Dose-response Analysis of Inhaled Treprostinil in Pulmonary Hypertension Associated with Interstitial Lung Disease and Its Effects on Clinical Worsening

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INCREASE

BACKGROUND

- INCREASE was a multicenter, randomized, double-blind, placebo-controlled, 16-week, parallel-group study.
- Inclusion criteria included confirmed diagnosis of pulmonary hypertension associated with interstitial lung disease (PH-ILD) by right heart catheterization and demonstrated evidence of diffuse parenchymal lung disease on computed tomography imaging.
- The study met its primary endpoint of change in 6-minute walk distance (6MWD) at Week 16.[1]
- Additionally, patients receiving inhaled treprostinil had a lower risk of clinical worsening than patients receiving placebo (hazard ratio 0.61; log-rank p=0.04). Clinical worsening was defined as either cardiopulmonary hospitalization, 6MWD decrease of >15% from baseline, lung transplantation, or death.
- In the INCREASE study, higher doses of inhaled treprostinil were associated with greater improvements in 6MWD. However, it is unknown whether higher doses of inhaled treprostinil in patients with PH-ILD are associated with other benefits such as decreased rates of clinical worsening.

METHODS

- INCREASE study procedures and endpoints have been previously reported.[1]
- In this post-hoc analysis, patients in the inhaled treprostinil treatment arm were divided based on maximum dose achieved into 2 groups, <9 and ≥9 breaths per session (bps).
- Kaplan-Meier estimates were used to evaluate time to clinical worsening. Log-rank test was used to compare overall rates of clinical worsening between groups.
- Individual components of the clinical worsening definition (i.e., cardiopulmonary hospitalization; 6MWD decrease of >15% from baseline; lung transplantation; death) were compared between dose groups using Fisher's exact test.

RESULTS

- Among the 163 patients in the inhaled treprostinil arm, 41 patients were in the <9 bps group and 122 patients were in the ≥9 bps group. The two dose groups had similar demographics, hemodynamics, and lung function at baseline (Table 1).
- The median doses in the <9 and ≥9 bps group were 6 and 12 bps, respectively Figure 1 shows a histogram of the number of patients at each specific dose.
- A total of 16 patients (39%) and 21 patients (17%) in the <9 and ≥9 bps groups respectively experienced a clinical worsening event (p<0.01).
- Patients in the ≥9 bps group had a significantly lower rate of clinical worsening (log-rank p<0.0001). Figure 2 displays the Kaplan-Meier estimates for clinical worsening for the two dose groups.

RESULTS (cont.)

- Significantly fewer patients died in the higher dose group compared to the lower dose group (3% vs. 15%, p=0.02).
- For the other components of the clinical worsening composite endpoint, there were lower incidences of 6MWD decline, cardiopulmonary hospitalization, and lung disease exacerbation in the ≥9 bps group but these differences did not reach significance (Table 2).

Table 1: Baseline Characteristics

Baseline Characteristics	<9 breaths per session (n=41)	≥9 breaths per session (n=122)	p-value
Age, mean (SD)	65.0 (13.5)	65.8 (12.5)	0.89
Sex, n (%)			
Male	19 (46%)	59 (48%)	0.82
Female	22 (54%)	63 (52%)	
Time since PH-ILD Diagnosis, years (median)	0.2	0.2	0.90
Etiology of PH-ILD, n (%)			
Idiopathic interstitial pneumonia	17 (42%)	48 (39%)	
CPFE	11 (27%)	31 (25%)	
Connective tissue disease	7 (17%)	33 (27%)	0.40
Chronic hypersensitivity pneumonitis	3 (7%)	7 (6%)	
Occupational lung disease	2 (5%)	3 (3%)	
Other	1 (2%)	0	
6-minute walk distance, m (median)	252	257	0.75
NT-proBNP, pg/mL (median)	543	558	0.99
Hemodynamics (median)			
mPAP, mmHg	35.0	35.5	0.37
PCWP, mmHg	9.0	10.0	0.14
PVR, Woods units	6.4	5.4	0.13
Pulmonary function tests (median)			
FEV1, % predicted	64%	63%	0.57
FVC, % predicted	61%	60%	0.45
TLC, % predicted	59%	63%	0.14
DLCO, % predicted	30%	28%	0.34

