Addition of Prostanoids in Pulmonary Hypertension Deteriorating on Oral Therapy

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Background: The aim of our study was to describe the efficacy of addition of intravenous or subcutaneous prostanoids in idiopathic pulmonary arterial hypertension (PAH) patients deteriorating on bosentan or on bosentan-sildenafil.

Methods: PAH treatment at our hospital is standardized with first-line oral therapy in New York Heart Association class III patients followed by addition of prostanoids on clinical worsening.

Results: Mean improvement in 6-minute walk distance after 4 months of prostanoids was 86 m (p < 0.01) in the bosentan group versus 41 m (p < 0.05) in the bosentan-sildenafil group, and these improvements persisted at long-term follow-up.

Conclusions: From these results we conclude that addition of subcutaneous or intravenous prostanoids can be efficacious in PAH deteriorating on oral therapy. J Heart Lung Transplant 2009;28:280–4. Copyright © 2009 by the International Society for Heart and Lung Transplantation.

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature, leading to right heart failure and death. Novel therapies target three different pathways of abnormal pulmonary artery smooth-muscle-cell proliferation and contraction: the prostacyclin, nitric oxide and endothelin pathways.1–4 Data on combining these therapies are limited. Sildenafil added to bosentan has been shown to improve exercise capacity.5–7 Bosentan added to beraprost or iloprost improves exercise capacity and hemodynamics.8,9 However, bosentan–epoprostenol given up-front showed no benefit versus epoprostenol in one study with a limited number of patients.10 Studies have shown contradictory results when inhaled iloprost was added to bosentan.11–15 Currently, first-line oral therapy is preferred,14–16 but 56% of patients require additional treatment within 2 years.17 The World Health Organization (WHO) recommends adding prostacyclin.18 No studies have described the efficacy of combination therapy with subcutaneous or intravenous prostanoids added to existing oral therapy. The aim of this study was to describe short- and long-term efficacy of intravenous epoprostenol or subcutaneous treprostinil in PAH deteriorating on oral therapy.

METHODS
Study Design and Patients

We performed an observational study of idiopathic PAH patients attending our hospital and starting first-line bosentan therapy from January 2002 to September 2007. Our hospital is a referral center for PAH in The Netherlands. Treatment is standardized. Diagnosis is confirmed by right heart catheterization. For New York Heart Association (NYHA) Class III patients the first-line therapy is bosentan (Tracleer; Actelion Pharmaceuticals) given at 62.5 mg twice daily, then increased to 125 mg twice daily after 1 month. Assessments are made at least every 4 months by symptoms, 6-minute walk distance (6MWD) and NYHA class. At our center clinical worsening is defined by a deterioration of NYHA class or a ≥10% decrease in 6MWD, measured on two occasions, in combination with increasing PAH symptoms, such as shortness of breath, collapse or signs of right heart failure. Upon clinical worsening, sildenafil is added and, with further clinical worsening, intravenous
or subcutaneous prostanoids are given. The addition of sildenafil has been an option since 2004. Patients treated with bosentan vs bosentan-sildenafil were compared for prostanoid efficacy.

**Addition of Prostanoids**

Prostanoid choice is a personal decision taking side effects and mode of delivery into consideration. Treprostinil (Remodulin; United Therapeutics) dose is gradually increased to 10 ng/kg/min after 1 week and 20 ng/kg/min after 6 weeks.

Epoprostenol (Flolan; GlaxoSmithKline) is titrated to the maximal tolerated dose, usually 6.0 to 8.0 ng/kg/min after 1 week. Further dose adjustments are made according to each patient’s need. Prostanoids are not started in patients unable to tolerate continuous pump infusion or if declined.

