Effects of the Dual Endothelin Receptor Antagonist Bosentan in Patients With Pulmonary Arterial Hypertension*

A 1-Year Follow-up Study

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Study objectives: We report on the long-term safety and efficacy of bosentan treatment in patients with pulmonary arterial hypertension (PAH).

Background: In a preceding study, bosentan was well tolerated and significantly improved the exercise capacity and hemodynamics of patients with PAH after 12 weeks of treatment.

Design: The present study was an open-label extension to the preceding double-blind, placebo-controlled study of 32 patients with PAH (primary or associated with scleroderma) who received bosentan or placebo at 125 mg bid for 3 to 7 months.

Patients: Twenty-nine of the original 32 patients received bosentan for an additional year (62.5 mg bid for 4 weeks and then 125 mg bid).

Interventions: Study end points included long-term safety, 6-min walk distance at week 4, modified New York Heart Association (NYHA) functional class of PAH at month 12, and the occurrence of withdrawal due to clinical worsening. Additional exploratory analyses included a walk test at month 6 for 19 patients and hemodynamic assessment at month 12 for 11 patients.

Results: At month 6, assessed patients continuing bosentan treatment maintained the improvement in walk distance observed at the end of the previous study (mean ± SEM, 60 ± 11 m), and patients starting bosentan treatment improved their walk distance by 45 ± 13 m. Long-term treatment with bosentan for >1 year was associated with an improvement in hemodynamic parameters and modified NYHA functional class. Overall, bosentan treatment was well tolerated. No patient underwent transplantation or died.

Conclusions: Long-term treatment with bosentan is safe and has sustained benefits on exercise capacity and hemodynamics in patients with PAH. (CHEST 2003; 124:247–254)

Key words: bosentan; endothelin receptors; endothelins; pulmonary hypertension; scleroderma

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = cardiac index; ET = endothelin; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PPH = primary pulmonary hypertension; PVR = pulmonary vascular resistance; ULN = upper limit of normal

Pulmonary hypertension (PH) is characterized by a progressive increase in pulmonary vascular resistance (PVR) leading to right ventricular failure.1,2 Primary PH (PPH) has an unknown etiology, whereas secondary PH occurs in association with collagen vascular disease3 or congenital heart disease or in response to a stimulus such as HIV.4 The term pulmonary arterial hypertension (PAH) has been

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proposed by the World Health Organization to regroup both PPH and secondary PH together, since the pulmonary vascular changes are nearly identical in both disorders indicating a similar pathologic process. Conventional therapy for PAH includes vasodilators, which are only effective in a small percentage of patients, and anticoagulants. For severely ill patients, who require more aggressive therapy, continuous IV epoprostenol (prostacyclin) infusion can substantially improve both the length and the quality of life; however, epoprostenol requires permanent IV access and is associated with numerous side effects and complications. The success of long-term IV epoprostenol stimulated the development of analog molecules that can be inhaled (iloprost), administered orally (beraprost), or subcutaneously (treprostinil), but it is uncertain whether these treatments will have the long-term beneficial effect of the IV therapy.

Increasing evidence regarding the role of endothelin (ET)-1 as a mediator of PAH suggests that ET antagonism may be an additional therapeutic approach. Bosentan is an orally active nonpeptide antagonist of both ET receptor subtypes (ET-A and ET-B). By blocking the actions of both receptors, bosentan affects the vasoconstricting, proliferative, and fibrotic effects of ET-1. These beneficial effects of bosentan are entirely derived from preclinical animal experiments.

In a double-blind, placebo-controlled study, we reported that bosentan significantly improved the exercise capacity and hemodynamics of patients with PAH after 12 weeks of treatment. Improvement in exercise capacity was maintained for at least 20 weeks. These findings were confirmed in a larger study by Rubin et al. Bosentan was generally well tolerated, although elevated liver aminotransferases were noted in a small number of patients in the second study. The long-term benefit of bosentan treatment is largely unknown, and in particular whether tolerance develops over time (as has been observed with some patients receiving epoprostenol) remains to be elucidated. Here, we describe the results of the open-label, follow-up study that was designed to assess the long-term safety and tolerability of bosentan treatment in patients with PAH.

