Bosentan Therapy in Patients With Eisenmenger Syndrome
A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study

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Background—Eisenmenger syndrome is characterized by the development of pulmonary arterial hypertension with consequent intracardiac right-to-left shunt and hypoxemia in patients with preexisting congenital heart disease. Because Eisenmenger syndrome is associated with increased endothelin expression, patients may benefit from endothelin receptor antagonist. Theoretically, interventions that have some effect on the systemic vascular bed could worsen the shunt and increase hypoxemia.

Methods and Results—The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) was a 16-week, multicenter, randomized, double-blind, placebo-controlled study evaluating the effect of bosentan, a dual endothelin receptor antagonist, on systemic pulse oximetry (primary safety end point) and pulmonary vascular resistance (primary efficacy end point) in patients with World Health Organization functional class III Eisenmenger syndrome. Hemodynamics were assessed by right- and left-heart catheterization. Secondary end points included exercise capacity assessed by 6-minute walk distance, additional hemodynamic parameters, functional capacity, and safety. Fifty-four patients were randomized 2:1 to bosentan (n=37) or placebo (n=17) for 16 weeks. The placebo-corrected effect on systemic pulse oximetry was 1.0% (95% confidence interval, −0.7 to 2.8), demonstrating that bosentan did not worsen oxygen saturation. Compared with placebo, bosentan reduced pulmonary vascular resistance index (−472.0 dyne·s·cm⁻²; P=0.0383). The mean pulmonary arterial pressure decreased (−5.5 mm Hg; P=0.0363), and the exercise capacity increased (53.1 m; P=0.0079). Four patients discontinued as a result of adverse events, 2 (5%) in the bosentan group and 2 (12%) in the placebo group.

Conclusions—In this first placebo-controlled trial in patients with Eisenmenger syndrome, bosentan was well tolerated and improved exercise capacity and hemodynamics without compromising peripheral oxygen saturation. (Circulation. 2006;114:48-54.)

Key Words: endothelin ■ heart septal defects ■ hypertension, pulmonary

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Eisenmenger syndrome is a multisystem disorder associated with numerous life-threatening complications, including hemoptysis, cerebrovascular accidents, brain abscesses, arrhythmias, and syncope. Exercise capacity is severely impaired in most patients with Eisenmenger syndrome. Although exercise limitation and exertional dyspnea may remain stable for years, poor exercise capacity identifies the patient at risk for hospitalization or death. Patients with Eisenmenger syndrome have a reduced life expectancy even if many can survive into their third or fourth decade. Oya et al reported a survival rate from the time of diagnostic catheterization of 98% at 1 year, 77% at 5 years, and 58% at 10 years.

Endothelin-1 is produced primarily by vascular endothelial cells and acts as a powerful vasoconstrictor and mitogen for smooth muscle. The endothelin-1 system appears to be
intimately involved in the pathobiology of PAH, and elevated endothelin-1 plasma and tissue levels have been observed in patients with Eisenmenger syndrome. Accordingly, targeting the endothelin-1 system with endothelin receptor antagonists may prove to be an effective treatment strategy. Bosentan is an orally active dual (ETβ and ETα) endothelin-1 receptor antagonist that is effective in the treatment of idiopathic PAH and PAH related to connective tissue disease in controlled clinical trials. A number of small, open, uncontrolled studies have suggested that bosentan improves exercise capacity and hemodynamics in adult patients with Eisenmenger syndrome. Thus, a controlled clinical trial is required to confirm safety and establish the real extent of efficacy. The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) was the first trial designed as a multicenter, double-blind, randomized (2:1), placebo-controlled study to assess the effects of bosentan on systemic oxygen saturation, pulmonary and systemic hemodynamics, and exercise capacity in patients with Eisenmenger syndrome.

