Original Article

The Effects of Bosentan on the Survival, Safety, and Tolerability in Pulmonary Hypertension as Related to Diffuse Cutaneous Systemic Sclerosis

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Pulmonary arterial hypertension [PAH] is a major cause of death in diffuse cutaneous Systemic Sclerosis [dcSSc] patients in functional class III with the least chances for improvement. Moreover, the unfavorable effects of pulmonary fibrosis in dcSSc threaten the mortality of these patients. This study examines the effects that bosentan monotherapy has on Functional Class III patients with PAH related to dcSSc with pulmonary fibrosis. Conducted between 1 March 2010 to 21 August 2014 at the Scleroderma Clinic of Srinagarind Hospital, Thailand, an open-labeled study was performed on these patients (rated as Function Class III by the WHO). During the 12 month period, they received bosentan and were then evaluated for survival, WHO Functional Class, safety, and tolerability. Of the 10 patients enrolled, all survived. Forty percent (40%) of patients improved from Class III to Class II by the end of month 6, and month 12. Seventy percent (70%) of patients showed significant improvement by making steady progress in the 6 minute walk test. No serious side-effects were detected. Bosentan can be used in dcSSc patients who suffer from WHO Functional Class III PAH.

Keywords: Pulmonary arterial hypertension, Systemic sclerosis, Bosentan, Lung fibrosis

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DcSSc is one of the most severe auto-immune diseases that can affect the life-span of patients. Generally, the survival rates of dcSSc patients are decreased. The reasons for the mortality of patients are related to fibrosis of the internal organs and the subsequent organ dysfunction. The following three conditions have led to death in Thai patients with systemic sclerosis [SSc]: a) pulmonary fibrosis with the presence or absence of pulmonary hypertension, b) heart failure, and c) renal failure[(1)]. Most studies from North America and Europe have focused on the clinical course of pulmonary hypertension in patients with connective tissue diseases without showing significant degrees of lung fibrosis. In the sub-group analysis conducted by these studies, systemic sclerosis patients had the worst outcomes. There have been few studies, that have examined the outcomes of the SSc patients who have had concomitant pulmonary fibrosis and PAH. The approval of the addition of sildenafil to the National List of Essential Medicines by the Thai FDA took place in 2014. During the years between 2010 to 2013, most Thai patients had been unable to afford the expensive PAH medications. Therefore, this study has been primarily designed to utilize patients, who had been previously unable to afford treatment. Furthermore, unlike previous Western studies, this study focuses on patients with dcSSc with accompanying PAH and with pulmonary fibrosis.

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Objective

The aims and objectives of this research study are as follows:

1) To study survival rates of dcSSc patients who have been diagnosed with pulmonary fibrosis and PAH (Functional Class III) and to evaluate their clinical

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response (include WHO functional class) to the medication.

2) To monitor dcSSc patients exhibiting PAH with respect to side-effects and the patient's ability to tolerate bosentan.

Definitions

1) The definition of systemic sclerosis was defined in the 1980 preliminary criteria for the classification of systemic cclerosis.

2) Pulmonary fibrosis must be determined by chest radiograph or by HRCT chest which can show the characteristics of the various stages of the interstitial lung infiltration.

3) After right heart catheterization [RHC], a diagnosis of Pulmonary arterial hypertension can be made if the value of the mean pulmonary arterial pressure ≥25 mmHg and the pulmonary capillary wedge pressure <15 mmHg.

4) In accordance with the World Health Organization [WHO] classification, a determination of the functional class of patients with PAH is to be made in order to decide the status of their functional class.

5) The worsening PAH events can be defined by any of the following events: (A) Death, (b) The worsening of the Functional Class, (C) Heart failure that requires intravenous diuretics or any other PAH-specific medications.

6) PAH-specific medications are as follows: (A) Phosphodiesterase-5 inhibitors, (B) Prostanoids, (C) Endothelin receptor antagonists.

Materials and Methods

The inclusion criteria for selecting the patient population were as follows: A) all patients were selected from the Scleroderma Clinic of Srinagarind Hospital at Khon Kaen University in Khon Kaen, Thailand during 1 March 2010 to 21 August 2014, B) the population of dcSSc patients had been previously diagnosed using the 1980 ACR classification criteria, C) Patients showed evidence of pulmonary fibrosis confirmed by HRCT chest, and D) had been diagnosed with Functional Class III (World Health Organization) pulmonary arterial hypertension, which had been confirmed by right heart catheterization. The patients in the study received bosentan (PAH-specific monotherapy) 62.5 mg twice daily for 1 month and then the dosage was raised to 125 mg twice daily for another 11 months. Another supportive treatments included; nifedipine, diuretics were allowed. After a 1 year of subscribing to the treatment regimen as outlined above, the following areas were examined: A) the survival rate of the patients, B) the amount of time to clinical decline defined by death, C) the amount of time leading to a worsening of the WHO Functional Class, D) the development of heart failure that required intravenous diuretics or other PAH specific medications, and E) a significantly positive change in their WHO functional class. The secondary desired outcome was that during the first six months of treatment the patients would be able to improve their ability to ambulate and walk a greater distance [6 MWD] than they had been able to when their initial baseline level was taken. This research protocol was approved by the KKU Institutional Research Ethics Committee.

