Background: Pulmonary arterial hypertension (PAH) is a serious and often progressive disorder that results in right ventricular dysfunction and mortality. Brain natriuretic peptide (BNP) is a useful cardiac biomarker for left-side heart failure. Reports about serial plasma BNP levels in PAH are limited. The aim of this article is to report serial plasma BNP determination in 6 PAH patients, who received therapy based on one of the endothelin receptor antagonists, bosentan.

Methods: Starting from September 2004 to September 2007, we enrolled 6 PAH patients (4 males, 2 females; mean age: 33 years) who received bosentan therapy. Four patients had been diagnosed with idiopathic pulmonary hypertension (IPAH) and two had PAH associated with systemic lupus erythematosus (SLE). All patients were in World Health Organization (WHO) functional class III. All the patients with IPAH received right-heart catheterization and acute vasoreactivity test with nitric oxide inhalation. Plasma BNP measurement, 6-min walk test, and echocardiographic evaluation of right ventricular function were performed regularly every 3 to 6 months and in case of clinical worsening.

Results: There was no mortality for a mean follow-up period of 33 months. During the follow-up period, the BNP levels fluctuated. There was a decrease in plasma BNP after bosentan therapy. Right-heart catheterization, 6-min walk distance, and echocardiography results were also presented in this report. During follow-up, 3 IPAH patients received combination therapy due to disease progression, 2 patients developed pericardial effusion, and 2 patients had an elevation of plasma BNP level with deterioration of clinical conditions.

Conclusion: There is an initial decrease in plasma BNP in PAH patients under treatment with oral bosentan. Serial measurement of plasma BNP may help clinical judgement and management in PAH.

Key Words: Brain natriuretic peptide • Combination therapy • Endothelin receptor antagonist • Pulmonary arterial hypertension

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a serious and often progressive disorder that results in right ventricular (RV) dysfunction and impairment in activity tolerance, and may lead to right heart failure and mortality.1,2 The pathogenesis of PAH is complex; both genetic and environmental factors play an important role in the changes in pulmonary vascular structure and function.3

Dramatic advancements in the treatment of PAH...
have been made over the past decade. Novel drugs such as endothelin receptor (ETR) antagonists, prostanoids, and phosphodiesterase (PDE) inhibitors have proved beneficial in the treatment of PAH.4 Also, the combination of these drugs has been found to be more effective in the management of PAH.5

Brain or B-type natriuretic peptide (BNP) is one of the new cardiac biomarkers employed in recent years. Plasma BNP is an endogenous polypeptide hormone which is released from the atrial and ventricular myocytes in response to volume expansion, pressure overload, and increase in wall tension.6,7 Plasma BNP has been used as a noninvasive marker in diagnostic evaluation, a prognostic indicator, and also for estimating the response to therapy of left-side heart failure.7 However, there are limited reports about serial plasma BNP testing associated with natural history and long-term outcome following medical treatment in PAH.8-11 A few studies showed that plasma BNP increases in proportion to the severity of RV dysfunction in PAH.8,10,12

We describe here 6 cases of PAH, which were treated with bosentan, an ETR antagonist, and studied with serial plasma BNP determination. Additionally, the 6-min walk distance (6MWD), hemodynamic variables, and echocardiographic indices of RV systolic function are also presented in this report.

MATERIALS AND METHODS

Starting from September 2004 to September 2007, we enrolled 6 patients (4 females, 2 males) with PAH to receive bosentan therapy. The mean age was 33 years (range, 20-54 years). Four patients were diagnosed with idiopathic pulmonary arterial hypertension (IPAH). One of the IPAH patients had received surgical correction for a small ventricular septal defect at the age of 10 and later developed severe PAH and hypertrophy of RV. Two patients had PAH associated with systemic lupus erythematosus (SLE) (Table 1). All patients were in World Health Organization (WHO) functional class III. All of the 4 patients with IPAH received right-heart catheterization (RHC) and acute vasoreactivity test with nitric oxide (NO) inhalation from 20 to 80 ppm.

