Bosentan Therapy for Inoperable Chronic Thromboembolic Pulmonary Hypertension*

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Background: Bosentan, an oral endothelin (ET)-A/ET-B receptor antagonist, is effective in the treatment of pulmonary arterial hypertension.

Objective: To investigate the safety and efficacy of bosentan therapy in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH).

Design: Case series.

Setting: Pulmonary Hypertension Unit of the Medical University of Vienna, Austria.

Patients: Sixteen patients (9 women and 7 men; mean age ± SD, 70 ± 13 years).

Intervention: Off-label bosentan treatment over 6 months.

Measurements: Changes from baseline in liver enzymes, New York Heart Association (NYHA) functional class, 6-min walking distance (6-MWD), and serum amino-terminal pro-brain natriuretic peptide (proBNP).

Results: After 6 months, NYHA functional class improved by one class in 11 patients. Mean 6-MWDs increased from 299 ± 131 m at baseline to 391 ± 110 m at 6 months (p = 0.01). In parallel, proBNP decreased from 3,365 ± 2,923 to 1,755 ± 1,812 pg/mL (p = 0.01). Neither aspartate aminotransferase (25 ± 2 U/L vs 25 ± 2 U/L, p = 0.25) nor alanine aminotransferase (23 ± 12 U/L vs 24 ± 9 U/L, p = 0.57) changed significantly. Limitations of the study were uncontrolled design and small sample size.

Conclusions: Our study suggests a beneficial effect of the oral dual ET receptor antagonist bosentan in patients with inoperable CTEPH, urging the need for a randomized, placebo-controlled trial.

Key words: bosentan; pulmonary hypertension; pulmonary thromboembolism

Abbreviations: BNP = brain natriuretic peptide; CTEPH = chronic thromboembolic pulmonary hypertension; ET = endothelin; 6-MWD = 6-min walking distance; NYHA = New York Heart Association; PEA = pulmonary endarterectomy; proBNP = pro-brain natriuretic peptide; PVR = pulmonary vascular resistance

Chronic thromboembolic pulmonary hypertension (CTEPH) has been observed in 0.1 to 3.8% of patients who have survived a pulmonary thromboembolic event1,2 and is associated with significant morbidity and mortality. It is characterized by the persistence of thromboemboli obstructing the pulmonary vascular bed as unique organization tissue3 that is distinct from acute pulmonary emboli. These organized residuae lead to an increase in pulmonary vascular resistance (PVR), right ventricular overload, and eventually to right ventricular failure.

The treatment of choice for CTEPH is surgical pulmonary endarterectomy (PEA), providing a potential cure of the disease.4 However, in our center, approximately 50% of patients cannot undergo surgery due to the distal location of pulmonary thromboemboli or severe comorbidity. Despite recent advances in the medical treatment of pulmonary hypertension,5 the subgroup of inoperable CTEPH patients faces the worst prognosis. In addition, approximately 10% of patients who undergo PEA obtain no relief and maintain a pulmonary hypertensive state.
Bosentan, an oral endothelin (ET)-A/ET-B receptor antagonist, has been shown to be effective and safe in the short-term and long-term treatment of nonthromboembolic pulmonary arterial hypertension. The aim of the present study was to evaluate its safety and efficacy in patients with inoperable CTEPH.

**MATERIALS AND METHODS**

**Setting**

The present study was conducted at the Pulmonary Hypertension Unit of the Medical University of Vienna between July 2003 and December 2004. PEA is a long-term successful treatment option of CTEPH, and this treatment is, in Austria, offered only at the Medical University of Vienna.

**Diagnostic Procedures**

All patients were referred for exertional or resting dyspnea. The diagnosis of CTEPH was established by chest radiography, transthoracic and transesophageal echocardiography with Doppler imaging, pulmonary function tests including arterial blood gas analysis at rest and exercise, right-heart catheterization, pulmonary angiography, ventilation-perfusion scan of the lungs, and multislice and high-resolution CT. A panel of cardiologists, pulmonologists, radiologists, and cardiothoracic surgeons reviewed each case. CTEPH type I–IV was classified as follows: type I, presence of a central thrombus; type II, thickened intima, with fibrous webs and bands in the main branches; type III, occlusions in the segmental and subsegmental branches; and type IV, very distal thrombi. Criteria for PEA at our institution are functional impairment, a resting PVR > 300 dynes·sec·cm⁻⁵, and the surgical accessibility of thromboembolic lesions. Inoperability was based on the following: a mismatch between the degree of hemodynamic compromise and the location of the most proximal thrombi, type IV disease, severe comorbidities, and patient refusal.

