Bosentan in Pulmonary Arterial Hypertension Secondary to Scleroderma

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ABSTRACT. ***Objective.*** To assess the efficacy and tolerability of bosentan in pulmonary arterial hypertension secondary to systemic sclerosis (SSc-PAH) including patients with restrictive lung disease.

Methods. We retrospectively reviewed 23 SSc-PAH patients with PAH at baseline [PA systolic pressure (PASP) ≥ 45 mm Hg by echocardiogram or mean PA pressure > 25 mm Hg at rest by cardiac catheterization], World Health Organization (WHO) functional classes II–IV, and with data available for 18 months. Bosentan dose was 62.5 mg twice daily for 1 month then 125 mg twice daily. Outcomes were WHO functional class, PASP, and pulmonary function tests (PFT) at 3-month intervals for 18 months.

Results. WHO class at baseline 3.1 ± 0.1 (mean ± SE); 3 months, 2.5 ± 0.2*; 6 months, 2.4 ± 0.2*; 9 months, 2.5 ± 0.2* (*p < 0.02 vs baseline, n = 21 to 23), indicating clinical improvement at 9 months. After 9 months, results were not significant versus baseline. Reduction in WHO class by at least one rank was 57% at 3 months; none worsened. After 9 months, WHO class tended to worsen compared to baseline. Baseline PASP was 54 ± 2 mm Hg (n = 23) and did not change significantly with therapy. Restriction (total lung capacity 76% ± 4% of predicted) and reduced diffusing capacity (39% ± 3% of predicted) were unchanged during therapy. Abnormal transaminases in 2 patients (9%) necessitated discontinuing drug in both.

Conclusion. Bosentan is clinically beneficial in patients with SSc-PAH including patients with restrictive lung disease, but pulmonary hemodynamics and PFT results remained stable during treatment. (J Rheumatol 2006;33:61–8)

Key Indexing Terms:
PULMONARY HYPERTENSION SYSTEMIC SCLERODERMA ENDOTHELINS
INTERSTITIAL LUNG DISEASES DYSPNEA RESPIRATORY FUNCTION TESTS

Diseases of the lung and pulmonary vasculature are the leading causes of morbidity and mortality in systemic sclerosis (SSc). In those SSc patients with restrictive lung disease, mortality is 40%–45% within 10 years of onset of SSc[1]. In those with pulmonary arterial hypertension (PAH), mortality is 20% within 20 months[2]. Newer treatments for PAH, including intravenous epoprostenol[3], intravenous and inhaled iloprost[4-7], subcutaneous treprostinil[8], and oral beraprost[9,10], have shown benefit in patients with PAH secondary to SSc (SSc-PAH). Bosentan, an orally bioavailable nonselective antagonist of endothelin at both the A and B receptors, has been found to improve exercise capacity and hemodynamics as well as to slow the time to clinical deterioration in 2 trials in patients with PAH[11,12]. Patients with SSc-PAH were underrepresented in these studies (52 total), which were short-term (12–16 weeks) and which excluded subjects with concomitant interstitial lung disease. Further, while patients with idiopathic (primary) pulmonary hypertension (PPH) improved their exercise capacity (6 minute walk distance) in comparison to placebo treated subjects, the subset with SSc-PAH remained at baseline status while the placebo treated group deteriorated[12]. The treatment difference between active drug and placebo was nonetheless comparable. The US Food and Drug Administration approved bosentan for SSc-PAH in December 2001. Firm conclusions about the safety and efficacy of bosentan in SSc-PAH cannot be made based on the available data.

The pharmacological action of endothelin receptor antagonism on modifying PAH likely involves antiproliferative and antifibrotic effects in addition to blocking vasoconstriction[13]. Bosentan has been shown to inhibit matrix protein biosynthesis and proliferation of SSc fibroblasts[14], inhibit

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proliferation of vascular smooth muscle cells[15], prevent collagen deposition in pulmonary arteries of experimental PAH[16], and inhibit the transcription factor nuclear factor-κB that mediates tissue inflammation[17]. Since noninflammatory obliterative vasculopathy contributes to other major complications of SSc such as renal crisis and digital ischemia, bosentan has theoretic benefit on modifying end-organ damage in other organs in patients with SSc.