Methods

Patients

Patients >12 years of age with World Health Organization (WHO) functional class III Eisenmenger syndrome were enrolled. Eisenmenger physiology was established echocardiographically as atrial septal defect with ≥2-cm effective diameter and/or ventricular septal defect with ≥1-cm effective diameter associated with right-to-left shunting. A systemic pulse oximetry (SpO2) between 70% and 90% at rest with room air and a baseline 6-minute walk distance between 150 and 450 m were required for inclusion. PAH was confirmed by cardiac catheterization as mean pulmonary arterial pressure >25 mm Hg, pulmonary capillary wedge pressure <15 mm Hg, and pulmonary vascular resistance >5 Wood units. Patients were excluded if they had patent ductus arteriosus (for hemodynamic assessment difficulties), complex congenital heart defect, left ventricular dysfunction (left ventricular ejection fraction <40%), restrictive lung disease (total lung capacity <70% predicted, with FEV1/forced vital capacity <50%), obstructive lung disease (forced expiratory volume in 1 second [FEV1] <70% predicted, with FEV1/forced vital capacity <60%), or previously diagnosed coronary artery disease. Medical therapy and clinical conditions had to be stable within 3 months of screening. Treatment with prostanooids, phosphodiesterase-V inhibitors, and endothelin receptor antagonists was not allowed during the study or within 1 month before screening. The study was conducted according to the most recent amendments to the Declaration of Helsinki and in adherence to good clinical practice guidelines. Local institutional review boards or independent ethics committees approved the protocol, and written informed consent was obtained from all patients.

Study Design and Procedures

BREATHE-5 was a 16-week, double-blind, randomized, placebo-controlled trial conducted in 15 centers in Europe, North America, and Australia. Eligible patients were randomized 2:1 to receive double-blind bosentan or placebo, respectively. Randomization was controlled by study medication packaging (Almedica HPS AG, Reinach, Switzerland). Patients were randomized in a consecutive order, starting with the lowest provided medication number. The investigators, patients, monitors, and sponsor personnel remained blinded to the treatment until closure of the clinical database. In addition to their background therapy for PAH (oral vasodilators, cardiac glycosides, diuretics, anticoagulants, supplemental oxygen), patients received bosentan 62.5 mg BID or matching placebo for 4 weeks and bosentan 125 mg BID or matching placebo for the remainder of the trial. Patients who did not tolerate the target dose of 125 mg BID could be downtitrated to the starting dose (62.5 mg BID). At study’s end, all patients were eligible to enter an open-label study of bosentan. Clinical examination, SpO2, and WHO functional class were assessed periodically. A 6-minute walk test and right- and left-heart catheterization were performed at baseline and at week 16. The following hemodynamic parameters were assessed: heart rate, right atrial pressure (RAP), left atrial pressure (LAP; in case of atrial septal defects), pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure, systemic arterial pressure (SAP), left ventricular end-diastolic pressure, superior vena cava O2 saturation, pulmonary arterial O2 saturation, systemic arterial O2 saturation, and pulmonary vein O2 saturation (measured in case of atrial septal defects, assumed as 96% in other cases). Pulmonary (Qpi) and systemic (Qsi) blood flow indexes were calculated according to Fick’s method using standard formulas and assuming an O2 consumption index of 125 mL·min⁻¹·m⁻². Pulmonary vascular resistance index (PVRi) and systemic vascular resistance index (SVRi) were calculated by the following formulas:

\[
PVRi = \frac{(meanPAP - meanLAP) \times 80}{Qpi}
\]

\[
SVRi = \frac{(meanSAP - meanRAP) \times 80}{Qsi}
\]

Adverse events, concomitant medications, hepatic function, renal function, and hematology values were monitored throughout the study.

At the end of the study, all patients were eligible to enter an open-label study of bosentan except those who were enrolled in Canada and Australia because of administrative limitations in those countries.

Statistical Analysis

Primary End Points

The first primary end point of the study was a safety end point, ie, the change in SpO2 from baseline to week 16 at rest on room air. For this end point, a noninferiority test was conducted comparing bosentan with placebo. The null hypothesis was that the mean difference between the bosentan and placebo groups was negative and ≥5%. Hypothesis testing was based on 2-sided 95% confidence intervals (using Student distribution). Assuming that the expected difference in means is 0% and the common standard deviation is 5.0%, in a sample of 51 evaluable patients randomized 2:1 to bosentan and placebo, respectively, a 2-group 0.025 one-sided test had 90% power to reject the null hypothesis in favor of the alternative hypothesis.

