ARTHRITIS & RHEUMATISM
Vol. 62, No. 7, July 2010, pp 2101–2108
DOI 10.1002/art.27466

Randomized, Prospective, Placebo-Controlled Trial of Bosentan in Interstitial Lung Disease Secondary to Systemic Sclerosis

J. R. Seibold,[1] C. P. Denton,[2] D. E. Furst,[3] L. Guillevin,[4] L. J. Rubin,[5] A. Wells,[6] M. Matucci Cerinic,[7] G. Riemekasten,[8] P. Emery,[9] H. Chadha-Boreham,[10] P. Charef,[10] S. Roux,[10] and C. M. Black[2]

Objective. **Endothelin is implicated as a participatory pathway in systemic sclerosis (SSc). We tested this hypothesis in a 12-month trial of bosentan, a nonselective endothelin receptor antagonist, as a therapy for SSc-related interstitial lung disease (ILD).**

Method. **Patients with SSc and significant ILD were recruited to this prospective, double-blind, randomized, placebo-controlled, parallel group study. The inclusion criteria were designed to select a cohort enriched for patients with active and progressive disease. Exclusion factors included significant pulmonary hypertension. Patients with a diffusing capacity for carbon monoxide of <80% predicted and a 6-minute walk distance of 150–500 meters or a 6-minute walk distance of ≥500 meters with a decrease in oxygen saturation received bosentan or placebo. The primary efficacy end point was a change in the 6-minute walk distance from baseline up to month 12. Secondary end points included time to death or worsening results of pulmonary function tests (PFTs). The safety and tolerability of bosentan were also assessed.**

Results. **Among the 163 patients, 77 were randomized to receive bosentan, and 86 were randomized to receive placebo. No significant difference between treatment groups was observed for change in the 6-minute walk distance up to month 12. No deaths occurred in this study group. Forced vital capacity and diffusing capacity for carbon monoxide remained stable in the majority of patients in both groups. Significant worsen-**

ClinicalTrials.gov identifier: NCT00070590.

Supported by Actelion Pharmaceuticals Ltd., Allschwil, Switzerland.

[1]J. R. Seibold, MD: University of Connecticut, Farmington; [2]C. P. Denton, MD, PhD, FRCP, C. M. Black, MD, FRCP, DBE: Royal Free and University College Medical School, London, UK; [3]D. E. Furst, MD: David Geffen School of Medicine at the University of California, Los Angeles; [4]L. Guillevin, MD: Hôpital Cochin, Paris, France; [5]L. J. Rubin, MD: University of California, San Diego; [6]A. Wells, MBChB, MD: National Heart and Lung Institute, London, UK; [7]M. Matucci Cerinic, MD: University of Florence, Florence, Italy; [8]G. Riemekasten, MD, PhD: Charité Universitätsmedizin Berlin, Berlin, Germany; [9]P. Emery, MA, MD, FRCP: Chapel Allerton Hospital and University of Leeds, Leeds, UK; [10]H. Chadha-Boreham, PhD, P. Charef, DVM, S. Roux, MD: Actelion Pharmaceuticals, Allschwil, Switzerland.

Dr. Seibold has received consulting fees and/or honoraria from Actelion, FibroGen, Pfizer (more than $10,000 each), Encysive, United Therapeutics, and FibroGen (less than $10,000 each); he has received research funding from Actelion, Pfizer, Encysive, FibroGen, Centocor, Bristol-Myers Squibb, Genzyme, Eli Lilly, Gilead Sciences, and United Therapeutics. Dr. Seibold's spouse is a full-time employee of Actelion. Dr. Denton has received consulting fees and/or honoraria from Actelion, Pfizer, Encysive, BioVitrum, GlaxoSmithKline, and Genzyme (less than $10,000 each); he has received research funding from Actelion, Encysive, Genzyme, and Aspreva. Dr. Furst has received consulting fees, speaking fees, advisory board service honoraria, and/or other honoraria from Abbott, Actelion, Amgen, Bristol-Myers Squibb, Biogen Idec, Centocor, Genentech, Gilead Sciences, GlaxoSmithKline, Merck, Nitec, Novartis, UCB, Wyeth and Xoma (less than $10,000 each); he has received research grants from Abbott, Actelion, Amgen, Bristol-Myers Squibb, Genentech, Gilead Sciences, GlaxoSmithKline, Nitec, Novartis, Roche, UCB, Wyeth, and Xoma. Dr. Guillevin has received consulting fees from Actelion (less than $10,000) and is a member of the Actelion France scientific council. Dr. Rubin has received consulting fees from Actelion (more than $10,000) and has served as the principal investigator for Actelion-funded research. Dr. Wells has received consulting fees and honoraria from Actelion (less than $10,000), has served on an Actelion speakers bureau, and has received research funding from Actelion. Dr. Matucci Cerinic has received a research grant from Actelion. Dr. Riemekasten has received consulting fees and honoraria from Actelion (less than $10,000), has served on an Actelion advisory board, and has received a research grant from Actelion. Dr. Emery has received consulting fees from Actelion (less than $10,000) and has received research funding from Actelion. Dr. Chadha-Boreham owns stock options in Actelion. Drs. Chadha-Boreham, Charef, and Roux are full-time employees of Actelion. Dr. Black has received consulting fees and honoraria from Actelion, Pfizer, Encysive, and Genzyme (less than $10,000 each). Drs. Seibold, Denton, Furst, Guillevin, Rubin, Wells, and Black were members of the steering committee for this study.

