Bosentan Therapy for Inoperable Chronic Thromboembolic Pulmonary Hypertension*

Marius M. Hoeper, MD; Thorsten Kramm, MD; Heinrike Wilkens, MD; Christine Schulze; Hans Joachim Schäfers, MD; Tobias Welte, MD; and Eckhard Mayer, MD

**Study objectives:** We performed an open-label multicenter study to evaluate the safety and efficacy of the dual endothelin receptor antagonist bosentan in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH).

**Patients:** Nineteen patients with inoperable CTEPH were enrolled.

**Measurements:** The primary end point was a change in pulmonary vascular resistance (PVR). Secondary end points included 6-min walk test, peak oxygen uptake ($V_\text{O}_2$), New York Heart Association functional class, serum levels of N-terminal-pro brain natriuretic peptide (NT-pro-BNP), and various other hemodynamic parameters.

**Results:** After 3 months of treatment with bosentan, PVR decreased from $914 \pm 329$ to $611 \pm 220$ dyne-s-cm$^{-5}$ ($p < 0.001$). Functional class and peak $V_\text{O}_2$ remained unchanged, but 6-min walk distance increased from $340 \pm 102$ to $413 \pm 130$ m ($p = 0.009$), and serum NT-pro BNP levels improved from $2,895 \pm 2,620$ to $2,179 \pm 2,301$ ($p = 0.027$). One patient died, presumably from influenza A infection, and another patient experienced progressive fluid retention despite reduction of PVR. Other than that, treatment was well tolerated by all patients.

**Conclusions:** This open-label pilot trial suggests that bosentan may offer a therapeutic option for patients with inoperable CTEPH. Randomized controlled trials are warranted to confirm these findings.

(CHEST 2005; 128:2363–2367)

**Key words:** hypertension, pulmonary; thromboembolism, endothelin

**Abbreviations:** CI = cardiac index; CPET = cardiopulmonary exercise testing; CTEPH = chronic thromboembolic pulmonary hypertension; INR = international normalized ratio; NT-pro-BNP = N terminal-pro brain natriuretic peptide; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAPm = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PEA = pulmonary endarterectomy; PVR = pulmonary vascular resistance; RAP = right atrial pressure; $Sv_\text{O}_2$ = mixed venous oxygen saturation; $V_\text{O}_2$ = oxygen uptake

Chronic thromboembolic pulmonary hypertension (CTEPH) develops in up to 3.8% of patients who survive acute pulmonary embolism. In addition, CTEPH is often identified during the diagnostic workup of patients with unexplained pulmonary hypertension, many of whom lacking a history suggestive of previous episodes of pulmonary embolism. Thus, the true incidence of CTEPH is unknown, but the entity has become a leading diagnosis in major referral centers for patients with severe pulmonary hypertension worldwide.

Left untreated, the prognosis of CTEPH is poor, and the 5-year mortality has been reported to approach 90% in patients when the mean pulmonary artery pressure (PAPm) is $> 30$ mm Hg. Surgical pulmonary endarterectomy (PEA) is the procedure of choice for patients with CTEPH, offering a chance for near-normalization of hemodynamics, exercise tolerance, and quality of life, and a 5-year survival rate of 75 to 80%. However, some patients may not be candidates for surgery because of predominant involvement of peripheral pulmonary arteries. In addition, an unknown number of oper...
ated patients may exhibit persistent or recurrent pulmonary hypertension not amenable to repeated surgery. In these patients, a “secondary” vasculopathy of peripheral pulmonary vessels is involved, with histologic features resembling those seen in pulmonary arterial hypertension (PAH),7 and they might therefore benefit from medical treatment with drugs that have been shown to be effective in PAH. Supporting this hypothesis, uncontrolled studies8–10 suggest that epoprostenol and sildenafil may improve hemodynamics and exercise capacity in patients with CTEPH.

Bosentan, a dual endothelin receptor antagonist, has beneficial effects in several types of PAH.11 Its role in the treatment of CTEPH has not yet been studied. We therefore conducted the present open-label pilot trial to assess whether there is any therapeutic potential of bosentan in patients with inoperable CTEPH.

