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CASE SERIES

Bosentan in pulmonary hypertension associated with hypoxaemic lung diseases

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ABSTRACT

Background: Pulmonary hypertension (PH) is associated with limitation of exercise capacity, poor clinical course and reduced survival in chronic, hypoxaemic lung diseases. Bosentan is an oral dual endothelin receptor antagonist with established efficacy in pulmonary arterial hypertension, either idiopathic or associated with other diseases. Treatment experience with the efficacy and safety of bosentan in PH associated with chronic hypoxeamic lung diseases is limited.

Methods: This case-series study reports six consecutive patients with chronic hypoxaemia on the basis of COPD, idiopathic pulmonary fibrosis, silicosis, pneumonectomy, or bronchiectasis. All patients were on long-term oxygen therapy.

Results: After 12 weeks' bosentan treatment, mean 6-minute walk distance increased by 44 meters (from 317 ± 40 m to 361 ± 43 m) and two patients had improved their functional class. Mean systolic pulmonary arterial pressure (PAP) decreased from 83 ± 5.3 to 75 ± 6.1 mmHg, mean partial pressure of arterial oxygen (PaO_2) increased from 52 ± 2.8 to 62 ± 4.5 mmHg. No patients presented with treatment-related adverse events.

Conclusion: Bosentan appears to be effective in enhancing gas exchange function in pulmonary hypertension associated with hypoxaemic lung diseases. These changes paralleled an increase in exercise capacity and functional class. Our experience suggests a possible role of dual endothelin receptor antagonists in the treatment of exercise capacity limitation and disease-related symptoms in chronic hypoxaemic patients.

Introduction

Several studies have assessed pulmonary arterial pressure (PAP0 in hypoxaemic lung diseases. Most studied patients with chronic obstructive pulmonary disease (COPD)[1] or some type of interstitial lung disease (ILD)[2] have a 20–40% prevalence of pulmonary hypertension (PH). Although PAP is usually mildly-to-moderately elevated and its progression slow compared to other categories of PH[3], it is an independent predictive factor of poorer clinical course[4] and impaired survival[5,6] and it has been hypothesised that PH could be a key factor in exercise-capacity limitation in these patients[7]. In addition, there is a subgroup of patients with severe forms of COPD and a concomitant severe manifestation of PH leading to a clinical course characterised by rapid progression and clinical deterioration as well as reduced survival[8].

Long-term oxygen therapy (LTOT) has been shown to improve exercise capacity and survival in COPD associated with hypoxaemia, and its benefits have been extrapolated to other hypoxaemic chronic respiratory disorders. Although LTOT appears to slow down progression of PH associated with severe

COPD, improvement of blood oxygenation does not return PAP to normal values[9]. Persistence of a high PAP in patients receiving LTOT is the single best predictor of mortality[5]. Long-term treatment of PH-associated COPD with non-selective vasodilators (i.e. calcium-channel blockers, CCB) causes minimal or no improvement in pulmonary haemodynamics[10] and can be accompanied by a worsening in gas exchange (increasing V/Q mismatch) and clinical deterioration.

Current concepts in the pathogenesis of PH in hypoxaemic lung diseases stress the importance of distal pulmonary vessel remodelling. Chronic hypoxia and cigarette smoke products are associated with endothelial dysfunction. There is a reduction of prostacyclin and nitrous oxide activity and over expression of ET-1 and ET receptors causing an imbalance towards vasoconstriction and vascular wall proliferation[1]. Anatomical findings in pulmonary distal arteries (primarily thickening of the intimae due to deposition of elastic and collagen fibres, medial smooth muscle cell proliferation and muscularisation of arterioles) are similar to those found in idiopathic pulmonary arterial hypertension or other secondary forms of PH[11].