The purpose of this retrospective study was to enlarge the clinical experience of bosentan in PAH-SSc in order to compare treatment efficacy and safety to results reported in randomized clinical trials (RCT) of patients with PAH including PAH-SSc. We reviewed clinical data of echocardiograms and/or cardiac catheterizations to assess PAH, World Health Organization (WHO) classification of functional capacity, and drug safety and tolerability in 23 patients during the first 18 months of therapy. We also studied whether bosentan could potentially modify the restrictive lung disease associated with SSc. To study this question, we measured changes in pulmonary function tests (PFT) in patients treated with bosentan.

MATERIALS AND METHODS

Design and hypotheses. This was a retrospective study of the efficacy and safety of the initial 18 month course of therapy with bosentan in treating SSc-PAH. Methods of data collection and analyses were predetermined. There were 3 main hypotheses tested: treatment improves functional capacity; treatment does not affect pulmonary artery (PA) pressure; treatment improves the restrictive disease and/or diffusing capacity in those patients with restrictive lung disease or impaired diffusing capacity. We also evaluated the safety profile of bosentan by comparing our results with those of published studies.

Patients and entry criteria. Subjects were recruited from the outpatient clinics of the University of Medicine and Dentistry of New Jersey Scleroderma Program. The diagnosis of PAH was suspected in SSc patients with progressive dyspnea or abnormalities suggesting PAH by physical examination, chest roentgenograms, or selected PFT results. Charts were screened for those subjects who met entry criteria and were treated with bosentan as the only therapy for PAH. Study-specific inclusion criteria were as follows: clinical diagnosis of SSc based on American College of Rheumatology criteria[18]; class II, III, or IV according to the WHO functional classification[19]; presence of PAH defined as a resting peak velocity of regurgitant tricuspid flow detected by Doppler echocardiogram of $\geq$ 45 mm Hg $\cdot$ s^{-1} or a resting mean PA pressure of > 25 mm Hg, a pulmonary capillary wedge pressure of < 15 mm Hg, a pulmonary vascular resistance > 240 dynes $\cdot$ s $\cdot$ cm^{-5} by cardiac catheterization that was not attributable to other cardiopulmonary diseases; and followup was likely for the subsequent 18 months. We used the value of PASP as $\geq$ 45 mm Hg by echocardiography since in patients with SSc-PAH the positive predictive accuracy of echocardiography compared to cardiac catheterization is 97% for values $\geq$ 45 mm Hg[20]. Exclusion criteria were age < 18 or > 80 years or contraindications for using bosentan [pregnancy, elevated liver function tests (LFT), use of glyburide or cyclosporine and other calcineurin phosphatase inhibitors]. The procedures were in accord with recommendations of the Helsinki Declaration of 1975 revised in 1983[21].

Data collection. The study population consisted of patients who had met entry criteria, taken bosentan, and signed a consent form. Most data were collected from charts since the majority of subjects were under treatment when the study was initiated. Followup data were collected during clinic visits or by a structured telephone interview. The start of the study was defined as the day bosentan therapy was initiated; the end as the date when patients completed 18 months of bosentan therapy, were lost to followup, or stopped bosentan therapy because of an adverse drug effect. Baseline data were defined as the most recent test results recorded prior to the study. Two investigators independently collected data from charts, and discrepancies were rectified by mutual agreement. From charts, we collected information on demographics, SSc classification, disease duration, hemodynamics, PFT, modified WHO functional class, and LFT results. The same followup data, as well as deaths and discontinuation of therapy, were collected from charts and/or clinic visits and telephone interviews at 3 month intervals. Data collection began 1 month after initiation of bosentan therapy. Data collected during subsequent 3 month periods were combined for analysis. For example, data accrued during months 2, 3, or 4 were referred to as 3 month, for months 5, 6, or 7 as 6 month, etc.

Bosentan therapy. We followed the guidelines for treatment with bosentan and for monitoring hepatic toxicity in accord with recommended practice[22]. Bosentan dose was 62.5 mg twice daily for 1 month followed by 125 mg twice daily thereafter. Transaminase levels were monitored prior to entry, at monthly intervals, and every 2 weeks if the dosage of bosentan was increased. Bosentan treatment was stopped or the dosage reduced if the transaminases were 3–5 times upper limit of normal (ULN), stopped and possibly reintroduced if 5–8 times ULN, and stopped and not reintroduced if > 8 times ULN. No patient developed symptoms of liver injury. Pregnancy tests were done monthly in women of childbearing age; none was positive.

Diagnosis of scleroderma. A senior rheumatologist (JRS) classified the SSc using the criteria of LeRoy and associates[23]: diffuse SSc, cutaneous sclerosis proximal to the elbows and/or knees, often the trunk, with or without facial involvement; or limited SSc, cutaneous sclerosis distal to the elbows and knees, with or without facial involvement. Duration of SSc was defined from the time of the first non-Raynaud manifestation.

