Long term effects of bosentan treatment in adult patients with pulmonary arterial hypertension related to congenital heart disease (Eisenmenger physiology): safety, tolerability, clinical, and haemodynamic effect

M D’Alto, C D Vizza, E Romeo, R Badagliaccia, G Santoro, R Poscia, B Sarubbi, M Mancone, P Argiento, F Ferrante, M G Russo, F Fedele, R Calabrò

Background: Oral bosentan is an established treatment for pulmonary arterial hypertension (PAH). Objective: To evaluate safety, tolerability, and clinical and haemodynamic effects of bosentan in patients with PAH related to congenital heart disease (CHD).

Patients: 22 patients with CHD related PAH (8 men, 14 women, mean (SD) age 38 (10) years) were treated with oral bosentan (62.5 mg×2/day for the first 4 weeks and then 125 mg×2/day).

Main outcome measures: Clinical status, liver enzymes, World Health Organisation (WHO) functional class, resting oxygen saturations and 6-min walk test (6MWT) were assessed at baseline and at 1, 3, 6, and 12 months. Haemodynamic evaluation with cardiac catheterisation was performed at baseline and at 12 month follow-up.

Results: 12 patients had ventricular septal defect, 5 atrioventricular canal, 4 single ventricle, and 1 atrial septal defect. All patients tolerated bosentan well. No major side effects were seen. After a year of treatment, an improvement was seen in WHO functional class (2.5 (0.7) v 3.1 (0.7); p<0.05), oxygen saturation at rest (87 (6%) v 81 (9%); p<0.001), heart rate at rest (81 (10) v 87 (14) bpm; p<0.05), distance travelled in the 6MWT (394 (73) v 320 (108) m; p<0.001), oxygen saturation at the end of the 6MWT (71 (14) v 63 (17%); p<0.05), Borg index (5.3 (1.8) v 6.5 (1.3); p<0.001), pulmonary vascular resistances index (14 (9) v 22 (12) WU m²; p<0.001), systemic vascular resistances index (23 (11) v 27 (10) WU m²; p<0.01), pulmonary vascular resistances index/systemic vascular resistances index (0.6 (0.5) v 0.9 (0.6); p<0.05); pulmonary (4.0 (1.3) v 2.8 (0.9) l/min/m²; p<0.001) and systemic cardiac output (4.2 (1.4) v 3.4 (1.1) l/min/m²; p<0.05).

Conclusions: Bosentan was safe and well tolerated in adults with CHD related PAH during 12 months of treatment. Clinical status, exercise tolerance, and pulmonary haemodynamics improved considerably.

CONGENITAL HEART DISEASES (CHDs) are the most common congenital malformations and account for about eight cases per 1000 births.1 Eisenmenger syndrome is defined as a congenital heart defect that initially causes a chronic large left-to-right shunt that induces severe pulmonary vascular disease and pulmonary arterial hypertension (PAH), with resultant reversal of the direction of shunting.2 Patients with Eisenmenger syndrome have a poor quality of life, but in most cases the disease progresses very slowly3 4 so they have a considerably longer life expectancy than those with idiopathic pulmonary arterial hypertension and comparable functional class.4 Because of its unique haemodynamics, the right ventricle maintains its characteristics from fetal life (that is, regression of wall thickness does not occur) and it can sustain an increased afterload. This is probably the reason why patients with Eisenmenger syndrome have a better prognosis than patients with other forms of PAH.5

In recent years, new treatment strategies have largely improved the clinical status and life expectancy of patients with PAH.6 7 Bosentan, an oral dual endothelin (ET-A/ET-B) receptor antagonist has been shown to be effective in patients with idiopathic PAH and PAH related to connective tissue disease, improving long term quality of life.6 8 15 Over the past few years, small open label studies have suggested that bosentan is safe and well tolerated in adults with CHD and improves functional status and exercise capacity.15 16 These pilot studies triggered the first large randomised controlled trial on bosentan in patients with Eisenmenger syndrome, showing a beneficial short term effect of bosentan on exercise capacity and haemodynamics without compromising systemic oxygen saturation.17

OBJECTIVE

The aim of this open label, single arm, prospective study was to evaluate the safety and tolerability of oral bosentan treatment in 24 adult patients with Eisenmenger physiology by assessing its long term effects on clinical status, exercise capacity, and cardiopulmonary haemodynamics.