Address correspondence and reprint requests to J. R. Seibold, MD, Division of Rheumatology, University of Connecticut Health Center, MARB MC 5353, Room N3020, 263 Farmington Avenue, Farmington, CT 06034. E-mail: jseibold@uchc.edu.

Submitted for publication April 8, 2009; accepted in revised form March 17, 2010.

ing of PFT results occurred in 25.6% of patients receiving placebo and 22.5% of those receiving bosentan (*P* not significant).

Conclusion. **No improvement in exercise capacity was observed in the bosentan-treated group compared with the placebo group, and no significant treatment effect was observed for the other end points. Although many outcome variables were stable, bosentan did not reduce the frequency of clinically important worsening. These data do not support the use of endothelin receptor antagonists as therapy for ILD secondary to SSc.**

Systemic sclerosis (SSc) is a systemic fibrosing connective tissue disease that affects the skin and internal organs and is associated with gastrointestinal, cardiac, and musculoskeletal complications. Pulmonary complications, including interstitial lung disease (ILD) and/or pulmonary arterial hypertension (PAH), are the leading causes of disease-related mortality in patients with SSc (1).

There is a need for effective treatment of ILD secondary to SSc (SSc-ILD). In contrast to idiopathic pulmonary fibrosis (IPF), which is an aggressive and rapidly progressive disease, SSc-ILD progresses more slowly (2). A recent placebo-controlled, double-blind study showed a statistically significant but modest (2.53%) beneficial effect of oral cyclophosphamide on lung function, as measured by forced vital capacity (FVC) (3). This small effect was not persistent at 1 year of followup (4), although the patients who had received cyclophosphamide still demonstrated a benefit in the dyspnea score.

As the understanding of SSc improves, the search for treatment options has focused on the more specific cellular and molecular mediators thought to play a role in disease progression. One of these factors is endothelin 1 (ET-1), which is implicated in the pathophysiology of lung fibrosis. ET-1 is known to induce fibroblast chemotaxis and proliferation (5), promote deposition of collagen (6), decrease collagenase activity, and increase levels of fibronectin. More specifically, ET-1 levels are elevated in the plasma and bronchoalveolar lavage fluid of patients with SSc-ILD (7). This raises the possibility that drugs targeting ET-1 or its receptors may be beneficial in the treatment of SSc-ILD.

Bosentan, a nonselective endothelin receptor antagonist, is a licensed treatment of PAH, including PAH associated with SSc (8,9). It was also shown to reduce the number of new digital ulcers in patients with SSc in 2 randomized, placebo-controlled trials (10,11) and has a favorable safety profile in patients with SSc. The current randomized, placebo-controlled trial was designed to investigate the possibility that treatment with bosentan for 12 months could alter the progression of SSc-ILD and therefore stabilize or improve exercise capacity in patients with SSc-ILD. Disease-related quality of life was also investigated.

PATIENTS AND METHODS

Trial design. The trial was a prospective, double-blind, randomized, placebo-controlled, parallel group study. Following a maximum screening period of 4 weeks, patients were randomized (1:1) to receive bosentan (62.5 mg twice daily, increasing to 125 mg twice daily after 4 weeks) or placebo. The double-blind period was fixed at 12 months, and patients were evaluated at the time of screening and randomization and then at the 3-month, 6-month, and 9-month visits and at month 12 or earlier in case of premature discontinuation (up to month 12).

All patients gave written informed consent to participate in the study, which was approved by the appropriate independent ethics committee or institutional review board and conducted in accordance with the principles of the Declaration of Helsinki and local laws and guidelines for Good Clinical Practice. The investigators who contributed patients to the clinical trial are shown in Appendix A.

