Additional Effects of Bosentan in Patients With Idiopathic Pulmonary Arterial Hypertension Already Treated With High-Dose Epoprostenol

Satoshi Akagi, MD; Hiromi Matsubara, MD; Katsumasa Miyaji, MD; Etsuko Ikeda, MD; Kazuhiro Dan, MD; Naoto Tokunaga, MD; Kenichi Hisamatsu, MD; Mitsuru Munemasa, MD; Yoshihisa Fujimoto, MD; Tohru Ohe, MD

Background  Combination therapy has been proposed in treatment algorithms for idiopathic pulmonary arterial hypertension (IPAH), so the additional effects of bosentan in IPAH patients already treated with high-dose epoprostenol (EPO) was evaluated in the present study.

Methods and Results  Bosentan (62.5 mg twice daily) was administered to 8 IPAH patients already being treated with high-dose EPO (average dose 99.6±43.4 ng·kg⁻¹·min⁻¹). Hemodynamics were assessed at baseline and at 2 days and then 1 year after the initiation of bosentan. Because a remarkable elevation of mixed venous oxygen saturation was observed at the initiation of bosentan, the dosage of EPO was reduced in 7 patients (from 99.6±43.4 to 82.8±31.3 ng·kg⁻¹·min⁻¹, p<0.05). There was a significant decrease from the baseline value for systolic pulmonary artery pressure (80.1±19.3 to 66.8±16.5 mmHg, <0.05). These effects were maintained for 1 year without progression of PAH in 6 patients whose condition had been stabilized at baseline.

Conclusions  The additional use of bosentan for IPAH patients whose condition has been stabilized by high-dose EPO is safe and effective.

Key Words: Bosentan; Combination therapy; Epoprostenol; Idiopathic pulmonary arterial hypertension

Dramatic advances have been made over the past decade in the treatment of pulmonary arterial hypertension (PAH). Current treatment algorithms recommend prostanoid analogs (iloprost, treprostinil), bosentan, sildenafil, and epoprostenol (EPO), depending on disease severity. Although each of these drugs has been reported to improve hemodynamics and exercise capacity in PAH patients, improvement of long-term survival in patients with idiopathic PAH (IPAH) has been achieved only with EPO together with treprostinil and bosentan.

PAH is a complex disease with multifactorial pathophysiology. More than 1 signaling pathway appears to be affected, including the endothelin, nitric oxide and prostaglandin signaling pathways. Treatment that targets more than 1 pathogenic mechanism at the same time by using a combination of agents with different modes of action might maximize the clinical benefit, so combination regimens have been studied. The combination of EPO and bosentan was studied in the BREATHE-2 trial, which showed a trend, but with no statistical significance, for improvement in hemodynamics or clinical improvement in PAH patients and the addition of bosentan to treatment of children with IPAH already treated with EPO enabled the EPO dosage to be reduced, which decreased its associated side-effects without deterioration of clinical and hemodynamic conditions.

The main therapy for PAH in Japan has been continuous intravenous infusion of EPO, because drugs that can improve hemodynamics and exercise capacity, such as iloprost, treprostinil, bosentan and sildenafil, were not approved for use in Japan until recently. Because of the lack of lung transplantation donors, the dosage of EPO had to be continuously increased until the patient’s condition stabilized, so most of our patients have been treated with high-dose EPO, and their survival is similar to that previously reported.

Recently, bosentan became available in Japan as a therapeutic agent for IPAH. Its pharmacological mechanism differs from that of EPO and we therefore expected that the additional use of bosentan would generate a synergistic effect in IPAH patients already treated with high-dose EPO. The aim of the present study was to evaluate the effects of additional bosentan therapy in patients with IPAH already treated with high-dose EPO.

