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Long-Term Use of Tyvaso DPI (Inhaled Treprostinil) Demonstrates Safety and Tolerability in Patients With Pulmonary Arterial Hypertension

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The long-term outcomes of the BREEZE (NCT03950739) study's optional extension phase (OEP) demonstrated the safety and tolerability of inhaled treprostinil (Tyvaso DPI, United Therapeutics) for patients with pulmonary arterial hypertension (PAH).¹ Bajwa and colleagues presented the results of the OEP as an oral presentation, "Long-Term Outcomes With Tyvaso DPI in Pulmonary Arterial Hypertension: Results From the BREEZE Optional Extension Phase," during the American College of Chest Physicians annual meeting, which took place October 6 to 9, 2024, in Boston, Massachusetts.¹

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Exacerbations in Chronic Obstructive Pulmonary Disease: The Impact of Type 2 Inflammation on Patient Care and Health Care Resource Strain

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A recent retrospective analysis has brought to light the unmet needs of a subset of patients with chronic obstructive pulmonary disease (COPD), specifically, those with type 2 inflammation who continue to experience exacerbations despite receiving maximum inhaled therapy. Data from this study have revealed that these patients have higher rates of COPD-related exacerbations and impose a greater burden on the health care system, underscoring the need for targeted therapies aimed at addressing type 2 inflammation as a potential treatment option.

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Tyvaso DPI (Continued from page 1)

Background, Prevalence, and Significance

PAH is a rare disease characterized by progressive increases in pulmonary vascular resistance (PVR) and right heart dysfunction, ultimately leading to death. PAH is hemodynamically characterized by a mean pulmonary arterial pressure (mPAP) greater than 20 mm Hg, PVR greater than 2 Wood units, and pulmonary arterial wedge pressure (PAWP) less than or equal to 15 mm Hg.² PAH affects 45,000 patients in the US and is more common in patients 60 years and older.³

Prostacyclin medications, including inhaled treprostinil, are a mainstay of PAH treatment.⁴ Treprostinil inhalation solution (nebulized Tyvaso, United Therapeutics) and inhaled treprostinil dry powder are indicated to improve exercise capacity in PAH and pulmonary hypertension associated with interstitial lung disease.^{5,6} Following approval of treprostinil inhalation solution, inhaled treprostinil was developed in the form of a small, disposable, high-resistance, low-effort inhaler.⁶

BREEZE and the BREEZE OEP

The BREEZE clinical trial was an open-label, multicenter clinical trial in which patients with PAH on a stable regimen of treprostinil inhalation solution switched to a corresponding dose of inhaled treprostinil. BREEZE demonstrated the safety and tolerability of transitioning from treprostinil inhalation solution to inhaled treprostinil in patients with PAH over the 3-week treatment phase.⁷

After 3 weeks of using inhaled treprostinil at the assigned corresponding dose, patients could then enroll in the OEP, in which inhaled treprostinil could be titrated at clinician discretion to a maximally tolerated dose. The primary objective of the OEP was to assess safety and tolerability through adverse events (AEs); secondary objectives included assessment of 6-minute walk distance (6MWD), the Preference Questionnaire for Inhaled Treprostinil Devices (PQ-ITD), and the Pulmonary

Arterial Hypertension Symptoms and Impact (PAH-SYMPACT) questionnaire. Inhaled treprostinil was administered 4 times daily, and dosing was reported in micrograms as well as corresponding breaths of treprostinil inhalation solution using the following pharmacokinetics-based formula: breaths = (µg × 9) ÷ 48. The mean and SD were reported for all numerical results.¹

Of the 51 patients who enrolled in BREEZE, 49 completed the 3-week treatment phase and chose to enter the OEP. The mean (SD) age was 56 (13) years and the mean (SD) time since diagnosis was 8.9 (6.6) years. Further, 84% of patients were female, 55% had idiopathic PAH, 29% had connective tissue disease, 84% were on dual background therapy and 16% were on monotherapy. Including the 3-week treatment phase, the mean (SD) time on inhaled treprostinil was 106 (49) weeks and the maximum time on inhaled treprostinil was 201 weeks. The mean (SD) dose at study completion was 72 (28) µg given 4 times daily (equivalent to 14 [5] breaths treprostinil inhalation solution); the highest dose achieved during the OEP was 176 µg given 4 times daily (equivalent to 33 breaths treprostinil inhalation solution). From baseline to week 107 (n = 19), the mean (SD) 6MWD increased from 420 (110) m to 446 (121) m, with a mean change from baseline of +15 m; at week 131 (n = 16), the mean (SD) 6MWD increased to 454 (86) m, with a mean change from baseline of +14 m. At the end-of-study visit, 35 patients with a mean follow-up time of 119 weeks completed the PAH-SYMPACT questionnaire. Disease symptoms and impacts were similar to those while on treprostinil inhalation solution; the change from baseline in scores for cardiopulmonary symptoms, cardiovascular symptoms, physical impacts, and cognitive/emotional impacts were 0.08, 0.01, 0.02, and 0.10, respectively. At the end-of-study visit, 23 patients with a mean follow-up time of 127 weeks completed the PQ-ITD; satisfaction was much improved with inhaled treprostinil compared with treprostinil inhalation solution. In response to the statement,