All the patients started bosentan therapy after detailed clinical evaluation. They received plasma BNP measurement (Triage® BNP Test, Biosite Incorporated, California, USA), 6-min walk test, and echocardiographic and Doppler evaluation of RV regularly every 3 to 6 months and in case of clinical worsening. The echocardiographic parameters included RV ejection fraction, RV fractional area change, RV myocardial performance index (Tei index), tissue Doppler maximal systolic velocity at the tricuspid annulus, estimated systolic pulmonary arterial pressure, and estimated pulmonary vascular resistance (PVR). The Tei index is defined as the ratio of isovolumic time intervals to RV ejection time. Estimated systolic pulmonary arterial pressure was calculated by summation of estimated right atrial pressure and the systolic trans-tricuspid pressure gradient. Estimated PVR was calculated by the ratio of peak tricuspid regurgitant velocity (TRV, m/s) to the RV outflow tract time-velocity

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Functional class#</th>
<th>Follow-up period (months)</th>
<th>Treatment</th>
</tr>
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<tbody>
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<td>1</td>
<td>54</td>
<td>female</td>
<td>IPAH</td>
<td>III</td>
<td>50.2</td>
<td>September 2004 bosentan was started; July 2007 combination with sildenafil.</td>
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<td>male</td>
<td>IPAH</td>
<td>III</td>
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<td>July 2005 bosentan was started; October 2007 combination with iloprost inhalation.</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>male</td>
<td>IPAH*</td>
<td>III</td>
<td>38.7</td>
<td>September 2005 bosentan was started; August 2007 combination with iloprost inhalation.</td>
</tr>
<tr>
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<td>female</td>
<td>IPAH</td>
<td>III</td>
<td>15.0</td>
<td>September 2007 bosentan was started.</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>female</td>
<td>SLE</td>
<td>III</td>
<td>30.0</td>
<td>June 2006 bosentan was started.</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>female</td>
<td>SLE</td>
<td>III</td>
<td>23.4</td>
<td>December 2006 bosentan was started.</td>
</tr>
</tbody>
</table>

# World Health Organization functional classification. * Surgical correction of a small ventricular septal defect at the age of 10 years. IPAH, idiopathic pulmonary hypertension; SLE, systemic lupus erythematosus.
integral (TVI_{RVOT}, \text{cm}) (PVR = \frac{TVI_{RVOT}}{TRV} \times 10 + 0.16).^{13,14}

RESULTS

The mean follow-up period was 33 months (range, 15.0-50.2 months). The Figure shows the serial plasma BNP levels and 6MWD in all 6 patients with PAH under bosentan therapy. During the follow-up period, the BNP levels fluctuated. Three patients with IPAH needed to escalate ETR antagonist treatment to combination therapy with a prostanoid or PDE inhibitor in the follow-up period due to progress in severity of the disease (Table 1 and Figure 1).

For the first patient, bosentan treatment was escalated into combination therapy with PDE-5 inhibitor sildenafil on the 33rd month of therapy owing to clinical worsening, which presented with aggravated symptoms of dyspnea on exertion and hemoptysis. The follow-up echocardiography showed development of pericardial effusion and increase in trans-tricuspid pressure gradient from 107 to 125 mmHg as compared to the previous month. Furthermore, there was a reduction in functional capacity of 6MWD from 360 to 310 m, and the BNP levels were increased from 310 to 335 pg/ml. Increase in 6MWD and decrease in BNP were found in the following months after the combination therapy.

For the second patient, bosentan treatment was escalated into combination therapy with inhaled prostenoid iloprost on the 27th month of follow-up due to progression of dyspnea on exertion and hemoptysis. The functional capacity

Figure 1. The serial plasma brain natriuretic peptide (BNP) and 6-min walk distance (6MWD) in patients with pulmonary arterial hypertension. The bars represent the BNP levels, and the lines represent 6MWD. The arrows are the time of combination therapy.
of 6MWD decreased without an increase in BNP levels. However, there was no increase in 6MWD in the following months after the combination therapy, although the patient’s clinical symptoms improved subjectively. Partial compliance of iloprost inhalation may be the reason for inadequate response.

The third patient had inhaled iloprost added to bosentan therapy on the 23rd month of follow-up because of exacerbation in dyspnea on exertion associated with leg edema. Echocardiography revealed the development of pericardial effusion. Additionally, serial plasma BNP showed gradually increase, with decrease in 6MWD. However, there was not much change in 6MWD after combination therapy, although the BNP decreased during follow-up. At the same time, the patient subjectively improved in symptom of dyspnea. Again, poor compliance with iloprost inhalation may have contributed to unsatisfactory effects of combination therapy.

Patients 4 and 6 had baseline BNP < 100 pg/ml, even during the follow-up period. Also, most of their functional capacities in the 6MWD was > 450 m. Patient 5 showed an increase in 6MWD during the initial 24 months of follow-up. Then, she developed pericardial effusion and aggravation in exertional dyspnea despite no increase in BNP levels. Meanwhile, menorrhea with hemoglobin decreased from 13.4 to 8.8 g/dl.

The effects of the therapy on echocardiographic and Doppler measures are listed in Table 2. The RV myocardial performance index and PVR decreased in the first 12 months of follow-up after bosentan treatment.

