Bosentan versus placebo in interstitial lung disease secondary to systemic sclerosis: The BUILD 2 study

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Abstract

Rationale: Bosentan is a dual endothelin (ET-1) receptor antagonist approved for pulmonary hypertension (PH) in SSc. The profibrotic effects of ET-1 are relevant in interstitial lung disease (ILD) in SSc. ET-1 levels are increased and ET-B receptors are overexpressed in involved lung. This study was designed to test the potential effects of bosentan therapy on clinical outcomes in patients with SSc-ILD.

Methods: This double-blind, randomized, placebo-controlled study evaluated exercise capacity by 6 min walk test (6MW). A sample of 132 patients permitted detection of a 45 m difference in the 6MW between groups after 1 year follow up (α 0.05, β 0.10). Other outcomes included time to death or worsening PFTs, dyspnea indices, quality of life, measures of SSc and safety and tolerability. Inclusion criteria required significant ILD by HRCT, DLco < 80%, 6MW ≥ 150m and ≤ 500m, and SSc < 3 yrs duration with dyspnea OR SSc > 3 yrs with worsening dyspnea and PFTs, new ILD by HRCT and/or abnormal lavage. Main exclusion criteria were FVC < 40% or DLco < 30% predicted or Doppler echo evidence of PH.

Results: 163 patients, mainly female (75%) with a mean age of 52 yrs (range 15–80) were enrolled in 29 centers with an average of 5.4 and 2.8 yrs since diagnosis of SSc and ILD, respectively. Mean baseline values were 6MW 398 m ± 84.3 m; Borg dyspnea index 2.8; and FVC 70.0%, DLco 45.7% predicted. Trial conduct is complete and results are expected in January 2006.

Conclusions: This trial will offer important information regarding the clinical usefulness of bosentan in SSc-ILD.

Introduction

- The process of fibrosis has not been addressed by current therapies
- In contrast to idiopathic pulmonary fibrosis (IPF), which is aggressive and progresses rapidly, ILD secondary to SSc (SSc-ILD) progresses more slowly[1]
- Pulmonary complications, including interstitial fibrosis and pulmonary vasculopathy are now the most common cause of death in patients with SSc
- Endothelin (ET-1) is implicated in the pathogenesis of SSc through a variety of mechanisms:
  - ET-1 induces fibroblast chemotaxis and proliferation
  - ET-1 promotes deposition of collagen, reduces collagenase activity and increases fibronectin
  - ET-1 levels are increased in both plasma and bronchoalveolar lavage (BAL) fluid in SSc-ILD[2]
  - ET-B receptors are over-expressed in involved tissues, including lung and skin
- The dual ET receptor antagonist, bosentan, is an established treatment for pulmonary arterial hypertension (PAH) associated with SSc, improving both exercise capacity[3] and long-term outcomes.[4] In addition, bosentan prevents the development of new digital ulcers (DU) secondary to SSc,[5] further supporting an important role for ET in the maintenance of vascular integrity and function

Study design and methods

- BUILD 2 was designed as part of a program to assess the effects of bosentan in IPF (BUILD 1) and SSc-ILD (BUILD 2)
- BUILD 2 was a multicenter, double-blind, randomized, placebo controlled study in patients with SSc-ILD and was designed to select patients with progressive disease. Patients were eligible for inclusion in the study according to criteria presented in Table 1. Patients were excluded if their FVC was < 40% or DLco was < 30% predicted, if they had ILD due to conditions other than SSc or if they had Doppler evidence of pulmonary hypertension
- The primary efficacy endpoint was change from baseline in 6 min walk test (6MW) at month 12
- Secondary endpoints included time to death or worsening in pulmonary function tests (PFTs), defined as a decrease from baseline ≥ 10% in FVC or a decrease from baseline ≥ 15% in DLco AND ≥ 6% in FVC. Improvement in PFTs was defined as an increase from baseline ≥ 10% in FVC or an increase from baseline ≥ 15% in DLco AND ≥ 6% in FVC
- A total of 132 patients were required to permit detection of a 45 m difference in the 6MW between groups at month 12 (SD = 75 m, two-sided α 0.05, β 0.10).

