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Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

This AJMC® Clinical Brief provides key information regarding a study by Aaron Waxman, MD, PhD, et al; results of this study were originally published in *The New England Journal of Medicine* (doi:10.1056/NEJMoa2008470). This study was funded and developed by United Therapeutics (NCT02630316). Please consult the full publication for complete study information and author affiliations. The authors of the original publication are Aaron Waxman, MD, PhD; Ricardo Restrepo-Jaramillo, MD; Thenappan Thenappan, MD; Ashwin Ravichandran, MD; Peter Engel, MD; Abubakr Bajwa, MD; Roblee Allen, MD; Jeremy Feldman, MD; Rahul Argula, MD; Peter Smith, PharmD; Kristan Rollins, PharmD; Chunqin Deng, MD, PhD; Leigh Peterson, PhD; Heidi Bell, MD; Victor Tapson, MD; and Steven D. Nathan, MD.

PULMONARY HYPERTENSION ASSOCIATED WITH INTERSTITIAL LUNG DISEASE

Pulmonary hypertension (PH), typically defined as a mean pulmonary arterial pressure (mPAP) at rest greater than 25 mm Hg, is a pathophysiological disorder that may involve multiple clinical conditions and can complicate the majority of cardiovascular and respiratory diseases.^{1,2} The World Health Organization (WHO) classifies PH into 5 different groups based on pathological findings, hemodynamic characteristics, and management.³ WHO Group 3 is defined as PH due to chronic lung disease and/or hypoxia; 1 of the disease states in this category is PH associated with interstitial lung disease (PH-ILD). The umbrella term ILD includes a broad, heterogeneous group of parenchymal lung diseases that cause progressive scarring of lung tissue, the most common of which is idiopathic interstitial pneumonia (IIP) inclusive of idiopathic pulmonary fibrosis (IPF).^{1,4}

TYVASO® (treprostinil) Inhalation Solution INDICATION

TYVASO (treprostinil) is a prostacyclin mimetic indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%).

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS

- TYVASO is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, TYVASO may produce symptomatic hypotension.
- TYVASO inhibits platelet aggregation and increases the risk of bleeding.
- Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness.

This clinical brief will provide an overview of the clinical burden and diagnostic challenges of PH-ILD and will highlight the historical lack of safe and effective therapies for patients living with PH-ILD. Additionally, key data from the pivotal INCREASE clinical trial (NCT02630316) will be presented; these results led to TYVASO (treprostinil) inhalation solution becoming the first and only FDA-approved treatment for PH-ILD on April 1, 2021.^{5,6}

Clinical Burden

PH in patients with ILD is associated with substantial clinical burden and poor health care outcomes, such as an increased need for supplemental oxygen, increased risk of acute exacerbations, decreased exercise capacity (based on tests such as the 6-minute walk distance [6MWD]), and worsened prognosis.^{7,8}

A single-center, retrospective analysis by Letteri et al published in *Chest* in 2006 found that PH is common among patients with advanced IPF and negatively impacts their survival.⁷ All the patients included in the study (n=79) had undergone right-sided cardiac catheterization (also referred to as right-heart catheterization [RHC]) and were evaluated for lung transplantation; of these, about 32% (n=25) had PH. During the observation period of June 1998 to December 2004, 60% of patients with PH died compared with 29.9% of those without PH (odds ratio, 2.6; 95% CI, 2.3-3.1; $P=.001$). Furthermore, 1-year mortality rates were higher among patients with PAH than patients without PH (28% vs 5.5%, respectively; $P=.002$).