“Overall, I am satisfied with the device,” 20 patients (87%) reported that they strongly agreed, 2 agreed, and 1 gave a neutral response. Of the 49 patients who enrolled in the OEP, 31 (61%) were still enrolled at formal study closure upon commercial availability of the drug. Reasons for early study discontinuation included: AEs (n=5), disease progression (n=5), investigator relocation (n=2), loss to follow-up (n=2), pregnancy (n=1), cancer (n=1), substance abuse (n=1), and death unrelated to study drug (n=1). During the OEP, AEs were consistent with the treatment phase and with previous studies of inhaled treprostinil in PAH (14% of patients reported cough, 14% headache, 12% dizziness, and 12% dyspnea). There were no serious AEs related to the study drug.¹

Study investigators concluded that in patients with PAH, inhaled treprostinil was safe and well tolerated. The persistent improvement in 6MWD observed in the BREEZE OEP may be attributed to continued dose titration, which has been seen in other studies of inhaled treprostinil, as well as to improved adherence to therapy. The lack of change in PAH symptoms and impact suggested no loss of efficacy compared with treprostinil inhalation solution and the positive changes in patient preference for inhaled treprostinil were expected given its size, portability, and reduced maintenance. This study was limited by the absence of a control group. The study was not designed to show efficacy, but rather to demonstrate comparability to treprostinil inhalation solution, assess safety/tolerability, and evaluate patient preferences and impacts on quality of life.¹

Conclusion

The study results of the BREEZE OEP demonstrated that long-term use of inhaled treprostinil was safe, tolerable, and provided maintenance of clinical stability. Spikes and colleagues also showed that inhaled treprostinil could be continuously titrated and that it was associated with high patient satisfaction.¹ ●

This article was reviewed by United Therapeutics for medical accuracy.

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Exacerbations in COPD (Continued from page 1)

The findings were presented at the CHEST 2024 annual meeting in Boston, Massachusetts, held from October 6 to 9, as a poster, “Exacerbations and Healthcare Resource Utilization in Patients With Chronic Obstructive Pulmonary Disease With Type 2 Inflammation Characterized by an Eosinophilic Phenotype: A US Claims Analysis”.¹

COPD is a heterogeneous and progressive inflammatory lung disease with airway and/or alveolar abnormalities leading to persistent airflow obstruction and respiratory symptoms.^{2,3} Patients with COPD who experience symptoms and acute exacerbations are typically treated with a combination of inhaled therapies: either a long-acting β_2 -agonist (LABA) and a long-acting muscarinic antagonist (LAMA), an inhaled corticosteroid (ICS) and a LABA, or triple therapy (TT), which includes an ICS, a LABA, and a LAMA for patients who do not respond to 2-drug regimens.⁴ However, despite receiving maximum inhaled therapy, some patients continue to experience exacerbations, leading to unfavorable clinical outcomes and negatively impacting

health-related quality of life.³ Type 2 inflammation in COPD, characterized by elevated blood eosinophils, is linked to an increased risk of COPD-related exacerbations.^{1,3} Given the lack of real-world data exploring exacerbations and health care resource utilization (HCRU) among patients with COPD with type 2 inflammation in the US, investigators conducted a retrospective analysis using de-identified data from Optum’s Clinformatics Data Mart Database.

To be included in the analysis, patients had to be 40 years or older as of the index date, have at least 2 COPD diagnosis claims at least 30 days apart between January 2018 and June 2022, be receiving TT, have continuous medical and pharmacy insurance coverage for at least 12 months before and after the index date, and have eligible baseline blood eosinophil counts (BEC). The index date was defined as the date of the last recorded COPD diagnosis claim. Patients with other selected respiratory diseases were excluded. Outcome measures included baseline demographic and clinical characteristics, rates of COPD-related

exacerbations, and COPD-related HCRU and costs during the 12-month post-index follow-up period.¹

A total of 12,834 patients who met the inclusion criteria were identified and stratified into 2 cohorts based on their BEC and frequency of COPD exacerbations at baseline. The “exacerbating patients with type 2 inflammation” group consisted of 1631 patients with a BEC of at least 300 cells/ μ L who had experienced at least 2 moderate or 1 severe COPD exacerbation during the 12-month pre-index period. Moderate exacerbations were defined as an outpatient (OP) or emergency department (ED) visit for COPD and dispensing of systemic corticosteroid and/or guideline-recommended antibiotics, while severe exacerbations were defined as inpatient hospitalizations for COPD. The remaining 11,203 patients formed the *reference* group, as they did not meet the BEC or exacerbation criteria. The mean (SD) ages at index were 72 (12) years in the exacerbating patients with type 2 inflammation group and 72 (11) years in the reference group. Females made up 56.5% and 55.7% of each group, respectively.¹

During the 1-year follow-up period, exacerbating patients with type 2 inflammation experienced a higher annual rate of COPD-related exacerbations, at 1.98 (95% CI, 1.88-2.09), compared with the reference group, at 1.14 (95% CI, 1.11-1.17). This difference was observed for both moderate exacerbations, with rates of 1.76 (95% CI, 1.66-1.86) in the exacerbating patients with type 2 inflammation group vs 1.01 (95% CI, 0.98-1.03) in the reference group, and, for severe exacerbations, with rates of 0.23 (95% CI, 0.19-0.26) vs 0.14 (95% CI, 0.13-0.14), respectively.¹