***Table 1** Inclusion criteria for BUILD 2*

Patients aged > 18 years
Diffuse or limited SSc
Significant ILD on HRCT scan
DLco < 80% predicted
6MW ≥ 150 m and < 500 m or ≥ 500 m with marked exercise desaturation
History of: SSc of < 3 years and dyspnea on exertion OR SSc > 3 years with signs of active ILD, i.e. the presence of **TWO** of the following (within the previous 12 months): – worsening FVC > 7% and/or in DLco > 10% – new area(s) of ILD on HRCT scan (ground glass or reticular) in at least 5% of lung parenchyma and extending to the level of the pulmonary venous confluence or higher – worsening of dyspnea – alveolitis on BAL (defined as a differential count in neutrophils ≥ 5% or in eosinophils ≥ 4%)

Results

- A total of 163 patients were randomised to receive bosentan (n = 77) or placebo (n = 86; Figure 1). The all-treated set comprised 152 patients (bosentan, n = 71; placebo, n = 81). Patient baseline demographics and characteristics are presented in Table 2
- At the 12-month evaluation point there was no significant difference in change from baseline 6MW between the two groups (Table 3). Changes in % predicted FVC and DLco were also similar (Figure 2)
- There was no treatment effect with respect to PFTs, which worsened in 25.6% and 22.5% and improved in 14.1% and 8.5% of patients in the placebo and bosentan groups, respectively
- No significant differences were observed in dyspnea, oximetry or modified Rodnan skin scores
- Overall, bosentan was well tolerated and the safety profile, including elevated LFTs, was consistent with earlier randomized clinical trials of bosentan

***Figure 1.** Study design and patient randomization*

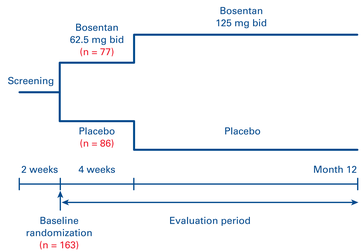


***Table 2.** Baseline patient demographics and characteristics in the all treated population*

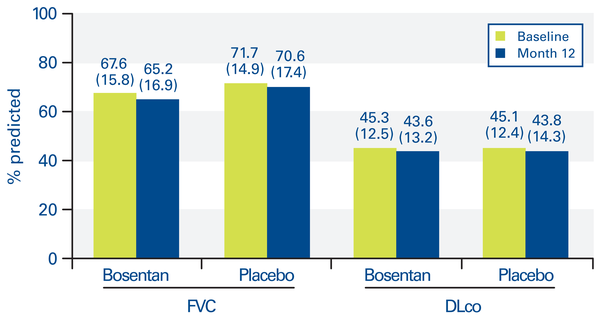
	Placebo (n = 81)	Bosentan (n = 71)
Gender (% female)	72.8	74.6
Ethnicity (%)		
Caucasian/white	84.0	77.5
Black	9.9	9.9
Other	6.2	12.6
Current smokers (%)	8.6	2.8
Mean age (years) (SD)	54.4 (11.1)	50.4 (12.0)
Mean weight (kg) (SD)	72.9 (16.8)	68.3 (14.3)
Mean no. DUs (SD)	0.23 (0.83)	0.72 (1.6)
Medsger Severity Score; General (SD)	0.26 (0.54)	0.56 (1.14)
Duration of SSc-ILD* (years) (SD)	2.5 (3.6)	3.0 (4.2)

*These data are for the safety set (n = 162) and are up to the randomization date

***Table 3.** 6MW – change from baseline to end of study*

	Placebo (n = 81)	Bosentan (n = 71)
Baseline Mean (SD)	404 m (86)	393 m (84)
End of study (month 12) Mean (SD)	413 m (123)	381 m (112)
Change from baseline Mean (SD) Median (95% CL)	+9 m (84) +13 m (3, 26)	-12 m (100) +16 m (-2, 21)
Treatment effect Mean (SE) Median (95% CL) P value (Mann-Whitney U-test)		-20 m (15) -8 m (-27, 9) NS

***Figure 2.** Key secondary outcomes – % predicted FVC and DLco at baseline and month 12 (SD)*



Conclusions

- There were no statisically significant differences in primary outcome (6MW) or key secondary outcomes (FVC, DLco, categorical changes in PFTs) between bosentan- and placebo-treated patients
- Any one or both of the following factors may have affected this result:
  - use of 6MW may not be appropriate to assess treatment effects in parenchymal lung disease
  - this study failed to select a population with expected level of disease progression as shown by the stability of PFTs in both groups. Trials in SSc-ILD may require a longer period of observation
- Bosentan is well tolerated in subjects with SSc-ILD

References

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