**Materials and Methods**

**Patient Selection**

In order to ensure diagnostic accuracy and to prevent inclusion of patients with operable disease, this study was carried out at the three largest referral centers for surgical treatment of CTEPH in Germany. All patients underwent standardized assessment at the centers including ventilation/perfusion scanning, helical CT of the chest, and pulmonary angiography. The final decision to classify the patient as inoperable was made together with the surgeon in charge of the PEA program. Patients who underwent PEA were followed up in the centers in 3- to 6-month intervals by echocardiography and clinical assessment. In patients with symptoms or signs of persistent pulmonary hypertension after PEA, a diagnostic right-heart catheterization was performed, and a repeated diagnostic workup was started when the patients were considered candidates for repeated surgery.

Inclusion criteria for this study were as follows: (1) CTEPH judged as inoperable because of peripheral location of vascular obliteration by an experienced surgeon; (2) persistent or recurrent pulmonary hypertension after PEA with no evidence of recurrent thromboembolism and not amenable to repeated surgery; and (3) hemodynamic evaluation showing precapillary pulmonary hypertension (pulmonary capillary wedge pressure [PCWP] < 15 mm Hg), with a PAPm > 35 mm Hg and a pulmonary vascular resistance (PVR) > 500 dynes-cm⁻². Exclusion criteria were as follows: (1) patients with other forms of pulmonary hypertension; (2) patients with CTEPH who had proximal occlusion of pulmonary arteries deemed operable by an experienced surgeon, but who declined operation or who were not considered operable due to other medical reasons; (3) pregnant or nursing women or women with child-bearing potential who did not use an acceptable method of contraception; and (4) patients with aspartate aminotransferase and/or alanine aminotransferase levels above three times the upper limit of normal. The study protocol was approved by the ethics committees of the participating centers, and all patients gave written informed consent.

**Results**

Between September 2003 and June 2004, 19 patients were enrolled into this study. Four patients had persistent/recurrent pulmonary hypertension after previous PEA (1.5 years, 4 years, 5 years, and 6 years after surgery, respectively); the others had nonoperable CTEPH. The interval between diagnosis of CTEPH and study entry was > 3 months in all patients and was > 12 months in 10 patients. All patients had received adequate treatment with oral anticoagulants since diagnosis. Demographics, clinical characteristics, and hemodynamics are depicted in Table 1. Eighteen patients completed this study; 1 patient died 6 weeks after the introduction of bosentan. This patient was a 41-year-old woman who underwent PEA 6 years before entering this study. After operation, she had persistent and progressive pulmonary hypertension and was in New York Heart Association (NYHA) functional class IV when she entered this study. After 4 weeks of bosentan treatment, her 6-min walk test had improved from 66 to 198 m. However, 2 weeks later, a febrile illness and...
Table 1—Baseline Characteristics of the Patients Who Completed a 3-Month Course of Bosentan Treatment*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>18</td>
</tr>
<tr>
<td>Female/male gender, No.</td>
<td>7/11</td>
</tr>
<tr>
<td>Age, yr</td>
<td>60 ± 8 (48–79)</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>n = 2</td>
</tr>
<tr>
<td>III</td>
<td>n = 14</td>
</tr>
<tr>
<td>IV</td>
<td>n = 2</td>
</tr>
<tr>
<td>6-min walk distance, m</td>
<td>340 ± 102 (191–490)</td>
</tr>
<tr>
<td>Peak VO₂, mL/min/kg</td>
<td>14.1 ± 3.2 (9.3–18.8)</td>
</tr>
</tbody>
</table>

Hemodynamics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before Treatment</th>
<th>3 Months of Treatment</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RAP, mm Hg</td>
<td>9 ± 4 (2–16)</td>
<td>9 ± 4 (2–16)</td>
<td></td>
</tr>
<tr>
<td>PAPm, mm Hg</td>
<td>48 ± 8 (36–63)</td>
<td>48 ± 8 (36–63)</td>
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<tr>
<td>Cardiac output, L/min</td>
<td>4.0 ± 1.1 (1.7–6.1)</td>
<td>4.0 ± 1.1 (1.7–6.1)</td>
<td></td>
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<tr>
<td>CI, L/min/m²</td>
<td>2.1 ± 0.4 (1.2–2.9)</td>
<td>2.1 ± 0.4 (1.2–2.9)</td>
<td></td>
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<tr>
<td>PVR, dyne-cm⁻⁵</td>
<td>914 ± 329 (501–1,776)</td>
<td>914 ± 329 (501–1,776)</td>
<td></td>
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<tr>
<td>PCWP, mm Hg</td>
<td>8 ± 3 (3–13)</td>
<td>8 ± 3 (3–13)</td>
<td></td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>54 ± 15 (25–82)</td>
<td>54 ± 15 (25–82)</td>
<td></td>
</tr>
<tr>
<td>SVO₂, %</td>
<td>59 ± 8 (40–66)</td>
<td>59 ± 8 (40–66)</td>
<td></td>
</tr>
</tbody>
</table>

