

Beneficial effects of long-term treatment with bosentan on the development of pulmonary arterial hypertension in patients with systemic sclerosis

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Abstract

Objective: To investigate the effects of long-term treatment with bosentan on pulmonary arterial hypertension (PAH) in patients with systemic sclerosis.

Methods: Patients with systemic sclerosis were followed between 2003 and 2014; those who developed digital ulcers were treated with standard regimens of bosentan. Patients were assessed at baseline and every 12 months using transthoracic Doppler echocardiography, 6-min walking distance test, Borg dyspnoea index and monitoring of plasma levels of 76-amino-acid N-terminal probrain natriuretic peptide. Patients who developed PAH underwent right heart catheterization to confirm the diagnosis.

Results: Sixty-nine patients with systemic sclerosis were enrolled in the study. Of these, 25 developed digital ulcers and received treatment with bosentan; the remaining 44 comprised the control group. None of the patients treated with bosentan developed PAH during the follow-up period. Furthermore, in these patients the mean \pm SD systolic pulmonary arterial pressure significantly decreased from 33.64 ± 2.91 mmHg at baseline to 26.20 ± 1.78 mmHg at the end of the follow-up period. In contrast, in the control group, seven patients developed PAH during the follow-up period, with the mean \pm SD systolic pulmonary arterial pressure significantly increasing from 33.57 ± 2.75 mmHg at baseline to 39.41 ± 4.11 mmHg at the end of the follow-up period.

Conclusion: Long-term treatment with bosentan reduces the risk of developing PAH in patients with systemic sclerosis.

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Keywords

Bosentan, endothelial dysfunction, pulmonary arterial hypertension, systemic sclerosis

Introduction

Pulmonary arterial hypertension (PAH) is a well known late complication of systemic sclerosis.¹ PAH is defined as a systolic pulmonary arterial pressure (sPAP) > 45 mmHg and is confirmed by right heart catheterization (mean pulmonary arterial pressure > 25 mmHg with a capillary wedge pressure \leq 15 mmHg). Endothelial impairment and vascular dysfunction may be the earliest pathogenetic changes that occur in systemic sclerosis.² Endothelin (ET) 1 is a potent mitogenic factor produced mainly by endothelial cells that interacts with two cell membrane-bound receptors ETA and ETB.³ Bosentan is an oral competitive specific dual ETA and ETB receptor antagonist⁴ that is used in the treatment of digital ulcers⁵ and which is also approved for the treatment of functional class II and III PAH (World Health Organization classification).⁶

Patients and methods

Between January and December 2003, patients aged \geq 18 years with systemic sclerosis (with a negative pregnancy test if female), treated at the Clinical Immunology Unit, University of Genoa, Genoa, Italy, were enrolled in the study and followed up until December 2014. Patients who developed digital ulcers were treated with bosentan 62.5 mg twice daily for 4 weeks, then 125 mg twice a day. The control group comprised the remaining patients who did not develop digital ulcers. Transthoracic Doppler echocardiography, 6-min walking distance test,⁷ Borg dyspnoea index⁸ and plasma levels of 76-amino-acid N-terminal probrain natriuretic peptide (NT-proBNP; a potential marker of heart failure), were performed at

baseline and every 12 months during the study period. Patients who developed PAH underwent right heart catheterization.

The primary endpoint was development of PAH. Secondary endpoints were a change in the 6-min walking distance test, Borg dyspnoea index or plasma levels of NT-proBNP over the follow-up period.

Written informed consent was obtained from all patients. The study was approved by the Regional Ethical Committee and conducted in accordance with the ethical principles of the Declaration of Helsinki Good Clinical Practice guidelines, as well as national and international regulatory requirements.

Statistical analyses

Data were reported as *n* (%) of patients or mean \pm SD. Differences between the two groups were analysed using χ^2 -test or Fisher's exact test. A *P*-value \leq 0.05 was considered to be statistically significant.

Results

Sixty-nine patients with systemic sclerosis were enrolled in the study, of whom 25 developed digital ulcers and were treated with bosentan. Baseline characteristics of the enrolled patients are given in Table 1.

The mean duration of treatment with bosentan was 6.75 ± 0.25 years. At baseline, no patients presented with clinical or echocardiographic indirect signs of PAH in either group (sPAP < 45 mmHg). There was no statistical difference in mean sPAP between the two groups at baseline.

None of the patients treated with bosentan developed PAH during the 12-year

Table 1. Baseline characteristics of patients with systemic sclerosis receiving standard treatment with bosentan (bosentan group) and those not receiving bosentan (control group).

Characteristic	Bosentan group <i>n</i> = 25	Control group <i>n</i> = 44
Sex		
Male	3 (12)	7 (16)
Female	22 (88)	37 (84)
Age, years	69 ± 8	69 ± 9
Disease duration, years	16 ± 4	15 ± 2
Limited systemic sclerosis	18 (72)	31 (70)
Diffuse systemic sclerosis	7 (28)	13 (30)
Anticentromere antibodies	18 (72)	30 (68)
Anti-Scl-70 antibodies	7 (28)	14 (32)
Systolic pulmonary arterial pressure, mmHg	33.64 ± 2.91	33.57 ± 2.75
6-min walking distance test, m	424.40 ± 52.26	475.34 ± 78.06
Borg dyspnoea index	4.20 ± 0.49	3.50 ± 0.82
NT-proBNP, ng/l	997.94 ± 919.86	711.82 ± 505.79

Data presented as *n* (%) of patients or mean ± SD.

