	-0.47	0.02
$ETCO_2$ and PVR (Fick-Dynes)	26	-0.42	0.03
Non-Hispanic			
ETCO2 AND PVR (TD-Dynes)	17	-0.15	0.57
$ETCO_2$ and PVR (Fick-Dynes)	18	-0.27	0.27
According to Race			
White			
ETCO2 AND PVR (TD-Dynes)	20	-0.28	0.24
$ETCO_2$ and PVR (Fick-Dynes)	21	-0.42	0.06
Other			
ETCO2 AND PVR (TD-Dynes)	23	-0.45	0.03
$ETCO_2$ and PVR (Fick-Dynes)	23	-0.31	0.15
According to Etiology			
Idiopathic			
ETCO2 AND PVR (TD-Dynes)	6	0.26	0.60
$ETCO_2$ and PVR (Fick-Dynes)	6	-0.62	0.19
HIV/HIV+Meth			
ETCO2 AND PVR (TD-Dynes)	4	0.40	0.59
$ETCO_2$ and PVR (Fick-Dynes)	4	-0.80	0.20
HHT/PVOD			
ETCO2 AND PVR (TD-Dynes)	4	-0.40	0.59

further research to explore these differences, aiming for more personalized and effective PAH management strategies. While the findings advocate for the role of $ETCO_2$ in reducing invasive monitoring, the small sample size affects the generalizability of the findings to a broader PAH population. Future investigators should aim at refining the application of $ETCO_2$ in PAH monitoring, with a larger sample size, multiple centers, and continue to consider factors like ethnicity, PAH etiology, and treatment approach to enhance patient care through less invasive methods.

GDF15 IS BIOMARKER AND DRIVER OF PULMONARY VASCULAR DISEASE

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Category: Basic Science
Subcategory: Therapeutic Strategies

Background: Pulmonary arterial hypertension (PAH) is a disorder of progressive vascular remodeling of the pulmonary circulation due to dysregulated proliferation, apoptosis, angiogenic activity of pulmonary vascular endothelial, smooth muscle, and adventitial cells. PAH is known to be critically influenced by dysregulated bone morphogenetic protein (BMP) and transforming growth factor-β (TGFβ) signaling. Growth and differentiation factor 15 (GDF15) is a BMP/TGFβ ligand that is known to be a pleiotropic regulator of proliferation, vascular tone, and angiogenesis in addition to serving as a central nervous system (CNS)–acting hormone regulating appetite and metabolism. GDF15 is expressed in response to tissue injury, metabolic or oxidative stress, hypoxia, and inflammation and has been shown to be elevated in the circulation and remodeled pulmonary vasculature of lung from patients with Group 1 PAH associated with scleroderma. We predicted that, in addition to serving as a biomarker, GDF15 has a causative role in pulmonary vascular disease.
Methods: Human plasma from 135 subjects with or without PAH were analyzed by ELISA for levels of circulating

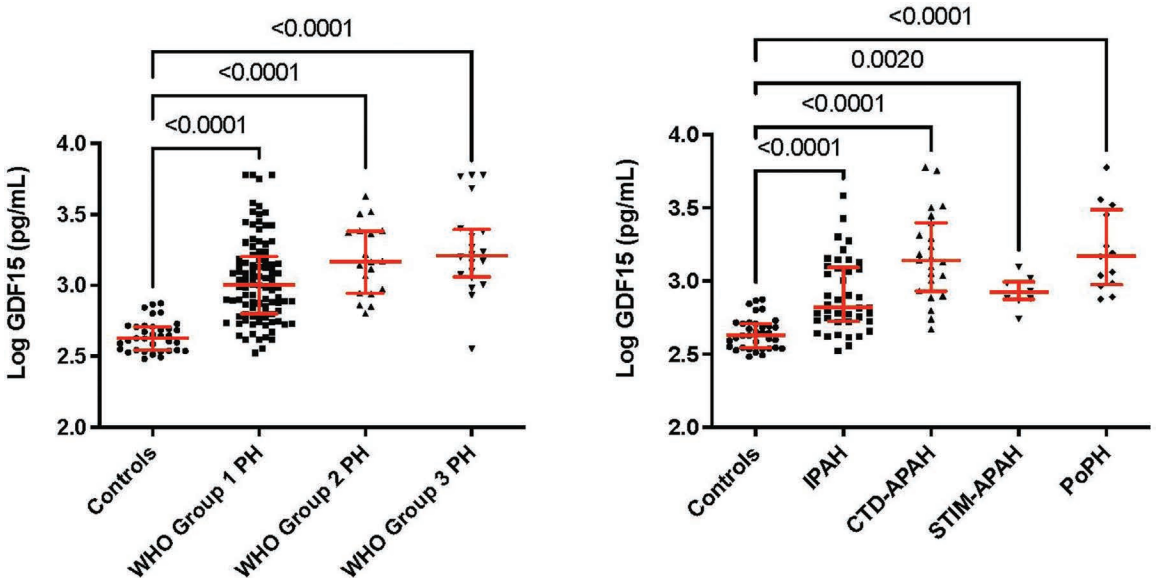

Figure 1: GDF15 is elevated in Group 1 PAH.

GDF15. Lungs from rats with monocrotaline-induced pulmonary hypertension were analyzed by RNA-Seq and immunohistochemistry. Human primary cultured pulmonary arterial smooth muscle cells (PASMC) were treated with recombinant human GDF15 from a variety of commercial sources and assessed for modulation of BMP-SMAD1/5/9 and TGFβ-SMAD2/3 signaling. Finally, mice with homozygous loss of GDF15 and wild-type littermates were treated with SU5416 (20 mg/kg s.c. weekly) and hypoxia (FIO2 = 0.1) for 3 weeks to induce experimental pulmonary hypertension (PH), assessed by invasive hemodynamics, and right ventricular (RV) remodeling, and histomorphometry.
See Figures 1 and 2.

Results: GDF15 was found to be elevated in all Group 1 PAH subjects including those with idiopathic, stimulant-associated and portopulmonary hypertension in addition to those associated with connective tissue disease. Exome profiling of lungs from monocrotaline-treated rats revealed GDF15 to be the most overexpressed ligand from among >80 BMP/TGFβ ligands, receptors, and signaling molecules analyzed. Purified recombinant human GDF15 was found to induce the activation of ERK1/2 in human PASMC but did not activate SMAD1/5/9 or SMAD2/3. GDF15 knockout mice, furthermore, were protected from SU5416/hypoxia-induced PH, exhibiting markedly reduced RV systolic pressures and essentially normalized RV hypertrophy to the level of non-PH control mice. Importantly, disruption of GDF15 did not affect normal weight gain in mice.

Conclusion: GDF15 is a biomarker of Group 1 PAH, reflecting dysregulated BMP/TGFβ signaling in human disease, that is also recapitulated in experimental PH. GDF15 is also a potential therapeutic target, with disruption of GDF15 in mice resulting in reduced experimental PH and normalized RV remodeling, but without effect on weight gain. Further studies are needed to discern the mechanisms by which GDF15 exerts its effects in the pulmonary vasculature and potentially the right ventricle.

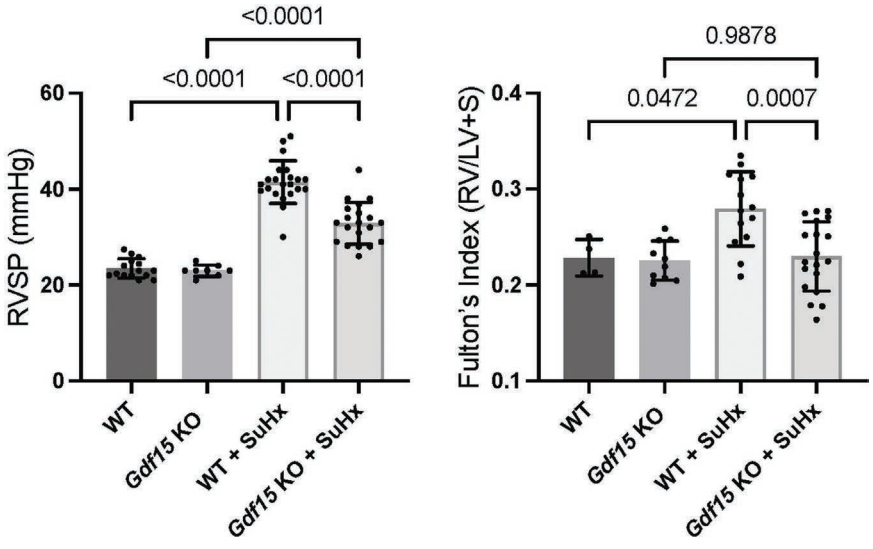

Figure 2: Loss of GDF15 is protective in rodent experimental PH.

HANK THE HEART AND PULMONARY HYPERTENSION MEDICATION MANAGEMENT: CHARACTER STORYTELLING ANIMATIONS DIGITAL MEDIA TOOL TO FURTHER EDUCATE AND ENGAGE PATIENTS AND FAMILIES WITH PULMONARY HYPERTENSION

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Category: Clinical Science
Subcategory: Pediatrics

Background: Pulmonary hypertension (PH) is a rare, complex disease affecting both children and adults. Efforts to provide health education are imperative, as patients or caregivers can feel overwhelmed or confused by the complexity of the disease and treatment options. Health literacy affects a patient's or caregiver's capacity to acquire, process, and understand health information and make informed health decisions. Enhancing health literacy improves patient or caregiver knowledge about illness, can alleviate anxiety about the disease, and plays a significant role in determining the degree of overall adherence to recommended therapies. An abundance of adult-centric patient educational materials, formatted as handouts and online readable materials, is available, but pediatric-specific material is scarce. The advent and availability of consumer technologies offers access to online educational materials. Unlike didactic education, videos accommodate visual and auditory learning styles and can be engaging for children and their caregivers, especially with increasingly electronically savvy generations. Educational videos can serve as an adjunct form of education for patients or caregivers and provide consistent reteaching opportunities. Our first video about PH in a series of planned educational videos received >20 000 views. Given this, we established the goal of developing content to include more educational topics for our patient population.
Methods: Cincinnati Children's Media Lab is an established animation team and multimedia lab which partners with institutional specialties to create brief, informative, and visually engaging animated educational videos. The PH team partnered with the Media Lab to create a series of character-based animations specific to PH. The animations were designed to be educational and engaging for the child and adult learner with content vetted and set at the sixth-grade fluency level by the organizational health literacy team. From idea to final product, the PH team collaborated with the Media Lab to assemble topic specific educational content, followed by development of a main character (i.e., Hank the Heart) and supporting scenes. A rough draft story board was assimilated where content, both audio and visual, could be edited. The final visual product was rendered with background music and voiceover added by sound engineers and a voice actor. Once complete, content can be uploaded and electronically shared.
Results: See Conclusions.
Conclusion: In a digital media–driven society, animation offers an alternative teaching tool for clinicians while educating both pediatric patients and their caregivers. We have a unique opportunity at our institution to partner with the Media Lab and develop such content. We expect that offering this unique education at an acceptable health literacy fluency level will positively affect the patient and family desire to acquire, process, and adhere to the recommended therapies. In addition, we anticipate it will alleviate anxiety about the disease and treatment while empowering patients and their caregivers to make informed health decisions.

HANK THE HEART GETS FOCUSED ON PHIGHTING PULMONARY HYPERTENSION

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Category: Clinical Science
Subcategory: Patient Education

Background: Pulmonary hypertension (PH) is a rare, complex disease affecting both children and adults. Efforts to provide health education are imperative, as patients or caregivers can feel overwhelmed or confused by the complexity of the disease and treatment options. An abundance of adult-centric patient educational materials is available, but pediatric-specific material is scarce. The advent and availability of consumer technologies offers access to online educational materials. Unlike didactic education, animations accommodate visual and auditory learning styles and can be engaging for children and their caregivers, especially with increasingly electronically savvy generations. Educational animations can serve as

an adjunct form of education for patients or caregivers and provide consistent reteaching opportunities. Hank the Heart was adapted to educate the PH population thus far in a 2-part series. We aim at studying the effect on patient and family education and health literacy.
Methods: Hank the Heart is an animated character created by Dr. Ryan Moore and the Digital Media Lab at Cincinnati Children's Hospital Medical Center (CCHMC) that is used for educational and informative animations for patients and families. Two animations have been developed surrounding education within PH. The overall utility and patient or family perception of these interventions is not yet known. We aimed at engaging families with preliminary animations to elicit feedback and impressions through focus groups which will inform implementation and further development of this type of educational content for patients and families.
Results: See Conclusions.
Conclusion: We have a unique opportunity at our institution to partner with the Media Lab and develop such content. We expect that offering this unique education at an acceptable health literacy fluency level will motivate the patient and family to understand and adhere to recommended therapies. In addition, we anticipate it will alleviate anxiety about the disease and treatment while empowering patients and their caregivers to make informed health decisions.

HIGH-RESOLUTION COMPUTED TOMOGRAPHY CHEST SCANS TO EXAMINE THE ASSOCIATION BETWEEN REGIONAL DRUG DEPOSITION OF LIQ861 (YUTREPIA™) AND VASODILATION IN PULMONARY HYPERTENSION IN INTERSTITIAL LUNG DISEASE POPULATION

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Category: Clinical Science
Subcategory: Diseases and Conditions Associated With PH

Background: Pulmonary hypertension (PH) is a frequent complication of interstitial lung disease (ILD) and is associated with substantially increased morbidity and mortality. Inhaled treprostinil is the only approved medical therapy indicated for treatment of PH-ILD. LIQ861 (Yutrepia™) is an investigational dry-powder inhaler (DPI) formulation of treprostinil. In this study, we assess the localized and dose-dependent vasodilatory effects of LIQ861 on the pulmonary vasculature and other lung structures using quantitative computed tomography (CT) analysis and computational fluid dynamics, by associating direct observation of vasodilation with local deposition.
Methods: The ASCENT study is an open-label, multicenter, prospective study that will enroll approximately 60 subjects with PH-ILD to be treated with LIQ861 for up to 52 weeks. Participants will receive inspiratory/expiratory, thin-slice, volumetric chest CT with intravenous contrast at baseline before initial dosing and at week 24 after dosing. Additional functional respiratory imaging (FRI) endpoints will quantify changes in pulmonary vascular volume in vessels with cross-sectional area <5 mm^2 (BV5%TBV) and >10 mm^2 (BV10%TBV) as well as reporting fibrosis score (siVfib), lung volume (iVlobe), and the volume of airways >~2 mm in diameter (iVaw). Computational fluid dynamic (CFD) deposition analysis will be performed at week 24 in a subset of patients. Blinded thoracic radiologists, in addition to assessing the pattern of ILD, will use semiquantitative scores to assess degree of fibrosis and total lung involvement.
Results: N/A.
Conclusion: ASCENT will be the first study in which quantitative CT imaging is used to examine the association between regional drug deposition of LIQ861 (Yutrepia) and vasodilation in a PH-ILD population. The use of intravenous (IV) contrast will improve the accuracy of vascular analysis by reducing the misclassification of interstitial markings as vasculature.

IDENTIFICATION OF KEY GENETIC FACTORS ASSOCIATED WITH HYPERTENSIVE HEART DISEASE IN AFRICAN AMERICANS IN THE UNITED STATES

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Category: Basic Science
Subcategory: Health Disparities/Social Determinants of Health

Background: Hypertensive heart disease (HHD) constitutes a significant contributor to mortality in the United States, particularly affecting the Black and African American (Black/AA) population with elevated mortality rates. The development of HHD involves a multifaceted interplay between genetic and environmental risk factors. Despite recent investigations into the genetic factors associated with early-onset HHD, genetic predictors within minority populations remain elusive. In this study, we use the latest whole-genome sequencing data from the All of Us research database to identify genetic predictors of early-onset HHD among the Black/AA population aged 18–45. These findings were systematically compared with age-matched non-Hispanic White (NHW) controls, with statistical analyses aimed at assessing the presence of genetic predictors within this population. Additionally, secondary comparisons were made with participants exhibiting

late-stage HHD. Further analyses were also conducted to investigate the intricate interplay between genetic factors and sex in both early-onset and late-stage HHD within the Black/AA population. In this study, we identified unique genetic loci associated with early-onset HHD, distinct from those found in the Black/AA population with late-stage HHD. Understanding this complex interplay between genetic factors, sex, and early-onset HHD within the Black/AA population is crucial for ensuring the delivery of high-quality health care and bridging the health disparities gap in communities most affected by the disease.

Methods: The study cohorts were extracted from the All of Us database. The All of Us research protocol has been approved by the All of Us Institutional Review Board. Study cohorts were identified as Black/AA AND early-onset HHD, NHWs AND early-onset HHD. All data collection, data analyses, and data storage were conducted within the secure Cloud hosted by the All of US research program following the study protocol. Inclusion criteria were individuals who developed HHD at either early stage (18–45 years of age) or late stage (>46 years of age). As Controlled Tier users within the All of Us research database, the Person Table (prepackaged data concept set "Demographics" in the dataset builder tool) was used to extract participant provided survey answers to determine sex at birth. Both male and female designations, based on participant-provided survey answers to the sex-at-birth question available in the database at the time of study, were included in the study. Lastly, a genome-wide association study (GWAS) approach was used with densely genotyped and imputed data and whole genetic sequencing (WGS) data to identify the causative locus for the HHD. See Figure 1.

Statistical Analysis: Logistic regression imputation was used for dichotomous data such as gender. Multinomial regression imputation was used for discrete data with >2 categories such as age group and hypertensive cardiovascular disease phenotype. The χ^2 tests, *t* test, analysis of variance (ANOVA), Mann-Whitney *U* test, and linear mixed effect model were used for comparisons of discrete and continuous variables. In sensitivity analysis, a 2-tailed *P* value of <.05 was considered statistically significant. Analysis was conducted using R version 4.3.1 in a Jupyter Notebook environment.

Results: We identified 2946 Black/AA participants with HHD and with short-read WGS available in the All of Us database. Based on these findings, we determined that the number of Black/AA's with available short-read WGS data HHD and short-read WGS data was sufficient patient information available for us to move forward with analyses. GWAS data present in the All of Us research database identified unique genetic predators of early-onset HHD among Black/AA as compared with NHW populations. Moreover, we noted that the Black/AA population exhibits unique variants or HHD-susceptible genetic loci that distinguish them from NHW controls. Black/AA's with early onset HHD share unique genetic predictors among the selected loci of 9p21, TARID/TCF21, LLPH/TMBIM4, FRMD3, and GRP20/CDH17 as compared with age-matched NHW controls (n = 2000). Further analyses will be conducted to establish the role of sex on genetic predictors of HHD in Black/AA's. Given that men are known to develop hypertension at younger ages than women, we predict that unique variants or HHD-susceptible genetic loci will be more prevalent in men than in women.

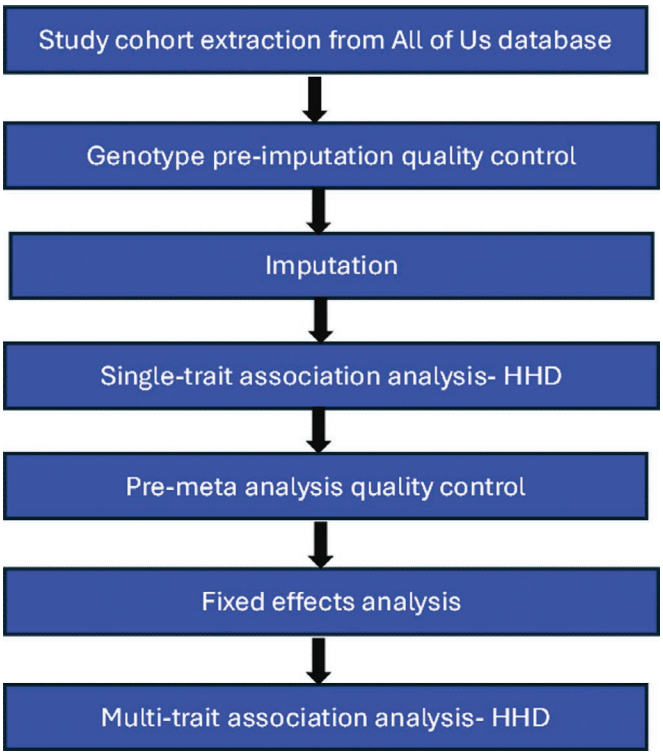

Figure 1: Research methods.

Conclusion: Further exploratory analyses will be conducted to correlate previously identified genetic markers to predict early onset HHD in the Black/AA population based on sex AND various social determinants of health measurements including years of education, income, perceived stress, and discrimination. Together, these findings will deepen our understanding of the genetic and environmental or societal risk factors that may synergistically combine to increase the prevalence of early onset HHD among Black/AA individuals as compared with age-matched NHW controls.

IMPLEMENTATION OF A DIGITAL PEER MENTOR SUPPORT PILOT PROJECT FOR PULMONARY HYPERTENSION PATIENTS

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Category: Clinical Science
Subcategory: Psychosocial Considerations/Aspects of Care

Background: Being diagnosed with pulmonary hypertension (PH) may be a time of fear, stress, anxiety, anger, isolation, and generally feeling overwhelmed. While being diagnosed can be challenging and require many health care provider visits, finding a PH expert care team and specific treatment plan can lead to feelings of calm and confidence regarding a serious diagnosis. Patients benefit from having close friends or family during this time, and many newly diagnosed patients find it helpful to connect with other people living with PH through patient mentor programs, online communities, or local support groups.

The patient-to-patient peer relationship is one that is nonhierarchical and reciprocal with peers sharing similar experiences and knowledge with others who have undergone similar challenges. Peer support is rooted in the belief that no one needs to travel their health care journey alone. The strategy of peer mentor programs is based on this premise that people who have gone through these experiences are best placed to assist others. Thus, a method by health care professionals to bring together peers, mentors, and mentees in formal patient-to-patient peer support programs may encourage improved decision-making, increased self-management, and improved health outcomes.

Currently, most PH centers provide a modest level of patient mentor-mentee support, although generally in an ad hoc manner, without a formal training or implementation program. Clearly, improvement of the overall quality and quantity of PH patient mentoring is needed for newly diagnosed patients.
Methods: With inTandem Health's formal Digital Peer Mentor Program, we are piloting the process and product with a small number of patient mentors and mentees. Patient mentors have undergone extensive training and have been matched with patient mentees and are currently engaged as matched pairs. Mentors may provide emotional support as well as educational materials regarding PH, mental wellness, or living with a chronic illness via the platform to mentees. Communication is managed with session notes. Feedback and evaluation are pending and will be provided. See Figures 1–4.
Results: We will report our preliminary results from the implementation of a pilot PH patient mentor program, including

Figure 1: Patient enrollment.

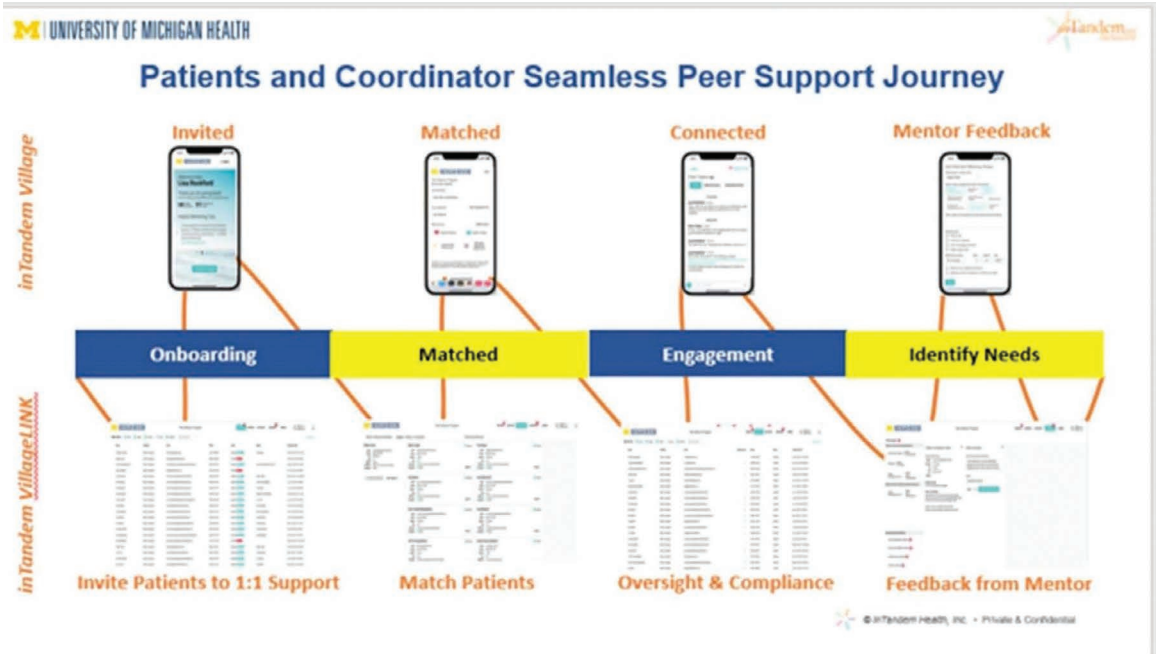

Figure 2: Seamless peer support journey.

