CHEST

Original Research

PULMONARY VASCULAR DISEASE

Bosentan for Sarcoidosis-Associated Pulmonary Hypertension

A Double-Blind Placebo Controlled Randomized Trial

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Background: **Sarcoidosis-associated pulmonary hypertension (SAPH) is a common problem in patients with persistent dyspneic sarcoidosis. The objective of this study was to determine the effect of bosentan therapy on pulmonary arterial hemodynamics in patients with SAPH.**

Methods: **This 16-week study was a double-blind, placebo-controlled trial of either bosentan or placebo in patients with SAPH confirmed by right-sided heart catheterization. Patients were enrolled from multiple academic centers specializing in sarcoidosis care. They were stable on sarcoidosis therapy and were receiving no therapy for pulmonary hypertension. The cohort was randomized two to one to receive bosentan at a maximal dose of 125 mg or placebo bid for 16 weeks. Pulmonary function studies, 6-min walk test, and right-sided heart hemodynamics, including pulmonary artery mean pressure and pulmonary vascular resistance (PVR), were performed before and after 16 weeks of therapy.**

Results: **Thirty-five patients completed 16 weeks of therapy (23 treated with bosentan, 12 with placebo). For those treated with bosentan, repeat hemodynamic studies at 16 weeks demonstrated a significant mean ± SD fall in PA mean pressure (−4 ± 6.6 mm Hg, $P = .0105$) and PVR (−1.7 ± 2.75 Wood units, $P = .0104$). For the patients treated with placebo, there was no significant change in either PA mean pressure (1 ± 3.7 mm Hg, $P > .05$) or PVR (0.1 ± 1.42 Wood units, $P > .05$). There was no significant change in 6-min walk distance for either group. Two patients treated with bosentan required an increase of supplemental oxygen by > 2 L after 16 weeks of therapy.**

Conclusions: **This study demonstrated that bosentan significantly improved pulmonary hemodynamics in patients with SAPH.**

Trial registry: **ClinicalTrials.gov; No: NCT00581607; URL: www.clinicaltrials.gov**

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Abbreviations: 6MWD = 6-min walk distance; 6MWT = 6-min walk test; NYHA = New York Heart Association; PA = pulmonary artery; PAOP = pulmonary artery occlusion pressure; PVR = pulmonary vascular resistance; SAPH = sarcoidosis-associated pulmonary hypertension; WHO = World Health Organization

Bosentan has been shown to be more effective than placebo in reducing pulmonary artery (PA) pressure in pulmonary arterial hypertension.[1] The drug has become a standard therapy for mild to moderately severe World Health Organization (WHO) group 1 pulmonary hypertension.[2,3] The use of endothelin receptor antagonists to treat group 1 pulmonary arterial hypertension has led to an overall improved survival in this group.[4]

Sarcoidosis-associated pulmonary hypertension (SAPH) is placed in group 5 of the current WHO classification system.[5] It may be found in a significant number of patients with persistent dyspnea.[6-8] The presence of pulmonary hypertension in patients with advanced pulmonary sarcoidosis is associated with increased mortality.[6,9] Several case series have suggested that treatment of pulmonary arterial hypertension with vasoactive drugs may reduce the level of pulmonary hypertension,[10-13] including in patients treated with bosentan alone or with other treatments.[12,14,15] To determine whether bosentan was effective in treating SAPH, we performed a double-blind, placebo-controlled trial of the agent.

Materials and Methods

Patients aged 18 to 90 years with sarcoidosis defined by standard criteria[16] were eligible for consideration. The patients were included if they had documented pulmonary hypertension with a PA mean pressure ≥ 25 mm Hg as measured by cardiac catheterization within 6 months of entry into the study. Pulmonary artery occlusion pressure (PAOP), left ventricular end-diastolic pressure, or both was < 15 mm Hg. Patients had to exhibit New York Heart Association (NYHA) functional class II or III symptoms. They had to have a 6-min walk distance (6MWD) of 100 to 500 m and a < 10% difference in the 6MWD performed on two separate occasions before receiving the first dose of bosentan. All patients were on stable immunotherapy for sarcoidosis, including prednisone, methotrexate, azathioprine, hydroxychloroquine, cyclophosphamide, thalidomide, and infliximab, for 3 months prior to the first dose of drug.