Results

The participants in this study were 10 dcSSc patients who met the inclusion criteria.

The baseline characteristics for the patients and hemodynamic parameters are shown in Table1. Most of the patients were female (60%), with a mean age of 55.1 (44 to 69) years. All patients had lung fibrosis defined by chest radiograph and HRCT chest. All patients were in Functional Class III as defined by the WHO. At the end of 12 months, all patients were still alive. The changes of WHO Functional Class and changes in 6 Minute Walking Distance in Meters during Study are shown in Table 2 and in Figure 1.

Several adverse events occurred during the time period of the study. Most events were not serious, but 3 of the participants were admitted as follows: A) Patient #1 was admitted due to upper gastro-intestinal hemorrhage, B) Patient #7 was admitted due to alveolitis, and C) Patient #8 was admitted due to pneumonia. Although Patient #3 had experienced mild right-sided heart failure between the 4th and 5th month of therapy, she was not admitted. According to this protocol, this event did not fulfill the definition of a worsening of the PAH event because she had responded well to the oral diuretic and therefore, did not require admission. During the course of treatment, Patient #10 had a painful complication with ulcerations on three toes which resulted in a marked decrease in the 6 MWD at the end of the study. All these events were classified as not related to the medication being studied. The details of adverse events of patients are shown in Table 3. There was no new onset anemia except for the #1 patient who had gastrointestinal bleeding from aspirin intake. Only two patients had transient modest elevation of liver enzyme (less than 1.5 ULN) during the course of treatment.

Table 1. Baseline characteristics of patients

No.	Age (years)	Gender	WHO class	6MWD (m)	RVSP (mmHg)	PVR (wood units)	mPAP (mmHg)	FVC (% predict)
1	69	Female	III	195	110	NA	39	85
2	44	Female	III	132	64	NA	30	34
3	52	Female	III	111	60	14.6	42	58
4	60	Male	III	165	85	8.5	44	58
5	63	Female	III	156	49	4.4	29	62
6	54	Female	III	108	114	16.7	57	45
7	54	Male	III	213	64	4.8	40	74
8	49	Male	III	306	58	5.5	35	49
9	53	Female	III	407	46	5.3	37	58
10	53	Male	III	348	58	6.4	35	90

Table 2. WHO functional class and changes in 6 minute walking distance in meters during study

No.	Baseline WHO functional class	6 month WHO functional class	12 month WHO functional class	Baseline 6MWD (m)	6 month 6MWD (m)	6 month walk distance increment (m)	12 month 6MWD (m)	12 month walk distance increment (m)
1	III	III	III	195	191	-4	207	12
2	III	III	III	132	342	210	343	211
3	III	II	III	111	243	132	234	123
4	III	II	III	165	327	162	327	162
5	III	II	II	156	378	222	387	231
6	III	II	II	108	294	186	324	216
7	III	III	II	213	272	59	390	177
8	III	III	III	306	354	48	307	1
9	III	III	II	407	396	-11	401	-6
10	III	III	III	348	463	115	261	-87

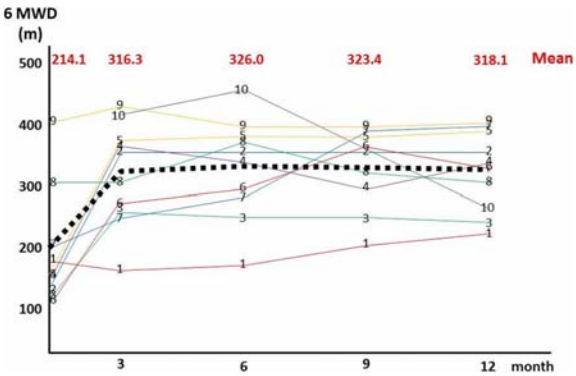

Figure 1. The changes in 6 minute walking distance in meters during study.