Functional classification. WHO functional class (classes I to IV, with higher classes indicating a greater loss of function), a metric of severity of patients' symptoms for ordinary activities, is based on the previous New York Heart Association (NYHA) classification[19]. One investigator (JRS) classified 95% of subjects by WHO functional class during a clinic visit or interview. No data on WHO functional classes were self-reported since these had been documented in charts prior to initiation of the study or were obtained at subsequent visits or telephone interviews. Standard measures of exercise performance, such as the 6 minute walk test, were not used on a consistent basis. The reasons included nonreimbursement by third-party payers citing redundancy in testing for PFT and lack of evidence that the 6 minute walk test is useful for adjusting doses of bosentan in PAH.

Changes in WHO functional class were analyzed in 3 ways. First, mean values for WHO class during each 3 month interval were compared. Second, change in functional status was analyzed by computing the percentage of patients at each 3 month interval that changed WHO class by at least one grade compared to the prior time period. For this analysis, we used paired data from consecutive time periods. Third, we compared the change in WHO functional class between baseline and 3 months to those reported in a published RCT, the Bosentan Randomized Trial of Endothelin Antagonist Trial-1 (BREATHE-1)[12], using a scoring system. Improvement in one or 2 classes was assigned a score of +1 or +2, respectively, and worsening as –1 or –2 for one or 2 classes, respectively. The change score for each study group was summed and expressed as a proportion to total number of patients (average improvement). We applied this scoring system only to patients in class III and IV at baseline since the comparison study (BREATHE-1, 125 mg dose at 16 weeks) consisted only of patients in classes III and IV at baseline[12].

Hemodynamics. Cardiac ultrasound machines were used to obtain Doppler measures, and Doppler-derived PASP was used as a noninvasive estimate of PA pressure at rest. The highest estimated pressure obtained from multiple echocardiographic views was used. For the echocardiograms, 94% were performed in one laboratory at this institution. In patients having cardiac catheterization, only those who met entry criteria were included.

Pulmonary function tests. PFT studies performed according to American Thoracic Society criteria[24,25] included forced vital capacity (FVC), forced vital capacity in 1 second (FEV_1), total lung capacity (TLC), and single-breath carbon monoxide diffusing capacity (DLCO). Restrictive lung disease was defined as a TLC < 70% predicted, obstructive disease as FEV_1/FVC < 70%, and reduced diffusing capacity as < 70% predicted, using the predicted values of Crapo and associates[26,27]. Total lung capacity rather than FVC was used to define restrictive lung disease because a reduced FVC may occur in severe obstructive lung disease[28] and obstructive lung disease was not an exclusion criterion for this study. Spirometry and DLCO were corrected for African American race[29], and DLCO was adjusted for hemoglobin level[30].

Published comparison groups. Three published studies were used for comparison to our results. First, a control group from a RCT reported by Badesch and associates[3] was used to determine if change in disease severity was affected by bosentan. We compared change in WHO class of our patients to change in NYHA functional class of the conventional treatment group from the study by Badesch and associates[3]. This was a RCT comparing intravenous epoprostenol to conventional therapy in patients with moderate to severe PAH secondary to SSc. Conventional therapy consisted of calcium channel blockers and warfarin in some patients. Change in exercise tolerance between baseline and 12 weeks using NYHA functional class was compared to changes we observed in WHO functional class between baseline and 3 months, recognizing that the WHO functional class is not a measure of exercise performance[19].

The other 2 studies, that of Channick and associates[11] and the larger BREATHE-1 study[12], were similar in design. Both were RCT that compared bosentan (62.5 mg twice daily for 1 month followed by 125 mg twice daily for 12 or 16 weeks) to placebo. Subjects included patients with PAH due to PPH, SSc, or systemic lupus erythematosus. The primary outcome in both studies was change in 6 minute walk test. Among the secondary outcomes, change from baseline in hemodynamic measurements (cardiac catheterization) was included in the study by Channick and associates[11] and WHO functional class in the BREATHE-1 study[12]. We used the baseline and WHO class data for the 125 mg bosentan group at 16 weeks of the BREATHE-1 study[12] to compare to our results of WHO classification. For comparison to our results for change in PA pressure, we used the mean PA pressure at baseline and 12 weeks of the study of Channick and associates[11]. (For BREATHE-1, analysis of echocardiographic data was done but results are reported only in abstract form[31].) To evaluate the frequency of abnormal LFT results and change or discontinuation of drug, we compared our results to those reported in the 125 mg bosentan group at 16 weeks in BREATHE-1[12].

