Bosentan in pulmonary arterial hypertension: a comparison between congenital heart disease and chronic pulmonary embolism

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Background. In patients with pulmonary hypertension, it is unknown whether the treatment effect of bosentan is dependent on the duration of pulmonary vessel changes. Therefore, we studied the response to bosentan in patients with life-long pulmonary vessel changes (pulmonary arterial

hypertension (PAH) due to congenital heart disease (CHD)) and in patients with subacutely induced pulmonary vessel changes (chronic thromboembolic pulmonary hypertension (CTEPH)).

Methods. In this open-label study, 18 patients with PAH due to CHD and 16 patients with CTEPH were treated with bosentan for at least one year. All patients were evaluated at baseline and during follow-up by means of the six-minute walk distance (6-MWD) and laboratory tests.

Results. Improvement of 6-MWD was comparable in patients with PAH due to CHD (444 ± 112 m to 471 ± 100 m, $p=0.02$), and in CTEPH (376 ± 152 m to 423 ± 141 m, $p=0.03$) after three months of treatment. After this improvement, 6-MWD stabilised in both groups.

Conclusion. Although duration of pulmonary vessel changes is strikingly different in patients with PAH due to CHD and CTEPH, the effect of one year of bosentan treatment was comparable. The main treatment effect appears to be disease stabilisation and decreasing the rate of deterioration. (*Neth Heart J* 2009;17:334-8.)

Keywords: pulmonary arterial hypertension, congenital heart disease, chronic thromboembolic pulmonary hypertension, bosentan treatment, response

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Pulmonary hypertension is a progressive disease, ultimately leading to right ventricular failure and death.¹⁻³ Pulmonary hypertension may develop in patients with congenital heart disease (CHD), and in patients with chronic pulmonary thromboembolism.¹

In CHD, approximately 6% of patients with a cardiac septal defect will develop pulmonary arterial hypertension (PAH), as a result of systemic-to-pulmonary shunting.⁴ Eventually, approximately 1% of CHD patients develop Eisenmenger syndrome in early childhood. Life expectancy of these patients is 20 to 50 years with a one-year survival of 98%.^{4,5}

In patients with incomplete resolution of acute pulmonary thromboembolism, chronic thromboembolic pulmonary hypertension (CTEPH) may develop in adult life.^{6,7} Although the chronic embolic material can be surgically removed by pulmonary endarterectomy,⁸ about 10% of patients who have undergone surgery will develop residual pulmonary hypertension.⁹ Moreover, about 50% of CTEPH patients are assumed to be inoperable due to the distal location of the chronic thromboembolism.^{8,10} Without treatment, the survival rate is low and proportionate to the severity of disease, with an estimated one-year survival of 40% in patients with mean pulmonary arterial pressure exceeding 50 mmHg.³

Treatment with bosentan, a dual endothelin receptor antagonist, has been reported to improve exercise capacity, and survival of patients with various forms of pulmonary hypertension, including both PAH due to CHD and inoperable CTEPH.¹⁰⁻¹⁵ However, since the duration of disease differs strikingly between these two groups of patients, we hypothesised that the extent of the response to bosentan would differ. Until now, the treatment effect of bosentan in patients with a different duration of pulmonary vessel changes is unknown. We hypothesised that pulmonary vessel changes in patients with CTEPH have a more reversible character, due to their shorter duration. Therefore, our hypothesis is that patients with CTEPH are more likely to respond positively to treatment with bosentan. To evaluate this influence we compared the one-year effect of bosentan treatment in adult patients with life-long pulmonary vessel changes (PAH due to CHD) with adult patients with subacutely induced pulmonary vessel changes (CTEPH).

