Chapter 4

Addition of prostanoids in pulmonary hypertension deteriorating on oral therapy

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Abstract

Background
The World Health Organisation recommends adding prostacyclin derivatives to oral therapy in deteriorating pulmonary arterial hypertension (PAH) patients. However there are no data defining the usefulness of intravenous or subcutaneous prostanoids in this setting. 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
Treatment at our hospital is according to a predefined protocol. First line therapy is bosentan. Upon clinical worsening, defined by a 10% decrease in 6 minute walk distance (6MWD) in combination with increasing PAH symptoms or deterioration of NYHA functional class, prostanoids are initiated. Response is assessed by change in 6MWD, NYHA class and after 2004 also by cardiac MRI and Nterminal-proBNP (BNP).

Results
63 idiopathic PAH (iPAH) started oral therapy. In 16 iPAH prostanoids were added after 20.6 ± 18.1 (± SD) months. Mean 6-minute walk distance improvement after 4 months prostanoids was +86m (p<0.01) in the bosentan group versus +41m (p<0.05) in the bosentan-sildenafil group and improvements persisted at long-term follow-up. NYHA class improved, BNP decreased and cardiac MRI functional parameters improved.

Conclusions
From these results we conclude that addition of subcutaneous or intravenous prostanoids can be efficacious in PAH deteriorating on oral therapy.
Introduction

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 improves exercise capacity.\(^5\)\(^-\)\(^7\) Bosentan added to beraprost or iloprost improves exercise capacity and hemodynamics.\(^8\)\(^,\)\(^9\) However, bosentan-epoprostenol up-front showed no benefit versus epoprostenol in limited patient numbers. However, this study was underpowered and therefore inconclusive.\(^10\) For inhaled iloprost added to bosentan studies are contradictory. McLaughlin showed improved exercise capacity. A study by Hoeper et al. failed to show a positive effect.\(^11\)\(^-\)\(^13\)

Currently first-line oral therapy is preferred.\(^14\)\(^-\)\(^16\) However 56% need additional treatment within 2 years.\(^17\) The WHO recommends adding a prostacyclin derivative in PAH worsening on oral therapy.\(^18\) No studies describe 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 attending our hospital and starting first line bosentan from January 2002–September 2007. Our hospital is a referral centre for PAH in the Netherlands. Treatment is standardized. Diagnosis is confirmed by right heart catheterisation. In New York Heart Association (NYHA) class III patients first-line therapy is bosentan (Tracleer®; Actelion Pharmaceuticals): 62.5mg b.i.d., increased to 125mg b.i.d. after one month. Assessment is at least every 4 months by symptoms, 6-minute walk distance (6MWD) and NYHA class. In our centre clinical worsening is defined by a deterioration of NYHA class or a greater than 10% decrease in 6MWD, measured on 2 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 upon further clinical worsening intravenous or subcutaneous prostanoids. Adding sildenafil is possible since 2004. Patients treated with bosentan versus 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®; UnitedTherapeutics, Silverspring, U.S.A.) dose is gradually increased to 10ng/kg/min after 1 week and 20ng/kg/min
after 6 weeks. Epoprostenol (Flolan®; GlaxoSmithKline, London, United Kingdom) is titrated to the maximal tolerated dose, usually 6.0-8.0 ng/kg/min after 1 week. Further dose adjustments are according to patient need. Prostanoids are not started in patients unable to deal with continuous pump infusion and if declined.

**Magnetic resonance imaging and N-terminal Pro-B-type natriuretic peptide**

Since 2004 cardiac MRI is performed during change of therapy as part of an ongoing study evaluating clinical value of MRI in PAH. A Siemens-1.5T-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). Strokevolume (SV) is calculated: LVEDV-LVESV=SV. Parameters are indexed for body surface area. NT-proBNP is measured by electrochemoluminescence immunoassay (ECLIARoche).

Requirements of hospital research and ethical review boards were met. Informed consent was obtained.

**Statistical analysis**

6MWD was analysed by ANOVA, MRI parameters and NT-proBNP by two-tailed t-test, NYHA class by Wilcoxon. Results are presented as mean±SE. Pearson correlation compared MRI parameter and 6MWD changes. GraphPad Prism® version 4 software was used.

**Results**

**Patient characteristics**

In the study period 63 idiopathic PAH 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 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 non-PAH cause (n=2; 1 pneumonia and 1 trauma), out of hospital death before initiation of prostanoids (n=2) and patient declination (n=1).

The characteristics of the 16 patients in whom prostanoids were added are depicted 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 was shorter for patients treated with bosentan compared to those treated with bosentan-sildenafil: 8.7±1.8 versus 27.8±7.0 months (p=0.06).
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**NYHA functional class, 6MWD and outcomes**

After prostanoid addition NYHA class improved by 1 class or more in 10 and remained unchanged in 6 (p = 0.002). In the 16 patients in whom prostanoids were added mean 6MWD was 400 ± 32m at baseline, 425 ± 27m after 4 months oral therapy, 363 ± 27m at start prostanoids and 427 ± 24m 4 months thereafter. A 61 ± 17m 6MWD decrease led to prostanoid addition. 4 months thereafter 6MWD improved 64 ± 18m (p<0.001; 95%CI 22.4 to 105.6; Fig 1). Treprostinil and epoprostenol efficacy were not significantly different (Table 2). After 4 months prostanoids all patients had stabilized or improved.