METHODS

Patients with PAH due to unoperated non-restrictive intracardiac communication with a bidirectional or a right-to-left shunt (Eisenmenger pathophysiology) were enrolled.

Concomitant causes of pulmonary hypertension such as lung or liver disease were excluded using mandatory chest x ray.

Abbreviations: CHD, congenital heart disease; 6MWT, 6-min walk test; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistances index; SVRI, systemic vascular resistances index; WHO, World Health Organisation

See end of article for authors’ affiliations

Correspondence to: Dr M D’Alto, Via D Fontana, 81, Naples 80128, Naples, Italy; mic.dalto@tin.it

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performed at baseline and at the 12 month follow-up evaluation; cardiac catheterisation was performed in a 25-m-long corridor in the same environmental conditions and at about the same time of day (± 2 h).

**Heart catheterisation**

Haemodynamic assessment was performed at baseline and after 12 months of treatment by right heart catheterisation. Pulmonary arterial, right atrial, and pulmonary capillary wedge pressures and systemic pressures were recorded at the end of a quiet respiratory cycle. Oxygen saturations in the superior vena cava, inferior vena cava, pulmonary artery, and femoral artery were obtained in triplicate.

Pulmonary vein saturation was assumed at 98%. Pulmonary and systemic flows were obtained by the Fick principle using table-derived oxygen consumption values and calculated oxygen content at the correspondent different sites. The transpulmonary pressure gradient was defined as the difference between the mean pulmonary arterial pressure and the mean pulmonary capillary wedge. Pulmonary and systemic vascular resistance indices were calculated using the standard formula.

**STATISTICAL ANALYSIS**

All values are presented as mean (SD) except when otherwise indicated. Changes from baseline to month 12 were evaluated with a paired t test for continuous variables and with Wilcoxon’s rank sum test for categorical variable. A value of p<0.05 was considered to be significant. All the reported p values were two tailed.

**RESULTS**

A total of 24 consecutive adult patients with pulmonary hypertension from CHD were enrolled. After 1–2 weeks of treatment, two patients (8.3%) withdrew from drug treatment because of severe leg oedema despite an increased diuretic dose and were not considered in the analysis.

In the 22 participating patients, conventional treatment with oxygen, diuretics, digoxin or warfarin was continued during the study, with little change. No patient used calcium channel blockers (tables 1 and 2).

**Aspartate aminotransferase and alanine aminotransferase plasma levels remained below three times the upper limit of normal in all but three patients throughout the observation period. In these three patients, showing a rise in the aminotransferase level of four times the upper limit of normal, the dose of bosentan at 2 months of observation was reduced from 125 mg twice a day to 62.5 mg twice a day, with a complete normalisation of the aminotransferase level. These three patients continued receiving 62.5 mg twice a day during the follow-up. One patient required a bosentan dose reduction in the sitting position, and the mean of three consecutive readings was recorded for analysis. Clinical findings such as pretibial oedema, jugular venous pulse, and hepatomegaly were observed.

Monitoring also included monthly measurements of liver enzymes, with a focus on alanine aminotransferase and aspartate aminotransferase and 3-monthly measurements of packed cell volume, haemoglobin, and serum iron.

**Effort tolerance**

Exercise capacity was evaluated with an non-encouraged 6MWT (at baseline 6-min walking distance was calculated as the best distance covered on two consecutive tests performed after 60–90 min). Heart rate, saturation of peripheral oxygen were recorded at rest and at the end of exercise, Borg dyspnoea index was evaluated at completion of the test. All 6MWTs were performed in a 25-m-long corridor in the same environmental conditions and at about the same time of day (± 2 h).

**Study design**

This was an open label, single arm, prospective study. Bosentan (Tracleer; Actelion Pharmaceuticals, Allschwil, Switzerland) was started at an oral dose of 62.5 mg twice a day and increased to the target dose of 125 mg twice a day after 4 weeks.

Clinical assessment and laboratory tests, including haemoglobin, packed cell volume, and liver function tests (aspartate aminotransferase/alanine aminotransferase) were performed at baseline (before initiating bosentan treatment) and monthly, or whenever the patients’ clinical status was determined. Evaluation of exercise tolerance with 6-min walk test (6MWT) was performed at baseline and at 1, 3, 6 and 12 month follow-up evaluation; cardiac catheterisation was performed at baseline and at the 12 month follow-up evaluation.

