Case report

Bosentan for pulmonary hypertension secondary to idiopathic pulmonary fibrosis

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**A B S T R A C T**

Pulmonary hypertension is a poor prognostic factor in patients with interstitial lung disease. No established treatment exists for pulmonary hypertension secondary to interstitial pneumonia. We describe the case of an 81-year-old woman with idiopathic pulmonary fibrosis (IPF), who was admitted to our hospital due to aggravation of dyspnea and decreased oxygen saturation, as well as onset of orthopnea and rapidly progressing edema. The transthoracic echocardiography and right heart catheterization showed the mean pulmonary artery pressure was 39 mmHg and the mean pulmonary capillary wedge pressure was 9 mmHg. After various examinations, the diagnoses of pulmonary hypertension (PH) due to IPF and of congestive heart failure secondary to PH were established. Diuretic therapy was started, but the patient’s condition showed poor improvement. Subsequent initiation of oral bosentan therapy led to improvement in symptoms and findings.

This report describes a case of successful treatment with bosentan for severe pulmonary hypertension in a patient with idiopathic pulmonary fibrosis. We also present a review of the literature on treatment of pulmonary hypertension in patients with chronic lung disease. Bosentan appears to be efficacious in some patients with pulmonary hypertension secondary to idiopathic interstitial pneumonitis.

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**Introduction**

The prevalence of pulmonary hypertension (PH) complicating the course of patients with idiopathic pulmonary fibrosis (IPF) has been reported to be 32%—85% [1]. According to the Dana Point 2008 classification of PH, this type of PH falls under group 3 (i.e., “Pulmonary hypertension secondary to lung diseases and/or hypoxemia”), and it is a determinant of the prognosis of patients with interstitial lung disease. No established treatment guideline has been available to treat this condition despite discussions at the fifth World Symposium of Pulmonary Hypertension [2]. We present a case of remarkable improvement of PH in a patient with idiopathic pulmonary fibrosis (IPF) after treatment with bosentan, an endothelin antagonist.

**Case report**

The patient was an 81-year-old woman. Around June 2012 she noticed difficult breathing while walking; then as the symptom mildly progressed, she was sent to our hospital due to worsening dyspnea and decreased oxygen saturation.
worsened she visited our hospital in October 2012. In December of the same year, bronchoscopy together with bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) were performed. The dominant cells in BAL fluid were monocytes, and TBLB demonstrated mild lymphocyte infiltration and fibroblast hyperplasia. Respiratory function tests showed restrictive lung disorder with a percentage vital capacity (%VC) of 63.0%, forced vital capacity (FVC) of 1.05 L, percentage forced expiratory volume in one second (%FEV1) of 105.1%, and percentage of predicted forced expiratory volume in one second (FEV1%) of 100.0%. Computed tomography (CT) showed honeycombing along with traction bronchiectasis in the subpleural and basal areas of both lungs (Fig. 1a). Findings of physical examination and blood tests showed no evidence of collagen-vascular disease or any other condition apart from idiopathic pulmonary fibrosis. Thus, based on clinical findings, the patient was diagnosed idiopathic pulmonary fibrosis (IPF). In addition, the transthoracic echocardiography showed a tricuspid regurgitation (TR) pressure gradient of 31.7 mmHg and a pulmonic regurgitation (PR) pressure gradient of 6.2 mmHg.

The patient was started on oral pirfenidone in February 2013, but this was discontinued in October 2013 because of difficulty taking oral medication. As for imaging examinations, in August 2013 these ruled out progression of IPF, but the patient showed aggravation of dyspnea and decreased oxygen saturation, as well as

![Fig. 1. Chest roentgenogram and computed tomography (a). Chest roentgenogram and computed tomography at the initial visit. Honeycombing along with traction bronchiectasis in the subpleural and basal areas of both lungs were detected. (b). Chest roentgenogram and computed tomography at exacerbation of pulmonary hypertension. Compared with Fig. 1a, the findings did not show marked progression of IPF, while congestion was prominent with an increased cardiothoracic ratio.](image-url)
onset of orthopnea and rapidly progressing edema. Transthoracic echocardiography demonstrated findings consistent with congestive heart failure secondary to pulmonary hypertension (PH), and thus the patient was started on diuretic therapy. However, her condition showed little improvement and the patient was thus hospitalized for detailed examination and treatment in October 2013. Findings of physical examination upon admission included body temperature 36.9 °C, blood pressure 94/52 mmHg, regular heart rate at 95 beats per minute, respiratory rate 25 breaths per minute, oxygen saturation 80% (on oxygen 3 L/min by nasal cannula), engorged jugular veins on inspection, and bilateral crepitations on auscultation.

