Improved low-risk criteria scores for combination therapy of sildenafil and generic bosentan in patients with congenital heart disease with severe pulmonary hypertension: A prospective open label study

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Abstract

Objective: We evaluated the efficacy and safety of the bosentan as a sequential add-on therapy with sildenafil in pulmonary arterial hypertension with congenital heart disease (PAH-CHD) patients.

Material and method: Twenty patients who were receiving sildenafil were given generic bosentan for up to a year. Hemodynamic data was collected from cardiac catheterization at pretreatment and at three months. Comparisons were made between the total scores of the four, low-risk criteria adapted from the 2015 ESC/ERS pulmonary hypertension guidelines, which are: 1) WHO functional class of I or II, 2) 6MWD of more than 440 m, 3) right atrial pressure of less than 8 mm Hg, and 4) cardiac index ≥ 2.5 L/min/m^2, performed at the beginning of therapy, 3-months, 6-months, and 1 year.

Results: Patients' average age was 27 ± 11 years old (12–53). PVRi decreased from 16.7 ± 9.5 to 12.7 ± 10.3 Wood unit (WU) m2 (p = 0.025) and PVRi/SVRi decreased from 0.69 ± 0.33 to 0.49 ± 0.32 (p = 0.001). During the follow-up, the composite scoring of the low risk scores for 19 patients was increased significantly from 1.8 ± 1.0 at baseline to 2.3 ± 0.9 at 3 months, to 2.9 ± 0.8 at 6 months, and 3 ± 0.7 at 1 year (p = 0.001).

Conclusion: We demonstrated intermediate term benefits for generic bosentan as an add-on therapy to sildenafil in patients with PAH-CHD by improving PVRi, and PVRi/SVRi at three months. A significant improvement was also seen in the combined scores of the low-risk criteria from below 2 to 3 at one year (p = 0.001).

Thai Clinical Trials Registry (TCTR): TCTR identification number is TCTR20200506006.

Introduction

Pulmonary arterial hypertension (PAH) is defined as an increase in mean pulmonary arterial pressure >20 mm Hg with pulmonary vascular resistance (PVR) ≥ 3 Wood units (WU) and pulmonary arterial wedge pressure (PAW) ≥ 15 mm Hg.[1–3] Patients who had pulmonary hypertension with congenital heart disease (PAH-CHD) such as Eisenmenger syndrome are

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known to benefit from bosentan treatment given as a monotherapy for 16 weeks with improving in 6-minute walk distance (6MWD) in the BREATH-5 study.[4] The subsequent COMPASS-2 trial[5] that added bosentan to sildenafil therapy did not show superior results compared to sildenafil monotherapy in delaying the time to the first morbidity/mortality event. Recently, the MAESTRO study (macitentan in Eisenmenger syndrome to restore exercise capacity) did not show results that were superior to placebo in regards to the primary end-point of change from baseline at the end of 16 weeks of treatment.[6] Nevertheless, the meta-analysis with 456 pooled PAH-CHD patients treated by bosentan as an adds on therapy[7] showed significant improvement in the 6MWD and with respect to the World Health Organization functional class (FC) and an additional statistically significant difference in mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance index (PVRi). These mixed outcomes led to a hesitation in adding combination therapy, as recommended by the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines for a risk assessment strategy.[8,9]

In Thailand, bosentan and other endothelin receptor antagonists have been considered as second-line add-on therapy to sildenafil, because of its high cost since 2008.[10–12] While considering the limited resources in our country, we designed a prospective single-arm, sequential combination therapy of the generic bosentan as an add-on to sildenafil in PAH-CHD patients.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice as outlined in the International Conference of Harmonization. This study was approved by the Siriraj Ethics Committee, Mahidol University No.161/2561 (EC1). Informed written consent was obtained from all participants before they were included in the study.

Materials and methods

This study is a prospective single-arm trial of combination therapy of sildenafil with sequential combination of the generic bosentan in PAH-CHD patients. All patients had received a stable dose of sildenafil for at least three months.