All 4 IPAH patients received RHC with acute vasoreactivity test. All of them were non-responders up to 80 ppm NO inhalation. Follow-up RHC was performed after 12 months of treatment (Table 3). All of them showed decrease in PVR. Additionally, increased cardiac output and decreased mean pulmonary arterial pressure were noted in 3 patients.

**DISCUSSION**

There was a decline in plasma BNP levels on treatment with ETR antagonist bosentan in both patients with IPAH and PAH associated with SLE. There is mounting evidence that BNP is a useful cardiac biomarker adjunct to clinical assessment to rule in or rule out left-side heart failure in patients presenting with shortness of breath.6,7 Furthermore, plasma BNP levels correlate well with the severity of heart failure and are independent predictors of heart failure mortality.15,16 Nevertheless, there are limited reports about serial plasma BNP determination in the prognosis of right-side heart failure and estimation of response to therapy in PAH.8,9,11

We studied the plasma BNP levels regularly in our patients to see whether this approach would play a role in improving the management of PAH, and thus delay

| Table 2. The plasma brain natriuretic peptide, 6-min walk distance, and echocardiographic parameters in patients with pulmonary arterial hypertension |
|----------------------------------|--|--|--|--|--|--|--|
|                                  | Baseline | 3 months | 6 months | 12 months | 18 months | 24 months | 30 months |
| BNP, pg/ml                       | n = 6     | n = 6     | n = 6     | n = 6     | n = 4      | n = 4      | n = 4      |
| 224 (20-269)                     | 136 (5-249) | 111 (13-231) | 125 (16-209) | 215 (14-352) | 193 (92-293) | 203 (81-376) |
| 6MWD, m                          | 423 (272-468) | 450 (267-478) | 460 (387-540) | 449 (412-492) | 432 (396-504) | 437 (414-479) | 360 (340-378) |
| sPAP, mmHg                       | 98 (50-163) | 92 (42-127) | 103 (37-142) | 92 (40-167) | 118 (28-143) | 118 (61-136) | 108 (87-117) |
| RVEF%                            | 30 (14-35) | 35 (15-60) | 39 (17-71) | 32 (15-83) | 45 (31-77) | 38 (20-50) | 28 (24-62) |
| RVFAC%                           | 22 (13-28) | 26 (9-49) | 27 (15-54) | 26 (16-66) | 35 (26-53) | 27 (16-33) | 21 (19-45) |
| Sm, cm/s                         | 9.1 (8.3-11.0) | 9.7 (7.9-10.9) | 8.6 (7.9-13.0) | 8.6 (7.9-14.7) | 7.7 (4.8-13.0) | 8.6 (6.7-10.2) | 6.9 (4.4-14.0) |
| Tei index                        | 0.85 (0.49-1.75) | 0.63 (0.33-1.49) | 0.55 (0.22-0.81) | 0.63 (0.17-0.87) | 0.70 (0.26-1.10) | 0.73 (0.62-1.08) | 0.67 (0.45-1.16) |
| PVR, Wood units                  | 5.1 (2.7-7.4) | 3.8 (2.2-5.4) | 4.0 (2.1-4.3) | 3.5 (2.1-4.0) | 4.2 (1.8-5.0) | 4.6 (4.0-4.9) | 4.8 (3.8-5.5) |

Values are median (range). BNP, brain natriuretic peptide; PVR, estimated pulmonary vascular resistance; RVEF, right ventricular ejection fraction; RVFAC, right ventricular fractional area change; sPAP, estimated systolic pulmonary pressure; Sm, tissue Doppler maximal systolic velocity at the tricuspid annulus; 6MWD, 6-min walk distance.

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unavoidable disease progression. All the patients are now leading normal lives. The extent of reduction in plasma BNP after therapy varied among patients. We observed fluctuation of BNP levels in the follow-up (Figure 1), as BNP changes with clinical conditions. In the study by Nagaya et al., plasma BNP measurement was repeated after 3 months of oral prostanoid beraprost therapy in patients with primary pulmonary hypertension. They found that plasma BNP was significantly decreased in survivors but increased in non-survivors during the 2-year follow-up. Accordingly, our patients have had favorable long-term outcome because they showed a decrease in plasma BNP levels in the 3-month follow up. Serial plasma BNP follow-up longer than 12 months has not been reported. In our study, we found that plasma BNP decreased in the first 12 months of follow up in those patients with baseline BNP > 100 pg/ml (Figure 1). Of note, later on, BNP levels elevated again. Partly, these results may be because the ETR antagonist bosentan, like other currently available drugs for PAH, causes only modification or slows down the progression of PAH instead of curing this disorder. In a multicenter study using a BNP level of 100 pg/ml as a diagnostic cut-off value, gave a sensitivity of 90% and a specificity of 76% in diagnosing heart failure in patients who came to the emergency department with acute dyspnea. There was no definite consensus cut-off level used in diagnosis or prognosis in PAH. Two of our patients who had relatively low baseline BNP levels (< 100 pg/ml in patients 4 and 6) seem to have had more favorable outcome, and the functional capacities in 6MWD were > 450 m most of the time during follow-up. It implies that low baseline BNP levels may indicate good prognosis.