Methods

Study population

For the present study, we retrospectively selected adult patients with PAH due to CHD and adult patients with CTEPH, who were treated with bosentan for at least one year. Patients with Down syndrome, with obstructions of the right ventricular outflow tract, pulmonary valve or pulmonary arteries, and patients receiving prostacyclin, glibenclamide or cyclosporin treatment were excluded. Among the CHD patients, PAH diagnosis was established by echocardiography using tricuspid regurgitation jet velocity and right arterial pressure (systolic pulmonary arterial pressure (sPAP) >40 mmHg).¹⁶ The Eisenmenger syndrome was defined as a congenital heart defect with a pulmonary-to-systemic shunt, observed by echo-

cardiography. The diagnosis of CTEPH was based on pulmonary angiography and right heart catheterisation (mean pulmonary arterial pressure (mPAP) >25 mmHg). To compare pulmonary arterial pressure between patients with PAH due to CHD and patients with CTEPH, we used sPAP estimated by echocardiography. All echocardiographic images were acquired and recorded digitally, and analysed offline by a single observer. The protocol was approved by the institutional review committee.

Study protocol

This was an open-label study. All patients were evaluated at baseline and during follow-up by six-minute walk test (6-MWT). The 6-MWT was performed according to the guidelines of the American Thoracic Society as described before, with continuous pulse oximetry monitoring, and was used to establish the treatment response.¹⁷ To exclude the potential effect of a learning curve, the 6-MWT at baseline was performed twice, and the second six-minute walk distance (6-MWD) was used as the baseline value. In addition, liver function, serum haemoglobin levels and serum NT-pro-BNP levels were monitored. NT-proBNP analysis was performed on an Modular E170 bench top analyser utilising a chemiluminescent assay with a coefficient of variation <5% (Roche Diagnostics, Lewes, UK).

Oral bosentan was initiated at 62.5 mg twice daily. Four weeks later, bosentan was increased to a maximum dose of 125 mg twice daily, if well tolerated. Treatment safety was evaluated during follow-up by monitoring flushing and nasal congestion, vital signs, pulse oximetry, and premature treatment discontinuation. Liver function tests and haemoglobin levels were checked every two weeks for the first two months and monthly thereafter. According to the bosentan summary of product characteristics, the standard threshold for liver function abnormality of >3 times the upper limit of normal was applied.

Statistical analysis

The descriptive data are presented as mean with standard deviation if normally distributed or as median with range as appropriate. Changes from baseline to three months and one year were evaluated with a paired t test for continuous variables (and with Wilcoxon's rank-sum test for categorical variables). A value of $p < 0.05$ was considered to be significant.

Results

Study population

Between September 2003 and September 2006, 36 eligible patients started oral bosentan treatment. Induction of bosentan therapy was well tolerated within both patient groups. In addition, in patients with PAH due to CHD, we could not observe a decrease in oxygen saturation during bosentan treatment.

During follow-up, one CTEPH patient withdrew from treatment because of severe liver function abnormalities. Another CTEPH patient had comorbidity (rheumatoid arthritis) and could therefore not perform a 6-MWT after one year of bosentan treatment. Consequently, the results of 34 patients are presented.

Baseline characteristics

Table 1 shows baseline characteristics of 34 patients (38% males, mean age 54, range 23 to 86 years). Eighteen (53%) patients were diagnosed with PAH due to CHD and 16 (47%) patients were diagnosed with CTEPH. Underlying diagnoses of the CHD patients were ventricular septal defect (n=8), atrial septal defect (n=6), univentricular heart (n=2), patent ductus arteriosus (n=1) and transposition of the great arteries (n=1). Of the CHD patients, four patients had persistent PAH after previous device closure of their septal defect, 13 patients (72%) had Eisenmenger syndrome, and one patient with transposition of the great arteries had persistent pulmonary hypertension after Mustard correction. Among the CTEPH patients, 11 patients had distal, inoperable CTEPH and five patients had residual pulmonary hypertension diagnosed six to 27 months after pulmonary endarterectomy.

The CHD patients were significantly younger (46 years, range 23 to 73 years vs. 63 years, 35 to 86 years, $p<0.01$) and had a lower oxygen saturation ($86\pm 9\%$ vs. $95\pm 4\%$, $p<0.01$) compared with the CTEPH patients.