Inclusion and exclusion criteria. The study was designed to select patients with active and progressive interstitial pulmonary disease but without significant pulmonary hypertension. Patients were considered for inclusion if they were older than 18 years and had a diagnosis of diffuse or limited SSc and significant ILD (as determined by the presence of reticular or ground glass changes extending at least to the venous confluence on high-resolution computed tomography [HRCT]). Other main inclusion criteria were a diffusing capacity for carbon monoxide (DLCO) of <80% of that predicted and a 6-minute walk distance of 150–500 meters or a distance of ≥500 meters with a decrease in oxygen saturation measured by pulse oximetry (SpO_2) of ≥4%. SSc of <3 years duration with dyspnea on exertion was required or SSc for ≥3 years with signs of active ILD, i.e., fulfillment of 2 of the following 4 criteria within the previous 12 months: 1) worsening dyspnea, 2) worsening results of pulmonary function tests (PFTs; i.e., worsening of FVC ≥7% and/or worsening of DLCO ≥10%), 3) new areas of ILD on HRCT scan (ground glass or reticular abnormalities) in at least 5% of overall lung parenchyma (or 15% of a lobe) and extending to the level of the pulmonary venous confluence or higher, and 4) neutrophilia and/or eosinophilia in bronchoalveolar lavage fluid (i.e., neutrophil differential count ≥5%, eosinophil differential count ≥4%) in the absence of infection.

The main exclusion criteria were the presence of ILD unrelated to SSc; FVC <40% predicted or DLCO <30% predicted; Doppler echocardiographic evidence of pulmonary hypertension, defined as a tricuspid regurgitation peak velocity of >3.2 meters per second (estimated systolic arterial pressure >50 mm Hg); SpO_2 <84% at rest; acute or chronic impairment (other than dyspnea) limiting the ability to comply with study requirements (e.g., intermittent claudication, angina

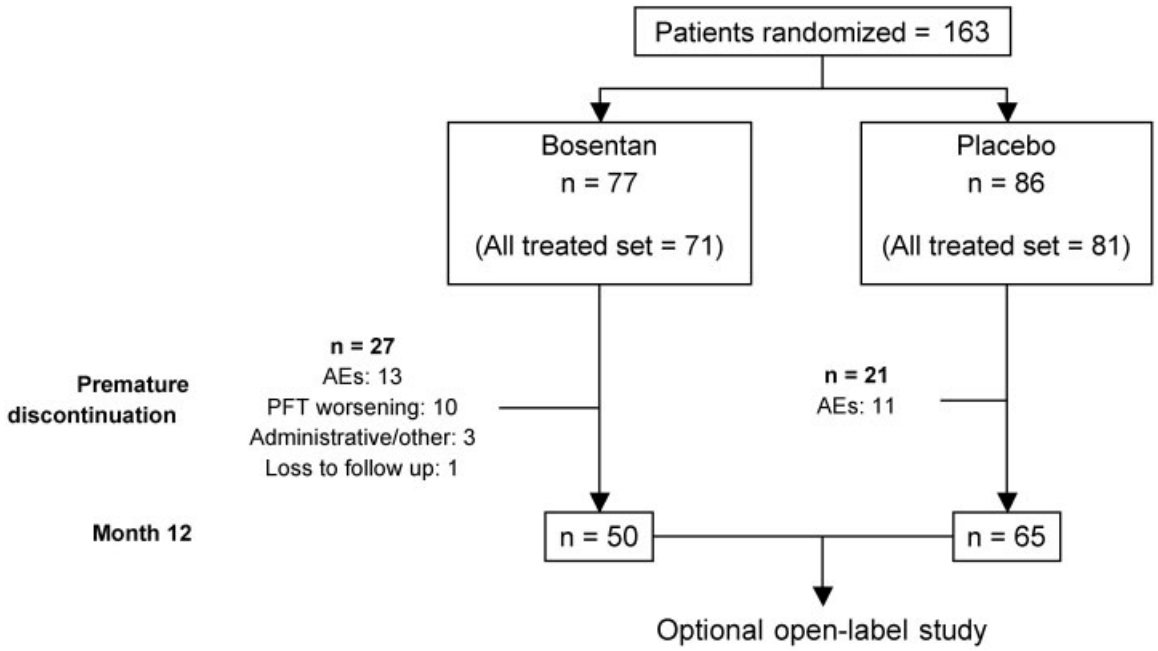

Figure 1. Patient disposition. AEs = adverse events; PFT = pulmonary function test.

pectoris, myositis); alanine aminotransferase/aspartate aminotransferase (ALT/AST) values ≥3-fold the upper limit of normal; severe heart failure; and treatment with high-dose corticosteroids, immunosuppressive agents, cytotoxic drugs, or antifibrotic drugs. However, patients were allowed to receive stable dosages of oral corticosteroids (≤10 mg/day of prednisone or equivalent).

End points. The primary end point for this study was a change in the 6-minute walk distance from baseline up to month 12. Secondary end points included time to death (all causes) or worsening PFT results up to month 12 and improvement or worsening of PFT scores at month 6 and up to month 12. Clinically significant worsening of PFT scores was defined as a decrease from baseline of ≥10% in FVC or ≥15% in DLco, with a decrease in FVC of ≥6%. Improving PFT scores were defined by an increase from baseline of ≥10% in FVC or ≥15% in DLco, with an increase in FVC of ≥6%.