If the null hypothesis concerning the SpO2 was rejected, a second test was to be performed concerning the second primary end point of the study, ie, the change in PVRi from baseline to week 16. For this end point, the superiority of bosentan compared with placebo was to be tested. The null hypothesis was that the mean change in PVRi from baseline to week 16 in the placebo group equals that in the bosentan group. The clinically relevant alternative was a difference of 250 dynes·cm⁻² between the treatment groups. With the assumption that the data were from approximately normal distributions with an SD of 250 dynes·cm⁻², the planned 51 patients randomized 2:1 to bosentan and placebo, respectively, provided 81% power to detect the abovementioned difference when the data were analyzed by means of the Student t test at 2-sided 0.05 significance level. Because of the study design characteristics, the primary analysis population was the per-protocol population, and a robustness analysis using the all-randomized population was to be performed on the second primary end point.

Secondary End Points

Secondary end points included the changes from baseline to week 16 in mean PAP, Qpi, Qsi, SVRi, SAP, mean RAP, 6-minute walk distance, and WHO functional class. Testing was based on the
Student t test. Secondary end points were analyzed using
the all-randomized population, and no correction for multiple testing
was done.

Substitution Rules
Any data missing at the week 16 assessment were derived from
predefined replacement rules. Patients who died, underwent lung
transplantation during the study, or discontinued study medication as
a result of worsening of their pulmonary hypertension and had no
assessment at the time of premature withdrawal were assigned the
worst value reported for SpO2 and WHO class and a walk distance of
0 m. Other patients, including those withdrawing for reasons other
than worsening of PAH or lost to follow-up had their last value
carried forward. Patients who had no PVRi assessment at the time of
discontinuation were analyzed using the worst percentage change from
baseline observed at the week 16 time point; no imputation rule
was applied to other hemodynamic parameters.

All reported probability values are 2 sided. Demographics/base-
line data are presented as mean±SE; efficacy end points are
presented as mean±SD; Student t test. Secondary end points were analyzed using
the all-randomized population, and no correction for multiple testing
was done.

Table 1. Baseline Clinical, Functional, and Hemodynamic
Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=17)</th>
<th>Bosentan (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>10 (59)</td>
<td>23 (62)</td>
</tr>
<tr>
<td>Age, y</td>
<td>44.2±8.5</td>
<td>37.2±12.0</td>
</tr>
<tr>
<td>Time from Eisenmenger syndrome</td>
<td>20.5±13.0</td>
<td>23.7±13.6</td>
</tr>
<tr>
<td>diagnosis, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>14 (82)</td>
<td>34 (92)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (12)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (6)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>63±18</td>
<td>64±14</td>
</tr>
<tr>
<td>Type of congenital heart defect, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defects</td>
<td>12 (71)</td>
<td>24 (65)</td>
</tr>
<tr>
<td>Atrial septal defects</td>
<td>5 (29)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Ventricular-atrial septal defects</td>
<td>...</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Previous or concomitant treatments, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombotic agents</td>
<td>11 (65)</td>
<td>25 (68)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>10 (53)</td>
<td>13 (35)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>4 (24)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>6-min walk distance, m</td>
<td>366.4±67.5</td>
<td>331.9±82.8</td>
</tr>
<tr>
<td>Systemic pulse oximetry, %</td>
<td>83.6±5.1</td>
<td>82.4±5.3</td>
</tr>
<tr>
<td>Hemodynamic variables*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>77.8±12.8</td>
<td>76.3±16.7</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure, mm Hg</td>
<td>72.1±19.4</td>
<td>77.8±15.2</td>
</tr>
<tr>
<td>Mean left atrial pressure, mm Hg</td>
<td>6.5±3.6</td>
<td>8.1±3.5</td>
</tr>
<tr>
<td>Pulmonary flow index, L·min⁻¹·m⁻²</td>
<td>2.0±0.5</td>
<td>1.9±1.1</td>
</tr>
<tr>
<td>Pulmonary vascular resistance index, dyne·s·cm⁻⁵</td>
<td>2870.0±1209.3</td>
<td>3425.1±1410.5</td>
</tr>
<tr>
<td>Mean systemic arterial pressure, mm Hg</td>
<td>93.9±17.3</td>
<td>90.7±14.6</td>
</tr>
<tr>
<td>Mean right atrial pressure, mm Hg</td>
<td>5.0±3.7</td>
<td>6.1±3.4</td>
</tr>
<tr>
<td>Systemic flow index, L·min⁻¹·m⁻²</td>
<td>2.1±0.7</td>
<td>2.7±2.3</td>
</tr>
<tr>
<td>Systemic vascular resistance index, dyne·s·cm⁻⁵</td>
<td>3658.1±1428.8</td>
<td>3244.2±1474.0</td>
</tr>
</tbody>
</table>