Patient selection

Twenty patients with PAH, according to the established criteria and classification,[12–14] were recruited. The inclusion criteria were: 1) male or female, older than 12 years-of age; 2) patients diagnosed with PAH-CHD by the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines;[8,9] 3) patients with WHO functional class (1988 WHO functional classification), level I or II who have had a stable disease for at least three months before participating; 4) patients who have had a 6MWD test equal to or greater than 100 m or less than 450 m; 5) patients have not previously been treated with any other endothelin receptor antagonist; 6) female patients of childbearing potential using one of the following methods of contraception: barrier-type device (e.g., condom, diaphragm) used only in combination with a spermicide, a double-barrier method is recommended, intrauterine devices (IUDs), or oral or implanted contraceptives, if used in combination with a barrier method; 7) patients providing written informed consent.

The exclusion criteria were: 1) pregnant patients, nursing mothers; 2) patients with left ventricular dysfunction (ejection fraction < 40%); 3) patients with systolic blood pressure less than 85 mm Hg; 4) patients with other conditions that may affect the ability to perform a 6-minute walk distance test; 5) patients with AST/ALT equal to or more than 3-times the upper limit normal; 6) patients with concurrent use of cyclosporine or glyburide; 7) patients unable to provide informed consent or comply with the patient protocol; 8) patients with planned surgical intervention during the study period; 9) patients with known hypersensitivity to bosentan or any of the excipients.

All of the patients received oral 20 mg sildenafil three-times daily as a stable dosage for three month and generic bosentan (Silkay125®, Unison Laboratories, Thailand) 1/2 tab was given twice daily for one month and 1 tab twice daily for up to one year. Patients who had a body weight of less than 40 kg were given bosentan as $1/2$ tab twice daily until the end of the study. Cardiac catheterization was performed at baseline and at 3-months using estimated oxygen consumption.[15] Baseline transcutaneous oxygen saturation, 6MWD, Borg dyspnea score, WHO functional class and laboratory parameters were measured at baseline, 3-months, 6-months, and 12-months.

Outcome measure

The primary objective of this study is to compare the hemodynamic parameters at baseline and at 3-month intervals during the study. We also compared a composite end-point by using a number of low-risk criteria adapted from the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines and risk assessment strategy[8,9] at the beginning of therapy, and at 3-months, 6-months, and 1-year. A score of 1 was given for each low-risk criteria, as follows: 1)

WHO/functional class of I or II; 2) 6MWD of more than 440 m; 3) echocardiography measurement using the same criteria as in the Swedish PAH Register (SPAHR)[16] and the estimated right atrial pressure by echocardiography criteria that has been widely used and validated in our hospital[17] of less than 8 mm Hg; and 4) cardiac index $\geq$2.5 L/min/m^2 measured by echocardiography.[2,16,18] The total of the maximal scores achieved for each follow-up period was 4.

We also followed the effect of treatment for up to one year by obtaining laboratory results including NTproBNP, complete blood count, aminotransferases and bilirubin levels at the beginning of therapy, and at 3-months, 6-months, and 1 year as shown in Table 3.

Statistical analysis

All variables were tested for normal distribution and all normally distributed variables were reported as mean $\pm$ standard deviation and tested with repeated measures of ANOVA. Non-normally distributed data was reported as median (range). Non-parametric statistics (Friedman's two-way ANOVA) was used to compare these types of variables. The number of achieved low-risk scores (0 = not achieve, and 1 = achieved) for each patient was reported as n (percentage), and each categorical variable was compared using Cochran's Q test.

The primary outcomes of the hemodynamic parameters by cardiac catheterization were compared at baseline and at 3-months with the paired t-test. Comparisons of the total, low-risk scores at baseline, 3-months, 6-months, and 12-months were done using repeated measures of ANOVA. The change in WHO functional class was compared using the Wilcoxon Signed Rank Test. A p-value of less than 0.05 was considered a statistically significant difference. All statistical analyses was performed using PASW Statistics (SPSS) 18.0 (SPSS Inc., Chicago, IL., USA).

