Long-term outcome and effects of oral bosentan therapy in Taiwanese patients with advanced idiopathic pulmonary arterial hypertension

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Bosentan; Endothelin receptor antagonist; Idiopathic pulmonary arterial hypertension

Summary

Study design: We report on the long-term outcome and effects of bosentan treatment in Taiwanese patients with advanced (functional class III or IV) idiopathic pulmonary arterial hypertension (IPAH).

Materials and methods: IPAH patients on stable bosentan therapy for more than 12 months and regularly monitored were eligible for this prospective uncontrolled study. Patients were evaluated for several clinical parameters, both measured at the time of initiation of bosentan therapy and after 12 months on therapy: New York Heart Association functional class (NYHA FC), change in 6-min walk distance (6MWD), right ventricle ejection fraction (RVEF), cardiothoracic ratio (CTR), and pulmonary functional status.

Results: Twelve of 15 patients met eligibility requirements and were enrolled. Their mean age was 37.6 ± 12.9 years and 92% were female. Six (50%) patients were in NYHA FC IV and the others were in NYHA FC III at baseline. Three (25%) patients were chronic hepatitis C virus (HCV) carriers, with normal liver function. After 12 months of bosentan treatment,
Introduction

Idiopathic pulmonary arterial hypertension (IPAH), formerly named primary pulmonary hypertension, is an uncommon disorder of unknown aetiology. The major characteristics are progressive increase in pulmonary artery pressure (PAP) and pulmonary vascular resistance, which often lead to right heart failure and death, especially in patients in New York Heart Association functional class (NYHA FC) III or IV. In the national North American Registry of 194 patients with IPAH, the median survival was only 2.8 years without specific treatment.

The treatment of IPAH has realized dramatic advances over the past decade. Bosentan (Tracleer, Actelion Pharmaceuticals, Allschwil, Switzerland), a non-peptide antagonist blocking both endothelin A and B receptors, is the first oral therapy approved for the treatment of pulmonary arterial hypertension (PAH) in North America and Europe. Recently, there were a number of clinical studies showing that bosentan therapy improved not only functional class and exercise performance, but also quality of life in symptomatic patients with PAH. Therefore, for many clinicians, bosentan provided an appealing alternative to epoprostenol as first line treatment in patients with severe symptomatic IPAH; however, much of this clinical research focused on the white population. Although Sasayama et al. demonstrated that 12 weeks of bosentan treatment resulted in improvement in symptoms, hemodynamics, and quality of life in 18 patients with PAH recruited from 11 Japan centres, the long-term outcome and benefits of bosentan therapy among the Asian populations are still largely unknown.

In Taiwan, recent history shows that clinicians relied on the use of prostanoids (intravenous epoprostenol or inhaled iloprost) for medical treatment of advanced IPAH. Since October 2003, oral bosentan was approved by health administrative official in Taiwan to treat advanced IPAH patients. Given the ease of administration and well-documented clinical benefits of bosentan, first-line treatment with bosentan for advanced IPAH patients is considered both reasonable and feasible. We describe the long-term outcome and effects of bosentan treatment on functional class, exercise capacity, clinical response, and adverse events in Taiwanese patients with severe symptomatic IPAH.