**PATIENTS AND METHODS**

*Patient Selection*

All eligible patients had participated in the preceding double-blind, placebo-controlled clinical study involving 3 to 7 months of treatment with 125 mg bid of bosentan or placebo. Inclusion/exclusion criteria for the preceding study have been described previously. Briefly, patients had symptomatic, severe PPH or PH associated with scleroderma in functional classes III-IV (according to the modified New York Heart Association [NYHA] classification, which ranks PAH severity in classes I to IV based on physical limitation), despite treatment including calcium-channel blockers, anticoagulants, diuretics, cardiac glycosides, or supplemental oxygen. They did not have an acute pulmonary vascular reactive component, or if they were vasoactive initially they failed to respond favorably to chronic calcium-channel blocker therapy. Epoprostenol was not allowed as concomitant medication in the preceding study but could be added, modified, or stopped in the present study. Use of glibenclamide (glyburide) and cyclosporine-A was not allowed due to potential drug interactions.

The study was conducted according to the Helsinki Declaration of 1975, as revised in 1983, and in adherence to local good clinical practice guidelines. The protocol was approved by the local ethics review committees, and written informed consent was obtained from all patients.

*Study Design*

The study was designed as an open-label, single-arm study, and was conducted in five centers in the United States and one center in France (Fig 1). Patients ending the preceding study were receiving 125 mg bid of bosentan or placebo. The design of that study required starting the open-label study without breaking the treatment codes (except for cases of clinical worsening). All patients started the present study with 62.5 mg bid of bosentan for the first 4 weeks and then received the target dose (125 mg bid). If clinical worsening of PAH occurred, bosentan could be up-titrated to 125 mg bid before week 4 or to 250 mg bid after week 4. In case of any drug-related adverse events (eg, hypotension), bosentan could be maintained at or down-titrated to 62.5 mg bid after week 4. At the clinical cutoff date (March 2001) corresponding to the 1-year follow-up data presented here, the study was still ongoing.

*Outcome Measures*

Patients were evaluated on an outpatient basis at 4 weeks and 12 weeks of therapy, at 6 months, and every 6 months thereafter. The primary assessments of the study were safety parameters: monitoring of adverse events, vital signs, and laboratory tests. Secondary efficacy end points included exercise capacity at week 4 (measured by the 6-min walk test); modified NYHA functional class of PAH at week 4, month 6, and month 12; and the occurrence of withdrawal due to clinical worsening. Additionally, a walk test was performed at month 6 for 19 patients, and hemodynamic parameters (cardiac index [CI], PVR, mean pulmonary artery pressure [mPAP], pulmonary capillary wedge pressure [PCWP], and mean right atrial pressure [mRAP]) were measured by right-heart catheterization for 11 patients (at baseline and at month 12). CI was computed as cardiac output divided by body surface area; PVR was calculated using the standard formula: (mPAP – PCWP)/cardiac output X 80.

*Statistical Analysis*

The baseline of the study was defined as the initiation of bosentan treatment and therefore corresponds to the beginning of the preceding study for the ex-bosentan group and to the beginning of the open-label study for the ex-placebo group. The significance of the effect of bosentan treatment on hemodynamic parameters compared to baseline was evaluated with the Wilcoxon rank-sum test.
A p value less than 0.05 was considered statistically significant. Data were expressed as mean ± SEM, except for demographic and treatment duration data, which were reported as mean ± SD.

Results

Of the 32 patients randomized in the preceding study to receive bosentan or placebo (2:1 ratio), 3 patients from the placebo group did not participate in the open-label study due to clinical worsening of PAH (Fig 1). Of the 29 enrolled patients, 21 patients had received bosentan in the preceding study ("ex-bosentan"; 100% of the eligible bosentan-treated patients) and 8 patients had received placebo in the preceding study ("ex-placebo"; 73% of the eligible placebo-treated patients). All 29 patients were included in the safety population. For 26 of these patients, treatment in the previous study was still blinded at the week 4 assessment.