Patients were excluded from the study if they had received specific therapy for pulmonary hypertension within 28 days of screening. The one exception was that patients who had been on a stable dose of calcium channel blocker for > 1 month prior to right-sided heart catheterization were allowed to continue the medication. Patients were excluded if they had severe airway obstruction as defined by $FEV_1/FVC < 35\%$; had an exercise limitation consistent with NYHA functional class IV; were pregnant or breast feeding; had significant left ventricular dysfunction (left ventricular ejection fraction < 35%); had a cardiac index < 2.0 L, right atrial pressure > 15 mm Hg, or both; had significant liver dysfunction not due to sarcoidosis; had other severe organ disease believed by the investigators to affect survival during the course of the study; were unable to perform the 6-min walk test (6MWT) at the time of screening; or were receiving either cyclosporine or glyburide. All patients provided written informed consent of an institutional review board-approved protocol (University of Cincinnati Institutional Review Board #7-3-22-1).

Before the first evaluation, patients underwent two 6MWTs using a standardized protocol.[17] Patients using supplemental oxygen as part of their standard care were maintained on the same level of oxygen. We recorded the oxygen flow rate as well as the oxygen saturation at rest and with exercise. Patients were believed to have significant oxygen desaturation if their lowest oxygen saturation was > 5% of rest value or if they required an increase in supplemental oxygen of at least 2 L/min. We measured FVC, FEV_1, and the FEV_1/FVC ratio. Percent predicted normal values were calculated with reference equations from the National Health and Nutrition Examination Survey.[18]

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Procedure

Patients were block randomized at each institution to receive either drug or placebo at a 2:1 ratio. Randomization was performed with a computer program, and the drug was supplied from a central institution (University of Cincinnati). For the first month, the patients received either 62.5 mg bosentan or placebo bid. After 1 month, a liver function test was performed. If stable, the dose was increased to 125 mg or two placebo tablets bid. Liver function testing was repeated monthly.

After 16 weeks, PA systolic, diastolic, and mean pressures and PAOP were measured. Cardiac output was determined by thermodilution method, and the pulmonary vascular resistance (PVR) was calculated. We did not collect cardiac output data as determined by the Fick method. Patients also underwent repeat pulmonary function testing, including spirometry and 6MWT.

Statistical Analysis

The predefined end point of the study was a change in PA mean pressure after 16 weeks of bosentan or placebo treatment. The sample size was based on the inhaled iloprost study.[10] In that study, patients with sarcoidosis prior to therapy had a mean ± SD PVR of 5.8 ± 4.669 Wood units. A sample size of 38 patients would provide 80% power to detect 50% difference in PVR between the two groups. The various measurements followed a normal distribution, and comparison within and between groups based on therapy was performed with Student *t* test. On the basis of a prior study,[12] a subgroup analysis of patients with an FVC ≤ 50% predicted vs those with a higher FVC was performed. Comparisons were again performed with Student *t* test, and linear correlation was calculated in some cases. $P < .05$ was considered significant.

Results

Forty-three patients from five sites were enrolled in the study over a 4-year period, ending in September 2011. Figure 1 summarizes the outcomes for these patients. Four patients were never randomized because of withdrawn consent (two patients) or ineligibility (one each for liver dysfunction and NYHA functional class IV). Of the 39 randomized patients, 35 completed 16 weeks of therapy. Five patients declined repeat right-sided heart catheterization but continued in the study. One patient had a repeat catheterization but could not perform the repeat 6MWT because of an above-knee amputation due to peripheral vascular disease. Patients with missing data were excluded from analysis.

The clinical features of the 35 patients who completed the full 16 weeks of the study are summarized in Table 1[20] by the CONSORT (Consolidated Standards of Reporting Trials) method.[19] There was no significant difference between the two groups. There was no difference in the baseline features of these 35 patients and the remaining eight who enrolled in the study but did not complete the 16 weeks of treatment. Approximately one-half of the patients in both groups had an FVC < 60% predicted, and one-half had Scadding stage IV chest radiographs. There was no difference in FVC or 6MWD at baseline between