Methods

Patient selection

From October 2003 to February 2005, 15 consecutive patients with advanced IPAH whose age was greater than 12 years and received bosentan as the first-line therapy in our institute were enrolled. All patients were classified as being in NYHA FC III or IV, despite optimal medical therapy, including the use of anticoagulants, diuretics, cardiac glycosides, vasodilators and supplemental oxygen. The diagnosis of IPAH was rendered by standard diagnostic criteria established at the third World Conference on Pulmonary Hypertension, held in Venice in 2003. Exclusion criteria were non-IPAH, a positive response to acute vasodilator challenge during right heart catheterization, impaired liver function (serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than two times the upper limit of normal (ULN)) at baseline and previous exposure to prostanoids (intravenous epoprostenol or inhaled iloprost). Three patients without pre-existing liver disease were excluded from this study in the initial 4 weeks after starting bosentan treatment. Two patients had elevation of hepatic aminotransferases greater than five times the ULN while on bosentan 62.5 mg twice daily and the other patient needed to combination therapy with inhaled iloprost due to clinical worsening of PAH while on bosentan. For patients with chronic hepatitis C virus (HCV) infection, the expert hepatologists were routinely consulted to confirm that there was no clinical evidence or symptoms of portal hypertension. Furthermore, serum alpha-fetoprotein (AFP), hepatic ultrasound, and the quantitative HCV RNA assay were examined at baseline and every 6 months after starting bosentan treatment to early detect the signs of hepatocellular carcinoma (HCC) development or active HCV replication. No patient was lost to follow up, and the vital statuses of all patients were confirmed in February 2006. This study was approved by our institutional review committee and the informed consent was obtained from all patients prior to their enrolment.

Bosentan treatment

Patients received a starting dose of bosentan 62.5 mg twice daily and this was increased and maintained at 125 mg twice daily after 4 weeks. ALT and AST were routinely monitored because of bosentan’s known adverse effects on hepatocellular enzymes. Follow-up visits were scheduled in the second and fourth weeks after starting bosentan therapy and then every 4 weeks thereafter. At each follow-up visit, data on clinical events, functional status, and adverse events were carefully recorded. If increases in ALT or AST levels were to a value greater than three times ULN, the bosentan dosage was reduced to 62.5 mg twice daily. If increases in ALT or AST levels were to a value greater than five times the ULN, bosentan treatment was discontinued...
and patients were shifted to inhaled iloprost or intravenous epoprostenol therapies.

Baseline characteristics

The baseline evaluation included a medical history, physical examination, routine blood tests and right heart catheterization using standard techniques. The clinical effects were determined by assessing the NYHA FC, 6-min walk distance (6MWD), right ventricle ejection fraction (RVEF), cardiothoracic ratio (CTR) and pulmonary function tests. All variables were examined prior to initiation of bosentan therapy and for 12 months thereafter.

NYHA FC assessment

The functional class of each patient was determined using a standardized protocol according to the Venice 2003 classification, including questions concerning the patient's daily life.

Six-minute walk test (6MWT)

This test provides a standardized, objective, integrated assessment of cardiopulmonary and musculoskeletal function that is relevant to daily activities. The self-paced 6MWT assesses the sub-maximal level of functional capacity and is widely applied as a long-term follow up effect for IPAH treatment. All patients were told to use their own pace, but to cover as much ground as possible in 6 min. Patients who were unable to perform the test were recorded as achieving a distance of 0 m.

Right ventricle ejection fraction

After injection with 20 mCi technetium 99m (99mTc)-labelled RBCs, radionuclide angiography using the gated blood pool technique was performed to measure the RVEF at rest. The results are shown as the RVEF percentage; the normal value in our institute is greater than 40%.

Cardiothoracic ratio

Cardiothoracic ratio was determined only where a standard posteroanterior (PA) chest film was available. It is the transverse cardiac diameter (the horizontal distance between the most rightward and leftward borders of the heart seen on a PA chest radiography) divided by the transverse chest diameter (measured from the inside rib margin at the widest point above the costophrenic angles on the PA chest film).

Pulmonary functional tests

The spirometric testing (forced vital capacity, FVC; forced expiratory volume in 1 s, FEV1) was performed according to the standards of the American Thoracic Society. Lung function reference values corrected for sex, age, and height were used. The FVC and FEV1 results are shown as percentages of predicted value, which were compared with the normative data that widely used as the reference data in our institute.

Statistical analysis

Baseline and follow-up information were summarised for the 12 patients who completed this study without missing data. All paired changes from baseline to month 12 were evaluated using the Wilcoxon signed-rank test. To avoid the potential of biasing the results of this uncontrolled, small-sample-size study, no imputation for missing values was used. Continuous variables were summarized as the means±SDs. All reported p values are two sided and p values less than 0.05 were considered statistically significant.

