A Post Marketing Surveillance Study on the Efficacy and Safety of Bosentan for Treatment of Pulmonary Arterial Hypertension among Adult Filipino Patients

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Abstract

Background: Pulmonary arterial hypertension (PAH) is a chronic, debilitating disease affecting millions of adults worldwide. With improved knowledge on PAH and better management, long-term survival in patients has significantly increased in the past 20 years. Bosentan is a nonselective, dual endothelin receptor antagonist used in the treatment of PAH. While the drug has already been established to improve exercise capacity and patient survival globally, no study has investigated its clinical effectiveness and safety among Filipino patients yet. A post marketing study was conducted to determine the efficacy and safety of bosentan (125 mg administered twice daily) among adult Filipino patients with PAH.

Methods: A non-randomized, non-comparative, open-label trial was conducted involving adult patients at a tertiary government hospital in Metro Manila. Study duration was from March to September 2012. Primary end points of the study were patients' response to efficacy and safety.

Results: A total of 14 patients were enrolled in the study and 13 included in the analysis. Mean age of the participants was 34 $\pm$ 11.54 years. Remarkable changes were observed for 6WMD and small improvements noted for Borg dyspnea index and CPET. There was no difference between baseline and 12th week WHO functional classification. FEV1/FVC, MVV, RV/TLC and sRaw showed modest improvement; there was a notable difference in the systolic PAP vs baseline; PVR, PVRI, SVR and SVRI demonstrated the largest changes via cardiac catherization and iloprost. Four patients experienced at least one serious adverse event, with one reported as suspected unexpected serious adverse reaction. Out of 13 patients, 10 (76.9%) considered bosentan as effective while 11 (84.6%) considered it safe.

Conclusion: Bosentan improved exercise capacity, pulmonary function and cardiopulmonary hemodynamics among study participants. The drug is generally well-tolerated and effective. Bosentan is among the useful options for treatment of adult Filipino patients with PAH.

Keywords: pulmonary arterial hypertension, bosentan, efficacy, safety

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a chronic, debilitating disease affecting millions of adults worldwide, higher in frequency with females but more fatal with males. PAH is a syndrome with diverse etiology and pathogenesis, but common to all types is the progressive increase in pulmonary vascular resistance (PVR), which may lead to right ventricular failure and mortality.[1]

Due to improved knowledge on PAH and better management, long term survival in patients has significantly improved in the past 20 years. In the 1980s, median patient survival was 2.8 years, compared to six years at present.[2] Various treatment strategies are currently available for PAH and are divided into three major categories: (1) general measures, (2) supportive therapies and (3) PAH-specific therapies.[3] Major predictors of PAH mortality are exercise capacity, WHO functional class and cardiopulmonary hemodynamics.[4]

Central to the pathogenesis of pulmonary arterial hypertension is pulmonary vascular endothelial cell dysfunction.[5] Bosentan, a PAH-specific therapy, is the first endothelin receptor antagonist (ERA) successfully used in the treatment of PAH[5], approved for use in North America and Europe in the early 2000s.[1] It is a nonselective, orally active, dual ERA which targets endothelin, a potent endogenous vasoconstrictor and smooth muscle mitogen that is overexpressed in the lungs and plasma of patients with PAH.[3]

A double-blind, randomized placebo-controlled trial (BREATHE-1) conducted in 27 centers in Europe, North America, Israel and Australia showed that bosentan 125 mg administered twice daily improved patients' six-minute walking distance (6MWD), Borg dyspnea index, WHO functional class and time to clinical worsening.[6] In another clinical trial (EARLY study), the drug demonstrated improvement of pulmonary vascular resistance and 6WMD in patients with mild symptoms (WHO functional class II).[7] Long-term studies have also demonstrated the effectiveness of bosentan in terms of improved overall survival,[4,8] 6WMD,[9,10] reduction of mean pulmonary arterial pressure,[9] slower clinical worsening[9] and maintenance/improvement of WHO functional class.[10]

While the drug has been globally established to improve exercise capacity and patient survival, most of these studies are from Western countries. Studies from East Asia[11-14] (China, Taiwan, South Korea, Japan) are available but no study has investigated its clinical effectiveness and safety among Filipino patients yet. A post marketing study was conducted to determine the efficacy and safety of bosentan among adult Filipino patients with pulmonary arterial hypertension (PAH).