The rate of COPD-related hospitalizations was higher among exacerbating patients with type 2 inflammation compared with the reference group, at 0.28 (95% CI, 0.24-0.32) vs 0.16 (95% CI, 0.15-0.17). ED visits were also more frequent, at 0.66 (95% CI, 0.58-0.73) vs 0.43 (95% CI, 0.41-0.45), as were OP visits, at 12.13 (95% CI, 11.3-13.0) vs 8.82 (95% CI, 8.57-9.07). Annual health care costs were higher among exacerbating patients with type 2

inflammation across all types of medical visits and overall. The mean annual cost for all COPD-related health care was \$9128 (95% CI, \$8063-\$10,193) for the exacerbating group compared with \$6013 (95% CI, \$5717-\$6310) for the reference group.¹

Potential limitations include the study’s reliance on claims data, which may have introduced coding errors that hindered the identification of eligible patients with COPD, as well as the accurate measurement of COPD-related exacerbations, HCRU, and medical costs.¹

This study demonstrated the substantial unmet needs among patients with COPD and type 2 inflammation characterized by elevated BEC who continue to experience exacerbations despite triple inhaled therapy. These patients experience approximately 2 clinically significant exacerbations per year on average, which is nearly twice as many as patients without type 2 inflammation and significant exacerbations at baseline, and place a heavy strain on health care resources. Investigators concluded that alternative therapies are needed to reduce COPD-related exacerbations and HCRU among US patients with COPD with type 2 inflammation, and targeted therapies against type 2 inflammation have the potential to address these unmet needs.¹ ●

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Comparing Hospitalization Differences in Patients With Pulmonary Hypertension Associated With Interstitial Lung Disease Who Initiated Inhaled Treprostinil Versus Those Who Remained Untreated

BENJAMIN WU, PHARMD, MS; AND KIMBERLY SIMPSON, PHARMD

In a retrospective claims analysis, patients with pulmonary hypertension associated with interstitial lung disease (PH-ILD) who initiated inhaled treprostinil (Tyvaso DPI, United Therapeutics) had fewer all-cause hospitalizations and intensive care unit (ICU)-related hospitalizations compared with patients with PH-ILD who did not initiate treatment. Cassidy and

colleagues presented these findings in an oral presentation, “Real-World Hospitalization Differences in Patients With Pulmonary Hypertension Due to Interstitial Lung Disease Initiating Inhaled Treprostinil Versus Those Who Remain Untreated,” at the American College of Chest Physicians annual meeting, which took place October 6 to 9, 2024, in Boston, Massachusetts.¹

Background, Prevalence, and Significance

PH-ILD is a disease categorized under the broader umbrella of pulmonary hypertension due to chronic lung diseases (group 3 PH).² PH-ILD specifically is pulmonary hypertension associated with interstitial lung disease (ILD); ILD encompasses a heterogeneous group of parenchymal lung diseases that cause progressive scarring of lung tissue. The most common subtypes of ILD include idiopathic interstitial pneumonias, which include idiopathic pulmonary fibrosis (IPF), connective tissue disease-related ILD, and environmental and occupational diseases like chronic hypersensitivity pneumonitis.³

Prevalence estimates of PH-ILD range widely depending on the underlying cause of ILD, disease severity, and diagnostic modality. In patients with IPF, the proportion of cases identified as having IPF range from 8% to 15% at initial diagnosis to more than 86% at time of lung transplant.⁴⁻⁷ Survival is poor in patients with PH-ILD. Data from the COMPERA registry, one of the largest pulmonary hypertension registries worldwide, show a 5-year survival rate of 14% in patients with pulmonary hypertension associated with fibrosing idiopathic interstitial pneumonias.⁸

Inhaled treprostinil was approved in 2021 for the treatment of PH-ILD.⁹ Studies of vasodilator therapies in PH-ILD conducted prior to the approval of inhaled treprostinil have revealed conflicting results. The INCREASE trial (NCT02630316) demonstrated that in patients with PH-ILD, treatment with inhaled treprostinil significantly improved 6-minute walk distance and decreased the time to clinical worsening by 39% compared with those given placebo. Additionally, patients with PH-ILD treated with inhaled treprostinil had significantly fewer exacerbations of underlying lung disease compared with those given placebo.¹⁰ The approval of inhaled treprostinil marked the first therapy indicated for treatment of PH-ILD. Trials of vasodilator therapies used for treatment of pulmonary arterial hypertension in patients with PH-ILD showed inconsistent results in exercise capacity and symptoms; some studies were stopped early due to lack of efficacy or increased harm in the PH-ILD population.

