

Lower Doses of Bosentan in Combination With Sildenafil Might be Beneficial in Pulmonary Arterial Hypertension

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Background: Endothelin-receptor-antagonist, bosentan, has been found to improve the functional capacity and cardiopulmonary hemodynamics in Pulmonary Arterial Hypertension (PAH). Clinical trials have shown the preferable dosage of 125 mg, twice daily, regarding both efficacy and safety.

Objectives: The purpose of this study was to investigate the effects of lower doses of bosentan (62.5 mg, twice daily) in combination with sildenafil on exercise capacity and clinical events, in 41 patients with idiopathic pulmonary hypertension or chronic thromboembolic pulmonary hypertension (CTEPH).

Patients and Methods: We assigned 41 patients with PAH (non-reactive idiopathic or non-operable chronic thromboembolic) to receive 62.5 mg of bosentan twice daily as combination therapy and evaluated the New York heart association (NYHA) functional class, 6-minutes-walk-distance (6MWD), time to clinical worsening, echocardiographic indexes and clinical events, for an average of 18.5 ± 9.5 months.

Results: No adverse drug reaction was observed during the follow-up. Clinical worsening occurred in six (14%) patients, at least one year after treatment, two of the cases failed to respond to 125 mg, twice daily and died. Eight (19%) remained in FC I_II, but didn't reach the goal of 380 meters for 6MWD. All other patients reached the treatment goals according to the latest European society of cardiology (ESC) guidelines.

Conclusions: We observed acceptable results regarding both efficacy and safety with 62.5 mg of bosentan, twice daily in this group of patients. Further clinical trials investigating PAH with lower dosages of bosentan may be warranted.

Keywords: Pulmonary Hypertension; Endothelin Receptor Antagonist; Bosentan; Chronic Thromboembolic Pulmonary Hypertension

1. Background

Pulmonary arterial hypertension (PAH) is defined as an increase in mean pulmonary arterial pressure (mPAP) of 25 mm Hg or greater at rest, as estimated by right-heart catheterization (RHC) (1).

Pulmonary hypertension (PH) is a complex and multi-disciplinary disorder. The term PH refers to the presence of high pulmonary vascular pressure, and can be the end result of a variety of different underlying disorders. New guidelines provide a clear classification of the major clinical subcategories of PH (1), where it is classified into five groups based upon shared pathophysiologic and clinical features: 1) pulmonary arterial hypertension (PAH); 2) pulmonary hypertension caused by left-sided heart disease (e.g. left ventricular dysfunction and valvular heart disease); 3) pulmonary hypertension caused by lung diseases and/or hypoxia; 4) pulmonary hypertension caused by chronic thromboembolic disease (CTEPH); and 5) pulmonary hypertension with unclear pulmonary multi-factorial mechanisms, such as sarcoidosis. Among these categories, PAH and CTEPH have been subject to the most

rapid advancement in terms of knowledge and treatment options in the past decades.

Endothelin-1 is a potent vasoconstrictor and smooth muscle mitogen, which contributes to the pathogenesis of PAH (2-4). Bosentan is an oral active dual endothelin-A and endothelin-B receptor antagonist and the first molecule of its class was artificially synthesized. This endothelin receptor antagonist (ERA) has been studied in multiple placebo-controlled trials of PAH. Evidence of pulmonary arteriopathy in CTEPH has been regarded as a rationale for the use of drugs approved for PAH, thus bosentan is also an option for these group of patients.

In the BREATHE-1 (bosentan randomized trial of endothelin receptor antagonist therapy for pulmonary hypertension) study, efficacy and safety of bosentan 125 mg and 250 mg twice daily on exercise capacity and the risk of clinical worsening was reported (5).

The BREATHE-1 study, a multicenter, randomized, placebo controlled trial of 213 functional class III and IV patients with PAH, demonstrated an improvement in

6 minute walking distance (6MWD) and the composite endpoint of time to clinical worsening over a period of 16 weeks (5).

2. Objectives

The objective of our study was to investigate the effects of bosentan at lower doses (62.5 mg twice daily) in combination with sildenafil 50 mg, twice daily, on exercise capacity. The idea came up as a consequence of economic constraints.