**Study Design**

This was a case series of patients treated off-label with bosentan. Consecutive patients with inoperable CTEPH were enrolled between July 2003 and July 2004. Compassionate use was sought and approved for each individual patient, including informed consent of each individual patient under a study protocol, in accordance with the Declaration of Helsinki of 1975 and amendments, and in adherence to the International Conference of Harmonization Good Clinical Practice Guidelines and the US Federal Register (1997). All patients started the study to inclusion.

**Outcome Measures**

Patients were evaluated on an outpatient basis at 4 weeks and 12 weeks and 6 months of therapy. Safety was assessed by monitoring liver enzymes, vital signs, and adverse events. Efficacy end points included exercise capacity after 6 months of treatment, measured by the New York Heart Association (NYHA) functional class and 6-min walking distance (6-MWD), as well as serum levels of amino terminal pro-brain natriuretic peptide (proBNP).

**Laboratory Analysis**

Venous blood samples were drawn at each visit from an antecubital vein of stable patients who were not receiving drug at baseline, into Vacutainer test tubes (BD Diagnostics; Franklin Lakes, NJ) after 30 min of supine rest. Serum separation was performed at 4°C, and proBNP was immediately determined (Elecsys NT-proBNP assay; Roche Diagnostics; Basel, Switzerland).

**Statistical Analysis**

Data are expressed as mean ± SD. Differences between patient groups were analyzed with analysis of variance and two-sample t test for continuous variables, and χ² test for categorical variables. The Mann-Whitney U test was used to compare outcome variables. Significance was determined at p < 0.05. For all analyses, statistical software was used (StatView version 5.0.1; SAS Institute; Cary, NC).

**RESULTS**

**Patients**

Patient baseline characteristics are shown in Table 1. Of the 33 patients who received a diagnosis of CTEPH at our center within the inclusion period, 16 patients (7 men and 9 women) were found to be inoperable. Mean age was 70 ± 13 years. Baseline hemodynamic data were as follows: mean cardiac index, 2.4 ± 0.5 L/min/m²; mean PVR, 712 ± 213 dyne·s⁻¹·cm⁻⁵; mean mixed venous saturation, 61 ± 9%; and mean pulmonary arterial pressure, 52 ± 10 mm Hg. None of the patients had elevated liver enzymes at baseline. All patients were in stable clinical condition and receiving supplemental oxygen, diuretics, and oral anticoagulants 1 month prior to inclusion.

**Exercise Capacity and Serum proBNP Levels**

All patients received the target dosage of bosentan, 125 mg bid. At study entry, two patients were in NYHA functional class II, nine patients were in class III, and five patients were in class IV. At the 6-month evaluation, 10 patients were in NYHA functional class II, 4 patients were in class III, and 2 patients remained in class IV, which was an overall significant improvement (p = 0.02). Accordingly, the mean 6-MWD increased from 299 ± 131 to 391 ± 110 m (p = 0.02; Fig 1). Mean serum proBNP level decreased from 3,366 ± 2,924 to 1,756 ± 1,812 pg/mL (p = 0.01; Fig 1).

**Safety**

None of the patients experienced liver enzyme elevations (aspartate aminotransferase, 25 ± 2 U/L.
of a perforated diverticulitis (patient 14).

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eration triggering an abnormal process of vascular remodeling due to a variety of factors, such as shear stress, pressure, inflammation, and the release of cytokines and vasculotrophic mediators. Changes in the ET-signaling system in CTEPH have been demonstrated as an increased production of ET-1 and altered ET receptor gene expression.11 CTEPH patients may benefit from ET receptor antagonism.

According to our experience, CTEPH is one of the most frequent forms of pulmonary hypertension. In contrast to patients with nonthromboembolic pulmo-
nary hypertension, CTEPH patients are character-