Diagnostic Challenges

To date, there are no standard methods for PH-ILD screening.⁹ Individually, several PH symptoms and fibrotic lung disease symptoms (eg, increased exertional dyspnea, fatigue, and cough) are nonspecific and frequently overlap.^{9,10} Consequently, PH-ILD is difficult to recognize and diagnose, and the estimated incidence of

PH-ILD varies widely and may be underestimated.⁹⁻¹² The majority of data on the prevalence of PH in patients with ILD are from IPF literature.¹³ PH has been identified in 8% to 15% of patients upon initial diagnosis of IPF and in more than 60% of patients with end-stage disease.¹²⁻¹⁵

Physical examinations lack sensitivity and are usually insufficient to accurately identify PH-ILD.⁹ The clinical manifestations of PH-ILD include lightheadedness, palpitations, lower-extremity edema, and chest pain.^{9,10} By the time these physical symptoms manifest, patients may already be experiencing the advanced stages of disease, during which the mPAP may be greater than 35 mm Hg, or it may be greater than 25 mm Hg with low cardiac index ($< 2.0 \text{ L/min/m}^2$).^{9,10,16,17}

The Proceedings of the 6th World Symposium on Pulmonary Hypertension by Nathan et al that was published in the *European Respiratory Journal* in 2019 included the latest information on detection and diagnosis of PH associated with ILD and other chronic lung diseases. As noted in this article, several noninvasive methods are available to detect the presence of PH in these patients, including screening for circulating biomarkers, pulmonary function testing, echocardiography (echo), and imaging.¹³

Elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP), a biomarker associated with right ventricular (RV) dysfunction, may be indicative of severe PH-ILD; this test, however, has less sensitivity and specificity in patients with moderate PH and could be confounded by left heart abnormalities. Also, PH in patients with ILD or chronic obstructive pulmonary disease (COPD) is generally associated with a reduced lower lung diffusion capacity (DL_{CO}), diminished exercise capacity, and more impaired gas exchange during exercise than would be expected based on ventilatory impairments in PH, ILD, or COPD alone.^{9,13} Echo is considered the best noninvasive modality to screen for chronic lung disease with PH. Among patients with

IMPORTANT SAFETY INFORMATION (Continued)

DRUG INTERACTIONS/SPECIFIC POPULATIONS

- The concomitant use of TYVASO with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension.
- Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor, gemfibrozil, increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer, rifampin, decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8.
- Limited case reports of treprostinil use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. However, pulmonary arterial hypertension is associated with an increased risk of maternal and fetal mortality. There are no data on the presence of treprostinil in human milk, the effects on the breastfed infant, or the effects on milk production.

PH-ILD, however, the ability to determine peak tricuspid regurgitation velocity to estimate the RV systolic pressure is limited in these patients. Potential alternative echo measures include RV outflow tract diameter, tricuspid annular plane systolic excursion, and qualitative assessment of right chamber structure and function. Furthermore, PH in COPD and IPF may also be predicted by calculating the ratio of the main pulmonary artery to ascending aorta diameter on imaging and using a ratio greater than 1 (range, 0.9-1.1) as a threshold. The accuracy of predicting PH-ILD could be improved by combining the pulmonary artery/aorta diameter ratio and other noninvasive measures, including echo and physiological variables.¹³

Ultimately, RHC is considered the “gold standard” for diagnosing PH-ILD. The authors recommend performing a RHC when significant PH is suspected and the patient’s management will likely be influenced by the the results.¹³

PH-ILD Treatment and Management

Aside from lung transplantation for patients with advanced disease, there were no FDA-approved treatment options that existed for PH-ILD prior to the TYVASO indication on April 1, 2021.^{5,6,13} Before this approval, clinicians often prescribed FDA-approved pulmonary vasodilator therapies indicated for WHO Group 1 PH (PAH without ILD) off label in patients with PH-ILD; this was primarily driven by the degree of pulmonary function impairment and RV dysfunction as important factors that influence the use of PAH therapy.¹⁸ The use of pulmonary vasodilator therapies were studied in patients with ILD and PH-ILD. Some studies failed to demonstrate any clear benefit while others were stopped early due to the risk of harm.¹⁹⁻²⁸

TYVASO, a stable analogue of prostacyclin, is indicated for the treatment of PH-ILD to improve exercise ability.³ It is intended for oral inhalation using the TYVASO inhalation system, which consists of an ultrasonic, pulsed delivery device and its accessories. The

major pharmacologic actions of TYVASO are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.^{5,29}

INCREASE TRIAL

As demonstrated from the results of completed pilot studies, patients with WHO Group 3 PH who are treated with TYVASO could experience improved hemodynamics and functional capacity.²⁹ The objective of INCREASE, a 16-week, phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial, was to evaluate the safety and efficacy of TYVASO therapy in patients with PH-ILD.

