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The efficacy of bosentan in inoperable chronic thromboembolic pulmonary hypertension: a 1-year follow-up study

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ABSTRACT: **The treatment of choice for chronic thromboembolic pulmonary hypertension (CTEPH) is pulmonary endarterectomy (PEA). However, many patients develop a severe progressive small vessel pulmonary arteriopathy that is inaccessible to surgical intervention and is associated with poor survival. The purpose of the present study was to evaluate the medium-term efficacy and safety of the dual endothelin receptor antagonist, bosentan, in inoperable CTEPH.**

Forty-seven patients with inoperable CTEPH (distal disease or persistent pulmonary hypertension following PEA) underwent evaluation after 1 yr of bosentan therapy. Outcomes included assessment of 6-min walk test (6MWT), haemodynamics and World Health Organization functional classification. Monitoring of serious adverse effects and changes in therapy was undertaken.

Patients showed sustained improvements in 6MWT (49±8 m), functional classification, cardiac index (+0.2±0.07 $L \cdot min^{-1} \cdot m^{-2}$) and total pulmonary resistance (-139±42 $dyn \cdot s \cdot cm^{-5}$). Those patients with persisting pulmonary hypertension following PEA showed the greatest improvement. One-yr survival was 96%, and bosentan was well tolerated with only one patient developing deranged liver function.

Although all patients with chronic thromboembolic pulmonary hypertension should be considered for pulmonary endarterectomy, bosentan provides an alternative medical therapy to improve function and delay the progression of this devastating disease in those in whom surgery is not suitable.

KEYWORDS: **Bosentan, chronic thromboembolic pulmonary hypertension, endothelin, pulmonary hypertension, thromboembolic**

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterised by obstruction of pulmonary arteries with organised fibrotic material, which results in a progressive increase in pulmonary vascular resistance, the development of right heart failure and markedly impaired survival [1–3]. The treatment of choice of this condition is that of surgical removal of this material from the central pulmonary arteries by means of pulmonary endarterectomy (PEA), a procedure that can be curative [4–6].

The underlying aetiology is thought to be on the basis of unresolved pulmonary emboli, with up to 3.8% of patients developing evidence of CTEPH within the first 2 yrs following an acute embolus [7]. However, in many patients, the distribution of this organised embolic material is confined to the subsegmental and smaller branches of the pulmonary vascular bed, which are inaccessible to surgical removal (so-called distal CTEPH) [8].

Recurrent pulmonary embolism and thrombosis *in situ* contribute further to this vascular obstruction and it is imperative that patients receive long-term anticoagulation. However, despite this intervention, the obliteration of the pulmonary vascular bed may continue to progress due to the

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development of a small vessel arteriopathy. The marked endothelial dysfunction and vascular remodelling seen in this process is similar to that seen in pulmonary arterial hypertension (PAH) and appears to develop in unobstructed areas of the pulmonary vascular bed exposed to high pressure load and shear stress [9]. However, the pathophysiology of these conditions is different, with CTEPH patients showing less tendency to plexiform lesion formation and reduced vasoresponsiveness to acute vasodilator challenge testing. In addition, the strong familial tendency and association with genetic mutations of the bone morphogenic protein receptor type II seen in idiopathic PAH has not been observed in the arteriopathy of CTEPH.

This process of small vessel arteriopathy not only occurs in patients with the more distal disease distribution, but can also develop in the setting of apparently surgically amenable central disease. This significantly increases the risk associated with PEA and explains the deterioration in function that some patients experience leading up to their surgery, despite commencing anticoagulation and the insertion of inferior vena caval filter. This also increases the likelihood that the patient will be left with residual pulmonary hypertension following the procedure.

At present, there are no licensed medical therapies for inoperable CTEPH. Several small case series have reported long-term improvements in markers of disease severity with the use of oral, inhaled and intravenous prostanoid therapies [10–15] and the phosphodiesterase-5 inhibitor, sildenafil [16]. One randomised clinical trial of inhaled iloprost in pulmonary hypertension has included patients with CTEPH within the study population, although sample size has been small and subgroup analysis of these subjects has not been reported [17].

Endothelin (ET)-1 is thought to play a key role in the small vessel remodelling that occurs in patients with CTEPH [18]. In animal models, circulating ET-1 levels correlate with disease severity and the ET receptor subtypes (ET_A and ET_B) seem unregulated in a similar fashion to that of PAH [19, 20]. The dual endothelin receptor antagonist, bosentan, has demonstrated significant clinical benefit in patients with PAH [21–23]. Whilst preliminary data of utilisation of this agent in inoperable CTEPH have suggested benefit [24–26], the longer term outcome from this approach is largely unknown.