Values are mean±SD when appropriate.
*The number of patients per treatment group varied slightly for each
parameter because of missing assessments.
†Directly assessed in the presence of an atrial septal defect or patent
foramen ovale, substituted with end-diastolic left ventricular pressure
or pulmonary capillary wedge pressure in other cases.

Results
Of the 76 patients screened for enrollment, 54 were included
in the study (22 screen failures) from September 2003 to
December 2004; 37 received bosentan and 17 received placebo
(Figure 1).

Baseline Characteristics
Treatment groups were well matched with respect to clinical,
functional, and hemodynamic baseline characteristics (Table
1), although patients randomized to bosentan tended to have
higher PVRi compared with those receiving placebo. Re-
duced SpO2, together with greater Qsi than Qpi, substantiates
net right-to-left shunt, confirming Eisenmenger syndrome.
All patients were in WHO functional class III, and baseline
6-minute walk distance was markedly reduced compared with
predicted normal values.19 Ventricular septal defect was the
most frequent congenital heart defect.

Systemic Pulse Oximetry
Systemic arterial blood oxygen saturation as assessed by SpO2
or directly measured during left-heart catheterization was similar in both
groups at baseline (83.6±5.1% versus
83.7±6.2% and 82.4±5.3% versus 80.2±8.9% in the placebo
and bosentan groups, respectively). The placebo-corrected

![Figure 1. Disposition of the patients.](http://circ.ahajournals.org/Article-Images/50/img1.jpg)
placebo and bosentan groups. TE indicates treatment effect.

Figure 2.

Exercise and Functional Capacity

The 6-minute walk distance decreased in the placebo group by 9.7 m and increased in the bosentan-treated patients by 22.3 m, resulting in a significant treatment effect of 33.6 m (P = 0.0176). Two patients in the placebo group (13%) improved to WHO class II compared with 13 patients in the bosentan group (35%); 1 patient in the placebo group (6%) and 1 patient in the bosentan group (3%) deteriorated to WHO class IV; all other patients remained in WHO class III.

Safety

Adverse events that occurred in a greater proportion of patients on bosentan than on placebo included peripheral edema (19% versus 6%), headache (14% versus 12%), palpitations (11% versus 0%), dizziness (8% versus 6%), and chest pain (8% versus 0%). Few adverse events were of severe intensity (8% in the bosentan group versus 18% in the placebo group).

Two patients randomized to placebo (12%) discontinued as a result of adverse events: 1 after 2 days because of fatigue and 1 after 20 days because of worsening of PAH. Two patients treated with bosentan (5%) were discontinued: 1 after 73 days because of angina pectoris and 1 after 99 days as a result of an increase in liver enzymes >5 times the upper limit of normal. All serious adverse events are reported in Table 3; 3 patients in the placebo group (18%) and 5 patients in the bosentan group (14%) had ≥1 serious adverse event.