**Clinical assessment and laboratory tests**

Clinical assessment included medical examination with WHO classification and measurement of systemic arterial pressure, transcutaneous oxygen saturation, and heart rate. Resting systemic arterial oxygen saturation was measured indirectly by non-invasive finger pulse oximetry after 5 min of absolute rest.

respiratory function, perfusion lung scan, high resolution computed tomography scan, spiral CT scan and abdominal ultrasound.

No patient was receiving calcium channel blockers as they were unresponsive to acute vasodilator testing in prior haemodynamic evaluation. No other drugs effective in PAH were used during the treatment period.

Informed patient consent was obtained before entering the study, and the protocol was approved by the institutional ethics committee. Enrolled patients weighed >40 kg, had been in a stable condition for at least 3 months before entering the study and were in World Health Organisation (WHO) functional class II–IV. Additionally, enrolled patients had resting systemic arterial oxygen saturations of <90% and >60% at rest in room air and were not pregnant.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients receiving treatment</th>
<th>Daily dose (mg)</th>
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<tbody>
<tr>
<td>Digoxin</td>
<td>12</td>
<td>0.125–0.25</td>
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<tr>
<td>Furosemide</td>
<td>18</td>
<td>25–125</td>
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<tr>
<td>Warfarin</td>
<td>15</td>
<td>2.5–6</td>
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<tr>
<td>Aldactone</td>
<td>13</td>
<td>25–100</td>
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<tr>
<td>Nifedipine</td>
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<td>Nitrites</td>
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<td>Amiodarone</td>
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**Table 1 Concomitant treatment**

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Bosentan treatment of pulmonary hypertension related to CHD

...functional status as well as exercise capacity in 33 adult patients with CHD related PAH at 2.1 year follow-up. In this study only 27 of 33 patients at baseline and 17 of 33 during the follow-up underwent heart catheterisation; no statistically significant haemodynamic modification was observed, despite slight trends in improvements in PVRI and right ventricular systolic pressure. Apostolopoulou et al,21 studying a heterogeneous population of 21 patients with PAH owing to differently operated or unoperated CHD, observed a short term (16 week treatment) improvement of clinical, exercise tolerance, and haemodynamics. These favourable findings in adults are further supported by data from a subset in an open, prospective trial of nine children with PAH-CHD in functional class II or III, all of whom stabilised or improved during 3 months' bosentan treatment.22,23

The Bosentan Randomised Trial of Endothelin Antagonist Therapy-5,17 a 16 week, multicentre, randomised, double blind, placebo controlled study, recently evaluated the effect of bosentan in 54 patients with WHO functional class III Eisenmenger syndrome. The placebo corrected effect on systemic pulse oximetry showed that bosentan did not worsen oxygen saturation. Moreover, compared with placebo, bosentan improved exercise capacity and haemodynamics: treatment effect on 6MWT of 53.1 m, and significant reduction of PVRI, mean pulmonary arterial pressure, SVRI, and mean systemic arterial pressure. In all, four patients discontinued the trial as a result of adverse events, two (5%) in the bosentan group and two (12%) in the placebo group.

Our results confirm these previous observations, suggesting that patients with CHD related PAH have a sustained benefit from long term bosentan therapy. Our findings agree with previous observations,15–23 ruling out the hypothesis that bosentan has a greater effect on systemic circulation than the obstructed pulmonary vascular bed of patients with Eisenmenger syndrome, and could worsen systemic hypoxaemia as a result of increased in right-to-left shunt.

After a year of treatment, we observed a considerable improvement in WHO functional class, 6-min walking, with a concomitant increase in pulmonary flow, systemic flow and reduction in PVRI, SVRI, PVRI/SVRI ratio. In our series, the significant reduction of the PVRI/SVRI ratio suggests a greater effect of bosentan on pulmonary rather than on systemic circulation. Although in patients with Eisenmenger syndrome small pulmonary arteries are affected by fixed obstructive pathological changes, it has been suggested that there may be