METHODS

The study was a non-randomized, non-comparative, open-label trial (Study No. DC.R.008.11) involving Filipino adult patients. Study duration was from 5 March 2012 to 25 September 2012, conducted at a tertiary government hospital in Metro Manila. Patients were assessed at 4th, 8th and 12 weeks of therapy. The primary end point of the study was the patients' response to efficacy and safety.

The participants' clinical and demographic characteristics were collected at baseline. Exercise capacity, arterial blood gas (ABG) levels, pulmonary function tests (i.e. spirometry, diffusion, lung volume/body plethysmography), hemodynamic monitoring parameters (i.e. systolic pulmonary arterial pressure by tricuspid jet, right atrial pressure, right ventricular size, left ventricular size, Doppler right ventricular index, color Doppler tricuspid area, left ventricular systolic function, left ventricular diastolic function, pulmonary artery size), cardiopulmonary hemodynamic parameters (via cardiac catheterization and vasoreactive testing using iloprost) and laboratory parameters (i.e. body mass index [BMI], pregnancy test, alkaline phosphatase levels, liver function test, bilirubin levels, complete blood count [with white blood cell differential count], bleeding/coagulation tests, serum uric acid, blood troponin and brain natriuretic peptide) were assessed during baseline, follow-ups and week 12. Owing to the large number of assessment/diagnostics performed, only the parameters deemed as essential are presented in this paper.

Quantitative data were summarized as mean ± standard deviation (SD), frequency (number) and percentage (%) distribution. Due to the small sample size, non-parametric tests were used to determine if there were significant changes from the baseline parameters. Wilcoxon matched pairs signed ranks test was used for ordinal data while McNemar test was utilized for dichotomous data.

RESULTS

Baseline Patient Characteristics

A total of 14 patients were enrolled in the study, with 13 as the final number of patients included in the analysis. One patient died before the drug was given and thereafter excluded from the study. Table 1 describes the clinical and demographic characteristics of participants.

The mean age of the patients was 34 ± 11.54 years. There were 12 females and only one male. The primary etiology of eight patients was congenital heart disease (CHD): four with atrial septal defect (ASD), two with ventricular septal defect (VSD), one with patent ductus arteriosus (PDA) and one with patent foramen ovale (PFO).

On the other hand, four had primary or idiopathic PAH and one had PAH associated with systemic lupus erythematosus (SLE).

Other Medications Taken Together with Study Drug

Thirteen (13) other medications were identified as used by participants simultaneously with bosentan during the study period. In descending order of frequency, these are: furosemide (8 or 61.5%), digoxin (7 or 53.8%), spironolactone (6 or 46.2%), sildenafil (3 or 23.1%), allopurinol (1 or 7.7%), aspirin (1 or 7.7%), clopidogrel (1 or 7.7%), diltiazem (1 or 7.7%), kalium durule (1 or 7.7%), levoxythroxine (1 or 7.7%), losartan (1 or 7.7%), prednisone (1 or 7.7%) and trimetazidine (1 or 7.7%).

Exercise Capacity, Body Mass Index (BMI) and WHO Functional Classification

As shown in Table 2, there was a mean increase in the patients' distance walked in 6 minutes (6MWD) (24.50 ± 69.66 meters) from baseline to week 12. There was no difference between the occurrence of dyspnea before and after performing the 6-minute walk test. There was a decrease in the Borg dyspnea index (0.50 ± 1.24) by week 12. To obtain more accurate evaluation of the exercise capacity of study participants, cardiopulmonary exercise testing (CPET) was done. A small improvement (0.73 ± 3.53) in CPET was noted by week 12. As for BMI and WHO functional classification of the patients, no changes were observed compared to baseline data.

Arterial Blood Gas (ABG)

Parameters under ABG (pH, PCO2, PO2, BHCO3, actual base excess [ABE] and oxygen [O2] saturation) showed some changes from baseline to week 12 (Table 2). Compared to other parameters, PCO2 (1.21 ± 4.17) and PO2 (1.28 ± 13.10) demonstrated notable differences in values.

Pulmonary Function Tests (PFTs)

As shown in Table 3, there were modest changes in spirometry and lung volume parameters. Among the remarkable differences were forced vital capacity/forced expiratory volume in 1 second (FEV1/FVC) (1.09 ± 4.78), maximum voluntary ventilation (MVV) (1.36 ± 9.18), residual volume/total lung capacity (RV/TLC) (2.82 ± 5.19) and specific airway resistance (sRaw) (3.03 ± 4.24).