Open-Label Continuation Study

Thirty-seven patients who completed the randomized study (11 patients treated with placebo, 26 treated with bosentan) were enrolled in an open-label extension study. After 24 weeks, all patients were alive; 24 patients had WHO functional class II and 13 patients had WHO functional class III limitations. No additional targeted treatments for pulmonary hypertension were initiated. Six-minute walk test data showed improvement in the patients who had been on placebo (33.2 ± 23.9 m) and maintenance of the effect in patients who had received bosentan (6.7 ± 10.0 m). Two

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**Table 2. Hemodynamic Effects of Placebo and Bosentan at Week 16**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change From Baseline</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=17)</td>
<td>Bosentan (n=37)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>−0.8 (2.7)</td>
<td>−2.0 (1.9)</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure, mm Hg</td>
<td>0.5 (1.4)</td>
<td>−5.0 (1.6)</td>
</tr>
<tr>
<td>Mean left atrial pressure, mm Hg</td>
<td>0.5 (1.2)</td>
<td>0.4 (0.6)</td>
</tr>
<tr>
<td>Pulmonary flow index, L·min⁻¹·m⁻²</td>
<td>0.0 (0.1)</td>
<td>0.1 (0.1)</td>
</tr>
<tr>
<td>Pulmonary vascular resistance index, dyne·s·cm⁻⁵</td>
<td>155.1 (134.0)</td>
<td>−316.9 (138.3)</td>
</tr>
<tr>
<td>Mean systemic arterial pressure, mm Hg</td>
<td>2.5 (2.2)</td>
<td>−3.8 (1.6)</td>
</tr>
<tr>
<td>Mean right atrial pressure, mm Hg</td>
<td>0.4 (0.9)</td>
<td>0.3 (0.5)</td>
</tr>
<tr>
<td>Systemic flow index, L·min⁻¹·m⁻²</td>
<td>−0.2 (0.1)</td>
<td>0.9 (0.8)</td>
</tr>
<tr>
<td>Systemic vascular resistance index, dyne·s·cm⁻⁵</td>
<td>378.9 (246.8)</td>
<td>−372.9 (244.6)</td>
</tr>
</tbody>
</table>

Values are expressed as means (SE).

*The number of patients per treatment group varied slightly for each parameter because of missing assessments.

†Directly assessed in the presence of an atrial septal defect or patent foramen ovale, substituted with end-diastolic left ventricular pressure or pulmonary capillary wedge pressure in other cases.
patients (5.4%) had an increase in liver aminotransferases $>3$ times the upper limit of normal. One patient had a marked decrease in hemoglobin. Two patients discontinued prematurely: 1 withdrew consent, and 1 developed adverse events (abdominal pain, diarrhea, lethargy, and nausea).

### Discussion

In this first-ever reported multicenter, randomized, double-blind, placebo-controlled trial for adults with Eisenmenger syndrome, bosentan significantly improved hemodynamics and exercise capacity without adversely affecting systemic arterial oxygen saturation.

The lack of change observed in $\text{SpO}_2$ can be explained by a limited influence of bosentan on the net right-to-left shunt because its effect on both PVRi and SVRI was similar. In patients with Eisenmenger syndrome, small pulmonary arteries are affected by fixed obstructive pathological changes (pulmonary hypertensive vasculopathy), whereas the supposedly normal systemic circulation could be considered more responsive to vasodilator stimuli. The results of this study allow rejection of the hypothesis that a prevalent effect of bosentan on the potentially more reactive systemic circulation compared with the obstructed pulmonary vascular bed could result in worsening of systemic hypoxemia as a result of an increase in right-to-left shunt. No changes in $\text{SpO}_2$ also were observed in an open multicenter study that included patients with Eisenmenger syndrome, and limited improvements were observed in smaller series.

In the present study, baseline 6-minute walk distance was similar to that of other studies on bosentan in PAH, although the patient population was about a decade younger (Table 1). These findings confirm the relevance of exercise limitation of patients with Eisenmenger syndrome compared with age-matched predicted normal values. The observed increase in 6-minute walk distance in bosentan-treated patients was comparable to that of other controlled studies in PAH. Exercise capacity improvements were maintained after 24 additional weeks of open-label bosentan administration. It should be emphasized that exercise capacity is a predictor of death in both patients with idiopathic PAH and patients with Eisenmenger syndrome and has been used as the primary efficacy end point in most clinical trials involving patients with PAH. Interestingly, after 16 weeks of treatment, a reduction in 6-minute walk distance was observed in placebo-treated patients of BREATHE-5, demonstrating that patients with WHO class III Eisenmenger syndrome tend to deteriorate in the same way as patients with other forms of PAH.