The pathophysiology of PAH is complex. Currently, there are three classes of medication approved for the treatment of PAH. Bosentan only blocks the ETR pathway, with difference in mechanism of action from prostanoids and PDE inhibitors. Combination therapy offers one option for patients insufficiently responding to monotherapy. In all, 3 of our 6 patients received combination therapy. Iloprost (a prostanoid) inhalation was added on bosentan in 2 patients and sildenafil (a PDE inhibitor) was added on bosentan in one patient. Although we studied the plasma BNP levels regularly in our patients, drug combination was primarily based upon worsening of clinical conditions. All 3 patients developed progression in dyspnea on exertion, and there was hemoptysis in 2 (patients 1 and 2). Two patients (patients 1 and 3) developed pericardial effusion, a poor prognostic sign for PAH in the follow-up. Two patients (patients 1 and 3) had an elevation of plasma BNP levels during deterioration of clinical conditions. Recently, Hoeper et al. published regarding goal-oriented and combination therapy in PAH. They set the treatment goals of 6MWD > 380 m, peak oxygen uptake > 10.4 ml/min/Kg, and peak systolic blood pressure > 120 mmHg during exercise. Combination therapy was given to the patients who did not reach the target in 2 to 6 months re-evaluation. The use of plasma BNP to guide left-side heart failure management has been associated with improved clinical outcomes and reduced health expense. Whether BNP-guided strategy will be helpful in the monotherapy or combination therapy in PAH remains unknown. Further analysis is needed.

<table>
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<tr>
<th>Patient no.</th>
<th>RAP, mmHg</th>
<th>mPAP, mmHg</th>
<th>PAWP, mmHg</th>
<th>CO, l/min</th>
<th>SVR, dynes/sec.cm²</th>
<th>PVR, dynes/sec.cm²</th>
<th>BNP, pg/ml</th>
<th>6MWD, m</th>
<th>RAP, mmHg</th>
<th>mPAP, mmHg</th>
<th>PAWP, mmHg</th>
<th>CO, l/min</th>
<th>SVR, dynes/sec.cm²</th>
<th>PVR, dynes/sec.cm²</th>
<th>BNP, pg/ml</th>
<th>6MWD, m</th>
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<tr>
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<td>5</td>
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<tr>
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<td>66</td>
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<td>3.1</td>
<td>2065</td>
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<td>30.7</td>
<td>465</td>
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</tbody>
</table>

BNP, brain natriuretic peptide; CO, cardiac output; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SVR, systemic vascular resistance; 6MWD, 6-min walk distance.
large-scale studies may clarify this aspect.

Echocardiography is an attractive method of assessing RV function in the follow-up and management of PAH patients. Because of its non-invasiveness, patients are more willing to accept examination repeatedly. Bosentan-based therapy improved echocardiographic and Doppler indices of RV systolic function in our findings. This is compatible with a previous report.21

We performed RHC in all four IPAH patients. All of them were non-responders in acute vasoreactivity test with NO inhalation. Only a small portion of IPAH has response to acute vaso-reactivity test. Sitbon et al. reported that 12.6% of IPAH patients displayed acute pulmonary vasoreactivity.22 The implication is that early diagnosis of this formidable disease is quite difficult. In repeated RHC after 12-month bosentan therapy, there was improvement in hemodynamic parameters including PVR and cardiac output in our study. Recently, a large randomized control clinical trial has demonstrated improvement of pulmonary hemodynamic variables after treatment with bosentan in PAH.23

The findings of our study have to be considered against the background of the limitations. Owing to the small number of patients studied, any inference from the current study appears difficult at first glance. We did not perform statistical analysis for our limited cases. However, several parameters like plasma BNP, 6MWD, Tei index, and estimated PVR by Doppler showed improvement. Some speculations regarding the usefulness of plasma BNP determination in PAH were therefore made.

**CONCLUSION**

There is a decline in plasma BNP levels in PAH patients when they are treated with bosentan. Serial measurement of plasma BNP may help clinical judgement and management in PAH. Further large-scale studies addressing this issue are needed in the near future.

**ACKNOWLEDGEMENT**

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**REFERENCES**