Real-world outcomes and health care utilization in patients with PH-ILD who were treated with inhaled treprostinil are not well characterized outside of clinical trials. Using claims data, Cassidy and colleagues sought to characterize health care utilization in patients with PH-ILD treated with inhaled treprostinil vs patients who remained treated without inhaled treprostinil.¹

Real-World Utilization of Inhaled Treprostinil

Study investigators conducted a retrospective cohort analysis of de-identified Optum Clinformatics Data Mart database claims from March 31, 2021, to June 30, 2023. Patients with PH-ILD were identified and indexed on the date of initiation of inhaled treprostinil therapy, and patients who remained untreated were indexed on the first observed PH diagnosis. Both cohorts were required to be at least 18 years old on the index date, to have 1

inpatient or 2 outpatient medical claims separated by at least 30 days for ILD in the 6-month pre-index period, and to have continuous enrollment 6 months pre-index. Patients treated with inhaled treprostinil were also required to have medical claims with a PH diagnosis in the 6-month pre-index period. For both cohorts, patients were excluded if they were treated with any pulmonary arterial hypertension therapy (ie, riociguat, endothelin receptor antagonist, or another prostacyclin) at any time in their record or if they had less than 1 month of follow-up. Each patient taking inhaled treprostinil was matched to up to 4 untreated patients based on age at index plus or minus 5 years,

“ Patients who initiated inhaled treprostinil had a 35% decreased risk of experiencing any hospitalization compared with untreated patients. ”

sex, race, insurance, Quan-Charlson Comorbidity Index score plus or minus 1, oxygen use, and any presence of pre-index hospitalization in the 6 months pre-index. Health care resource utilization (eg, inpatient care and ICU care) was compared between the 6-month pre-index period and the variable postindex date.¹

After applying selection criteria and matching, 153 patients treated with inhaled treprostinil and 380 untreated patients were included in the cohort. Mean all-cause per-member per-month hospitalizations remained unchanged in the 6-month pre-index and variable postindex periods in the inhaled treprostinil cohort but significantly increased in untreated patients ($P < .01$). Among patients who were hospitalized, length of stay was significantly lower in the variable postindex period in the inhaled treprostinil cohort compared with untreated patients (2.46 vs 4.99 days; $P < .01$). ICU utilization remained unchanged in the 6-month pre-index and variable postindex periods for patients treated with inhaled treprostinil compared with the untreated cohort ($P < .01$).¹

Controlling for baseline comorbidities, patients who initiated inhaled treprostinil had a 35% decreased risk of experiencing any hospitalization compared with untreated patients ($P < .01$).¹

Conclusion

Study investigators concluded that utilization of inhaled treprostinil in patients with PH-ILD resulted in fewer all-cause hospitalizations, shorter length of stay, and fewer ICU hospitalizations compared with patients with PH-ILD who remained untreated. Outcomes were similar between patients using treprostinil inhalation solution (nebulized Tyvaso, United Therapeutics) and patients using the inhaled treprostinil dry

powder formulation. Investigators noted that these results demonstrated better health outcomes among patients with PH-ILD who were treated with inhaled treprostinil, while patients who remained untreated had greater health burdens. ●

This article was reviewed by United Therapeutics for medical accuracy.

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Results of Claims Analysis Reveal Comparable Efficacy Between 2 Inhaled Corticosteroid/Long-Acting β_2 -Agonist Combinations

MELANIE DOLAN

The results of a recent retrospective cohort analysis of real-world claims data demonstrated similar effectiveness between 2 inhaled corticosteroid/long-acting β_2 -agonist (ICS/LABA) combinations in patients with moderate-to-severe asthma. Based on proportion of days covered (PDC), there was a trend toward greater adherence to fixed-dose fluticasone propionate/salmeterol (FP/SAL) than to budesonide/formoterol (BUD/FOR).¹ Study findings were presented as a poster entitled “Comparative Effectiveness of Fixed-Dose Fluticasone Propionate/Salmeterol and Budesonide/Formoterol Combinations in Asthma: A United States Database Analysis” at the American College of Chest Physicians (CHEST) 2024 Annual Meeting held from October 6 to 9, 2024, in Boston, Massachusetts.

The Global Initiative for Asthma (GINA) recommends the use of an ICS/LABA combination for patients with moderate-to-severe asthma.¹ According to the GINA guide, if asthma is not controlled with ICS monotherapy, a LABA can be added to improve asthma control instead of doubling the ICS dosage.² The use of an ICS/LABA combination can improve asthma symptoms and lung function and reduce exacerbation more rapidly than can administration of an ICS alone.² FP/SAL and BUD/FOR have demonstrated similar efficacy in patients with moderate-to-severe asthma in clinical trials.^{1,3} The goal of this study was to compare the effectiveness of FP/SAL with that of BUD/FOR in a real-world setting.¹

Researchers analyzed data from Optum’s Market Clarity claims-clinical integrated database from July 1, 2010, to

December 31, 2019. This database includes electronic health records (EHR) data and adjudicated medical and pharmacy claims data.¹ Eligible patients included those who were at least 18 years of age at the index date, who received asthma treatment in accordance with GINA guidelines (steps 3-4), who had at least 1 pharmacy claim for either FP/SAL (dosage: 100/50, 200/50, or 500/50 μg) or BUD/FOR (dosage: 80/4.5 or 160/4.5 μg) during the identification period, who had continuous medical and pharmacy coverage for at least 12 months before and after the index date, and who had at least 1 asthma-related medical claim at baseline.¹ To adjust for confounding, the investigators estimated the weighted-average treatment effect.¹ For both the FP/SAL and BUD/FOR cohorts, descriptive analyses of baseline demographic and clinical characteristics were presented after weighting.¹