Baseline Characteristics

Patients were predominantly white and female. The ex-placebo and ex-bosentan groups were well matched with respect to baseline characteristics (Table 1). In both groups, PPH was more common than PH associated with scleroderma (17 patients vs 4 patients in the ex-bosentan group, and 7 patients vs 1 patient in the ex-placebo group). Both groups were similar in terms of concomitant medication, including anticoagulants, vasodilators, and diuretics. All patients except one were in modified NYHA functional class III prior to initiation of bosentan treatment.

Duration of Exposure to Bosentan

Patients were exposed to different durations of bosentan treatment depending on their treatment group in the preceding study. Ex-bosentan patients received bosentan for a mean of 4.4 ± 1.2 months in the preceding study and for 12.4 ± 0.3 months in the open-label study (16.8 ± 1.4 months in total). Ex-placebo patients received bosentan treatment in the open-label study for 11.4 ± 3.2 months; therefore, the overall mean exposure to bosentan in the two studies up to the clinical cutoff date was 15.3 ± 3.2 months.

Exercise Capacity

The improvement in walk distance observed at the end of the preceding study for the ex-bosentan group was 321 ± 116 m, while the improvement for the ex-placebo group was 292 ± 116 m. The difference was statistically significant (p < 0.05).
patients was maintained during the first 6 months of the open-label study (+60 ± 11 m [n = 16] after a total of 10 ± 1 months of treatment with bosentan) despite a dose reduction from 125 to 62.5 mg bid during the first 4 weeks of the open-label study (Table 2). For the ex-placebo patients, treatment with bosentan improved the walk distance by 22 ± 14 m (n = 8) at week 4 and by 45 ± 13 m (n = 3) at month 6.

Cardiopulmonary Hemodynamics

Eleven patients underwent right-heart catheterization after 15 ± 4 months (range, 8 to 22 months) of treatment with bosentan. For these patients, CI and PVR had significantly improved from the value at baseline (Table 3, Fig 2). Treatment with bosentan also had a slight beneficial effect on mPAP and mRAP, but these decreases did not reach a statistical significance.

The improvements in hemodynamic parameters observed with bosentan were not associated with a clinically relevant change in heart rate (Table 3). A decline in mean arterial BP was observed (Table 3), but symptomatic hypotension did not occur in any of the patients.

Modified NYHA Functional Class

Long-term bosentan treatment improved the functional class of PAH (Fig 3). All patients were in class III at baseline except for one patient who was in class I. At the 6-month evaluation, 41.4% of patients showed an improvement from baseline compared with 32.1% at week 4, and this improvement remained stable at the 1-year evaluation (41.4%). After at least 1 year of treatment, 11 patients had improved to class II and 1 patient to class I. One patient deteriorated to class IV and was withdrawn from the study to receive epoprostenol therapy.

Code Breaks

For two patients whose clinical condition deteriorated near the end of the preceding study, individual codes were broken to decide between initiation of epoprostenol therapy or enrollment in the open-label study. Since both patients had been receiving placebo, they were enrolled in the open-label study to receive treatment with bosentan. Individual codes were also broken for one patient presenting signs of aggravated PAH after 1 week of treatment with bosentan at 62.5 mg bid. This patient had been receiving bosentan at 125 mg bid in the previous study and restoring the 125-mg bid dose improved the symptoms.

Need for Up-titration of Bosentan

Four patients experiencing a significant deterioration of their walk distance (>15%) had a bosentan dose increase to 250 mg bid until the clinical cutoff date. Walk distance in two of these patients subsequently improved, and two patients remained in stable condition.

Safety Results

No patient died during the course of the study. Overall, bosentan treatment was well tolerated. Nearly all patients have experienced an adverse event, but only individual events were reported by more than two patients. The most common adverse events were headache and upper respiratory tract infection (nine patients for each event), dyspnea (eight patients), chest pain, aggravated PAH, and sinusitis (seven patients for each event) [Table 4]. During the open-label study, one patient was discontinued for aggravated PAH and placed on epoprostenol therapy. Four patients experienced six serious adverse events that were unrelated or remotely related to study medication (gastroenteritis, atrial fibrillation, hypercalcemia/hyperparathyroidism, palpitations, and chest pain), but all either recovered or