**Magnetic Resonance Imaging and N-terminal Pro–B-type Natriuretic Peptide**

Since 2004, cardiac magnetic resonance imaging (MRI) is performed during change of therapy as part of an ongoing study evaluating the clinical value of MRI in PAH. A Siemens 1.5-T Sonata scanner is used to acquire short-axis cine images from apex to base. Endocardial contours are delineated manually by a blinded observer and processed using Mass software (Department of Radiology, Leiden University Medical Centre) to obtain right and left ventricular end-diastolic volume (RVEDV and LVEDV) and left ventricular end-systolic volume (LVESV). Stroke volume (SV) is calculated by: LVEDV - LVESV = SV. Parameters are indexed for body surface area. N-terminal pro–B-type natriuretic peptide (NT-proBNP) is measured by electrochemiluminescence immunoassay (ECLI; Roche).

The requirements of the hospital research and ethics review boards were met and informed consent was obtained from all participants.

**Statistical Analysis**

The 6MWD was analyzed by analysis of variance (ANOVA), MRI parameters and NT-proBNP by 2-tailed t-test, and NYHA class by Wilcoxon’s test. Results are presented as mean ± SE. Pearson’s correlation was used to compare MRI parameters and 6MWD changes. Prism version 4 (GraphPad) software was used for analyses.

**RESULTS**

**Patient Characteristics**

In the study period, 63 idiopathic PAH patients were started oral therapy. Follow-up was 32.8 ± 18.1 months. At end of the observation period, 19 of these patients remained stable on bosentan, 18 were stable on bosentan-sildenafil, and in 16 prostanoids were added. In 10 patients, clinical worsening and death occurred without prostanoid initiation. Reasons for not starting prostanoids despite clinical worsening and death were: inability to deal with pump infusion (n = 5); death from a non-PAH cause (n = 2; 1 pneumonia and 1 trauma); out-of-hospital death before initiation of prostanoids (n = 2); and patient refusal (n = 1).

The characteristics of the 16 patients in whom prostanoids were added are given in Table 1. In 6 patients, prostanoids were added to bosentan, and in 10 to bosentan-sildenafil. Mean time between start oral therapy and addition of prostacyclin was 20.6 ± 5.0 months. This duration was shorter for patients treated with bosentan compared to those treated with bosentan-sildenafil: 8.7 ± 1.8 vs 27.8 ± 7.0 months (p = 0.06), respectively.

**NYHA Class, 6MWD and Outcomes**

NYHA class improved after prostanoid addition (p = 0.002). In the 16 patients in whom prostanoids were added, mean 6MWD was 400 ± 32 m at baseline, 425 ± 27 m after 4 months of oral therapy, 363 ± 27 m at start of prostanoids, and 427 ± 24 m 4 months thereafter. A decrease of 61 ± 17 m in 6MWD led to prostanoid addition. Four months thereafter 6MWD improved 64 ± 18 m (p < 0.001; 95% confidence interval [CI] 22.4 to 105.6; Figure 1). Treprostinil and epoprostenol efficacy were not significantly different (Table 2). After 4 months of prostanoid treatment all patients had stabilized or improved.

At the end of observation, after 18.4 ± 3.9 months, prostacyclin 6MWD was 436 ± 22 m, showing a persisting 73 ± 22 m improvement compared with 6MWD at the start of prostanoid therapy (p = 0.005; 95% CI 25.6 to 119.7). The 6MWD was still better than at start of oral therapy 37.0 ± 4.4 months earlier. Of the 16 patients, there was 1 death (6%), which occurred in the bosentan–prostanoid group after 15 months of prostanoid treatment. Post-mortem examination revealed

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
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<tr>
<td>Subjects (n)</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Age, in years (mean ± SD)</td>
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<tr>
<td>Prostanoid added</td>
</tr>
<tr>
<td>Epoprostenol</td>
</tr>
<tr>
<td>Treprostinil</td>
</tr>
<tr>
<td>Right heart catheterization at baseline</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
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<tr>
<td>RAP (mm Hg)</td>
</tr>
<tr>
<td>SVO₂ (%)</td>
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<tr>
<td>CI (liters/min/m²)</td>
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</table>

Data are represented as mean ± SE where appropriate; MPAP, mean pulmonary artery pressure; RAP, right atrial pressure; SVO₂, mixed venous oxygen saturation; CI, cardiac index.
pulmonary veno-occlusive disease. The remaining 15 patients showed continued clinical improvement.