ized by numerous severe comorbidities, a lack of gender or age predominance, and a lack of heritable factors. Few data exist on vasodilator treatment in CTEPH because this patient population was excluded from the majority of large randomized trials. In a small uncontrolled series, sildenafil had a ben-
eficial effect on exercise capacity and hemodynamics in patients with inoperable CTEPH.12 Application of IV prostacyclin (epoprostenol) may improve exercise capacity and hemodynamic parameters in CTEPH patients listed for PEA.13 The major drawback of prostacyclin therapy in this patient population is the need for a permanent IV access that increases the risk of infection and thrombosis, potentially complicated by new thromboembolism. The use of inhaled iloprost in CTEPH has not been sufficiently evaluated. Subgroup analyses from the randomized iloprost study14 demonstrated that in contrast to patients with nonthromboembolic pulmo-
nary hypertension, CTEPH patients did not benefit from this treatment. In accord with these data, a previous study15 of CTEPH patients in our center under inhaled iloprost over 1 year of treatment has demonstrated a lack of effectiveness of this therapy. The mean age of our study patients was > 70 years, and one third were > 80 years old. Bosentan is an oral drug and therefore represents

vs 25 ± 2 U/L, p = 0.25; alanine aminotransferase, 23 ± 12 U/L vs 24 ± 9 U/L, p = 0.57), which has been reported as the most frequent side effect of bosentan treatment (occurring in 11.2% in the piv-
otal trials).6 No patient experienced symptomatic hypotension. From baseline to follow-up, heart rate (74 ± 7 beats/min vs 77 ± 10 beats/min, p = 0.31), systolic BP (134 ± 18 mm Hg vs 133 ± 20 mm Hg, p = 0.24), diastolic BP (80 ± 17 mm Hg vs 79 ± 13 mm Hg, p = 0.68), body weight (85 ± 21 kg vs 83 ± 14 kg, p = 0.14), and hemoglobin (14.3 ± 2.4 g/dL vs 14.5 ± 2.4 g/dL, p = 0.92) did not change significantly. Two patients required hospitalization during the study period, one for warfarin-dependent bleeding (patient 12), and the other patient because of a perforated diverticulitis (patient 14).

### Discussion

Our study suggests a beneficial effect of the oral dual ET receptor antagonist bosentan in patients with inoperable CTEPH. Currently, no specific random-
domized trial-based therapeutic recommendations exist for this patient population. The pathogenesis of CTEPH is still unclear, but it is widely accepted that the disease is determined by thromboembolic obliteration triggering an abnormal process of vascular remodeling due to a variety of factors, such as shear stress, pressure, inflammation, and the release of cytokines and vasculotrophic mediators. Changes in the ET-signaling system in CTEPH have been demonstrated as an increased production of ET-1 and altered ET receptor gene expression.11 CTEPH patients may benefit from ET receptor antagonism.

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<table>
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<th>Patient No.</th>
<th>Age, yr</th>
<th>Gender</th>
<th>Cardiac Index, L/min/m²</th>
<th>PVR, dynes/cm²</th>
<th>mPAP, mm Hg</th>
<th>NYHA Functional Class</th>
<th>6-MWD, m</th>
<th>CTEPH Type</th>
<th>Reason for Inoperability*</th>
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*Severe comorbidities were cardiomyopathy in patient 3 and parenchymal lung disease in patient 5 and patient 10. mPAP = mean pulmonary artery pressure; ND = not done.
Measurement of plasma brain natriuretic peptide (BNP) is simple, noninvasive, and relatively inexpensive. It is a peptide that is produced by the cardiac ventricles and is elevated in patients with pulmonary hypertension. BNP levels have been shown to positively correlate with PVR and pulmonary arterial pressure, and an inverse correlation exists between BNP and cardiac index, suggesting that it may serve as a noninvasive prognostic indicator of pulmonary hypertension. In the present study, proBNP, a more stable peptide prohormone, was found to be significantly decreased after 6 months of bosentan therapy. Patients in NYHA functional class IV had significantly higher proBNP serum levels than those in class III, indicating an active process of right ventricular remodeling. The significant decrease in serum proBNP levels after 6 months of treatment argues against a placebo effect on the 6-MWD. Also, the magnitude of change in mean 6-MWD was comparable to the changes observed in the randomized placebo-controlled trials.

**Study Limitations**

Experimental data suggest that blockade of ET could directly reduce BNP levels, independent of a hemodynamic effect. Thus, the observed decrease in proBNP serum levels at the end of the study period may be explained by this phenomenon. Furthermore, the present study utilized a noncomparative design and investigated a small sample size. Objective parameters of improvement, ie, pulmonary arterial pressures and cardiac output by hemodynamic assessment, were not accomplished within the study period. It cannot be excluded that the observed improvement in 6-MWD was due to a placebo effect. Despite these major limitations, our initial experience with bosentan therapy in patients with inoperable CTEPH is promising and urges the need for a randomized, placebo-controlled trial.

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