Study Design

A total of 426 adults were screened for eligibility based upon specific inclusion and exclusion criteria (Table 1).^{29,30} The study enrolled 326 adult patients with a confirmed diagnosis of WHO Group 3 PH based on the results of CT scans performed within 6 months of the trial that showed evidence of diffuse parenchymal lung disease and an RHC performed within 1 year before randomization to confirm WHO Group 3 PH.

Patients were randomized 1:1 to treatment with either TYVASO (n=136) or placebo (n=136).²⁹ The starting dose was 3 breaths taken 4 times daily during waking hours. Dose escalations of 1 breath taken 4 times daily were permitted to occur up to every 3 days, with a target maintenance dose of 9 breaths taken 4 times daily and a maximum of 12 breaths taken 4 times daily, as clinically tolerated.

Efficacy and Safety End Points

The primary end point of the trial was the change in 6MWD measured at peak exposure (between 10 and 60 minutes after most recent dose) from baseline to week 16 between patients treated with TYVASO

IMPORTANT SAFETY INFORMATION (Continued)

DRUG INTERACTIONS/SPECIFIC POPULATIONS (Continued)

- Safety and effectiveness in pediatric patients have not been established.
- Across clinical studies used to establish the effectiveness of TYVASO in patients with pulmonary arterial hypertension (PAH) and PH-ILD, 268 (47.8%) patients aged 65 years and over were enrolled. The treatment effects and safety profile observed in geriatric patients were similar to younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

ADVERSE REACTIONS

Pulmonary Hypertension Associated with ILD (WHO Group 3)

In a 16-week, placebo-controlled study (INCREASE) of 326 patients with PH-ILD (WHO Group 3), adverse events were similar to the experience in studies of PAH. The most common adverse reactions seen with TYVASO in $\geq 4\%$ of PAH patients and more than 3% greater than placebo in the placebo-controlled study (TRIUMPH I) were cough (54% vs 29%), headache (41% vs 23%), throat irritation/pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%). In addition, adverse reactions occurring in $\geq 4\%$ of patients were dizziness and diarrhea.

Table 1. Key Inclusion and Exclusion Criteria for the INCREASE Clinical Trial^{29,30}

Key inclusion criteria	Key exclusion criteria
<p>Patients ≥18 years of age were eligible to enroll if they had:</p> <ul style="list-style-type: none"> • A confirmed diagnosis of WHO Group 3 PH based on CT imaging within 6 months prior to randomization and demonstrated evidence of any form of ILD or CPFE • RHC within 1 year prior to randomization, with the following documented parameters: <ul style="list-style-type: none"> » PVR > 3 WU » PCWP ≤ 15 mm Hg » mPAP ≥ 25 mm Hg • Baseline 6MWD ≥ 100 meters • A stable and optimized dose for ≥ 30 days prior to randomization if on a chronic medication for underlying lung disease (ie, pirfenidone, nintedanib) • Baseline FVC < 70% in patients with connective tissue disease 	<p>Patients were not eligible to enroll if they had:</p> <ul style="list-style-type: none"> • Diagnosis of PAH or PH for reasons other than WHO Group 3 PH-ILD • Use of any PAH-approved therapy within 60 days of randomization • Evidence of clinically significant left-sided heart disease (PCWP > 15 mm Hg and LVEF < 40%) • Use of > 10 L/min oxygen supplementation by any mode of delivery at baseline • Exacerbation of underlying lung disease or active pulmonary or upper respiratory infection within 30 days of randomization • Initiation of pulmonary rehabilitation within 12 weeks prior to randomization • Diagnosis of acute pulmonary embolism within 90 days of randomization

6MWD, 6-minute walk distance; CPFE, combined pulmonary fibrosis and emphysema; CT, computed tomography; FVC, forced vital capacity; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PH-ILD, PH associated with interstitial lung disease; PVR, pulmonary vascular resistance; RHC, right-heart catheterization; WHO, World Health Organization; WU, Wood units.

vs placebo.²⁹ Secondary efficacy end points in order of statistical testing hierarchy were the change in NT-proBNP level from baseline to week 16, the time to first clinical worsening event from time of randomization until study discontinuation, the change in peak 6MWD at week 12, and the change in trough 6MWD at week 15.