Of the 2,177,928 patients with moderate-to-severe asthma identified, 57,000 individuals (FP/SAL, 28,639 patients; BUD/FOR, 28,361 patients) met the study inclusion criteria.¹ Patient demographics were well balanced across cohorts at the beginning of the study.¹ The most common comorbidity among participants was respiratory infections (51.39% in the FP/SAL arm vs 52.20% in the BUD/FOR arm; $P = .092$).¹ The blood eosinophil counts of most patients at baseline were 30 to 300 cells/ μL (FP/SAL, 58.03%; BUD/FOR 58.53%; not significant).¹ At baseline, there were differences between the cohorts in the proportion of patients with an asthma exacerbation (17.19% in the FP/SAL group vs 18.67% in the BUD/FOR group, $P < .001$), patients who were treated with an oral corticosteroid (47.66% vs 50.10%, respectively; $P < .001$),

and those who refilled prescriptions of short-acting β_2 -agonists (SABA) at least 3 times (22.27% vs 23.29%; $P = .010$).¹

During the 12-month follow-up, the mean (SD) annual asthma exacerbation rate was 0.14 (0.45) for both the FP/SAL and BUD/FOR arms ($P = .853$).¹ The groups had similar proportions of patients who had an asthma exacerbation–related emergency department visit or hospitalization,¹ and 47.05% of patients overall had 3 or more refills of SABA prescriptions.¹ The FP/SAL group, when compared with the BUD/FOR group, had more patients with at least 0.8 PDC (5.37% vs 4.43%, respectively; $P < .001$) and at least 0.5 PDC (15.53% vs 14.58%; $P = .007$).¹

The results of this evaluation of EHR and claims data showed a similar benefit with FP/SAL and BUD/FOR among patients with asthma. Based on PDC, a trend toward greater adherence to FP/SAL

than BUD/FOR was observed.¹ Although further exploration in a global population is needed to assess the effectiveness of FP/SAL vs BUD/FOR, all doses of the 2 combinations showed comparable efficacy in treating patients with moderate to severe asthma.¹ ●

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Lung Cancer Experts Encourage Use of System-Based Interventions to Address Racial Disparities

BROOKE MCCORMICK

Experts at the 2024 American College of Chest Physicians (CHEST) annual meeting in Boston, Massachusetts, highlighted significant racial and ethnic disparities in lung cancer and recommended using system-based interventions that leverage transparency, accountability, and enhanced communication to mitigate these differences.

During the session “Addressing Disparities in Lung Cancer Care,” Neelima Naluvuri, MD, assistant professor of medicine at the Duke University School of Medicine, stated that lung cancer screening rates are unacceptably low, with the average rate being 5.8% among eligible patients in 2022.

Even with this small percentage, racial disparities still exist among those who receive lung cancer screenings. In 2018, Naluvuri reported that lung cancer screening rates were significantly lower in Black patients than in non-Black patients even though the risk of lung cancer among Black or Hispanic patients is equivalent to or greater than that of White patients with histories of tobacco use.

These differences in screening rates directly correlate to disparities in the rates of lung cancer incidence, morbidity, and survival among patients of color, as discussed by Francesca Duncan, MD, MS, assistant professor of medicine at the Indiana University School of Medicine.

She noted that Black males have the highest incidence rate of lung cancer, whereas American Indian and Alaskan Native females have the highest mortality rate. Also, Black patients are less likely to be diagnosed with early-stage disease and, therefore, have worse survival than do White patients.

These statistics were further demonstrated by Duncan’s study, “Racial Disparities in Staging, Treatment, and Mortality in Non–Small Cell Lung Cancer (NSCLC).”¹ The results showed that a greater percentage of Black patients was diagnosed with lung cancer when aged 50 to 64 years; in comparison, White patients were more likely to be diagnosed at 65 years or older. Also, a larger percentage of Black patients than of White patients was diagnosed at an advanced disease.

Factors associated with advanced-stage diagnosis included being male, uninsured, and of Black race. Similarly, the study found worse overall survival rates among patients who were Black, male, uninsured, or single compared with their counterparts. Based on these findings, Duncan tasked attendees to ensure that their organizations prioritize understanding and address lung cancer disparities.

“While I’m very happy to be here, my hope is that in 40 to 50 years, we’re not sitting here in these same seats having the same conversation about lung cancer disparities,” she said.

Similar trends were reported by Stella Ogake, MD, FCCP, assistant professor of medicine at The Ohio State University College of Medicine, who presented information on disparities in the treatment of lung cancer.

She first highlighted that the standard of care for patients with early-stage NSCLC is anatomic lung resection with a multistation lymph node dissection. Postresection survival can be over 85% at 5 years among patients with early-stage NSCLC. However, Ogake noted that patients of color are significantly less likely to undergo surgery—and, in some cases, they receive no treatment at all.

She highlighted the outcomes of a study that showed Black patients to be least likely to receive surgery regardless of whether they were treated in an integrated or nonintegrated care setting.² Conversely, Asian and White patients were equally likely to receive surgery in either setting. In terms of care setting, results of another study showed that Black patients were more likely to undergo surgery at an academic facility than at a community facility (odds ratio [OR], 1.12; 95% CI, 1.01-1.24; $P = .04$).³ Consequently, Black patients treated at academic facilities had significantly higher overall survival.

Lastly, she highlighted a study that examined the level of adherence to predefined, stage-specific, guideline-concordant treatment among US patients with lung cancer of different age and racial groups.⁴ It determined that non-Hispanic Black patients were less likely to receive guideline-concordant treatment (OR, 0.82; 95% CI, 0.81-0.84); this association persisted after adjusting for covariates (adjusted OR, 0.78; 95% CI, 0.76-0.08).