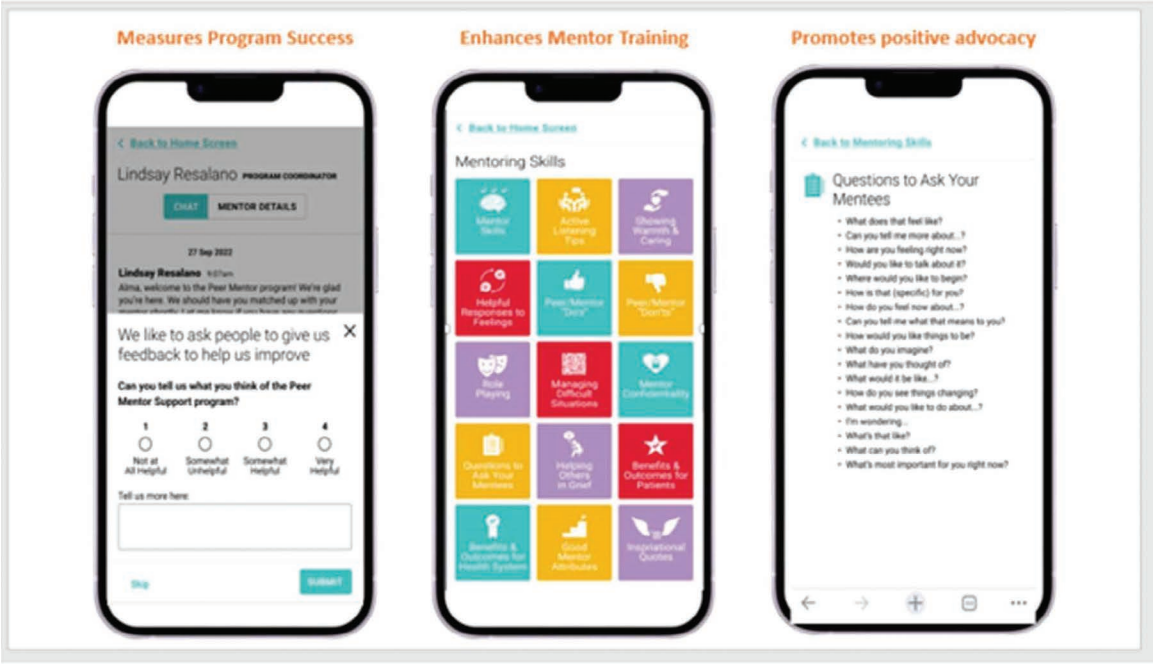

Figure 3: Program highlights.

effect on patient satisfaction, patient access, and time spent in nonclinical tasks on the clinical team, with a goal of improving health outcomes, increasing patient retention, and enabling scale to provide more mentors to patients.

Conclusion: The inTandem Health Digital Peer Mentor Support Project allows for 3 fundamental shifts to support patient mentoring including moving from (1) a fragmented manual peer coordination to a centralized solution, (2) using notebooks and Excel to a secure technology platform, and (3) using personal devices to a secure, HIPAA-compliant communication tool. We plan to measure outcomes as well as patient mentor, patient mentee, and health care provider satisfaction after the first 3 months of implementation. This platform has the potential to significantly increase patient mentor reach to positively affect the PH patient journey.

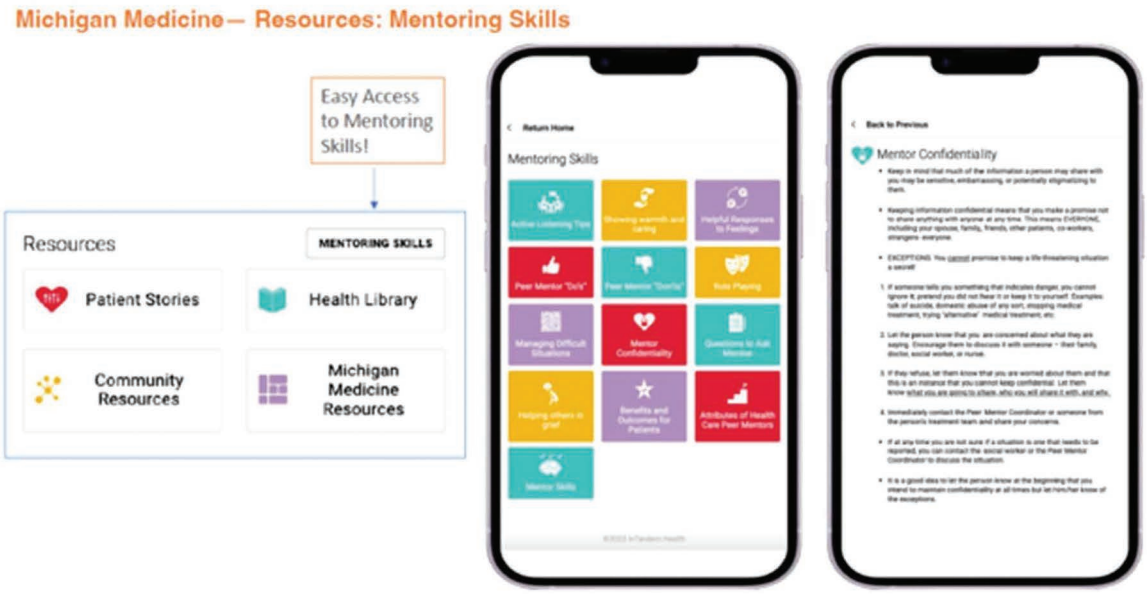

Figure 4: Mentoring skills resources.

IMPROVED OUTCOMES WITH EARLY INITIATION OF COMBINATION TRIPLE THERAPY IN NEWLY DIAGNOSED INTERMEDIATE TO HIGH-RISK PULMONARY ARTERIAL HYPERTENSION

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Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Treatment of pulmonary arterial hypertension (PAH) involves targeting 3 distinct therapeutic pathways. Studies are limited in which authors have investigated outcomes associated with early initiation of a combined 3-drug regimen targeting each pathway in patients newly diagnosed with intermediate- to high-risk PAH.
Methods: A single-center retrospective review was conducted on 36 patients with intermediate-risk (N = 26) to high-risk (N = 10) PAH by REVEAL Lite 2 scoring who were initiated on combination triple therapy at the time of their initial diagnosis. Combination triple therapy included a combined 3-drug regimen of agents targeting each of the distinct therapeutic pathways. High-risk patients were treated with a combination regimen that included a parenteral prostacyclin analogue. The primary analysis involved paired comparative tests per patient of conventional noninvasive cardiovascular indices measured before initiation of combination triple therapy and following at least 6 months of optimization on the combined regimen. Comparisons were made using paired *t*-test and Wilcoxon signed rank test where appropriate. All tests were 2-tailed, and a *P* value of <.05 was considered statistically significant.
Results: A summary of the primary analysis is presented in Table 1.
Conclusion: Early initiation of combination triple therapy for newly diagnosed intermediate- to high-risk PAH showed a significant improvement in measured clinical outcomes.

Table 1. Comparison of Measured Indices Precombination and Postcombination Triple Therapy (N = 36)

	Pre	Post	P-value
NTproBNP (pg/mL)	728 (189.5 - 3401.5)	187.5 (114.0 - 341.0)	<0.0001
REVEAL Lite 2.0 score	8 (3)	5 (2)	<0.0001
RVSP (mm Hg)	72.3 (36.4)	44.7 (28.0)	<0.0001
WHO/NYHA Functional Class	3 (3 - 3.5)	2 (2 - 3)	<0.0001
6MWT (m)	299.0 (195.0 - 336.0)	333.0 (276.0 - 429.0)	<0.0001

IN VIVO MODELING OF ARTERIOVENOUS MALFORMATIONS AND HEREDITARY HEMORRHAGIC TELANGIECTASIA MIMICRY DUE TO PROSPECTIVE PULMONARY ARTERIAL HYPERTENSION THERAPIES

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Category: Basic Science
Subcategory: Diseases and Conditions Associated With PH

Background: Pulmonary arterial hypertension (PAH) and hereditary hemorrhagic telangiectasia (HHT) are congenital vascular syndromes arising from mutations in a common set of genes of the bone morphogenetic protein (BMP), activin, and TGFβ signaling pathway; however, the factors that dictate which phenotype arises from common mutations are unknown. Prospective therapies for PAH-targeting activin and/or BMP signaling have been associated with telangiectasias and arteriovenous malformations (AVMs), suggesting perturbation of BMP/activin/TGFβ signaling in PAH can lead to phenotypes that mimic HHT. To identify the ligands potentially responsible for driving HHT mimicry, we tested a panel of molecules with different activities against BMP and activin ligands. We predicted that ligands within the TGFβ superfamily are responsible for AVM formation in HHT-prone mice.
Methods: We tested several recombinant proteins or antibodies known to have potential therapeutic effects in experimental or human pulmonary hypertension: anti-BMP9, anti-BMP10, ALK1-Fc (a BMP9/BMP10 ligand trap), ACTRIIA-Fc a.k.a. sotatercept, ACTRIIB-Fc (a combined activin/GDF/BMP9/BMP10 ligand trap), and isotype control Ab. These were administered to juvenile 129X1/SvJ mice that are prone to HHT. Recombinant BMP/activin ligand-traps or neutralizing Abs were tested in 3- or 6-week old mice (5–10 mg/kg twice weekly) for 15 weeks, with weekly paw and digital skin surveys, and blood counts and whole body computed tomography (CT) angiography performed at time of euthanasia.
Results: Treatment with ACTRIIB-Fc, ALK1-Fc, or anti-BMP10 led to prominent digital and tail AVM formation at high frequency but with distinct distributions, within 30 days when initiated at 3 weeks of age, and within 60 days when initiated at 6 weeks of age. Treatment with ALK1-Fc, ACTRIIA-Fc, and anti-BMP9 led to less frequent and milder AVMs, and at a delayed interval compared with ACTRIIB-Fc, ALK1-Fc, or anti-BMP10. Treatment with ACTRIIB-Fc promoted weight gain, consistent with known anabolic effects on muscle and bone.
Conclusion: Combined antagonism of BMP9/BMP10 via ACTRIIB-Fc or ALK1-Fc exerted strongest HHT mimicry in susceptible mice, while selective or weaker antagonism of BMP9 or BMP10 via neutralizing antibodies or ACTRIIA-Fc was less potent. HHT-susceptible strains of mice challenged with prospective PAH therapies can be used to reveal potential for HHT mimicry due to BMP9/BMP10 antagonism in an age-dependent fashion. This model or similar preclinical models could be used to screen for potential risk of AVMs in future clinical trials of novel therapies for PAH.

INCREMENTAL BURDEN OF PULMONARY HYPERTENSION AMONG PATIENTS WITH CONNECTIVE TISSUE DISEASE-RELATED INTERSTITIAL LUNG DISEASE IN THE REAL-WORLD SETTING

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Category: Clinical Science
Subcategory: Databases and Registries

Background: Interstitial lung disease (ILD) is a serious manifestation of connective tissue diseases (CTDs) associated with increased morbidity and mortality and with a clinical spectrum ranging from self-limiting disease to progressive irreversible pulmonary fibrosis. Pulmonary hypertension (PH), a common complication in patients with ILD, may impose a substantial additional burden. The objective of this study was to assess hospitalization rates over 2 years among patients with CTD-ILD with PH compared with those without PH, in real-world settings.
Methods: This retrospective cohort study included patients in the US Marketscan® Claims Database with ≥2 outpatient claims (on different dates) or 1 inpatient claim for ILD and CTD from January 1, 2017, to December 31, 2019. Patients aged ≥18 years with ≥12 months continuous enrollment before and ≥24 months after index (date of first ILD claim) were included. Subcohorts were patients with or without PH (≥2 outpatient or 1 inpatient claim for PH) during the study period (January 1, 2016, to December 31, 2021). Heart failure (HF)–related and all-cause hospitalizations were assessed, with subcohorts compared by χ^2 test for categorical variables and Student's *t*-test for continuous variables. Multivariate analyses included logistic regression (odds ratio [OR]) and Poisson regression (incidence rate ratio [IRR]) to adjust for confounding comorbidities identified during the 12-month baseline (preindex) period.
Results: A total of 4545 patients with CTD-ILD was identified; 663 (15%) had PH. Patients with PH were older (age = 54.5 ± 12.2 versus 50.5 ± 13.5 years) and more likely to have comorbid conditions (including chronic obstructive pulmonary disease, congestive HF, dyslipidemia, gastroesophageal reflux disease, hypertension, and ischemic heart disease). A significantly higher proportion of patients with PH compared with patients without PH had HF-related and all-cause hospitalizations during baseline, 1-year, and 2-years follow-up (P < .0001 for all; Figure 1), with the percentage-point difference between groups ranging from 7% to 19%. PH was associated with a significantly greater risk of HF-related hospitalizations per patient per year at 1-year (IRR [95% confidence interval

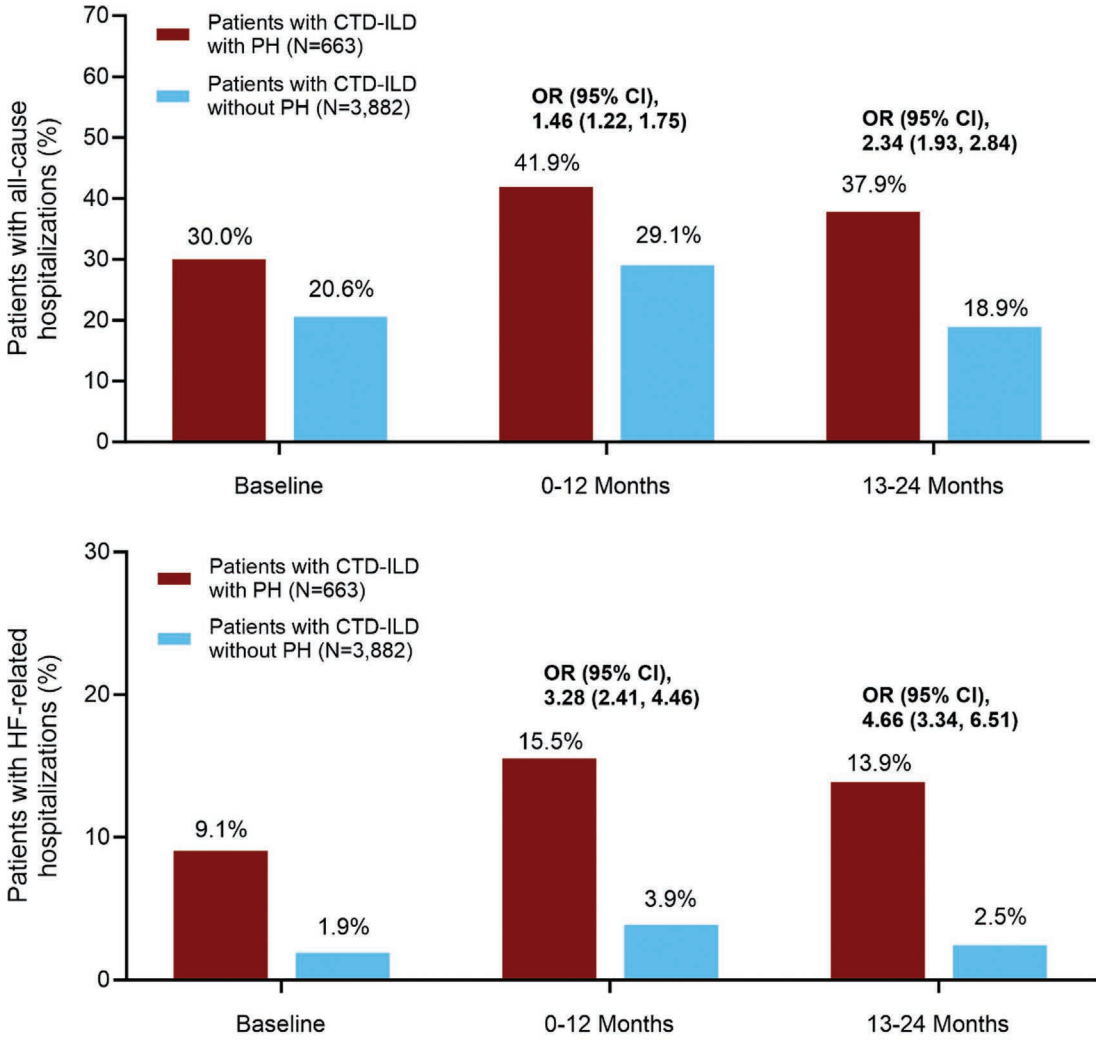

Figure 1: Proportion of patients with CTD-ILD with and without PH with all-cause and HF-related hospitalizations.

(CI)] = 2.41 [1.94, 2.99]) and 2-years (4.09 [3.24, 5.15]) follow-up. In addition, a higher percentage of patients with CTD-ILD with PH versus those without PH who had hospitalization at baseline had subsequent hospitalizations during 1-year follow-up (HF-related, 50% versus 42%; all-cause, 60% versus 50%).

Conclusion: Both HF-related and all-cause hospitalizations were significantly higher in patients with CTD-ILD with PH compared with those without PH, with differences even more pronounced during follow-up. Data from this study suggest that, in patients with CTD-ILD, PH adds a significant clinical burden.

INTERIM RESULTS FROM THE PHASE 1B AND PHASE 2 TORREY OPEN-LABEL EXTENSION STUDY OF SERALUTINIB IN PULMONARY ARTERIAL HYPERTENSION

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Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Seralutinib is a highly potent inhibitor of PDGFRα/β, CSF1R, and c-KIT kinase pathways driving vascular remodeling in PAH. The Phase 2 TORREY study in pulmonary arterial hypertension (PAH; NCT04456998) met its primary endpoint of reduction in pulmonary vascular resistance (PVR) from baseline to week 24 (W24; –14.3%; *P* = .0310). We present interim results (as of October 26, 2023) from an open-label extension (OLE) study (NCT04816604) to evaluate the long-term safety, tolerability, and efficacy of seralutinib.
Methods: Here, 73/80 patients from TORREY (World Health Organization [WHO] Group 1 pulmonary hypertension [PH] on stable PAH-specific background medications) and 1/8 patients from a Phase 1B study (NCT03926793) enrolled and received seralutinib 90 mg BID by dry-powder inhaler. The primary endpoint was safety and tolerability; treatment-emergent adverse events (TEAEs) were recorded. PVR was measured at TORREY BL and OLE W24 and week 72 (W72). Analyses are descriptive.
Results: At OLE entry (OE), 34 patients continued seralutinib (S–S), and 40 switched from placebo to seralutinib (P–S), mean age 50 years, 89.2% female. WHO Functional

Table 1. PVR Results, as of October 26, 2023

	Seralutinib-to-seralutinib (n=26)	Placebo-to-seralutinib (n=24)
Median PVR at OLE entry	500.0	644.5
Change in PVR from Week 24 to 72, median (%)	-47.5 (-9.1)	-47.0 (-7.3)
Change in PVR ≥10% from Week 24 to 72, n (%)	15 (57.7)	11 (45.8)
Change in PVR from TORREY baseline to Week 72, median (%)	-143.0 (-23.6)	-71.0 (-10.5)

Data are presented as dyne*s/cm^5, unless otherwise indicated.

Class (FC) I/II/III/IV for S–S, 5.9%/76.5%/17.6%/0; P–S, 7.5%/45%/40%/7.5%. Here, 37.8%/56.8% had 2/3 background PAH medications. Most common TEAEs were headache (24.3%), COVID-19 (23%), and cough (21.6%). Cough was less frequent in the OLE (W72: S–S 20.6%; P–S 22.5%) than in TORREY (seralutinib 43.2%; placebo 38.1%). TEAEs led to study discontinuation in 18 (24.3%) patients, most due to cough. Two patients discontinued seralutinib (1/group) for increased ALT/AST, resolving upon discontinuation. Three deaths occurred unrelated to seralutinib. At OE, median PVR was higher in the P–S versus S-S group (Table 1). From W24 to W72, median PVR change was similar in both groups. Overall, 73% S-S and 75% P-S patients improved or maintained PVR at W72.

Conclusion: Seralutinib was well tolerated for up to 72 weeks. No new safety signals were identified. Further PVR reductions from W24 to W72 with S–S suggest treatment effect persistence. PVR improved with P–S for ≤48 weeks. A Phase 3 study of seralutinib in PAH is enrolling (PROSERA, NCT05934526).

MAKING A SPLASH… IN SEARCH OF A SAFE WAY TO SUBMERGE ON SUBCUTANEOUS TREPROSTINIL THERAPY

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Category: Clinical Science
Subcategory: Quality of Life

Background: Subcutaneous (SQ) site maintenance is burdensome for patients on continuous treprostinil therapy. Patients self-administer a small catheter via a needle injection device under the skin. Setting each new site often results in 5–7 days of debilitating pain and erythema, often referred to as "hell week." Promoting longevity of sites up to 3 months is therefore of utmost importance. Although the Remunity pump itself may be submerged for a short time under water, it is the site that is most difficult to maintain. Patients frequently report that the supplies allotted from specialty pharmacies to protect sites from water during showering or bathing are often ineffective. To achieve a more normal lifestyle, some patients have been noted to interrupt their continuous infusions to shower or swim. With a half-life of 4 hours, patients have a false sense of security that they are safe to disconnect from their treprostinil pumps without complications. Our patient herein admits to having previously disconnected the pump to swim after reading on social media sites that other patients disconnect to submerge. This is not only against medical advice, but it is also dangerous. Unfortunately, not enough research has been performed on best practices to waterproof SQ sites. Our patient took it upon herself to find a better solution and found that Allevyn Life Dressing afforded reliable waterproofing. One case study patient on a Remunity pump spent a family vacation on the beach in North Carolina. The patient kept her Subcutaneous Remunity (SQR) site completely waterproof while swimming in the ocean for several hours by covering the existing site, intravenous (IV) 300 dressing, tubing, and Remunity pump with Allevyn Life Dressing. After swimming, the dressing was carefully removed, and the site, tubing, and pump remained completely intact. Upon diagnosis in 2019, the case study patient was devastated to learn that she could never swim. She scoured the Internet for solutions. She learned many patients on Facebook Websites reported disconnecting their medication to swim. She disconnected her SQR for several hours, then reported violent nausea, vomiting, flushing, headaches, diarrhea, and significant increases in her dyspnea for several hours after resuming her SQR infusion at 135 ng/k/m. Interruption of therapy is not medically recommended and may result in worsening PAH symptoms. Patients not only suffer adverse physical events from SQ therapy, but their quality of life can be affected. The waterproof capacity of Allevyn Life Dressing will be tested on SQ patients receiving Remodulin via a Remunity pump upon approval of an Institutional Review Board (IRB) at the Ohio State University Wexner Medical Center.

Methods: The existing SQR site is covered by an IV 3000 dressing. The site, tubing, and pump are secured with tape for extra support. A test strip which detects the presence of moisture is placed beside the SQR site. Allevyn Life Dressing (8.25 × 8.25 in) is applied, smoothed out completely with no wrinkles or buckles, and the patient will submerge in water for 20 minutes. Upon exiting the pool, the Allevyn Life Dressing is removed. The IV 3000 dressing over the existing SQR site is shown to be completely dry. The test strip shows no evidence of moisture, thereby demonstrating the waterproof capability of Allevyn Life Dressing.