The aim of the present study is to report the efficacy and safety of the compassionate use of bosentan in patients with inoperable CTEPH after at least 1 yr of therapy.

PATIENTS AND METHODS

Subject selection

The present study included patients with inoperable CTEPH commenced on bosentan between February 2002 and August 2004 at three European specialist centres (Pulmonary Vascular Diseases Unit, Papworth Hospital, Cambridge, UK; Antoine Béclére, Clarmart, France; and Medical University of Vienna, Vienna, Austria) routinely performing PEA. All patients had established pulmonary hypertension as confirmed by a mean pulmonary artery pressure (mPAP) of >25 mmHg, and wedge pressure of <15 mmHg at rest during a right heart catheterisation. The diagnosis of CTEPH was based on multiple imaging modalities, which included multislice computed tomography, direct pulmonary angiography, ventilation perfusion scanning and magnetic resonance angiography. Two groups of patients were included: those with distal CTEPH, in whom the distribution of disease was considered unsuitable for PEA; and those who had persisting pulmonary hypertension following PEA (median duration since PEA 9 months, range 4–18). The investigations of all patients were reviewed by the multidisciplinary PEA assessment team, which included surgeons, cardiologists, pulmonologists and radiologists, and patients were deemed to be unsuitable for surgery on the basis of an unfavourable distribution of their disease on imaging.

This retrospective study was conducted in accordance with the Declaration of Helsinki 1975 and with adherence to local good clinical practice guidelines and legislative requirements. Compassionate use was sought and approved for each individual patient. All data were made anonymous and held within a secure database. Specific written informed consent was only obtained for repeat right heart catheterisation in those centres where this procedure was not considered as part of routine clinical assessment. However, all patients were informed that they were receiving a novel drug for the management of their CTEPH, were fully advised of the potential adverse effects, and gave consent to be treated with bosentan.

Study design

All patients received anticoagulation therapy for at least 3 months prior to commencing bosentan. Routine evaluation to assess the severity of their pulmonary hypertension was performed on all patients within the month prior to commencing bosentan. This included right heart catheterisation, 6-min walk test (6MWT), determination of World Health Organization (WHO) functional classification and appropriate imaging. In addition, 26 patients also underwent acute vasodilator testing with nitric oxide at baseline at two of the centres (Antoine Béclére, Clarmart, France, and Medical University of Vienna, Vienna, Austria). All of these studies showed absent responses to nitric oxide (fall in mPAP by at least 10 mmHg from baseline to a level <40 mmHg).

All subjects were then commenced on bosentan 62.5 mg *b.i.d.*, which was subsequently increased to 125 mg *b.i.d.* (if liver function remained within normal limits). Patients were reviewed clinically on a 3–4 monthly basis at the investigating centre. If clinical worsening of symptoms occurred, bosentan could be increased further to 250 mg *b.i.d.*, or additional advanced therapy could be added. Liver function was monitored on a monthly basis and bosentan was reduced to 62.5 mg *b.i.d.* or discontinued if significant liver function abnormalities occurred (sustained increase in transaminases >3 times the upper limit of the normal reference range). Any other significant adverse effect, such as anaemia (fall in haemoglobin >2 $g \cdot dL^{-1}$), was also recorded.

The primary outcomes were those of 6MWT and WHO functional classification following 1 yr of therapy. Additionally, 28 patients underwent repeat right heart catheterisation for cardiac index (CI), mPAP, pulmonary capillary wedge pressure and mean right atrial pressure at baseline and after 12 months.

TABLE 1 Baseline demographic characteristics of patients included

Characteristics	
Mean age yrs	59.5 (27–82)
Female/male	27/20
Previous PEA	8 (17)
WHO Class II/III/IV	10/32/5
6MWT m	291±116
mPAP mmHg	51±11.3
TPR dyn·s·cm^{-5}	1122±398
CI L·min^{-1}·m^{-2}	2.1±0.5
Long-term oxygen therapy	11 (23)
Diuretic therapy	30 (64)
Anticoagulation	47 (100)

Data are presented as mean (range), n, n (%) or mean±SD, unless otherwise indicated. PEA: pulmonary endarterectomy; WHO: World Health Organization; 6MWT: 6-min walk test; mPAP: mean pulmonary artery pressure; TPR: total pulmonary resistance; CI: cardiac index.