The trial also incorporated several exploratory end points, including a change from baseline to month 6 and up to month 12 in the Borg Dyspnea Index and a change from baseline in FVC, DLco, and SpO_2 (at rest and during exercise). The modified Rodnan skin thickness score (12) and the Medsger disease severity score (13) were investigated, as were the Scleroderma Health Assessment Questionnaire (SHAQ) (14) and its disability index and visual analog scales (VAS) as measures of patient functional status at baseline, month 6, and month 12. Adverse events (AEs) and concomitant medications were recorded on an ongoing basis. Laboratory safety parameters were assessed monthly.

Statistical analysis. The study was designed to detect a mean difference between the treatment groups of 45 meters in the 6-minute walk distance, assuming normal distributions with a common SD of 75 meters. A sample size of 132 patients (66 per treatment group) was required to demonstrate this treatment effect with a 0.05 significance level and 90% power, using the nonparametric Mann-Whitney 2-tailed U test. The nonparametric test was used in the main analysis of the 6-minute walk distance, because the replacement rules of missing data lead to a skewed distribution.

The median placebo-corrected treatment effect and its confidence interval were estimated using the Hodges-Lehmann method (15,16). An approach similar to that of the primary end point analysis was used for secondary and exploratory end points when they were on a continuous scale. The comparison between the 2 treatment groups for the distribution of categorical ordinal data was performed using the

Table 1. Baseline demographics of the all-treated set of patients

Characteristic	Bosentan (n = 71)	Placebo (n = 81)
Female, no. (%)	53 (74.6)	59 (72.8)
Age, years		
Mean ± SD	50.4 ± 12.0	54.4 ± 11.1
Median	52.0	55.0
Range	15.0–74.0	21.0–80.0
Weight, kg		
Mean ± SD	68.3 ± 14.3	72.9 ± 16.8
Median	68.0	71.0
Smoking status		
Current smoker, no. (%)	2 (2.8)	7 (8.6)
Nonsmoker, no. (%)	69 (97.2)	74 (91.4)
Race		
Caucasian/white, no. (%)	55 (77.5)	68 (84.0)
Other, no. (%)	16 (22.5)	13 (16.0)

Table 2. Baseline disease characteristics of the all-treated set of patients*

Characteristic	Bosentan (n = 71)	Placebo (n = 81)
Duration of ILD, years		
Mean ± SD	2.9 ± 3.8	2.6 ± 3.7
Median (95% CI)	1.2 (0.9, 2.1)	1.3 (0.9, 1.8)
Forced vital capacity, % predicted		
Mean ± SD	67.6 ± 15.8	71.7 ± 14.9
Median (95% CI)	67.7 (61.0, 71.1)	70.5 (66.6, 73.7)
DLco, % predicted		
Mean ± SD	45.3 ± 12.5	45.1 ± 12.4
Median (95% CI)	43.2 (39.1, 49.2)	43.3 (40.9, 48.8)
Borg Dyspnea Index		
Mean ± SD	2.9 ± 2.0	2.7 ± 2.0
Median (95% CI)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)
SHAQ DI, overall derived		
Mean ± SD	1.00 ± 0.70	0.89 ± 0.67
Median (95% CI)	0.88 (0.75, 1.13)	0.88 (0.63, 1.00)
SHAQ VAS, overall		
Mean ± SD	1.50 ± 0.79	1.32 ± 0.77
Median (95% CI)	1.46 (1.20, 1.76)	1.37 (1.04, 1.50)
6-minute walk distance, meters		
Mean ± SD	393 ± 84	404 ± 86
Median (95% CI)	395 (370, 425)	408 (394, 429)
MRSS		
Mean ± SD	15.7 ± 10.3	13.8 ± 10.9
Median (95% CI)	12.5 (2, 48)	9.0 (0, 45)
Medsger disease severity score, general		
Mean ± SD	0.56 ± 1.14	0.26 ± 0.54
Median	0.0	0.0

* ILD = interstitial lung disease; 95% CI = 95% confidence interval; DLco = diffusing capacity for carbon monoxide; SHAQ DI = Scleroderma Health Assessment Questionnaire disability index; VAS = visual analog scale; MRSS = Modified Rodnan skin thickness score.

nonparametric Mann-Whitney U test. For dichotomous data, the 95% confidence interval (95% CI) of a proportion was based on the exact binomial distribution (Clopper-Pearson approximation), and the between-treatment comparison of proportions was performed using Fisher's exact test. Comparison between treatments for time-to-event data was performed using the log-rank test.

The all-treated set of patients was used for the main analysis of efficacy end points. This set included randomized patients who had received the study treatment at least once and had at least 1 valid postbaseline value for the primary end point. Sensitivity analyses were performed using the per-protocol set of patients (i.e., those in the all-treated set who did not have major protocol deviations) and the parametric 2-sample *t*-test. Missing postbaseline values for efficacy and quality of life end points were imputed prior to unblinding by carrying forward the last available value. Those patients who were unable to perform the 6-minute walk distance test because of death, worsening PFT results, or an SpO_2 value at rest of ≤80% had their values substituted with the worst case value (0 meters).