NT-proBNP, 76-amino-acid N-terminal probrain natriuretic peptide.

follow-up period. Furthermore, the mean ± SD sPAP significantly decreased from 33.64 ± 2.91 mmHg at baseline to 26.20 ± 1.78 mmHg at the end of the follow-up period ($P < 0.0001$) (Figure 1). In contrast, in the control group, seven patients developed PAH, confirmed by right heart catheterization, during follow-up, with the mean ± SD sPAP increasing significantly from 33.57 ± 2.75 mmHg at baseline to 39.41 ± 4.11 mmHg at the end of the follow-up period ($P < 0.0001$) (Figure 1).

During the follow-up period, patients receiving bosentan showed a significant overall improvement in the 6-min walking distance test and the Borg dyspnoea index values ($P < 0.0001$), whereas in the control group, both the 6-min walking distance test and the Borg dyspnoea index values worsened ($P < 0.0001$ for both) (data not shown). NT-proBNP levels significantly decreased in patients receiving bosentan and significantly increased in controls ($P = 0.004$ and $P = 0.008$, respectively) (data not shown).

Discussion

In the present study, no patients treated with bosentan developed PAH during the follow-up period, which supports the clinical efficacy of long-term bosentan treatment in reducing the risk of developing PAH in patients with systemic sclerosis. These findings are in agreement with those reported in a long-term observational study showing the low occurrence of digital ulcers in patients with systemic sclerosis receiving bosentan for PAH.⁹ Increased ET-1 activity inhibits nitric oxide synthesis, which has been found to be impaired in patients with systemic sclerosis.¹⁰ Bosentan improves exercise-induced and flow-mediated pulmonary vasodilatation and thus restores endothelial function by increasing nitric oxide production.¹⁰

In conclusion, long-term treatment with bosentan improves endothelial function and reduces the risk of PAH development in patients with systemic sclerosis. Early initiation of bosentan

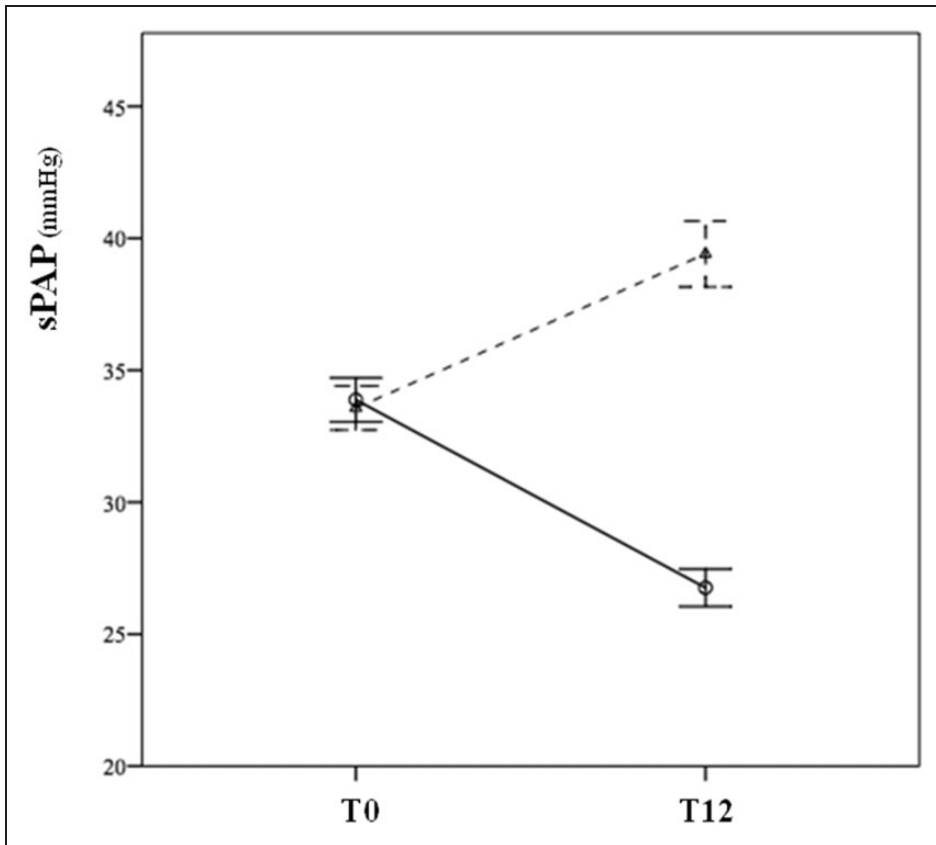


Figure 1. Systolic pulmonary arterial pressure (sPAP) in patients with systemic sclerosis receiving standard treatment with bosentan (circles) and those not receiving bosentan (triangles) at baseline in 2003 (T0) and at the end of the follow-up period in 2014 (T12).

treatment may reduce the progression of pulmonary arterial impairment in these patients.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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