Future Testing: Upon approval of an IRB, patients on Remunity pumps will trial the Allevyn dressing while walking

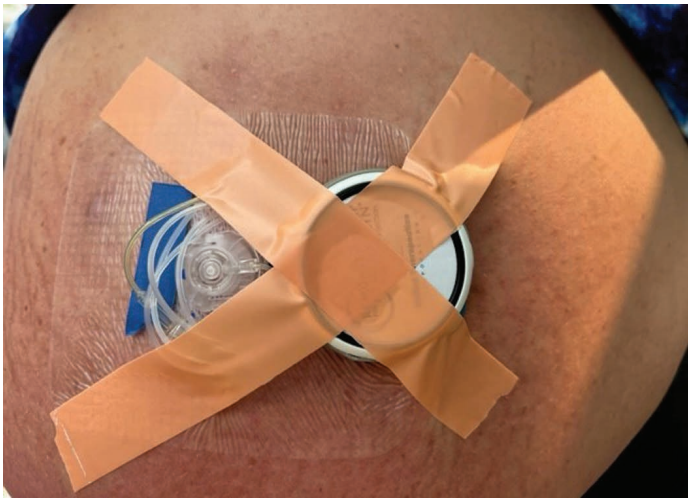

Figure 1: SQR site with tubing and Remunity pump.

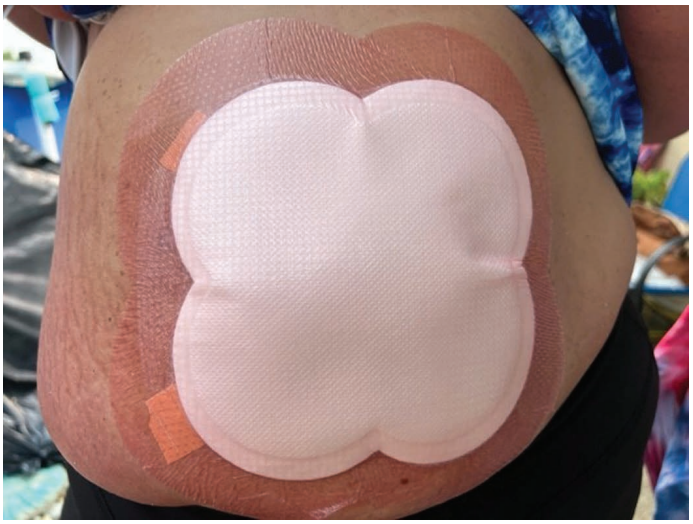

Figure 2: Allevyn before swimming.

in a pool for 15–20 minutes. Moisture test strips will be used to ensure dressing is occlusive and prevents water leakage to site. A quality-of-life survey will be completed pretrial and posttrial to assess how the dressing affects patients' quality of life. See Figures 1–3.

Figure 3: Submerged in pool.

Results: Allevyn Life Dressing by Smith & Nephew was successfully used by 1 patient to reliably waterproof their pump and site while submerging in water. Quality-of-life surveys will be administered. Results will be submitted after the testing occurs.

Conclusion: Pending IRB approval, we intend to further investigate the reliability of this dressing by having other patients on SQ therapy use it to submerge in water in a controlled setting. Moisture strips will be used to ensure that the dressing is occlusive. Surveys of trial patients will be conducted before and after using the dressing to assess satisfaction with Allevyn Life Dressing compared with current dressings. The surveys will also gauge the effect on quality of life, as patients may now submerge in water.

MANAGING PATIENT EXPECTATIONS WHEN TREATED WITH ORAL SELEXIPAG FOR PULMONARY ARTERIAL HYPERTENSION: RESULTS FROM A DELPHI CONSENSUS SURVEY

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Category: Clinical Science
Subcategory: Psychosocial Considerations/Aspects of Care

Background: Oral selexipag is approved for patients with pulmonary arterial hypertension (PAH) to delay disease progression and reduce hospitalizations, based on a robust evidence base. Oral selexipag is associated with a range of expected prostacyclin pathway side effects (SEs) more frequently seen during titration. Patient and health care professional (HCP) management of these SEs is essential to help determine the individual maximum tolerated dose for each patient. We sought to identify best practices for HCPs to optimize patient expectations when treated with selexipag.
Methods: US HCPs (n = 11 physicians, n = 5 nurse practitioners, and n = 1 registered nurse) were convened as a modified Delphi panel (2 online survey rounds and a virtual consensus meeting). Consensus was defined as ≥80% of the panel in agreement using a 9-point Likert scale.
Results: Panelists agreed that an integrated and collaborative approach is optimal in clinical management and maintaining patient engagement for patients on oral selexipag. They agreed that a patient beginning selexipag therapy should be informed of its effectiveness, benefits, expected SEs, and the titration plan. Approaches to implementing these methods incorporated educational resources, face-to-face conversations with HCPs (i.e., physicians, nurse practitioners, nurses, pharmacists), phone conversations with members of the HCP team, and connecting patients to specialty pharmacy nurses or pharmacists. Consensus was also agreed that family members can be helpful in assisting the patient manage expected SEs. Insights highlighted that approaches to treatment initiation, titration, and SE management are best individualized to suit each patient. Panelists revealed that their clinical decision-making was primarily based on patient characteristics and treatment preference. For example, a provider would adjust the dose of selexipag if the patient had SEs but expressed that he or she was tolerating the SEs with his or her care team. In addition, the panel identified the common selexipag SEs of headache, diarrhea, and nausea were burdensome for patients, while flushing and jaw pain were not as burdensome. Strategies to manage these specific SEs and expectations were also defined by the Delphi panelists. The panel agreed that telehealth, support groups, setting treatment goals, and close monitoring with the patient would maximize patient care with oral selexipag. For example, support groups are a useful resource for patients in making fear of the unknown easier to handle.
Conclusion: The Delphi panel of experts achieved consensus on current management practices on the clinical use of oral selexipag in addition to suggestions to optimize the patient experience. These insights support the development of best practices that prioritize patients' needs when initiating or titrating oral selexipag and managing SEs.

NEW CANDIDATE GENES IMPLICATED IN THE DEVELOPMENT OF PULMONARY ARTERIAL HYPERTENSION

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Category: Basic Science
Subcategory: Diagnosis/Screening and Physiologic Studies

Background: Pulmonary arterial hypertension (PAH) is a rare disease characterized by elevated blood pressure in the pulmonary arteries, leading to progressive heart failure and premature death. In this study, we aim at selecting and validating pathogenic variants in genes previously associated with PAH and investigating new genes and potentially implicated variants in the development of the disease.
Methods: A total of 55 clinically diagnosed PAH patients and 21 unaffected family members was analyzed using whole exome sequencing (WES). Variant prioritization was conducted through a bioinformatic algorithm.
Results: Genetic analysis revealed pathogenic or uncertain significance variants (VUSs) in 30.9% of genes previously linked to PAH. Additionally, 3 VUSs were identified in 4 new candidate genes: ATF2, HDAC5, VASH1, and UACA.
Conclusion: Variants in ATF2, VASH1, and UACA may influence hyperproliferation and resistance to apoptosis of pulmonary vascular cells, contributing to PAH development. Furthermore, malfunctions in the posttranslational protein acetylation regulatory mechanisms involving the HDAC5 gene also contribute to PAH development, producing an aberrant epigenetic signature that exacerbates the characteristic vascular remodeling process. WES enables the expansion of the study in inconclusive cases to identify variants in new genes potentially implicated in the disease, although further research is needed to describe the involvement of these genes in PAH.

PULMONARY ARTERIAL HYPERTENSION 1-YEAR SURVIVAL PREDICTION USING INTEGRATIVE NONINVASIVE LAB AND MAGNETIC RESONANCE IMAGING VARIABLES

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Category: Basic Science
Subcategory: Risk Assessment

Background: Current pulmonary arterial hypertension (PAH) risk assessment tools are integral to selecting appropriate PAH treatments. It is therefore of interest to explore how different statistical methods and data can improve risk assessment. Right heart catheterization (RHC) is an invasive but standard procedure for diagnosing PAH. The current REVEAL 2.0 assessment tool includes 2 RHC variables: mean right atrial pressure (mRAP) and pulmonary vascular resistance (PVR). On the other hand, magnetic resonance imaging (MRI) is noninvasive, and the variables extracted from the images of the heart could potentially be of value as replacements for the invasive RHC variables.

Methods: The dataset analyzed contains information on 2592 cardiac MRI (cMRI) exams performed in the UK. Exploratory analysis showed it was best to focus on a subset of 343 prevalent subjects. The MRI data on these subjects were first analyzed using the Leiden community detection algorithm to generate communities of similar variables. Principal component analysis (PCA) was then done on each of the communities to reduce dimensionality. A generalized boosted regression classifier (GBM) was then used to predict 1-year survival. Various models incorporating combinations of non-MRI (with or without invasive variables) and MRI (all variables, selected variables, or 2 leading MRI PCs) variables were examined using a GBM classifier with fivefold cross-validation. Results on the testing folds were then analyzed using several measures, including accuracy, sensitivity, specificity, and area under the receiver operator characteristic curves (AUCs).

Results: Six communities of imaging variables were detected, corresponding to 6 well-defined modules as labeled in Figure 1 (LV, LV/RV, RV/PA, LA, RA, and PA). Of the total of

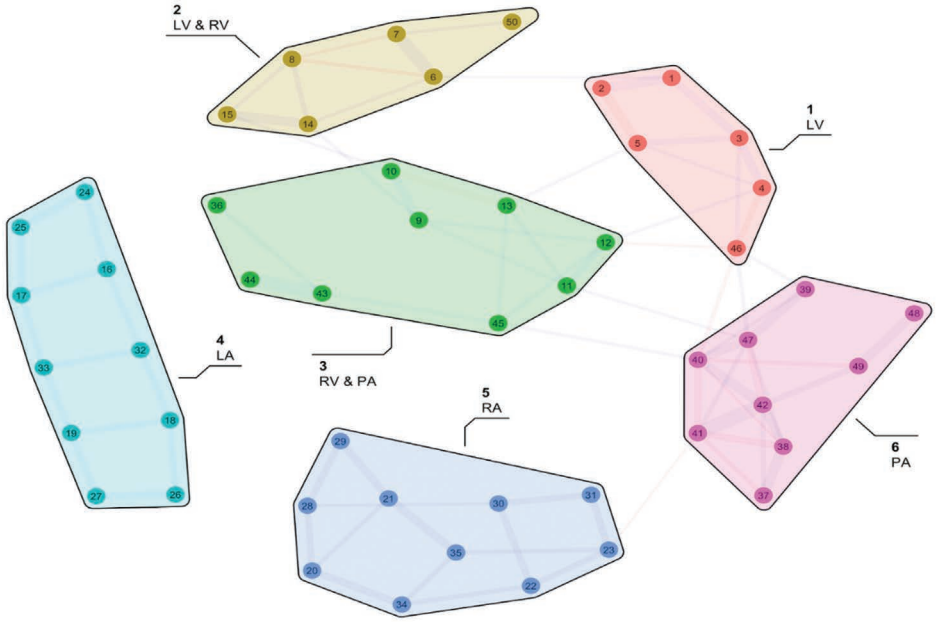

Figure 1: Six communities (with labeling) of the MRI variables detected by the Leiden algorithm.

29 models considered (Figure 2), we are the most interested in head-to-head comparison between models containing only nonimaging variables (e.g., REVEAL 2.0—Model 1 or all nonimaging—Model 2) versus nonimaging without invasive but with imaging variables (e.g., REVEAL 2.0–invasive + PC—Model 1PC, all nonimaging–invasive + PC—Model 2PC, all nonimaging–invasive + 4 imaging—Model 2Four, or all nonimaging–invasive + all imaging—Model 2MRI). Note that the PCs are as described above, whereas the 4 imaging variables were obtained from the literature. Specifically, the AUCs for Model 1 and Model 1PC are 0.747 and 0.763, respectively, indicating that the imaging variables do indeed contain information that can be used in lieu of invasive RHC variables in 1-year survival prediction. The AUCs for Model 2, Model 2PC, and Model 2Four are 0.845, 0.822, and 0.813, respectively, solidifying the value of imaging variables. Finally, Model 2MRI, using more variables than any of the other models, achieved an AUC of only 0.77, possibly due to overfitting. **Conclusion:** Based on the results using nonimaging and imaging variables and exploring over many models, it is clearly seen that replacing the invasive RHC variables with MRI data did not lead to worsening performance of 1-year survival prediction for PAH patients. These results substantiate the hypothesis set forth in our purpose of this study. Further, judicious handling of many MRI variables should be exercised to avoid the pitfall of overfitting.

Model parameters: n.trees = 500, shrinkage = 0.05, CV = 5 folds	Accuracy	Sensitivity	Specificity	'Optimal' Threshold	AUC
REVEAL 2.0	0.7524297	0.7551763	0.7084127	0.20430221	0.7468281
REVEAL 2.0 - invasive	0.7929241	0.7972759	0.6984127	0.23136443	0.7401402
All non-imaging	0.7898124	0.7783155	0.8928571	0.04888257	0.8484174
All non-imaging - invasive	0.7492754	0.7392116	0.8806349	0.04690229	0.8224869
Four variables	0.621185	0.6200779	0.6525397	0.06307617	0.601444
All imaging	0.5394288	0.5359746	0.5953968	0.03259103	0.5515456
2 PCs	0.6234442	0.6184462	0.6361905	0.07488765	0.6017235
All imaging + ESV/SV	0.5394288	0.5359746	0.5953968	0.03258783	0.5515456
2PCs + ESV/SV	0.5737852	0.5614806	0.7012698	0.05671039	0.6819454
REVEAL 2.0 + Four variables	0.7379795	0.7344315	0.8084127	0.05396841	0.7793257
REVEAL 2.0 + All imaging	0.714578	0.7247972	0.6453968	0.0380295	0.6836754
REVEAL 2.0 + 2 PCs	0.7060529	0.6966722	0.8306349	0.03906074	0.7816825
REVEAL 2.0 + All imaging + ESV/SV	0.714578	0.7247972	0.6453968	0.0380295	0.6836754
REVEAL 2.0 + 2PCs + ESV/SV	0.7813725	0.7759203	0.8028571	0.13477809	0.7882121
REVEAL 2.0 - invasive + Four variables	0.7730179	0.776294	0.7584127	0.0641009	0.764828
REVEAL 2.0 - invasive + All imaging	0.7871697	0.8056067	0.5953968	0.15854371	0.6726923
REVEAL 2.0 - invasive + 2 PCs	0.7901961	0.7958502	0.7084127	0.15133426	0.7630293
REVEAL 2.0 - invasive + All imaging + ESV/SV	0.7871697	0.8056067	0.5953968	0.15854371	0.6726923
REVEAL 2.0 - invasive + 2PCs + ESV/SV	0.7695652	0.7690555	0.7306349	0.13990448	0.7681416
All non-imaging + Four variables	0.8014066	0.7971199	0.8206349	0.05506569	0.8448337
All non-imaging + All imaging	0.769139	0.768634	0.7761905	0.0519207	0.8091264
All non-imaging + 2 PCs	0.7957374	0.7881129	0.8706349	0.0561769	0.8330606
All non-imaging + All imaging + ESV/SV	0.769139	0.768634	0.7761905	0.0519207	0.8091264
All non-imaging + 2PCs + ESV/SV	0.798295	0.7925415	0.8206349	0.06280444	0.8396597
All non-imaging - invasive + Four variables	0.7576726	0.746699	0.8592063	0.05234477	0.8131366
All non-imaging - invasive + All imaging	0.7110827	0.7053071	0.7798413	0.03629493	0.7774208
All non-imaging - invasive + 2 PCs	0.7841858	0.7796246	0.8306349	0.04488763	0.8223866
All non-imaging - invasive + All imaging + ESV/SV	0.7110827	0.7053071	0.7798413	0.03629493	0.7774208
All non-imaging - invasive + 2PCs + ESV/SV	0.7518329	0.7401968	0.8806349	0.03538709	0.821958

Figure 2: Performance characteristics—accuracy, sensitivity, specificity, and AUC—of 29 models.

PATIENT PREFERENCES REGARDING THE USE OF COMBINATION ERA+PDE5I FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION: RESULTS FROM A DISCRETE CHOICE EXPERIMENT

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Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Pulmonary arterial hypertension (PAH) is a life-threatening condition where the arteries of the lung become narrowed, thickened, or stiff. According to current guidelines, combination treatment with an endothelin receptor antagonist (ERA) and a phosphodiesterase type 5 inhibitor (PDE5i) is recommended for most low- and intermediate-risk patients. Here, we examined patients' perceptions of these combination therapies, including factors likely to increase or decrease their acceptance (e.g., single-tablet combination therapy [STCT]).
Methods: A purposive sample of 201 PAH patients completed an online, cross-sectional survey; all patients were required to have used an oral PAH medication in the past year. Patients' willingness to use double combination ERA+PDE5i was assessed using a discrete choice experiment (DCE). This experiment evaluated 7 treatment-level attributes (listed in Table 1a). The results of the DCE are reported as attribute relative importance scores, where higher percentages indicate greater importance to patients' decision-making. The role of STCT on ERA+PDE5i acceptance was assessed with 1–5 Likert scales.
Results: Respondents were predominantly White (86.1%) and female (88.6%), with a median age of 59 years. Most were not employed (70.2%), with over one-third reporting a disability (38.3%). Over half of respondents were currently using some combination of ERA+PDE5i at time of survey (either double ERA+PDE5i therapy = 17.9% or triple PDE5i+ERA+prostacyclin therapy = 36.8%). The 2 main factors that influenced patients' acceptance of ERA+PDE5i in the DCE were out-of-pocket costs (33.7%) and dosing frequency (31.5%; Table 1a). Individual preference weights confirmed that patients were most accepting of ERA+PDE5i therapies when available at the lowest out-of-pocket cost and the least frequent dosing regimen (i.e., 1 pill/day). Most respondents reported that STCT would reduce pill consumption (83.1%) and time spent managing prescriptions (68.7%; Table 1b), whereas one-third reported benefits to treatment adherence (39.3%) and initiation (34.8%; Table 1c).
Conclusion: Dosing frequency and out-of-pocket costs were both highly influential in determining PAH patients' willingness to accept double combination treatment with ERA+PDE5i. Most patients were receptive to STCT to streamline prescriptions and reduce pill burden, and a substantial portion noted that STCT may accelerate treatment initiation and improve adherence. Despite these advantages, cost considerations remain a significant factor driving patient decision-making.

Table 1. Patients Preferences in Treating PAH

Table 1. Patients Preferences in Treating PAH	
a) Treatment Attributes Influencing ERA+PDE5i Use	**Mean Relative Importance, %****
Out-of-Pocket Costs	33.7
Dosing Frequency	31.5
Patient Support Program	9.3
Discontinuation Due to Side Effects*	8.0
Pharmacies	6.9
Prior Authorization	5.6
Dose Increase (Titration)	5.0
b) Pros of STCT	**>50% Respondents Selected, %**
Be able to take less pills	83.1
Spend less time managing prescriptions	68.7
c) Influence of STCT on Treatment Behavior	**Respondents Reporting "Always/Often" or "Strongly Agree/Agree", %**
Would result in less missed doses	39.3
Would have started therapy sooner	34.8

* Presented to respondents in the DCE as "the percentage of patients that stopped medication due to side effects.", **Results sum to 100%.

PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ASSOCIATED PULMONARY HYPERTENSION DEMONSTRATE REDUCTION IN EXERTIONAL VENTRICULAR-ARTERIAL COUPLING: A PILOT STUDY USING INVASIVE CARDIOPULMONARY EXERCISE TESTING

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Category: Clinical Science
Subcategory: Diseases and Conditions Associated With PH

Background: Chronic obstructive pulmonary disease (COPD) affects 8%–12% of adults ≥40 years. Pulmonary hypertension (PH) affects up to 70% of patients with COPD, impairing functional capacity and increasing COPD exacerbations and mortality. The negative effects of PH are mediated by right ventricular (RV) dysfunction, and treatments are lacking. The objective of this pilot study was to generate hypotheses regarding pathophysiological mechanisms of exertional RV dysfunction among patients with COPD and associated PH.
Methods: Patients with COPD and pulmonary artery enlargement (pulmonary artery/aorta >1 on computed tomography) were recruited. Patients were excluded if a primary etiology of PH other than COPD was identified. Spirometry was performed. An oxygen titration test was performed which included 2–4 minutes upright cycling without resistance while supplemental oxygen was adjusted for goal oxygen saturation 90%–93%. Supplemental oxygen was provided at that level through the remainder of testing. Baseline hemodynamics were obtained by Swan-Ganz catheter. Thereafter, the catheter was exchanged for a conductance catheter (CDLeycom, Hengelo, Netherlands) for RV pressure-volume analysis during rest and invasive cardiopulmonary exercise testing on an upright cycle ergometer. Pressure-volume measurements were obtained at rest, submaximal (20 Watts) and maximal exercise. Data are presented as mean [range]. Data across exercise conditions are compared using 1-way analysis of variance.
Results: Three participants were studied (62 [60–67] years, 2 females/1 male, all former smokers, none on pulmonary vasodilators, forced expiratory volume in 1 second 29% predicted [22%–42%], supplemental fraction of inspired oxygen 43% [36%–48%]). Resting hemodynamics included right atrial pressure 5 [2–10] mmHg, mean pulmonary artery pressure 25 [18–36] mmHg, and pulmonary artery wedge pressure 9 [5–16] mmHg. Maximal oxygen uptake and workload were reduced compared with population norms (16.9 [12.4–25.3] ml/kg/min, 43 [30–50] Watts). Pressure-volume analysis results are summarized in Table 1. RV afterload was increased at rest compared with published data in healthy adults and increased with exercise. Metrics of RV contractility were increased at rest and only modestly increased with exercise. As a result, ventricular-arterial coupling, determined by the ratio of end-systolic elastance (Ees) to effective arterial elastance (EA), decreased by 20% during exercise.
Conclusion: Among patients with COPD and associated PH, RV afterload increased during exercise. While contractility increased, this was not sufficient to maintain ventricular-arterial coupling, and ventricular-arterial coupling decreased during exercise. In this pilot study, we suggest that RV contractile reserve is reduced among patients with COPD and associated PH. Impaired RV contractile reserve may contribute to exertional RV dysfunction and exercise limitation.