<table>
<thead>
<tr>
<th>Time</th>
<th>Ex-placebo</th>
<th>Ex-bosentan</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline†</td>
<td>394 ± 38 (n = 8)</td>
<td>360 ± 19 (n = 21)</td>
<td>370 ± 17 (n = 29)</td>
</tr>
<tr>
<td>Study start†‡</td>
<td>394 ± 38 (n = 8)</td>
<td>439 ± 14 (n = 21)</td>
<td>426 ± 15 (n = 29)</td>
</tr>
<tr>
<td>Week 4</td>
<td>416 ± 25 (n = 8)</td>
<td>442 ± 15 (n = 21)</td>
<td>435 ± 13 (n = 29)</td>
</tr>
<tr>
<td>Month 6</td>
<td>406 ± 23 (n = 3)</td>
<td>434 ± 19 (n = 16)</td>
<td>430 ± 17 (n = 19)</td>
</tr>
</tbody>
</table>

Table 2—Walk Distance After a Minimum of 6 Months of Bosentan Treatment*

*Values are given as mean ± SEM.
†The beginning of the preceding study for the ex-bosentan group and the beginning of the open-label study for the ex-placebo group. At month 6 of the open-label study, the total duration of bosentan treatment was 10 ± 1 months for the ex-bosentan group and 6 months for the ex-placebo group (9 ± 2 months for all patients combined).
‡The beginning of the open-label study.
* p < 0.0001 for treatment vs baseline with the Wilcoxon rank test.
improved. Hemoglobin concentrations decreased for three patients by 19%, 21%, and 24%, but remained superior to 10.4 g/dL. Three patients experienced transient elevations in liver alanine aminotransferase (ALT) and aspartate aminotransferases (AST) above the upper limit of normal (ULN). For one ex-bosentan patient, ALT increased to 113 U/L (four times ULN) during the double-blind study. For another ex-bosentan patient, ALT increased to 81 U/L (three times ULN) and AST to 67 U/L (three times ULN) during the double-blind study, and then ALT increased again to 68 U/L (two times ULN) during the open-label study. For one ex-placebo patient, ALT increased to 81 U/L (three times ULN) and AST to 67 U/L (three times ULN) during the double-blind study, and then ALT increased again to 68 U/L (two times ULN) during the open-label study. However, neither liver nor hemoglobin abnormalities warranted discontinuation of bosentan treatment.

**DISCUSSION**

The present study is the first trial investigating the long-term safety and efficacy of bosentan in the treatment of PAH. In the preceding double-blind, placebo-controlled study, bosentan demonstrated favorable hemodynamic effects—including decreases in pulmonary pressures and resistances—after 3 months of treatment. These effects were accompanied by an increase in exercise capacity, an improvement in functional class, and a reduction in the incidence of clinical deterioration. In this open-label extension study, the improvement of exercise capacity was sustained for an additional 6-month period. Long-term treatment for over a year was associated with a significant reduction in PVR and an increase in CI. Although there was no control group in this study, the observed hemodynamic improvement is unlikely to have occurred spontaneously in patients with PAH and may be attributed to the vascular remodeling effect of bosentan due to ET blockade, as suggested in preclinical studies. The long-term efficacy of bosentan is further supported by the improvement in the modified NYHA functional class and the low incidence of clinical worsening. Seven patients (24%) had a worsening of PAH during the study. In four of them, an increase in the bosentan daily dose to 250 mg bid has led to clinical improvement. In addition, there was only one withdrawal due to clinical worsening, as a result of lack of compliance with the treatment. The fact that none of the patients with PAH followed up for > 1 year died during this study is indicative of the potential of bosentan therapy; however, a larger cohort of patients is warranted to draw further conclusions.

PAH is a progressive and fatal disease with few effective long-term treatment options. Calcium-channel blocking agents can sometimes induce sustained beneficial effects, including long-term reduction in PVR, but only in a limited number of patients. Epoprostenol has been associated with long-term improvement in clinical and pulmonary hemodynamic responses. In three long-term studies, continuous IV epoprostenol significantly reduced PVR and increased CI and exercise capacity. Improvement was also observed, though to a lesser extent, after 1 year of treatment with inhaled iloprost. In the present study, improvement of hemodynamics and exercise capacity was sustained with oral bosentan treatment for > 1 year, without increasing the dosage over time. However, additional long-term studies will be necessary to fully compare treatment efficacy in patients with PAH.