RESULTS

Patient characteristics. Of the 163 patients in the study, 77 were randomized to receive bosentan, and 86 were randomized to receive placebo. The all-treated set comprised 152 patients (71 assigned to bosentan and 81 assigned to placebo) (Figure 1). In total, 48 patients discontinued participation in the study prematurely (Figure 1). Treatment groups were generally well matched with regard to demographics (Table 1). However, some imbalance was noted in disease characteristics, especially the Medsger disease severity score (Table 2).

Efficacy. No significant difference was observed between the bosentan and placebo groups with respect to the primary end point, a change in the 6-minute walk distance up to month 12. The mean ± SD change from baseline in the bosentan group was –12 ± 100 meters compared with 9 ± 84 meters in the placebo group. The

Table 3. Summary of treatment effects in the all-treated set of patients*

End point	Bosentan (n = 71)	Placebo (n = 81)	Placebo-controlled treatment effect
Change in 6MWD			
Median (95% CI), meters	+16 (−2, 21)	+13 (3, 26)	−8 (−27, 9)
P			0.404†
Worsening PFT scores			
No. (%) [95% CI]	16 (22.5) [13.5, 34.0]	20 (25.6) [16.5, 36.8]	0.88 (0.50, 1.56)
P			0.705‡
Improved PFT scores			
No. (%) [95% CI]	6 (8.5) [3.2, 17.5]	11 (14.1) [7.3, 23.8]	0.6 (0.23, 1.54)
P			0.313‡

* For worsening or improved pulmonary function test (PFT) score, the treatment effect is shown as the relative risk (95% confidence interval [95% CI]). For change in the 6-minute walk distance (6MWD), the treatment effect is shown as the difference between the 2 groups (95% CI). None of the treatment effects was statistically significant. Three patients in the placebo group could not be analyzed for worsening or improved PFT scores, due to the lack of a PFT value at baseline. 6MWD = 6-minute walk distance.
† By Mann-Whitney U test.
‡ By Fisher's exact test.

mean placebo-corrected treatment effect (mean treatment effect) was –20 meters (95% CI –50, 9 [$P = 0.176$]), and the median placebo-corrected treatment effect (median treatment effect) was –8 meters (95% CI –27, 9 [$P = 0.404$]) (Table 3).

Bosentan had no effect on time to death or worsening PFT scores (hazard ratio 1.10, 95% CI 0.56, 2.14 [$P = 0.783$]). PFT scores remained stable for the majority of patients in both the bosentan (69.0%) and placebo (60.3%) groups, whereas 22.5% and 25.6% of patients in the bosentan and placebo groups, respectively, experienced clinically significant worsening at month 12 (relative risk 0.88, 95% CI 0.50, 1.56 [$P = 0.705$]) (Table 3). No deaths occurred during the controlled phase of this study.

The change in the median FVC as a percentage of predicted values was –1.6% up to month 12 for the bosentan group and –1.2% for the placebo group, representing a median treatment effect of –0.9% of the predicted values (95% CI –3.4, 1.2 [$P = 0.422$]). The median change in DLCO as a percentage of the predicted values was –1.3% up to month 12 in the bosentan group and –0.9% in the placebo group, with a median treatment effect of –0.2% of predicted values (95% CI –2.7, 2.0 [$P = 0.860$]).

The median treatment effects for the disability index of the SHAQ and the SHAQ VAS up to month 12 were 0.08 (95% CI –0.10, 0.25 [$P = 0.226$]) and 0.12 (95% CI –1.0, 0.35 [$P = 0.294$]), respectively. The median treatment effect on the Borg Dyspnea Index was 0.0 up to month 12 (95% CI –0.5, 0.5 [$P = 0.939$]). The median treatment effect on the general Medsger disease severity score up to month 12 was 0.44 (95% CI −0.76, 0.97 [$P = 0.212$]), and the median treatment effect on the total Rodnan skin thickness score up to month 12 was –0.3 (95% CI –1.9, 1.5 [$P = 0.649$]).

Safety. The mean exposure to study treatment was 42.7 weeks (range 1.1–60.1 weeks) for patients receiving bosentan and 46.8 weeks (range 4.0–66.1 weeks) for the placebo group. The overall incidence of AEs was similar for both bosentan-treated (97.4%) and placebo-treated (94.2%) patients. Skin ulcers, worsening PFT scores, fatigue, upper respiratory tract infection, cough, arthralgia, peripheral edema, diarrhea, bronchitis, sinusitis, and anemia were the most commonly reported AEs (each occurring in >10% of patients in the bosentan arm). Elevated liver aminotransferase levels (ALT/AST values >3-fold the upper limit of normal) were observed in 11.3% of bosentan-treated patients and 1.2% of patients receiving placebo.