3. Patients and Methods

We enrolled 41 patients with symptomatic, severe pulmonary arterial hypertension (NYHA functional class II-IV). Pulmonary hypertension was either pulmonary arterial hypertension (Class 1) or associated with non-operable distal type chronic thromboembolic hypertension. The inclusion criteria were New York heart association (NYHA) class II-IV, resting mean pulmonary artery pressure equal or greater than 25 mmHg, pulmonary capillary wedge pressure of less than 15 mmHg, and pulmonary vascular resistance greater than three woods. Patients needed to be naïve in treatment (not receiving any kind of pulmonary vasodilator). Patients were excluded if they had received or had been scheduled to receive calcium-channel blockers. The protocol was reviewed and approved by the ethics committee of Rajaie Cardiovascular, medical and research center. Written informed consent was obtained from all patients according to the ethical standards of the declaration of Helsinki

3.1. Study Design

In our single-center cohort study, 41 patients were assigned to receive combination pulmonary vasodilator therapy with an Endothelin Receptor Antagonist (62.5 mg bosentan twice daily) and a phosphodiesterase inhibitor (50 mg sildenafil, twice daily).

The recommended interval between outpatient visits is three to six months according to the latest guidelines, thus patients were evaluated on an outpatient basis after one, four, eight, eleven, fifteen and eighteen months of therapy. The primary end point was the change in exercise capacity (from base line over the duration of study); defined as the change in the distance a patient could walk during six minutes (6MWD). Six-minute walk test is technically a simple, inexpensive, reproducible, and well standardized test (6). In addition to the distance walked, dyspnea on exertion (Borg scale) and finger O₂ saturation were recorded. Walking distances <332 m, or <250 m and O₂ desaturation >10 % indicated impaired prognosis in PAH (7-9). Absolute values of more than 380 m following treatment correlated with improved survival in PAH patients.

The secondary end points were the change from base line to 18th month NYHA functional class and the time to clinical worsening (defined as lack of clinical improve-

ment, worsening of clinical condition, hospitalization for pulmonary hypertension, atrial septostomy or death).

All patients underwent an echocardiographic examination at baseline and after 18 months of follow up. Apical and parasternal views were obtained according to the American Society of Echocardiography guidelines. From apical four-chamber and parasternal views, right ventricular (RV) end diastolic diameter, tricuspid annular plane systolic excursion (TAPSE), right atrial area, tissue Doppler-derived lateral tricuspid annular systolic velocity, right ventricular fractional area change and pericardial effusion size were determined.

Patients were also followed for increase in liver aminotransferase levels. If the increase in these enzymes were between five and eight times the upper limit of normal, the dose of bosentan was decreased to 62.5 mg daily. If increase in liver aminotransferases were to a value greater than eight times the upper limit of normal, bosentan was discontinued.

3.2. Statistical Analysis

Statistical analysis was performed with SPSS 15 for Windows (SPSS Inc., Chicago, Illinois). Data were expressed as mean values \pm standard deviation for interval and count (%), for categorical variables. All variables were tested for normal distribution with Kolmogorov-Smirnov test. Repeated measures Analysis of Variance (ANOVA) followed by Bonferroni post-test were used to assess parametric distributions. For non-parametric distributions, Friedman test was applied. P values of < 0.05 were considered significant.

4. Results

Forty-one patients were included in this study. The mean duration of treatment was 18.5 ± 9.5 months. No instance of incomplete treatment occurred.

4.1. Base-line Characteristics

Table 1 summarizes the demographic data and hemodynamic measurements of the study population. The mean age was 37 years, 75.6% were female, and most patients (85%) were diagnosed as having idiopathic PAH and the rest had inoperable distal type CTEPH (6%). The time between baseline measurements and the end of the study represented a median follow-up period of 18.5 ± 9.5 months.