Methods

Patient Selection

Sixteen patients were being treated with EPO in the Division of Cardiology, National Hospital Organization, Okayama Medical Center and were followed up under a diagnosis of IPAH based on the World Health Organization (WHO) criteria. Patients selected for this study were clinically stable, had not required an increase in the dosage of EPO for at least 6 months, were in WHO functional class II, and had no clinical evidence of heart failure.
who did not clearly meet these criteria were excluded from the study and a total of 8 patients were enrolled. Diuretics and supplemental oxygen were being used by all patients, and digitalis was used by 2 patients. All the enrolled patients were stabilized with current medication, which had not been changed for more than 6 months before the initiation of bosentan. Patients were aware that bosentan is a novel drug with unexplored long-term safety and efficacy, and that studies on combination treatment are lacking. The local institutional review boards approved the study protocol and all patients gave written informed consent for participation in the study.

Study Design
Baseline information, including demographic data, current medical therapy and clinical characteristics prior to the initiation of bosentan, was available for all patients. Chest radiography, electrocardiography, blood examination and 6-min walking test were performed within 1 week prior to the initiation of bosentan. Patients remained on concomitant medications after the initiation of bosentan.

Bosentan therapy was initiated at a dose of 62.5 mg twice daily under hemodynamic monitoring with a Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA, USA). Cardiopulmonary hemodynamic parameters (systolic pulmonary artery pressure [sPAP], right atrial pressure [RAP], mixed venous oxygen saturation [SvO2], pulmonary vascular resistance [PVR], noninvasive blood pressure [NIBP], and heart rate [HR]) were determined before and 2 h after bosentan administration at 2 days after the initiation of treatment. If the SvO2 value increased, the dosage of EPO was safely decreased from 99.6±43.4 to 82.8±48.0 ng·kg−1·min−1 (41.0–189.1) for a long duration (average 1,239±527.4 days [713–2,217]) at baseline. None of the patients had elevated liver enzymes at baseline and all were in a stable clinical condition.

Cardiopulmonary Hemodynamics, Dosage of EPO and Value of SvO2
Changes in various hemodynamic measurements are shown in Fig 1. A significant decrease in sPAP (from 110.7±20.7 mmHg to 80.1±19.3 mmHg, p<0.05) and a significant increase in SvO2 (from 64.6±9.4% to 75.3±4.9%, p<0.05) occurred after the start of EPO therapy.

At the initiation of bosentan, 7 patients showed remarkable elevation of SvO2 and had complaints such as flushing and headache because of the high cardiac output. The dose of EPO was safely decreased from 99.6±43.4 to 82.8±31.3 ng·kg−1·min−1 (p<0.05), with a maximal decrease of 50 ng·kg−1·min−1 in patient no. 6 (from 189.1 to 140.0 ng·kg−1·min−1) (Fig IA). Despite efforts to maintain the initial value of SvO2, a slight but significant increase from baseline values occurred (from 75.3±4.9% to 79.7±3.2%, p<0.05) (Fig IB).

Significant decreases from baseline values occurred for sPAP (from 80.1±19.3 to 66.8±16.5 mmHg, p<0.05) (Fig IC) and PVR (from 9.7±3.1 to 8.1±3.2 Wood units, p<0.05); however, there were no significant changes in RAP (from 6.4±1.7 to 5.0±1.4 mmHg, p=0.17), HR or systolic NIBP.

WHO Functional Class and 6-min Walking Test
The WHO functional class at study entry improved in comparison with the value at the start of EPO therapy. At study entry, all patients were in WHO functional class II. At 1 week after the initiation of bosentan, the WHO functional class had not changed in any of the patients. The distance attained in the 6-min walking test tended to increase at 1 week after the initiation of bosentan.

Side-Effects and Safety
Side-effects of EPO were monitored after the initiation of bosentan. All patients experienced flushing and 1 had nausea and headache; however, these side-effects were relieved by reducing the EPO dosage. None of the patients showed elevation of liver enzyme levels at 1 week after the initiation of bosentan (aspartate aminotransferase, from 20.7 to 19.3 IU/L, p=0.48; alanine aminotransferase, from 527.4 to 527.4 IU/L, p=0.03). None of the patients experienced any adverse effects leading to discontinuation of bosentan and there were no deaths during the observation period.
Follow-up After Initiation of Bosentan

The combination of EPO and bosentan was continued in 6 patients for an average of 381 ± 120 days. It had to be discontinued in 1 patient because of adverse events (patient no. 7) who had an asymptomatic elevation of liver enzyme levels at 2 months after the initiation of bosentan, which was subsequently discontinued, and EPO was returned to

Table 1 Patients’ Characteristics and Hemodynamic Effects Before and After the Addition of Bosentan to EPO Therapy

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Sex</th>
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<th>NISBP</th>
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<td>151</td>
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<td>205</td>
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Late failure; *p<0.05 vs start of EPO therapy.