Statistical analysis. Continuous variables were compared using paired one-way ANOVA and ordinal values by the Mann-Whitney rank-sum test using the SigmaStat statistical software package (v. 3.01A; Systat Software, Richmond, CA, USA). All reported p values are 2 sided. A p value < 0.05 was considered significant.

RESULTS

Patients. Of the 51 patients screened, 28 were excluded because they did not meet entry criteria. The exclusions were for a PASP < 45 mm Hg by Doppler echocardiogram or failure to meet the entry criteria for cardiac catheterization (24 patients), SSc in association with features of other connective tissue diseases (3 patients), and termination of medical insurance (one patient). Characteristics of the 23 subjects who entered the study are shown in Table 1. There were no differences in any baseline variables listed in Table 1 between subjects enrolled and those excluded from the study except for mean PASP (data not shown).

Table 1. Characteristics of patients at entry into the study.

No.	23
Age, yrs, mean (range)	59 ± 3 (34–80)
Sex, no. (%)	
Male	7 (30)
Female	16 (70)
Ethnicity, no. (%)	
Caucasian	21 (92)
African American	1 (4)
Hispanic	1 (4)
Scleroderma type, no. (%)	
Diffuse	10 (43)
Limited	13 (57)
Disease duration, yrs, mean (range)	11 ± 2 (2–37)
Hemodynamics	
Echocardiogram, n = 21	
Pulmonary artery systolic pressure, mm Hg, mean (range)	53 ± 3 (45–84)
Cardiac catheterization, n = 2	
Pulmonary artery pressures, mm Hg, systolic/diastolic	45/20, 53/21
WHO class, no. (%)	
I	0 (0)
II	3 (13)
III	14 (61)
IV	6 (26)

Data are mean ± SE. WHO class: World Health Organization classification (classes I to IV, with higher classes indicating greater severity of disease).

Study completion and number of observations. Four of the 23 subjects who entered the study did not complete 18 months of bosentan therapy. One subject was lost to followup after 6 months. Two discontinued bosentan after 9 months because of increased transaminase levels, and one discontinued at 9 months because of fluid retention. No deaths occurred during the study period. Results are reported only for those patients who were undergoing bosentan therapy when data were collected. Consequently, the number of observations varied during the study period (Table 2).

Functional classification. Mean ± SE of WHO functional class was as follows: baseline, 3.1 ± 0.1 (n = 23); 3 months 2.5 ± 0.2 (n = 21); 6 months 2.4 ± 0.2 (n = 23); 9 months 2.5 ± 0.2 (n = 21) (all p < 0.02 vs baseline by Mann-Whitney rank-sum test). These results indicate improvement in function during the first 9 months of bosentan therapy. Mean WHO functional classes at 12, 15, and 18 months were not significantly different from baseline (data not shown). Compared to baseline, we observed a trend toward lower WHO classes, i.e., improved function, at the 3 and 6 month periods and a trend toward higher numbers after 12 months (Figure 1).

Change in functional status was also analyzed by computing the percentage of patients at each 3 month interval that changed WHO class by at least one grade compared to the prior time period (Table 3). Between baseline and 3 months, 57% of the patients improved and none worsened. Roughly the same percentage of patients improved or wors-

Table 2. Observations at each time period.

Variable	Baseline	3 mo	6 mo	9 mo	12 mo	15 mo	18 mo
Taking bosentan, no.	23	23	23	21	19	19	19
WHO class, no. (%)	23 (100)	21 (91)	23 (100)	21 (100)	19 (100)	15 (79)	17 (89)
Hemodynamics, no. (%)	23 (100)	7 (30)	10 (43)	8 (38)	8 (42)	3 (16)	5 (26)
PFT, no. (%)	20 (87)	7 (30)	15 (65)	8 (38)	9 (47)	3 (16)	7 (37)

Numbers in the first row indicate the number of subjects who completed 18 months of bosentan therapy at each time period. For each variable, no. indicates the number of tests available for analysis and (%) indicates the percentage of patients taking bosentan whose tests were available at each time. Hemodynamics refers to pulmonary artery systolic pressure measured by echocardiography or by cardiac catheterization. Baseline refers to data collected prior to study entry; mo refers to the 3-month intervals during which data were combined. WHO: World Health Organization; PFT: pulmonary function tests.