Bosentan at 125 mg bid was generally well tolerated, and no patient discontinued treatment because of adverse events. These results are in concordance with previous data obtained from clinical studies with bosentan, which suggest that bosentan is well tolerated at a dose of 125 mg bid. For the ex-bosentan patients, decreasing the dose from 125 mg bid in the preceding study to 62.5 mg bid at the

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**Table 3—Hemodynamic Characteristics for 11 Patients Treated With Long-term Bosentan**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline†</th>
<th>After 15 ± 4 Months of Bosentan</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac output, L/min</strong></td>
<td>4.1 ± 0.3</td>
<td>5.1 ± 0.4</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>CI, L/min</strong></td>
<td>2.2 ± 0.2</td>
<td>2.6 ± 0.2</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>PVR, dyne s cm⁻⁵</strong></td>
<td>1.049 ± 122</td>
<td>862 ± 145</td>
<td>0.016</td>
</tr>
<tr>
<td><strong>mPAP, mm Hg</strong></td>
<td>61 ± 4</td>
<td>57 ± 4</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>PCWP, mm Hg</strong></td>
<td>10.3 ± 0.8</td>
<td>9.5 ± 1.2</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>mRAP, mm Hg</strong></td>
<td>11.5 ± 2.0</td>
<td>9.1 ± 1.7</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Heart rate, beats/min‡</strong></td>
<td>83 ± 6</td>
<td>88 ± 3</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Mean BP, mm Hg‡</strong></td>
<td>96 ± 3</td>
<td>88 ± 4</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Values are given as mean ± SEM (except for treatment duration, which is expressed as mean ± SD).
†The beginning of the preceding study for the ex-bosentan group and the beginning of the open-label study for the ex-placebo group.
‡Wilcoxon rank test.
§n = 10 (one patient did not have heart rate and BP measurement at 1 year).
beginning of the present open-label study did not provoke any rebound effect, although the lower dose may not have been sufficient for some patients to maintain a favorable clinical status. For patients presenting with clinical signs of aggravated PAH while receiving the 125-mg bid dosage, a dose increase to 250 mg bid appears to be an additional option before epoprostenol treatment has to be considered. Only 4 of 29 patients required such a dose increase during the 1-year extension study. Among them, three patients continued on high-dose bosentan, whereas one patient transitioned to long-term IV infusion of epoprostenol after 400 days of bosentan treatment.

Asymptomatic increases in liver aminotransferase levels have been observed previously, especially...
in patients treated with a higher dose of bosentan (250 mg or 500 mg bid), but also in a few patients treated with 125 mg bid; therefore, liver monitoring is recommended at bosentan treatment initiation and at monthly intervals thereafter to ensure safe use of the medication. In the present study, increases in liver aminotransferase levels were reported for three patients; however, these were not severe and did not warrant discontinuation of bosentan treatment.

Although the results of this study are promising, there are a number of limitations, inherent to the small number of enrolled patients (29 patients treated in six separate centers): the study involved few male patients (all in the bosentan group), no class IV patients at baseline, and more patients with PPH than with PAH related to scleroderma. (There were no patients with other PH etiologies such as congenital heart disease, portal hypertension, or infection with HIV.) The study is also limited by the unknown impact of the duration of the disease prior to treatment initiation.

In conclusion, we provide evidence that the initial clinical efficacy of bosentan, an oral dual ET receptor antagonist, is maintained over a period of 1 year. This study supports the long-term use of bosentan as an efficacious approach in the treatment of PAH, which could expand the few therapeutic options currently available for this indication.

APPENDIX

Olivier Sitbon, MD; David B. Badesch, MD; Richard N. Channick, MD; Adaani Frost, MD; Ivan M. Robbins, MD; Victor F. Tapson, MD; Gérald Simonneau, MD; and Lewis J. Rubin, MD, contributed to study recruitment and assessments, and to the preparation of the article. Dr. Sitbon collected long-term hemodynamic data. Frédéric Bodin, MD; Maurizio Rainizio, PhD; and
Sébastien Roux, MD, designed the study, monitored the clinical and laboratory assessments, performed the study analysis, and contributed to the preparation of the manuscript.

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