Based on the concern that treating WHO Group 3 PH with pulmonary vasodilators could worsen ventilation-perfusion (V/Q) matching in patients, pulmonary function tests and exacerbations were included

as safety end points.^{9,29} An exacerbation was defined as an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality, as determined by the investigator.

Additional safety end points included in the study were abnormal laboratory results, oxygenation as measured by pulse oximetry and supplemental oxygen requirement, and hospitalization for a cardio-pulmonary indication.²⁹

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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Baseline characteristics

Baseline characteristics were similar between the TYVASO and placebo groups.²⁹ The mean patient age was 66.5 years, 46.9% of participants were women, and the most common diagnosis was IIP.

The mean patient 6MWD was 259.6 meters, the mean pulmonary vascular resistance was 6.2 Wood units, and the mean NT-proBNP level was 1832.9 pg/mL.²⁹

Efficacy Results**Change in 6MWD (meters) From Baseline Through Week 16**

In the TYVASO group, patients took a median of 11 breaths from the inhaler (66 µg) at each of the 4 daily sessions at week 12, and 12 breaths (72 µg) per session at week 16. In the placebo group, patients took a median of 12 breaths from the inhaler per session at weeks 12 and 16.²⁹

Efficacy results indicated that patients with PH-ILD who took TYVASO walked farther than patients treated with placebo (Table 2).²⁹ At week 16, a mixed-model repeat-measurement analysis (MMRM) demonstrated that patients who took TYVASO had a placebo-corrected difference in peak 6MWD of 31.12 ± 7.25 meters.²⁹ MMRM uses all available data at all time points and does not require imputation of individual missing data points. The change from baseline to week 15 in trough 6MWD was 21.99 meters greater in the TYVASO group ($P = .004$).

Improvements in 6MWD with TYVASO were observed across a range of patient subgroups, including etiology of PH-ILD, disease severity (measured by baseline 6MWD), age, sex, baseline hemodynamics, and dose group.^{29,30}

Clinical Worsening Events

Overall, incidence of any clinical worsening event was 22.7% for TYVASO and 33.1% for placebo (hazard ratio [HR], 0.61; 95% CI, 0.40–0.92; $P = .04$).^{29,30} Clinical worsening events included hospitalization due to a cardiopulmonary indication (11% TYVASO vs 14.7% placebo),

Table 2. Change in Peak 6MWD in Meters From Baseline Through Week 16^{29,30,a,b}

Week	TYVASO	Placebo
4	2.8	-2.52
8	14.69	-9.45
12	18.77 ^c	-12.52
16	21.08 ^c	-10.04

6MWD, 6-minute walk distance; MMRM, mixed model repeated measurement.

^aThe effect of inhaled TYVASO as compared with placebo on the change in 6MWD was evaluated with the use of an MMRM, with the change from baseline in peak 6MWD as the dependent variable; treatment, week, and treatment-by-week interaction as the fixed effects; baseline 6MWD as the covariate; and subject as the random effect.

^bWeeks 4 and 8 were exploratory end points, week 12 was a secondary end point, and week 16 was the primary end point.

^c $P < .001$.

decrease in 6MWD greater than 15% from baseline (8% TYVASO vs 16% placebo), death—all causes (2.5% TYVASO vs 2.5% placebo), and lung transplantation (1.2% TYVASO vs 0% placebo).²⁹

NT-proBNP

At week 16, compared with baseline, TYVASO therapy resulted in a 15% reduction in NT-proBNP vs a 46% increase in NT-proBNP for placebo ($P < .001$).^{29,30} Elevated levels of BNP and NT-proBNP are biomarkers that indicate RV dysfunction.³¹ The role of NT-proBNP in PH-ILD and the clinical significance of changes associated with therapy are unknown.

