Medical Treatment for an Adult Patient With Eisenmenger Syndrome

A Case Report

Atsushi Yao, MD

Summary

Previous studies examining the use of pulmonary arterial hypertension (PAH) drugs in patients with Eisenmenger syndrome (ES) have shown that it may have beneficial effects in some patients with ES; however, experience with additional cases is necessary to confirm its efficacy and appropriate clinical use. We herein report our experience of an adult patient with ES who benefitted from treatment with PAH drugs. A 32-year-old Japanese man with severe ES induced by a ventricular septal defect associated with Down syndrome began treatment with bosentan at 62.5 mg. Eleven months later, he was admitted for tadalafil (40 mg) add-on therapy because his 6-minute walking distance and brain natriuretic peptide (BNP) level had not improved and his hepatic enzyme levels had increased. However, marked hypotension developed, and the tadalafil dose was decreased. His BNP level subsequently increased, so the bosentan dose was increased to 125 mg. The bosentan was then abruptly stopped because of a low platelet count and high liver enzyme levels. Ambrisentan was then administered for these side effects, but because severe dyspnea developed, the bosentan was started again at 62.5 mg. This resulted in immediate clinical improvement. The patient was finally switched to ambrisentan (5 mg), which was well tolerated. The findings in this particular case show that although it should be used with caution, bosentan may be beneficial in select patients with ES. In addition, ambrisentan may be considered as first-line treatment in some patients as long as liver enzymes and platelets are carefully monitored. (Int Heart J 2015; 56: S8-S11)

Key words: Pulmonary arterial hypertension, Ventricular septal defect, Patent ductus arteriosus, Down syndrome, Bosentan, Ambrisentan, Tadalafil, 6-minute walking distance, Endothelin receptor antagonists

Until bosentan was approved for clinical treatment of pulmonary arterial hypertension (PAH), no medical treatment had been recognized to be effective for patients with Eisenmenger syndrome (ES). The only effective treatment was lung and heart transplantation, which has been performed on a restricted number of patients.

Several reports have described the effectiveness of PAH drugs for patients with ES. Fernandes, et al reported the usefulness of intravenous epoprostenol for patients with ES. For the first time in a multicenter, randomized, double-blind, placebo-controlled study (BREATHE-5), Galíe, et al showed that medical monotherapy with bosentan not only significantly improved 6-minute walking distance, but also decreased pulmonary vascular resistance in patients with ES. At almost the same time, Singh, et al showed significantly beneficial effects of sildenafil on exercise tolerance and hemodynamic parameters in patients with ES. Mukhopadhyay, et al reported similar effects of tadalafil. Considering the results of these reports, it may be reasonable to routinely use PAH drugs for patients with ES. In fact, Dimopoulos, et al reported that advanced therapy with PAH drugs improved the prognosis of patients with ES, which is the only report to show the prognostic benefit of PAH drugs for such patients. Accordingly, we herein present a case report of a Japanese patient with severe ES treated with PAH drugs.

Case Report

A 32-year-old male patient with ES induced by a ventricular septal defect (VSD) due to Down syndrome visited our hospital in March 2009, accompanied by his parents. He was being treated with digoxin (0.125 mg), furosemide (40 mg), aspirin (100 mg), and allopurinol (200 mg). The purpose of their visit was to inquire about new treatments available for ES. Physical examination revealed clubbed fingers with cyanotic skin, a prominent single second heart sound with no apparent murmur, and decreased respiratory sounds in the left lower lung field. Electrocardiography showed right ventricular hypertrophy (Figure 1A). Chest X-ray revealed an enlarged pulmonary artery, a large bulla in the upper field of the right lung, and a pneumonia shadow in the lower left lung field (Figure 1B). A VSD was confirmed by transthoracic echocardiography, and a large patent ductus arteriosus (PDA) was inciden-
tally found by three-dimensional computed tomography (Figure 2A); both were further visualized by angiography. Additionally observed were minor pulmonary embolisms with no significant defects in perfusion scintigraphy, renal infarctions, or multiple hepatic arteriovenous shunts (Figure 2B–D). A hemodynamic study with oximetric analysis confirmed ES physiology as indicated by severely higher pulmonary vascular resistance than systemic vascular resistance and markedly decreased pulmonary blood flow, resulting in severe hypoxia (Table). Because the decrease in the arterial oxygen saturation was not observed over the ostium of the PDA, prominent right-to-left shunt flow most likely originated through the VSD at rest (Table). Bosentan at minimal dose of 62.5 mg was then initiated on an outpatient basis because his liver enzyme levels were slightly increased. Eleven months later, he was admitted for add-on therapy with tadalafil. Tadalafil at 40 mg was added to the bosentan therapy with no significant side effects during hospitalization. However, his systolic blood pressure at home had decreased to < 80 mmHg and did not recover even after the tadalafil dose was reduced to 20 mg. Therefore, we decided to stop the tadalafil therapy. The plasma brain natriuretic peptide (BNP) level gradually increased (Figure 3), causing us to increase the dose of bosentan to 125 mg. The platelet count then gradually decreased, finally reaching < 50 × 10^3/µL, and the liver enzyme levels mildly increased. Because these changes were likely to be side effects of bosentan, the bosentan was abruptly stopped. We planned to begin administration of ambrisentan after elimination of the side effects. A few days later, his mother called and stated that he could not move from his bed because of worsened dyspnea. This suggested that his World Health Organization functional class had worsened from III to IV. We recommended readministration of 62.5 mg of bosentan, which immediately reversed his clinical status. After this event, we directly switched the 62.5-mg bosentan therapy to 5 mg of ambrisentan under hospitalization. For more than 6 months, the ambrisentan seemed to be successfully tolerated, although the patient’s 6-minute walking distance did not improve.