Table 1. Right Ventricular Pressure-Volume Analysis

	Rest	Submaximal Exercise	Maximal Exercise	P-value
Contractility				
Maximum rate of pressure change (dP/dt_{max}), mmHg/second	348 [268-501]	577 [464-648]	720 [639-840]	<0.05
Preload recruitable stroke work, mmHg	26 [18-39]	30 [20-37]	39 [35-46]	0.26
End-systolic elastance (E_{es}), mmHg/mL	0.74 [0.34-1.34]	0.77 [0.39-1.24]	1.20 [0.41-1.89]	0.57
Lusitropy				
Minimum rate of pressure change (dP/dt_{min}), mmHg/second	-321 [-229- -458]	-583 [-461- -653]	-727 [-815- -682]	<0.01
Energetics				
Stroke work, mmHg·mL	5,180 [1918- 11,154]	6,790 [3,145-12,963]	8,947 [3,721-18,805]	0.79
Afterload				
Effective arterial elastance (E_A), mmHg/mL	0.54 [0.24-1.00]	0.63 [0.30-1.11]	1.06 [0.37-1.62]	0.44
Ventricular-arterial coupling				
E_{es}/E_A	1.41 [1.35-1.50]	1.24 [1.05-1.36]	1.13 [1.09-1.17]	0.05

PATTERNS AND OUTCOMES OF EPOPROSTENOL USE IN INFANTS WITH CONGENITAL DIAPHRAGMATIC HERNIA REQUIRING EXTRACORPOREAL LIFE SUPPORT

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Category: Clinical Science
Subcategory: Diseases and Conditions Associated With PH

Background: Pulmonary hypertension (PH) remains the Achilles' heel of severe congenital diaphragmatic hernia (CDH). Various pharmacologic therapies have demonstrated inconsistent benefit. We aimed at describing our experience using epoprostenol in infants with CDH requiring extracorporeal life support (ECLS).
Methods: A single-center retrospective review (2013–2023) was conducted, investigating infants diagnosed with CDH who required ECLS and were treated with intravenous epoprostenol during their hospitalization. Demographics, disease characteristics, medication administration patterns, and outcomes were analyzed between survivors and nonsurvivors. Chi-squared/Fisher's exact and Kruskal-Wallis tests were used, with significance $P < .05$.
Results: Forty infants met inclusion criteria: 24 infants (60%) survived to hospital discharge (survivors), and 16 (40%) did not (nonsurvivors). Both groups had similar prenatal indicators of disease severity (Table 1). Most (80%) hernia defects were classified as Type C/D, and most (68%) were repaired early (<72 hours) after ECLS cannulation with a patch or muscle flap. The median age at initiation of epoprostenol was 6 days (interquartile range [IQR], 4–7) in survivors and 8 (IQR, 7–16) in nonsurvivors ($P = .012$). Most patients (85%) were started on epoprostenol while on circuit. Median time to

Table 1. Comparison of Prenatal Predictors, Disease Severity, Defect Characteristics, and Repair Details Between Survivors and Nonsurvivors

Prenatal Characteristic Median (IQR) or n(%)		Survivors (n=24)	Non-Survivors (n=16)	p-value
U/S Lung-to-Head Ratio		1.05 (0.8–1.2)	1.00 (0.7–1.3)	0.652
U/S Observed/Expected Ratio Lung-to-Head (o/e LHR)		31.1% (23.9–37)	34.6% (24–44)	0.494
MRI Observed/Expected Ratio Total Fetal Lung Volume (o/e TFLV)		20% (17–28)	19% (15.8–23.1)	0.361
Defect Laterality				
	Right	12 (50%)	5 (31.3%)	0.240
	Left	12 (50%)	11 (68.7%)	
Liver Position				
	Up	22 (91.7%)	14 (87.5%)	0.667
	Down	2 (8.3%)	2 (12.6%)	
CDH Severity				
	Mild	0 (0%)	0 (0%)	
	Moderate	10 (40%)	3 (20%)	0.256
	Severe	10 (40%)	10 (66.7%)	
	Extreme	5 (20%)	2 (13.3%)	
Concurrent Cardiac Defect		4 (16.7%)	3 (18.8%)	0.865
Defect Type				
	A	0 (0%)	0 (0%)	
	B	5 (20.8%)	3 (18.8%)	0.281
	C	14 (58.3%)	6 (37.5%)	
	D	5 (20.8%)	7 (43.8%)	
CDH Repair Timing				
	Early on ECLS (<72h)	13 (54.2%)	14 (87.5%)	
	Late on ECLS (>72h)	4 (16.7%)	1 (6.3%)	0.085
	After ECLS	7 (29.2%)	1 (6.3%)	
Repair Type				
	Patch or Flap	20 (83.3%)	15 (93.8%)	0.329
	Primary Repair	4 (16.7%)	1 (6.2%)	

initiation was 4 days (IQR, 3–7) after cannulation in survivors compared with 8 days (IQR, 8–15) in nonsurvivors (P = .012). No differences were found in incidence of intracranial hemorrhage (8.3 versus 18.3%, P = .329) or major bleeding complications (4.2 versus 6.3%, P = .767). Survivors had significantly shorter durations of ECLS (11 versus 20 days, P = .049) and had significantly more ventilator-free days in the first 60 days of life (18 versus 0, P = .003). Of nonsurvivors (n = 16), refractory PH was the cause of death for 13 infants (80%), with most undergoing palliative decannulation (n = 8, 50%) or declining recannulation (n = 4, 25%).
Conclusion: Our results suggest that, in infants with CDH requiring ECLS, addition of epoprostenol appears promising, and earlier initiation may affect survival. However, despite ECLS and pharmacologic therapy, recalcitrant PH remains an unsolved problem.

PERCEPTIONS OF THE PROSTACYCLIN PATHWAY: INSIGHTS FROM A PULMONARY ARTERIAL HYPERTENSION PATIENT ENGAGEMENT RESEARCH COUNCIL

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Category: Clinical Science
Subcategory: Patient Engagement Strategies

Background: The prostacyclin pathway represents a key foundational pathway in treating pulmonary arterial hypertension (PAH); however, targeting the pathway comes with challenges related to associated side effects and, for some therapies, a burden of administration. As a result of these challenges, patient engagement often plays a factor in therapeutic persistence. Currently, knowledge is limited of patients' understanding of the prostacyclin pathway and their perspective on the prostacyclin pathway agent (PPA) treatment experience.
Methods: Johnson & Johnson engaged a Patient Engagement Research Council (PERC) that was facilitated by a third-party vendor (CorEvitas). The PAH PERC is a focus group of contracted patient consultants, adults residing in the US with a self-reported diagnosis of PAH. For this specific engagement, PERC members were required to have familiarity with the prostacyclin pathway. CorEvitas conducted 3 virtual focus group sessions with 10 eligible PAH PERC members. All engagements are product agnostic.
Results: Participants were typically introduced to PPAs when providers were considering additional therapy at a time of deterioration and disease progression. The PERC members reported they felt insufficient information was provided about the value of the prostacyclin pathway and PPAs, but instead, PPAs were presented as a "necessary evil" for those with "increased pressures." Participants were also neither aware of nor made aware of different PPA formulations and did not fully understand the differences between them, leading to confusion when engaging with clinicians during treatment discussions. While all 10 participants were familiar with PPAs, 3 did not realize they were taking or had taken a PPA because PPAs were perceived as intravenous medications only. Several noted that providers may not fully appreciate the intensity of side effects and effect on daily life because their experiences did not reflect the expectations conveyed to them. Participants felt they would benefit from more information about how long the side effects last, options for side effect management, different formulations, and more time to decide about initiating therapy. When discussing potential benefits of PPAs, participants suggested the best communication strategy was to present data, including placebo outcomes, in plain language and to emphasize the consequences of not taking a PPA.
Conclusion: Insights provided by this group of PAH patients provided a unique perspective into their experiences on different formulations of PPAs. They conveyed a desire to be more informed and engaged in treatment decisions. A better understanding of gaps in communication and education can inform strategies for better shared decision-making and patient engagement to optimize outcomes.

PULMONARY HYPERTENSION ASSOCIATION REGISTRY CARE STANDARDS FOR PARTICIPATING PATIENTS WITH WORLD HEALTH ORGANIZATION GROUP 1 PULMONARY ARTERIAL HYPERTENSION POSITIVELY INFLUENCE CARE PROVIDED TO COMPARABLE PATIENTS NOT ENROLLED IN THE REGISTRY

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Category: Clinical Science
Subcategory: Databases and Registries

Background: The Pulmonary Hypertension Association (PHA) Registry (PHAR) has proven to be a highly valuable research tool for the accumulation of information about the longitudinal experiences of patients with pulmonary arterial hypertension (PAH). Participation in the PHAR elevates the standard of care for patients with PAH, which in turn should improve outcomes. We hypothesized that those patients who, for one reason or another, are not participants in the PHAR program at our pulmonary hypertension (PH) treatment center also benefit from this elevated standard of care. In other words, the PHAR standard of care and its benefits extend beyond the select patients who are enrolled in the PHAR program.
Methods: The East Tennessee Pulmonary Hypertension Center (ETPHC) maintains an internal PAH treatment database which serves to track patient treatment trajectories over time. We performed an audit of management practices for our World Health Organization (WHO) Group 1 PAH patients not participating in the PHAR and receiving treatment from January 1, 2018, through January 1, 2024. Our first PHAR enrollment occurred in October 2019. We used PHAR tracking parameters to compare our management practices during 2 time periods: 1 for a 2-year period before PHAR participation (period 1: January 1, 2018, through January 1, 2020) and a second 2-year period beginning after 2 years of PHAR participation (period 2: January 1, 2022, through January 1, 2024). We reviewed charts and extracted data pertaining to the relative roles of physician or midlevel provider, number of regular or urgent PAH outpatient visits, number of hospitalizations for PAH reasons, frequency of assessments including 6-minute walk (6MW), biomarkers, echocardiogram, right heart catheterization (RHC), and risk analysis. We critically evaluated documentation of referrals to supportive services including pulmonary rehabilitation, lung transplant evaluation, palliative care services, and immunization status. Finally, we determined compliance with documentation of safety concerns for women of childbearing age.
Results: Database review identified 21 non-PHAR WHO Group 1 patients who received continuous care during the defined study period. During period 1, a greater percentage of patient visits were provided by the PH nurse practitioner (NP); 67.1% NP and 32.9% medical doctor (MD). In contrast, more patient visits were provided by the MD during period 2; 21.7% NP and 78.3% MD. The numbers of PAH-related urgent visits and hospitalizations were similar for both time periods. 6MW testing was performed for 62% of all patient visits during period 1 and 64% of all visits during period 2. A significant increase was found in frequency of biomarker measurement during period 2 with testing completed for 60% of all patient visits versus 19% of all period 1 visits. A risk score was determined for 1 of the 21 patients during period 1 compared with multiple risk scores determined and documented for 10 of the study patients during period 2. No difference was found in the frequency of echocardiogram monitoring in either period. Repeat RHC was performed 3 times during period 1 and 5 times in the comparison period. Documentation of influenza and pneumococcal vaccination improved with the rate of documentation for influenza at 62% in period 1 and 95% in period 2, pneumococcal vaccination 24% in period 1 and 71% in period 2. Documentation of discussion or referral for supportive services improved from period 1 to period 2; 28% versus 57% for pulmonary rehabilitation, 33% versus 57% for lung transplantation, and 28% versus 52% for palliative care. Chart documentation of reproductive risk to patients was more commonly documented in period 2 at a rate of 67% versus 33% of the patient progress reports.
Conclusion: This practice audit demonstrated that participation in PHAR has improved patient care practices and extended more consistent guideline-based care to the broader PAH patient population served by the ETPHC whether PHAR participants or otherwise. Specific improvements in care included physician involvement, biomarker monitoring and risk analysis, and documentation of immunizations and referrals for other supportive services beneficial to PAH patients. Findings also provide guidance for areas needing further improvement.

PLATELET-DERIVED GROWTH FACTOR-BB ANTAGONIST MONOCLONAL ANTIBODY AS A THERAPY FOR PULMONARY ARTERIAL HYPERTENSION

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Category: Basic Science
Subcategory: Therapeutic Strategies

Background: Pulmonary arterial hypertension (PAH) is a rare, progressive pulmonary vascular disease characterized by small pulmonary artery cell hyperplasia, leading to vascular luminal obstruction. Platelet-derived growth factor (PDGF)-BB is a potent mitogen for cells of mesenchymal origin, including fibroblasts, smooth muscle cells, and endothelial cells. Extracellular PDGF-BB binds and activates PDGF-αα, PDGF-αβ, and PDGF-ββ receptors, triggering cellular proliferation, differentiation, and migration and inhibiting apoptosis. Neutralizing PDGF-B may provide efficacy in PAH by reducing PDGF-BB/AB-induced proliferation and cellular migration of both smooth muscle cells and fibroblasts that actively contribute to promote adverse vessel remodeling.
Methods: Affinity of PDGF-B antibody REGN13335 binding to recombinant human, monkey, rabbit, rat, and mouse PDGF-BB and human PDGF-AA and PDGF-AB dimer reagents was measured. In vitro potency of REGN13335-blocking PDGF-AB- or PDGF-BB-induced PDGFR-B activation was evaluated in both engineering HEK293/SREluc/hPDGFRβ cells and human primary pulmonary artery smooth muscle cells (PASMCs). The in vivo efficacy of REGN13335 was evaluated in the hypoxia/Sugen 5416 (Hy/Su) mouse model and the monocrotaline (MCT) rat model. The Hy/Su model was induced by exposing mice to 10% oxygen and weekly Sugen 5416 dosing. The MCT rat model was induced by subcutaneous injection of 40 mg/kg MCT in saline. REGN13335 was dosed subcutaneously at 1–25 mg/kg either preventatively or therapeutically. PAH functional endpoints include right ventricle systolic pressure (RVSP) and Fulton index as a measure of right ventricular hypertrophy (RVH).
Results: REGN13335 displayed subnanomolar binding affinity to recombinant PDGF-BB of human, monkey, rat, rabbit, and mouse. REGN13335 inhibited PDGF-BB- and PDGF-AB-induced HEK293/SRE-luc/hPDGFRβ engineering cells activation. In addition, REGN13335 completely blocked PDGFRβ phosphorylation and PASMCs proliferation and activation. In the in vivo efficacy studies, REGN13335 treatment significantly reduced RVSP and RVH (Fulton index) in both the Hy/Su mouse and MCT rat models. Furthermore, therapeutic treatment with REGN13335 in the high dose MCT model significantly improved survival time by 50%.
Conclusion: PDGF-B antagonist REGN13335 demonstrated robust efficacy mitigating PAH related endpoints in various experimental PAH models. Our results implicate PDGF-B antagonist as a potential therapy for PAH.

PORTOPULMONARY HYPERTENSION COMPLICATED BY LIVER CANCER: JOURNEY TO A SUCCESSFUL LIVER TRANSPLANT

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Category: Case Report
Subcategory: Diseases and Conditions Associated With PH

Introduction: We investigated how often people referred for transplantation are accepted and how they can be treated to become acceptable candidates.

Case Description: Portopulmonary hypertension (POPH) is a complex disease. About 4%–6% of patients referred for liver transplant evaluation have pulmonary hypertension, and a large portion of these patients have POPH. Patients with POPH have worse prognosis compared with idiopathic pulmonary arterial hypertension (PAH). The treatment of these patients is complex and requires a multidisciplinary approach. It includes specific PAH therapies and supportive management to improve their hemodynamics, right ventricular function, tricuspid regurgitation, and functional capacity to allow patients to be ready for transplantation, which ultimately improves their survival. We present a case of a 66-year-old Hispanic female with a history of decompensated cirrhosis secondary to chronic hepatitis C complicated by POPH with hepatocellular carcinoma. Her evaluation in December 2015 revealed severe pulmonary hypertension confirmed by right heart catheterization showing right atrial (RA) pressure of 7 mmHg, pulmonary artery (PA) 75/27 (47), pulmonary artery wedge pressure (PAWP) 18, cardiac output (CO) 7.6/min, cardiac index (CI) 4.37 L/min, and pulmonary vascular resistance (PVR) 3.8 WU. She was started on Tadalafil 40 mg daily and Ambrisentan 10 mg daily according to the Ambition protocol.
Discussion: After 6 months of PAH therapy, her hemodynamics significantly improved, allowing us to list her for liver transplant, which she underwent without complications in February 2017. This case study highlights 1 patient's journey from diagnosis of POPH in the setting of cirrhosis secondary to chronic hepatitis C with liver cancer who was treated with PAH therapies, which lead to the outcome of a successful liver transplant without complications. To this date, this patient remains well and without any PAH therapies.

PRACTICAL MANAGEMENT OF ORAL TREPROSTINIL AND ADVERSE EFFECTS: LESSONS FROM THE ADAPT REGISTRY AND EXPERT CONSENSUS

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Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Oral treprostinil (TRE) is a prostacyclin analog approved to treat pulmonary arterial hypertension (PAH). Higher doses of oral TRE correlate with increased treatment benefit. As with all prostacyclins, oral TRE has an expected adverse effect profile, which can affect a patient's ability to up-titrate doses.
Methods: Management techniques for oral TRE adverse effects were derived from literature and expert recommendations. Data on real-world management of oral TRE therapy in adults with PAH were obtained from the multicenter, prospective, observational ADAPT registry (NCT03045029).
Results: From expert recommendations, patients who are candidates for oral TRE therapy and are prostacyclin naïve may be initiated with de novo oral dosing or receive parenteral prostacyclin induction and transition to oral TRE. The latter allows for faster dose escalation. Patients with PAH should be educated about the expected adverse effects of prostacyclin therapy, especially before initiating and up-titrating the dose. A proactive management plan for common adverse effects (ie, diarrhea, headache, nausea) can include recommendations for over-the-counter (OTC) or prescription medications as needed (Table 1). In the real-world ADAPT registry study, common OTC treatments were effective in managing adverse effects. Patients reported adverse effects becoming less bothersome over time (Figure 1).
Conclusion: Proactive management and prophylactic treatment of expected prostacyclin-related adverse effects may be beneficial to aid in titration and persistence on therapy and to help patients obtain the optimal therapeutic benefits of oral TRE.

Table 1. Management Strategies for Side Effects of Treprostinil Therapy

Side effect	First-line	Second-line	Refractory
Headache	Acetaminophen	Tramadol NSAID	Gabapentin Amitriptyline Opioid if severe
Nausea, vomiting	Ondansetron	Prochlorperazine Proton pump inhibitors	Metoclopramide Promethazine
Diarrhea	Loperamide	Diphenoxylate/atropine	Dicyclomine
Dizziness, hypotension	Assess volume status	Decrease dose of diuretic or BP medication	
Abdominal discomfort	Bismuth subsalicylate	Loperamide Dicyclomine Acetaminophen	
Extremity pain	Acetaminophen	Gabapentin Pregabalin Tramadol Ibuprofen	Duloxetine Opioid Massage
Jaw pain	Reassurance		
Flushing	Reassurance Cold packs		

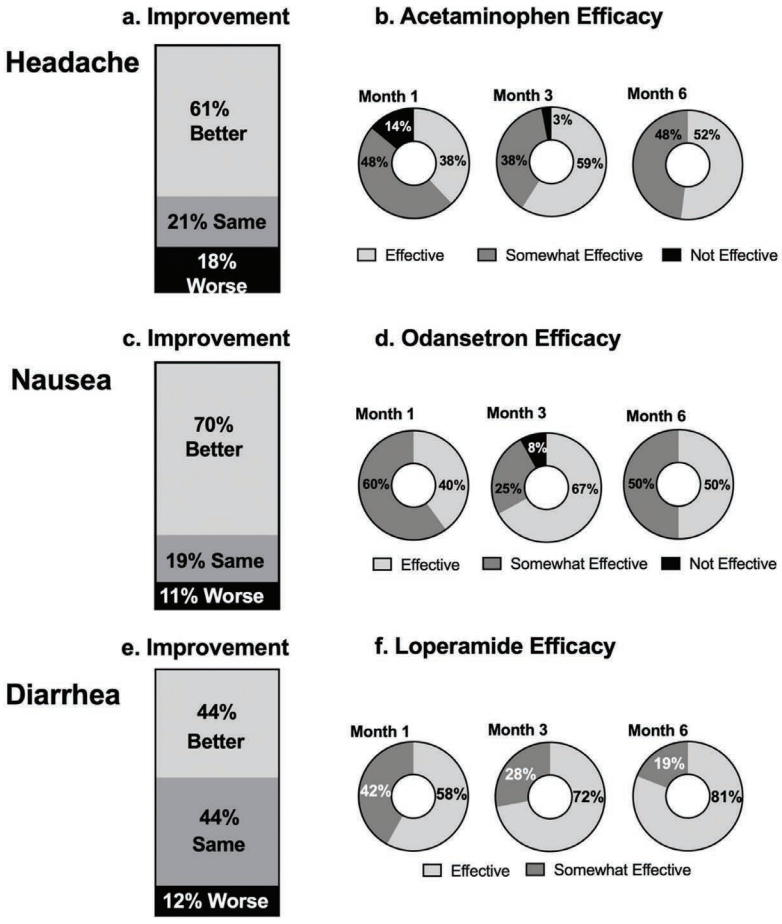

Figure 1: Real-world outcomes of common side effects of oral TRE therapy and common OTC and prescription medication management. Patient-reported incidence and treatment of common side effects associated with oral TRE therapy were collected prospectively in ADAPT to better understand side effect management and tolerability. Left column (a), (c), (e) shows calculated improvement of the bothersome score. This was calculated by comparing the earliest report to month 6 reports. If a previously reported side effect was not reported in month 6, it was considered better. Patients missing an early or a month 6 report were not included in these analyses. For headache, n = 44; nausea, n = 27; diarrhea, n = 41. The right column (b), (d), (f) shows all patient-reported effectiveness of common OTC and prescription medications given to a portion of those patients reporting the side effect. Early therapy was defined as ≤5 months in this analysis and represents the first reported data from the patient during this period. Month 6 is defined as Weeks 22–25.

PRELIMINARY LONG-TERM DATA FROM ADVANCE EXTENSION, A PHASE 3, OPEN-LABEL STUDY EVALUATING RALINEPAG FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

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Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Ralinepag, a potent, titratable, once-daily, oral prostacyclin receptor agonist, is in Phase 3 trials to treat pulmonary arterial hypertension (PAH). The primary goal of ADVANCE EXTENSION (open-label extension [OLE]) is to evaluate long-term safety and tolerability of ralinepag. This is an interim analysis of the long-term effects of ralinepag on 6-minute walk distance (6MWD), risk scores, N-terminal pro-brain natriuretic peptide (NT-proBNP), and World Health Organization (WHO) Functional Class (FC).

Methods: Participants entered the OLE after a clinical worsening event in the blinded, placebo-controlled parent study (ADVANCE OUTCOMES). All participants received ralinepag with an individualized dose-titration period in the OLE. On-site clinical assessments occurred until discontinuation.

Results: At the time of interim data analysis, 106 participants had transitioned to the OLE. Participants were a mean age of 50 years, 83% were female, 71% were White, and 75% were WHO FC III at OLE baseline. Median treatment duration was 49.6 weeks in the OLE with a median dose of 300 mcg at week 28. Mean 6MWD increased from OLE baseline at weeks 4, 16, 28, and 52 by 42, 58, 64, and 65 m, respectively (Figure 1). WHO FC improved in 32% and 43% of participants and French noninvasive risk scores improved in 42% and 39% from OLE baseline to weeks 28 and 52, respectively. Median NT-proBNP decreased by −45.0 and −59.0 pg/mL at weeks 28 and 52, respectively.

Adverse events (AEs) were consistent with the safety profile of prostacyclin therapies, with headache (69.5%), diarrhea (45.7%), and nausea (33.3%) reported most. Only 4.7% of participants discontinued the study due to AEs.

Conclusion: Initial ADVANCE EXTENSION data indicate ralinepag is well tolerated and produces durable, clinically meaningful benefits by addressing a key PAH pathway.

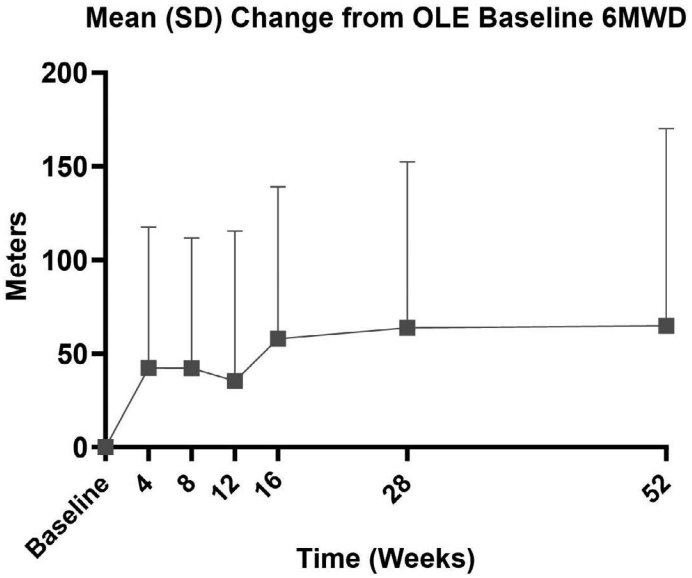

Figure 1: Mean (SD) change from OLE baseline 6MWD.

PRIOR AUTHORIZATION RESTRICTIVENESS NEGATIVELY AFFECTS TIME TO RECEIPT OF ENDOTHELIN RECEPTOR ANTAGONIST THERAPY FOR PULMONARY ARTERIAL HYPERTENSION

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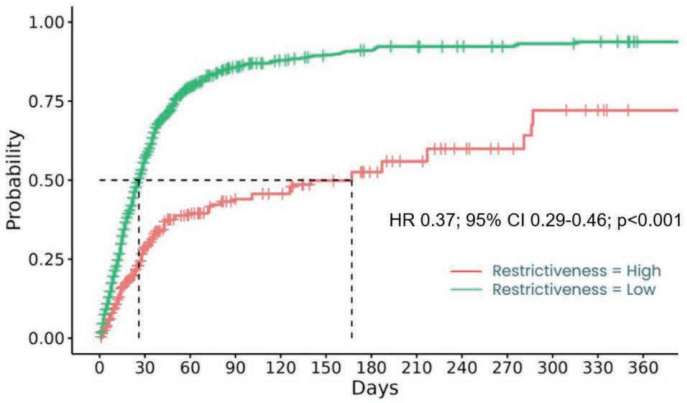
Category: Clinical Science
Subcategory: Real-World Data and Evidence Studies

Background: Health plan coverage is critical for medical care access and for access to medications. Often, access to specialty medications is subject to use management tools including prior authorizations (PAs), which can pose significant challenges for patients and providers. As most pulmonary arterial hypertension (PAH) therapies require a PA, in this study, we examined the effect of PA restrictiveness on time to receipt of endothelin receptor antagonist (ERA) therapy (TTR).
Methods: This retrospective study used Prospection's US open-network claims data (January 2018 to April 2023) and Managed Markets Information Technology Payer and Formulary data. PA restrictiveness was based on formulary requirements beyond the label (e.g., specialty prescriber, step therapy, pulmonary vascular resistance measurement, and/or concomitant PAH-targeted therapy), with low/high restrictiveness defined as 0/≥1 formulary requirement. A weighted Cox regression model was used to estimate the association between PA restrictiveness and TTR, with entropy balancing to account for differences between restrictiveness levels.
Results: Data from 3681 patients with PAH receiving an ERA (macitentan, ambrisentan, or bosentan) were analyzed. Patients in the high restrictiveness cohort (n = 1398) were 63% more likely to have longer TTR versus the low restrictiveness cohort (n = 2283; heart rate [HR] = 0.37; $P < .001$; Figure 1). The median (Q1, Q3) TTR was 26 (13, 50) days in the low versus 167 (28, not reached [NR]) days in the high restrictiveness cohort. The TTR was significantly longer if patients were on Medicaid versus Medicare (HR = 0.21; 95% confidence interval [CI] = 0.07, 0.68; $P = .009$) or had a severe (versus negligible) comorbidity index (HR = 0.79; 95% CI = 0.66, 0.94; $P = .008$). TTR was significantly shorter for patients aged 25–34 versus ≥65 years (HR = 2.58; 95% CI = 1.52, 4.4; $P < .001$) and 55–65 versus ≥65 years (HR = 1.28; 95% CI = 1.09, 1.5; $P = .003$). By specific ERA, the median (Q1, Q3) TTR in the high versus low restrictiveness cohorts was 187 (33, NR) versus 27 (14, 50) days for macitentan, 72 (19, NR) versus 21 (9, 53) days for ambrisentan, and 37 (37, 41) versus 29 (11, 34) days for bosentan.
Conclusion: PA restrictiveness is associated with longer times to receipt of ERA therapy for PAH. This may delay or prevent patients from receiving appropriate ERA treatment, result in treatment abandonment, and may detrimentally affect patient outcomes.