Results

Twenty patients were enrolled, including six males and fourteen females. Their average age was 27 ± 11 years (range 12–53 years) and their average weight was 48 ± 12 kg (range 27–81 kg). Their diagnoses were unoperated atrial septal defect (ASD) (6 cases, including 2 patients with small ASD), ventricular septal defect (VSD) (3 cases), patent ductus arteriosus (5 cases), and atrioventricular canal (AVC) (2 cases). Post-operative pulmonary atresia ventricular septal defect (PA/VSD) was seen (3 cases), and complete transposition of great arteries (DTGA) (1 case). One patient (a 26-year-old female), who had unrepaired sinus venous defect ASD had finished 3 months of follow-up including cardiac catheterization and then had sudden cardiac arrest from ventricular fibrillation and passed away at 4 months after enrolling in the study. The other 19 patients tolerated Silkay125$^{®}$ during treatment for a 12-month period. No significant side-effects were reported during the study period. Baseline characteristics, including WHO functional class, 6MWD, BORG dyspnea, Ao saturation, and NTproBNP are shown in Table 1. Hemodynamic data obtained during cardiac catheterization; specifically, cardiac index (CI), PVRi, mPAP), PVRi/systemic vascular resistance index (SVRi) and right atrial pressure (RA) at baseline and

Table 1. Hemodynamic characteristics including WHO functional class, 6MWD, BORG dyspnea, Ao saturation, NTproBNP, and hemodynamic data including cardiac index, PVRi, mean pulmonary artery pressure (mPAP), PVRi/SVRi and right atrial pressure (RA) obtained at baseline, 1-month, 3-months, 6-months, and 12-months (cardiac catheterization only at baseline and at 3-months).

Hemodynamic	Baseline	3-months	6-months	12-months	p-value
FC I/II	16	18	19	18	0.290
6MWD (meters)	342 ± 94	362 ± 78	362 ± 78	361 ± 122	0.622
BORG	5.9 ± 2.2	5.5 ± 2.2	6.8 ± 1.4	5.8 ± 2.1	0.144
AoSat (%)	91.7 ± 6.8	89.6 ± 9.0	90.7 ± 7.2	91.5 ± 8.3	0.440
NTproBNP (ng/L)	640 (9–9602)	582 (10–6852)	621 (6–6519)	462 (13–5509)	0.145
CI(L/min/m^2) cath	3.06 ± 0.86	3.12 ± 0.9			0.542
mPAP (mm Hg) cath	65 ± 19	63 ± 23			0.797
PVRi (WU·m2) cath	16.8 (3–31)	8.1 (3.1–45)			0.025
PVRi/SVRi cath	0.68 ± 0.33	0.49 ± 0.32			0.001
RAP (mm Hg) cath	12.8 ± 6.5	11.1 ± 4.4			0.004
CI (L/min/m^2) echo	3.06 ± 1.0	3.8 ± 1.7	4.4 ± 3.5	6.1 ± 5.5	0.006
RAP (mm Hg) echo	18.4 ± 2.7	18.3 ± 3.5	16.6 ± 3.5	13.7 ± 3.4	0.001

FC I/II: functional class I/II; 6MWD: six-minute walk distance; BORG: Borg dyspnea index; Ao sat: aortic oxygen saturation; NTproBNP: N-terminal pro b-type natriuretic peptide in median (range); CI =cardiac index; cath: by cardiac catheterization; mPAP: mean pulmonary artery pressure; PVRi: pulmonary arteriolar resistance index to body surface area (Wood unit m^2) in median (range); PVRi/SVRi: ratio of pulmonary vascular resistance to systemic vascular resistance); RAP: right atrial pressure (mm Hg); echo: by echocardiography, statistically significant at p-value $<$ 0.05.

at 3-months are also shown in Table 1. PVRi decreased from 16.8 WU·m^2 (3–31) to 8.1 WU·m^2 (3.1–45) (p = 0.025). The mean difference between PVRi at the 1st and 2nd catheterization was reduced by 3.9 ± 7.2 WU·m^2. PVRi/SVRi decreased from 0.68 ± 0.33 to 0.49 ± 0.32 (p = 0.001). No significant change in the cardiac index was seen between the 1st and 2nd cardiac catherization. Right atrial pressure, measured by cardiac catheterization, was lowered from 12.8 ± 6.5 mm Hg to 11.1 ± 4.4 mm Hg (p = 0.004). During a one-year follow-up, the hemodynamic data was obtained by echocardiography for long-term comparison. The calculated cardiac index increased from 3.06 ± 1.0 L/min/m^2 at baseline to 6.1 ± 5.5 L/min/m^2 (p = 0.006) at the end of 12 months. The estimated RAP decreased from 18.4 ± 2.7 mm Hg to 13.7 ± 3.3 mm Hg (p = 0.001) from baseline to 12 months. No significant change was seen in 6MWD, BORG dyspnea, Ao saturation, mean PAP, and NTproBNP from baseline and during the follow-up period.

