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

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Prostanoid; Endothelin receptor antagonist; Right heart failure

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.

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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.\textsuperscript{1,2} Intravenous prostacyclin (PG) was the first FDA approved therapy to treat PAH.\textsuperscript{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).\textsuperscript{4,6,7}

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{9,10,11} 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.\textsuperscript{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 ± 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>
<thead>
<tr>
<th>Patient no.</th>
<th>Gender</th>
<th>Age, year</th>
<th>Race</th>
<th>Etiology of PAH</th>
<th>Duration of illness at transition, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Female</td>
<td>50</td>
<td>Caucasian</td>
<td>IPAH</td>
<td>36</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>74</td>
<td>Caucasian</td>
<td>IPAH</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>79</td>
<td>Caucasian</td>
<td>CVD</td>
<td>58</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>38</td>
<td>Caucasian</td>
<td>IPAH</td>
<td>46</td>
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<tr>
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<td>Female</td>
<td>51</td>
<td>Hispanic</td>
<td>CVD</td>
<td>59</td>
</tr>
<tr>
<td>12</td>
<td>Female</td>
<td>43</td>
<td>Caucasian</td>
<td>IPAH</td>
<td>60</td>
</tr>
<tr>
<td>13</td>
<td>Male</td>
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<td>Hispanic</td>
<td>IPAH</td>
<td>112</td>
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<td>17</td>
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<td>50</td>
<td>Africo-American</td>
<td>CVD</td>
<td>28</td>
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<td>65</td>
<td>Caucasian</td>
<td>CVD</td>
<td>45</td>
</tr>
<tr>
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<td>35</td>
<td>Africo-American</td>
<td>PAH (HIV)</td>
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<td>23</td>
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<td>62</td>
<td>Caucasian</td>
<td>CVD</td>
<td>68</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>54 ± 14</td>
<td>50 ± 25</td>
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</tbody>
</table>

IPAH, idiopathic pulmonary arterial hypertension; and CVD, collagen vascular disease.
maintained in 9 patients at the time of last follow-up. The hemodynamic data was obtained from the echocardiogram post-transition and compared with the echocardiogram at last follow-up. There was no significant change over the time of follow-up in right ventricular systolic pressures ($p = 0.87$) (Fig. 2) and cardiac output ($p = 0.29$) (Fig. 3).

**Discussion**

Parenteral prostanoid remain the gold standard of therapy for treating patients with severe PAH.12,13 We had previously reported the successful transition of eleven PAH patients who were on PG to oral bosentan.4 At the time of our original transition study, bosentan was the only FDA approved ERA available in USA.14,15 In this one center study, many patients resumed PG (64%) but had a prolonged prostanoid free honeymoon period. In these patients six-minute walk distance and functional class was unchanged. PAH is a progressive disease that requires escalation of therapy over time.8 In our study, 45% had a second oral

![Figure 1](image1.png)  
**Figure 1** Six-minute walk distance post-transition and at last follow-up. Six-minute walk distance (meters) after transition to oral bosentan and at the time of last follow-up. Patient 8 refused the reinstatement of PG therapy. Patient 9 relocated to another state 5 months after transition to oral bosentan (11/20/2002) and later died (8/4/2004). Patient 7 relocated 5 years after transition and was on epoprostenol at that time. Patient 12 relocated 4 years and 2 months after transition and was on subcutaneous treprostinil. Patient 18 relocated 3 years after the transition while on epoprostenol (6/23/2005) and later died (9/19/2005).

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>PG type</th>
<th>PG dose at transition (ng/kg/min)</th>
<th>PG resumed</th>
<th>Current PG dose (ng/kg/min)</th>
<th>Duration on oral therapy, months</th>
<th>PDE5-i</th>
<th>ERA</th>
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<tr>
<td>7a</td>
<td>EPO</td>
<td>16</td>
<td>EPO</td>
<td>18</td>
<td>30</td>
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<tr>
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<td>None</td>
<td>62</td>
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<td>Yes</td>
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<tr>
<td>9a,b</td>
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<td>NA</td>
<td>NA</td>
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<td>70</td>
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<td>11</td>
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<td>TRE-o</td>
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<td>12a</td>
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<td>TRE-sc</td>
<td>60</td>
<td>9</td>
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<tr>
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<td>EPO</td>
<td>54</td>
<td>EPO</td>
<td>70</td>
<td>18</td>
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</tr>
<tr>
<td>17</td>
<td>TRE</td>
<td>18</td>
<td>EPO</td>
<td>14</td>
<td>33</td>
<td>No</td>
<td>No</td>
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<tr>
<td>18a,b</td>
<td>TRE</td>
<td>19</td>
<td>None</td>
<td>None</td>
<td>37</td>
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<td>No</td>
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<tr>
<td>22</td>
<td>EPO</td>
<td>10</td>
<td>EPO</td>
<td>16</td>
<td>35</td>
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<td>No</td>
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<tr>
<td>23</td>
<td>TRE</td>
<td>9</td>
<td>EPO</td>
<td>Lung transplant</td>
<td>3</td>
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<tr>
<td>Mean ± SD</td>
<td>26 ± 15</td>
<td></td>
<td>31 ± 27</td>
<td>34 ± 24</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PG, prostacyclin; EPO, epoprostenol; TRE-o, oral treprostinil; TRE-sc, subcutaneous treprostinil; PDE5-i, phosphodiesterase 5-inhibitor; ERA, endothelin receptor antagonist; and NA, not available.

