

# Sildenafil And Atorvastatin Added To Bosentan As Therapy For Pulmonary Hypertension

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## Citation

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## Abstract

**Background:** The efficacy and safety of combination therapies for pulmonary hypertension are unknown.

**Methods:** Patients with symptomatic pulmonary hypertension on 125 mg bosentan 2 times daily were randomized by a 2:1 randomization to sildenafil 50 mg 3 times daily and atorvastatin 20 mg daily versus placebo. The primary endpoint in the trial was treadmill time.

**Results:** 22 patients age  $47.4 \pm 14$  years were enrolled. Fifteen patients were randomized to receive active therapy, 7 to placebo. After 12 weeks the treadmill time increased from  $459 \pm 152$  to  $623 \pm 230$  seconds (36%),  $p = 0.004$  in those receiving active therapy, largely attributable to the effects in 5 patients. There was an increase in treadmill time from  $279 \pm 127$  to  $359 \pm 141$  seconds (28%),  $p = 0.06$  in the placebo group.

**Conclusions:** Although the addition of sildenafil and atorvastatin to bosentan produced beneficial effects in some patients with pulmonary hypertension, the imbalance in baseline treadmill times, and the small sample size makes it difficult to conclude that the combination is favorable.

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## INTRODUCTION

Pulmonary arterial hypertension (PAH) is a disease that previously had few treatment options. Patients now have choices of oral, inhaled, subcutaneous and intravenous treatments. The chronic care of PAH remains challenging, and the morbidity and mortality remain high. The available

medications work differently at the cellular level, and it is unknown if combining therapies is safe or if it will improve outcomes.

Bosentan, an oral endothelin receptor antagonist, improves exercise tolerance in patients with PAH.<sup>1,2</sup> As patients with PAH often have elevated endothelin levels,<sup>3</sup> it is presumed that blocking receptor stimulation decreases the inflammatory and vasoconstrictive process. Sildenafil is an oral phosphodiesterase 5 (PDE5) inhibitor developed for erectile dysfunction. However, several studies have shown its efficacy in blocking the PDE5 enzyme in the pulmonary circulation resulting in elevation of cyclic GMP levels and a lowering of pulmonary artery pressure.<sup>4,5</sup> Atorvastatin is a HMGCoA reductase inhibitor drug that effectively lowers serum cholesterol levels. Recently several studies suggest that the statin drug class improve endothelial cell function and inhibit inflammation,<sup>6,7,8</sup> and in an open label observational study, improved exercise capacity in pulmonary hypertension patients.<sup>9</sup>

This trial was initiated at a time when bosentan was the only

commercially available oral therapy. Both sildenafil and atorvastatin have favorable records of chronic safety, and offer the possibility of having a beneficial effect in patients with PAH via different mechanisms. Since the action of sildenafil is dependant on an endothelial cell response, and atorvastatin improves endothelial cell function, we reasoned that the combination was rational.

## METHODS

The study was approved by the Institutional Review Boards at Rush University Medical Center and at The University of Chicago Hospitals, and all subjects gave written informed consent for their participation. This was a single center double-blind randomized placebo controlled trial testing the combination of atorvastatin 20 mg daily, and sildenafil 50 mg 3 times a day in subjects with PAH on chronic bosentan therapy. By design, this study was double-blinded, placebo controlled with a 2:1 randomization scheme, combining use of sildenafil with atorvastatin as active therapy compared to placebo. The subjects were treated for a period of 12 weeks.

The primary end point in this study was a change in exercise time between baseline and 12 weeks determined by a Naughton-Balke protocol, the standard exercise assessment for pulmonary hypertension by our institution.<sup>10</sup> Secondary endpoints were a change in symptoms as assessed by the dyspnea fatigue score (DFS), and change in WHO Functional Class (FC) from baseline to 12 weeks.