Results

Baseline characteristics

From October 2003 to February 2005, 12 patients with severe IPAH were eligible for this analysis. The baseline demographic and haemodynamic characteristics of these patients are shown in Table 1. Patients ranged in age from 14 to 57 years, with a mean age of 37.6±12.9 years. Eleven of the patients were female and 3 of 9 (75%) patients with mean pulmonary artery pressure (MPAP) greater than 50 mmHg. Six (50%) patients presented in NYHA FC IV and eight (75%) patients had a history of right heart failure. Three (25%) patients were diagnosed as HCV carriers, based on positive test results for antibodies to HCV (by second-generation enzyme-linked immunosorbent). Two patients had cirrhotic livers based on characteristic ultrasonographic patterns. All three patients presented with normal liver function, normal serum AFP levels, and undetectable serum HCV RNA by quantitative assays before initiation of bosentan.

Clinical parameter changes

Of the 12 patients enrolled in the trial, six (50%) were in NYHA FC III and 6 patients (50%) were in class IV at baseline. The NYHA functional status significantly improved from 3.5 at baseline to 2.25 after 12 months of treatment (p = 0.002) (Table 2). At month 12, 9 patients (75%) were reclassified to class II and 3 patients (25%) were reclassified to class III (Fig. 1): 4 patients improved from class IV to II, 2 patients improved from class IV to III, 5 patients improved from class III to II, and 1 patient remained in class III although their 6MWD lengthened by 20 m. Two of the three HCV carriers improved from class IV to II, and the other improved from class IV to III. None of the 12 patients completing the 12-month study deteriorated or were reclassified to class IV (Fig. 1).

For all patients, 6MWD increased from 326±138 m at baseline to 446±119 m at month 12, an increase of 37% (p = 0.002) (Table 2). The RVEF percentage increased from 31.0±17.1% at baseline to 54.5±12.2% at month 12 (p = 0.004). The CTR decreased, i.e., improved from 0.551±0.066 at baseline to 0.508±0.049 at month
The percentages of predicted values of FVC and FEV₁ improved from 84.2 ± 14.7% and 77.1 ± 17.7% at baseline to 95.3 ± 16.1% (p = 0.003) and 84.0 ± 17.0% (p = 0.019) at month 12, respectively.

Withdraw and adverse events

Three of our original 15 patients were excluded from this study in the initial 4 weeks due to serious adverse events (Table 3). Two patients were excluded due to asymptomatic increases in hepatic aminotransferase levels 5 times the ULN on bosentan dosage 62.5 mg twice daily. These increases returned to normal after discontinuing bosentan and both patients were switched to prostanoid therapy. The other one patient needed combination therapy with prostanoid treatment due to clinical worsening of PAH. Thus, although 15 patients were enrolled and 12-month data were only available for 12 patients, the 3 patients not completing the 12-month evaluation were included in the adverse events assessments (Table 3). Except for the serious adverse events, the most frequent adverse events were headache and flushing, both of which were reported in 20% of patients. Additional adverse events included leg oedema, pain in the limbs, arthralgia, and cough. For 3 IPAH patients with chronic HCV infection, there was no episode of abnormal hepatic function that necessitated the adjusted of bosentan dosage or discontinance of the treatment during the 12 months of bosentan treatment. In addition, no clinical sign of HCC development was detectable and the serum HCV RNA levels were persistently undetectable during and after the 12 months of bosentan treatment. Overall, bosentan treatment was well tolerated in the 12 IPAH patients, regardless of whether or not they were chronic HCV carriers.
Discussion

