Long-Term Effect of Bosentan Therapy on Cardiac Function and Symptomatic Benefits in Adult Patients With Eisenmenger Syndrome

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ABSTRACT

Background: Bosentan improves symptoms in patients with Eisenmenger syndrome (ES). This study evaluated the effect of long-term bosentan therapy on cardiac function and its relation to symptomatic benefits in ES patients.

Methods and Results: Twenty-three consecutive adult ES patients (15 with ventricular septal defect, 6 with atrial septal defect, and 2 with patent ductus arteriosus) underwent standard and tissue Doppler echocardiography before and 24 ± 9 months after bosentan therapy. Echocardiographic measurements included pulmonary arterial systolic pressure (PASP), myocardial performance index (MPI), tricuspid and lateral mitral annular pulsed-wave tissue Doppler systolic (Sa) and early diastolic (Ea) long-axis motions. Patients' World Health Organization (WHO) functional class, 6-minute walk distance (6MWD), and systemic arterial oxygen saturations (SaO_2) were also recorded. The PASP, WHO functional class, 6MWD, and SaO_2 all improved (118 ± 22 to 111 ± 19 mm Hg, 3.2 ± 0.4 to 2.4 ± 0.5, 286 ± 129 m to 395 ± 120 m, and 84.6 ± 6.5% to 88.8 ± 3.9%, respectively; all $P < .01$) after therapy. There was also significant improvement in right ventricular (RV) MPI (by 23.9%: 0.46 ± 0.15 to 0.35 ± 0.09) and biventricular long-axis function (tricuspid Sa and Ea: 6.7 ± 1.5 to 8.8 ± 1.7 cm/s and 5.7 ± 1.3 to 7.0 ± 1.2 cm/s, respectively; lateral Sa and Ea: 6.8 ± 1.3 to 8.4 ± 1.5 cm/s and 7.6 ± 2.0 to 8.5 ± 2.1 cm/s, respectively; all $P < .05$). Posttherapy RV MPI was moderately correlated with PASP and 6MWD.

Conclusions: Sustained improvement of pulmonary arterial hypertension and RV function in ES patients was evident 2 years after bosentan therapy, and this may provide insights on the symptomatic benefits gained in these patients. (*J Cardiac Fail 2012;18:379–384*)

Key Words: Bosentan, Eisenmenger syndrome, myocardial performance index, long-axis function.

Eisenmenger syndrome (ES) refers to the reversal of the left-to-right shunt in patients with intracardiac systemic-to-pulmonary communications as a result of severe pulmonary vascular disease.[1] In the past, treatment options for ES patients were mainly supportive, and heart-lung transplantation or lung transplantation with corrective cardiac surgery is usually not feasible, owing to the lack of potential organ donors. Bosentan is a safe and effective oral endothelin dual-receptor antagonist for treating patients with pulmonary arterial hypertension associated with congenital heart disease,[2–6] mainly by improving short-term exercise capacity in patients.[5–8] Recent (2010) European Society of Cardiology guidelines for the management of grown-up congenital heart disease also recommends bosentan therapy in World Health

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Manuscript received September 15, 2011; revised manuscript received January 10, 2012; revised manuscript accepted February 6, 2012.

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1071-9164/$ - see front matter

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doi:10.1016/j.cardfail.2012.02.004

Organization (WHO) functional class III patients based on those short-term studies.[9] However, there is a lack of long-term echocardiographic studies to address the underlying mechanisms for the observed clinical improvement.

ES patients have increased pulmonary vascular resistance, leading to chronic pressure overload on the right ventricle (RV) with subsequent dilatation and failure.[10] Assessment of global RV systolic function by the biplane Simpson method is often inaccurate owing to complex RV geometry.[11] RV diastology studied by transtricuspid pulsed-wave Doppler filling indices (peak E- and A-wave velocities, E-wave deceleration time, and isovolumic relaxation time) have the drawbacks of heart rate and load dependency as well as the lack of generally acceptable reference values, particularly for different age groups.[12] On the other hand, myocardial performance index (MPI), initially described by Tei et al as a surrogate of combined left ventricular (LV) systolic and diastolic function,[13] has been widely applied to congenital heart diseases predominately affecting the RV. Moreover, Gatzoulis et al showed an improvement in RV long-axis function 3 months after bosentan therapy in 10 ES patients.[6] Their findings are in agreement with our observation that ventricular long-axis function is more sensitive than global LV or RV ejection fraction in unveiling cardiac dysfunction in other congenital conditions.[12,14]

The aims of the present study were therefore: 1) to assess the long-term clinical benefits of bosentan therapy in ES patients; and 2) to prospectively characterize the change in cardiac long-axis function after therapy and its relation to clinical benefits.