Endothelin-1 (ET-1) is an endothelium-derived peptide that binds to two receptors subtypes, ET_A and ET_B, present in vascular smooth muscle cell, fibroblasts and endothelial cells. It exerts a variety of actions: vessel-wall hypertrophy, fibrosis, vasoconstriction and inflammation. ET-1 is a known pathogenic mediator in several forms of PH, either idiopathic or associated with other pathologies. High ET-1 plasma levels have been found in patients with COPD and ILD[12,13] and ET-1 over expression in lung tissue from patients with PH associated with lung disease correlates with pulmonary vascular resistance severity[14]. In animal models of chronic hypoxia, bosentan reverses the detrimental effect of higher ET-1 activity and prevents hypoxic PH[15].

Bosentan is an oral dual endothelin receptor antagonist that blocks the detrimental effects of ET-1 under pathological conditions[16]. In patients with pulmonary arterial hypertension (PAH) bosentan decreases mean PAP and pulmonary vascular resistance and increases cardiac index measured by right heart catheterisation with no effect on systemic arterial pressure, thus indicating selectivity on pulmonary circulation. Compared to placebo, bosentan improves exercise capacity, delays clinical worsening and increases survival in PAH[17,18]. An initial open-label study with bosentan in PH due to respiratory disease and hypoxaemia has recently been reported, in which it appeared to be safe and effective[19]. Apart from this report, bosentan data are sparse in this indication. Thus, we report here our case-series experience in the use of bosentan in patients with severe PH associated with hypoxaemic chronic pulmonary diseases.

Material and methods

Setting and subjects

The present case-series study was conducted in a respiratory diseases unit in the outpatient facility of a tertiary hospital. At the unit, lung function tests, including partial pressure of oxygen in arterial blood sample (PaO_2) and capacity of CO transfer (diffusion capacity for carbon monoxide (DL_{CO}), single-breath carbon monoxide transfer coefficient (KCO), and systolic PAP (sPAP) measured by transthoracic Doppler echocardiography (TTDE) are routinely assessed. Adult patients affected by hypoxaemic (defined as $PaO_2 < 65$ mmHg, breathing room air), stable, chronic pulmonary diseases, and moderate-to-severe PH, estimated by a sPAP > 65 mmHg, were screened through a battery of tests for other causes of PH as described in Table 1.

All consecutive patients who presented with PH associated with hypoxaemia and had no other secondary causes of PH were offered bosentan through a compassionate-use programme. According to local legislation patients' informed consent was obtained and each case was assessed by local clinical and pharmacy committees. Compassionate-use procedures were reviewed and endorsed by national health authorities.

Study design and methods

Patients received oral bosentan on top of their usual medication at a dose of 62.5 mg b.i.d. for the first 4 weeks followed by the target dose of 125 mg b.i.d. for at least eight additional weeks, at which point therapy maintenance was considered based on observed efficacy

Table 1. *Screening tests of other pulmonary hypertension-associated pathologies*

Image techniques	Transthoracic Doppler echocardiography Abdominal echography Ventilation/perfusion lung scan Conventional thorax CT and angio-CT
Serological analysis	Antinuclear antibodies (AB), antithyro globulin AB, antiperoxidase AB, antitissue ABs HIV, hepatitis B and C serological screening
Thyroid function	T_3, free T_4 and TSH
Sleep-disordered breathing	Cardiorespiratory polygraphy

and safety. Other drugs and oxygen therapy were not modified during the observational period. Standard prospective follow-up was performed in an open-label fashion. Efficacy was assessed by WHO functional class (modified from NYHA classification), 6-minute walk test distance (6MWD), sPAP measured by TTDE, partial oxygen pressure (P_aO_2) and KCO at baseline and after 12 weeks. Safety evaluations included blood analysis and liver function tests at baseline, biweekly for the first month and on a monthly basis thereafter. Other safety signals were recorded as treatment-emergent adverse events (AEs).

Statistical analysis

Baseline characteristics are described for each patient individually. Quantitative variables are presented as mean and standard error of the estimate (SEE) at baseline and after 12 weeks' follow-up. Categorical variables are given as the total number of patients in each category at baseline and 12 weeks. Due to the small sample size and heterogeneity of the sample no statistical test was performed.

