Best Practices When Referring a Patient With Suspected PH-ILD for Right Heart Catheterization (RHC)

PH-ILD=pulmonary hypertension associated with interstitial lung disease.

Establish your rationale for suspecting PH-ILD and referring the patient for RHC

To build clinical suspicion, include any of the following indicators of PH-ILD that apply to your patient[1-3]:

- **Physical signs and symptoms**
  - Rapid recent deterioration
  - Fatigue
  - Unexplained dyspnea
- **Evidence of PH on CT scan**
  - RV enlargement (eg, RV:LV ratio >1)[4]
  - PA enlargement (eg, PA >32 mm)
  - Flattening of the septum
  - Enlarged pulmonary arteries in the lung periphery
- **PFT results**
  - Low D_{LCO} (≤40% predicted)
  - Disproportionate decline in D_{LCO} vs FVC*
- **Oxygen saturation**
  - Any need for supplemental oxygen
- **Poor results during exercise testing**
  - Marked or worsening desaturation or dyspnea†
  - Severely reduced distance, particularly with stable PFTs†
  - Impaired heart rate recovery†
- **Elevated or increasing levels of BNP or NT-proBNP**

*WSPH recommends using an FVC/D_{LCO} ratio >1.6 as a threshold for suspecting PH in patients with ILD.[1]
†Based on studies using the 6MWT. Impaired heart rate recovery has been identified as a predictor of PH in patients with IPF.[1,2,5]

Describe your patient's Echo results in the complete clinical context

- **Note elevated RVSP and/or any other indicators of PH that were reported in your patient's Echo study[1-3]**
- ***If your patient's Echo study does not clearly establish a high probability of PH:***
  - Note that **Echo is not sensitive enough to rule out PH** and often has inferior performance characteristics in patients with chronic lung diseases due to[1,3,6,7]:
    - Poor acoustic windows
    - Altered location of the heart in the chest cavity
    - Interference from lung tissue overlying the heart
  - Include any **specific limitations** that were indicated for your patient's Echo study

In a cohort of patients who were **clinically suspected** of having PH-ILD (N=265)

40% of those with an Echo showing a low likelihood of PH were confirmed to have PH-ILD by RHC[6‡,§]

‡Clinical suspicion was determined following review of all available relevant information (ie, physical exam, Echo, PFTs, other tests) by an expert PH physician.[6]
§Probability was determined based on modified 2015 ESC/ERS screening recommendations. "Low probability" of PH was defined as TRV ≤2.8 m/s or unmeasurable, with no other Echo signs of PH. PH was defined as mPAP ≥25 mm Hg. Out of 43 patients with low Echo probability of PH, 17 (40%) were confirmed to have PH by RHC.[6]

Explain how the RHC results will impact how you manage your patient‖

- **Indicate that an RHC is needed for your patient to confirm a PH-ILD diagnosis and develop a treatment plan (eg, therapy and/or referral to an expert center)[1-3]**
  - TYVASO and TYVASO DPI are approved for the treatment of PH-ILD to improve exercise ability[8,9]
- ***Request all 3 parameters below in the RHC report. The thresholds listed are required to qualify for treatment coverage by Medicare (and other payers)[10]:***
  - mPAP ≥25 mm Hg (at rest)
  - PAWP ≤15 mm Hg
  - PVR ≥3 WU¶

‖United Therapeutics does not provide medical advice.

¶When calculating PVR, cardiac output should be assessed via thermodilution (mean: ≥3 measurements) or the direct Fick method. Thermodilution should not be used in the presence of shunts. The indirect Fick method is unreliable due to inaccuracies in the estimation of oxygen consumption, particularly in the presence of PH.[3,11]

SELECT IMPORTANT SAFETY INFORMATION FOR TYVASO AND TYVASO DPI:

WARNINGS AND PRECAUTIONS

- May cause symptomatic hypotension in patients with low systemic arterial pressure.
- Inhibits platelet aggregation and increases the risk of bleeding.
- Dosage adjustments may be necessary with changes in CYP2C8 inhibitor or inducer use.
- May cause bronchospasm, particularly in patients with a history of hyperactive airway disease.