Subjects with symptomatic PAH who were on therapy with bosentan for ≥3 months time were eligible for the trial. Subjects were medically stable for the past 30 days, had a recent assessment of the severity of their pulmonary hypertension which included a treadmill exercise test showing an exercise time of ≥2 minutes (2 METS) and < 12 minutes (8 METS) and a pulmonary vascular resistance of greater than 5 units documented on a right heart catheterization. Only patients 18 years or older were eligible.

Safety was assessed at repeat office visits, and by laboratory testing that included a CBC, chemistry profile, and lipid profile. Compliance was assessed by pill counts at the 6 and 12 week visits. Following the study completion, patients were given the option to start or continue on open label sildenafil, while the atorvastatin was discontinued in all subjects. Repeat outpatient assessments were done at 24 weeks.

Descriptive analyses of all variables were examined. Data are presented as percentages for categorical variables or

mean values ± SD for continuous variables. Comparisons of characteristics between those in the treatment group compared to placebo group were performed using the Mann-Whitney two-sample statistic for continuous variables or the  $\chi^2$  test for categorical variables. The change in exercise treadmill test characteristic within each individual and within each treatment group was performed using the paired Wilcoxon signed-rank test. A p-value of ≤ 0.05 level was taken as statistically significant. Patients whose exercise time increased by >200 seconds were analyzed separately as this was deemed a clinically significant improvement (correlating with an increase in exercise of >2 METS). Statistical analysis was performed using STATA 8.0 (College Station, Texas). The study was funded by a grant by Pfizer Inc. The sample size was limited by the parameters of the grant.

## RESULTS

Twenty-two subjects (18 female, 4 male) with PAH (WHO Category I) were enrolled into the trial. Fifteen patients were randomized to receive the investigational drug combination, 7 to placebo. The mean age was  $47.4 \pm 14.6$  years. Eleven subjects had primary pulmonary hypertension (PPH), 6 had connective tissue disease, and 5 had surgically repaired congenital heart disease. At baseline their Functional Class was  $2.8 \pm 0.4$ . The mean exercise time on treadmill was  $409.2 \pm 156.4$  seconds and the mean pulmonary vascular resistance was  $13.3 \pm 5.8$  units. (Table 1: Baseline Demographics)

**Figure 1**

Table 1: Baseline characteristics of study participants

Characteristic	N=22
Age (years)	$47.4 \pm 15$
Female/Male (%)	82%/18%
Mean Pulmonary Artery Pressure (mm-Hg)	$56 \pm 12$
Pulmonary Vascular Resistance (Wood units)	$13.3 \pm 6$
Cardiac Output (L/min)	$4.1 \pm 1.1$
Cardiac Index (L/min/m <sup>2</sup> )	$2.3 \pm 0.6$
Right Atrial Pressure (mm-Hg)	$9 \pm 6$
Treadmill time (seconds)	$409 \pm 156$
Dyspnea Fatigue Scale	$7 \pm 1.5$
World Health Organization Functional Class	$2.8 \pm 0.4$
Aspartate Aminotransferase (U/L)	$28 \pm 10$
Alanine Aminotransferase (U/L)	$32 \pm 17$
Bilirubin (mg/dl)	$0.6 \pm 0.4$
Alkaline Phosphatase (U/L)	$85 \pm 23$
Cholesterol (mg/dL)	$160 \pm 42$

Three patients did not complete the trial. Two patients randomized to active therapy dropped from the study prematurely secondary to side effects which were felt to be

related to the medication, (headache and lightheadedness). One patient, on placebo, was withdrawn from the trial by the investigators because of lack of compliance with study medication.

There were no significant differences in baseline demographics between active and placebo groups except for baseline treadmill time ( $p=0.02$ ). (Table 2) After 12 weeks of therapy the treadmill time increased from  $459\pm152$  to  $623\pm230$  seconds (36%)  $p=0.004$  in the 13 patients receiving active therapy, and also increased, but not significantly, from  $279\pm127$  to  $359\pm141$  seconds (29%)  $p=0.08$  in the 6 patients receiving placebo (Figure 1). There was no significant change in functional class in either the active group (2.8 to 2.4,  $p=0.1$ ), or the placebo group (2.8 to 3.0,  $p=0.3$ ). The dyspnea fatigue score, however, increased from 7.1 to 8.8

( $p=0.01$ ) in the active group but was not significantly changed from 6.6 to 7.0 ( $p=0.5$ ) in the placebo group.