Safety Results

TYVASO was well tolerated in the INCREASE trial. The safety population included all patients who underwent randomization and received at

IMPORTANT SAFETY INFORMATION (Continued)**DRUG INTERACTIONS/SPECIFIC POPULATIONS**

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least 1 dose of TYVASO or placebo.²⁹ The most frequently occurring adverse events (AEs) that occurred in greater than 10% of patients in the TYVASO or placebo groups, respectively, were cough (43.6% vs 33.1%), headache (27.6% vs 19.6%), dyspnea (25.2% vs 31.3%), dizziness (18.4% vs 14.1%), nausea (15.3% vs 16.0%), fatigue (14.1% vs 14.1%), diarrhea (13.5% vs 11.7%), throat irritation (12.3% vs 3.7%), and oropharyngeal pain (11% vs 2.5%).^{29,30} Serious AEs occurred in 23.3% of patients who received TYVASO and in 25.8% of those who received placebo.

During the 16-week study, fewer patients in the TYVASO group had exacerbations of underlying lung disease.²⁹ Overall, 43 patients (26.4%) in the TYVASO group experienced an exacerbation of underlying lung disease during the study compared with 63 patients (38.7%) in the placebo group ($P=.02$ by Fisher exact test).

There was no evidence that TYVASO worsened oxygenation, suggesting that it does not contribute to the undesirable effects of V/Q mismatching.^{29,30} Treatment with TYVASO did not show any negative impact on any pulmonary function test variable during the trial, and no significant treatment-related changes in pulse oximetry or supplemental oxygen use in either group were observed over the trial period.

Study Limitations

The investigators noted several study limitations.²⁹ The study was conducted over just 16 weeks. Between the first week and the final week of the trial, 68 enrolled patients (21%) discontinued treatment. The number of early discontinuations was similar in the inhaled TYVASO and placebo groups (40 vs 38 patients, respectively). An independent review committee did not adjudicate events of clinical worsening and exacerbation of underlying lung disease; AEs were reported by investigators.

Another study limitation noted by the investigators was that the size of the favorable treatment effect of TYVASO on 6MWD

that was observed in this study was similar to estimates of the minimum clinically important difference for this test in patients with pulmonary disease reported in studies by Nathan et al and du Bois et al (21.7-37 meters and 24-45 meters, respectively).^{29,32,33}

CONCLUSIONS

In adult patients with PH-ILD enrolled in the INCREASE trial, TYVASO therapy was associated with significant improvement in exercise capacity, lower risk of clinical worsening, reduction of NT-proBNP levels, and fewer exacerbations of underlying lung disease over 16 weeks in comparison with placebo.^{29,30} TYVASO therapy was not associated with negative effects on pulmonary function during the trial or significant treatment-related changes in pulse oximetry or supplemental oxygen use. TYVASO therapy was also not associated with worsened V/Q matching or peripheral oxygen saturation in the INCREASE trial. •

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IMPORTANT SAFETY INFORMATION (Continued)

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- TYVASO is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, TYVASO may produce symptomatic hypotension.
- TYVASO inhibits platelet aggregation and increases the risk of bleeding.
- Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness.

Q&A WITH AARON B. WAXMAN, MD, PHD

Pulmonary hypertension (PH) is a complication that can occur in patients with interstitial lung diseases (ILDs). Based on your experience in clinical practice, can you discuss the potential challenges that clinicians may experience when screening patients for and diagnosing PH in their patients with ILD? What strategies can be implemented to address diagnostic challenges?

One thing [that] we've learned is that [PH] in the setting of [ILDs] is not uncommon. The hard part is that patients present with shortness of breath, which is true for both ILD and PH. When these 2 diseases overlap, shortness of breath can worsen, but it can also worsen as ILD progresses. It requires awareness and consideration of the development of pulmonary vascular remodeling in ILD.