Ogake said that these treatment disparities are driven by social determinants of health such as care access, education level, and insurance status. Other factors impacting care disparities include guideline-concordant treatment differences, being treated at an academic institution vs a community institution, and implicit bias.

Consequently, Samuel Cykert, MD, professor of medicine at the University of North Carolina (UNC) at Chapel Hill School of Medicine, emphasized the need for system-level interventions with real-time transparency, accountability, and enhanced communication to mitigate these lung cancer disparities.

Cykert shared the example of the racial equity analysis and solution used by the Greensboro Health Disparities Collaborative through the UNC's Accountability for Cancer Care through Undoing Racism and Equity (ACCURE) project, which helped to improve care for Black patients by reducing racial disparities. Using electronic medical records, Cykert explained, a warning system was created to alert providers when patients—especially those of color—missed appointments or care milestones. Also, regular audits identified care disparities,

and ACCURE navigators helped patients to overcome barriers like transportation, finances, and mistrust in the health care system.

The intervention's impact was analyzed among patients with early-stage lung cancer in 5 cancer centers, he noted.⁵ At baseline, the crude treatment rates were 78% for White patients vs 69% for Black patients ($P < .001$); these were confirmed after adjusting for comorbidities (OR, 0.66; 95% CI, 0.51-0.85; $P = .001$).

After the solution was implemented, the crude treatment rate was 96.5% for Black patients vs 95% for White patients ($P = .56$), which was confirmed in the adjusted analysis (OR, 2.1; 95% CI, 0.41-10.4; $P = .39$). Therefore, this method helped to mitigate disparities and improve care for all patients, not just 1 group. In light of these positive findings, Cykert encouraged other cancer centers to adopt similar interventions to help mitigate care disparities.

“If we work with affected communities to determine appropriate outcome measures—and if we apply the interventions in real time using transparency, accountability, and excellent communication—system-based interventions cause inequities to be mitigated, and care is improved for everyone,” he concluded. ●

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Safety and Efficacy of Inhaled Treprostinil in Patients With and Without Connective Tissue Disorder–Associated Pulmonary Arterial Hypertension From the TRIUMPH Study

KAITLYN N. PAXTON, PHARMD, MBA; AND KIMBERLY SIMPSON, PHARMD

A post hoc analysis of the TRIUMPH study (NCT00147199) assessed a subgroup of patients with pulmonary arterial hypertension (PAH) who had connective tissue disorder–associated

PAH (CTD-PAH). Highland and colleagues presented their findings in a rapid-fire presentation titled “Inhaled Treprostinil for the Treatment of Connective Tissue–Associated Pulmonary Arterial

Hypertension” at the American College of Chest Physicians annual meeting, which took place October 6 to 9, 2024, in Boston, Massachusetts.¹

Background

Pulmonary hypertension (PH) is a progressive, life-threatening disease that is categorized into 5 clinical groups. Group 1 PH, PAH, is characterized by progressive increases in pulmonary vascular resistance and right heart dysfunction, ultimately leading to death.² PAH affects 45,000 patients in the US and is more common in patients 60 years and older.³

PAH is composed of multiple etiologies including idiopathic, heritable, drug- and toxin-induced, and PAH associated with conditions such as connective tissue disease, HIV infection, portal hypertension, congenital heart disease, and schistosomiasis. PAH associated with another condition comprises approximately 50.7% of PAH cases in the US. Of that 50.7%, approximately 50% are cases of PAH associated with connective tissue disease (CTD-PAH). CTD-PAH is the second-most common etiology with the most severe disease characteristics and the highest mortality of all PAH etiologies.⁴

The TRIUMPH study was the basis of FDA approval for the use of inhaled treprostinil (Tyvaso DPI, United Therapeutics) to treat PAH to improve exercise ability. Inhaled treprostinil is administered in 4 separate treatment sessions daily, approximately 4 hours apart, with target maintenance doses of 9 to 12 breaths per treatment session.^{5,6}

TRIUMPH Study and the CTD-PAH Subgroup

TRIUMPH was an international, multicenter, double-blind, placebo-controlled trial that examined the safety and efficacy of inhaled treprostinil in PAH patients receiving oral therapy, and it met its primary end point of peak 6-minute walk distance (6MWD) at 12 weeks.⁵ In this post hoc analysis, Highland and colleagues assessed the CTD-PAH subgroup relative to those without CTD-PAH in the overall study population, evaluating 6MWD, N-terminal pro B-type natriuretic peptide (NT-proBNP), dosing, and changes in New York Heart Association functional class.¹

In the TRIUMPH study, a total of 235 patients with PAH were randomly assigned to inhaled treprostinil (n=115) or placebo (n=120); 77 patients had CTD-PAH (inhaled treprostinil, n=40; placebo, n=37) and 158 patients had non-CTD-PAH (inhaled treprostinil, n=75; placebo, n=83). In the CTD-PAH inhaled treprostinil group, the mean age was 58.4 years, with 90% being female. The mean 6MWD was 342 m, and the median NT-proBNP was 422 pg per mL; patients were on background therapy for a median of 26 weeks. For the non-CTD-PAH inhaled treprostinil group, the mean age was 53.9 years, with 76% being female. The mean 6MWD was 349 m, and the median NT-proBNP was 782 pg per mL; patients were on background therapy for a median of 85 weeks. The CTD-PAH inhaled treprostinil group

and the non-CTD-PAH inhaled treprostinil group had similar functional class and background therapies but demonstrated a big difference in baseline NT-proBNP and weeks of background therapy. Etiologies of the associated connective tissue diseases were not collected.^{1,5}