The most common adverse reactions observed with TYVASO are cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, syncope, dizziness and diarrhea.

Please see Important Safety Information on back and accompanying Full Prescribing Information and Instructions for Use for TYVASO and TYVASO DPI in pocket.

TYVASO DPI® (treprostinil) INHALATION POWDER

TYVASO® (treprostinil) INHALATION SOLUTION

TYVASO® (treprostinil) Inhalation Solution
TYVASO DPI® (treprostinil) Inhalation Powder

INDICATION

TYVASO (treprostinil) Inhalation Solution and TYVASO DPI (treprostinil) Inhalation Powder are prostacyclin mimetics indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study with TYVASO 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 and TYVASO DPI are pulmonary and systemic vasodilators. In patients with low systemic arterial pressure, either product may produce symptomatic hypotension.
- Both products inhibit platelet aggregation and increase 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.
- Like other inhaled prostaglandins, TYVASO and TYVASO DPI may cause acute bronchospasm. Patients with asthma or chronic obstructive pulmonary disease (COPD), or other bronchial hyperreactivity, are at increased risk for bronchospasm. Ensure that such patients are treated optimally for reactive airway disease prior to and during treatment with TYVASO and TYVASO DPI.

DRUG INTERACTIONS/SPECIFIC POPULATIONS

- The concomitant use of either product 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.
- 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 reactions with TYVASO were similar to the experience in studies of PAH. The most common adverse reactions seen with TYVASO in ≥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 ≥4% of patients were dizziness and diarrhea.

Please see Full Prescribing Information for TYVASO or TYVASO DPI, Instructions for Use manuals for TD-100 and TD-300 TYVASO® Inhalation System and TYVASO DPI® Inhalation Powder, and additional information at www.TYVASOHCP.com or call 1-844-UNITHER (1-844-864-8437).

TYVISIhcpSEP2024(PH-ILD)

6MWT=6-minute walk test; BNP=B-type natriuretic peptide; CT=computed tomography; D_{LCO}= diffusing capacity for carbon monoxide; ERS=European Respiratory Society; ESC=European Society of Cardiology; FVC=forced vital capacity; IPF=idiopathic pulmonary fibrosis; LV=left ventricle; mPAP=mean pulmonary arterial pressure; NT-proBNP=N-terminal pro–B-type natriuretic peptide; PA=pulmonary artery; PAWP=pulmonary artery wedge pressure; PFT=pulmonary function test; PVR=pulmonary vascular resistance; RHC=right heart catheterization; RV=right ventricle; RVSP=right ventricular systolic pressure; TRV=tricuspid regurgitation velocity; WHO=World Health Organization; WSPH=World Symposium on Pulmonary Hypertension; WU=Wood unit.

References: 1. Shlobin OA, et al. *Eur Respir J.* 2024;64(4):2401200. **2.** Rahaghi FF, et al. *Chest.* 2022;162(1):145-155. **3.** Humbert M, et al. *Eur Heart J.* 2022;43(38):3618-3731. **4.** King CS, Shlobin OA. *Chest.* 2020;158(4):1651-1664. **5.** Swigris JJ, et al. *Respirology.* 2011;16(3):439-445. **6.** Keir GJ, et al. *Respirology.* 2018;23(7):687-694. **7.** Fisher MR, et al. *Am J Respir Crit Care Med.* 2009;179(7):615-621. **8.** TYVASO [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2022. **9.** TYVASO DPI [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2024. **10.** Centers for Medicare & Medicaid Services. Medicare Part B Durable Medical Equipment Local Coverage Determination DL33370: Nebulizers. Effective June 5, 2022. **11.** Opotowsky AR, et al. *JAMA Cardiol.* 2017;2(10):1090-1099.

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