Results

Efficacy

Patients' baseline characteristics are shown in Table 2. KCO was severely impaired in all but one patient (patient 5 had a KCO of 103% its expected value; four of five patients had KCO under 50% of its expected value). Patient 4 had undergone left pneumonectomy 12 years previously due to lung epidermoid carcinoma; this patient underwent a bronchoscopy and PET scan with negative results thus ruling out primary disease recurrence. All patients fulfilled the criteria of chronic respiratory failure (PaO_2 < 60 mmHg breathing room air) and were receiving long-term oxygen therapy (LTOT). No patient was receiving specific vasodilator therapy (CCB, prostanoids, PDE-5 inhibitors, endothelin receptor antagonists).

Pre- and post-intervention efficacy outcome values are described in Table 3. All patients but one improved in 6MWD, sPAP, PaO_2 and KCO measures. Two patients (2 and 4) also improved in WHO functional class. Patient 3 (complicated silicosis in advance lung disease stage) was the only patient in WHO functional class IV at baseline. During the 12-week follow-up bosentan did not improve functional class in patient 4 and was unable to modify the rapid progression of the disease. Figure 1 represents the change in the 6MWD for each individual patient.

Tolerability

At baseline no patient presented abnormalities in liver function tests or blood count. During the study, liver enzymes in all patients stayed within normal range and abnormalities were not detected with other analytical parameters. No bosentan-related AEs were reported and tolerance was good.

Table 2. *Baseline characteristics of the case series of six patients*

Patient No.	Age (years)	Sex	Primary respiratory disease	Time since PH detection (months)	Baseline PaO_2 (mmHg)	Baseline PAP (mmHg)	Baseline KCO (%)*	Current drug therapies†
1	68	F	Diffuse bronchiectasis	11	58	66	40	β2-adrenergic agonists *N*-acetylcysteine
2	58	F	Idiopathic pulmonary fibrosis	3	58	89	51	Prednisone Azathioprine
3	74	M	Complicated silicosis	24	56	76	42	β2-adrenergic agonists Theophylline Inhaled steroids Diuretics
4	71	M	Left pneumonectomy	4	49	103	34	Diuretics Digoxin
5	45	M	COPD	12	48	74	103	β2-adrenergic agonists Tiotropium
6	65	M	COPD	24	41	88	26	β2-adrenergic agonists Inhaled steroids Tiotropium

*Percentage of expected value
†All patients were receiving long-term oxygen therapy (LTOT)
PH, pulmonary hypertension; KCO, carbon monoxide transfer coefficient; PaO_2, partial pressure of O_2 in arterial blood; PAP, pulmonary arterial pressure

Table 3. *Efficacy outcomes at baseline and 12 weeks for the case series of patients (N = 6) treated with bosentan*

	Baseline, *n*	12 weeks, *n*
WHO functional class		
II	1	3
III	4	2
IV	1	1
6MWD (m)	317 ± 40*	361 ± 43
sPAP (mmHg)	83 ± 5.3	75 ± 6.1
PaO_2 (mmHg)	52 ± 2.8	62 ± 4.5
KCO (% of expected value)	49 ± 14.7	58 ± 13.5

*Quantitative variables are expressed as mean ± SEE
n, Number of patients in each class
6MWD, 6-minute walk distance; KCO, carbon monoxide transfer coefficient; sPAP, systolic pulmonary arterial pressure; PaO_2, partial pressure of O_2 in arterial blood; SEE, standard error of the estimate; WHO, World Health Organization

