Abstract

Pulmonary arterial hypertension (PAH) is a frequent complication in patients with systemic sclerosis (SSc) and is the leading cause of disease-related death. It has been reported that the survival of patients with PAH related to SSc is worse than that of patients with other forms of PAH despite having similar hemodynamics (1). The serum levels of endothelin (ET)-1 are increased in SSc patients (2, 3); therefore, ET-1 appears to be crucial in the pathogenesis of SSc-related PAH. Bosentan, a non-selective, oral ET-1 receptor antagonist, has been recommended for symptomatic PAH patients (4, 5); however, it is difficult to treat patients with advanced PAH. It might be possible to prevent the progression of pulmonary vascular remodeling by administering bosentan from an early stage in patients with SSc, who are patients at high risk for PAH; however, it has not been determined whether or not bosentan ameliorates the progression of PAH in patients with systemic sclerosis who have no PAH-related symptoms.

We present a case of systemic sclerosis with no PAH-related symptoms in which bosentan ameliorated exercise-induced PAH evaluated by 6-minute walk stress echocardiography, brachial flow-mediated dilation, and skin temperature of hands and feet. The results suggest that administration of bosentan in patients with early-stage PAH ameliorates pulmonary arterial vasodilatation through improvement of endothelial function.

Key words: endothelin-1, pulmonary arterial remodeling, flow-mediated dilation, stress echocardiography

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Introduction

Pulmonary arterial hypertension (PAH) is a frequent complication in patients with systemic sclerosis (SSc) and is the leading cause of disease-related death. It has been reported that the survival of patients with PAH related to SSc is worse than that of patients with other forms of PAH despite having similar hemodynamics (1). The serum levels of endothelin (ET)-1 are increased in SSc patients (2, 3); therefore, ET-1 appears to be crucial in the pathogenesis of SSc-related PAH. Bosentan, a non-selective, oral ET-1 receptor antagonist, has been recommended for symptomatic PAH patients (4, 5); however, it is difficult to treat patients with advanced PAH. It might be possible to prevent the progression of pulmonary vascular remodeling by administering bosentan from an early stage in patients with SSc, who are patients at high risk for PAH; however, it has not been determined whether or not bosentan ameliorates the progression of PAH in patients with systemic sclerosis who have no PAH-related symptoms.

Here, we present a case of systemic sclerosis with no PAH-related symptoms in which bosentan ameliorated exercise-induced PAH evaluated by 6-minute walk stress echocardiography, brachial flow-mediated dilation (FMD), and skin temperature of hands and feet.

Case Report

A woman in her 60s was referred to a clinic for Raynaud’s phenomenon five years ago. She was diagnosed with limited SSc in the clinic and prescribed prostaglandin agents. From 2 years ago, her symptoms became worse and ulceration developed in the right index finger. She suffered pain from the digital ulceration and was admitted to our hospital. We diagnosed peripheral circulatory insufficiency due to SSc, the same as at the previous clinic, based on results of physical and serological examinations (anti-
Bosentan ameliorated exercise-induced pulmonary arterial hypertension and desaturation. Before bosentan therapy After 12 weeks of bosentan therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Exercise</th>
<th>After Exercise</th>
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<th>After Exercise</th>
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</thead>
<tbody>
<tr>
<td>Walk distance (m)</td>
<td>540</td>
<td>560</td>
<td>120</td>
<td>178</td>
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<tr>
<td>Tricuspid pressure gradient (mmHg)</td>
<td>32</td>
<td>64</td>
<td>16</td>
<td>32</td>
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<tr>
<td>Blood pressure (mmHg)</td>
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<td>170/74</td>
<td>120/58</td>
<td>178/82</td>
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<tr>
<td>Heart rate (b.p.m.)</td>
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<td>76</td>
<td>66</td>
<td>74</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>95</td>
<td>80</td>
<td>98</td>
<td>98</td>
</tr>
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Figure 1. Parameters of the 6-minute walk test before and after the start of bosentan therapy.

Figure 2. Brachial flow-mediated dilation (FMD) before and after the start of bosentan therapy. Bosentan improved brachial flow-mediated dilation as indicated by arrows. (left, before treatment; right, after the start of treatment)