Data were also analysed for the primary outcomes following at least 4 months of therapy to demonstrate the trend over time and rate of response to bosentan therapy. For 29 of the included patients, these interim data have been published in previous reports [24, 26], and are included for completeness with the permission of the authors. However, only those patients who had been reassessed after completing 12 months of bosentan therapy at the time of this review have been included in this analysis.

Statistical analysis

The baseline assessment was defined as the date of initiation of bosentan therapy. Patient characteristics and treatments are expressed as mean±SD. Wilcoxon analysis was used to compare baseline, and 4- and 12-month continuous variables for all patients alive at 1 yr, and are expressed as mean±SEM. All reported p-values are paired and two-tailed. A p-value of <0.05 was considered statistically significant.

A survival estimate associated with longer term administration of bosentan was conducted by means of Kaplan–Meier analysis.

RESULTS

Baseline

Forty-seven subjects with inoperable CTEPH were commenced on bosentan during the study period. The baseline characteristics are presented in table 1. The majority of patients (80%) were WHO Class III or IV at baseline, with a significant proportion receiving chronic diuretic and oxygen therapy (table 1). One subject was anticoagulated with full-dose low molecular weight heparin rather than oral anticoagulation due to a previous haemorrhagic pericardial effusion with tamponade. All other patients received long-term oral coumadin-based anticoagulation.

Four-month review

All patients remained on bosentan at the 4-month review (mean 4.4±1.5 months). At this time, the mean 6MWT had increased by 49±8.4 m ($p<0.001$) from baseline. Eight patients (17%) had improved by at least one WHO functional class, whilst one patient had deteriorated (fig. 1).

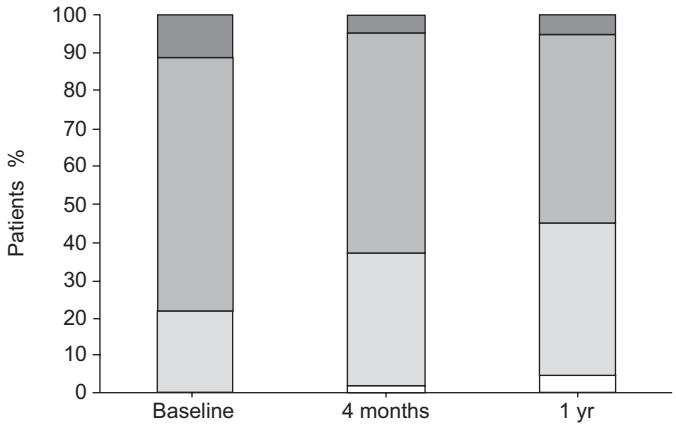

FIGURE 1. World Health Organization classification at baseline, and following 4 months and 1 yr (13.6±2.1 months) of bosentan therapy. □: class I; ▒: class II; ▒: class III; ■: class IV.

Review after 1 yr

One year after commencing bosentan (mean 13.6±2.1 months), two patients had died (one of progressive right heart failure, one of peritonitis), two had been commenced on alternative advanced therapy (one *i.v.* epoprostenol, one subcutaneous treprostinil) and, in three patients, the dose of bosentan had been increased to 250 mg *b.i.d.* due to functional deterioration. In the 45 patients still alive who had been started on bosentan as first-line therapy, the mean 6MWT had increased by 52±10 m ($p<0.001$) from baseline (table 2). The improvement in 6MWT was most marked in the eight patients who had previously undergone PEA (102 m *versus* 40 m, $p=0.001$; fig. 2). The WHO functional class had improved from baseline in 11 patients (24%), whilst in the remainder it was stable (fig. 1).

TABLE 2 Paired 6-min walk test (6MWT)[#] and haemodynamic data[¶] following 1 yr (13.6±2.1 months) of bosentan treatment

	Baseline±SEM	1 yr±SEM	p-value
6MWT m	312±17	364±18	0.000
Borg score	3.9±0.3	3.6±0.3	0.24
mRAP mmHg	10±1	8±1	0.24
mPAP mmHg	50±2	49±2	0.45
CI L·min^{-1}·m^{-2}	2.1±0.1	2.3±0.1	0.004
TPR dyn·s·cm^{-5}	1107±63	969±62	0.003
PVR dyn·s·cm^{-5}[+]	916±77	841±81	0.171
S_{V,O_2} %	60±2	62±1	0.147

Data are presented as mean±SEM. mRAP: mean right atrial pressure; mPAP: mean peripheral artery pressure; CI: cardiac index; TPR: total pulmonary resistance; PVR: pulmonary vascular resistance; S_{V,O_2}: mixed venous oxygen saturation. [#]: n=45; [¶]: n=28; [+]: n=18.