**Discussion**

ES is a progressive disease with a poor prognosis. In the present case, the endothelin receptor antagonists (ERAs) bosentan and ambrisentan did not prevent the progression of clinical worsening as indicated by the 6-minute walking distance. These results are inconsistent with those of previous reports on the effects of ERAs in patients with ES. One reason for this discrepancy might be the low doses of ERAs used in this case; ie, 62.5 mg of bosentan and 5 mg of ambrisentan. Another possible reason might be the severity of this case. In previous reports, the mean values of various hemodynamic parameters were 72.1 mmHg and 61.8 mmHg for pulmonary arterial pressure; 28.3 Wood units, 20.8 Wood units, and (2870 dyne·sec·cm^−5·m^2) for pulmonary vascular resistance,

![Figure 1. Electrocardiography (ECG) and chest X-ray findings.](image1.png)

**Figure 1.** Electrocardiography (ECG) and chest X-ray findings. A: ECG shows right axis deviation with a prominent R wave in the V1 lead and a deep S wave in the V4-6 leads, suggesting right ventricular hypertrophy. B: Chest X-ray shows an enlarged pulmonary artery, large bulla in the right upper lung field, and old inflammatory change with pleural effusion in the left lower lung field.

![Figure 2. Computed tomography and pulmonary perfusion scintigram findings.](image2.png)

**Figure 2.** Computed tomography and pulmonary perfusion scintigram findings. A: Three-dimensional cardiovascular imaging clearly demonstrates a patent duc
tus arteriosus (PDA). B: A pulmonary embolism is likely present as indicated by the left panel of the computed tomography scan. However, a pulmonary perfusion scintigram (left panel) only shows a large defect likely secondary to the bulla in the left upper lobe. The computed tomography scan also shows (C) multiple intrahepatic arteriovenous shunts and (D) a small renal embolism.

<table>
<thead>
<tr>
<th>Table. Hemodynamic Study with Oxymetric Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure (mmHg)</td>
</tr>
<tr>
<td>IVC 5 58.8</td>
</tr>
<tr>
<td>SVC 7 64.4</td>
</tr>
<tr>
<td>RA 6 61.2</td>
</tr>
<tr>
<td>RV 110/6 63.8</td>
</tr>
<tr>
<td>PA 116/72 65.3</td>
</tr>
<tr>
<td>PCW 6</td>
</tr>
<tr>
<td>LV 1067 73.6</td>
</tr>
<tr>
<td>Asc. Ao 100/60 74.5</td>
</tr>
<tr>
<td>Dsc. Ao 76.7</td>
</tr>
<tr>
<td>FA 76.6</td>
</tr>
<tr>
<td>Qp/Qs (L/minute) 1.71/4.0 = 0.43</td>
</tr>
<tr>
<td>LR shunt 0.17 L/minute</td>
</tr>
<tr>
<td>RL shunt 2.46 L/minute</td>
</tr>
<tr>
<td>Rp/Rs (dyne·sec·cm^−5·m^2) 3789/1560</td>
</tr>
</tbody>
</table>