**DISCUSSION**

This study is the first prospective relatively long term haemodynamic evaluation of bosentan treatment in patients with CHD related PAH. Bosentan treatment was investigated in several small, uncontrolled case series in the present indications. Christensen et al10 treated nine patients with CHD related PAH with oral bosentan. Clinical and non-invasive evaluation showed a significant improvement of oxygenation and functional status with minimal side effects at a 9.5-month follow-up. Gatzoulis et al15 reported a substantial improvement in clinical status, 6-min walking distance, and haemodynamics in 10 adult patients with Eisenmenger physiology after a short term (3 months) treatment. Recently, in an open label, prospective, multicentred study, Schulze-Neick et al16 observed that bosentan treatment was well tolerated and improved functional status as well as exercise capacity in 33 adult patients with CHD related PAH at 2.1 year follow-up. In this study only 27 of 33 patients at baseline and 17 of 33 during the follow-up underwent heart catheterisation; no statistically significant haemodynamic modification was observed, despite slight trends in improvements in PVRI and right ventricular systolic pressure. Apostolopoulou et al,21 studying a heterogeneous population of 21 patients with PAH owing to differently operated or unoperated CHD, observed a short term (16 week treatment) improvement of clinical, exercise tolerance, and haemodynamics. These favourable findings in adults are further supported by data from a subset in an open, prospective trial of nine children with PAH-CHD in functional class II or III, all of whom stabilised or improved during 3 months' bosentan treatment.22,23

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**Figure 1** (A) Travelled distance at 6-min walk test (6MWT). (B) Heart rate at the end of 6MWT. Open bars: basal condition; black bars: 1 year follow-up.

**Figure 2** (A) Oxygen saturation at the end of 6-min walk test (6MWT). (B) Borg index at 6MWT. Open bars: basal condition; black bars: 1 year follow-up.
reverse remodelling of pulmonary vascular changes with endothelin receptor antagonists on the basis of their anti-proliferative properties.81 1

The decrease in pulmonary vascular resistance seen in our study is in the range of 20–25% from baseline, similar to the results obtained in randomised controlled studies conducted in patients with idiopathic and CHD related PAH. 81 41 7

Experimental data showed that endothelin-1 not only modulates vascular smooth muscle tone 24 but also promotes cellular proliferation, 25 initiates cardiac myocyte, 26 and non-myocyte27 hypertrophy, and regulates secretion of neurohormonal mediators of cardiac and vascular hypertrophy. 28 Bosentan, an oral ET-A/ET-B inhibitor, not only prevents the development of pulmonary hypertension but can also reverse established pulmonary hypertension and pulmonary vascular remodelling induced by chronic hypoxia.29 These experimental observations may explain the long term efficacy of oral bosentan in patients with Eisenmenger physiology as a result of its favourable effect on pulmonary vessel remodelling.

In patients with Eisenmenger syndrome there remains a theoretical point of concern using a non-selective pulmonary vasodilator: the possible increase in right-to-left shunt. However, in our population during bosentan treatment we saw no reduction in resting or exercise saturation of peripheral oxygen compared with baseline.

Bosentan treatment for 1 year caused a greater reduction in right ventricular than in the left ventricular afterload, resulting in a reduction in the right-to-left shunt, an improvement in pulmonary blood flow, and ultimately, in systemic oxygen delivery. This pathophysiological mechanism explains the significant improvement in clinical status and effort tolerance seen during the follow-up.

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STUDY LIMITATION

These results need to be viewed against the background of several potential limitations.

Firstly, this study was not controlled, and therefore, the contribution of a placebo effect is unknown. However, an attempt was made to exclude this effect by allowing no less than a 9 month treatment. Placebo effects disappear after 1–2 months in randomised controlled studies.30 Secondly, in the absence of randomisation procedures, the influence of unknown bias—for example, through patient selection, cannot be determined. Finally, the specific type of intracardiac abnormality largely determines the natural history and