The present study reports the first trial investigating the long-term outcome and effects of bosentan in the treatment of advanced IPAH among Asian patients. In this study, bosentan demonstrated favourable exercise effects, including improved NYHA functional status and 6MWD after 12 months of treatment. These effects were accompanied by an increase in RVEF, improvements in FVC and FEV$_1$, and a reduction in CTR. Except for the 3 patients who withdrew in the initial 4 weeks, the long-term effects of bosentan was further supported by the fact that none of the 12 patients with advanced IPAH monitored for more than 1 year presented with clinical worsening of PAH during this study. Furthermore, after 12 months of treatment, there was no episode of apparently abnormal hepatic function, no evidence of active HCV replication, and no sign of HCC development in the 3 patients with chronic HCV infection.

Meyer et al.\textsuperscript{10} reported that FVC and FEV$_1$ were significantly reduced among the 171 IPAH patients they characterized, compared to the predicted values of 64 non-smoking control volunteers without pulmonary or cardiac dysfunction. They reported that peripheral airway obstruction was common in IPAH and was more pronounced in severe disease. One of the reasons for poor pulmonary test results is that the increased production of cytokines and growth mediators in the pulmonary vasculature in IPAH might cause proliferation in adjacent small airways.\textsuperscript{11} Another reason is that decreased endothelial synthesis of the vasodilator nitric oxide and increased levels of the vasoconstrictor endothelin-1 (ET-1) in IPAH patients might also affect peripheral airway function since both mediators have similar effects on vascular and airway smooth musculature.\textsuperscript{12–14} However, it remained to be determined whether an increase in an ET-1 receptor antagonist, such as bosentan, could improve the function of peripheral airways in IPAH patients. In this study, we demonstrated that FVC and FEV$_1$ both significantly improved after 12 months of bosentan treatment in patients with severe IPAH. Since expiratory airflow limitation may contribute to symptoms and exercise limitation in patients with advanced IPAH, long-term bosentan treatment could pharmacologically reverse the phenomenon of peripheral airway obstruction. This finding implies that the functional limitations of patients with IPAH are not only caused by progressive right heart failure and impaired pulmonary gas exchange, but also by peripheral airway obstruction, which can be pharmacologically reversed by long-term bosentan treatment.

There are few well-documented non-invasive parameters to predict right heart function and efficacy of bosentan treatment in IPAH patients. Radionuclide angiographic measurement of ejection fraction is a widely used method for the non-invasive assessment of ventricular function. Gated imaging of the equilibrium blood pool was the first reliable and reproducible radionuclide technique proposed for the measurement of RVEF.\textsuperscript{15–18} Furthermore, the size of the heart, as assessed by CTR on chest radiography is often used as a screening test for the presence of heart failure and for assessing its severity.\textsuperscript{19,20} In our study, the significant improvements in RVEF and reduction in CTR after 12 months of bosentan therapy implied improvement in right heart function and the effectiveness of bosentan treatment in IPAH. Long-term observation and survival analysis in a large number of IPAH patients are needed to determine whether or not these factors could be of non-invasive prognostic value in IPAH treatment.

Both the NYHA FC and 6MWD are independent predictors of mortality in IPAH.\textsuperscript{21,22} After 12 months of bosentan therapy, the NYHA FC improved significantly in almost all patients. Eleven of the 12 patients had at least a one class improvement in NYHA FC, and no patient worsened. The difference in 6MWD between baseline and the 12-month follow-up was 120 m and the increase in length was high relative to that of other clinical trials. One potential explanation for the relative improvement is that sicker patients may have a tendency to improve more with regard to 6MWD than less severely ill patients.\textsuperscript{23} In this study, 6 of the 12 patients were classified in NYHA FC IV at baseline and, furthermore, the mean baseline walk distance of 326 m in the 12 patients was even lower than in the pivotal trial by Sitbon and colleagues (351 m for the bosentan group).\textsuperscript{24} The other explanation is that all the changes in clinical parameters after 12 months of therapy contributed to the final clinical status in the patients receiving bosentan. The significant improvements in the RVEF and pulmonary function, and the reduction in CTR contributed to enhance the exercise tolerance. Our results imply that the significant improvements in exercise capacity, RVEF, pulmonary function and reduced CTR correlated well with the clinical response in these patients and reinforced the efficacy of oral bosentan therapy. Because the small size of our study precludes generalisation to larger IPAH patient populations, larger studies will be required in order to confirm our results.