**Figure 2**

Table 2: Baseline Characteristics by Treatment Category

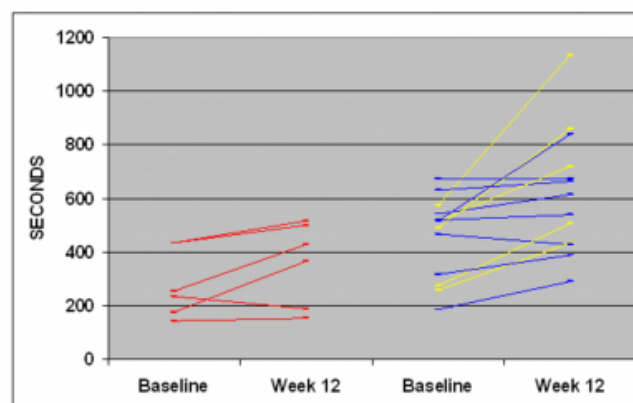
	Drug (N=13)	Placebo (N=6)	P-value
Age (years)	46 $\pm$ 4	52 $\pm$ 6	0.57
Female/Male (%)	77%/13%	100%/0	0.20
Mean Pulmonary Artery Pressure (mmHg)	54 $\pm$ 4	62 $\pm$ 4	0.14
Pulmonary Vascular Resistance (Wood units)	14 $\pm$ 2	15 $\pm$ 2	0.67
Cardiac Output (L/min)	4.2 $\pm$ 0.4	3.8 $\pm$ 0.3	0.67
Cardiac Index(L/min/m <sup>2</sup> )	2.3 $\pm$ 0.2	2.1 $\pm$ 0.2	0.54
Mean Right Atrial Pressure (mmHg)	8 $\pm$ 1	9.5 $\pm$ 2	0.36
Dypnea Fatigue Scale	7.1 $\pm$ 0.4	6.5 $\pm$ 0.8	0.36
World Health Organization Functional Class	2.8 $\pm$ 0.1	2.8 $\pm$ 0.2	0.76
Treadmill Time (seconds)	459 $\pm$ 152	279 $\pm$ 127	0.02

**Figure 3**

Figure 1: The change in treadmill times between baseline and 12 weeks of treatment is shown in the patients randomized to active therapy (left) vs. those randomized to placebo (right). Within the group randomized to active therapy, a subset of patients had improvements of >200 seconds, vs. none of the patients receiving placebo.

PLACEBO THERAPY- Red

ACTIVE THERAPY- Yellow= Subjects with >200 second increase in treadmill time  
Blue= Subjects with <200 second increase in treadmill time



Within the group treated with active therapy, 5 of the patients had an increase in exercise time of greater than 200 seconds compared with none of the patients who were randomized to placebo. (Figure 1) When these patients were analyzed separately with respect to their baseline characteristics, there were no distinguishing features about them compared to the group as a whole.

Side effects in subjects assigned to active therapy included: headache (6), lightheaded (2), edema (6), cough (1), flushing (3), chest pain/angina (2), dry eyes (3), nasal congestion (3), diarrhea (1), and shortness of breath (1). One subject had a syncopal event that was not reported until follow-up visit and did not require hospitalization. Side effects in subjects assigned to placebo therapy included: headache (2), lightheaded (2), edema (1), cough (2), nausea (1), and dry eyes (1). Headaches occurred mostly within first couple weeks and then dissipated by week 6. There were no serious adverse events during the 12 week study. There was no evidence of liver toxicity with the combination therapy (bosentan + sildenafil + atorvastatin) in any patient.