The number of low-risk criteria, adapted from the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines[8,9] at beginning of therapy, 3-months, 6-months, and 1-year are shown in Table 2. A significant improvement can be seen in CI > 2.5 L/min/^{2} and RAP pressure by echocardiography, though no significant changes occurred in the WHO functional class or 6MWD. The combined composite scores for the low-risk criteria increased significantly from 1.8 ± 1.0 at baseline to 2.3 ± 0.9 at 3 months, 2.9 ± 0.8 at 6 months, and 3 ± 0.7 at one year (p = 0.001). In conclusion, the addition of bosentan to sildenafil can increase the average low-risk score from below 2 at baseline to just above 3 at 12 months.

Safety and tolerability of medication

All patients tolerated treatments of both sildenafil and bosentan for the 12–month period. Complete blood count, and aminotransferase and bilirubin levels were obtained at baseline, 1-month, 3-months, 6–months, and 12-months. A slight decrease in hemoglobin was seen at 3 months, though this finding was not statistically significant. A mild increase occurred in total bilirubin from 0.71 (0.38–2.16) mg/dL to 0.74 (0.25–1.36) mg/dL, p = 0.047; however, this was not of clinical significance.

Discussion

In 2006, BREATHE-5 (Bosentan Randomized Trial of Endothelin Antagonist Therapy-5),[4] a bosentan monotherapy study, was the first study to show improvements in 6MWD and a decrease in PVRi for Eisenmenger patients treated with bosentan for 16 weeks regardless of the primary cardiac defect.[19] In

Table 2. Individual low-risk scores adapted from the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines at beginning of therapy, 3-months, 6-months, and 1-year. A score of 1 was given if the patient reached the WHO/functional class of I or II, 6MWD ≥ 440 m, right atrial pressure (RAP) < 8 mm Hg and cardiac index (CI) ≥ 2.5 L/min/m2. If any criterion was not reached, a score of 0 was given for that category. The average for the total number of low risk scores are shown as mean ± standard deviation. The maximal score for each follow-up period was 4.

Hemodynamic	Baseline	3 months	6 months	12 month	p-value
FC I/II	16 (80%)	18 (90%)	19 (95%)	18 (90%)	0.290
6MWD > 440 meters	3 (15%)	4 (20%)	4 (20%)	6 (31%)	0.631
CI ≥2.5 l/min/m^2*	13 (65%)	18 (80%)	18 (90%)	18 (94.7%)	0.015
RAP* ≤ 8 mm Hg*	4 (20%)	9 (45%)	6 (30%)	8 (42.1%)	0.029
Low risk Score**	1.8 ± 0.1	2.3 ± 0.9	2.9 ± 0.9	3 ± 0.7	0.001

FC I/II: functional class I/II; 6MWD: six-minute walk distance; *CI: cardiac index (L/min/m^2) by echocardiography; *RAP: right atrial pressure (mm Hg) by cardiac catheterization at 0 and 3rd month and by echocardiography at 6th and 12th month (17).
**Low-risk score (mean ± standard error).
Statistical significance at p-value < 0.05.

Table 3. Laboratory safety data at 3-months, 6-months, and 12-months.

Safety monitoring	Baseline	3-months	6-months	12-months	p-value
Hb (g/dL)	15.2 ± 3.5	14.0 ± 3.4	14.6 ± 2.7	15.1 ± 2.3	0.085
ALT (U/L)	16 (7–60)	16 (6–78)	16 (6–97)	15 (7–61)	0.665
Direct bilirubin (mg/dL)	0.28 (0–1)	0.29 (0.12–.91)	0.24 (0.09- 0.94)	0.19 (0.11–0.77)	0.057
Total bilirubin (mg/dL)	0.71 (0.38–2.16)	0.61 (0.22–1.49)	0.69 (0.21–1.47)	0.74 (0.25–1.36)	0.047

Hb: hemoglobin level; ALT: alanine aminotransferase.