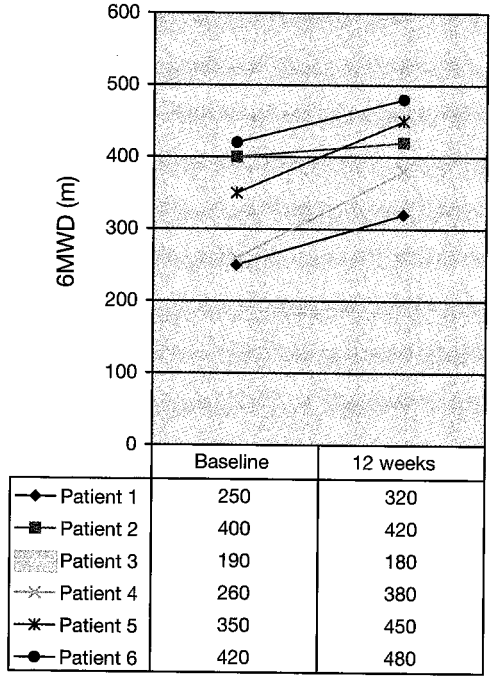

Figure 1. *Change in 6-minute walk distance (6MWD) from baseline to 12 weeks for the case series of six patients treated with bosentan*

Discussion

This initial experience suggests bosentan has a beneficial effect on exercise capacity, PAP and gas exchange function of patients with PH associated with hypoxaemic lung diseases. Despite differences in baseline characteristics, improvements in mean 6MWD (Δ 44 m) and sPAP (Δ –8 mmHg) are comparable to those obtained in a similar open-label study conducted by Sulica *et al.*[19] (6MWD, Δ 55 m and mPAP measured by right heart catheter, Δ –5.5 mmHg).

One of the main concerns of the investigators was to monitor a possible increase in *V*/*Q* mismatch that could have led to a worsening of gas exchange and respiratory failure. This effect has been previously described in non-selective vasodilators (CCB) and is attributed to reversal of 'physiological' pulmonary vasoconstriction due to hypoxia. Not only was no desaturation episode detected, but the 12-week mean PaO_2 improved from 52 to 62 mmHg (Δ 10 mmHg) in those patients with a severely impaired gas exchange function. Again these data were consistent with the findings of Sulica's group that reported that ten of 49 patients decreased their requirements for supplemental O_2 (including five patients who were taken off LTOT) and O_2 saturation increased from 91.7 to 93.8% in 32 patients in whom LTOT dosage was not modified.

Blood oxygenation improvement paralleled a KCO value increase from 49 to 58% of its expected value. Dual ET_A and ET_B receptors blockade reduce PAP through their vasodilator and anti-remodelling action[20] thus diminishing pulmonary vascular resistance. Subsequently increased cardiac index is a plausible underlying factor to explain both KCO and PaO_2 improvement. However ET-1 also has pro-fibrotic and pro-inflammatory activity and bosentan has been shown to reverse its action in animal models of chronic hypoxic PH[21,22], so a direct action on capillary–alveolar interface could also play a role in gas exchange improvement.

Limitations of this case-series include the small sample size and heterogeneity of the population studied. Despite different primary diseases, patients had chronic respiratory failure and PH in common. Chronic hypoxia is a known causal factor of PH *in vivo* in a high-altitude population[23] and hypoxia increases ET-1 activity (as higher plasma and lung tissue ET-1, higher ET receptor expression) in animal models[15] and *in vitro* human cultured cells[24,25]. However, PH is far from being the rule in the natural progression of chronic hypoxic diseases which individuals present a wide range of PAP values[3], and it has been hypothesised that genetic susceptibility is crucial to PH development[26]. Current PH severity in the sample may have selected

'out of proportion PH' patients for their underlying lung disease, a subgroup that is supposed to represent best responder profile to selective vasodilators.

The second main limitation is short-term follow-up. Although the 6MWD is a reliable measure of submaximal exercise capacity in chronic lung diseases, and a 6MWD change is widely used as the primary outcome in drug trials, its interpretation in an open-label design must be treated with caution. On the other hand the benefit observed in exercise capacity is paralleled by the improvement in PAP and blood oxygenation (more 'objective' outcomes), thus giving consistency to the data. 6MWD change and final value are strongly related to exercise capacity, quality of life and survival in chronic lung diseases and in other PH trials.

In conclusion, bosentan appears to be safe and effective in the short term in a population of patients with severe PH associated with hypoxaemic lung diseases, improving exercise capacity, reducing PAP and improving blood oxygenation and gas exchange function. These results from a small sample and short-term experience highlight the need to further explore the utility of endothelin receptor blockade in hypoxaemic PH.

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