Because of interaction with bile-salt excretion from hepatocytes, liver toxicity is a typical side effect, which occurs in approximately 5–10% of patients.\textsuperscript{13,14} In this study, 2 (13%) of our initial 15 patients were excluded from the study due to asymptomatic elevated liver function tests in the first 4 weeks of bosentan therapy. However, these increases quickly returned to normal after discontinuing bosentan, without any consequent complication. After a mean treatment period of 19.4 ± 5 months, 12 (80%) of the original

### Table 3  Adverse events (n = 15).

<table>
<thead>
<tr>
<th>Variables</th>
<th>n (%)</th>
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<tbody>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
</tr>
<tr>
<td>Abnormal hepatic function</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Aggravated pulmonary hypertension</td>
<td>1 (7)</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Flushing</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Leg oedema</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Pain in limb</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (7)</td>
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</table>
15 patients tolerated bosentan treatment very well, without complications of hepatic dysfunction requiring dosage adjustment or discontinuation. Chronic HCV infection, although generally indolent, could lead to liver cirrhosis or HCC. There are serious safety concerns regarding the administration of bosentan in IPAH patients with pre-existing hepatic disease since potential hepatotoxicity is a well-recognised side-effect of bosentan. Hoeper et al. reported that bosentan was efficacious and safe in their eleven patients with portopulmonary hypertension; however, the majority of their aetiology was alcoholic liver disease. In this study, 3 IPAH patients diagnosed as HCV carriers without symptoms of portal hypertension tolerated bosentan therapy well for more than 12 months. At month 12, two patients' symptoms had improved such that they were reclassified into NYHA FC II, while the other was reclassified into NYHA FC III. Most notably, there was no evidence for drug-induced liver toxicity that required bosentan dosage adjustment or any episode of severe adverse event leading to withdrawal from this study. Hepatic aminotransferase levels were normal or slightly abnormal (less than 3 times the ULN). The quantitative assays of HCV RNA, which indicate the status of hepatitis C virus replications, were persistently undetectable before and after 12 months of bosentan treatment. At month 12, patient 2 remained free from cirrhosis, based on ultrasonographic characteristics, and all the 3 patients had no clinical evidence of HCC according to serum AFP tests and hepatic ultrasonographic findings. These findings suggested that long-term bosentan therapy may offer a therapeutic option in patients with chronic HCV infection; however, study of a larger cohort of patients is warranted to confirm the result.

Although the results of our study are promising, the limitations are still obvious. Firstly, this single-centre prospective study enrolled a small number of patients with advanced IPAH. It needs to be emphasised that the total number of IPAH patients who received regular bosentan therapy in Taiwan was fewer than 50 until January 2006. Additionally, this study excluded patients less than 12 years of age because some of the paediatric patients could not obey the orders required to complete the clinical examinations. Secondly, the patients and investigators were not blinded and there was also no control group due to ethical considerations. Thirdly, we did not repeat right heart catheterizations at 12 months of bosentan treatment because we preferred to reserve this invasive follow-up measurement for unclear situations, difficult therapeutic decisions or to use it prior to combination therapies when IPAH was clinically worsening.

**Conclusion**

This single-centre study of 12 Taiwanese patients with advanced IPAH treated with long-term oral bosentan found significant improvements in NYHA FC, 6MWD, RVEF and pulmonary function, as well as decreases in CTR compared with baseline. Our observations suggest that long-term bosentan therapy has favourable outcome and beneficial effects in Taiwanese IPAH patients, whether or not the patients had chronic HCV infection.

**References**