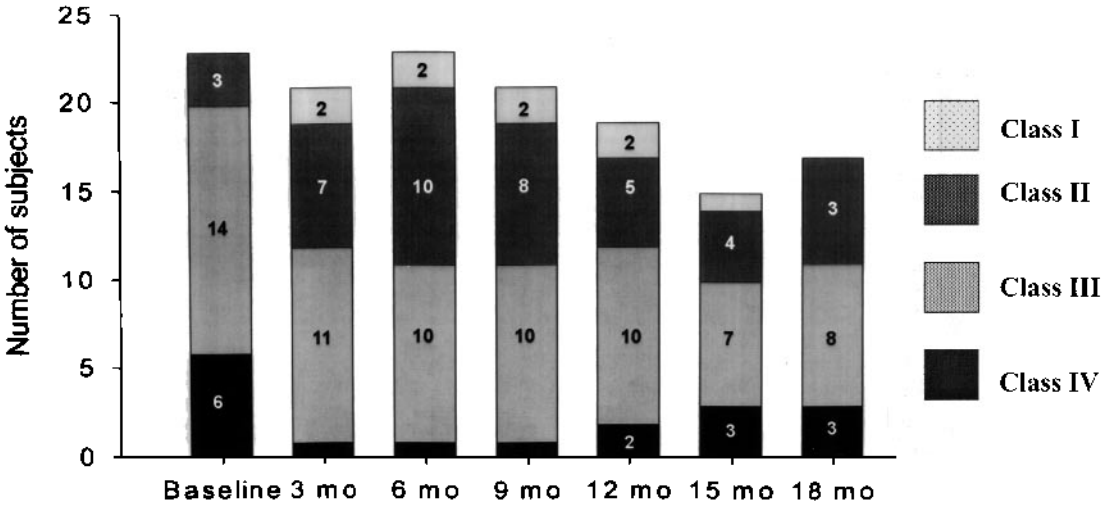

Figure 1. WHO functional classes of patients in the study population. These data include patients in classes II, III, and IV at baseline. Baseline indicates most recent data collected prior to initiation of bosentan therapy. Numbers of months indicate the 3 month intervals of data collection beginning 1 month after initiation of bosentan therapy. For example, data accrued during months 2, 3, or 4 are referred to as 3 month, for months 5, 6, or 7 as 6 month, etc. Higher number of WHO class represents more severe functional impairment. Numbers in each bar segment represent the number of subjects in each class. In bar segments without a number, n = 1.

Table 3. Changes in World Health Organization (WHO) classification.

Change in WHO Class	Baseline vs 3 mo (n = 21)*	3 mo vs 6 mo (n = 21)*	6 mo vs 9 mo (n = 21)*	9 mo vs 12 mo (n = 19)*	12 mo vs 15 mo (n = 15)*	15 mo vs 18 mo (n = 14)*
+2	14	0	0	0	0	0
+1	43	14	0	5	5	7
–1	0	14	5	16	5	21
–2	0	0	0	0	5	0

Numbers indicate the percentage of patients with baseline WHO functional class III or IV that changed WHO class compared to the prior period. A positive number indicates improvement of one or 2 classes; a negative number a worsening of one or 2 classes. Baseline refers to data collected prior to study entry, mo refers to the 3-month intervals during which data were combined. * n refers to number of paired data from consecutive time periods; this number may differ from the number of WHO class observations for individual time periods (Table 2).

ened during the 3 versus the 6 month period. After 6 months, 5%–21% of patients worsened and 5%–7% improved.

To compare our change in WHO functional class at 3 months with those of a RCT, we used a change score for those patients in only WHO functional classes III and IV at baseline. These results were compared to the BREATHE-1

study[12], which also included only classes III and IV patients. For our patients, the raw change score from baseline to 3 months was +13 (n = 19), and the average improvement at 3 months was +0.65. The raw change score for those patients in BREATHE-1 was +29 (n = 72) and the average improvement at 16 weeks was +0.40. It appears that, in class III or IV patients, the patients in our group had at least as great an improvement in function at 3 months as was observed in the BREATHE-1 group (125 mg bosentan dose, 16 weeks). Taking the findings of these analyses together, our results show improvement in functional class during the first 3 months after bosentan therapy, stabilization between 3 and 6 months, and a trend toward worsening after 12 months.