Prostanoid Efficacy: Bosentan vs Bosentan–Sildenafil

The 6MWD in the bosentan group was 323 ± 53 m at addition of prostanoids, 409 ± 48 m at 4 months, and 447 ± 48 m at end of observation. The 6MWDs in the bosentan–sildenafil group were 387 ± 30 m, 428 ± 23 m and 429 ± 23 m at start, 4 months and end of observation, respectively. Improvement in 6MWD at 4 months with prostanoids was 86 m (p < 0.01) for bosentan and 41 m (p < 0.05) for bosentan–sildenafil (Figure 2). The 6MWD improvement in the bosentan group was not significantly different from that in the bosentan–sildenafil group (p = 0.10). Time on prostanoids was 27.0 ± 7.7 months in the bosentan group and 13.2 ± 3.5 months in the bosentan–sildenafil group.

Cardiac MRI and N-terminal-proBNP Serum Levels

MRI was performed on 10 patients before and 6 months after prostanoid addition (Table 3). MRI parameter and 6MWD improvements were correlated; Pearson’s correlation values were as follows: r = 0.94 (p < 0.001) for LVEDVI; r = −0.49 (p = 0.18) for RVEDVI; r = 0.64 (p = 0.06) for SVI; and r = 0.57 (p = 0.11) for CI.

Table 2. Change in 6MWD Distances in the Treprostinil and Epoprostenol Subgroup After 4 Months of Prostanoid Therapy

<table>
<thead>
<tr>
<th>Prostanoid</th>
<th>6MWD at start</th>
<th>Change in 6MWD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol</td>
<td>263 ± 48</td>
<td>+ 83</td>
<td>+14 to +152</td>
</tr>
<tr>
<td>Treprostinil</td>
<td>421 ± 93</td>
<td>+ 57</td>
<td>+ 8 to +107</td>
</tr>
</tbody>
</table>

6MWD, 6-minute walk distance (in meters); CI, confidence interval.

NT-proBNP was measured in 11 patients. After prostanoids, NT-proBNP decreased from 2,830 ± 818 ng/liter to 1,574 ± 447 ng/liter. Mean decrease was 1,256 ± 430 ng/liter (p < 0.05; 95% CI 298 to 2,215 ng/liter). The BNP decrease was 987 ± 1,224 ng/liter in the bosentan group and 1,316 ± 489 ng/liter in the bosentan–sildenafil group, with no significant difference between the two groups (p = 0.78).

Prostanoid Dose and Adverse Effects

At the end of the observation the treprostinil dose was 38.4 ± 5.7 ng/kg/min and the epoprostenol dose was 16.0 ± 2.8 ng/kg/min. Maximal doses were reached after 16.2 ± 5.9 and 7.3 ± 2.8 months, respectively. There were no treatment-related deaths.

Four of 10 treprostinil patients had irritation at the needle insertion site, although symptoms generally subsided. One of these patients was switched to epoprostenol. Two treprostinil patients reported headaches and 1 had nausea. Their symptoms subsided spontaneously. One diarrhea case was treated with loperamide.

Four of 6 epoprostenol patients had intravenous portacath-related infections, for which the device was replaced. In 2 patients, infections recurred, which required a switch to subcutaneous treprostinil. The rate of infusion-related infections was 0.7 per 1,000 prostanoid infusion days.