When I'm concerned about progressive shortness of breath in a patient with ILD, I assess for changes that might suggest progression of [ILD], such as a CT scan or pulmonary function testing. Are there changes that might make one think about other causes of worsening shortness of breath, like [PH]? For that, the CT scan is not necessarily helpful, although sometimes you can see enlargement of the right side of the heart. Pulmonary function testing can be helpful, as the diffusing capacity might be worsening out of proportion to the restrictive physiology.

Because of those kinds of changes, or even just the fact that the patient is getting worse, the clinician should consider getting an echocardiogram [echo]. The echo can be helpful as a screening tool, but it can be problematic, because lung disease itself can

make the interpretation of an echo more difficult. Ultimately, a right heart catheterization [RHC] is critical.

However, a lot of people worry that an RHC is difficult and dangerous. It's actually very safe and very easy. If the test is normal, it takes less than 10 minutes in experienced hands. If the test is abnormal, we can really sort out whether it's precapillary [PH]. We can do vasodilator testing, and we can take selective angiographic pictures that provide a lot of information. RHC is an easy way to sort out if the patient has [PH] and [whether] we should treat them with a pulmonary vasodilator.

How does development of PH associated with ILD (PH-ILD) impact a patient's prognosis?

There's no question that it worsens the prognosis both from the standpoint of survival as well as quality of life and exercise tolerance. That's true with pretty much any disease to which you add [PH]; the patients are going to do worse.

What are some of the key clinical and economic considerations regarding the burden of disease and management of patients with PH-ILD?

There are a couple of key things that we see. There's no question that, clinically, these patients do worse. [They have more shortness] of breath, they're functionally more limited, [and] many of them are probably not able to work to the same degree—if at all—than they did before. There [are] also concerns about worsening exacerbations of their underlying lung disease, worsening infectious complications, and worsening of their

IMPORTANT SAFETY INFORMATION (Continued)

DRUG INTERACTIONS/SPECIFIC POPULATIONS

- The concomitant use of TYVASO with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension.
- Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor, gemfibrozil, increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer, rifampin, decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8.
- Limited case reports of treprostinil use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. However, pulmonary arterial hypertension is associated with an increased risk of maternal and fetal mortality. There are no data on the presence of treprostinil in human milk, the effects on the breastfed infant, or the effects on milk production.

quality of life. From an economic standpoint, all of those things would add to the cost of their care. These patients require more medications, more antibiotics, [and] more frequent hospital admissions, and they are more frequently out of work.

How can the implementation of screening recommendations within the clinical workup support the early diagnosis of PH-ILD, and how would this implementation address unmet clinical and economic burdens?

Just thinking about [PH] in the setting of ILD is important—and then [looking] for it, because someone has to specifically do that. Many pulmonologists who see these patients do routine pulmonary function testing. Ideally, they will add a diffusing capacity as a screening tool. They should also consider including echos on an annual basis or as soon as they observe clinical changes in these patients. The sooner [that] we can find the disease, the sooner [that] we can introduce treatment and, ideally, improve a patient's overall condition.

What were the historical challenges that clinicians and patients experienced in the management of PH-ILD?

All physicians want to try to improve their patient's trajectory, and if a patient is short of breath, they want to treat them with something. The easiest thing is to try to use the drugs that are currently available for [pulmonary arterial hypertension] (PAH); most of those are systemic pulmonary vasodilators.

Importantly, the lung is always trying to match ventilation and perfusion to optimize its function. When there is a diseased region of lung, that region attempts to minimize its influence by diverting blood flow to better preserved regions of lung. If a

patient is treated with a systemic vasodilator—which [accounts for] most of the drugs we use right now—that can override the normal response to underlying lung pathology. It can actually make oxygenation worse, because you are now perfusing these regions of diseased lung with greater blood flow. That's not going [to] result in efficient oxygenation; it's really wasted blood flow.

When one looks at the prior clinical trials [that studied the treatment of patients with PH-ILD with pulmonary vasodilators approved for PAH], the results were mixed. It's important to consider the mechanism of action of these drugs, especially systemically administered drugs, and figure out whether or not they actually help patients.