Hemodynamics. At baseline, the mean PASP of the patients having PAH diagnosed by echocardiography was 54 ± 2 mm Hg (n = 21). The mean PA pressures of the 2 patients who had catheterization at baseline were > 25 mm Hg. Since the PASP of these 2 patients were ≥ 45 mm Hg (45 and 53 mm Hg), data for PASP from the echocardiograms and cardiac catheterizations at baseline were combined for analysis. Followup estimates of PASP, all by echocardiography, were made on 39 occasions, with all patients having at least one followup, 39% having 2, and 17% having at least 3. For patients who were under bosentan therapy, mean values of PASP at 3 month intervals were not significantly different compared to baseline (data not shown). Trends in PASP at 3 month intervals were plotted for individual patients (Figure 2). About one-third of patients tended to improve, one-third tended to remain the same, and one-third tended to worsen over time. Thus, there was no overall change in PSAP during the study period.

Pulmonary function tests. At baseline, restriction defined as TLC < 70% of predicted was present in 7/20 (35%) of patients, obstruction in 3/20 (15%), and reduced DLCO in 20/20 (100%). Baseline FVC was 2.4 ± 0.2 l (72% ± 5% predicted), TLC was 3.9 ± 0.2 l (76% ± 4% predicted), and DLCO was 9.4 ± 0.7 ml/min/mm Hg (39% ± 3% predicted) (n = 20 for all). There were no significant differences in numerical or percentage-predicted values of FVC, TLC, or DLCO at any time compared to baseline (data not shown). Plots of individual numerical values of TLC at 3 month intervals showed a tendency toward decline (Figure 3). When results from DLCO were plotted, there also was an apparent downward trend in numerical values for DLCO (data not shown).

Adverse effects. Two subjects had elevations of transaminase concentrations during the 18 month study period requiring discontinuation of bosentan. One had 5–8 times ULN and the other a 3–5 times ULN elevation of transaminases; both occurred during the 6 month interval. Among our patients, 9% had hepatic toxicity. This compares to a 5% incidence over 16 weeks in the BREATHE-1 study[12]. In our study, both patients had to permanently discontinue drug compared to none in BREATHE-1. One other patient had to permanently discontinue bosentan because of excessive fluid retention that occurred 9 months after bosentan therapy was started. Thus, 13% of our subjects had to discontinue bosentan therapy permanently.

DISCUSSION

To broaden the clinical experience in using bosentan to treat PAH secondary to SSc, we report a retrospective study of 23 patients during the first 18 months of therapy. Improved functional class occurred during the first 3 months of treatment, since 57% of patients improved their WHO functional class (on a scale of I to IV, higher number representing increased severity of functional impairment) and none worsened. Improvement was durable and sustained between 3

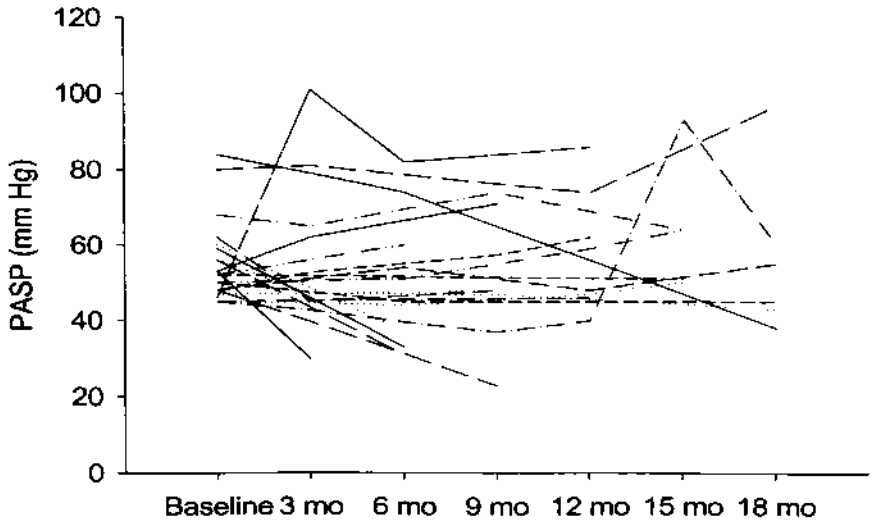

Figure 2. Each line of the graph represents values for pulmonary artery systolic pressure (mm Hg) for an individual patient over time. The number of months is defined in the legend for Figure 1.