At week 12, investigators observed a significant difference in change in 6MWD between the inhaled treprostinil and placebo groups in both the CTD-PAH ($P=.01$) and non-CTD-PAH subgroups ($P=.02$). The treatment effect in the 6MWD in the CTD-PAH subgroup was 28.2 m, which was comparable to the treatment effect in the non-CTD-PAH group of 29 m. The inhaled treprostinil group with CTD-PAH experienced an average increase of 24.8 m at week 12 in their 6MWD compared to baseline; the increase was 37 m in the non-CTD-PAH treatment group. Median NT-proBNP levels in the inhaled treprostinil group were 27% lower compared with the placebo group in the CTD-PAH subgroup ($P=.07$) at week 12 compared with 34% in the non-CTD-PAH subgroup ($P=.05$).

“ With inhaled treprostinil, patients had statistically significant improvements in 6MWD and reductions in NT-proBNP.”

The mean dose at week 12 in the CTD-PAH inhaled treprostinil group was 8.5 breaths per session, while the non-CTD-PAH inhaled treprostinil group received a mean dose of 7.9 breaths per session. Most patients had no change in functional class in both the CTD-PAH and non-CTD-PAH groups, and no patients who received inhaled treprostinil worsened from baseline to week 12.

Early discontinuation due to adverse events was similar between groups. Cough, headache, and dizziness were the most common adverse events in both groups.¹

Conclusion

Highland and colleagues concluded that following 12 weeks of treatment with inhaled treprostinil in TRIUMPH, patients had statistically significant improvements in 6MWD and reductions in NT-proBNP regardless of PAH etiology. Treatment effect was numerically similar between patients with CTD-PAH and those with non-CTD-PAH. Safety was similar between patients with and without CTD-PAH in the TRIUMPH study.¹ ●

This article was reviewed by United Therapeutics for medical accuracy.

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Experts Highlight AI’s Potential to Enhance ILD Diagnostic Accuracy Amid Limitations

BROOKE MCCORMICK

Experts at the 2024 American College of Chest Physicians (CHEST) annual meeting in Boston, Massachusetts, discussed how artificial intelligence (AI) tools can enhance diagnostic accuracy for interstitial lung diseases (ILDs) amid their limitations.

Michael Morris, MD, associate professor at the University of Arizona College of Medicine, uses AI tools for image interpretation. During the session “AI in ILD Imaging: The Future is Here,” he noted that most senior radiologists only achieve diagnostic accuracy about 80% of the time, leaving room for improvement that AI may help address.

“With numerous AI algorithms available, radiologists should select one that aligns with their practice’s needs and determine whether the algorithm works with their data.”

Bruno Hochhegger, MD, PhD, clinical professor of radiology at the University of Florida College of Medicine, provided an overview of 2 commonly used AI techniques: machine learning and deep learning. He explained that machine learning relies on labeled data, with labels representing the *gold standard* for what the AI is trying to identify. Therefore, the AI system compares the input data to these labels to make classifications.

In the context of ILD, Hochhegger noted that machine learning requires a radiologist to label specific features of a lung CT scan that indicates honeycombing, which is a sign of end-stage ILD. The AI system then compares this labeled data with a large database of lung CT scans to help identify and diagnose ILD cases. Machine learning methods do not require extensive technology;

however, he emphasized, the radiologist must confirm whether AI’s identification of honeycombing is accurate.

Conversely, deep learning typically uses neural networks to analyze data without the need for explicit labels, allowing the algorithm to discover patterns and insights independently. These models automatically learn features from the data by using its structure to categorize objects and identify patterns.

Hochhegger explained that deep learning algorithms break down ILD lung CT scans into numerous small segments and compare them with a large database of lung CT scans. Deep learning algorithms can identify patterns in these segments and draw conclusions about the scan without relying on pre-labeled data. Morris added that more advanced deep learning algorithms can identify features invisible to the human eye.

Although deep learning requires more computational power than does machine learning, Hochhegger highlighted, it has the advantage of not needing manual label input from a radiologist.

Consequently, unlike for machine learning, it is unclear what aspect of the *black box* of deep learning is used to predict outcomes; he considered this a limitation. To ensure accurate ILD identification by AI, especially with deep learning, Hochhegger suggested using large databases of diverse patients. Exposure to patients of diverse backgrounds can help improve the algorithms’ accuracy in diagnosing ILD.

Kevin Brown, MD, professor and chair of the department of medicine at National Jewish Health, listed additional AI limitations that may impact ILD diagnoses. These include data bias, which leads to outcomes that do not accurately reflect the reality being modeled; technical bias, resulting from changes in the underlying technology; and automation bias, in which individuals favor AI decisions over conflicting data or human judgments.

While AI is not yet ready to replace radiologists entirely, Morris emphasized, these algorithms can enhance diagnostic accuracy beyond what radiologists achieve alone, particularly when they integrate clinical information with imaging data. Therefore, AI

should not be relied upon entirely; instead, it should be used as a tool by radiologists to make a proper ILD diagnosis. With numerous AI algorithms available, he recommended, radiologists should select one that aligns with their practice's needs and then ask, "Does this algorithm work with my particular data?"