Exercise capacity

All included patients were treated with bosentan for at least one year (median follow-up 1.9 years, range 1.3 to 4 years). During the first three months of treatment, mean 6-MWD improved significantly with 36 ± 53 m (from 414 ± 133 m to 450 ± 120 m, $p<0.01$), after which the mean 6-MWD appeared to stabilise during the following nine months. Compared with baseline a persistent, but small increase of 19 ± 56 m ($p=0.06$) remained after one year of treatment.

In CHD patients, mean 6-MWD increased from 444 ± 112 m at baseline to 471 ± 100 m ($p=0.02$) after three months of bosentan treatment. During the following nine months of treatment, 6-MWD gradually returned to baseline values. After one year of treatment, a slight increase in 6-MWD remained (14 ± 47 m; $p=0.2$) compared with baseline.

Mean 6-MWD in CTEPH patients increased during the first three months of treatment from 376 ± 152 m at baseline to 423 ± 141 m ($p=0.03$). As in CHD patients, after one year of treatment only a slight increase in 6-MWD (24 ± 65 m; $p=0.2$) remained in patients with CTEPH (figure 1). No correlation was found between time after pulmonary endarterectomy and observed changes in 6-MWD during follow-up ($r=0.4$, $p=0.5$).

Figure 1. Mean six-minute walk distance (6-MWD) during one year of bosentan treatment among patients with pulmonary arterial hypertension due to congenital heart disease (CHD) and patients with chronic thromboembolic pulmonary hypertension (CTEPH). In both patient groups, the greatest magnitude of improvement is shown during the first three months. After one year of bosentan treatment, 6-MWD tends to stabilise.

Table 1. Baseline characteristics.

	Total (n=34)	CHD (n=18)	CTEPH (n=16)	P
Age (years)	54 (23-86)	46 (23-73)	63 (35-86)	0.003
Male (%)	13 (38)	5 (28)	8 (50)	0.2
Eisenmenger syndrome (%)	11 (32)	11 (61)		
6-MWD, mean±SD (m.)	414±133	444±112	376±152	0.2
Oxygen saturation, mean±SD (%)	90±8	86±9	95±4	0.002
NT-pro-BNP, median, range (µg/l)	466 (97-9693)	460 (97-5815)	1126 (99-9693)	0.5
sPAP, mean±SD (mmHg)	80±19	85±21	77±18	0.3

CHD=pulmonary arterial hypertension due to congenital heart disease, CTEPH=chronic thromboembolic pulmonary hypertension, 6-MWD=six-minute walk distance, sPAP=systolic pulmonary arterial pressure.

Although the extent of response after three months of bosentan treatment seemed more pronounced in CTEPH patients, treatment effect was statistically comparable ($p=0.3$) in CHD and CTEPH patients. After one year of bosentan treatment, mean 6-MWD had gradually returned to baseline values in both patients with PAH due to CHD as well as CTEPH patients, with a slight but persistent and comparable increase remaining of 14 ± 47 m and 24 ± 65 m ($p=0.6$), respectively. No correlations were found between the effect size of treatment and any of the baseline parameters in both patient groups.

NT-pro-BNP

Median NT-pro-BNP was elevated at baseline in patients with PAH due to CHD and in patients with CTEPH (460 ng/l, range 97 to 5815 ng/l vs. 1126 ng/l, range 99 to 9693 ng/l; $p=0.5$). After one year of treatment, median NT-pro-BNP remained unchanged in both patient groups compared with baseline. Changes in NT-pro-BNP during treatment were not related to 6-MWD.

Discussion

Although pulmonary vessel changes exist much longer in patients with PAH due to CHD compared with patients with CTEPH, no differences were observed in treatment effect between the two groups. During the first three months of treatment, mean 6-MWD improved significantly, after which 6-MWD appeared to stabilise during one-year follow-up.