Exacerbation of IPF was unlikely because the only significant finding from imaging examination and blood tests was elevated KL-6 that was attributed to influence of diuretic therapy given since before her admission and influence of congestion (Table 1 and Fig. 1b). In addition, after admission, transthoracic echocardiography and right heart catheterization were performed. The transthoracic echocardiographic finding suggested severe PH and a congestive condition (TR pressure gradient was 86.6 mmHg and PR pressure gradient was 16.1 mmHg total ejection isovolumetric (Tei) index was 0.44 and tricuspid annular plane systolic excursion (TAPSE) was 1.13 cm). (Fig. 2a).

Right heart catheterization showed systolic and diastolic pulmonary artery pressure (PAP) of 54 and 24 mmHg, respectively (mean PAP was 39 mmHg) and a systolic and diastolic pulmonary capillary wedge pressure (PCWP) of 16 and 0 mmHg, respectively (mean PCWP was 9 mmHg) (Table 2). After various examinations including lung perfusion scintigraphy that ruled out other diseases causative of PH, the diagnosis of PH due to IPF was established. Since treatments such as diuretic therapy and oxygen therapy do not improve circulatory failure associated with PH, on Day 12 of hospitalization the patient was started on oral bosentan at a dose of 125 mg/day, leading to rapid improvement of circulatory failure associated with PH. The dose of bosentan was increased to 250 mg/day from hospital Day 25 onward. After improvement of symptoms and findings, the patient was discharged from the hospital on long-term oxygen therapy (using Oxymizer®; dose of oxygen was 3 L/min at rest and 6 L/min on exertion) (Table 2). At the follow-up assessment one year later her pulmonary function showed no significant changes and no apparent worsening of arterial blood gases, with evident improvement of PH, WHO functional class, maximum exercise tolerance on treadmill exercise testing, right heart catheterization, and transthoracic echocardiography (Table 2 and Fig. 2b).

### Table 1

| Blood data at the initial visit and admission. | At the initial visit | At admission in Oct. 2013 |
|-----------------------------------------------|---------------------|---------------------|
| White blood cells (×10³/µL)                   | 7180                | 11,650              |
| Red blood cells                               | 4.81                | 4.28                |
| Hemoglobin (g/dl)                             | 14.4                | 13.3                |
| Hematocrit (%)                                | 45.0                | 40.8                |
| Platelets (×10⁹/mm³)                          | 25.5                | 24.2                |
| AST (U/L)                                     | 23                  | 38                  |
| ALT (U/L)                                     | 12                  | 23                  |
| LDH (U/L)                                     | 225                 | 260                 |
| ALP (U/L)                                     | 152                 | 232                 |
| γ-GTP (U/L)                                   | 14                  | 29                  |
| CPK (U/L)                                     | 48                  | 57                  |
| T-Bil (mg/dl)                                 | 0.5                 | 0.4                 |
| BUN (mg/dl)                                   | 13.8                | 35.5                |
| Cre (mg/dl)                                   | 0.66                | 0.68                |
| Na (mEq/L)                                    | 138                 | 143                 |
| K (mEq/L)                                     | 4.4                 | 4.5                 |
| Cl (mEq/L)                                    | 105                 | 109                 |
| Total Protein (g/dl)                          | 7.0                 | 6.7                 |
| Albumin (g/dl)                                | 3.6                 | 3.4                 |
| C-Reactive Protein (mg/dl)                    | <0.05               | 0.90                |
| BNP (pg/ml)                                   | 27.7                | 1671.82             |
| KL-6 (U/ml)                                   | 1848                | 2435                |
| SP-D (ng/ml)                                  | 305.8               | 420.2               |
| ANA (EIA)                                     | 15.7                | 11.4                |
| MMP-3 (ng/ml)                                 | 40.7                | 90.2                |
| Anti-CCP Ab (U/ml)                            | 1.0                 | 1.0                 |
| Anti-DNA Ab (RIA)                             | 9.2                 | 14.9                |
| Anti-RNP Ab (EIA)                             | 5.8                 | <5.0                |
| Anti-Sm Ab (EIA)                              | <5.0                | <5.0                |
| Anti-SS-A Ab (EIA)                            | <5.0                | <5.0                |
| Anti-SS-B Ab (EIA)                            | <5.0                | <5.0                |
| Anti-Sc170 Ab (EIA)                           | <5.0                | <5.0                |
| Anti-jo-1 Ab (EIA)                            | <5.0                | <5.0                |
| Anti-cardiolipin Ab (U/ml)                    | 0.0                 | 1.0                 |
| Anti-centromere Ab                            | <5.0                | <5.0                |
| MPO-ANCA (U/ml)                               | <1.3                | <1.3                |
| PR3-ANCA (U/ml)                               | 2.3                 | <1.3                |