addition, the open label extension study of the same group of patients for up to 40 weeks, still showed an overall improvement in 6MWD of 61.3 ± 8.1 m (95% confidence interval: [44.7, 78.0]) for the ex-bosentan group.[20] A longer-term effect of bosentan for patients with PAH-CHD was also reported by Hascoet et al.[21] for patients being treated for more than 20 years with bosentan. The PVRi decrease was 5.1 WU m^2 (-1.4, -12.6) ($p = 0.0001$); the increase in pulmonary blood flow index from cardiac catheterization was $+0.4$ L/min/m^2 (0, $+0.9$) ($p < 0.0001$); and the increase in 6MWD was $+49$ m ($+15$, $+93$) ($p = 0.0003$). The result was especially encouraging as the persistent long-term improvement was 68% in all patients.

We enrolled 20 patients with PAH-CHD, with an average age of 27 ± 11 years. Our main findings showed a decrease in their PVRi from 16.8 (3–31) at baseline to 8.1 (3.1–45) WU·m^2 at 3 months ($p = 0.025$) and PVRi/SVRi decreased from 0.68 ± 0.33 to 0.49 ± 0.32 ($p = 0.001$) from baseline to 3 months. PVRi, obtained by cardiac catheterization, is widely used as the surrogate end-point, though it is known to be inaccurate for cyanosis heart patients using estimated oxygen consumption during cardiac catheterization.[22]

Recently, a simplified risk-assessment tool, adapted from the 2015 European Society of Cardiology (ESC)/ European Respiratory Society (ERS) guidelines for the diagnosis and treatment of pulmonary hypertension has been used to evaluate therapy in this group of patients. Certain low-risk criteria are associated with better prognoses of PAH.[8,9,23] In addition, subsequent assessments have shown that the low-risk criteria at diagnosis and during the first year of treatment can discriminate the risk of death or lung transplantation.

Hence, we evaluated the result of treatment using a risk assessment model and substituting part of hemodynamic data with a validated echocardiography measurement.[2,8,9,17,18] After excluding one patient who had sudden cardiac arrest from ventricular fibrillation, the composite scoring of the low-risk criteria for the remaining 19 patients increased significantly from 1.8 ± 1.0 at baseline to 2.3 ± 0.9 at 3 months, 2.9 ± 0.8 at 6 months, and 3 ± 0.7 at 1 year ($p = 0.001$). No significant side-effects (anemia, elevated liver enzymes or bilirubin) were seen during the 12-month period.

We used a total of four, specific low-risk criteria[9] to be achieved in the first year of treatment, which are known to be related to long-term prognosis. They reflect the importance of individual responses to PAH therapy[9] rather than using individual end points as has been done in previous studies.[4–6] Patients who achieved three or four low-risk criteria at reevaluation were known to have similar prognoses as for the four low-risk criteria at baseline.[9]

Conclusions

We demonstrated that incremental treatment with the generic bosentan as an add-on to sildenafil in patients with PAH-CHD improves their PVRi and PVRi/SVRi. Significant improvement was seen in the composite scores of the low-risk criteria adapted from the 2015 ESC/ERS PH guidelines from 1.8 ± 0.9 at baseline to 3 ± 0.7 at one year ($p = 0.001$). Oral bosentan, in its locally made formula (Silkay125®) is safe and effective to be used as an add-on to sildenafil.

Limitations of study

This study was not a head-to-head comparison of add-on bosentan with sildenafil to sildenafil monotherapy. Further, the study only showed improved scores for the low-risk criteria of bosentan compared to the background therapy. Moreover, we did not monitor plasma concentrations of bosentan and sildenafil. Although interactions between sildenafil and bosentan have been reported previously, at this point, dose adjustments of the two drugs are not yet needed.[8]

Ethical approval

This study was approved by the Siriraj Ethics Committee, Mahidol University No.161/2561 (EC1). Informed written consent was obtained from all participants before they were included in the study.

Guarantor

Kritvikrom Durongpisitkul, M.D.

Contributorship

Study conception & design: KD, PaC, PC
Funding acquisition: KD, PaC
Project administration: PaC

Data acquisition/survey dissemination: KD, PaC
Data analyses: KD, PC, CV
Interpretation of results: KD, PC, CV, JS, SK
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