The INCREASE clinical trial was designed to assess the efficacy and safety of TYVASO (treprostinil) inhalation solution in patients with PH-ILD. In this study, 6-minute walk distance (6MWD) was selected as the measure to assess the primary end point for efficacy. What is the clinical significance of this metric?

Well, the [6MWD] test has been the standard for pretty much every clinical trial that's been done since the 1990s. It used to be easy to use a [6MWD] test, because we were testing 1 drug at a time. Now that we have multiple drugs for PAH, that [6MWD] test has become more difficult, because you can only get so much benefit out of any good drug.

The difference with PH-ILD is that we had no drugs that were approved, so we could do a single-agent trial, which allowed us to go back to using a simple test like the [6MWD] to assess the efficacy. The [6MWD] test has a lot of limitations, some of which are the patient's musculoskeletal condition (such as arthritis) or

IMPORTANT SAFETY INFORMATION (Continued)

DRUG INTERACTIONS/SPECIFIC POPULATIONS (Continued)

- Safety and effectiveness in pediatric patients have not been established.
- Across clinical studies used to establish the effectiveness of TYVASO in patients with pulmonary arterial hypertension (PAH) and PH-ILD, 268 (47.8%) patients aged 65 years and over were enrolled. The treatment effects and safety profile observed in geriatric patients were similar to younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

ADVERSE REACTIONS

Pulmonary Hypertension Associated with ILD (WHO Group 3)

In a 16-week, placebo-controlled study (INCREASE) of 326 patients with PH-ILD (WHO Group 3), adverse events were similar to the experience in studies of PAH. The most common adverse reactions seen with TYVASO in $\geq 4\%$ of PAH patients and more than 3% greater than placebo in the placebo-controlled study (TRIUMPH I) were cough (54% vs 29%), headache (41% vs 23%), throat irritation/pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%). In addition, adverse reactions occurring in $\geq 4\%$ of patients were dizziness and diarrhea.

if there are things in the hallway, including various distractions (such as stretchers or other people) that affect the test. But in this case, because no other drugs were approved for PH-ILD, it was applicable and gave us an important, significant readout.

Can you explain why patients treated with treprostinil in the INCREASE trial did not experience worsening peripheral oxygen saturation and why oxygenation seemed to improve in some of the patients who participated in the trial?

When you use an inhaled medication, you're actually optimizing the drug delivery to regions of lung that are well-ventilated and [that] are going to be better perfused.

What were the clinical implications of the findings from the INCREASE study?

The most important clinical implication is that we now have the opportunity to use an effective therapy in patients who have this complex disease. We had nothing before.

Were there any results from the study that you found surprising?

Yes, some of the safety readouts that we planned for the study [were surprising]. I was surprised when we actually saw positive findings, which included a reduction in the number of exacerbations of the underlying lung disease and improvements in certain aspects of patients' pulmonary function testing.

When you use an inhaled medication, you're actually optimizing the drug delivery to regions of lung that are well-ventilated and [that] are going to be better perfused.

What are the most important data from your study that you think managed care professionals should consider, and how can they apply this information in practice?

Inhaled treprostinil has a very clear and positive impact on a patient's exercise tolerance, which should translate into the ability of that patient to continue to contribute [to] and be an active member of society rather than being sick in a hospital or sick at home [and] not doing anything. I think we should aggressively seek these patients out and treat them.

Will there be additional follow-up clinical trials of treprostinil, and, if so, what can you tell us about them?

Yes. As I mentioned, we saw improvement in pulmonary function testing in patients with PH-ILD, which was unexpected. We also saw reductions in underlying disease exacerbations. We are now embarking on a phase 3 clinical trial in patients with [ILD] agnostic of [PH] status to see if patients in that population derive the same benefits. •

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Please see Full Prescribing Information, the TD-100 and TD-300 TYVASO® Inhalation System Instructions for Use manuals, and other additional information at www.tyvaso.com or call 1-877-UNITHER (1-877-864-8437).

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