Figure 1: Dosing Among Patients Randomized to Inhaled Treprostinil

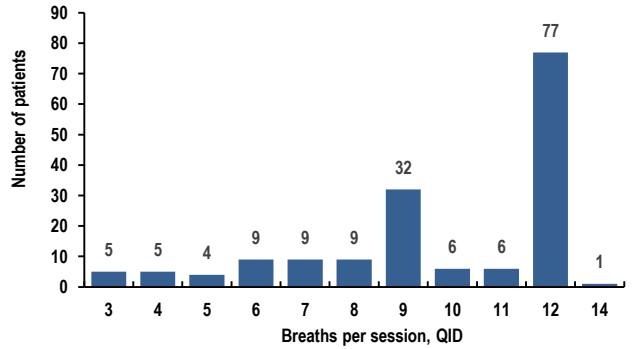
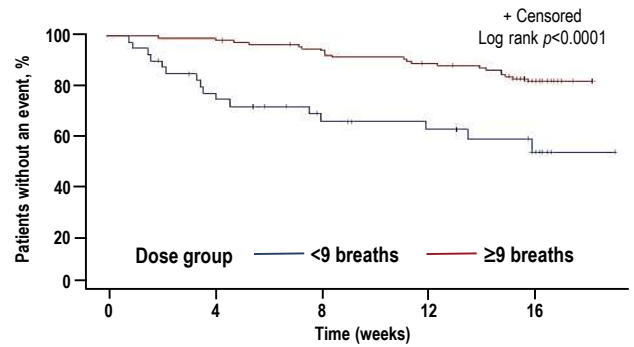


Figure 2: Kaplan-Meier Curves for Time to First Clinical Worsening Event



CI, confidence interval; HR, hazard ratio; Pearson chi-square test was used to compare overall rates of clinical worsening between groups. Individual components of the clinical worsening definition were compared between groups using Fisher exact test.

Table 2: Incidences of Clinical Worsening Components by Dose Group

	<9 bps (n=41)	≥9 bps (n=122)	p-value
Death	6 (15%)	4 (3%)	0.02
Lung transplantation	2 (5%)	0	0.06
Decrease in 6MWD >15% from Baseline	5 (12%)	8 (7%)	0.32
Cardiopulmonary hospitalization	8 (20%)	13 (11%)	0.14
Exacerbation	13 (32%)	31 (25%)	0.43

DISCUSSION

- In patients with PH-ILD in the INCREASE trial, higher doses of inhaled treprostinil were associated with a lower risk of clinical worsening.
- Kaplan-Meier curves separate early on, after patients have uptitrated on dose, demonstrating that the dose-response on clinical worsening occurs early in the treatment course.
- The majority of patients (n=122, 75%) were able to achieve a dose of ≥9 breaths per session QID, suggesting that titrating to efficacious doses of inhaled treprostinil is feasible in this patient population in the context of appropriate adverse event management.
- Results from this analysis in patients with PH-ILD are similar to previous reports in WHO Group 1 pulmonary arterial hypertension that suggest that higher doses of inhaled treprostinil have beneficial effects on survival and delayed time to parenteral therapy.[2]
- Limitations of this analysis include a small sample size in the <9 bps group and the relatively short duration of the study. Additionally, the analysis separated patients based on maximum dose achieved and did not include the time spent (i.e. number of weeks) at the maximum dose.

CLINICAL IMPLICATIONS

- This post-hoc analysis suggests that a higher dose of inhaled treprostinil has beneficial effects on clinical worsening in patients with PH-ILD.
- Our results underscore the importance and benefits of titrating inhaled treprostinil to the maximum tolerated dose for patients with PH-ILD.

REFERENCES

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