The observed initial improvement in exercise capacity is in agreement with previously reported results.^{10,13,15,18-21} However, inconsistent data have been reported on treatment response after one-year follow-up. Several studies in PAH due to CHD reported a persistent beneficial effect of bosentan on exercise capacity during longer term follow-up.^{12,14,22} In contrast, Apostolopoulou et al. reported a gradual return to baseline of exercise capacity after two years bosentan treatment in patients with PAH due to CHD.¹¹ In a previous study in our institution among patients with PAH due to CHD, we demonstrated similar findings. Bosentan treatment resulted in short-term improvement in both adults and children with PAH associated with systemic-to-pulmonary shunt. At long-term follow-up, however, a gradual decline in the beneficial effect of bosentan was observed. The decline appeared to be particularly pronounced in paediatric patients who, in this study, tended to have more severe disease at baseline.²³ In CTEPH, however, one open-label multicentre study demonstrated a sustained effect on 6-MWD after one year of treatment with bosentan.²⁴

Stabilisation of exercise capacity after one year of bosentan treatment could be considered beneficial. Unfortunately, therapeutic options are still limited and treatment is aimed to increase time to clinical worsening. In CTEPH patients, disease stabilisation

is more valuable compared with patients with PAH due to CHD as survival of untreated CTEPH patients remains poor, with an estimated one-year survival of 40% in patients with an mPAP exceeding 50 mmHg. In contrast, patients with PAH due to CHD are known to remain stable for several years without treatment.^{3,5} This difference in prognosis could be due to a better preserved right ventricular function in patients with PAH due to CHD. In these patients, the right ventricle has been subjected to high pressures from early childhood.²⁵ As a consequence, the right ventricle of patients with a cardiac septal defect may be better adjusted to support systemic pulmonary pressures compared with structurally normal hearts.²⁶

The relatively worse cardiac status of the CTEPH patients could have been a reason for the observed lower exercise capacity in CTEPH patients at baseline and during follow-up. Moreover, the older age of CTEPH patients could also have played a role, as 6-MWD is known to decrease with age.²⁷

Taking the decreased prognosis into consideration, disease stabilisation could be considered a more favourable response in CTEPH patients compared with patients with PAH due to CHD, as we hypothesised that, in view of the shorter duration of pulmonary vessel changes, reversibility of the pathological process was more likely in these patients. However, the duration of the vascular changes did not appear to be of influence on the extent and dynamics of response on bosentan treatment. Patients with life-long pulmonary vessel changes (PAH due to CHD) and patients with subacute pulmonary vessel changes (CTEPH) showed a comparable treatment response. A possible explanation for this comparable treatment response could be found in similar pathological changes of the pulmonary microvasculature and marked endothelial dysfunction in both diseases.^{1,28} Another explanation might be that more extensive improvements of vascular changes in the CTEPH patients are masked by right ventricular dysfunction. A direct effect of bosentan on the right ventricle is still subject to investigation.

In addition, in patients with pulmonary hypertension health-related quality of life is significantly impaired and from the patients' perspective, quality of life is one of the most important measures of treatment effect.²⁹ Therefore, quality of life should be also assessed in the future as outcome parameter of treatment effect in patients with PAH.

Study limitations

Limitations of this study include the lack of a placebo group and the heterogeneity of the subgroups. Due to the relatively small sample size, analyses in subpopulations could not be performed. Moreover, in the two groups, the exact duration of pulmonary vessel changes is unknown and data on the natural course of 6-MWD are lacking. In addition, right heart catheterisation data were unavailable in patients with PAH due

to CHD and follow-up data were incomplete for patients with CTEPH. As a result, we could not observe changes in haemodynamics over time. Prospective studies with larger numbers and longer follow-up duration are warranted.

Conclusion

The extent and dynamics of response to one year of bosentan treatment was comparable in patients with PAH due to CHD and patients with CTEPH. Differences in pulmonary vessel change duration between both groups did not influence treatment effect. Although treatment effect seems to be mainly one of disease stabilisation and decreasing the rate of deterioration, this could be considered an advantage in these patients with decreased prognosis. ■

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