### Discussion

The prevalence of pulmonary hypertension (PH) complicating the course of patients with idiopathic pulmonary fibrosis (IPF) has been reported to vary between 32% and 85%. According to the Dana Point 2008 classification of PH, this type of PH falls under group 3 [3,4]. The pathologic condition has been said to consist of (1) pulmonary artery vasoconstriction associated with chronic hypoxemia; (2) structural damage with decreased vascular bed; and (3) progression of pulmonary vascular lesions due to inflammatory cytokines and other mediators. No established treatment exists for PH due to lung disease [1,2]. The mainstay of treatment is oxygen therapy in addition to basal treatment of the primary disease, but it is unclear if this approach has beneficial effects on the outcome. Patients typically receive symptomatic treatment with diuretics, digitalis, and anticoagulants as required. Vasodilators have not been documented to be efficacious; rather, they may lead to decreased systemic blood pressure, aggravation of ventilation perfusion ratio inequality, and worsening of hypoxemia [4]. In this case, elevation of KL-6 was the only finding that could be suggestive of exacerbation of IPF, but the elevated KL-6 upon admission was attributed to congestive heart failure on the basis of absence of elevation in surfactant protein D (SP-D) or other parameters suggestive of exacerbation of IPF along with the elevated KL-6. Bosentan was effective for PH associated with the underlying lung disease, and did not cause any adverse effects such as worsening of the patient respiratory condition. Diuretic therapy failed to improve congestive heart failure due to PH, but the add-on use of bosentan improved pulmonary circulation leading to improvement of systemic hemodynamics. This indicated that bosentan not only improved congestive heart failure but also directly improved PH. A published study on ambrisentan, which is another endothelin antagonist with affinity for the endothelin A receptor, showed that ambrisentan was associated with IPF disease progression and significantly increased the number of hospitalizations due to respiratory problems (i.e., acute exacerbation of IPF or aggravated respiratory condition) [4]. On the other hand, a study of bosentan, a non-selective endothelin receptor antagonist, reported that bosentan did not improve activities of daily living or slowed progression of symptoms or disease condition in patients with IPF, but when compared with placebo, bosentan did not worsen IPF, unlike the endothelin antagonist ambrisentan [5]. While treatment of PH associated with lung disease remains controversial in many ways, the present case indicates that bosentan can be efficacious in some patients with PH associated with idiopathic interstitial pneumonitis, although it cannot be completely ruled out that our patient...
Fig. 2. Images from transthoracic echocardiography. (a) Transthoracic echocardiography after admission in Oct. 2013. Upper panels: The right ventricle was enlarged and the interventricular septum was straightened or bowed into the left ventricle. Middle panels: Severe tricuspid regurgitation (TR) was detected. TR pressure gradient was 86.6 mmHg. Lower panel: Mild pulmonary regurgitation (PR) was detected. PR pressure gradient was 16.1 mmHg. Total ejection isovolumetric (Tei) index was 0.44 and tricuspid annular plane systolic excursion (TAPSE) was 1.13 cm. (b) Transthoracic echocardiography at 1 year from start of bosentan therapy. Upper panels: Findings improved compared with Fig. 2a. Middle panels: Severe TR was noted. TR pressure gradient was 48.2 mmHg. Lower panel: Mild PR was noted. PR pressure gradient was too small to measure. Tei index was 0.40 and tricuspid annular plane systolic excursion (TAPSE) was 1.6 cm.
might have had an undetected disease independent of the lung disease responsible for PH, including pulmonary artery hypertension.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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Table 2
Clinical course.

| WHO functional class | At the start of bosentan | At 1 year of therapy |
|----------------------|--------------------------|----------------------|
| Treadmill exercise test | 1METs | 1.7METs |
| BNP (pg/ml) | 1671.82 | 24.10 |

**Right cardiac catheterization**

| PAP: Systolic/Diastolic (mean) | 54/24 (39) mmHg | 48/14 (27) mmHg |
|--------------------------------|----------------|----------------|
| BNP (pg/ml) | 15/–1 (9) mmHg | 15/–2 (7) mmHg |
| CO (L/min) | 3.2 | 3.4 |
| PVR (dyne-sec/cm³) | 750.0 | 470.59 |
| KL-6 | 2435 U/ml | 1085 U/ml |
| SP-D | 420.2 U/ml | 363.9 U/ml |

**Arterial blood gases (on oxygen 3 L/minute by Oxymizer)**

| pH | 7.409 | 7.344 |
| PO₂ | 56.6 mmHg | 91.5 mmHg |
| PCO₂ | 50.5 mmHg | 48.5 mmHg |

**Pulmonary function tests**

| FVC(%) | 0.91 L (50.6%) | 0.89 L (50.0%) |
| FEV₁(%) | 0.91 L (113.8%) | 0.89 L (115.8%) |
| FEV₁%(G) | 100% | 100% |

METS: metabolic equivalents, PAP: Pulmonary artery pressure, PCWP: pulmonary capillary wedge pressure, PO₂: arterial O₂ pressure, PCO₂: arterial CO₂ pressure, FVC: forced vital capacity, FEV₁(%): forced expiratory volume in one second (% predicted FEV₁), FEV₁%(G): percentage of forced expiratory volume in one second.

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