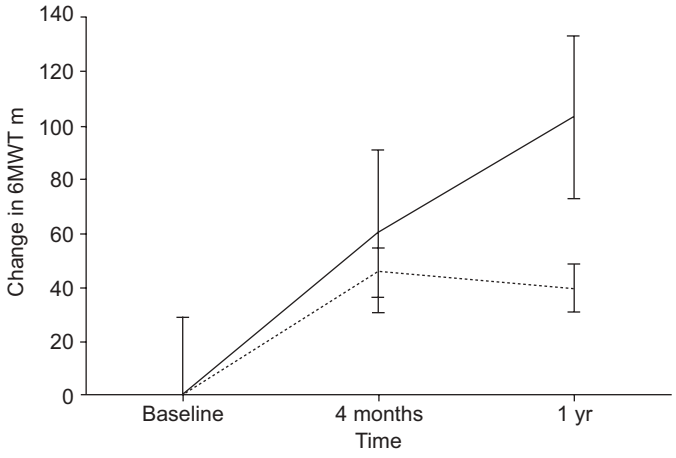

FIGURE 2. Change in 6-min walk distance at baseline and following 4 months and 1 yr (13.6±2.1 months) of bosentan therapy (n=45). Data are presented as mean±SEM. 6MWT: 6-min walk test. ·····: nonoperated patients; ——: post-pulmonary endarterectomy patients.

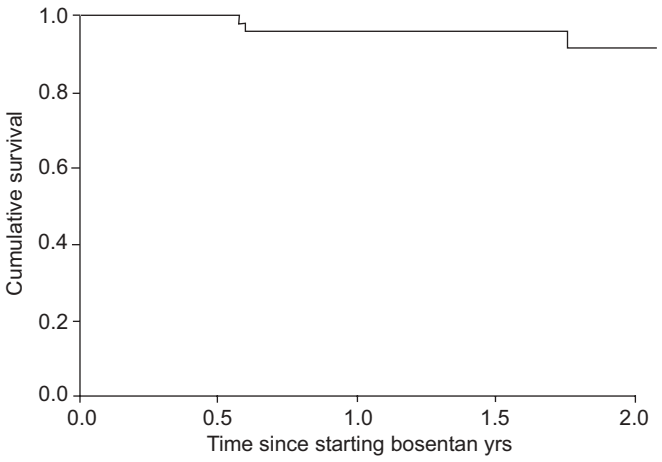

FIGURE 3. Long-term survival for patients commenced on bosentan therapy as first-line therapy for inoperable chronic thromboembolic pulmonary hypertension.

Twenty-eight subjects consented to repeat right heart catheterisation. There were significant improvements in CI, which increased by 0.2 ± 0.07 L·min^{-1}·m^{-2} ($p=0.004$), and total pulmonary resistance (TPR), which fell by 138 ± 42 dyn·s·cm^{-5} ($p=0.003$). These improvements were more marked in the eight patients who had undergone PEA, where the CI rose by 0.4 ± 0.07 L·min^{-1}·m^{-2} ($p=0.001$) and TPR fell by 255 ± 57 dyn·s·cm^{-5} ($p=0.003$).

Two-yr efficacy and adverse effects

At the time of the analysis, 18 patients had completed at least 2 yrs of therapy with bosentan. During this period, alternative advanced therapy had been required in three patients, whilst the remaining 15 subjects remained on bosentan monotherapy.

Bosentan was discontinued in one patient due to persistently deranged liver function (>3 times the upper limit of the normal range), despite a dose reduction after 2.5 yrs of therapy. No other serious adverse effects, significant reduction in haemoglobin level or discontinuations occurred. Overall, the mean duration of exposure to bosentan was 20 months (range 7–41). During the course of this longer term follow-up, three further patients died, all as a result of progressive right heart failure (fig. 3). All five patients who died during the course of long-term review had not undergone PEA.