centromere antibody positive, anti-scl-70 negative). Echocardiography showed a tricuspid pressure gradient of 32 mmHg, indicating high-normal systolic pulmonary arterial pressure, and the 6-minute walk distance was 540 m, indicating almost normal exercise capacity; however, the tricuspid pressure gradient just after the 6-minute walk exercise test was elevated to 64 mmHg, indicating a poor pulmonary vascular response. Oxygen saturation was also decreased from 95% to 80% by exercise; however, she had never experienced PAH-related symptoms such as exertional dyspnea. Cardiac catheter examination at rest showed a mean pulmonary arterial pressure of 18 mmHg, which did not meet the criteria of PAH, left ventricular end-diastolic pressure of 10 mmHg, and cardiac index of 2.7 L/min/m², with normal left ventricular ejection fraction and no coronary artery lesion. She was prescribed bosentan for peripheral circulatory insufficiency including digital ulceration and Raynaud’s phenomenon at an initial dose of 125 mg, which was increased to 250 mg after 4 weeks in accordance with the protocol of bosentan for PAH (6, 7). Bosentan improved her digital pain and Raynaud’s phenomenon without healing of the digital ulceration. After bosentan therapy for 12 weeks the 6-minute walk distance remained nearly unchanged (from 540 m to 560 m). However, bosentan decreased the exercise-induced elevation of tricuspid pressure gradient from 64 mg to 32 mmHg and it diminished exercise-induced desaturation (Fig. 1). Moreover, bosentan therapy improved brachial FMD from 3.0% to 6.9%, indicating that bosentan improved endothelial function (Fig. 2). Bosentan also improved the decrease in skin temperature in hands and feet as evaluated by cold stress thermography (Fig. 3). Because bosentan could not improve the digital ulceration of the right index finger, she underwent amputation of the finger. After the bosentan therapy and amputation of the finger, her digital pain disappeared, and she was discharged with bosentan medication at a dose of 250 mg/day. She was observed as an outpatient, and there was no exacerbation of PAH (tricuspid pressure gradient at rest: 29 mm Hg) while taking bosentan at a dose of 250 mg/day 2 years after the start of bosentan treatment.
Figure 3. Thermography of hands and feet 10 minutes after cold stress. Bosentan improved skin temperature evaluated by cold stress thermography. (left, before treatment; right, after the start of treatment)

Discussion

The present case showed that bosentan ameliorated peripheral circulation evaluated by cold stress thermography and brachial FMD and also ameliorated exercise-induced PAH. Collagen diseases, especially SSc, cause peripheral circulation insufficiency and PAH by pulmonary arterial remodeling. ET-1 plays an important role not only in systemic vascular contraction but also in pulmonary vascular contraction and remodeling, which consists of obstruction of alveolar capillaries and narrowing of small arteries and arterioles with medial thickening. Increased production of ET-1 and decreased expression of ETB receptor in endothelial cells associated with increased expression of ETA receptor in vascular smooth muscle cells stimulates vascular contraction and proliferation of vascular smooth muscle and fibroblast cells (8, 9). This suggests that bosentan therapy from an early stage in patients with SSc leads to prevention of peripheral and pulmonary arterial contraction and remodeling (9, 10).

Bosentan has been approved for use only in patients with symptomatic PAH of WHO class III or IV in Japan; however, it has recently been recommended that bosentan be used from a stage of WHO class II in Europe and the United States (4, 11). It is difficult to treat symptomatic advanced PAH; therefore, early detection of PAH by a sensitive method is important. Annual cardiac echocardiography or exercise echocardiography is recommended for the detection of early-stage PAH (12, 13). The present case showed that 6-minute walk stress echocardiography was a sensitive procedure for detection of PAH; therefore, patients at high risk for PAH such as those with SSc should undergo 6-minute walk stress echocardiography not only for evaluation of exercise capacity but also for detection of early-stage PAH, even if their resting pulmonary arterial pressure is normal.

In the present case, bosentan suppressed exercise-induced PAH. Exercise-induced PAH is caused by insufficient pulmonary vasodilatation in response to an increase of pulmonary blood flow associated with increased cardiac output during exercise. In a normal physiological state, enhancement of shear stress to the pulmonary arterial wall increases nitric oxide release from the pulmonary arterial endothelium, leading to pulmonary arterial dilatation. However, in a pathological state, the release of nitric oxide from damaged pulmonary arterial endothelium decreases, leading to attenuated pulmonary vascular dilatation during exercise (8). Our speculation from these findings is that bosentan may improve exercise-induced and flow-mediated pulmonary vasodilation. In addition, bosentan also improved brachial FMD. Since FMD is thought to be endothelium dependent, blocking the ET-1 action in patients with SSc might improve systemic and pulmonary endothelial function. Accumulation of cases
is needed to assess these issues.

There is a possibility that long-term use of bosentan in patients with an early stage of PAH prevents organic pulmonary arterial remodeling through improvement of vascular endothelial function and leads to a reduction of morbidity and improvement of mortality. Physicians therefore should perform exercise stress examination for detecting latent PAH in patients with a high risk for PAH such as patients with collagen diseases. In addition, large-scale clinical investigations are required to assess and clarify the effect of bosentan in patients with early-stage PAH.

In conclusion, we presented a case of systemic sclerosis with no PAH-related symptoms in which bosentan ameliorated exercise-induced PAH, brachial FMD and skin temperature. Administration of bosentan in patients with early-stage PAH may ameliorate pulmonary arterial vasodilatation through improvement of endothelial function.

References


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