| Table 3 Clinical, haematological, and haemodynamic variables before and after oral bosentan treatment |
|-----------------|-----------------|-----------------|-----------------|
| Clinical status | Basal           | End of observation | p Value |
| Sat art O2 (%)  | 81 (9)          | 87 (6)           | <0.001         |
| HR (bpm)        | 87 (14)         | 81 (10)          | <0.05          |
| WHO functional class | 3.1 (0.7) | 2.5 (0.7) | <0.05 |
| Exercise tolerance: 6MWT | 320 (108) | 394 (73) | <0.001 |
| HR at the end (bpm) | 119 (17) | 112 (24) | NS |
| Sat art O2 at the end (%) | 63 (17) | 71 (14) | <0.05 |
| Borg index      | 6.5 (1.3)       | 5.3 (1.8)       | <0.001         |
| Heart catheterisation pressure |       |                 |               |
| RA (mm Hg)      | 12 (4)          | 11 (3)           | NS             |
| dPAP (mm Hg)    | 104 (28)        | 105 (37)         | NS             |
| dPAP (mm Hg)    | 52 (6)          | 49 (16)          | NS             |
| mPAP (mm Hg)    | 73 (18)         | 71 (22)          | NS             |
| mCWP (mm Hg)    | 12 (3)          | 12 (4)           | NS             |
| mSAP (mm Hg)    | 84 (14)         | 83 (18)          | NS             |
| Blood flow      |                 |                 |                 |
| QP (l/m/m²)     | 2.8 (0.9)       | 4.0 (1.3)        | <0.001         |
| QS (l/m/m²)     | 3.4 (1.1)       | 4.2 (1.4)        | <0.05          |
| QP/QS           | 0.9 (0.3)       | 1.0 (0.3)        | NS             |
| Vascular resistances |        |                 |                 |
| PVRi (WU.m²)    | 22 (12)         | 14 (9)           | <0.001         |
| SVRi (WU.m²)    | 27 (10)         | 23 (11)          | <0.01          |
| PVRi/SV Ri      | 0.9 (0.6)       | 0.6 (0.5)        | <0.05          |
| Biochemistry     |                 |                 |                 |
| Packed cell volume (%) | 57 (7) | 55 (7) | NS |
| Hb (mg/l)       | 180 (40)        | 170 (60)         | NS             |
| Pts (1000/µl)   | 198 (73)        | 179 (67)         | NS             |
| WCC (1000/µl)   | 7.4 (2.3)       | 7.2 (2.8)        | NS             |
| Aspartate aminotransferase (U/l) | 24 (9) | 28 (12) | NS |
| Alanine aminotransferase (U/l) | 31 (21) | 31 (19) | NS |
| pH              | 7.37 (0.05)     | 7.38 (0.07)      | NS             |
| PaO₂ (mm Hg)    | 45.5 (5.2)      | 50.3 (10.1)      | NS             |
| PaCO₂ (mm Hg)   | 39.3 (8.4)      | 38.9 (7.3)       | NS             |

dPAP, diastolic pulmonary arterial pressure; Hb, haemoglobin; HR, heart rate; mCWP, mean capillary wedge pressure; mPAP, mean pulmonary arterial pressure; mSAP, mean systemic arterial pressure; 6MWT, 6-min walk test; NS, not significant; PacO₂, systemic arterial CO₂; PaO₂, systemic arterial O₂; pH, systemic arterial pH; Plts, platelets; PVRi, pulmonary vascular resistances index; PVRi/SV Ri, pulmonary to systemic vascular resistances ratio; QP, pulmonary cardiac output; QP/QS, pulmonary to systemic cardiac output ratio; QS, systemic cardiac output; RA, right atrial pressure; Sat art O₂, transcutaneous oxygen saturation; sPAP, systolic pulmonary arterial pressure; SVRi, systemic vascular resistances index; WCC, white cell count; WHO, World Health Organisation.

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therefore, ideally, the response to any treatment should be compared with the long term outcome in that particular abnormality.

CONCLUSION
Our study, in agreement with previous observations, suggests that long term bosentan treatment is safe, well tolerated, and effective in patients with pulmonary hypertension related to CHD. Careful patient management is recommended in the current monitoring schedule and flowchart for modifying the dosing schedule in cases of increased liver function tests or significant side effects (that is, leg oedema). This is especially relevant in patients with Eisenmenger physiology who usually have multiorgan involvement, and thus may be at greater risk for liver or other organ dysfunction.\textsuperscript{17} Our safety experience is consistent with the results of the controlled clinical trials\textsuperscript{14} and the wide experience from the bosentan post-marketing surveillance database, in which a large number of patients with PAH-CHD are included.\textsuperscript{20} A recent larger multicentre, randomised, double blind, placebo controlled study with bosentan in patients with Eisenmenger syndrome confirms these results.\textsuperscript{17}

Authors’ affiliations
M D’Alto*, E Romeo, G Santoro, B Sarubbi, P Argiento, M G Russo, R Calabrò, Second University of Naples, A O Mondaldi, Naples, Italy
C D Vizza*, R Badagliacca, P Roscia, M Mancone, F Ferrante, F Fedele, Department of Cardiovascular and Respiratory Sciences, University La Sapienza, Rome, Italy

* M D’Alto and C D Vizza contributed equally to this study.

Competing interests: None.

REFERENCES
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