Hemodynamic Monitoring and Cardiopulmonary Hemodynamic Parameters

There was a notable decrease in the systolic pulmonary arterial pressure (PAP) by tricuspid jet (10.75 ± 30.84) from baseline. Right atrial pressure (1.00 ± 3.59) and left ventricular systolic function (2.50 ± 4.80) had small changes. As for the rest of the hemodynamic parameters (i.e. right ventricular size, left ventricular size, doppler right ventricular index, color doppler tricuspid area, left ventricular diastolic function, pulmonary artery size), differences observed were minimal.

For cardiopulmonary hemodynamic parameters via cardiac catheterization, noteworthy changes in pulmonary vascular resistance (PVR) (182.20 ± 386.72), pulmonary vascular resistance index (PVRI) (175.68 ± 465.49), systemic vascular resistance (SVR) (938.84 ± 1523.01) and systemic

vascular resistance index (SVRI) (1244.23 ± 2642.15) during invasive cardiac catheterization were demonstrated.

On the other hand, results under mean right atrial pressure (mRAP), mean left atrial pressure (mLAP), mean pulmonary arterial pressure (mPAP), mean systemic arterial pressure (mSAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), cardiac index (CI), mixed venous oxygen saturation (SVO2%) and left ventricular end-diastolic pressure (LVEDP) showed minimal differences from baseline and week 12.

As for cardiopulmonary hemodynamic parameters through vasoreactive testing using iloprost, results were similar with cardiac catheterization. PVR (149.66 ± 458.01), PVRI (291.12 ± 634.73), SVR (323.04 ± 1057.56) and SVRI (333.25 ± 1467.22) showed remarkable changes from baseline.

Bosentan-related Clinical Worsening

No patient experienced hospitalization, development of right heart failure, worsening pulmonary hypertension or death due to bosentan therapy at week 4, week 8 and week 12 of the study.

Laboratory Parameters

Among laboratory parameters (Table 4), notable differences between baseline and follow-up levels in alkaline phosphatase (26.23 ± 92.37), SGOT (26.31 ± 97.60) and SGPT (16.62 ± 71.26) were observed on the 4th week, while there was a modest change in indirect bilirubin levels (5.20 ± 3.82) on the 12th week

Safety and Tolerability

Respiratory tract infection was one of the medical events experienced by two patients (one from baseline to 12th week of observation period and one on the 12th week follow-up). Three patients experienced headache, one from baseline to 12th week, one on the 4th week only and one on the 12th week follow- up. One patient had edema, another had flushing and one was reported to experience palpitations and hypotension. There was no significant change in liver size observed among the participants.

As shown in Table 5, four patients experienced at least one serious adverse event. One case was assessed as suspected unexpected serious adverse reaction (SUSAR) during the review period: a 23- year old female patient with PAH associated with CHD experienced medically significant headache and numbness of extremities at the time of bosentan up-titration, one month after initiation of the study drug. Following administration of paracetamol, the said medical events resolved within one day while bosentan was continued. The investigators assessed them as related to bosentan.

Another participant experienced medically significant elevation of liver function test (LFT) results (see Table 4) which resolved following drug discontinuation. This was reported as related to bosentan.

One patient experienced medically significant, progressive deterioration of PAH associated with SLE and was hospitalized for fever, cough and abdominal distention. All events were reported as unrelated to bosentan which remained ongoing. The fever, cough and abdominal distention eventually resolved; however, the outcome for PAH deterioration on this patient was not provided.

Another patient underwent prolonged hospitalization due to palpitations and transient decrease in blood pressure (hypotension) following protocol-mandated pulmonary function testing. These resolved while bosentan was ongoing and afterwards reported as a medical event unrelated to the study drug.

One patient experienced a non-serious urinary tract infection (UTI) which was reported as unrelated to bosentan. The outcome was not provided.

One patient was hospitalized and subsequently died due to pulmonary hypertensive crisis following right heart catheterization prior to initiation of bosentan. Following the death of this patient, the protocol and informed consent form of the study were amended to include a new paragraph on the potential risks of right heart catheterization.

Overall, two (15.4%) out of six adverse events were reported as related to the study drug.

At study endpoint, efficacy and safety were assessed. Among 13 patients, 10 (76.9%) considered bosentan as effective while 11 (84.6%) considered it safe. "Effective" was defined as the ability to produce desired results and "safe" was defined as the absence of adverse drug events or minimal adverse drug events.

DISCUSSION

In this post marketing surveillance study, administration of bosentan 125 mg twice daily for 12 weeks generally improved exercise capacity, pulmonary function and cardiopulmonary hemodynamics of the patients involved.