DISCUSSION

These present data are the first to describe the efficacy and long-term follow-up of intravenous or subcutaneous prostanoids added in PAH deteriorating on oral therapy. Both 6MWD and NYHA class showed improve-
ment. This improvement persisted at long-term follow-up. Findings were corroborated by improvements in cardiac function measured by MRI and decreased NT-proBNP serum levels. NYHA class, 6MWD, NT-proBNP, stroke volume and right and left ventricular end-diastolic volume are all known to correlate with disease severity and outcome in PAH.19–22

The 64-m increase in 6MWD after prostanoid addition compares favorably with the 30-m increase reported for inhaled iloprost added to bosentan.11 The improvement may have been a sole effect of prostacyclin2; however, the BREATHE-2 study showed a tendency toward improved hemodynamics with first-line bosentan–epoprostenol compared with epoprostenol alone.10 Because oral therapy was continued, a synergistic effect cannot be excluded.

This study did not aim to investigate the effects of sildenafil added to bosentan. Earlier studies5–7 showed that this strategy leads to improved exercise capacity.

In our study time to addition of prostacyclin increased from 8.7 ± 1.8 to 27.8 ± 7.0 months after the introduction of sildenafil. It remains unclear whether prostacyclin addition is beneficial in non-deteriorating PAH. Furthermore, we cannot exclude a differential treatment effect between epoprostenol and treprostinil. Mortality in our patients was similar to rates recently reported.17 Initial improvement with oral therapy is in line with earlier study results.

Adverse effects of prostanoid addition were few and mainly related to infectious and inflammatory complications at the prostanoid infusion site. The rate of this complication was similar to earlier findings.23 Post-mortem evaluation in the only PAH death after addition of prostanoids revealed pulmonary veno-occlusive disease, thus explaining her bad outcome.

Study limitations include lack of a control group and limited patient numbers. Performing an adequately sized, randomized, placebo-controlled trial addressing the issue of adding subcutaneous or intravenous prostanoids in patients worsening on oral therapy deprives deteriorating patients of the chance of improvement on prostanoids. Considering the limited life expectancy of these patients this would not be ethically sound practice. Data on safety and long-term efficacy of combination therapy in PAH are sparse. Due to the rarity of this disorder it is practically impossible to obtain answers to all questions regarding efficacy, adverse effects and long-term outcome with combination therapy from randomized, controlled trials. Some of the most relevant data currently available have not been derived from formal trials but rather from large pulmonary hypertension centers presenting long-term experiences with their therapeutic approaches.24 To support the findings of this uncontrolled study, we used NT-proBNP and MRI measurements. These data show that addition of prostacyclin improves pulmonary hemodynamics and right ventricular function. For these reasons we believe this observational study has high clinical value.

In conclusion, adding subcutaneous and intravenous prostanoids in deterioration on oral therapy is an effective approach to treatment of idiopathic PAH.

REFERENCES


Table 3. Cardiac MRI Parameters Before and 6 Months After Addition of Prostanoid Therapy (n = 10)

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>Mean change</th>
<th>95% CI</th>
<th>p-value</th>
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<tbody>
<tr>
<td>SVI (ml/m²)</td>
<td>27.1 ± 3.0</td>
<td>36.1 ± 2.7</td>
<td>+9.0</td>
<td>+5.4 to +12.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDVI (ml/m²)</td>
<td>42.1 ± 3.4</td>
<td>53.2 ± 4.6</td>
<td>+11.1</td>
<td>+6.2 to +16.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVEDVI (ml/m²)</td>
<td>84.0 ± 7.8</td>
<td>76.5 ± 7.0</td>
<td>−7.5</td>
<td>−0.9 to −14.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CO (liters/min)</td>
<td>4.0 ± 0.3</td>
<td>4.7 ± 0.4</td>
<td>+0.7</td>
<td>0.0 to +1.5</td>
<td>=0.06</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>33 ± 5</td>
<td>44 ± 6</td>
<td>+12</td>
<td>+4 to +9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>66 ± 5</td>
<td>70 ± 3</td>
<td>+6</td>
<td>−3 to +14</td>
<td>=0.19</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SE. SVI, stroke volume index; LVEDVI, left ventricular end-diastolic volume index; RVEDVI, right ventricular end-diastolic volume index; CO, cardiac output; RVEF, right ventricular ejection fraction; LVEF, left ventricular ejection fraction.