CI, confidence interval; **HR**, hazard ratio; **PAH**, pulmonary arterial hypertension.

Figure 1: Time to receipt of PAH medication by restrictiveness cohort.

PRIOR AUTHORIZATIONS FOR PEDIATRIC PULMONARY HYPERTENSION MEDICATIONS

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Category: Clinical Science
Subcategory: Psychosocial Considerations/Aspects of Care

Background: Pediatric patients with pulmonary hypertension (PH) are treated with expensive PH medications that may not be approved for children. Insurance companies often require prior authorization (PA) to determine coverage. Few publications about the burden of the PA process exist, but it is anecdotally time-consuming and unnecessary. We sought to understand our center's PA burden and eventual outcome, as this may lead to process improvement and clarity for care providers, insurance companies, and families.

Methods: All patients followed by the PH team at Seattle Children's Hospital were queried using Epic, the electronic health record, for PH prescriptions between 2021 and 2023. Specific tools in Epic, such as SlicerDicer and Reports, were used to assist in collecting patient demographics, insurance information, and PA documentation. Each PH medication was counted as 1 prescription per patient per year, even if multiple prescriptions were written in that year. Patient demographics, including PH diagnostic group and insurance type, were collected (Table 1). The number of PAs, denials, and approvals were recorded by year and medication (Tables 2 and 3). If a medication was denied but could be obtained in a different formulation (e.g., tablets versus compound liquid), it was not counted as a final denial.

Results: There were 283 prescriptions and 215 PAs (76% of prescriptions) in 53 patients (Table 2). Each patient had a mean of 1.8 prescriptions per year. By year, the percentage of PAs per prescription was stable, but the percent of initial and final denials increased from 6% to 12% and 2% to 5%, respectively. Thirteen (4%) PAs were for compounding. PAs were least commonly required for prescriptions of Food and Drug Administration (FDA)–approved sildenafil (27%) and bosentan (44%). PAs are required for all (100%) ambrisentan prescriptions, and >1 PA (143%) is often needed for selexipag, due to multiple tablet strengths. Only 6 (3%) final denials occurred: 2 selexipag and 3 ambrisentan were covered by patient assistance programs, and 1 selexipag was ultimately approved after a failed trial of inhaled treprostinil (Table 3).

Conclusion: At our center, PAs are an enormous burden with 76% of all prescriptions requiring PA, yet they could be considered unnecessary, as 97% were finally approved, and all patients were ultimately able to receive the prescribed medication. The initial denial rate may be increasing over time, and insurance companies may be denying medications that are available through pharmaceutical company patient assistance programs. Further work on types of insurance and pharmacies associated with PA is needed.

Table 1. Patient Demographics

	N = 53
Male sex	26 (49%)
Age, y, mean ± SD	11 ± 6.2
Race	
White	32
Asian	6
Black	3
American Indian	1
Alaska Native	2
Other	7
Multiple	2
Ethnicity	
Hispanic	5
Primary insurance	
Medicaid	26
Private	17
Military	3
Kaiser	3
Self-funded	4
Diagnosis	
WHO Group 1	45
WHO Group 3	5
WHO Group 5 (single ventricle)	3

Table 2. Prior Authorizations by Year[a]

Year	Prescriptions (Rx) written	Prior auth (PA), (% of all Rx)	Initial denial (% of all PA)	Final denial (% of all PA)
2021	76	53 (70%)	3 (6%)	1 (2%)
2022	97	79 (81%)	7 (9%)	1 (1%)
2023	109	83 (76%)	10 (12%)	4 (5%)
Total	283	215 (76%)	20 (9%)	6 (3%)

[a]The number of PAs are different in Tables 2 and 3 due to additional PA being required for compounding and not for specific medications.

Table 3. Prior Authorizations by Medication[a]

Medication	Prescriptions (Rx) written	Prior auth (PA), (% of all Rx)	Initial denial (% of all PA)	Final denial (% of all PA)
Amlodipine	10	5 (50%)	1 (10%)	0 (0%)
Sildenafil	48	13 (27%)	1 (8%)	0 (0%)
Tadalafil	89	64 (72%)	4 (6%)	0 (0%)
Bosentan	32	14 (44%)	1 (3%)	0 (0%)
Ambrisentan	27	27 (100%)	3 (11%)	3 (11%)
Macitentan	8	4 (50%)	0 (0%)	0 (0%)
Selexipag	44	57 (130%)	9 (16%)	3 (5%)
Treprostinil	26	13 (50%)	3 (23%)	0 (0%)
Total	283	202 (72%)	22 (11%)	6 (3%)

[a]The number of PAs are different in Tables 2 and 3 due to additional PA being required for compounding and not for specific medications.

PULMONARY HYPERTENSION ASSOCIATION REGISTRY: A STATUS UPDATE AND RESOURCE FOR RESEARCH

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Category: Clinical Science
Subcategory: Databases and Registries

Background: The Pulmonary Hypertension Association Registry (PHAR) is the largest active longitudinal registry of patients diagnosed with World Health Organization (WHO) diagnostic Group 1 pulmonary arterial hypertension or Group 4 chronic thromboembolic pulmonary hypertension. The principal purpose of the PHAR was to measure and improve adherence to published guidelines and quality of care for patients with pulmonary hypertension (PH) and subsequently improve outcomes. To facilitate that aim, the data repository has been leveraged for ongoing research by PHAR investigators.
Methods: Demographic and clinical data were collected from the PHAR data repository as of October 2023. Research proposals were reviewed and assessed by committee. Both abstracts and manuscripts were quantitated with focused areas highlighted.

Table 1. Demographics of PHAR Participants

Description	All (N = 2743)
Sex	
Male	762 (27.8%)
Female	1957 (71.3%)
Missing	24 (0.9%)
Age	
Mean ± SD	54.8 ± 17.0
Median (IQR)	56.9 (43.2, 68.0)
Missing	36 (1.3%)
Race	
Chinese	11 (0.4%)
Filipino	23 (0.8%)
Japanese	4 (0.1%)
Korean	4 (0.1%)
Vietnamese	15 (0.5%)
Other Asian	16 (0.6%)
Black or African American	361 (13.2%)
Native Hawaiian or Pacific Islander	9 (0.3%)
White	2026 (73.9%)
American Indian	26 (0.9%)
Asian Indian	32 (1.2%)
1 race	50 (1.8%)
Unknown, not reported, or missing	165 (6.0%)
Missing	1 (0.0%)
Ethnicity	
Hispanic or Latino	269 (9.8%)
Not Hispanic or Latino	2323 (84.7%)
Unknown or not reported	151 (5.5%)
Missing	0 (0%)
Health insurance	
Private health insurance	1283 (46.8%)
Medicare	1154 (42.1%)
Medicaid	442 (16.1%)
Medi-Gap	104 (3.8%)
SCHIP	30 (1.1%)
Military health care (TRICARE/VA, Champ-VA)	95 (3.5%)
Indian Health Service	12 (0.4%)
State-sponsored health plan	120 (4.4%)
Other government program	147 (5.4%)
Single service plan (eg, dental, vision, prescription)	43 (1.6%)
No coverage	51 (1.9%)
Education	
<18 y old	57 (2.1%)
Did not graduate high school	175 (6.4%)
High school, GED, or vocational education graduate	813 (29.6%)
Some college or university	464 (16.9%)
Graduated from college or university	706 (25.7%)
Professional training beyond ^{4}-y college or university	282 (10.3%)
Missing or do not know	26 (0.9%)

Results: Of 86 accredited PH Care Centers (PHCCs), 71 (82.5%) participated in PHAR. Sixty-nine (80.2%) centers have enrolled at least 1 patient, with over 2700 patients total (Table 1). Most were Caucasian women in their mid-50s; 2.1% were <18 years of age. Most were Group 1 pulmonary arterial hypertension, somewhat evenly split between idiopathic and associated (Figure 1). Most were modified New York Heart Association (NYHA) Functional Class III with average 6-minute walk distance nearly 340 m (Table 2A). Mean pulmonary artery pressure was moderately elevated

Table 2. Baseline Clinical Characteristics of PHAR Participants

	All (N = 2743)
A. Baseline characteristic	
6-min walk distance, m	
Mean ± SD	335 ± 126
Median (25%ile, 75%ile)	340 (245, 420)
Missing	525 (19.1%)
NYHA/WHO Functional Class	
I	208 (7.6%)
II	953 (34.7%)
III	1223 (44.6%)
IV	157 (5.7%)
Missing	202 (7.4%)
B. Hemodynamics	
Right atrial pressure, mmHg	
Mean ± SD	9.8 ± 5.9
Median (IQR)	9 (5, 13)
Missing, No. (%)	191 (7%)
Pressure (mPAP), mmHg	
Mean ± SD	48.5 ± 13.7
Median (IQR)	48 (39, 57)
Missing, No. (%)	122 (4.4%)
Pulmonary artery wedge pressure (PAWP), mmHg	
Mean ± SD	11.0 ± 5.6
Median (IQR)	10 (7, 14)
Missing, No. (%)	235 (8.6%)
Left ventricular end-diastolic pressure (LVEDP), mmHg	
Mean ± SD	11.8 ± 5
Median (IQR)	11 (8, 14)
Missing, No. (%)	2245 (81.8%)
Pulmonary vascular resistance (PVR), Wood units	
Mean ± SD	9.8 ± 5.5
Median (IQR)	8.8 (5.7, 12.5)
Missing, No. (%)	395 (14.4%)
Cardiac output (CO), L/min	
Mean ± SD	4.35 ± 1.49
Median (IQR)	4.1 (3.3, 5.17)
Missing, No. (%)	265 (9.7%)
Cardiac index (CI), L/min/m^2	
Mean ± SD	2.31 ± 0.78
Median (IQR)	2.18 (1.78, 2.7)
Missing, No. (%)	311 (11.3%)

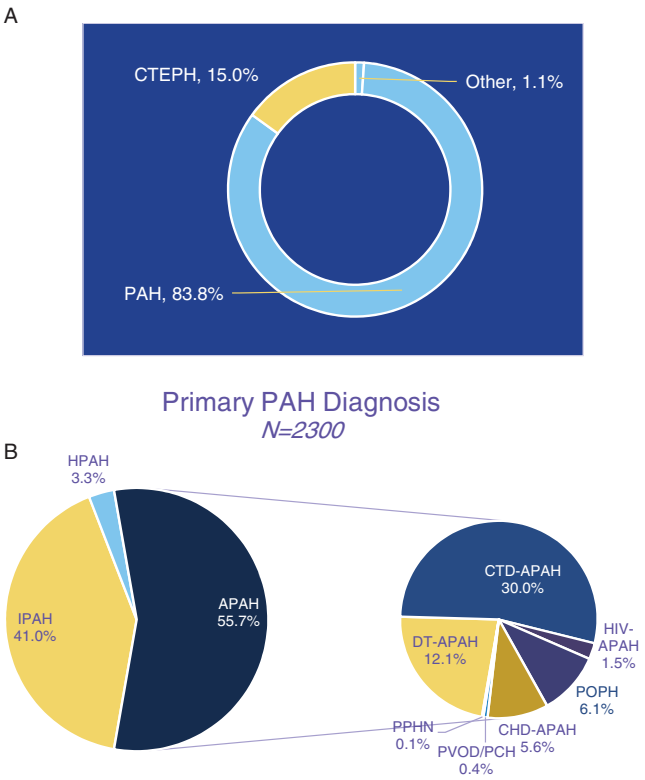

Figure 1: A and B, Diagnostic group and subgroup classification of PHAR participants.

Table 3. Medication Patterns for PHAR Participants

PH-targeted treatment: baseline, Group 1 PAH patients	N = 2331
PH medications now	
None	312 (13.4%)
1	620 (26.6%)
2	1012 (43.4%)
3	376 (16.1%)
≥4	11 (0.5%)
Medications at enrollment (w/in 6 mo)	
Endothelin receptor antagonists (ERA)	1327 (56.9%)
PDE5 inhibitors	1805 (77.4%)
Soluble guanylate cyclase (sGC) stimulators	128 (5.5%)
Prostanoid (inhaled)	157 (6.7%)
Prostanoid (oral)	231 (9.9%)
Prostanoid (parenteral)	569 (24.4%)
Prostanoid (any)	846 (36.3%)

and pulmonary vascular resistance just under 10 Wood units (Table 2B). Most PHAR participants were on combination therapy with the most common agents phosphodiesterase-5 inhibitors and endothelin receptor blockers (Table 3). The average EmPHasis-10 score was 25.09 ± 12.3. Forty-nine proposals for research were submitted and reviewed, resulting in 43 (88%) approvals and 17 manuscripts published to date. There were also 30 abstracts, 6 of which were for 2023 national society meetings. The primary focus of the published manuscripts was distributed as follows: cause-related outcome 6, health care disparities 3, demographics 2, quality of life 2, treatment 2, and hospitalization or mortality 2. Four ancillary studies include 1 completed, 3 in progress potentially including those PHAR participants (88%) who agreed to additional research. Pharmaceutical companies have used PHAR data in support of drug delivery and development.

Conclusion: The PHAR represented a collaborative effort of the majority of PHCCs that enrolled a significant number of patients diagnosed with either Group 1 or Group 4 pulmonary hypertension. The data collected represented demographic and clinical characteristics of those patients along with prospectively collected outcomes. Investigators at PHAR sites submitted multiple proposals for data queries with a broad range of research aims that resulted in several published manuscripts over the last 3 years. Ancillary and industry-related studies offer ongoing opportunities.

PULMONARY HYPERTENSION IS ASSOCIATED WITH MORBIDITY, MORTALITY AND PROLONGED HOSPITALIZATION IN PREMATURE INFANTS WITH BRONCHOPULMONARY DYSPLASIA

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Category: Clinical Science
Subcategory: Pediatrics

Background: Pulmonary hypertension (PH) is a common comorbidity in premature infants with bronchopulmonary dysplasia (BPD). We sought to assess factors associated with PH and determine its association with morbidity and mortality in a large contemporary BPD cohort.

Methods: In this single-center retrospective cohort study, we identified all infants with BPD born 2010–2021. BPD severity was defined by previously established literature guidelines. PH was defined at ≥36 weeks postmenstrual age by echocardiography (right ventricular [RV] pressure > 40 mmHg, eccentricity index > 1.1), cardiac catheterization (mean pulmonary artery pressure > 20 mmHg, pulmonary capillary wedge pressure ≤ 15 mmHg, and pulmonary vascular resistance ≥ 3 iWU), or treatment with enteral pulmonary vasodilators. Outcomes of death, tracheostomy, hospital duration, and comorbidities were compared against a positive PH diagnosis. Univariate and multivariable models were used to assess associations of PH and covariates with clinical outcomes.

Results: The sample cohort consisted of 726 neonates (median gestational age [GA] = 26 weeks [interquartile ratio (IQR), 25.0–28.0], 48.4% female) with PH diagnoses in 190 (26%). Ninety-two PH patients received enteral PH therapy, with 84 (44%) on mono and 8 (5%) on dual therapy, which was discontinued by a median age of 9.5 months (IQR, 6.6–15.3). Lower GA (P = .016), higher BPD severity (P < .0001), and non-White race (P = .002) were associated with PH by multivariable models. PH was associated with higher mortality rate (18% versus 5%, P < .0001), higher tracheostomy rate (50% versus 16%, P < .0001), and longer hospitalization (116 [IQR, 61–182] versus 58 [IQR, 11–132] days, P = .001) in univariate and multivariable models. PH was also associated with pulmonary vein stenosis (9% versus 1%, P = .001) but by multivariable modeling only. Common complications in premature infants including necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), or intraventricular hemorrhage (IVH) were not associated with a PH diagnosis.

Conclusion: In this study, we demonstrate that BPD-PH carries an independent risk for mortality and morbidity including BPD severity, tracheostomy, pulmonary vein stenosis, and longer hospitalization when compared with BPD alone. Enteral pulmonary vasodilators were used in almost half of all PH patients, with resolution of PH within 1 year of diagnosis in most infants.

QUALITY OF LIFE IN PULMONARY ARTERIAL HYPERTENSION PATIENTS RECEIVING AN INHALED DRY-POWDER TREPROSTINIL (LIQ861) IN THE INSPIRE STUDY

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Category: Clinical Science
Subcategory: Quality of Life

Background: Health-related quality of life (HRQoL) is severely impaired in patients with pulmonary arterial hypertension (PAH), with better quality-of-life outcomes reported for patients administered therapies that improve functional outcomes, such as exercise capacity. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is a HRQoL questionnaire widely used by patients with heart failure (HF). The MLHFQ is an instrument used to investigate HRQoL and evaluate patients' daily lives and well-being, which cannot be obtained directly from clinical endpoints. The MLHFQ contains 21 questions to determine how HF affects patients' well-being and other standard physical and social functions. The total score of the MLHFQ comprises scores provided from 2 dimensions, physical and emotional. A clinically meaningful effect is defined as a >5-point reduction in the total score.

Treprostinil is a prostacyclin analog that has been approved for inhaled administration to patients with PAH via nebulized Tyvaso® Inhalation Solution with a target dose range of 54–72 µg via 9–12 breaths, 4 times per day (QID). The time required for nebulizer preparation, dose administration, and cleaning can be burdensome to patients. A more convenient system to deliver this medication directly and deeply to the lungs may offer a meaningful improvement over the current nebulized therapy. Liquidia has developed LIQ861, a dry-powder formulation of treprostinil using PRINT® technology, designed to enhance deep-lung delivery and enable QID delivery of doses in 2 breaths per capsule via a convenient, palm-sized dry-powder inhaler (DPI). PRINT technology produces drug particles that are precise in size, shape, and composition.
Methods: The INSPIRE trial was a Phase 3, open-label, multicenter trial (LTI-301) that enrolled patients with PAH ≥18 years of age who transitioned to LIQ861 from nebulized treprostinil (Transition) or added LIQ861 to ≤2 nonprostacyclin oral therapies, prostacyclin naïve (Naïve). The MLHFQ survey was administered at baseline, 2 months, and 4 months during the trial.
Results: One hundred and twenty-one patients were enrolled in the trial, including 55 in the Transition group and 66 in the Naïve group. Most patients were female, White, and non-Hispanic, with a mean age of 54.2 years. Approximately two-thirds of the patients were New York Heart Association (NYHA) Functional Class (FC) II, the remaining being NYHA FC III. Most patients received background PAH medications, with 71% receiving a combination of endothelin receptor antagonist and phosphodiesterase 5 inhibitor or soluble guanylate cyclase agonists. By month 4 (N = 104), a clinically meaningful improvement was found in the total MLHFQ score for all patients from baseline. Overall, the mean score of 36.0 at baseline decreased to 25.8; at month 4, both physical and emotional dimension scores decreased from 16.2 to 11.8 and 7.8 to 5.2, respectively. Improvements were seen in both the Transition and Naïve patient groups.
Conclusion: Treatment with LIQ861 may help improve HRQoL, which has been shown to be impaired in PAH patients.

REAL-WORLD DISCONTINUATION RATE OF INHALED TREPROSTINIL IN PATIENTS WITH PULMONARY HYPERTENSION IN INTERSTITIAL LUNG DISEASE

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Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: While pulmonary hypertension (PH) therapies can be lifesaving, medication adherence can be challenging.[1] This is especially true for nonenteral delivery routes or therapies that require frequent administration.[2,3] We aimed to analyze a real-world PH-interstitial lung disease (ILD) population's inhaled treprostinil (InTrep) use and discontinuation rates and identify the most common reasons for therapy discontinuation. The lessons learned can be applied to address future therapy starts and could help decrease our discontinuation rates.
Methods: We conducted a retrospective study of patients who received InTrep in the PH program of a large tertiary academic medical center, with an additional focus on those with PH-ILD or concomitant ILD. Patients were included if they had received InTrep between January 2018 and January 2024. The analysis included patient demographics, PH group, ILD characteristics, additional PH therapies, InTrep therapy duration, side effects, and adherence.
Results: We identified 33 patients who received InTrep during the study period. Most were male (56%), with a mean age of 67.6 years. For those with an identified ILD (n = 20), 50% had idiopathic pulmonary fibrosis, and 25% had connective tissue disease (CTD)–associated ILD. Baseline hemodynamics for the entire group revealed the following: median, mean pulmonary artery pressure of 46 mmHg, median thermodilution cardiac output of 3.7 L/min, and median pulmonary vascular resistance of 9.1 Wood units. The mean InTrep therapy duration was 19 months (median 11.5 months). A total of 9 patients discontinued InTrep (27%) after a mean duration of 2.5 months (median 3 months). At least two-thirds of these patients were receiving >6 QID inhalations. The main reason for discontinuation was dyspnea or hypoxia (3/9), cough (2/9), and lack of perceived benefit (2/9).
Conclusion: Our cohort's InTrep discontinuation rate was over 25% after a mean duration of 2.5 months. Most patients who stopped treatment were receiving 6 or more QID inhalations at the time of stoppage. The main reasons for stopping were dyspnea, cough, and lack of perceived benefit. We could not identify baseline factors that predicted future InTrep discontinuation.
Clinical Implications: Given the significant increase in InTrep use due to its benefit in PH-ILD, our real-world discontinuation rate of InTrep is concerning. If similar rates are identified in other PH centers, early identification of patients at risk for discontinuation and specific interventions to improve adherence should be explored.

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REAL-WORLD SAFETY AND EFFICACY OF RIOCIGUAT IN ADULTS WITH PULMONARY ARTERIAL HYPERTENSION: 6-MONTH DATA FROM THE RIOCIGUAT USERS (ROAR) REGISTRY

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Category: Clinical Science
Subcategory: Databases and Registries

Background: The RiOciguAt UseRs (ROAR) Registry (NCT04813926) was designed to obtain real-world data on

riociguat therapy in US adults with pulmonary arterial hypertension (PAH), as such data were lacking.
Methods: This is a prospective, observational cohort study of US adults with PAH who are riociguat naïve or have initiated riociguat in the previous 90 days.
Results: Ninety-four patients (68% female, 62% White, 13% Black, and 23% Hispanic or Latino) had baseline data for analysis. Median (interquartile range) age and PAH duration: 55 (43 – 69) and 0.5 (0.2–1.9) years, respectively. PAH etiologies: idiopathic 53%, connective tissue disease 13%, congenital heart disease 5%, HIV infection 4%, drug or toxin induced 17%, heritable 3%, and other 4%. At enrollment, 40 of 94 patients (43%) were receiving riociguat monotherapy; 32 (34%) first-line, 7 (7%) after transition from phosphodiesterase 5 inhibitors (PDE5i), 1 (1%) after transition from an endothelin receptor antagonist (ERA). Fifty-four (57%) were receiving combination therapy; riociguat was part of initial combination therapy in 20 of those 54. The rest had transitioned from PDE5i (n = 18) or other agents (n = 16). Baseline combinations at enrollment: riociguat/ERA, 26 of 54 patients (48%); riociguat/ERA/prostacyclin analog (PCA), 19 (35%); riociguat/PCA, 9 (17%). Six-month follow-up data were available for 73 patients; 28 (38%) remained on riociguat monotherapy, 43 (59%) continued riociguat combination therapy, 2 (3%) had discontinued riociguat. Of 71 patients on treatment at 6 months, 47 (66%) were receiving riociguat 2.5 mg 3 times daily (tid), 5 (7%) 2 mg tid, 6 (8%) 1.5 mg tid, and 13 (18%) 0.5 or 1 mg tid. Disease parameters and PAH risk status improved at 6 months versus baseline (Table 1). Most common adverse events (AEs) were dizziness (16%), headache (14%), nausea (14%), and dyspnea (11%). Most common serious AEs were chest pain (5%), acute respiratory failure (4%), dyspnea (4%), hypervolemia (4%), and hypoxia (4%).
Conclusion: Riociguat was prescribed as monotherapy and as part of various combinations for PAH; 25 of 94 patients (27%) had transitioned from PDE5i. Preliminary, uncontrolled data between baseline and 6 months suggest modest improvements in functional class, PAH risk scores, right-ventricular function, and 6-minute walk distance. No new safety signals were found.