The most common AE leading to discontinuation of treatment was worsening PFT results, which occurred in 15.8% of bosentan-treated patients and 11.6% of those receiving placebo. Pulmonary hypertension developed in 5 patients (5.8%) in the placebo group compared with 1 patient (1.3%) in the bosentan group. The proportion of patients with at least 1 serious adverse event, including those considered unrelated to treatment, was 21.1% in the bosentan group and 18.6% in the placebo group.

One hundred patients with a mean ± SD drug exposure of 29.5 ± 15.8 weeks entered the open-label followup. During this period, 1 patient receiving bosentan died of cardiac arrest, and 1 patient died of complications of diverticular disease occurring 60 days after discontinuation of bosentan. The open-label followup phase had been designed to permit bosentan treatment during the interval from study completion to preliminary analysis of efficacy from the blinded phase of treatment. No analysis of efficacy measures was performed.

DISCUSSION

The majority of pulmonary complications associated with SSc are attributable to pulmonary hypertension or ILD (1). Although bosentan has been studied in PAH secondary to SSc, no systematic investigations have been carried out in SSc-ILD. This trial represents an important study in the treatment of this patient population; it is the first randomized clinical trial investigating treatment with endothelin antagonists in SSc-ILD and is one of the largest trials in this disease area to date.

A relatively slow rate of progression of SSc-ILD was confirmed in this study. Little change in DLCO and FVC was seen in patients with SSc-ILD. Overall, FVC scores were reduced by <2%, and PFT scores up to month 12 remained stable in the majority of patients across both groups. This contrasts with IPF, for example, in which DLCO has been shown to decrease by >7% in ~13 months (17).

However, some patients enrolled into the study had clearly more progressive disease, and PFT values worsened at a clinically meaningful level in ~25% of patients in this trial. This is consistent with the frequency of decline over a 1-year period described in the literature (2) and confirms that the selected inclusion criteria did in fact incorporate a cohort enriched for the risk of worsening. This is in contrast to the US cyclophosphamide study cohort (3), in which only 19 (13.1%) of 145 patients lost at least 10% of FVC during 1 year of treatment. Recent data have suggested that the progressivity of ILD in SSc can be predicted by the extent of

disease as measured by HRCT, and that the contribution of ground glass changes offers no predictive value (18,19). The results of the cyclophosphamide study suggested a stronger treatment effect based on the level of HRCT-defined parenchymal involvement, implying that disease severity has a strong influence on the clinical and physiologic course (3). The present trial required HRCT evidence of either reticular or ground glass change to the venous confluence, whereas the cyclophosphamide trial protocol required only evidence of any ground glass changes. Thus, the present study reflected a cohort enriched for the progressivity of ILD, and the lack of differences between bosentan and placebo in forestalling the event of major deterioration provides strong evidence against an important role for ET-1 in disease progression.

The overall slow disease progression may also have contributed to the lack of a significant response in exercise tests and quality of life measurements. The selected tests and measurements for this trial may not be suitable to detect a treatment effect on mechanistic factors involved in fibrosis progression. In contrast, other studies of corticosteroids and/or immunosuppressants have shown limited effects on FVC and DLCO in patients with SSc-ILD (3,20–22).

No significant treatment effect was observed for the 6-minute walk distance, which was the primary end point of this study. However, this finding should be interpreted with caution. The 6-minute walk distance end point has been widely used and has been validated as an indicator of disease progression in PAH (9) and chronic heart failure (23). It has also been used in one ILD study (24). However, a recent report on the analysis of the baseline 6-minute walk distance in patients with SSc-ILD indicated that the 6-minute walk distance may not be the most appropriate measure of treatment effect in this specific patient population (25). Whereas patients with SSc-ILD performed the test with a high level of consistency, no relationship was observed between the 6-minute walk distance and either FVC or DLCO. This lack of correlation suggests that the reduced exercise capacity in patients with SSc-ILD may be the result of SSc affecting multiple organ systems. This idea is supported by a recent study detailing the musculoskeletal complications of SSc and suggesting they may be rate-limiting on the walking capacity of this patient population (26).

Exercise capacity is influenced by cardiac, pulmonary, and locomotor systems as well as patient motivation. It is not surprising that the effect of therapies directed at one component of exercise may be blunted by the effects of other factors. As such, the validity of the 6-minute walk distance as an end point in patients with stable ILD is questionable. Furthermore, as was also reported in recent studies of IPF, the 6-minute walk distance exhibited major variability in both directions over the period of study (27,28), as shown by an SD of ~85 meters for changes between the initial and final tests. These observations suggest that factors other than the severity of ILD are responsible for large changes in the 6-minute walk distance, possibly including deconditioning, variable levels of fatigue, and, in SSc, extrapulmonary disease features. There may have been some degree of imbalance in favor of patients in the placebo group, in whom disease may have been less severe. This possibility was supported by the general Medsger disease severity score (see Table 1), which also indicated that patients randomized to receive placebo may have had less severe disease. In any case, the present data do not support use of the 6-minute walk distance as an outcome measure in future studies of ILD secondary to SSc.