For exercise capacity, remarkable changes were observed in the patients' 6MWD, while there was a small improvement in the Borg dyspnea index and CPET. For WHO functional classification, there was no difference between baseline and 12th week values.

As for for pulmonary function parameters, FEV1/FVC, MVV, RV/TLC and sRaw showed modest improvement. For hemodynamic parameters, there was a notable difference in the systolic PAP (by tricuspid jet) compared to baseline.

For cardiopulmonary hemodynamic parameters, PVR, PVRI, SVR and SVRI demonstrated the largest changes both via cardiac catheterization and iloprost.

The results of the study is consistent with other clinical studies[6,7,9,10] in terms of improvement in 6WMD, mean systolic PAP and pulmonary vascular resistance. However, no statistical test was performed as the sample size (13) was too small to allow for hypothesis testing, therefore limiting the extent to which generalizations can be drawn.

It is interesting to note that lung function abnormalities in PAH while modest and considered less probable to significantly affect patients' symptoms[15] should warrant further attention. Pathophysiological changes in the pulmonary circulation (arterioles and capillaries) begin early in PAH[15] and detectable alterations in cardiopulmonary hemodynamic parameters and manifestation of symptoms usually appear at the late or advanced stage of the disease.[15,16] Pulmonary function changes and related respiratory symptoms may be more sensitive to short-term bosentan therapy compared to exercise capacity and cardiopulmonary hemodynamic parameters. Further studies with larger sample size and longer period is recommended to accurately determine the effectiveness of the drug among Filipino patients.

Except for the SUSAR (i.e. headache and numbness of extremities associated with bosentan up-titration), all adverse events reported were consistent with prior studies. Headache with numbness of extremities associated with administration of the study drug is reported for the first time in this study. This underscores the importance of vigilant monitoring of adverse events, especially those that were unexpected and serious, for appropriate intervention and reporting.

Out of 13 patients, 10 (76.9%) considered bosentan as effective while 11 (84.6%) deemed it safe. Liver function test results of the participants were consistent with previous studies. Only one patient necessitated discontinuation of the study drug due to medically relevant elevation of LFT.

CONCLUSION

Bosentan 125 mg administered twice daily generally improved exercise capacity, pulmonary function and cardiopulmonary hemodynamics, with pulmonary function demonstrating the most number of significant results. The drug is generally well-tolerated and effective. However, further studies with larger samples and longer duration is recommended. Bosentan is currently among the useful options for treatment of adult Filipino patients with PAH.

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DISCLOSURE

This post-marketing surveillance study was conducted by Menarini Philippines – Actelion's local partner for the sales and marketing of bosentan – from 5 March 2012 to 25 September 2012 as part of the regulatory requirements under monitored release of bosentan (Tracleer). Actelion was acquired by Johnson & Johnson in 2017, resulting to the transfer of marketing authorization for bosentan in the country from Menarini to Johnson & Johnson (Philippines), Inc. (JJPI) in July 2018. The preparation of this manuscript is supported by both JJPI and Actelion.

Table 1. Demographic and Clinical Characteristics of Patients in the Study

CHARACTERISTIC	Mean ± SD	No. (%)
Age (years)	34.00 ± 11.54	
Weight (kg)	47.60 ± 10.26	
Sex		
Male		1 (7.70)
Female		12 (92.30)
Occupation		
Nurse		1 (7.70)
Student		1 (7.70)
Teacher		1 (7.70)
Unemployed		8 (61.50)
Not indicated		2 (15.40)
Etiology		
Primary (idiopathic) pulmonary hypertension		4 (30.80)
PAH associated with congenital heart defect (CHD)		8 (61.50)
Atrial septal defect (ASD)		1 (7.70)
Patent ductus arteriosus (PDA)		1 (7.70)
Patent foramen ovale (PFO)		2 (15.40)
Ventricular septal defect (VSD)		1 (7.70)
PAH associated with systemic lupus erythematosus (SLE)		1 (7.70)
Pulmonary hypertension associated with other illnesses		0 (0.00)