Table 1. ROAR Registry: Disease Parameters at Baseline and 6 Months[a]

Parameter	Baseline	6 mo
6-min walk distance, m	n = 24	n = 24
Mean ± SD	313 ± 108	335 ± 113
WHO FC, No. (%)	n = 64	n = 64
I	1 (2)	2 (3)
II	22 (34)	30 (47)
III	40 (63)	30 (47)
IV	1 (2)	2 (3)
Right ventricular function, No. (%)[b]	n = 17	n = 17
Normal	6 (35)	7 (41)
Mild dysfunction	4 (24)	5 (29)
Moderate dysfunction	1 (6)	3 (18)
Severe dysfunction	6 (35)	2 (12)
REVEAL Lite 2 risk status, No. (%)	n = 51	n = 51
High	23 (45)	19 (37)
Intermediate	12 (24)	15 (29)
Low	16 (31)	17 (33)
COMPERA 2.0 risk status, No. (%)	n = 13	n = 13
Intermediate-high	7 (54)	5 (38)
Intermediate-low	3 (23)	5 (38)
Low	3 (23)	3 (23)
BNP, pg/mL[c]	n = 41	n = 29
Median (IQR)	105 (41, 218)	58 (28, 152)
NT-proBNP, pg/mL[†]	n = 49	n = 21
Median (IQR)	360 (168, 821)	279 (105, 1014)

BNP, brain natriuretic peptide; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension 2.0; FC, functional class; IQR, interquartile range; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; SD, standard deviation; WHO, World Health Organization.

[a]Table shows data for patients with values at both times. Percentages may not total 100 because of rounding.

[b]Qualitative assessment based on echocardiographic parameters.

[c]Excluding outliers.

RIGHT HEART CATHETERIZATION PRACTICE PATTERNS IN PULMONARY HYPERTENSION DIAGNOSIS IN THE UNITED STATES: A CROSS-SECTIONAL ANALYSIS

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Category: Clinical Science
Subcategory: Diagnosis/Screening and Physiologic Studies

Background: Guidelines support a standardized hemodynamic evaluation of patients with pulmonary hypertension (PH). However, considerable variability exists among PH specialists in the performance of right heart catheterization (RHC) and hemodynamic data interpretation. Therefore, we sought to identify current hemodynamic practice patterns among PH physicians in the US.
Methods: We designed a REDCap semiquantitative online survey for physicians with expertise in diagnosing and treating patients with PH. We surveyed PH physicians in the Pulmonary Hypertension Association (PHA) PH Clinicians and Researchers Network (PHCR). The main inclusion criteria required that the providers identify as physicians caring for PH patients and prescribe pulmonary arterial hypertension (PAH) medications. The survey contained 45 questions addressing the RHC technique, hemodynamic assessment, PH diagnosis, PH provocative maneuvers, and hemodynamic follow-up. See Figures 1–4.
Results: One hundred and forty-five physicians completed the survey. Most are male (68%), are in the 30–60 age range (85%), are pulmonologists (71%), and primarily treat adult PH patients (89%). They are evenly distributed throughout the US regions. Half of the physicians (50%) practice in nonaccredited PHA centers. Most perform RHCs in the cardiac catheterization lab (96%).

Of those who perform the RHCs themselves (46%), approximately two-thirds are pulmonologists, and one-third are cardiologists. When the RHC is performed by someone other than the treating PH physician, up to 26% do not independently review the tracings and rely solely on the final report. Most physicians (86%) measure the pulmonary artery occlusion pressure (PAOP) at end expiration. Up to 73% routinely confirm a wedged catheter location by fluoroscopy, but only 42% routinely check a PAOP O_2 saturation for confirmation. Most respondents (99%) do not measure esophageal pressure in obese patients to adjust the PAOP measurement. The cardiac output (CO) method of choice is either a combination of thermodilution (TD) and estimated Fick (eFICK) (54%), TD alone (18%), or eFICK alone (12%). Most providers (80%) consider pulmonary vascular resistance (PVR) >3 Wood units to be the abnormal cutoff that warrants treatment. When deciding between TD and eFICK, if PVR is elevated by one method and normal by the other, 66% use TD as the tiebreaker, 20% choose eFICK, and 10% do not know which one to trust. When asked which CO-related variable provides the best prognostic information, most (65%) chose the cardiac index, and only 19% of the respondents selected the stroke volume index. Nitric oxide is the vasodilator agent of choice (83%).
Conclusion: In this study, we provide a unique snapshot of RHC practices by PH physicians in the US. Almost half of physicians perform the RHC themselves. Still, up to 26% of those not performing the procedure do not independently

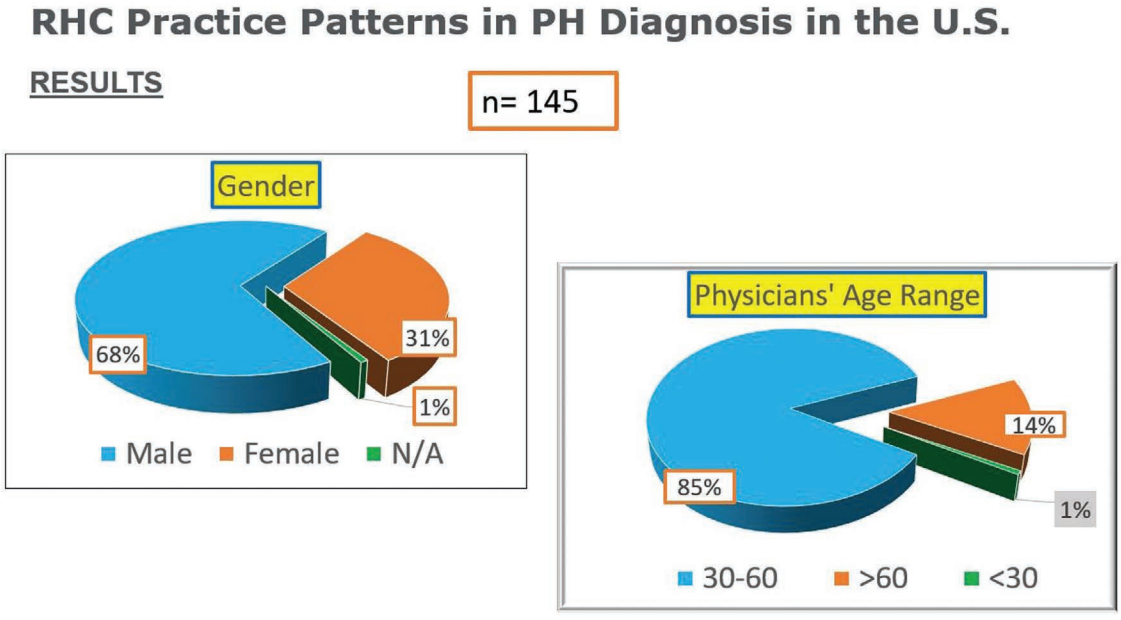

Figure 1: Respondents' demographics.

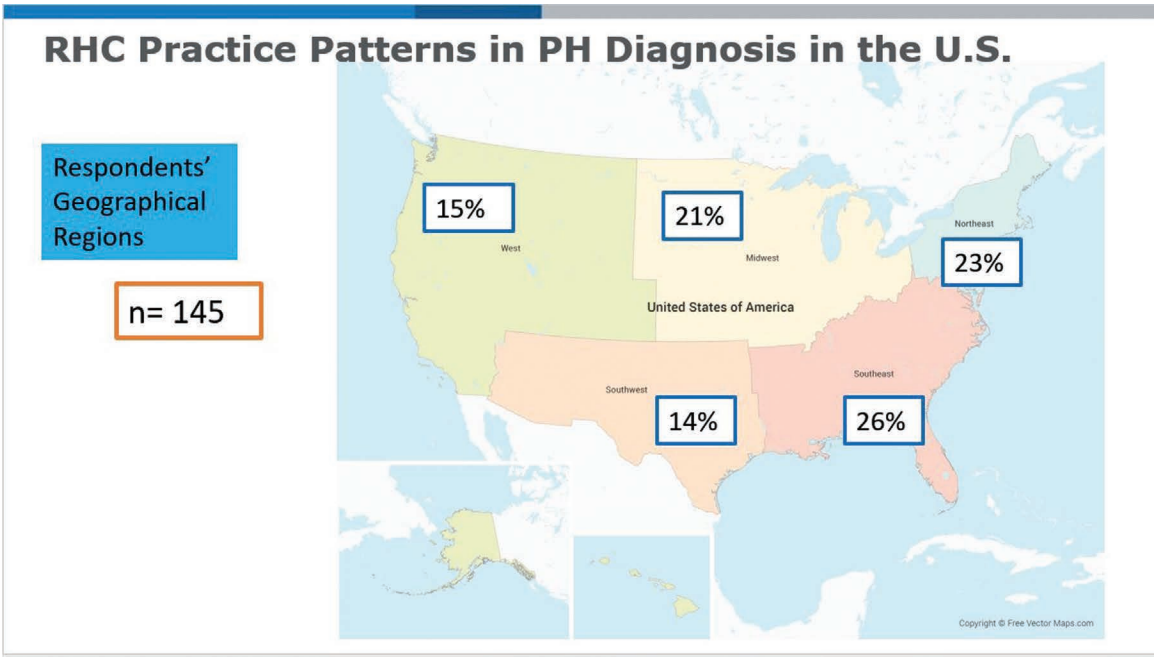

Figure 2: Respondents' geographical distribution.

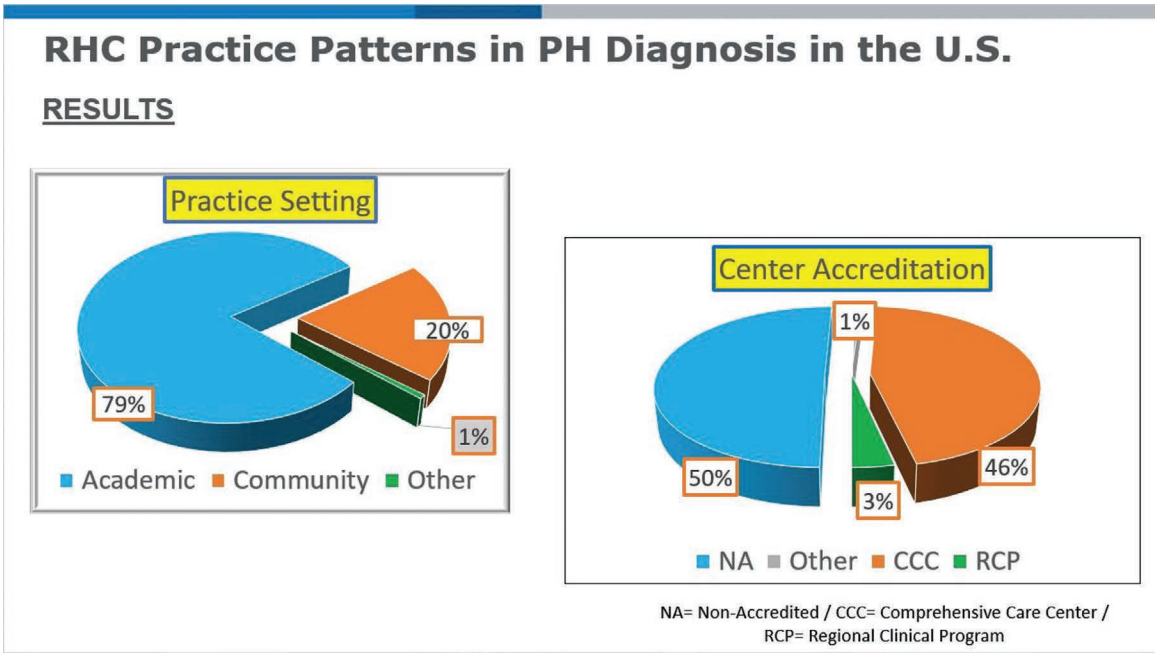

Figure 3: Respondents' practice settings.

review the tracings. In addition, we found significant variability in the measurement and confirmation of the PAOP accuracy, a critical cutoff value to determine PH phenotype and treatment. Recent European Respiratory Society (ERS)/European Society of Cardiology (ESC) guidelines for change in PVR cutoff and optimal CO measurement methods were not consistently followed in this group.

Clinical Implications: Standardization of RHC performance and hemodynamic evaluation is vital for the accurate diagnosis of PH patients. Since major therapeutic decisions in PH are made based on strict hemodynamic cutoffs, achieving a more uniform hemodynamic assessment is a priority to ensure appropriate PH management.

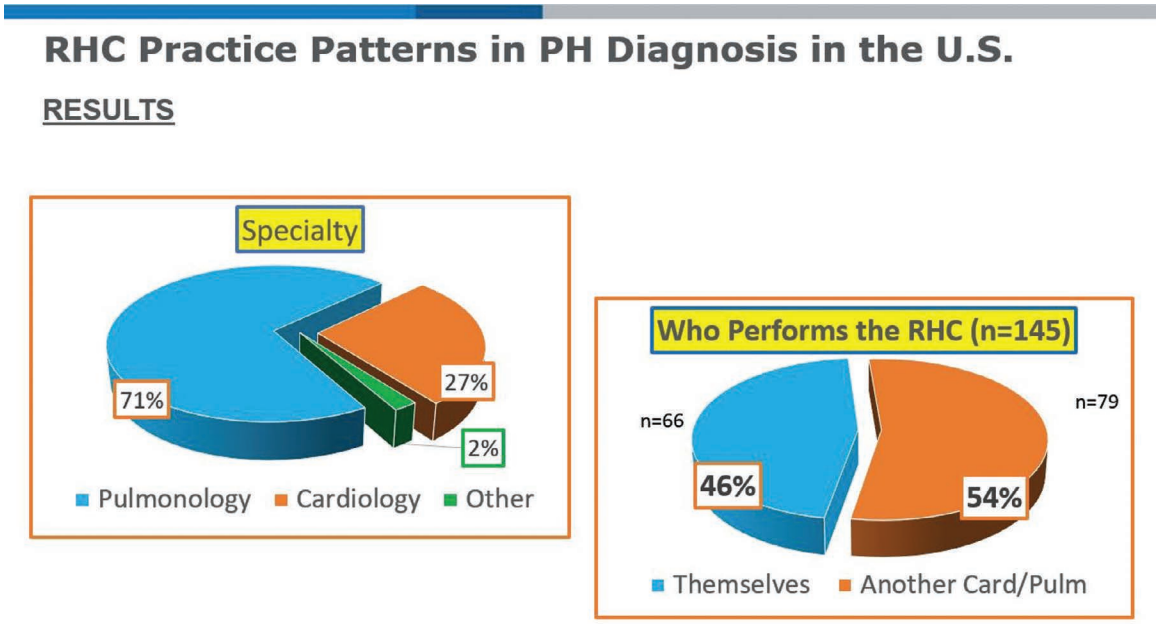

Figure 4: RHC operators and specialties.

RISK ASSESSMENT IN PULMONARY ARTERIAL HYPERTENSION: INSIGHTS FROM THE INSPIRE STUDY WITH LIQ861 (YUTREPIATM)

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Category: Clinical Science
Subcategory: Diseases and Conditions Associated With PH

Background: The objective of this analysis was to assess risk status improvement in pulmonary arterial hypertension (PAH) patients receiving an inhaled dry-powder treprostinil, LIQ861 (Yutrepia™) in the INSPIRE trial.
Methods: INSPIRE was a Phase 3, open-label, multicenter study of World Health Organization (WHO) Group I PAH patients to evaluate the long-term safety and tolerability of LIQ861. Patients with New York Heart Association (NYHA) Functional Class (FC) II or III PAH who were either transitioned to LIQ861 after receiving a stable dose of Tyvaso® for ≥3 months (Transition) or were started on LIQ861 as prostacyclin-naïve (Naïve) patients in addition to background therapy with an ERA and/or phosphodiesterase type 5 inhibitor (PDE5i) or soluble guanylate cyclase (sGC). Transition patients received an initial dose of LIQ861 that was comparable with their Tyvaso dose. Naïve patients initiated LIQ861 at a dose of 26.5 mcg 4 times/day. Dose increments in both groups were 26.5 mcg as tolerated.

Three risk variables (NYHA FC, 6-minute walk distance [6MWD], and N-terminal pro-brain natriuretic peptide [NT-pro BNP]) were measured at baseline and during LIQ861 treatment. The percent of patients who achieved low-risk as defined by the 2019 European Society of Cardiology (ESC)/European Respiratory Society (ERS) low-risk guidelines (NYHA FC: I–II; 6MWD > 440 m; NT-pro BNP < 300ng/L) were assessed at baseline, month 2, month 4, and month 8 in Transition, Naïve, and overall groups.
Results: A total of 121 patients were enrolled (55 Transition; 66 Add-On) in the trial. Overall, 51% of patients met 2 or 3 low-risk variables at baseline. At month 2 (n = 103), month 4 (n = 99), and month 8 (n = 91), 65%, 63%, and 76% of patients met 2 or 3 low-risk variables, respectively. Overall, a larger percentage of patients met 2 or 3 PAH low-risk variables at month 8 than at baseline. The percentage of patients increased from 51% at baseline to 76% overall, and the shift was more pronounced in the Naïve group (from 42% to 73%) than the Transition group (62% to 79%).
Conclusion: In WHO Group 1 PAH patients, LIQ861 was shown to improve risk stratification using the 2019 ESC/ERS low-risk guidelines.

SAFETY AND TOLERABILITY OF LIQ861 (YUTREPIA™ IN PULMONARY ARTERIAL HYPERTENSION: RESULTS FROM THE INSPIRE STUDY

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Category: Clinical Science
Subcategory: Diseases and Conditions Associated With PH

Background: The INSPIRE study assessed the safety and tolerability of LIQ861 (Yutrepia™), an innovative dry-powder treprostinil formulation. Using PRINT® technology, Yutrepia produces uniformly sized and shaped 1-µm particles. This formulation is delivered through a user-friendly, low-resistance dry-powder inhaler, for the treatment pulmonary arterial hypertension (PAH).
Methods: INSPIRE, a Phase 3, open-label, multicenter study, involved World Health Organization (WHO) Group I PAH patients in New York Heart Association (NYHA) Functional Class (FC) II or III. Participants transitioned to Yutrepia after a stable Tyvaso® dose (Transition) or were prostacyclin naïve, adding Yutrepia to up to 2 oral PAH therapies (Naïve). Transition patients' initial Yutrepia dose mirrored their Tyvaso dosage. Naïve patients started with 26.5 mcg 4 times daily, with dose adjustments based on tolerance and symptom relief. The primary goal was to evaluate the long-term safety and tolerability of LIQ861, with an optional extension.
Results: In this study, 121 patients (55 Transition, 66 Add-On) were enrolled, predominantly female (82%) and in FC II (66%). Median exposure was nearly 12 months. Final median LIQ861 dose was 106 mcg. About 79% experienced ≥1 treatment-related adverse event (TEAE), mostly mild (48%) or moderate (28%), with 3% severe. Common TEAEs included cough, headache, throat irritation, and dizziness. Seven percent discontinued due to adverse events. No Transition patient discontinued due to cough, and 2 Naïve patients (3%) discontinued due to cough at 1 year. No deaths occurred.
Conclusion: Except for expected prostanoid-related events, the inhaled delivery of Yutrepia showed no significant adverse safety effects in the INSPIRE trial. Yutrepia, as a treprostinil dry-powder formulation, offers a safe, tolerable option for treating PAH patients.

SCARRED PHOR LIFE: TIP OF THE ICEBERG

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Category: Case Report
Subcategory: Diseases and Conditions Associated With PH

Background: Combined pulmonary fibrosis and emphysema (CPFE) is a complex disease that is poorly recognized and understood. Moderate to severe pulmonary arterial hypertension (PAH) is the most common complication of CPFE. CPFE constituted 25% of patients in the INCREASE trial. This phenotype is associated with poor outcomes. We illustrate a case of an unfortunate patient with scleroderma, CPFE, and severe World Health Organization (WHO) Group I PAH.[1–3]
Methods: This study is a case report. The patient was selected based on his CPFE diagnosis and underwent thorough evaluation, treatment, and follow-up. Patient consent and anonymity were maintained throughout this process.
Results: A 58-year-old White male presented with weight loss, chronic cough, and shortness of breath. Labs showed positive Scl-70 antibodies, indicative of scleroderma. He also demonstrated evidence of heart strain (B-type natriuretic peptide [BNP] > 1600). Spirometry showed mixed ventilatory impairment. High-resolution computed tomography (HRCT) revealed advanced chronic interstitial lung disease (ILD) with usual interstitial pneumonia (UIP) pattern in the lung bases and emphysema changes in the upper zones, indicative of CPFE (Figure 1). Right heart catheterization confirmed severe WHO Group I/Group III PAH (mean right atrial pressure [mRAP] 10, pulmonary artery [PA] pressure 70/25, mean pulmonary artery pressure [mPAP] 40, pulmonary artery wedge pressure [PAWP] 8, cardiac output [CO] 3.44, and pulmonary vascular resistance [PVR] 9.4). Pulmonary therapies can be summarized as follows: home oxygen, mycophenolate, nintedanib, and inhaled treprostinil. Treprostinil and mycophenolate were not well tolerated and eventually stopped. Lung transplantation could not be considered due to chronic active smoking status, social barriers, and patient's expressed wishes. Relentless progression was noted in this patient. Hospice care was initiated 18 months after diagnosis.
Conclusion: CPFE carries a 1-year survival rate of 60% in patients with PAH, with lower median survival time than individuals with idiopathic pulmonary fibrosis alone. Males with smoking history are at highest risk for developing CPFE, and those with connective tissue disease have lower diffusion capacity and higher pulmonary pressures. Pirfenidone is a useful antifibrotic but has not been tested in disease with an emphysema component. Nintedanib demonstrated slower progression of forced vital capacity (FVC) decline, but the effectiveness of this drug is difficult to assess due to counterbalancing effects

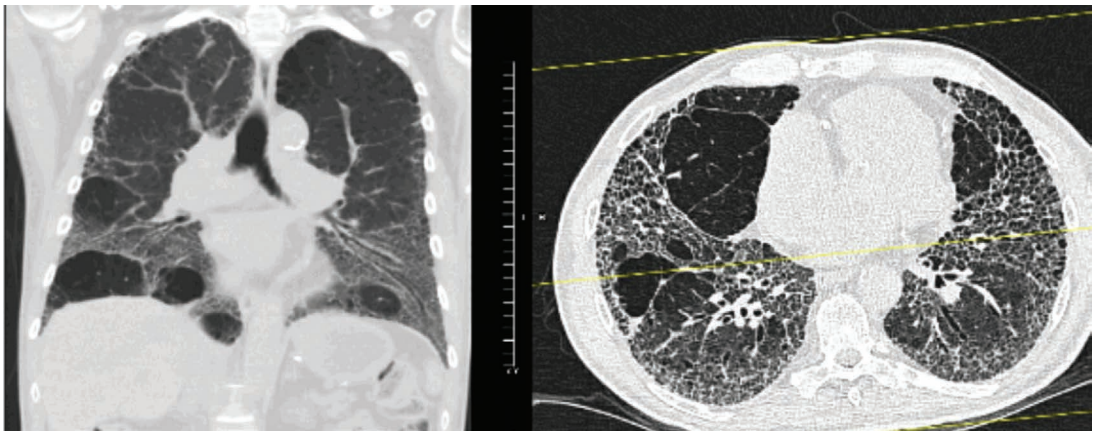

Figure 1: UIP pattern with combined emphysema changes.

of restrictive and obstructive components on spirometry. Common PAH medications have not proven benefit, and some may worsen ventilation/perfusion mismatch. More instances of CPFE must be studied to characterize this disease and identify successful treatment for CPFE complicated by PAH and connective tissue disease. CPFE remains poorly recognized and is associated with poor outcomes. This phenotype can be considered an unmet need and merits more focused attention in future clinical studies.[4–6]

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SINGLE CENTER EXPERIENCE WITH THE USE OF AMBRISENTAN IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE

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Category: Clinical Science
Subcategory: Pediatrics

Background: Approved pharmacotherapy for pediatric pulmonary hypertension (PH) is limited, though off-label use of adult therapies is frequently used. The oral endothelin receptor antagonist bosentan is approved for pulmonary arterial hypertension in patients aged 3 years and older; however, administration is twice daily, and side effects can present as severe. Alternative endothelin receptor antagonists, such as ambrisentan, require less monitoring and are administered once daily. Pharmacokinetic data for ambrisentan in pediatrics exist, though the mean age in that cohort was around 10 years of age. Because of its favorable side effect profile and frequency of administration, ambrisentan is of interest for the neonatal and pediatric population <2 years of age. It has been used in this population at Riley Hospital for Children, and we aimed at characterizing dosing, World Health Organization (WHO) classification, concurrent pharmacotherapy, and side effects.
Methods: We retrospectively reviewed dosing and side effects of ambrisentan in neonates and children <2 years of age with pulmonary hypertension over a 5-year period from 2019 to 2024.
Results: Twenty patients <2 years of age were with a mean gestational age of 37.4 ± 3 weeks were initiated on ambrisentan. The mean age at initiation was 189 days (range, 11–504 days). At initiation, patients had a mean corrected age of 60.8 ± 18.1 weeks. Ninety percent of patients were on

additional targeted pulmonary vasodilatory therapy, including sildenafil (85%), parenteral prostacyclins (20%), and oral prostacyclin agonists (10%). Ten percent of patients experienced side effects. One patient experienced peripheral edema associated with ambrisentan while receiving concurrent sildenafil and selexipag, and 1 patient, also on concurrent sildenafil, had elevated transaminases which resulted in therapy discontinuation. Consistent with existing literature, the mean dose of ambrisentan used was 0.2 mg/kg (range, 0.11–0.67 mg/kg), with 19 out of 20 patients started on 1 mg. All patients received ambrisentan once daily.