EPO, epoprostenol; WHO, World Health Organization; 6MWD, 6-min walking distance; BNP, B-type natriuretic peptide; NISBP, non-invasive systolic blood pressure; HR, heart rate; S, start of EPO therapy; B, baseline; 1 week, 1 week after initiation of bosentan; FU, follow-up; 2-day, 2 days after initiation of bosentan.
the original dosage. Right-heart failure occurred in 1 patient (patient no. 3), who required hospitalization for an episode of hemoptysis at 9 months after the initiation of bosentan. Right-heart catheterization was performed, and sPAP was found to be elevated (from 97 to 116 mmHg). The patient required diuretic medication and increased dosage of EPO after the catheterization. The other 6 patients did not experience liver dysfunction or right heart failure leading to hospitalization.

Right-heart catheterization was performed in 7 patients, including the patient with right-heart failure. Various assessments of these patients are shown in Fig 1 and Table 1. The dose of EPO (from 86.8±31.6 to 83.7±32.3 ng·kg⁻¹·min⁻¹, p=0.79), SvO₂ (from 79.6±3.4% to 77.7±3.2%, p=0.21), sPAP (from 65.9±17.6 to 69.7±22.0 mmHg, p=0.51) and PVR (from 10.2±4.1 to 7.9±1.5 Wood units, p=0.41) were not significantly different from the values immediately after the initiation of bosentan.

The distance attained in the 6-min walking test tended to be decreased at 1 year after the initiation of bosentan. The serum BNP level was not significantly different from that immediately after the initiation of bosentan.

**Discussion**

The results of the present study suggest that the addition of bosentan to high-dose EPO could have synergistic effects in patients with IPAH. SvO₂ significantly increased in all patients on initiation of bosentan, resulting in a high cardiac output state in 7 patients, and the dose of EPO had to be decreased despite a significantly decrease in sPAP. Furthermore, these effects were maintained for at least 1 year without progression of PAH in 6 patients.

Based on the known pathobiological mechanisms of PAH, combination therapy with agents targeting different pathways has been proposed in treatment algorithms, although the criteria for instituting combination therapy have not been defined. Combination therapy is used in 3 scenarios. First, drugs with different actions are additionally administered to PAH patients with an insufficient response to monotherapy. Hoeper et al reported that the addition of bosentan led to marked improvements in refractory patients already receiving iloprost or beraprost, and Channick et al found that the addition of inhaled treprostinil for PAH patients who were symptomatic despite bosentan therapy led to improvement. Second, drugs with different actions are administered to patients who are in transition from infusion therapy, such as EPO or treprostinil, to less complicated oral therapy. Third, drugs with different actions are administered to patients whose condition has been stabilized by monotherapy to enable further clinical improvement or to suppress side-effects resulting from high doses. In the present study, we administered additional bosentan to patients whose condition had been stabilized with EPO therapy in order to achieve further clinical and hemodynamic improvements. Hemodynamic parameters improved in 7 patients at the initiation of bosentan and these improvements were maintained in 6 patients. The dose of EPO was decreased because the addition of bosentan led to high cardiac output. Although patients experienced flushing, nausea and headache because of this, these symptoms quickly improved after reducing the dosage of EPO. There have been a few studies in which the possibility of reducing the EPO dose was examined. In a study of children, Ivy et al demonstrated that bosentan facilitated a reduction in the EPO dose, and the associated side-effect severity, without deterioration of clinical and hemodynamic parameters. Patients with a successful reduction were treated with high-dose (average dose 86±37 ng·kg⁻¹·min⁻¹) and long-term EPO (average duration 7.6±2.3 years) and showed normal or near normal PAP (mean PAP of 49±27 mmHg). Our results also suggest that the addition of bosentan enabled a reduction of the EPO dose in patients whose condition had already been stabilized by high-dose and long-term EPO therapy. In our study, patients with a successful reduction in the EPO dose had been treated by high-dose (average dose 104.5±48.6 ng·kg⁻¹·min⁻¹) and long-term (average duration 3.69±1.6 years) therapy.