Table 2. Outcome Measures by Observation Period

OUTCOME MEASURE	NO.	BASELINE Mean ± SD / No. (%)	WEEK 12 Mean ± SD / No. (%)	DIFFERENCE Mean ± SD / No. (%)
Exercise capacity				
6-minute walk distance (m)	12	355.00 ± 91.01	380.00 ± 101.45	24.50 ± 69.66
Dyspnea after 6-minute walk test Yes No TOTAL		 10 (83.3) 2 (16.7) 12 (100.0)		
Dyspnea index (Borg scale)	12	2.29 ± 1.42	1.79 ± 1.44	0.50 ± 1.24
Body mass index (BMI)	12	19.46 ± 2.56	19.46 ± 2.56	0.00
WHO functional classification 3.0 3.5 TOTAL		 12 (100.0) 0 (0.0) 12 (100.0)	 11 (9.7) 1 (8.3) 12 (100.0)	
Cardiopulmonary exercise testing (CPET)	10	15.68 ± 4.78	16.41 ± 6.59	0.73 ± 3.53
Arterial blood gas (ABG at room air)				
pH	11	7.47 ± 0.03	7.45 ± 0.03	0.02 ± 0.03
PCO_2	11	29.89 ± 3.09	31.10 ± 4.69	1.21 ± 4.17
PO_2	11	77.97 ± 16.27	76.00 ± 15.82	1.28 ± 13.10
$BHCO_3$	11	21.33 ± 2.28	21.16 ± 2.40	0.16 ± 3.50
Actual base excess (ABE)	11	-1.02 ± 2.16	-1.51 ± 1.93	0.49 ± 3.33
O_2 saturation	11	95.27 ± 2.58	94.69 ± 3.06	0.58 ± 2.04

Table 4. Assessment of Laboratory Parameters by Observation Periods

PARAMETER	NO.	BASELINE Mean ± SD / No. (%)	WEEK 12 Mean ± SD / No. (%)	DIFFERENCE Mean ± SD / No. (%)
Alkaline phosphatase				
4th week	13	96.38 ± 57.09	122.62 ± 145.42	26.23 ± 92.37
8th week	12	82.50 ± 28.66	87.58 ± 34.87	5.08 ± 15.78
12th week	12	82.50 ± 28.66	84.83 ± 31.84	2.33 ± 13.92
Liver function test (LFT)				
SGOT (ALT)				
4th week	13	36.77 ± 20.16	63.08 ± 114.80	26.31 ± 97.60
8th week	12	32.00 ± 11.00	33.08 ± 13.41	1.08 ± 9.96
12th week	12	32.00 ± 11.00	34.42 ± 8.64	2.42 ± 7.90
SGPT (AST)				
4th week	13	38.92 ± 21.76	55.54 ± 84.29	16.62 ± 71.26
8th week	12	35.25 ± 18.03	31.17 ± 9.51	4.08 ± 14.56
12th week	12	35.25 ± 18.03	37.33 ± 13.23	2.08 ± 11.23
Bilirubin				
Total bilirubin				
4th week	13	14.68 ± 9.72	16.32 ± 8.93	1.65 ± 8.33
8th week	12	14.68 ± 9.72	17.43 ± 10.36	2.75 ± 5.90
12th week	12	15.04 ± 10.06	12.46 ± 5.04	2.58 ± 7.14
Direct bilirubin				
4th week	13	1.45 ± 4.19	2.52 ± 3.89	1.07 ± 2.28
8th week	12	1.45 ± 4.19	2.88 ± 4.52	1.43 ± 1.62
12th week	12	1.45 ± 4.19	3.07 ± 4.33	1.62 ± 6.24
Indirect bilirubin				
4th week	13	14.22 ± 5.36	13.42 ± 6.88	0.80 ± 6.59
8th week	12	14.59 ± 5.42	13.78 ± 7.71	0.82 ± 4.68
12th week	12	14.59 ± 5.42	9.39 ± 6.40	5.20 ± 3.82

Table 5. Adverse Events Experienced by Study Participants

ADVERSE EVENT	OUTCOME			SERIOUSNESS		
	Total No. (%)	Resolved	Not Indicated	Medically Significant	New Hospitalization	Prolonged Hospitalization
Possibly related to the study drug	**2**					
Elevated liver function test	1	1	-	1	-	-
Headache and numbness of extremities	1	1	-	1	-	-
Not related to the study drug	**4**					
Serious progressive deterioration of PAH secondary to SLE	1	-	1	1	-	-
Urinary tract infection	1	1	-	-	-	-
Fever and cough	1	1	-	-	1	-
Palpitation and hypotension	1	1	-	-	-	1
EVENT RATE	6 (46.2)					
EVENT RELATED TO STUDY DRUG	2 (15.4)					

*PAH, Pulmonary arterial hypertension; SLE, systemic lupus erythematosus