Conclusion: Ambrisentan in this population was dosed at weight-based doses and intervals used in older pediatric patients and in a dosing increment that makes administration of a dissolved tablet possible. Our data suggest that ambrisentan is well tolerated at weight-based doses that are similar to what is described in older pediatric patients. Larger analyses, including pharmacokinetic studies, are needed to identify optimal dosing for this unique population.

TBX4 SYNDROME: A PARADIGM OF HERITABLE PULMONARY ARTERIAL HYPERTENSION AFFECTING PEDIATRIC AND ADULT POPULATIONS

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Category: Clinical Science
Subcategory: Diseases and Conditions Associated With PH

Background: Heritable pulmonary arterial hypertension (HPAH) remains a complex and challenging condition affecting both children and adults. Among the myriad genetic factors implicated, TBX4 syndrome has emerged as a distinctive example, with mutations in the TBX4 gene associated with pulmonary hypertension (PH) as well as other complicating features including developmental and interstitial lung disease and skeletal disorders. The broad age spectrum affected by TBX4 syndrome underscores its relevance in both pediatric and adult populations.

Methods: TBX4Life seeks to elucidate the phenotypic and genetic complexities of TBX4 syndrome, emphasizing the role of the TBX4 gene as a causative factor for HPAH and its effect on other abnormal processes including developmental and interstitial lung-spectrum disease processes. Efforts are underway to explore the genetic landscape, clinical manifestations, and the broader implications for affected individuals and their families.

Results: Multiple patients and families affected by TBX4 gene mutations have been identified across the world, many not yet reported, consistent with the variable phenotypic spectrum of TBX4 mutation carriers. Mutations in the TBX4 gene have been identified as significant contributors to pulmonary vascular and developmental lung diseases in particular, portraying TBX4 syndrome as a prototypical genetic disorder within the spectrum of HPAH with additional effects including skeletal irregularities. The effect of mutations in this gene extends beyond the affected individuals, influencing entire families and often spanning multiple generations.

Conclusion: Understanding TBX4 syndrome will provide a unique perspective on the genetic basis of HPAH and lung development while also expanding its relevance in diverse age groups. TBX4Life aims to elucidate the broad implications of TBX4 mutations and variations in related genes while also supporting efforts that target comprehensive care and genetic counseling for affected individuals and their families across generations.

THE ASCENT STUDY: AN OPEN-LABEL PROSPECTIVE MULTICENTER STUDY TO EVALUATE SAFETY AND TOLERABILITY OF DRY-POWDER INHALED TREPROSTINIL IN PULMONARY HYPERTENSION

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Category: Clinical Science
Subcategory: Diseases and Conditions Associated With PH

Background: Study LTI-401 is an open-label, prospective, multicenter study to evaluate the safety and tolerability of a dry-powder inhaled (DPI) treprostinil, LIQ861 (Yutrepia™) in patients who have World Health Organization (WHO) Group 1 and 3 PH.

Yutrepia is a novel, inhaled, dry-powder formulation of treprostinil designed using the proprietary PRINT® technology that enables the development of drug particles that are precise and uniform in size, shape, and composition.

Methods: ASCENT (NCT: NCT06129240): Cohort A will include approximately 60 subjects who have WHO Group 3 pulmonary hypertension associated with interstitial lung disease (PH-ILD). Study visits include screening, baseline, week 8, week 16, week 24, and week 52.

Results: The primary endpoint is safety and tolerability. Exploratory endpoints include dose titration, patient-reported outcomes (EmPHasis10, Dyspnea 12, and simplified cough score), WHO Functional Class (FC), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), 6-minute walk distance (6MWD), cardiac effort, quantitative computed tomography (CT) chest scan with functional respiratory imaging, pulmonary function tests (PFTs), peak inspiratory flow rate, and echocardiogram parameters.

Key inclusion criteria are a baseline 6MWD > 125 m, RHC with mean pulmonary artery pressure (mPAP) > 30, pulmonary vascular resistance (PVR) > 3 with a limited exploratory subset of patients with mPAP > 21 and PVR > 3 and confirmed diagnosis of WHO Group 3 PH-ILD based on CT chest imaging and first second of forced expiration (FEV1)/forced vital capacity (FVC) > 70%.

Conclusion: ASCENT is the first an open-label, prospective, multicenter investigation designed to evaluate the safety and tolerability of DPI administered treprostinil (Yutrepia) in prostacyclin naïve patients with PH-ILD, including combined pulmonary fibrosis and emphysema (CPFE) patients.

THE CLINICAL DEVELOPMENT OF INHALED SERALUTINIB FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

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Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Pulmonary arterial hypertension (PAH) is a multifactorial, progressive disease characterized by pulmonary vascular remodeling and an increase in pulmonary vascular resistance (PVR). Inflammation, proliferation, and fibrosis contribute to the vascular remodeling process. Signaling through several tyrosine kinase pathways (PDGFRα/β, CSF1R, and c-KIT) has been implicated in PAH pathogenesis; therefore, the development of tyrosine kinase inhibitors (TKIs) targeting these pathways has been of interest as a promising therapeutic approach. Orally administered TKIs, while demonstrating efficacy, lacked specificity for target pathways and produced

serious side effects. Seralutinib, a potent, inhaled TKI, was intentionally designed as a treatment for PAH to target these pathways with high specificity. Seralutinib is formulated for delivery by a hand-held, dry-powder inhaler to reach the site of disease and minimize systemic side effects.
Methods: Seralutinib is an investigational compound, evaluated preclinically, in Phase 1 trials in healthy volunteers and patients with PAH, and in a double-blind, placebo-controlled Phase 2 trial in patients with PAH receiving standard of care (SOC) therapy (TORREY; NCT04456998), with a companion open-label extension study, in which all patients received seralutinib (OLE; NCT04816604). Patient enrollment is ongoing for a registrational Phase 3 trial (PROSERA; NCT05934526).
Results: Seralutinib as a new chemical entity was chosen based on its selectivity and potency. Preclinical characterization in biochemical and cell-based assays demonstrated greater potency than imatinib. Authors of studies in 2 animal models replicating features of human PAH demonstrated efficacy as measured by improvements in hemodynamics and histopathology of lung sections. These animal models also demonstrated an increase in lung BMPR2 levels. Characterization of inhaled pharmacokinetics in animals indicated an average seralutinib lung-to-plasma ratio of 30 and a pharmacokinetic profile consistent with limited systemic exposure. Following preclinical characterization, seralutinib was evaluated in the 24-week Phase 2 TORREY trial. The study met its primary endpoint of significant reduction in PVR in the seralutinib group compared with placebo. Authors of the study further demonstrated that seralutinib treatment improved right heart function and blood flow to the smaller lung vessels typically affected by PAH, supporting the idea that seralutinib was inhibiting the previously mentioned kinase pathways to improve the underlying disease process. Inhaled seralutinib was generally well tolerated with a good safety profile. In the longer-term OLE, seralutinib treatment continued to be generally well tolerated and safe. Increasing efficacy was observed in patients receiving seralutinib during TORREY and continued in the ongoing OLE. Patients who switched to active drug in the OLE experienced improvements.
Conclusion: In patients with PAH on SOC medication, authors of studies evaluating inhaled seralutinib in PAH have shown promising effects on the pulmonary vasculature that are suggestive of reverse remodeling, with good tolerability and a favorable safety profile. As a result of these findings, the global pivotal Phase 3 PROSERA study is now enrolling.

TRANSITIONING BETWEEN TREPROSTINIL FORMULATIONS: EVIDENCE AND STRATEGIES

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Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Transitions between treprostinil formulations occur frequently due to patient preference, tolerability, changes in acuity of care, and worsening Functional Class status. Each formulation is associated with advantages and limitations. Remodulin (treprostinil) injection and Tyvaso (treprostinil) inhalation solution require device management that may be cumbersome for patients. The inhaled formulation requires frequent dosing and a patient-specific device. Orenitram (treprostinil) extended-release tablets allow patients to retain their independence; however, the incidence of headache and diarrhea may be dose limiting. At present, no consensus exists for how to perform each transition.
Methods: A literature search was performed to identify studies in which authors have reported transitions between treprostinil products. Products included were Remodulin, Tyvaso, and Orenitram. Tyvaso DPI (treprostinil) inhalation powder was excluded, given the paucity of data. Data collected included type of publication, reason for transition, setting of transition, duration of transition, dosing, rate of titration, and any limitations or adverse events.

Table 1. Number of Publications by Type of Transition

Type of transition	No. prospective analyses	No. retrospective analyses	No. case reports	No. Delphi analyses
Remodulin to Orenitram	3	6	8	
Remodulin to Tyvaso	1	4	5	
Tyvaso to Orenitram	1	5	3	1
Tyvaso to Remodulin		1	1	
Orenitram to Remodulin		1	1	
Orenitram to Tyvaso		1		

Results: In a review of published literature (Table 1), outpatient transitions from parenteral to oral treprostinil occurred in 140 patients over an average of 27 days, resulting in an average total daily dose of 28 mg. Inpatient transition from parenteral to oral treprostinil occurred over an average of 4 days, resulting in an average total daily dose of 22 mg. Most parenteral-to-inhaled treprostinil transitions occurred in the inpatient setting. The average inhaled treprostinil dose following transition from parenteral treprostinil was 9 breaths 4 times daily. Reasons patients transitioned to parenteral treprostinil included clinical deterioration, lack of clinical improvement, pregnancy, changes in acuity of care, and nothing-by-mouth (NPO) status. The most common reason for failed transition was tolerability.
Conclusion: Transitions between treprostinil formulations are frequently performed in clinical practice. Guidance and consensus are needed to ensure successful transitions are performed.

TREPROSTINIL PALMITIL HYDROLYSIS IS FACILITATED BY ENDOGENOUS LUNG ENZYMES

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Category: Basic Science
Subcategory: Therapeutic Strategies

Background: Treprostinil palmitil inhalation powder (TPIP) is a dry-powder formulation in development for the treatment of pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease.[1] Its core pharmaceutical ingredient—the long-acting prodrug treprostinil palmitil (TP)—is composed of treprostinil (TRE) linked to a palmityl group via an ester bond. In the lung, the ester bond is hydrolyzed, and TRE is released slowly over 24 hours leading to prolonged vasodilation and vascular remodeling effects.[2,3] To understand the underlying mechanisms accountable for the slow TRE release, we investigated the involvement of various lung enzymes and the potential limiting factors in the TP hydrolysis reaction.

Methods: TP was incubated with purified, biologically active recombinant human carboxylesterase type 1 (CES1), type 2 (CES2), acetylcholinesterase (AChE), butyrylcholinesterase (BChE), paraoxonase type 2 (PON2), esterase D (ESD), lipoprotein lipase (LPL), monoglyceride lipase (MGL), phosphodiesterase 5 (PDE5), and phospholipid phosphatase 1 (PLPP1). After 24 hours, TRE converted from TP was quantified by liquid chromatography with tandem mass spectrometry (LC-MS/MS).
Results: LPL was the most active enzyme in TP conversion, followed by CES1, CES2, and BChE. Other enzymes—AChE, ESD, PON2, PDE5, MGL, and PLPP1—showed limited activity. In LPL-facilitated TP conversion, excess enzymatic activity was found with respect to the availability of TP for enzyme interaction, which was likely due to the limited availability or accessibility of TP in the aqueous reaction buffer.
Conclusion: LPL is likely the key enzyme in the in vivo conversion of TP to the pharmaceutically active TRE, while several other enzymes may also contribute to this conversion but to a lesser extent. Mechanistically, the availability of TP to enzymes in aqueous environments is likely the rate-limiting step for enzymatic TP conversion. Normal variations among individuals in lung endogenous enzymes may not significantly alter TP conversion rate following TPIP inhalation.

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TRIAL IN PROGRESS: PROSERA, A PHASE 3 STUDY OF THE EFFICACY AND SAFETY OF SERALUTINIB IN ADULTS WITH PULMONARY ARTERIAL HYPERTENSION

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Category: Clinical Science
Subcategory: Therapeutic Strategies

Background: Seralutinib is a highly potent inhibitor of PDGFRα, PDGFRβ, CSF1R, and c-KIT kinase pathways that activate inflammation, proliferation, and fibrosis and drive vascular remodeling in pulmonary arterial hypertension (PAH). Seralutinib is the first tyrosine kinase inhibitor specifically formulated for inhaled delivery to achieve deep lung deposition while minimizing systemic exposure. The Phase 2 TORREY study of seralutinib in patients with World Health Organization (WHO) Group I pulmonary hypertension (PH) receiving standard of care (SOC) therapy met its primary endpoint, demonstrating a statistically significant reduction in pulmonary vascular resistance (PVR) compared with placebo, with favorable tolerability (NCT04456998). Significant improvements in N-terminal pro B-type natriuretic peptide (NT-proBNP) and right heart function by echocardiography were also observed.
Methods: PROSERA is a global Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of inhaled seralutinib in adults with WHO Group 1 PH, Functional Class (FC) II or III, PVR ≥ 400 dyne·s/cm^5, 6-minute walk distance (6MWD) 150–450 m, either REVEAL Lite 2 Risk Score ≥ 5 or NT-proBNP ≥ 300 ng/L, and on stable treatment with up to 3 SOC PAH background therapies, including parenteral prostacyclins (NCT05934526). A total of 350 patients will be enrolled and randomized to receive either seralutinib 90 mg or placebo by dry-powder inhaler twice daily for up to 48 weeks. The primary endpoint is change in 6MWD from baseline to week 24. Key secondary endpoints (measured from baseline) are time to first event of clinical worsening through week 48, proportion of patients achieving clinical improvement (week 24), change in NT-proBNP (week 24), and proportion of patients with ≥1 point decrease in REVEAL Lite 2 risk score (week 24). Other secondary endpoints (measured from baseline) include proportion of patients with each of the clinical worsening outcomes (through week 48), proportion of patients who improve

in WHO FC or maintain WHO FC II (through week 48) and change in health-related quality of life (PAH-SYMPACT, EQ-5D-5L; week 24). Patients who complete the study on blinded treatment may be eligible to enroll in a separate open-label extension study. In a functional respiratory imaging substudy, researchers will examine the effect of seralutinib on pulmonary vascular remodeling.
Results: N/A, trial in progress.
Conclusion: N/A, trial in progress.

TRPV4 CONTRIBUTES TO ANGIOTENSIN II-INDUCED RIGHT VENTRICULAR HYPERCONTRACTILITY IN ISOLATED HEARTS OF TYPE 3 PULMONARY HYPERTENSIVE MICE

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Category: Basic Science
Subcategory: Mechanistic Physiology Studies

Background: TRPV4 is a nonselective cation channel that is upregulated in cardiomyocytes of the left ventricle (LV) in the setting of pressure overload. Angiotensin II has been shown to stimulate TRPV4 activity. Pulmonary hypertensive patients and animal models of pulmonary hypertension (PH) display elevated circulating levels of angiotensin II. The role of TRPV4 in the hypercontractile response in the right ventricle (RV) during PH is currently unknown.
Methods: Both male (m) and female (f) C57BL6 mice were treated with intratracheal saline (Sham) or bleomycin (Bleo; 0.025 units) to induce pulmonary fibrosis and Type 3 PH. On days 21–24 posttreatment, hearts were excised and perfused with an oxygenated Krebs-Henseleit buffer (KHB) via a modified Langendorf perfusion technique. Hearts from the 2 groups of mice were perfused with KHB containing either the TRPV4 antagonist HC-067047 (HC; 1 μM) or vehicle control (DMSO; 1.0 × 10-4%) creating 4 separate groups: Sham-DMSO (n = 5; 4m, 1f), Sham-HC (n = 4; 4m), Bleo-DMSO (n = 7; 4m, 3f), and Bleo-HC (n = 7; 4m, 3f). A pressure catheter was inserted into the RV to monitor pressure development. Each heart was equilibrated for a 30-minute baseline period in its respective perfusate, then administered angiotensin II (10 nM) for a subsequent 30-minute interval. See Figure 1.
Results: Fulton index (RV/LV+Septum ratio) was enhanced ($P < .01$, *t*-test) in hearts of Bleo-treated mice (0.25 ± 0.01) versus hearts of all Sham-treated mice (0.18 ± 0.01), consistent with the development of PH with Bleo treatment. RV pressure development (Pdev) was significantly greater in hearts of pulmonary hypertensive mice during baseline conditions than hearts of saline-treated mice (Bleo-DMSO: 19.3 ± 3.0 mmHg, Bleo-HC: 15.6 ± 1.6 mmHg versus Sham-DMSO: 10.1 ± 1.0 mmHg, Sham-HC: 9.8 ± 0.9 mmHg; main effect $P < .001$, 2-way analysis of variance [ANOVA]). After angiotensin II treatment, Bleo-DMSO hearts exhibited greater

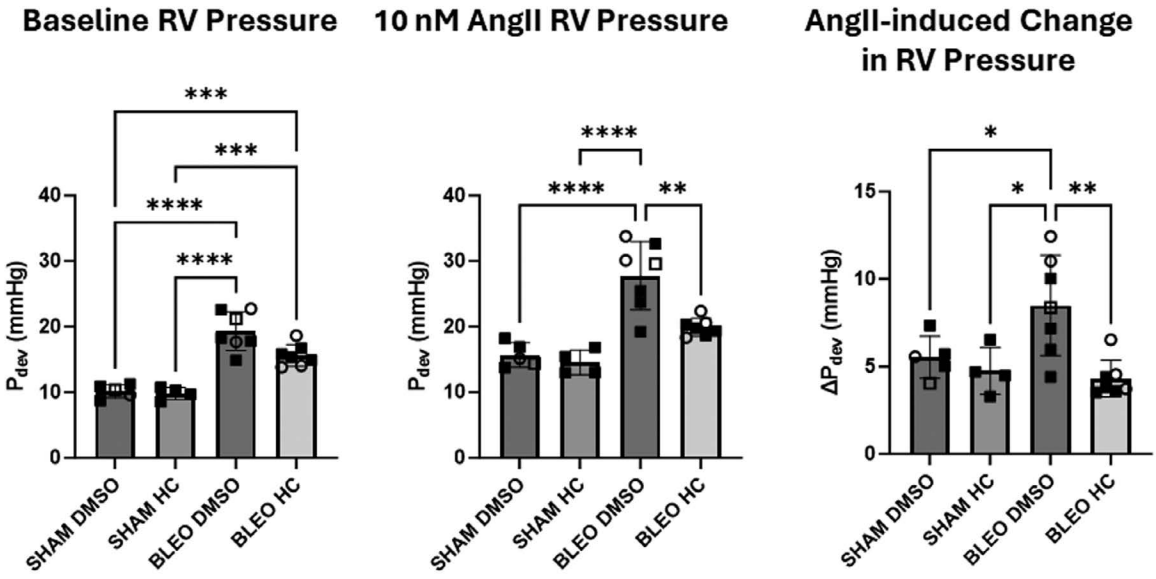

Figure 1: RV pressure development under baseline, angiotensin II perfusion, and change in pressure development.

Pdev than all other groups (Bleo-DMSO: 27.8 ± 5.2 mmHg versus Bleo-HC:19.9 ± 1.4 mmHg, Sham-DMSO: 15.7 ± 1.9 mmHg, Sham-HC: 14.6 ± 1.9 mmHg; interaction $P < .05$, 2-way ANOVA, Bonferroni post hoc test). Furthermore, angiotensin II–dependent increases in Pdev were larger in Bleo-DMSO hearts than all other groups (Bleo-DMSO: 8.5 ± 2.8 mmHg versus Bleo-HC: 4.3 ± 1.1 mmHg, Sham-DMSO: 5.5 ± 1.2 mmHg, Sham-HC: 4.8 ± 1.3 mmHg, interaction $P < .05$, 2-way ANOVA, Bonferroni post hoc test).
Conclusion: In this study, we identify TRPV4 channel activity as a novel mechanism of RV hypercontractility in PH and may be targeted therapeutically.

UNDER PRESSURE: A CASE OF PROGRESSIVE PERICARDIAL EFFUSION IN A PULMONARY HYPERTENSION PATIENT

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Category: Case Report
Subcategory: Diseases and Conditions Associated With PH

Background: Pericardial effusions in patients with pulmonary arterial hypertension (PAH) are associated with a high risk of early mortality, and the reason behind this is unknown. Currently, no guidelines are in place regarding treatment of pericardial effusion in PAH patients.
Methods: A 68-year-old female with a medical history of connective tissue disease and World Health Organization (WHO) Group I PAH presented to the hospital with progressive dyspnea with exertion. She had a known pericardial effusion that had been increasing based on serial echocardiograms. Her medication regimen for PAH included macitentan, riociguat, and selexipag. The patient was hemodynamically stable. The patient's echocardiogram on admission showed a large circumferential pericardial effusion with mild swinging motion of the heart. Although no echocardiographic evidence showed tamponade, impending tamponade was a concern. She underwent pericardiocentesis, and 1 L of fluid was removed. A drain remained in place during admission and approximately 2 L in total of fluid were removed with resolution of effusion on echocardiogram. The patient reported improvement in dyspnea, and she was discharged home. Fluid was sent for analysis, but no definitive cause for effusion was identified. Within 3 weeks, the large pericardial effusion reaccumulated. She was rehospitalized for a pericardial window with removal of 1.5 L of fluid. The patient was discharged home and has since been doing well.