Baseline hemodynamic data of both treatment groups (Table 1) are consistent with severe PAH with markedly elevated PVRi. Despite the common concept that hemodynamics of patients with Eisenmenger syndrome are remarkably stable over time, we have observed in the placebo group of this study a trend to increased PVRi (5.4%) and SVRI (10.4%), consistent with progressive deterioration over the 16-week study period. It seems that the patient population of this study, characterized by WHO class III, represents a subgroup with advanced disease and more rapid progression.

The observed reductions in PVRi and mean PAP (Table 2) in bosentan-treated patients are remarkably similar to those observed in another controlled clinical trial with the same compound including subjects with idiopathic PAH or PAH related to connective tissue disease. Although the time from diagnosis to the initiation of the investigational treatment was much longer in this study on patients with Eisenmenger syndrome compared with other clinical trials with different types of PAH ($>2$ decades versus 2 to 3 years, respectively), bosentan therapy appears to be equally effective. It is not clear what mechanisms are involved in the hemodynamic improvements seen in patients with PAH who have long-standing fixed pulmonary vascular obstructive lesions. It has been suggested that there is possible reverse remodeling of pulmonary vascular changes with endothelin receptor antagonists on the basis of their antiproliferative properties.

Reductions in PVRi and mean PAP also were observed in an uncontrolled study on patients with Eisenmenger syndrome but not in another series. However, in the latter study, surgically corrected patients also were included, and invasive hemodynamics were performed only in selected cases.

Reductions in SVRI and mean systemic arterial pressure were observed in bosentan-treated patients in BREATHE-5. The mechanisms involved may include a direct effect of endothelin-1 antagonism on the systemic circulation and/or the interconnection between right and left ventricles in ventricular septal defects (the most frequent defect in this study), which implies the reciprocal influence of pressure changes in the 2 chambers. In any case, the reduction in systemic arterial pressure was well tolerated because only 1 episode of vasovagal syncope (Table 3) was observed in 1 patient (3%) after the initial dose of bosentan (on standing up after 12 hours of bed rest as a result of heart catheterization), whereas no additional symptoms were detected with the continuation of treatment.

The reductions in PVRi, mean PAP, SVRI, and mean systemic arterial pressure decrease the workload of the right and left ventricles and may contribute to delaying the progression of heart failure.

No unexpected side effects were observed in the bosentan-treated group, and the profile of adverse events in patients with Eisenmenger syndrome was comparable to that reported...
for other PAH forms.12,13 Similar to previous studies of bosentan, the increases in liver enzymes were reversible on dose reduction or discontinuation and confirm the necessity of routine monitoring liver function tests on a monthly basis. The limitations of the present study are related to the theoretical assumptions made for the assessment of O2 consumption and pulmonary venous O2 saturation in patients with isolated ventricular septal defects.

We adopted an assumed O2 consumption because, in the setting of a multicenter study, the variability of directly measured O2 consumption was considered high.22 We chose to assume pulmonary venous O2 saturation in patients with ventricular septal defects because a direct measurement would have required 2 transseptal procedures that were considered too risky and unethical. In addition, the assumed O2 consumption based on body mass index tables is used in common practice in hemodynamic laboratories. The randomized and blinding procedures of this study should have allowed equal distribution of any possible error related to these assumptions.

Conclusions

In this trial, the safety profile of bosentan was confirmed in patients with Eisenmenger syndrome. Furthermore, bosentan produced favorable hemodynamic and functional effects that were similar to those reported in other randomized studies of other forms of PAH. These results indicate that bosentan may be a new treatment option in patients with Eisenmenger syndrome.

