Novel Analysis of Treprostinil Dose-response Relationship Using Weight-normalized Dosing

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INTRODUCTION

- Treprostinil is a prostacyclin analogue available in intravenous, subcutaneous (SC), inhaled, and oral administration routes for pulmonary arterial hypertension (PAH).
- Doses are titrated based on tolerability and clinical response.
- Because doses are individualized, conventional dose-response studies using randomized drug exposure are difficult to employ.
- In this novel analysis, we report outcomes with weight-normalized doses to SC and oral treprostinil.

METHODS

- Data from patients receiving active therapy (i.e. not placebo) in the SC treprostinil registration study were combined with patient data from the FREEDOM-M study of oral treprostinil.[1,2]
- Both were 12 weeks long, had the same endpoints of 6-minute walk distance (6MWD) at week 12, studied systemically administered treprosintil monotherapy, and titrated treprostinil to the maximum tolerated dose.
- To facilitate pooling of dosing data, oral doses were converted to weight-based continuous doses (ng/kg/min), accounting for patient weight and bioavailability (see formula below).
- Patients were grouped into dose tertiles, based on doses achieved at week 12 of the clinical studies.
- Measures of efficacy:
  - 6MWD, Borg dyspnea score (BDS), World Health Organization (WHO) functional class (FC).
- Statistical Analysis:
  - Last observation carried forward (LOCF) was used to impute last observations of 6MWD, Borg dyspnea score, WHO FC, and dose.
  - One-way analysis of variance (ANOVA) and Jonckheere-Terpstra tests were used to assess differences and linear trends in 6MWD, BDS, and WHO FC based on treprostinil dose received.

Oral treprostinil daily dose (mg/day) converted to weight-based continuous dose (ng/kg/min):

$$\frac{\text{X mg}}{\text{day}} \times \underset{\text{Step 1}}{\frac{1{,}000{,}000\ \text{ng}}{\text{mg}}} \times \underset{\text{Step 2}}{0.2} \times \underset{\text{Step 3}}{\frac{1}{\text{wt (kg)}}} \times \underset{\text{Step 4}}{\frac{1\ \text{day}}{1440\ \text{min}}}$$

Step 1
- Multiply oral treprostinil dose by 1,000,000 to convert from milligrams to nanograms.

Step 2
- Multiple the daily dose in nanograms by 0.2 to account for increased bioavailability of SC treprostinil.

Step 3
- Divide the daily dose by the patient's weight (kg) to calculate weight-based daily dose.

Step 4
- Divide the weight-based daily dose by 1440 (minutes/day) to convert weight-based daily dose (ng/kg) to weight-based continuous dose (ng/kg/min).

Table 1. Patient Baseline Demographics

Baseline Characteristic	Low Dose (n=151)	Medium Dose (n=159)	High Dose (n=156)	p-value 1 (low vs. medium)	p-value 2 (medium vs. high)	p-value 3 (low vs. high)
SC treprostinil (%)	92 (60.9)	86 (54.1)	55 (35.3)	--	--	--
Oral treprostinil (%)	59 (39.1)	73 (45.9)	101 (64.7)	--	--	--
Mean age, years (SD)	44.8 (12.8)	45.1 (14.5)	37.6 (14.6)	0.890	<0.001*	<0.001*
Female, %	86.1	79.2	72.4	0.457	0.158	0.001
Mean weight, kg (SD)	72.5 (20.2)	71.1 (19.7)	65.3 (20.7)	0.457	0.001*	0.001*
Mean duration of PAH, months (SD)	8.7 (17.4)	11.8 (25.6)	5.0 (10.1)	0.715	0.009*	0.016*
WHO FC, score (%) I II III IV	 2 (1.8) 21 (18.8) 85 (75.9) 4 (3.6)	 3 (1.9) 35 (22.7) 108 (70.1) 8 (5.2)	 2 (1.3) 47 (30.5) 102 (66.2) 3 (1.9)	0.800	0.222	0.143
Median 6MWD, m (IQR)	335 (264, 385)	340 (278, 389)	357 (285, 395)	0.531	0.247	0.077
Median BDS	4.0 (3.0, 5.0)	3.5 (2.0, 5.0)	3.5 (2.0, 5.0)	0.252	0.667	0.446

6MWD, 6 minute walking distance; BDS, Borg dyspnea score; WHO FC, World Health Organization functional class; IQR, interquartile range | *Statistically significant value