The present data are interesting in the context of a similar study of bosentan for the treatment of IPD (27). Although that study also failed to show improvement in the 6-minute walk distance, there were trends in favor of bosentan in delayed time to death or disease progression and improvement in measures of quality of life.

The potential benefit of endothelin receptor antagonists in SSc-ILD is particularly relevant in this disease, because these agents have measurable benefits in patients with PAH secondary to SSc (9,29). However, available data suggest that patients with pulmonary hypertension associated with ILD have a 5-fold increased risk of death compared with patients with PAH in spite of the use of endothelin receptor antagonists (30).

Overall, bosentan was safe and well tolerated in this study. The incidences of peripheral edema, anemia, and elevated liver aminotransferase levels in bosentan-treated patients were similar to those reported in previous studies of bosentan (8,9). The safety profile was consistent with that observed for bosentan in patients with PAH and patients with SSc who have digital ulcerations (10,11) and is also comparable with those reported in other recent studies in the treatment of IPF (27,31).

In conclusion, treatment with the nonselective endothelin receptor antagonist bosentan did not show any effect on exercise capacity in the target patient population in this trial. There was also no effect on FVC,

DL_{CO}, patient functional status, or the frequency of clinically meaningful deterioration in pulmonary function.

ACKNOWLEDGMENTS

We thank Tom Newton, who is associated with Elements Communications, for providing medical writing assistance supported by Actelion Pharmaceuticals Ltd. We would also like to acknowledge the contribution of Dr. J. Korn, who was a member of the clinical trial Steering Committee and played an important role in the project, but who, sadly, died before this manuscript could be finalized.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Seibold had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Seibold, Denton, Furst, Guillevin, Rubin, Chadha-Boreham, Charef, Roux, Black.

Acquisition of data. Seibold, Furst, Guillevin, Rubin, Riemekasten, Emery, Chadha-Boreham, Roux.

Analysis and interpretation of data. Seibold, Denton, Furst, Rubin, Wells, Matucci Cerinic, Chadha-Boreham, Charef, Roux, Black.

ROLE OF THE STUDY SPONSOR

The study sponsor was involved in the study design and in the collection, analysis, and interpretation of data. All authors had full access to the study data and had the final responsibility for the decision to submit the article for publication. Publication of this article was not contingent on approval by the study sponsor.

REFERENCES

1. Steen VD, Medsger TA Jr. Changes in causes of death in systemic sclerosis, 1972–2002. Ann Rheum Dis 2007;66:940–4.
2. Wells AU, Cullinan P, Hansell DM, Rubens MB, Black CM, Newman-Taylor AJ, et al. Fibrosing alveolitis associated with systemic sclerosis has a better prognosis than lone cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 1994;149:1583–90.
3. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al, for the Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655–66.
4. Tashkin DP, Elashoff R, Clements PJ, Roth MD, Furst DE, Silver R, et al. Effects of a one-year treatment with cyclophosphamide on outcomes at two years in scleroderma lung disease. Am J Respir Crit Care Med 2007;176:1026–34.
5. Peacock AJ, Dawes KE, Shock A, Gray AJ, Reeves JT, Laurent GJ. Endothelin-1 and endothelin-3 induce chemotaxis and replication of pulmonary artery fibroblasts. Am J Respir Cell Mol Biol 1992;7:492–9.
6. Shi-Wen X, Denton CP, Dashwood MR, Holmes AM, Bou-Gharios G, Pearson JD, et al. Fibroblast matrix gene expression and connective tissue remodeling: role of endothelin-1. J Invest Dermatol 2001;116:417–25.
7. Reichenberger F, Schauer J, Kellner K, Sack U, Stiehl P, Winkler J. Different expression of endothelin in the bronchoalveolar lavage in patients with pulmonary diseases. Lung 2001;179:163–74.
8. Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet 2001;358:1119–23.
9. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896–903.
10. Korn JH, Mayes M, Matucci Cerinic M, Rainisio M, Pope J, Hachulla E, et al, for the RAPIDS-1 Study Group. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. Arthritis Rheum 2004;50:3985–93.
11. Seibold JR, Denton CP, Furst DE, Matucci Cerinic M, Mayes MD, Morganti A, et al. for the RAPIDS-2 Investigators. Bosentan reduces the number of new digital ulcers in patients with systemic sclerosis [abstract]. Ann Rheum Dis 2006;65:S90.
12. Clements P, Lachenbruch P, Siebold J, White B, Weiner S, Martin R, et al. Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. J Rheumatol 1995;22:1281–5.
13. Medsger TA Jr, Silman AJ, Steen VD, Black CM, Akesson A, Bacon PA, et al. A disease severity scale for systemic sclerosis: development and testing. J Rheumatol 1999;26:2159–67.
14. Steen VD, Medsger TA Jr. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum 1997;40:1984–91.
15. Hodges JL, Lehmann EL. Estimates of location based on rank tests. Ann Math Stat 1963;34:598–611.
16. Hettmansperger TP. Statistical inference based on ranks. New York: John Wiley & Sons; 1984.
17. Battista G, Zompatori M, Fasano L, Pacilli A, Basile B. Progressive worsening of idiopathic pulmonary fibrosis: high resolution computed tomography (HRCT) study with functional correlations. Radiol Med (Torino) 2003;105:2–11.
18. Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med 2008;177:1248–54.
19. Strange C, Seibold JR. Scleroderma lung disease: if you don't know where you are going, any road will take you there [editorial]. Am J Respir Crit Care Med 2008;177:1178–9.
20. Pakas I, Ioannidis JP, Malagari K, Skopouli FN, Moutsopoulos HM, Vlachoyiannopoulos PG. Cyclophosphamide with low or high dose prednisolone for systemic sclerosis lung disease. J Rheumatol 2002;29:298–304.
21. Beretta L, Caronni M, Raimondi M, Ponti A, Viscuso T, Origgi L, et al. Oral cyclophosphamide improves pulmonary function in scleroderma patients with fibrosing alveolitis: experience in one centre. Clin Rheumatol 2007;26:168–72.
22. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum 2006;54:3962–70.
23. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J 1985;132:919–23.
24. Chetta A, Aiello M, Foresi A, Marangio E, D'Ippolito R, Castagnaro A, et al. Relationship between outcome measures of six-minute walk test and baseline lung function in patients with interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis 2001;18:170–5.