Concomitant medication, %

- Oral anticoagulants (n = 18) 100
- Diuretics (n = 11) 61
- Digitalis (n = 1) 6

*Data are presented as mean ± SD (range) or mean ± SD (%) unless otherwise indicated.

Symptoms suggestive of influenza A infection developed (an influenza A epidemic was sweeping over Germany during that time). The patient died suddenly 2 days after the onset of fever. Death was considered unrelated to medical treatment by the investigators and the hospital ethics committee. This patient was excluded from all further analysis.

**Hemodynamic Responses**

Results of cardiac catheterization at baseline and after 3 months of bosentan treatment are shown in Table 2 and Figure 1. PVR declined from 914 ± 329 to 611 ± 220 dyne-cm⁻⁵ (p < 0.001). PAPm fell from 48 ± 8 to 42 ± 8 mm Hg (p = 0.004), and cardiac output rose from 4.0 ± 1.1 to 4.7 ± 1.3 L/min (p < 0.001). Stroke volume increased from 54 ± 15 to 64 ± 21 mL (p = 0.009), and the SVO₂ increased from 59 ± 8 to 64 ± 8% (p = 0.005). There were no significant changes in heart rate, RAP, PCWP, and systemic arterial pressure.

**Functional Assessment, 6-min Walk Distance, and CPET**

At baseline, 2 patients were in NYHA functional class II, 14 patients were in NYHA class III, and 2 patients were in NYHA class IV. After 3 months of bosentan treatment, one patient had progressed from NYHA functional class III to functional class IV, three patients had improved from functional class III to functional class II, and one patient improved from class IV to class III; the remaining patients were assigned the same functional class as at baseline.

As shown in Figure 2, the 6-min walk distance increased significantly from 340 ± 102 to 413 ± 130 m (p = 0.009). The Borg dyspnea score remained unchanged (5.7 ± 2.0 at baseline vs 5.3 ± 2.4 after 3 months, p = 0.19).

Results from CPET were nonconclusive, which may be partly due to the fact that complete sets of pretreatment and posttreatment measurements were obtained only from 12 patients. Missing values were due to either technical reasons or the incapability of some patients to perform CPET. Analysis of the 12 patients who completed the procedure revealed a nonsignificant increase in peak VO₂ from 14.1 ± 3.2 to 15.1 ± 3.8 mL/min/kg (p = 0.17) and an increase...
in oxygen pulse from 8.6 ± 3.1 to 9.5 ± 3.1 mL that was of borderline significance (p = 0.058). Ventilatory efficacy for carbon dioxide at the anaerobic threshold declined from 52 ± 10 to 47 ± 7 (p = 0.064), suggesting a trend toward improved pulmonary perfusion during exercise.

Laboratory Values

During bosentan treatment, plasma levels of alanine aminotransferase and aspartate aminotransferase were above the upper level of normal in four patients (22%) but remained below the mark of three times the upper limit of normal in all patients. There were no dose adjustments or treatment interruptions due to liver dysfunction.

In order to maintain INR values in the target range between 2.5 and 3.0, the dose of phenprocoumon (and oral anticoagulant widely used in Germany instead of warfarin) had to be increased between 25% and 100% from baseline, which is consistent with the known stimulatory effects of bosentan on cytochrome oxidase-dependent metabolic pathways. Serum levels of troponin T were below the detection limit of < 0.01 µg/L in all patients at all times during the study.

Serum levels of NT-pro-BNP were elevated in all patients at baseline (mean ± SD, 2,895 ± 2,620 ng/L; range, 536 to 11,114 ng/L; upper limit of normal, 200 ng/L). After 3 months of bosentan treatment, NT-pro-BNP levels decreased to 2,179 ± 2,301 ng/L (p = 0.027).

