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Outcome of pulmonary hypertension subjects transitioned from intravenous prostacyclin to oral bosentan

Zeenat Safdar*

Division of Pulmonary-Critical Care Medicine, Baylor College of Medicine, 6620 Main Street, Suite 11B.09, Houston, Texas 77030, USA

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Summary
Introduction: Prostacyclin (PG) remains the gold standard therapy for severe pulmonary arterial hypertension (PAH). Previously, we reported the successful transitioning of PAH subjects from intravenous prostacyclin to oral bosentan (Suleman et al. Chest 2004;126:808–15). We report here the 5-year follow-up data.
Methods: In the transition study, 11 PAH subjects were successfully transitioned to oral bosentan in 12 weeks. Two subjects who subsequently developed liver function test (LFT) abnormalities were taken off bosentan and switched to another endothelin receptor antagonist. Demographics, six-minute walk distance (6MWD), WHO functional class (FC), and survival data was collected.
Results: 10 Females and 1 male ranging in age from 35 to 79 were successfully transitioned. Mean duration of illness prior to transition was 50.55 ± 26 months. Mean duration that these subjects remained on oral therapy was 34 ± 24 months. Mean duration that patients remained off PG was 28 ± 21 months. In 7 of the 11 subjects (64%), PG was resumed due to clinical deterioration. One patient remained on bosentan as monotherapy, five had phosphodiesterase 5-inhibitor added. 9 Of the 11 subjects were WHO FC II post-transition and 5 of the 7 subjects at follow-up were WHO FC II (82% vs 67%). Post-transition 6MWD was 386 ± 85 in 10 subjects and at follow-up 6MWD was 396 ± 99 in 9 subjects ($p = 0.81$).
Conclusions: In this study, patients frequently required prostanoid resumption after transition from intravenous prostanoid to oral therapy. However, in these carefully selected patients, transition to oral therapy offered prolonged stable FC and 6MWD, cost savings and substantial quality of life benefits.

* Tel.: +1 713 798 2400; fax: +1 713 798 2688.
E-mail address: safdar@bcm.edu

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Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease that results from remodeling of pulmonary arteries and leads to right heart failure.[1,2] Intravenous prostacyclin (PG) was the first FDA approved therapy to treat PAH.[3] Subsequently, oral agents became available and several papers indicated that carefully selected PAH patients could be successfully transitioned from systemic prostanoids (epoprostenol IV or treprostinil subcutaneously) to oral agents such as an endothelin receptor antagonist (ERA) or phosphodiesterase 5-inhibitor (PDE5-i).[4–6]

Although prostanoids remain the preferred treatment for PAH patients with severe disease, this therapy has socioeconomic and psychological impact on the patients. A chronic indwelling catheter and the side-effect profile of PG can influence the quality of life in these patients. Various studies have shown that patients transitioned to oral agent can maintained their stable functional status and walk distance over a short period of time.[4,6,7] However, long-term follow-up data after the successful transition to oral therapy is missing. This is important, as PAH is a progressive disease and most patients require escalation of therapies over time.[8] In addition, with the FDA approval of newer agents since the initial approval of epoprostenol, offers an option to start patients on these agents.[9–11] In addition, availability of newer agents as part of a research protocols may be an option for these patients.

We present our long-term data for up to 70 months on eleven patients that were successfully transitioned from continuous systemic prostanoids (treprostinil — TRE; or epoprostenol — EPO) to oral bosentan in 2002–2003 in our previously reported study.

Methods

In the previous study, 11 PAH subjects were successfully transitioned to oral bosentan in 12 weeks.[4] Two PAH subjects subsequently developed liver function abnormalities and were switched to another ERA and nine were continued on bosentan. Demographic, six-minute walk distance (6MWD), WHO functional class (FC), and long-term data was obtained.

Immediate post-transition data and data at last clinic follow-up were obtained. Except for the four patients that relocated to other areas, the last date for the data collection was August 2008. One patient relocated 5 months after transition and therefore no data could be obtained (patient 9), the remaining 3 patients relocated 2.5 years, 5 years and 7 years after the transition. Estimated pulmonary artery systolic pressure and cardiac output were obtained from an echocardiogram.

Statistical analysis: Data presented as mean $\pm$ SD. p-value considered significant at 0.05.

Results

10 Females and 1 male that were successfully transitioned to oral bosentan had ages ranging from 35 to 79 (Table 1). Duration of illness at the time of transition ranged from 17 to 112 months. Mean duration that these subjects remained on oral therapy (ERA and PDE5-i) was 34 ± 24 months (range 3–70 months) (Table 2). Mean duration that patients remained off PG was 28 ± 21 months.

Prostacyclin therapy was resumed in seven of the eleven subjects due to clinical deterioration (range 3–68 months). The dose of the PG at the time of follow-up was similar to the dose prior to transition ($p = 0.62$). One patient remained on bosentan monotherapy 70 months after successful transition. One patient who was on bosentan monotherapy relocated 5 months following transition and died two years later at the age of 75. Four patients remain off any prostacyclin therapy at the time of last clinic follow-up. One patient was started on oral treprostinil (as part of a research protocol). One patient who was started on epoprostenol underwent successful lung transplantation and following that was not on any PAH therapy. Five had a PDE5-i added to their regimen.

9 Of the 11 subjects were WHO FC II post-transition and 6 of the 9 subjects at last follow-up were WHO FC II (82% vs 67%) (Fig. 4). Post-transition 6MWD was 386 ± 85 in 10 subjects and at follow-up 6MWD was 396 ± 99 in 9 subjects ($p = 0.81$) (Fig. 1). The six-minute walk distance was

Table 1 Demographics of successful transitions.

Patient no.	Gender	Age, year	Race	Etiology of PAH	Duration of illness at transition, months
7	Female	50	Caucasian	IPAH	36
8	Female	74	Caucasian	IPAH	17
9	Female	79	Caucasian	CVD	58
10	Female	38	Caucasian	IPAH	46
11	Female	51	Hispanic	CVD	59
12	Female	43	Caucasian	IPAH	60
13	Male	47	Hispanic	IPAH	112
17	Female	50	Afrco-American	CVD	28
18	Female	65	Caucasian	CVD	45
22	Female	35	Afrco-American	PAH (HIV)	27
23	Female	62	Caucasian	CVD	68
Mean $\pm$ SD		54 ± 14			50 ± 25

IPAH, idiopathic pulmonary arterial hypertension; and CVD, collagen vascular disease.