Overall, Morris explained that AI is helping to democratize access to ILD diagnoses, leveling the playing field among health care providers. Staff at academic institutions are often most qualified in making ILD diagnoses, yet AI is helping to

distribute this expertise to a broader range of clinicians and health care settings.

"AI is really key in terms of democratizing access for both US clinicians and patients in terms of receiving the best possible care," Morris concluded. "Hopefully, we can use AI to help improve and facilitate medical diagnoses and ultimately improve outcomes." ●

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Preapproval Process Intervention for Patients With Pulmonary Arterial Hypertension Leads to Reduced Hospital Length of Stay

JABIR BHUIYAN, MS

Pulmonary arterial hypertension (PAH) is a rare, chronic, progressive, and life-threatening condition that can severely impact patients' quality of life.^{1,3} PAH is often misdiagnosed due to the ambiguity of the signs and symptoms such as fatigue and dyspnea that overlap with other conditions.³ Difficulty in diagnosis is compounded by the wide range of ages it can affect as well comorbid conditions with which PAH is commonly associated.^{3,4} The disease carries a substantial risk of mortality and no cure currently exists, limiting treatment to alleviation of symptoms and delay of disease progression.^{1,3} Patients diagnosed with PAH require considerable therapy and health care resource use, placing enormous economic burden on patients and the US health care system.¹

Patients frequently face delays in diagnosis and treatment, with more than 2 years elapsing between symptom presentation and diagnosis of PAH, on average.^{2,4} European guidelines for the diagnosis and treatment of PAH note that collaboration among first-line physicians and clinicians in more specialized centers throughout the diagnostic process can help improve time to diagnosis and management and thus improve outcomes.⁴

Although there is no cure for PAH, therapies that can slow clinical progression are available. Brewster and colleagues evaluated the potential benefits of implementing a preapproval process for patients who have been prescribed medication for PAH. They presented the results of their study titled "Impact of a Pharmacist-Driven Preapproval Process for Parenteral Pulmonary Arterial Hypertension Therapies on Hospital Length of Stay" during the 2024 CHEST Conference in Boston, Massachusetts, on October 6, 2024.⁵

In this single-center retrospective study, patient chart data were evaluated to determine the impact of implementing a proactive approach to accessing parenteral therapy for the treatment of PAH on hospital length of stay (LOS). As part of the intervention, for patients who were initiating a parenteral PAH therapy, a

clinical pharmacist would work with specialty pharmacies to obtain drug approvals and provide patients with education before their admission to the hospital to begin treatment.⁵

Patients included in the analysis were admitted between January 1, 2022, and March 2024 for initiation of parenteral PAH therapy.⁵ Patients who were in the proactive access process (study) group were compared with patients who were not (control group). The primary outcome for the study was the difference in hospital LOS between the study group and the control group. Secondary outcomes included difference in intensive care unit (ICU) LOS, readmission within 30 days, all-cause and PAH-related readmission within 90 days, rates of compliance with post discharge follow-up appointments for PAH, and use of patient assistance resources to obtain medications. Excluded from the study were patients who were discharged to hospice, who left the clinic against medical advice, who were discharged to locations other than their homes, or who were initially admitted for acute decompensated PAH.⁵

“ Significant reductions in hospital LOS were seen within the study group of patients who went through the proactive access process compared with the control group who did not. ”

The final analysis included 16 patients, 6 in the study group and 10 in the control group. The majority of patients (63%) were classified as World Health Organization functional class III, indicating that they had limited physical activity; 81% of the patients were female. At the time of admission, 6% of patients

were being treated with monotherapy, 44% with dual therapy, and 6% with triple therapy; 44% of patients were treatment naive. Nearly all patients (94%) were naive for prostacyclin treatment.⁵

Significant reductions in hospital LOS were seen within the study group of patients who went through the proactive access process compared with the control group who did not (5.41 vs 16.4 days, $P = .003$).⁵ LOS for the ICU was also observed to be significantly shorter among patients who received the intervention (3.8 vs 8.9 days, $P < .05$). When accounting for whether the patient received education about drug therapy and devices before admission, further improvements were observed in hospital LOS. Patients who received education had a reduced hospital LOS compared with those who did not (3 vs 10 days). Readmission rates for both the intervention group and the control group were low, with 1 patient in each group readmitted within 30 days. However, investigators noted that the patient in the intervention group was readmitted due to a non-PAH-related cause, whereas the patient in the control group was readmitted due to PAH. In the intervention group, an average of 22 days passed (range, 4-33 days) from when the clinician decided to start parenteral therapy and when the patient was admitted to the hospital to begin treatment.⁵

In this study, the implementation of a proactive access process for parenteral prostacyclin treatment substantially

decreased hospital LOS for patients who were admitted for PAH therapy initiation. Furthermore, patients who participated in the proactive process and who received education about their medication and device before hospitalization were able to more quickly switch to self-management and be discharged to their homes.⁵

The investigators noted that the implementation of a proactive access process before hospital admission for eligible patients who are initiating parenteral prostacyclin therapy may reduce health care resource use and cost and improve patient satisfaction.⁵ ●

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