This patient was diagnosed with PAH by right heart catheterization (RHC) with a mean pulmonary artery pressure (PAP) of 60 mm Hg and pulmonary vascular resistance of 17 Woods units. She was initiated on pulmonary arterial vasodilators with continued follow-up in the outpatient setting. Echocardiogram before initial RHC showed a small pericardial effusion, and follow-up echocardiogram 8 months later showed a medium to large circumferential effusion with normal right ventricular function. RHC was performed the day of pericardiocentesis that showed a reduction in the mean PAP at 50 mmHg and an improvement in cardiac output compared with diagnostic RHC.
Results: Patients with PAH can have reduced right ventricular function and elevated estimated right atrial pressure on echocardiography which over time can result in pericardial effusion. Furthermore, pericardial effusion in patients with PAH has been associated with connective tissue disease, which could potentially be the cause in this patient's case. The presence of pericardial effusion in patients with PAH is associated with a high risk of early mortality, but no correlation between the size of effusion and mortality has been found. Tamponade physiology develops in large pericardial effusions due to elevated intrapericardial pressure causing diastolic collapse of the ventricles and atria. This classic presentation can be masked in PAH patients due to their elevated right heart pressures at baseline. The patient in this case showed concern for impending tamponade but did not develop tamponade physiology possibly due to her continued elevated right heart pressures. The patient had improved right heart pressures after initiation of PAH treatment, but oddly, the pericardial effusion worsened. A degree of improvement in her right heart pressure and function may be the reason why she had a positive outcome after pericardiocentesis and pericardial window.
Conclusion: In this case, our patient with worsening pericardial effusion after starting vasodilator treatment for PAH required pericardiocentesis and later a pericardial window. Fortunately, she is doing well after the procedure despite the high morbidity and mortality associated with these procedures in PAH patients. This warrants further investigation to examine the pathophysiology of pericardial effusion in PAH patients as well as the development of guidelines for treatment in PAH patients with effusion.

UNMASKING LEFT VENTRICULAR DIASTOLIC DYSFUNCTION: IMPLICATIONS OF GROUP 1 PULMONARY HYPERTENSION TREATMENT

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Category: Case Report
Subcategory: Diseases and Conditions Associated With PH

Background: The incidence of pulmonary arterial hypertension is rising alongside an increase in targeted pharmaceutical treatment options. Despite their diverse mechanisms of action, these medications collectively decrease right ventricular afterload, potentially unmasking left ventricular diastolic dysfunction because of increased left ventricular filling pressures. Here, we present 2 cases where treatment of pulmonary arterial hypertension unmasked, new onset left ventricular dysfunction.
Methods: Case 1: 67-year-old male with a history of obstructive sleep apnea, chronic obstructive pulmonary disease, hypertension, hyperlipidemia, morbid obesity, and type 2 diabetes who initially presented with progressive dyspnea. He underwent a right heart catheterization that revealed elevated precapillary right-sided filling pressures: right atrium (RA) pressure of 7 mmHg, right ventricle (RV) pressure of 58/5 mmHg, pulmonary artery (PA) pressure of 58/23 mmHg, mean pulmonary artery pressure (mPAP) 37 mmHg, pulmonary capillary wedge pressure (PCWP) 9 mmHg, and pulmonary vascular resistance (PVR) of 6 WU. He was subsequently started on tadalafil 40 mg/daily, ambrisentan 10 mg/daily, and treprostinil for World Health Organization (WHO) Group 1 pulmonary hypertension. His repeat right heart catheterization 1 year later revealed a reduction in his right-sided pressures including a decreased RV pressure from 58/5 to 46/8 mmHg, a decrease in PA pressures from 58/23 to 46/20 mmHg, a decrease in mPAP from 37 to 33 mmHg, and a reduction in PVR from 6 to 2 WU. Interestingly, his transpulmonary gradient decreased from 29 to 14 mmHg with an increase in his PCWP from 9 to 19 mmHg with a normal left ventricular ejection fraction, all indicative of new onset diastolic dysfunction.

Case 2: 72-year-old male history of coronary artery bypass surgery, atrial fibrillation, hypertension, and hyperlipidemia underwent a right heart catheterization in September 2023 that revealed elevated precapillary right-sided filling pressures: RA 9 mmHg, PA pressure 77/22 mmHg, mPAP 40 mmHg, PCWP 12 mmHg, and PVR of 6.4 WU. He was subsequently started on tadalafil and ambrisentan, after which he complained of progressive weight gain and edema despite increasing diuretic doses. He underwent a follow-up right heart catheterization in December 2023 which revealed an improvement in his PVR from 6.4 to 3.7 WU; however, his PCWP increased to 22 mmHg, also indicative of new onset diastolic dysfunction.
Results: These cases are unique in that the treatment of Group 1 pulmonary hypertension unmasked diastolic dysfunction. The hypothesis is that persistent pulmonary arterial hypertension attributed to increased right ventricular afterload, which was seen with elevated precapillary pressures and increased PVR. Multimodal treatment for pulmonary arterial hypertension, involving medications such as phosphodiesterase type 5 inhibitors, endothelin receptor antagonists, and prostacyclin pathway agonists, results in decreased pulmonary arterial pressures and reduced right ventricular afterload. We hypothesize that decreasing pulmonary vascular resistance and RV afterload leads to an increase in RV output and can result in increased LV filling pressures in susceptible individuals with existing risk factors for diastolic dysfunction.
Conclusion: Treatment of long-standing WHO Group 1 pulmonary hypertension can lead to unmasking of diastolic dysfunction. The physiological changes that result in reversal of pulmonary arterial hypertension can lead to reduction in right ventricle afterload, which ultimately can lead to elevated left ventricular filling pressures—a common etiology of diastolic dysfunction. Therefore, these cases highlight the importance of using surveillance echocardiograms in addition to right heart catheterization when monitoring for response in patients treated for pulmonary arterial hypertension, as patients can potentially develop new diastolic heart failure. Further research is needed to understand the specific risk factors of patients more likely to develop diastolic heart failure with treatment of pulmonary arterial hypertension.

THE DEVELOPMENT OF A MULTIDISCIPLINARY PULMONARY HYPERTENSION CLINIC AT A COMMUNITY HEALTH SYSTEM

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Category: Case Report
Subcategory: Multidisciplinary Care/Community Health

Background: Pulmonary hypertension (PH) is a complex disease process which requires the care of multiple specialty providers. The guideline for the evaluation and treatment of PH recommends a comprehensive evaluation for both pulmonary and cardiovascular disease. As the prevalence of PH increases, more patients will require treatment in community-based health systems. Standardization of evaluation and collaboration among specialists in a multidisciplinary PH clinic is imperative for optimal patient care.
Methods: In December 2022, a multidisciplinary work group was created. This work group met monthly to discuss the development and implementation of the PH clinic. The work group included a cardiologist, pulmonologist, PH nurse navigator, practice administrators, clinical nurse manager, business operations manager, and service line advisor. This group focused on workflow for patient referrals and patient scheduling, navigation of the patient visit, optimization of provider and nursing time during the clinic appointment, and individual provider billing.
Results: The first patients were seen in June 2023. For the first 6 months, only new patient referrals were seen in this clinic. Patients were evaluated independently by both a pulmonologist and cardiologist at each clinic visit. Clinic templates were built to optimize patient throughput and provider time including separate time for collaboration. The PH nurse navigator assisted with order entry, scheduled testing and follow-up visit, and gave patient instructions. A pharmacist was available offsite via electronic medical record messaging if needed. Most patients only had an echocardiogram completed at the time of the initial clinic visit. The most common procedures ordered were right heart catheterization, lung imaging, and pulmonary function testing. After the results of right heart catheterization and other testing were reviewed, many patients had an adjustment to their diuretics and/or afterload reduction medication. In addition, about 30% of patients were started on pulmonary vasodilators. In most cases, long-term follow-up with either cardiology or pulmonology was determined to be appropriate based on the etiology of PH. However, in early 2024, complex patients with advanced heart and lung disease returned to the PH clinic for multidisciplinary follow-up. Many clinic days had late cancellations due to patients being hospitalized. This speaks to the complexity and acuity of this patient population.
Conclusion: A comprehensive evaluation for both pulmonary and cardiac disease is recommended by PH guidelines. Seeing patients in a multidisciplinary PH clinic helps to streamline care of these complex patients. In the future, we plan to simplify the referral process and add advanced practice PH providers. Additionally, we will compare our processes and data to determine if differences in patient care and outcomes occur when seen in this multidisciplinary clinic compared with our individual practices.

REGULAR ARTICLE

Rapid Transition From Oral Selexipag to Intravenous Treprostinil in a Patient With Severe Pulmonary Arterial Hypertension

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Purpose: Certain patients may require transition from selexipag to intravenous (IV) treprostinil due to clinical deterioration or worsening pulmonary arterial hypertension. However, consensus on how to transition between these agents is lacking.
Summary: Herein, we report a 44-year-old woman diagnosed with pulmonary arterial hypertension treated with oral triple therapy (sildenafil 40 mg 3 times daily, bosentan 125 mg twice daily, and selexipag 1600 mg twice daily), who required transition from oral selexipag to IV treprostinil due to worsening clinical parameters. Right heart catheterization revealed mean right atrial pressure of 3 mmHg, mean pulmonary artery pressure of 48 mmHg, mean pulmonary capillary wedge pressure of 5 mmHg, pulmonary vascular resistance of 12 WU, and cardiac index (indirect Fick) of 2.12 L/min/m^2. Upon admission to the intensive care unit, selexipag was weaned down over 3 days while IV treprostinil was up-titrated to 35 ng/kg/min. Our patient experienced improvements in echocardiographic parameters as well as clinical symptoms after the transition was completed.
Conclusion: In this case report, we demonstrate the feasibility of faster transition without increasing the risk of adverse effects, if performed in a monitored setting.

INTRODUCTION

Selexipag is an oral selective prostacyclin receptor agonist (IP-receptor) indicated for patients who have World Health Organization (WHO) functional class (FC) II–III pulmonary arterial hypertension (PAH). It has increasingly been used based on its efficacy, favorable adverse effect profile, and availability as an oral formulation.[1] Despite this, conversion to parenteral prostacyclin therapy may be indicated for patients who have rapid progression or high-risk PAH. Published data on transitioning from oral selexipag to parenteral treprostinil are limited, and no formal guideline recommendations exist, despite this conversion being commonly performed at pulmonary hypertension centers. In this case report, we outline the rapid transition from selexipag to intravenous (IV) treprostinil at a specialized pulmonary hypertension center.

CASE REPORT

A 44-year-old woman with WHO Group 1, FC IV idiopathic PAH underwent a planned admission to transition from oral selexipag to IV treprostinil due to worsening parameters on echocardiogram and right heart catheterization (RHC). Her past medical history was significant for renal artery stenosis successfully treated with balloon angioplasty with resolution of her systemic hypertension. The patient was diagnosed with PAH at the age of 32 after she presented with progressive dyspnea on exertion. Through the years, she required treatment escalation of her PAH medications due to declining FC and right ventricular function, with reasonable, short-lived improvement after each escalation. She was also resistant to the idea of IV prostacyclin when it was first recommended, several years after diagnosis, and with disease progression on sildenafil and bosentan. She eventually agreed to oral prostacyclins. At the time of current admission, she was on sildenafil 40 mg 3 times daily, bosentan 125 mg twice daily, and selexipag 1600 mg twice daily. The patient had received selexipag for approximately 5 years.
The triple regimen was generally well tolerated with occasional mild headaches (treated with acetaminophen) and constipation. Other medications included spironolactone 50 mg daily and torsemide 10 mg twice daily. Her 6-minute walk distance (6MWD) on dual therapy before selexipag initiation was 336 m. Her 6MWD on triple therapy and prior to transition was not available. A transthoracic echocardiogram on this regimen identified a D-shaped interventricular septum suggestive of elevated right-sided pressure as well as a moderately dilated right ventricle with moderately reduced function. She did not have a sufficient tricuspid regurgitation jet to estimate right ventricular systolic pressure. Subsequently, she underwent a RHC which showed a mean right atrial pressure of 3 mmHg, mean pulmonary

Key Words—prostacyclin receptor agonist, pulmonary hypertension
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Disclosure: All of the authors declare they have no conflicts of interest to disclose.

Table 1. Hemodynamic Values Before, During, and After Initiation of Intravenous Treprostinil Administration

Day	6MWT (m)	HR (beats/min)	RA mean (mm Hg)	PA (mean), (mm Hg)	PCWP mean (mm Hg)	PVR (WU)	CO (L/min)	CI (FICK), (L/min/m^2)
2 mo prior to treprostinil infusion (on triple therapy)	NA	54	7	89/34 (53)	19	11.97	2.84	1.74
Day 0 (upon admission), prior to initiation of treprostinil infusion	NA	69	3	75/32 (48)	5	12	3.39	2.12
Titration of treprostinil to 10 ng (day 2)	NA	60	3	63/28 (40)	5	8.19	4.27	2.58
Titration of treprostinil to 25 ng (day 3)	NA	69	1	64/32 (42)	5[a]	10.45[b]	3.54	2.19
Titration of treprostinil to 30 ng (day 4)	NA	72	3	54/29 (38)	5[a]	9.5	3.88	2.38
4 months after target dose of 40 ng/kg/min was achieved	549	68	1	52/25 (35)	4	8.05	3.85	2.46

Abbreviations: 6MWT indicates 6-minute walk test; CI, cardiac index; CO, cardiac output; HR, heart rate; NA, not available; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PVT, pulmonary vascular resistance; RA, right atrium.

[a] Unable to obtain PCWP from Swan-Ganz; therefore, estimated from right heart catheterization.

[b] Estimated.

artery pressure of 48 mmHg, mean pulmonary capillary wedge pressure of 5 mmHg, pulmonary vascular resistance (PVR) of 12 WU, and cardiac index (CI, indirect Fick) of 2.12 L/min/m^2 (Table 1). Based on these findings, a decision to undergo transition to IV treprostinil was made. A subcutaneous route of administration was offered. However, the patient refused due to the potential for injection site reactions.

On admission, the patient had a brain natriuretic peptide of 21 pg/mL, with normal liver and kidney chemistries, and a total body weight of 56.7 kg (body mass index = 21.46 kg/m^2). She was hemodynamically stable with an oxygen saturation of 99% on room air. She was admitted to the intensive care unit (ICU), and a Swan-Ganz catheter was placed. Down-titration of selexipag was started by 400 mcg every 12 hours until 400 mcg was reached from her initial dose of 1600 mcg (Table 2). Then it was decreased by 200 mcg until completed (on day 3). Concurrently, IV treprostinil was titrated rapidly by 5–7.5 ng/kg/min every 12 hours until 25 ng/kg/min was reached. Subsequently, the rate of titration was lowered to 2.5 mg/kg/min every 12 hours until a final dose of 35 ng/kg/min was reached. Overall, this transition occurred over the course of 3 days and was generally well tolerated except for complaints of minimal headaches and constipation. She did not endorse any muscle pains, flushing, flulike symptoms, symptomatic hypotension, diarrhea, nausea, or vomiting. No significant changes in heart rate or blood pressure were noted during the transition process. She did not require any vasopressor support or fluid administration and was maintained on her home diuretic regimen of spironolactone 50 mg daily and torsemide 10 mg twice daily during the in-patient treatment. Via the Swan-Ganz catheter, a decrease in PVR was seen from 12 to 10.5 WU over these initial 3 days. The remainder of the hospital stay was insignificant, and the patient was discharged home on day 8 after teaching and logistics of home therapy were in place. Treprostinil was up-titrated as an outpatient over several weeks to reach a target dose of 40 ng/kg/min (see details in discussion). Her functional capacity continued to improve, and she continued to work full time. A follow-up RHC at 4 months after achieving the target dose of 40 ng/kg/min showed continued improvement in her hemodynamics, as demonstrated in Table 1. Notable findings include an overall decrease in PVR from 12 to 8.05 WU as well as an increase in CI (via indirect Fick) from 2.12 to 2.46 L/min/m^2. Her echocardiogram at 4 months showed resolution of the previously seen D-shaped interventricular septum with an associated improvement of right ventricular function (Figure 1). The REVEAL Lite 2 risk score improved from 7 at baseline to 2 at week 16, representing a shift from intermediate- to low-risk strata.[2]

DISCUSSION

In this case report, we describe the rapid transition from oral selexipag to IV treprostinil therapy due to disease progression despite oral triple regimen. Transition was safely completed over 3 days in an ICU, without the patient experiencing any significant adverse effects. Our patient experienced improvements in echocardiographic parameters as well as clinical symptoms after the transition was completed. WHO FC improved from IV to I, and she reported increased endurance at work. We acknowledge that some of the hemodynamic numbers obtained throughout this process such as PVR were variable, which may be in part due to the limitations of an indirect Fick.

Selexipag is an oral prostacyclin receptor agonist with a nonprostanoid structure approved for patients with PAH who have WHO FC II and III.[1] The starting dose of selexipag is 200 mcg twice daily titrated to a maximum dose of 1600 mcg twice daily.[3] It achieves rapid absorption with maximum plasma concentration achieved within 1–2 hours, bioavailability of 49%, and a terminal half-life of 0.8–2.5 hours.[3] In the landmark GRIPHON

Table 2. Doses of Selexipag and Intravenous Treprostinil, Vital Signs, Side Effects, and BNP Levels During the Transition

Day	Selexipag AM (mcg)	Selexipag PM (mcg)	Treprostinil AM (ng/kg/min)	Treprostinil PM (ng/kg/min)	Blood pressure (MAP range)	Adverse effects	BNP	Titration comments
0	1600	1600	0	0	NA	NA	NA	NA
1	1600	1200	0	5	74–89	None	21	Increase treprostinil by 5 ng/kg/min every 12 h
2	800	400	10	17.5	80–107	None	NA	Increase treprostinil by 7.5 ng/kg/min every 12 h
3	200	NA	25	27.5	70–102	Mild headache and constipation	NA	Increase treprostinil by 2.5 ng/kg/min every 12 h
4	NA	NA	30	32.5	70–101	Constipation	NA	Increase treprostinil by 2.5 ng/kg/min every 12 h
5	NA	NA	35	35	87–102	Mild headache and constipation	<10	NA

Abbreviations: BNP indicates brain natriuretic peptide; MAP, mean arterial pressure; NA, not available.

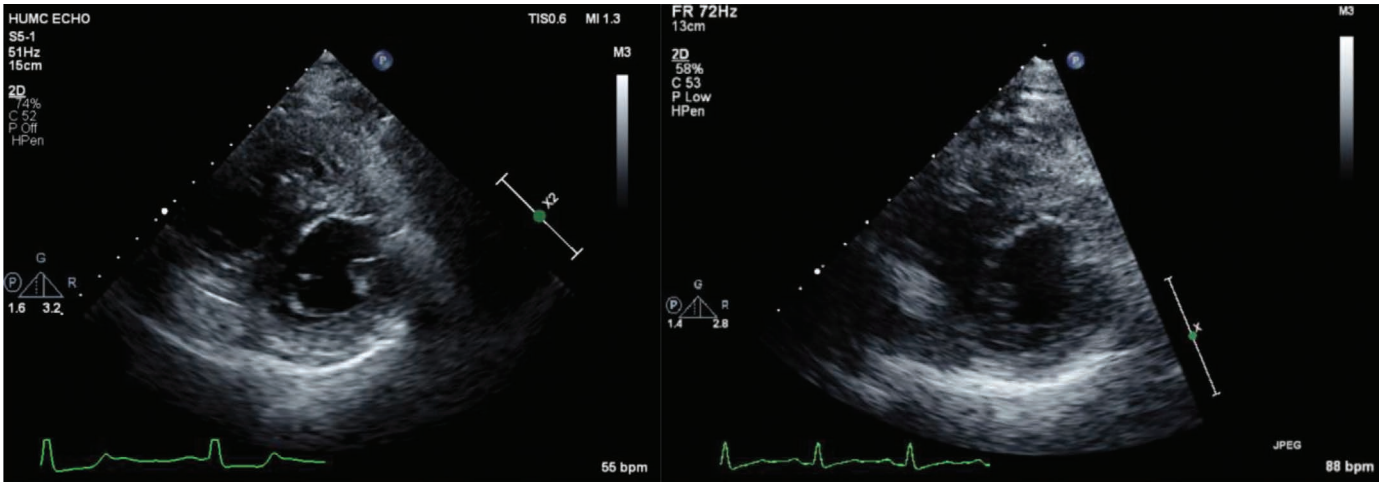

Figure 1: Echocardiogram 2 months prior to the transition and 4 months after intravenous treprostinil administration.

trial, selexipag was associated with a reduction in hospitalization and slower disease progression.[1] A reduction in all-cause mortality was not observed.[1] Treprostinil is a prostacyclin analog with a half-life of 2–4 hours and achieves 100% bioavailability with IV administration.[4] Since they both target the prostacyclin pathway, they share common adverse effects including headache, diarrhea, nausea, flulike symptoms, and flushing. The IV route of treprostinil is also associated with bloodstream infections.[4]

Despite receiving maximum doses of selexipag, our patient demonstrated disease progression requiring transition from oral selexipag to IV treprostinil. We found no standardized dose conversion strategy for transitioning from oral selexipag to IV treprostinil. Several case reports have been published describing transition from selexipag to subcutaneous treprostinil due to patient preference but lack consistent practices.[5,6] Cases of transition to IV treprostinil are limited to 1 report.[7] Since considerably less guidance is available for conversion between selexipag and IV treprostinil, we were challenged with optimal titration rate for achieving a rapid response while minimizing adverse effects. Additionally, it was difficult to extrapolate previous conversion schedules since dose requirements vary between patients, making it difficult to know an individual's target therapeutic dose ahead of time when the predominant reason for transitioning is typically worsening symptoms. We derived our conversion strategy based on a previous study in which authors estimated dose equivalency of selexipag

200 mcg twice daily to subcutaneously treprostinil 5 ng/kg/min.[5] Using this conversion strategy, the corresponding equivalent dose of IV treprostinil dose would be 40 ng/kg/min. In the present case, 40 ng/kg/min dosage of IV treprostinil improved hemodynamics parameters better than the 1600 mcg twice daily dosage of selexipag.[8] Despite its proven efficacy, selexipag has relatively low oral bioavailability at approximately 49%. The patient's favorable response to an equivalent dose of IV treprostinil may be better explained by the consistent drug delivery of the IV formulation, which reduces the fluctuations associated with oral dosing. This practice is in line with previous reports in which authors have suggested that the route of administration may influence treatment efficacy.[5] Low-risk patients seem to tolerate oral agents compared with patients that experience deterioration requiring IV therapy. Another explanation for improved hemodynamics may lie in the dose equivalency that was used in this case. In contrast with the previous article, Furukawa et al[8] have suggested selexipag 1600 mcg twice daily provides vasodilating effects that are roughly equivalent to parenteral treprostinil 20 ng/kg/min. The discrepancy in dose equivalency adds to the confusion on how to safely transition between the 2 agents and highlights the need for additional literature.

The duration over which the transitions are implemented has also varied across studies.[5–12] Most reported conversions occurred over several days to a few weeks, depending on the setting (inpatient versus outpatient). However, in one study, a rapid transition was completed over 30 hours in a patient with mixed-etiology PAH who was receiving therapy with selexipag 1600 mg twice daily and macitentan 10 mg daily.[12] During the rapid escalation of treprostinil, the patient experienced minor adverse effects.[12] Authors of most reports have suggested titrating parenteral treprostinil by 5 ng/kg/min once daily, with corresponding selexipag dose reduction by 200 mcg twice daily.[5,9] We created an individualized, rapid titration approach for our patient after having an extensive discussion among the treating team, including the pulmonary hypertension attending and advanced practice provider, ICU intensivist, pulmonary fellow, and a critical care pharmacist. A discussion on the risk to benefit profile of rapid titration was addressed, including hypotension and other relevant side effects. Thereafter, we derived our titration protocol to involve reducing the dose of selexipag by 400 mcg twice daily, which is double the previously recommended reduction in selexipag dosing. Our patient tolerated it quite well without any major adverse effects. Prior exposure to a prostacyclin therapy likely contributed to both the rapid titration and overall tolerability, as noted in a previous report.[13] Given the variability in response, a one-size-fits-all approach may not be practical; instead, an individualized approach should be attempted based on tolerability, especially in a monitored inpatient setting.

This case report is novel, as it provides a faster transition strategy without complications, allowing for a shortened ICU and hospital length of stay. This is critical in an era when hospital beds are in dire need and rapid turnover of beds is desired. None of the authors of previous reports described this faster rate of titration considering the target dose of treprostinil required in our patient. At our institution, patients requiring de novo prostacyclin therapy or any dose titrations must be cared for in an ICU for monitoring purposes. Additional data are needed to add to the literature regarding the safety of rapid conversion from selexipag to IV treprostinil.

Despite increased use of oral prostanoids, certain patients will require transition to IV prostanoid therapy. Guidance on how to transition between these agents is an unmet need. In this case report, we add to the current literature by providing a faster strategy on transitioning from oral selexipag to IV treprostinil that was well tolerated.

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