The BREATHE-2 study showed that the combination of bosentan and EPO was effective for improving hemodynamics, exercise capacity and WHO functional class, but had no significant benefit compared with EPO monotherapy. Those results differ from ours, because the patients enrolled in the BREATHE-2 study were untreated and in a serious condition without stabilization, whereas almost all of the present patients were already stabilized. We had to discontinue combination therapy in 1 patient because of progression of right-heart failure. The sPAP and BNP levels in that patient were higher than those in other patients at baseline, so PAH might not have been completely stabilized by EPO at enrollment, and the dosage of EPO would therefore have been insufficient. Thus, combination therapy might not be successful in IPAH patients who have not been stabilized.

To generate synergistic effects by the addition of bosentan, baseline stabilization of PAH with high-dose EPO appears to be necessary. We speculate that high-dose EPO therapy would alter the vasoreactivity of the pulmonary artery to different drugs, so selection of patients stabilized on EPO therapy is necessary for successful combination therapy. Most of the significant hemodynamic improvements occurred at the initiation of bosentan and would be the result of vasodilatation caused by bosentan. The additional effects at the initiation of bosentan could be maintained for at least 1 year, a chronic effect that might be related to inhibition of disease activity, such as pulmonary artery remodeling. However, further synergistic effects were not achieved, so bosentan can not reverse established pulmonary artery remodeling.

The dosage of bosentan was maintained at 62.5 mg twice daily and was not titrated to 125 mg twice daily, which might have given further chronic clinical and hemodynamic improvements. The dosage of bosentan was based on the data presented by Humbert et al in the BREATHE-2 study: dose of bosentan per body weight was 3.11 mg/kg (2.00–5.45 mg/kg). Therefore, the dose of bosentan used in the present study (2.62 mg/kg [1.68–3.37 mg/kg]) was seemed sufficient and it was thought that up-titration of bosentan would not provide further improvements.

**Study Limitations**

The patient population was small and the study design was non-randomized, non-blinded, and open label. We could not increase the number of patients in our sample because almost all of the recent patients had already been treated with bosentan at the time of their first visit to us. Significant results could not be achieved because of the small sample size, so we decided we could not conduct a double-blind and controlled study. Although the addition of bosentan was successful in 6 patients treated with high-dose EPO, the possibility of reducing the EPO dose after reducing the dosage of EPO. There have been a few studies in which the possibility of reducing the EPO dose was examined. In a study of children, Ivy et al demonstrated that bosentan facilitated a reduction in the EPO dose, and the associated side-effect severity, without deterioration of clinical and hemodynamic parameters. Patients with a successful reduction were treated with high-dose (average dose 86±37 ng·kg⁻¹·min⁻¹) and long-term EPO (average duration 7.6±2.3 years) and showed normal or near normal PAP (mean PAP of 49±27 mmHg). Our results also suggest that the addition of bosentan enabled a reduction of the EPO dose in patients whose condition had already been stabilized by high-dose and long-term EPO therapy. In our study, patients with a successful reduction in the EPO dose had been treated by high-dose (average dose 104.5±48.6 ng·kg⁻¹·min⁻¹) and long-term (average duration 3.69±1.6 years) therapy.

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EPO, the median follow-up for hemodynamic data was only 1 year, which does not necessarily constitute “long-term” follow-up. Thus, no conclusions regarding long-term safety and efficacy can be reached. However, significant hemodynamic improvements during the introduction period and the maintenance of these effects for 1 year indicate a benefit of the addition of bosentan to high-dose EPO therapy. Large-scale and long-term investigations are required to prove the effectiveness of the combination of bosentan and high-dose EPO therapy.

Conclusion

The addition of bosentan to the treatment of IPAH patients whose condition has been stabilized by high-dose EPO can generate synergistic effects.

References