RESULTS

- A total of 466 patients were included in this analysis (SC, N=233; oral, N=233). The mean SC and oral treprostinil dose at week 12 was 9.3 ng/kg/min and 13.8 ng/kg/min, respectively.
- In this analysis, the median doses in the low (<6.3 ng/kg/min), medium (6.3 to 13.4 ng/kg/min), and high dose (>13.5 ng/kg/min) groups were 3.7, 9.1, and 18.5 ng/kg/min, respectively and the groups had respective median 6MWD improvements of 13, 22, and 30 meters. [Table 2]
- There was a statistically significant difference in 6MWD improvement between low/high dose groups (p=0.013) and a statistically significant linear trend for 6MWD improvement with higher doses (Jonckheere-Terpstra test, one-sided p=0.0052).
- Significant differences in Borg dyspnea score were found between low/medium groups (p=0.007) and low/high groups (p<0.001) with median improvements of 0.0, 1.0, and 1.0 in the low, medium, and high groups, respectively. [Table 3]
- There were differences observed in WHO FC improvements between dose groups but these differences did not reach statistical significance.

Table 2. Change in 6MWD, BDS, and WHO FC by Dose Tertile

	Low (n = 151)	Medium (n = 159)	High (n = 156)
Median dose at week 12, ng/kg/min (range)	3.7 (0.4 to 6.1)	9.1 (6.3 to 13.4)	18.5 (13.5 to 60.4)
Median change in 6MWD, m (IQR)	13 (-18, 55)	22 (-13, 58)	30 (-6, 70)
Median change in BDS, (score)	0.0 (-1.0, 1.0)	-1.0 (-2.0, 0.0)	-1.0 (-2.0, 0.0)
Change in WHO FC Unchanged; worsened, n (%) Improved, n (%)	 57 (50.9) 55 (49.1)	 62 (40.3) 92 (59.7)	 73 (47.4) 81 (52.6)

Table 3. Differences in 6MWD, BDS, and WHO FC Between Dose Tertile

	Low vs Medium	Medium vs High	Low vs High
6MWD	0.287	0.112	0.013*
BDS	0.007*	0.191	<0.001*
WHO FC	0.085	0.207	0.574

6MWD, 6 minute walking distance; BDS, Borg dyspnea score; WHO FC, World Health Organization functional class; IQR, interquartile range | *Statistically significant value

Figure 1. Comparative Histogram for Treatment Subjects

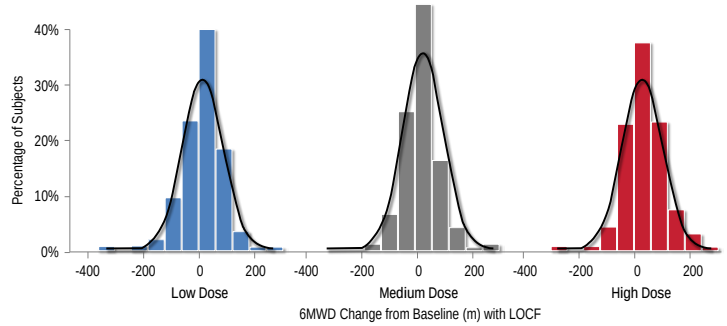
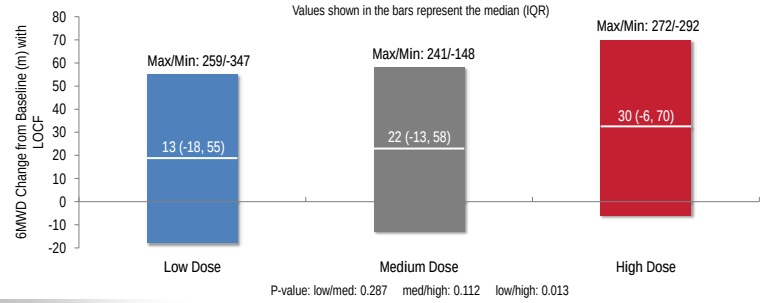


Figure 2. Change in Exercise Capacity by Trepostinil Dose Tertile



CONCLUSIONS

- This combined analysis of SC and oral treprostinil provides evidence for the dose-response relationship of treprostinil.
- Increased treprostinil dose is associated with improvements in 6MWD and Borg dyspnea score.
- Although these results are modest, the treprostinil doses used in both studies are relatively low compared to those used in clinical practice today. For instance, the median dose in the high dose group was 18.5 ng/kg/min, which approximately corresponds to an oral treprostinil regimen of 3 mg TID.
- Despite a strong correlation between 6MWD change and dosing tertile, the existence of patient variation for 6MWD change within dosing tertiles limits the predictability of a dose-dependent response.
- Results from this novel post-hoc analysis suggest that systemically administered treprostinil, in oral or SC formulations, produces statistically and clinically significant, dose-dependent therapeutic responses.

REFERENCES:
1. Simmoneau G et al. *Am J Respir Crit Care Med*. 2002 Mar 15;165(6):800-4.
2. Jing ZC et al. *Circulation*. 2013 Feb 5;127(5):624-33.

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