Methods

Population

We prospectively studied 23 consecutive ES patients who were followed in an adult congenital heart disease clinic and received transthoracic echocardiography in 2005−2008. Enrolled patients were in WHO functional class III and IV and free from decompensated heart failure, severe arrhythmias causing hemodynamic compromise, and hemoptysis for ≥3 months before study entry. ES was defined as all of the following: 1) known intracardiac or great artery shunt; 2) comparable pulmonary arterial systolic pressure to systemic pressure; and 3) reversed or bidirectional shunt resulting in hypoxemia (systemic arterial oxygen saturation [SaO_2] <92% at rest or <87% with exercise).[10] Patients with suboptimal echocardiographic windows, more-than-mild valvular heart disease, coronary artery disease, or significant hepatic and renal dysfunction and those with contraindication to bosentan therapy were excluded from the study. Informed consent was obtained from each of the studied patients, and the study was approved by the local ethics committee.

Transthoracic echocardiography was performed at baseline and 1 month, 3 months, and every 3 months after starting bosentan therapy according to the study protocol. Clinical information collected at baseline and during scheduled follow-ups included: WHO functional class, systemic blood pressure, SaO_2 in room air, and 6-minute walk distance (6MWD). Patients' right arm systolic and diastolic blood pressures were measured with the use of a sphygmomanometer with the patient lying supine. SaO_2 was measured by resting finger pulse oximetry. Exercise capacity was evaluated by 6MWD.[15]

Medications

Baseline medications, including angiotensin-converting enzyme inhibitors, digoxin, diuretics, and antithrombotic agents, were continued during follow-up. Bosentan (Tracleer; Actelion Pharmaceuticals, Allschwil, Switzerland) was started at a dose of 62.5 mg twice per day and was subsequently titrated to the target dose of 125 mg twice per day after 4 weeks. It was initiated in the hospital setting with close monitoring of SaO_2 and blood pressure. Physical examinations and laboratory tests, particularly hemoglobin and hepatic transaminase levels, were performed monthly or as clinically indicated. Derangement of liver function was defined as an elevation of hepatic transaminase level >3 times the upper limit of normal.

Echocardiographic Examination

Echocardiograms were recorded according to the guidelines of the American Society of Echocardiography[16] by using a Vivid 7 (GE-Vingmed Ultrasound, Horten, Norway). At least 3 consecutive beats in sinus rhythm were recorded, and the average values were taken for analysis. The LV end-diastolic and end-systolic dimensions (LVEDD and LVESD, respectively) and RV end-diastolic dimension (RVEDD) were measured from M-mode recordings in the parasternal long-axis view. LV ejection fraction was calculated by biplane Simpson estimates. Right and left atrial dimensions were measured in the apical 4-chamber view. The LV mass was calculated with the Devereux formula.

LV filling velocities were obtained by placing a 2-mm pulsed-wave Doppler sample volume at the tips of mitral valve leaflets from the apical 4-chamber view. Peak early LV filling velocity (E-wave), peak atrial filling velocity (A-wave), E/A ratio, and E-wave deceleration time were all measured. The LV filling pattern was characterized as a normal pattern, an abnormal relaxation pattern (ARP), a pseudonormal pattern, or a restrictive filling pattern as previously described.[17]

LV and RV MPI were calculated from pulsed-wave Doppler recordings of LV and RV inflows and outflows as previously described.[13,18] Segmental myocardial long-axis function was assessed by recording longitudinal motions at tricuspid and lateral mitral annular sites with pulsed-wave tissue Doppler imaging technique.[19] Long-axis peak systolic (Sa), early diastolic (Ea), and late diastolic (Aa) velocities were measured. E/Ea ratios were then calculated. Tricuspid regurgitation (TR) was assessed by color-flow and continuous-wave Doppler from the apical 4-chamber view. Pulmonary artery systolic pressure (PASP) was estimated from RV systolic pressure (peak retrograde) as TR pressure drop + right atrial pressure (RAP). The RAP was assessed at subcostal view by inferior vena caval (IVC) size and collapsibility as recommended by American Society of Echocardiography. An IVC diameter of ≤2.1 cm that collapsed >50% with a sniff suggested a normal RAP of 3 mm Hg, whereas an IVC diameter of >2.1 cm that collapsed <50% with a sniff suggested a high RAP of 15 mm Hg. In indeterminate cases in which the IVC diameter and collapse did not fit this paradigm, an intermediate value of 8 mm Hg was used. The pulmonary acceleration time and ejection time were calculated from pulsed-wave Doppler recordings at pulmonary valve level. All echocardiographic

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