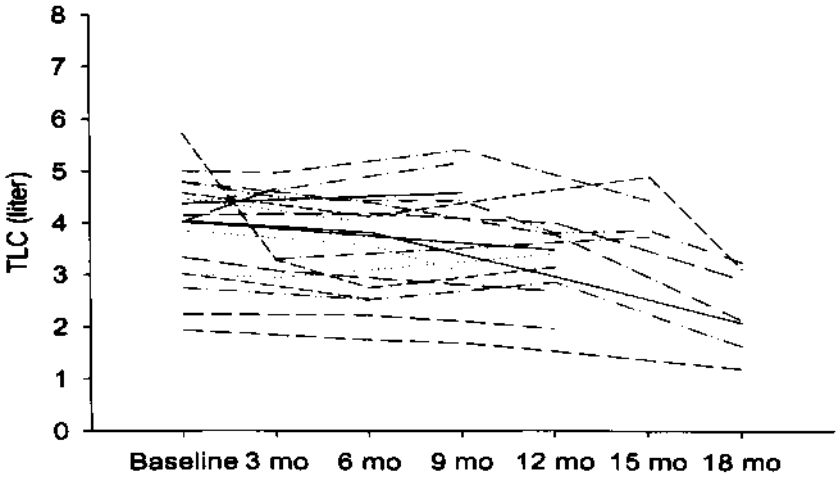

Figure 3. Each line of the graph represents total lung capacity (liters) for an individual patient over time. The number of months is defined in the legend for Figure 1.

and 6 months, but tended to worsen between 12 and 18 months.

We compared our experience to a published group of patients with PAH secondary to SSc. Badesch and colleagues[3] compared intravenous epoprostenol to conventional treatment in a RCT, and we used the conventional treatment arm of that study as an external comparison group. Initial severity of PAH and study duration were similar. Badesch and colleagues[3] used the NYHA functional class as a secondary outcome measure whereas we used the WHO classification. Comparing the 2 classification systems is reasonable since the WHO scheme is based on the previous NYHA classification[19]. Fifty-seven percent of patients treated with bosentan in our study decreased functional class, i.e., improved, at 3 months compared to none of the external comparison group. It is reasonable to conclude that the functional improvement in our group was attributable to bosentan therapy.

Change in WHO class at 3 months of treatment in our patients who were class III or IV at baseline was compared to data of a treated group in BREATHE-1[12], a large RCT that included patients with PPH as well as connective tissue diseases. We used a scoring system by assigning a number to each patient who changed class, a positive value for improvement and a negative value for worsening. Our average improvement (+0.65) was at least as good as that derived from the comparably treated group in BREATHE-1 (+0.40). Interestingly, a subgroup analysis of BREATHE-1 compared exercise performance by disease (PPH vs SSc) using the 6 minute walk test, and found that patients with PPH improved, but those with SSc stayed about the same[32]. This result suggests bosentan therapy prevented disease deterioration in patients with SSc, but improved performance in PPH. Our results showed improved functional performance by WHO classification in SSc patients treated with bosentan compared to no change in the subgroup analysis of BREATHE-1.

We found no change in PAH assessed by echocardiography between baseline and 3 month intervals following bosentan therapy. Channick and associates[11] reported lowering of PAH in patients with predominately PPH treated with bosentan for 12 weeks as determined by cardiac catheterization. Channick and associates[11] evaluated change in mean PA pressure using between-treatment group differences. The difference between the treated and placebo groups was accounted for by a rise of +5.1 mm Hg pressure in the placebo group and a decrease of –1.6 mm Hg in the treated group. They concluded that the hemodynamic effect of bosentan on PAH is to stabilize PA pressure at baseline levels rather than lowering blood pressure. Our results are consistent with this conclusion.

We measured serial PFT in our patients to determine if bosentan treatment affects the progression of restrictive lung disease in patients with SSc. We found no statistical change in FVC, TLC, or DLCO during the treatment period, although there appeared to be a downward trend when numerical values for TLC and DLCO were plotted over the study period. On this basis, we conclude that bosentan does not influence the restrictive lung disease or reduced diffusing capacity in SSc when given for 18 months. Our data do not permit conclusions about potential antiinflammatory effects of endothelin receptor antagonism because bronchoalveolar lavage, lung biopsy, and serial high-resolution computed tomography of the thorax were not employed in this clinical experience.