At end of observation after 18.4 ± 3.9 months prostacyclin 6MWD was 436 ± 22 m, showing a persisting 73 ± 22m improvement compared to 6MWD at start prostanoids (p=0.005; 95% CI 25.6 to 119.7). 6MWD was still better than at start oral therapy 37.0 ± 4.4 months earlier. 1/16(6%) death had occurred. This was in the bosentan-prostanoid group after 15 months prostanoids. Post-mortem revealed pulmonary veno-occlusive disease. The 15 remaining showed persisting clinical improvement.

**Prostanoid efficacy: bosentan versus bosentan-sildenafil**

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

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Subjects n</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>3</td>
</tr>
<tr>
<td>Women</td>
<td>13</td>
</tr>
<tr>
<td>Age yrs ± SD</td>
<td>37.0 ± 10.9</td>
</tr>
</tbody>
</table>

**Prostanoid added:**

- Epoprostenol: 6
- Treprostinil: 10

**Right heart catheterisation at baseline**

| MPAP, mmHg | 56 ± 4 |
| RAP, mmHg  | 7.1 ± 1.2 |
| SvO₂, %    | 66 ± 2 |
| CI, l/min/m² | 2.6 ± 0.15 |

* Data are represented as mean ± SE where appropriate; m = months; yrs = years; PAP = pulmonary artery pressure; RAP = right atrial pressure; SvO₂ = mixed venous O₂ saturation; CI = cardiac index.
Table 2. Change in 6-minute walk distance (6MWD) in metres in treprostinil and epoprostenol subgroup after 4 months of prostanoid therapy.

<table>
<thead>
<tr>
<th>Prostanoid</th>
<th>6MWD at start prostanoid</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>

Table 3. Cardiac MRI parameters before and 6 months after addition of prostanoid therapy (n=10)*.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
<th>Mean change</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<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 (L/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>P=0.06</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>33 ± 5</td>
<td>44 ± 6</td>
<td>+ 12</td>
<td>+ 4 to + 19</td>
<td>P&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>P=0.19</td>
</tr>
</tbody>
</table>

* Values are given 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.

Figure 1. Mean 6-minute walk distance (6MWD) in meters ± SE in 16 idiopathic pulmonary arterial hypertension patients treated with first-line oral therapy and addition of prostanoids on clinical worsening. 6MWD is depicted at baseline, after 4 months oral therapy (4m), at addition prostanoid, after 4 months prostanoid (4m Pr) and at end of observation (End obs). Significant improvements occur after prostanoid addition (p<0.001). Prostanoid addition is after 20.6 ± 5.0 months oral therapy. End observation is after 18.4 ± 3.9 months prostanoid treatment.
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Cardiac MRI and N-terminal-proBNP serum levels

MRI was performed in 10 patients before and 6 months after prostanoid addition. Results in table 3 show improved RVEF, stroke volume and improved RV and LV end-diastolic volumes after prostanoid addition. MRI parameter and 6MWD improvements pearson r correlation values were 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.

NT-proBNP was measured in 11 patients. After prostanoids NT-proBNP decreased from 2830 ± 818nanog/L to 1574±447nanog/L. Mean decrease was 1256 ± 430nanog/L (95%CI 298 to 2215; p<0.05). BNP decrease was 987 ± 1224nanog/L in bosentan and 1316 ± 489 nanog/L in bosentan-sildenafil and not significantly different between both groups (p=0.78).

Prostanoid dose and adverse effects

At end observation treprostinil dose was 38.4 ± 5.7 ng/kg/min and epoprostenol dose 16.0±2.8ng/kg/min. Maximal doses were reached after respectively 16.2 ± 5.9 and 7.3 ± 2.8 months. No treatment related deaths occurred.

4/10 treprostinil had needle insertion site irritation. Usually symptoms subsided. One was switched to epoprostenol. 2 treprostinil patients reported headaches and 1 nausea. Symptoms subsided spontaneously. 1 diarrhoea was treated with loperamide. 4/6 epoprostenol had intravenous portacath catheter infections, for which it was replaced. In 2 infections recurred and these were switched to subcutaneous treprostinil. Rate of infusion related infections was 0.7/1000 prostanoid infusion days.
Discussion

These data are the first describing efficacy and long-term follow-up of intravenous or subcutaneous prostanoids added in PAH deteriorating on oral therapy. 6MWD and NYHA class improve. This improvement persists at long-term follow-up. Our data are further supported by an improvement 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.\textsuperscript{19,22}

The 64m increase in 6MWD after prostanoid addition compares favourably to the 30m increase reported for inhaled iloprost added to bosentan.\textsuperscript{11} The improvement could be a sole effect of prostacyclin.\textsuperscript{2} However the BREATHE-2 study showed a tendency towards improved hemodynamics with first-line bosentan-epoprostenol compared to epoprostenol alone.\textsuperscript{10} Since oral therapy was continued a synergistic effect cannot be excluded.

This study did not aim to investigate effects of sildenafil added to bosentan. Earlier studies\textsuperscript{5-7} showed this strategy leads to improved exercise capacity. In our study time till addition of prostanoyl 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 is similar to rates recently reported.\textsuperscript{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 reported figures.\textsuperscript{23} Post-mortem 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 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 the disorder it is practically impossible to obtain answers to all questions regarding efficacy, adverse effects and long-term outcome with combination therapy from randomised controlled trials. Some of the most relevant data currently available have not been derived from formal trials but from large pulmonary hypertension centres presenting long-term experiences with their therapeutic concepts.\textsuperscript{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 all above reasons we believe this observational study has high clinical value.
Conclusion

The results of this study show that adding subcutaneous or intravenous prostanoids in patients deterioration on oral therapy is an effective treatment approach in idiopathic PAH.

References