25. Buch MH, Denton CP, Furst DE, Guillevin L, Rubin LJ, Wells AU, et al. Submaximal exercise testing in the assessment of interstitial lung disease secondary to systemic sclerosis: reproducibility and correlations of the 6-min walk test. Ann Rheum Dis 2007;66:169–73.
26. Mimura Y, Ihn H, Jinnin M, Asano Y, Yamane K, Tamaki K. Clinical and laboratory features of scleroderma patients developing skeletal myopathy. Clin Rheumatol 2005;24:99–102.
27. King TE Jr, Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, et al. Build-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2008;177:75–81.
28. Raghu R, Brown KK, Costabel U, Cottin V, du Bois RM, Lasky JA, et al. Treatment of idiopathic pulmonary fibrosis with etanercept: an exploratory, placebo-controlled trial. Am J Respir Crit Care Med 2008;178:948–55.
29. Girgis RE, Frost AE, Hill NS, Horn EM, Langleben D, McLaughlin VV, et al. Selective endothelin A antagonism with sitaxsentan for pulmonary arterial hypertension associated with connective tissue disease. Ann Rheum Dis 2007;66:1467–72.
30. Mathai SC, Hummers LK, Champion HC, Wigley FM, Zaiman A, Hassoun PM, et al. Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases: impact of interstitial lung disease. Arthritis Rheum 2009;60:569–77.
31. Gunther A, Enke B, Markart P, Hammerl P, Morr H, Behr J, et al. Safety and tolerability of bosentan in idiopathic pulmonary fibrosis: open label study. Eur Respir J 2007;29:713–9.

APPENDIX A: INVESTIGATORS WHO CONTRIBUTED PATIENTS TO THE CLINICAL TRIAL

Investigators who contributed patients to the clinical trial are as follows: Eric Rich (Centre Hospitalier, Montreal, Canada), Jean Cabane (Hopital St. Antoine, Paris, France), Patrick Carpentier (CHU de Grenoble, Grenoble, France), Eric Hachulla (CHRU Claude Huriez, Lille, France), Mordechai Kramer (Rabin Medical Center, Petach Tikva, Israel), Raffaella Scorza (Ospedale Maggiore, Milano, Italy), Silvano Todesco (Policlinico Unversitario, Padova, Italy), Frank H. J. van den Hoogen (Sint Maartenskliniek, Nijmegen, The Netherlands), Anita Akesson (Lund University, Lund, Sweden), Pius Bruhlmann (UniversitatsSpital Zurich, Zurich, Switzerland), Soumya Chatterjee (Wayne State University, Detroit, MI), David Collier (Denver Health Medical Center, Denver, CO), Nora Sandorfi (Thomas Jefferson University, Philadelphia, PA), Maureen D. Mayes (University of Texas at Houston, Houston, TX), Jerry Molitor (Virginia Mason Medical Center, Seattle, WA), Ganesh Raghu (University of Washington, Seattle, WA), Vivien M. Hsu (UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ), Lee Shapiro (The Center for Rheumatology, Albany, NY), Richard M. Silver (Medical University of South Carolina, Charleston, SC), Virginia D. Steen (Georgetown University, Washington, DC), John Varga (University of Illinois at Chicago, Chicago, IL), Mariana Kaplan (University of Michigan, Ann Arbor, MI).