Although not part of the original protocol, following the 12 week assessment the trial was unblinded and subjects were offered open label sildenafil, with recommendations to add or continue the therapy based on their symptomatic response, and a return assessment at 24 weeks for functional class determination and treadmill testing. We chose to

discontinue the atorvastatin to see if it would have any obvious impact on the other therapies. 10 of the subjects randomized to active therapy continued on the sildenafil with BOS without the atorvastatin, and 4 subjects in the placebo group. No patient randomized to active therapy during the 12 week trial reported any worsening in symptoms or functional class after discontinuation of atorvastatin at 24 weeks.

After 24 weeks, all 14 subjects had WHO Class assessment. Treadmill times in the 10 subjects on 24 week of bosentan and sildenafil therapy tended to further improve from

591 ± 253 seconds to 705 ± 251 seconds with persistence of functional class (2.4 ± 0.5 to 2.4 ± 0.5). In the 4 subjects from the placebo group who were given sildenafil along with their bosentan from weeks 12 to 24, there was no significant change in treadmill time 363 ± 149 to 372 ± 145 seconds or in WHO class 3.0 ± 0 to 2.8 ± 0.4.

### **DISCUSSION**

Bosentan is a non-selective endothelin receptor blocker that has been FDA approved based on improvement in 6 minute walk distance in randomized clinical trials in patients with pulmonary arterial hypertension.<sup>11</sup> However, approximately 60% of patients receiving bosentan for PAH remained in Functional Class III or IV.<sup>11</sup> Sildenafil is a PDE5 inhibitor that has been demonstrated to be a potent and selective pulmonary vasodilator. Recently it has been shown to have similar efficacy in PAH as other therapies based on 6 minute walk testing.<sup>12</sup>

HMG-COA reductase inhibitors, statins, attenuate vascular smooth muscle growth and neointimal proliferation. In further support, simvastatin exerted potent effects on vascular wall proliferation and inflammation in pulmonary hypertensive animals.<sup>13</sup> Subjects treated with simvastatin in an open labeled observational study had improvements in 6 minute walk test and hemodynamics.<sup>9</sup> We questioned whether these cellular effects of the statin drugs might allow for a more favorable response to sildenafil.

Although our study showed a significant improvement in exercise tolerance and DFS in patients on bosentan given the combination of sildenafil and atorvastatin, the study was underpowered. We attribute the clinical benefits seen to the addition of sildenafil as all subjects were discontinued off of their atorvastatin following the trial, and we did not notice any deterioration when they were reevaluated 12 weeks later. It is of note that most of the benefit was attributable to

5 subjects whose exercise time improved by more than 200 seconds in the active group but none in the controls. This variable responsiveness is common in clinical trials, and is the reason for using the randomized placebo controlled design. To date there have been other reports of clinical benefit using combination therapies in open label studies which are hard to interpret.<sup>14,15</sup> One small open-label study reported benefit with the combination of bosentan and sildenafil in subjects with PAH,<sup>16</sup> but the only other randomized placebo controlled trial of combination therapy tested adding bosentan to patients being initiated on epoprostenol and failed to show any clinical benefit.<sup>17</sup>

After the trial was initiated, a pharmacokinetic interaction between sildenafil and bosentan in patients with PAH was reported.<sup>18</sup> Because of interference in liver metabolism, bosentan levels tend to increase, whereas sildenafil levels are reduced. This may have affected the treatment effect in some way.

Although several agents have shown to benefit patients with pulmonary hypertension, it is uncommon for any patient to have dramatic reversal of their disease process. Thus, there is a continuing need for physicians to continue to test combination medication regimens to determine efficacy. Although our study supports that sildenafil added to bosentan may be of clinical benefit in a subset of patients, we cannot draw the conclusion that this combination should be adopted. The imbalance in baseline treadmill times underscores that future trials need to be adequately powered, and need to have a randomized placebo design.

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