DISCUSSION

The present study demonstrates sustained improvements in exercise capacity, WHO functional class and haemodynamic markers of disease severity after 1 yr of bosentan therapy for inoperable CTEPH. One-yr survival was 96%, with 43 patients (91%) remaining on bosentan monotherapy. This is the first study to demonstrate the longer term efficacy of endothelin receptor antagonists in this difficult-to-treat patient group. The natural history of this condition is that of progressive increase in pulmonary vascular resistance, TPR and reduced right ventricular function resulting in worsening exertional breathlessness and right heart failure [1]. The observed improvements in TPR and CI at 1 yr are clinically significant, and are likely to reflect a partial reversal of the vascular remodelling of the small vessel pulmonary arteriopathy, rather than any effect on the fixed obstructive lesions. There appears to be a plateau in the improvement after 4 months of therapy, suggesting that the majority of this effect has occurred within this time period.

The improvement in 6MWT and WHO functional class noted after 4 months of therapy are in keeping with the results obtained from a recently published open-label, short-term study [25]. These results are also of similar magnitude to those observed in clinical trials of bosentan in patients with pulmonary arterial hypertension [21]. Although there are some differences in the aetiology and pathophysiology of these conditions, it would appear that blockade of the deleterious effects of ET-1 is of similar importance in impeding disease progression. The effects of bosentan treatment seen after 4 months may be due to a variety of mechanisms: as endothelin receptor antagonists have an antiproliferative effect, they may act at least in part on pulmonary vascular remodelling. However, the observation that there was no further improvement after 12 months may either argue against this mechanism or indicate that initial antiremodelling effect with this agent is indeed incomplete, as is suggested in PAH therapy [22]. Other potential mechanisms, such as a pulmonary vasodilator effect of bosentan, may be of importance in the long term, although it is well demonstrated that this subgroup of patients do not respond acutely to vasodilators such as nitric oxide or prostacyclin. Additional effects on cardiac function have also been considered previously [27].

Despite similar baseline haemodynamic, exercise capacity and functional status, there is a suggestion of more marked improvements in those patients with persisting pulmonary hypertension following PEA. In this small subgroup, the 6MWT continued to improve throughout the first year of therapy with bosentan. This is not an unexpected result, given that much of the subsegmental obstruction will have been removed with the proximal fibrotic material during the endarterectomy. Any persisting resistance to flow is more likely to result from the potentially reversible small vessel arteriopathic component. All of these patients had been either stable or deteriorating prior to commencing bosentan, and in

most cases bosentan was initiated many months after the PEA. It is therefore unlikely that the observed improvements in this group are solely due to delayed recovery or reconditioning following the surgery [28]. However, these results should be interpreted with caution, given the small sample size of this subgroup.

The limitation of this study is the lack of a control population. The majority of the patients included in this study had severe pulmonary hypertension, with rapid functional decline prior to commencing bosentan consistent with a very poor prognosis. Given the considerable evidence of benefit from bosentan in other forms of pulmonary hypertension, it was considered unethical to conduct a long-term placebo-controlled study. Historical data in this condition are limited but suggest that survival is directly related to the severity of haemodynamic markers at the time of diagnosis. In the study by RIEDEL *et al.* [29], which included all forms of CTEPH including those with a proximal disease, a mPAP of >50 mmHg was associated with 40% survival at 1 yr. Given the severity of the haemodynamic compromise noted in the current population (mPAP 51 mmHg), the observed survival of 96% at 1 yr is likely to represent a significant improvement in outcome. However, the sample size is small, and it is necessary to confirm these findings in a larger study population. A multicentric randomised trial, which includes a 4-month placebo-controlled phase, is currently being undertaken. By including both nonoperated patients and those with persisting pulmonary hypertension following PEA, it is hoped that this larger study will be able to further explore any potential difference in response to bosentan between these subgroups, as noted in the current study.

Bosentan was generally well tolerated in the study population, with only one patient having therapy withdrawn as a result of hepatic dysfunction after 2.5 yrs of therapy. These data are in concordance with previous studies of bosentan in patients with PAH, showing that doses up to 250 mg twice daily can be safely administered under strict monitoring [21, 22].

In conclusion, the results of this study suggest that therapy with the dual endothelin receptor antagonist, bosentan, was well tolerated and can result in sustained improvement in function, exercise capacity and markers of disease severity, and may improve survival in patients with inoperable chronic thromboembolic pulmonary hypertension. Whilst all patients with chronic thromboembolic pulmonary hypertension should receive long-term anticoagulation and be assessed for suitability for a potentially curative pulmonary endarterectomy procedure, bosentan may offer an effective therapeutic option for those patients unsuitable for surgery.

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