The overall incidence of hepatic toxicity, the most serious toxic effect of bosentan, was slightly greater in our study than that reported in a larger RCT. We found in a small sample of 23 patients that about 9% of SSc patients had abnormal LFT, defined as greater than 3 times ULN levels

of transaminases over the 18 months of therapy. All our subjects had sufficient levels of elevated transaminases to mandate permanent discontinuation of bosentan. The incidence in the BREATHE-1 study[12] was lower, since about 5% of patients had abnormal LFT over 18 weeks and none had to permanently discontinue the drug. In the Randomized, Placebo–controlled Study on the Prevention of Ischemic Digital Ulcers Secondary to Systemic Sclerosis (RAPIDS 1), the incidence of abnormal LFT results leading to permanent discontinuation of bosentan was 6% compared to none in the placebo treated group[33]. In that study, the dosing regimen of bosentan was identical to that used here, and the observations were made at 16 weeks of therapy. Our data and those of RAPIDS 1 suggest that, compared to patients with PPH treated with bosentan, patients with SSc may be at somewhat greater risk of hepatic toxicity from bosentan. Occurrence of abnormal LFT is generally accepted to be a feature of early phases of drug treatment. In our study, however, instances of LFT abnormalities occurred after 3 months of therapy and tended to persist or rapidly recur on reintroduction of bosentan, necessitating drug withdrawal in both subjects. Surveillance of bosentan hepatic toxicity utilizing data from the open label periods of 2 RCT (Channick and associates[11] and BREATHE-1[12]) showed an incidence of abnormal LFT of 13% over 2.1 years. Continued surveillance of patients taking bosentan is required to determine if there is a disease-specific risk of bosentan toxicity in patients with SSc, or whether the risk of adverse effects increases with duration of therapy.

Our study has methodological limitations that affect the interpretation of our results. Limitations include retrospective design, use of an indirect measurement of PAH, incomplete followup data, and inclusion of subjects with restrictive lung disease as well as obstructive lung disease. Another limitation of the study is that the WHO functional classification is not an objective measurement of exercise capacity[19]. Pulmonary hypertension in SSc can be due to a broad range of causes, including thromboembolic lung disease, hypoxia due to lung disease, underlying heart disease, or the isolated pulmonary vascular disease associated with SSc[32]. These various causes of PAH were not completely defined, since echocardiography was the only method used to evaluate the hemodynamics in almost all patients in this population. It is possible that inclusion of some patients with PAH due to diseases for which bosentan therapy is inappropriate may have influenced the response to treatment. Despite these limitations, it is important that we used predetermined objective measurements to assess change of function and echocardiography, and our goal was to determine the general direction of change in severity, not to perform a precise comparison with published data. Considering that it is unethical to conduct a placebo controlled trial on an FDA approved drug, this limitation is likely to impede more rigorous analysis of the efficacy of bosentan on a relatively rare disease such as SSc.

A major observation of this study is that mean functional capacity, as determined by change in WHO functional class, improved during the first 6 months of bosentan therapy compared to baseline, and was then followed by a trend toward worsening between 12 and 18 months of therapy. The importance of functional capacity in assessing prognosis of PAH was underscored by a recent report of McLaughlin and associates[34] that analyzed the baseline variables that predicted survival of patients with PPH treated with bosentan. In a 2.1 year followup of 169 patients who participated in the open-label portion of 2 RCT (Channick and associates[11] and BREATHE-1[12]), it was found that noninvasive studies (WHO functional class and 6 minute walk test) were better predictors of survival than hemodynamic measurements performed by cardiac catheterization[34]. Functional measurements were not collected during the open-label phase of these trials. If functional measurements are a better predictor of survival than hemodynamic measurements in patients with PPH, it is possible that functional measurements may be better predictors of response to therapy as well.

During bosentan therapy, it is possible that the improvement in functional class (assessed during activity) without a decrease in PASP (assessed at rest) might be due to a drug related increase in oxygen delivery to the exercising muscles. However, a study in rats showed that administration of an endothelin A receptor blocker decreased blood flow to active muscles and increased blood flow to internal organs during exercise[35]. If these results apply to humans, it is unlikely that improvement in functional class can be explained by enhanced delivery of oxygen to skeletal muscles during bosentan therapy.

Our study adds validity to published RCT showing that 3 months' treatment with bosentan improves function during ordinary activities in patients with PAH secondary to SSc. We show it is possible, within limits, to perform comparative analyses on the effect an FDA approved drug in a relatively rare disease using published data. By expanding the clinical experience of bosentan in PAH secondary to SSc, our results have uncovered an effect that was unexpected from the RCT: improved function during ordinary activities during early bosentan therapy. Although bosentan appears beneficial in treating PAH in patients with SSc, continued assessment of its efficacy and safety is needed.

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