a Pt relocated.
b Patient died.
agent added to their regimen. A second agent and sometimes a third agent were added to maintain clinical status in PAH subjects. More than half of the patients were continued on the ERA and three of the seven patients (43%) that resumed PG were also started on a second oral agent. These data suggest that it may be possible to maintain the walk distance and functional status by adding a second agent after resuming the PG. Most of the patients that continued on oral therapy ultimately required combination therapy—an as yet unproven treatment modality although as demonstrated here a common clinical practice. Clinical trials testing different combination of PAH drugs are underway to determine the efficacy and safety of the combination therapies.

In a previous single center study by Diaz-Guzman et al. 15 of the 21 patients were successfully transitioned to oral therapy and maintained on an oral agent 24 month after transition. In this study, successfully transitioned patients were older than those that failed transition. The successfully transitioned patients had longer duration of prostanooid therapy, though not significantly different. There were no significant differences in 6MWD, BNP, or RVSP between the groups. Moreover, the duration of weaning period was similar, and the dose of PG was not different between the two groups.

In the study by Suleman et al, although there was a trend towards longer duration of PG therapy, higher doses of PG, and higher PAPs by ECHO in patients that failed transition, these were not statistically significant. In addition, there was no difference in age or etiology of PAH between the successfully and failed transitioned groups.

In the study by Steiner et al, successfully transitioned patients had lower PG dose, and lower PA pressures as compared to failed group. There was a trend towards better WHO FC, 6MWD, and Borg Dyspnea score in the transitioned patients at baseline. Johnson et al conducted a retrospective review of 13 patients that were transitioned to oral bosentan or sildenafil from intravenous epoprostenol. The mean dose of PG before weaning was 23 ng/kg/min, similar to the mean dose reported by Steiner, and Suleman et al. Three patients were re-started back on prostacyclin and nine patients remained on an oral agent (69%).

In all these studies, patients that were considered for transitioning to oral therapy had to meet certain criteria for disease stability. The two criteria that were considered important in each of these studies were (1) infrequent or no change in PG dose and (2) no evidence of right heart failure. The mean duration of weaning period was 3, 4.5, 6 and 11 months in the studies by Suleman, Steiner, Johnson and Diaz-Guzman respectively. Given the small number of patients that were transitioned, data on duration of PG therapy, 6MWD and hemodynamic is difficult to interpret.

In our study, patients were continued on bosentan as monotherapy for a mean duration of 25 months and on combination oral therapy for a mean duration of 34 months excluding oral prostacyclin. Many patients (57%) remained stable for substantial period of time on an oral agent.

In the study by Steiner et al 22 patients were identified from 5 PH centers and ten were successfully transitioned to oral bosentan. Seven of these ten patients (70%) were maintained on oral therapy after a mean follow-up of 17.7 months with stable walk distance, WHO functional class, and PA systolic pressures. This is in line with our observation where most patients that were re-started on a prostacyclin therapy maintained stable clinical status with unchanged functional status and walk distance.

In our study, none of the patients died immediately after transitioning to an oral agent. Two patients on an ERA relocated, and later died. One patient had PDE5-i added prior to relocation. No deaths could be attributable to the transition. Two patients that developed liver function abnormalities were taken off bosentan. After the normalization of their liver function test they were switched to another oral ERA as part of a research protocol. Another
patient who was on oral therapy for 68 months was started on oral PG as part of a research protocol while being continued on the ERA. These options were not available to treat these patients when they were initially transitioned to oral bosentan.

Intravenous PG though life-saving therapy for severe PAH patients involves an indwelling catheter with continuous infusions. Oral agents can provide a prolonged, safe and beneficial period without the risk of line infection, pain, prostanoid side-effects and limitation to quality of life imposed by parenteral drug administration. The option to transition patients that are on stable PG is an attractive one. These patients had other therapies added during the course of their illness. Although majority of the patients were resumed on PG, walk distance, functional status, and hemodynamics were maintained. Carefully selected patients can be transitioned to oral therapy while maintaining their walk distance and functional status. In these patients, resuming PG does not result in decline of their clinical status. These results suggest that transition to oral therapy may be a viable option in carefully selected patients and that these patients could maintain stable clinical status while enjoying a prolonged prostanoid free honeymoon period.

Conflict of interest statement

Dr Safdar is on the Scientific Advisory Board and Speaker for Gilead Sciences, Actelion and United Therapeutics.

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References