Discussion

The 2015 ESC/ERS guidelines for the diagnosis and treatment of PAH[2] categorize patients by their functional class to decide which of PAH specific medication(s) should be given to the patient. In patient with Functional Classes II and III, monotherapy with PAH specific medication can be begun. In patients, who did not respond to the first medication, the treatment regimen could be combined with other medications in different groups. However, in Thailand, the treatment of pulmonary hypertension is expensive. Before the year 2014, most of Thai patients could receive only nifedipine for treatment, and as a result, they died prematurely by natural causes as described in our previous publication[3]. Bosentan is a PAH specific agent, belonging to a group of drugs called endothelin receptor antagonists. It has been reported to be efficacious in the treatment of scleroderma-related pulmonary arterial hypertension[4]. Launay, et al

Table 3. Adverse events in individual patients

Patient number	Adverse events
1	Upper gastrointestinal hemorrhage, anemia, digital ulcers on fingers
2	Cystitis
3	Mild right-sided heart failure
4	Digital ulcers on fingers
5	None
6	Elevation of ALT, AST less than 2 time ULN
7	Alveolitis
8	Pneumonia, bronchitis
9	None
10	Hypotension, digital ulcers on toes, arthralgia

reported that more patients had NYHA functional class II after 4 months of bosentan treatment (6 patients vs. 16 patients from the overall 44 patients). However, in their report, no significant improvement in 6MWD was detected. In our series, bosentan was able to provide clinical improvement of patients as defined by change to WHO functional class III to WHO functional class II in 4 patients(40%).Although, the 6 MWD in systemic sclerosis patient may be affected by other factors, such as joint contraction, muscle problems, and foot ulcer conditions, a meaningful clinical improvement of 6 MWD of more than 54 meters[5] was found in 7 patients (70%) at month#6, and at the end of study (60%). Patients with underlying connective tissue disease, that was related to pulmonary arterial hypertension, may receive benefit from immunosuppressive treatment, mostly in SLE, Sjogren, and mixed connective tissue disease[6], but not in systemic sclerosis. 50% of patients in our study had significant alveolitis, and as a result, received oral cyclophosphamide for treatment. The authors could not find any difference results in either groups in terms of functional class improvement or the 6MWD. There was no death during the 12 month treatment period. After completion of this study, all patients were enrolled to the extension study in order to evaluate their long-term clinical outcomes and survival. Patients were provided with the PAH-specific medications. In accordance with each patient's level of health coverage, for 2 of the patients, bosentan continued to be prescribed, while the other 8 patients were switched to sildenafil. The results of the survival and other outcomes of these 10 patients will be followed and will be reported at a later date.

The adverse reactions in the present study were similar to other studies. For example, hepatitis was mild and transient. No patients withdrew from the treatment during 12 month period. Although, bosentan can prevent digital ulcers[7] in patients with systemic sclerosis, three of our patients developed new digital ulcers; two displayed finger ulcers, and one displayed foot ulcers during treatment with 125 mg bid of bosentan. Despite this fact, the ulcers were able to heal without the use of any added PDE-5 inhibitors or prostanoids.

Conclusion

Bosentan can be used as a form of monotherapy in dcSSc patients with pulmonary fibrosis who are suffering from WHO Functional Class III PAH. Moreover, this drug (which has a good level of tolerability) can, with respect to exercise endurance of patients, provide clinical improvement as has been demonstrated by improvements in the patients' WHO Functional Class and their 6MWD.

What is known about this topic?

Bosentan is an effective treatment for primary pulmonary hypertension. It can be use as monotherapy or in combination with other PAH specific drugs. Its efficacy in SSc related pulmonary hypertension who has significant interstitial lung disease was not known because it is an exclusion for almost all studies.

What this study adds?

Bosentan can be used as a form of monotherapy in dcSSc with pulmonary fibrosis.

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Disclosure

In the present study, the medication, bosentan, was provided by Actelion. However, no additional support was received from the company.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Ruangjutipopan S, Kasitanon N, Louthrenoo W, Sukitawut W, Wichainun R. Causes of death and poor survival prognostic factors in thai patients with systemic sclerosis. J Med Assoc Thai 2002;85:

1204-9.
2. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67-119.
3. Foocharoen C, Nanagara R, Kiatchoosakun S, Suwannaroj S, Mahakkanukrauh A. Prognostic factors of mortality and 2-year survival analysis of systemic sclerosis with pulmonary arterial hypertension in Thailand. Int J Rheum Dis 2011;14:282-9.
4. Launay D, Sitbon O, Le Pavec J, Savale L, Tcherakian C, Yaici A, et al. Long-term outcome of systemic sclerosis-associated pulmonary arterial hypertension treated with bosentan as first-line monotherapy followed or not by the addition of prostanoids or sildenafil. Rheumatology (Oxford) 2010;49:490-500.
5. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. Am J Respir Crit Care Med 1997;155:1278-82.
6. Sanchez O, Sitbon O, Jais X, Simonneau G, Humbert M. Immunosuppressive therapy in connective tissue diseases-associated pulmonary arterial hypertension. Chest 2006;130:182-9.
7. Matucci-Cerinic M, Denton CP, Furst DE, Mayes MD, Hsu VM, Carpentier P, et al. Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. Ann Rheum Dis 2011;70:32-8.