Acknowledgments

We acknowledge the collaboration and commitment of all the local investigators and their staff: Australia: David Celerier-Majd, MD, Central Clinical School, Camperdown; Leeanne Grigg, Royal Melbourne Hospital, Parkville. Austria: Helmut Baumgartner, MD, Universitätssklinik für Innere Medizin, Wien. Belgium: Luc Mertens, MD, UZ Gasthuisberg, Leuven. Canada: Michael Connelly, MD, Peter Lougheed Centre, Calgary; Rima Hosn, MD, Toronto General Hospital, Pavia, Netherlands: Petronella G. Pieper, MD, University Medical Center Groningen. Spain: José María Oliver, MD, Hospital La Paz, Madrid. United Kingdom: W. Stewart Hills, MD, Scottish Vascular Unit, Glasgow; Carl Harries, BSc RN, Royal Brompton Hospital, London. United States: Ronald G. Grijka, MD, Texas Children’s Hospital, Houston, Tex; Dorothy D. Pearson, PA-C, Boston Adult Congenital Heart and Pulmonary Hypertension Group, Children’s Hospital, Boston, Mass.

Sources of Funding

This study was supported by Actelion Pharmaceuticals Ltd, Allschwil, Switzerland. Dr Galié has received grant support from Pfizer, Actelion, Schering, Encysive, and Myogen. Dr Beghetti has received grant support from Actelion and Schering. Drs Gatzoulis and Berger have received grant support from Actelion. Dr Granton has received grant support from Pfizer, Actelion, GlaxoSmithKline, and AGA Medical and has received trial grant support from Actelion, Myogen, Pfizer, NITROX, NMT Medical, and AGA Medical.

Disclosures

Dr Galié has served on the advisory boards of Pfizer, Actelion Pharmaceuticals Ltd, Schering, Encysive, Myogen, and Mondobiotec and has received lecture fees from Actelion and Schering. Dr Beghetti has served on the advisory boards of Actelion, INO Therapeutics, and Mondobiotec and has received lecture fees from Actelion, INO Therapeutics, and Schering. Dr Gatzoulis has served on the advisory boards of Pfizer and Actelion and has received lecture fees from Actelion. Dr Granton has served on the advisory board of and has received lecture fees from Actelion. Dr Lauer and E. Chiossi are employees of and have ownership interest in Actelion.

References


**CLINICAL PERSPECTIVE**

Congenital heart disease is the most common inborn defect with a worldwide incidence of approx. 1%, and Eisenmenger syndrome represents the most advanced form of pulmonary arterial hypertension related to unrepaired congenital heart disease. Eisenmenger syndrome is a multisystem disorder associated with numerous life-threatening complications, including hemoptysis, erythrocytosis, cerebrovascular accidents, brain abscesses, arrhythmias, and syncope. Despite major advances in the diagnosis and treatment of congenital heart diseases that allow most children now to survive into adulthood, a significant proportion of these patients develop pulmonary hypertension, particularly those with absent or delayed repair of large left-to-right shunts. No evidence-based medical treatment approach currently exists for patients with Eisenmenger syndrome, and guidelines are based mainly on empirical expert recommendations. The present study reports the results of the first-ever performed multicenter, randomized, double-blind, placebo-controlled trial for adults with Eisenmenger syndrome. Because this condition is associated with increased endothelin expression, patients may benefit from endothelin receptor antagonism. The hypothesis that the oral active dual endothelin-1 receptor antagonist bosentan was safe and effective was tested in 54 patients with large atrial and/or ventricular unrepaired congenital septal defects. After 16 weeks of therapy, bosentan compared with placebo was well tolerated and improved exercise capacity and hemodynamics without compromising peripheral oxygen saturation. Exercise capacity improvements were maintained after 24 additional weeks of open-label bosentan administration period. These data may constitute the confirmation for considering bosentan as a new evidence-based treatment option in patients with Eisenmenger syndrome.
Bosentan Therapy in Patients With Eisenmenger Syndrome: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study
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Circulation. 2006;114:48-54; originally published online June 26, 2006;
doi: 10.1161/CIRCULATIONAHA.106.630715
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/114/1/48

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