Side Effects and Adverse Events

The death of one patient and elevations of transaminases have been addressed above. In addition, one patient complained about mild upper-abdominal pain after the bosentan dose was increased to 125 mg bid, which resolved completely within a few days without dose adjustment. A total of four patients experienced fluid retention, which was transient and manageable except for one patient, who had signs and symptoms of progressive right-heart failure with an increase in RAP from 10 to 24 mm Hg and a decrease in cardiac output from 3.8 to 3.2 L/min (since the PAPm also declined and the PCWP increased, the calculated PVR formally improved). In this patient, bosentan treatment was stopped after 3 months. Other than that, no adverse events were observed.

Discussion

This open-label pilot trial, despite limited by its relatively small sample size and its uncontrolled design, shows that the dual endothelin receptor antagonist bosentan may have beneficial effects in selected patients with inoperable CTEPH. On first glance, it may seem counterintuitive to use a vasoactive treatment in a disease that is characterized by mechanical obstruction of pulmonary vessels. However, several lines of evidence suggest that, after the initializing event of single, multiple, or recurrent pulmonary embolism, vascular remodeling may ensue with morphologic changes resembling those seen in PAH. As time elapses, these secondary changes may have a more potent impact on the PVR than the original thromboembolic events. Some degree of pulmonary vasoreactivity may be preserved in patients with CTEPH, and preliminary observations suggest that IV epoprostenol and sildenafil may yield beneficial hemodynamic and clinical effects in selected CTEPH patients.

Plasma levels of big-endothelin-1, the precursor of endothelin-1, are increased in patients with CTEPH compared to control subjects. In addition, selective upregulation of endothelin B receptors has been demonstrated in pulmonary arterial smooth-muscle cells of patients with this disease. These data provide a rationale for the use of dual endothelin receptor antagonists as potential treatments for CTEPH.
had substantial responses (a fact that is clearly visible in Fig 2). The clinical response to bosentan in patients with CTEPH appears to be highly variable, and it will be a task for future clinical trials to find out which patients among the CTEPH population will gain the highest benefit from medical treatment. Perhaps vasoreactivity testing might be a helpful tool, but this remains to be investigated.

Although the comparison of different clinical trials has obvious limitations, the observed effects of bosentan in CTEPH are strikingly similar to the results reported with the phosphodiesterase-5-inhibitor sildenafil in a similar patient population. Ghofrani et al treated 12 patients with inoperable CTEPH over a 6-month period with sildenafil and found an increase in mean 6-min walk distance from 312 m at baseline to 366 m at the end of the observation period (+17%), which is comparable to the increase from 340 to 413 m that we observed with bosentan treatment (+21%). The change in PVR (−30% with sildenafil treatment and −33% with bosentan treatment) was almost identical in both studies. It is impossible to judge by the present data whether any of these drugs will turn out to have superior effects in CTEPH, and both treatment strategies require more extensive long-term evaluation in controlled clinical trials, ideally alone as well as in combination.

The present study was restricted to patients with predominant peripheral vascular involvement precluding successful desobliteration according to the judgement of an experienced surgeon. However, experiences with epoprostenol suggest that medical treatment may also be temporarily used in patients with operable disease to obtain hemodynamic improvement prior to surgery. Thus, several subgroups of patients with CTEPH may be candidates for medical treatment. However, with the perspective of medical treatment becoming available for treatment of CTEPH, there is also the potential caveat that physicians may use medical remedies in patients with operable disease. PEA, when performed at an experienced center, offers the chance for substantial improvement in physical capacity and quality of life, as well as for near-normalization of hemodynamics, longevity, and even cure. However, PEA is a high-risk procedure with mortality rates between 4.4% and 10.9% in experienced centers, and surgery may not be the best therapeutic option for every patient. Effective medical treatments may be used in the preoperative period to improve hemodynamics, right-heart function and, possibly, postoperative outcome, but also as an alternative treatment for patients who are less than optimal candidates for surgery.

The present data suggest that bosentan may offer a therapeutic option for selected patients with inoperable disease. It is warranted to conduct larger, randomized controlled trials to confirm these findings.

REFERENCES