4.2. Exercise Capacity

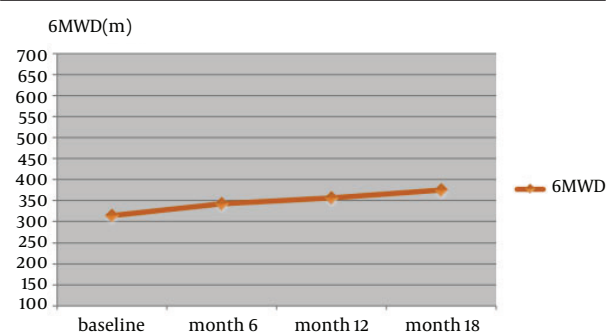
Improvements in 6MWD were observed in 36 patients, which were maintained till the end of the study. Baseline 6MWD was 330 ± 64 meters. After 18 months of treatment the walked distance increased to 390 ± 36 meters and this improvement was statistically significant ($P = 0.01$). Furthermore, 80% of patients reached the goal of 6MWD over 380 meters (Figure 1 and Table 2).

Table 1. Baseline Demographic, Clinical and Hemodynamic Characteristics ^{a,b}

Variables	Values
Gender	
Male	10 (24)
Female	31 (76)
Age, y	
Mean	37
Range	13 - 59
Weight, kg	69
Cause of pulmonary arterial hypertension	
Primary	35 (85)
CTEPH	6 (15)
Previous or concomitant treatment	
Diuretics	23
Supplemental oxygen	2
6 minute walking test, m	330 ± 64
NYHA Functional Class	
II	14 (34)
III	23 (56)
IV	4 (10)
Cardiac index, L/min/m²	2.4 ± 0.6
Pulmonary Vascular Resistance, dyn-sec-cm-5	940 ± 436
Mean Pulmonary arterial pressure, mmHg	56 ± 14
Pulmonary capillary wedge pressure, mmHg	9.4 ± 3
Right Atrial Pressure, mmHg	10.1 ± 5

^a Abbreviations: CTEPH, Chronic Thromboembolic Pulmonary Hypertension; NYHA, New York Heart Association.

^b Data are presented as No. (%) or Mean ± SD.

**Figure 1.** Significant Improvement in Six-Minute Walking Distance (6MWD) During Follow-up**Table 2.** Changes in Six-Minute Walking Distance and New York Heart Association (NYHA) Functional Class

NYHA Functional Class ^a	Baseline	18th month	P Value
I	0	17	0.01
II	34	54	
III	56	24	
IV	10	5	
Six Minute Walking Distance, m	330 ± 64	390 ± 36	0.01

^a Data are presented as (%).

4.3. New York Heart Association Functional Class

At base-line 56% of patients were in the world health organization (WHO) functional class III and 1% in WHO functional class IV. At the end of study, nearly 70% of patients were in NYHA functional class I or II. The improvement in NYHA functional class was statistically significant ($P = 0.01$; Table 2)

4.4. Echocardiography

Analysis of echocardiographic parameters after 18 months of treatment showed significant improvement in RV end diastolic diameter, TAPSE and RV fractional area change. There was no significant change in right atrial area and in number of patients with pericardial effusion. Table 3 depicts echocardiographic data at baseline and after 18 months.

4.5. Clinical Worsening

Across the study, clinical worsening and hospitalization for pulmonary hypertension occurred in six (14%) patients at least one year after treatment and we had to increase bosentan to 125 mg twice daily. Two patients with idiopathic pulmonary hypertension failed to respond to 125 mg twice daily and passed away. Deterioration of NYHA functional class was the most frequent feature of clinical worsening.

4.6. Safety

No adverse effects were observed during the follow-up period. The majority of serious events were due to PAH-related conditions. Increases in hepatic aminotransferase levels were not observed in the patients.

Table 3. Echocardiographic Changes ^{a,b}

Parameter	Baseline	18th Month	P Value
RVEDD, mm	46 ± 1.3	44 ± 1.1	0.01
RVSm, cm/s	9.1 ± 2.6	9.7 ± 2.1	0.01
TAPSE, mm	14.3 ± 3.1	16.5 ± 3	0.001
RVFAC, %	22.5 ± 6.1	24.9 ± 7.5	0.02
RAA index, cm²/m²	13.3 ± 6	13.1 ± 5.8	NS
Pericardial effusion, % ^c	26.8	24.3	NS

^a Abbreviations: NS, not significant; RAA, right atrium area; RV, right ventricle; RVEDD, right ventricular end diastolic diameter; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion.