IVC indicates inferior vena cava; SVC, superior vena cava; RA, right atrium; RV, right ventricle; PA, pulmonary artery; PCW, pulmonary capillary wedge; LV, left ventricle; Asc, Ascending; Ao, aorta; Dsc, descending; FA, femoral artery; Qp, pulmonary blood flow; Qs, systemic blood flow; LR, left-to-right; RL, right-to-left; Rp, pulmonary vascular resistance; and Rs, systemic resistance.
S10

YAO, ET AL

Int Heart J 2015

(106x453 to 478x702)

Figure 3. Clinical course. Bosentan at 62.5 mg was first administered, but neither the 6-minute walking distance (6MWD) nor the brain natriuretic peptide (BNP) level was improved. Because the hepatic enzyme and glutamic-pyruvic transaminase (GPT) levels were slightly elevated after the initiation of bosentan, tadalafil was added instead of uptitrating the bosentan. The addition of tadalafil (40 mg) decreased the BNP level, but was not tolerated even after the dose was reduced to 20 mg because of marked hypotension. The dose of bosentan was then increased to 125 mg. However, the GPT level increased and the platelet (Plt) count decreased to < 50 × 10^3/µL, which led us to discontinue the bosentan. Two days later, the patient’s World Health Organization functional class progressed from III to IV because of worsened dyspnea. Thus, bosentan was re-started at 62.5 mg, resulting in immediate improvement of his symptoms. Therefore, instead of the uptitration of bosentan, the 62.5 mg of bosentan was directly switched to 5 mg of ambrisentan with no clinical worsening or increase in the BNP level, although the GPT level slightly increased and the Plt count slightly decreased. During the clinical course, the white blood cell (WBC) count and C-reactive protein (CRP) level intermittently increased, reflecting the activity of pneumonia.

Oral combination therapy for patients with ES has also been investigated. The addition of sildenafil to bosentan was recently reported to be effective for patients with ES, especially after failure of bosentan monotherapy. In this case, we chose to add tadalafil instead of sildenafil, but we did not continue the tadalafil because of marked hypotension. Long-term effects of the combination therapy would have been expected to some extent in this patient because the plasma level of BNP was actually reduced after started treatment with this combina-

(index); and 2.6 L/minute and (2.0 L/minute/m^2) for pulmonary blood flow (index). Compared with these values, our patient showed a markedly progressed hemodynamic status (Table). This may be one reason why bosentan no longer improved 6-minute walking distance. However, the abrupt cessation of bosentan led to further clinical deterioration, which was reversed by immediate readministration of bosentan, strongly suggesting that bosentan exerted some beneficial effects in this case. The direct switch from bosentan to ambrisentan was safely accomplished and well tolerated. In addition, similarly to bosentan, ambrisentan exerted beneficial effects while not preventing the worsening of 6-minute walking distance. The uptitration of ambrisentan may exert additional benefits and should be considered as first-line treatment, although careful monitoring of slightly increased liver enzyme levels and mildly decreased platelet counts is important (Figure 3).

Oral combination therapy for patients with ES has also been investigated. The addition of sildenafil to bosentan was recently reported to be effective for patients with ES, especially after failure of bosentan monotherapy. In this case, we chose to add tadalafil instead of sildenafil, but we did not continue the tadalafil because of marked hypotension. Long-term effects of the combination therapy would have been expected to some extent in this patient because the plasma level of BNP was actually reduced after started treatment with this combina-

(index). Therefore, combination therapy may be worth rechallenging if it is tolerated. The chronic use of bosentan is well known to decrease the plasma concentration of both tadalafil and sildenafil but not ambrisentan. Thus, retreatment with tadalafil added on to ambrisentan would very likely reinduce more severe hypotension. Instead, a low initial dose of short-acting sildenafil may be the next best choice with ambrisentan under careful monitoring of the systemic blood pressure.

Despite recently available PAH drugs, ES remains difficult to manage. Even if the progression of PAH were prevented or reversed, severe hypoxia and shunt-induced complications such as thromboembolism, infection, and sudden death could remain serious problems. Thus, medical therapy for PAH seems to be critically limited for patients with ES. Nonetheless, advanced therapy with PAH drugs should be considered for patients with ES because improvements in exercise tolerance and prognosis may be expected.

ACKNOWLEDGMENTS

The authors would like to thank Springer Healthcare, which was funded by Actelion Pharmaceuticals Japan Ltd.
REFERENCES