National Jewish Health
Breathing Science is Life.

JOURNAL CLUB

Article Summary by: Mohammad Dalabih, MBBS, MHA & Patricia George, MD

ARTICLE

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

Waxman A et al. NEJM 2021; 384: 325-34. DOI: 10.1056/NEJMoa2008470

CLINICAL QUESTION

Is inhaled treprostinil safe and effective in patients with pulmonary hypertension due to interstitial lung disease?

SUMMARY

This was a randomized, multicenter, double blind, placebo controlled 16-week trial of inhaled trepostinil versus placebo in patients with pulmonary hypertension (defined by right heart catheterization showing a PVR > 3 Wood Units (WU), mPAP $\geq$ 25 mmHg and a pulmonary capillary wedge pressure $\leq$ 15 mmHg) and interstitial lung disease (ILD), diagnosed by presence of diffuse parenchymal lung disease on CT scan and an FVC < 70% of predicted in patients with connective tissue disease. Subjects had to be stable on ILD therapies and those already receiving pulmonary hypertension specific therapy were excluded. Inhaled treprostinil was delivered using an ultrasonic nebulizer starting at 3 breaths four times daily and increased up to 12 breaths four times daily. The primary end point was change in six-minute walk distance from baseline at 16 weeks. Secondary end points were the change in NT-proBNP at 16 weeks and the time to clinical worsening. Safety measures including pulse oximetry, oxygen requirement, pulmonary function tests, ILD exacerbations, progression of underlying lung disease were also assessed.
A total of 326 patients were enrolled in a 1:1 randomization to inhaled treprostinil vs. placebo. The least squares mean difference in the change in 6-minute walk distance at 16 weeks between the two groups was 31 m greater in the treprostinil group (P < 0.001). NT-proBNP decreased by 15% in the treprostinil group and increased by 46% in the placebo group (P < 0.001). Clinical worsening occurred in 22.7% patients in the treprostinil group and 33.1% in the placebo group (P = 0.04). There was no treatment-related adverse impact on oxygenation or pulmonary function testing, and there were fewer ILD exacerbations in the treprostinil group (26.4%) vs 38.7% in the placebo group.

National Jewish Health
Breathing Science is Life.

JOURNAL CLUB

Article Summary by: Mohammad Dalabih, MBBS, MHA & Patricia George, MD

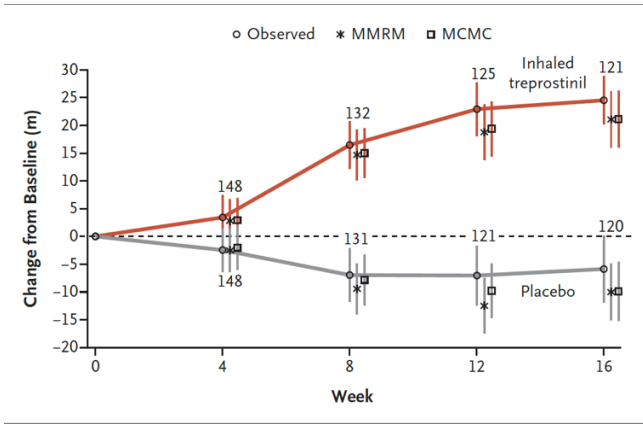

Table 2. Summary of Primary and Secondary End Points.*

End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
Primary end point				
Change in peak 6-minute walk distance from baseline to wk 16 — m†	21.08±5.12	−10.04±5.12	31.12±7.25 (16.85 to 45.39)‡	<0.001
Secondary end points§				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change — pg/ml	−396.35±1904.90	1453.95±7296.20		
Median — pg/ml	−22.65	20.65		
Range — pg/ml	−11,433.0 to 5373.1	−5483.3 to 87,148.3		
Ratio to baseline	0.85±0.06	1.46±0.11	0.58±0.06 (0.47 to 0.72)‖	<0.001
Occurrence of clinical worsening — no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6-minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		
Least-squares mean change in peak 6-minute walk distance from baseline to wk 12 — m†	18.77±4.99	−12.52±5.01	31.29±7.07 (17.37 to 45.21)‡	<0.001
Least-squares mean change in trough 6-minute walk distance from baseline to wk 15 — m	9.3±5.5	−12.7±5.5	21.99±7.7 (6.85 to 37.14)‡	0.005††

GROUP OPINION

This is the first randomized controlled trial in PH-ILD that supports the use of a PH-specific therapy in this population. Prior to this study there were no FDA-approved medications for group 3 pulmonary hypertension due to numerous negative clinical trials and in the case of two clinical trials, findings that oral and parenteral PH medications were associated with harm in patients with idiopathic pulmonary fibrosis. There has been a concern that off-label use of pulmonary vasodilators could worsen ventilation/perfusion mismatch and hypoxia in this population. With a lack of approved therapies, some physicians have utilized inhaled therapies off-label in patients who had severe PH and ILD, with idea that these therapies may be less likely to contribute to V/Q mismatch and hypoxemia.

This clinical trial provides important evidence supporting the use of inhaled treprostinil in this patient population, with improved exercise capacity measured by 6-minute walk test, lower NT-proBNP, and decreased risk of clinical worsening without worsening hypoxia. That said the treatment effect on the primary outcome was modest, as the six-minute walk distance difference met the minimal clinically significant limit in patients with lung disease. The study was relatively short in duration, and there was no difference in patient-reported quality of life assessment by St. George's Respiratory Questionnaire. The study also raises the question of whether the inhalational route should be explored for other classes of PH-specific medications in patients with underlying lung disease.

On behalf of the PH Physicians: Mohammad Dalabih, MBBS, MHA; Andrew Freeman, MD; Marjorie P. George, MD; Darlene Kim, MD; Suraj Sunder, MD

PH Journal Club dates and times njhealth.org/PHJournalClub