^b Data are presented as mean ± standard deviation.

^c Percent of patients with pericardial effusion.

5. Discussion

Pulmonary vasodilators are the mainstay of pulmonary arterial hypertension (PAH) treatment. Patients with type IV (distal) CTEPH should similarly receive standard pulmonary vasodilator therapy. Bosentan, a dual endothelin receptor antagonist, has been shown to effectively increase exercise capacity in PAH.

In the first placebo controlled study of bosentan in PAH, Channick et al. studied patients with either idiopathic PAH or scleroderma associated PAH who were randomly assigned to receive bosentan (62.5 mg taken twice daily for four weeks then 125 mg twice daily) or placebo. This study showed improvement in NYHA class, 6MWD and cardiac index, while a decrease in pulmonary vascular resistance (10). BREATHE-1 (bosentan randomized trial of endothelin receptor antagonist therapy for pulmonary hypertension) investigated the effect of bosentan on exercise capacity in patients with PAH and also compared two different doses (62.5 mg vs. 125 mg, twice daily). Although both bosentan doses induced a significant treatment effect, the placebo-corrected improvement was more pronounced for the dose of 125 mg twice daily, than for 62.5 mg twice daily. However, increasing the dose to 125 mg twice daily led to a greater frequency of increased aminotransferase levels (5). In fact, no dose-response relationship for efficacy could be ascertained.

Clinical trials have shown the preferable dosing of 125 mg twice daily, regarding both efficacy and safety. The efficacy of treatment with bosentan in CTEPH has been the aim of many clinical trials. Nishikawa and colleagues investigated the effect of bosentan in patients with CTEPH, who were not eligible for pulmonary endarterectomy, and showed that Long-term advanced therapy with bosentan significantly improves symptoms, pulmonary vascular resistance, plasma BNP concentration, and time to clinical worsening in Japanese patients with inoperable CTEPH (11). Surie and colleagues showed that bosentan in patients with inoperable CTEPH was associated with a significant improvement in cMRI parameters of RV function and remodeling (12). Six-minute walking distance remains the only food and drug administration- and European Agency for the evaluation of medicinal products-accepted exercise endpoint for studies evaluating treatment effects in PAH. In this study, in accordance with previous studies, patients (including idiopathic PH or CTEPH) treated with bosentan, had an improved 6MWT, and 65% of patients reached the goal of 380 meters, which was statistically significant. Bosentan (at dose of 62.5 mg, twice daily) also improved the NYHA functional class and increased the time to clinical worsening.

Despite all the guideline recommendations, there is always a major issue with the cost of medications, resulting in poor adherence and frequent drug discontinuation. Bosentan was ranked as an overpriced medication in our country at the time of this study, and a trend towards lower efficacious dosing could have helped many

patients benefit from this drug. In our study we showed acceptable safety measures and efficacy endpoints (functional class and 6MWT improvement) with the combination of 62.5 mg bosentan and 50 mg sildenafil, twice daily. This finding can be taken as a concept to perform head to head studies comparing this combination with 125 mg bosentan, twice daily, and if the results confirm the efficacy of this dose, a recommendation to start PAH patients on this regimen instead of standard 125 mg bosentan, twice daily, might be reasonable for our country. It should be noted that without a placebo control, these results should be interpreted with caution and further studies to look at this combination regimen are crucial before any recommendations.

Our study demonstrated that treatment with bosentan at lower doses improves exercise capacity and that this treatment appears to be safe, well-tolerated and cost effective. Further clinical trials to look at treating primary pulmonary hypertension with lower dosage of bosentan may be warranted.

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Authors' Contributions

Ahmad Amin: study concept and design, analysis and interpretation of data, study supervision, and critical revision of the manuscript for important intellectual content. Arezoo Mohamadifar: acquisition of data, and drafting of the manuscript. Sepideh Taghavi: analysis and interpretation of data. Nasim Naderi: analysis and interpretation of data. Hosnolah Sadeghi: analysis and interpretation of data.

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