

Effect of transition from sitaxsentan to ambrisentan in pulmonary arterial hypertension

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Introduction: Currently available endothelin receptor antagonists for treating pulmonary arterial hypertension block either the endothelin (ET) receptor A or both A and B receptors. Transition from one endothelin receptor antagonist to another may theoretically alter side-effects or efficacy. We report our experience of a transition from sitaxsentan to ambrisentan, both predominant ET_A receptor antagonists, in pulmonary arterial hypertension patients.

Methods: At Baylor Pulmonary Hypertension Center, 18 patients enrolled in the open-label extension phase of the original sitaxsentan studies (Sitaxsentan To Relieve Impaired Exercise) were transitioned to ambrisentan (from July 2007 to September 2007) at the time of study closure. Pre-transition (PreT), 1 month (1Mth) and 1 year (1Yr) post-transition assessments of 6-minute walk distance (6MWD), brain natriuretic peptide (BNP) levels, WHO functional class (WHO FC), Borg dyspnea score (BDS), oxygen saturation, liver function, and peripheral edema were compared.

Results: 6MWD was 356 ± 126 m at PreT, 361 ± 125 m at 1Mth, and 394 ± 114 m at 1Yr (mean \pm SD). There was no difference in the walk distance at 1Mth and 1Yr post transition compared with PreT ($P = 0.92$, 0.41 respectively). Oxygen saturation was no different at 1Mth and 1Yr to PreT level ($P = 0.49$ and $P = 0.06$ respectively). BNP was 178 ± 244 pg/mL at PreT, 129 ± 144 pg/mL at 1Mth and 157 ± 201 at 1Yr. Peripheral edema was present in 7/18 patients at PreT, in 8/16 patients at 1Mth, and in 6/13 patients at 1Yr post transition. Proportions of patients with edema over these 3 time points did not change significantly ($P = 0.803$). At 1Yr, 2 patients had died, 1 had undergone lung transplantation, 1 had relocated, and 1 patient was started on intravenous prostacyclin therapy. Over 3 points (baseline, 1 month, and 1 year), there was no significant change in function class ($P = 0.672$).

Conclusion: Our limited data suggest that ET_A receptor antagonists can be switched from one to another with sustained exercise capacity and maintained WHO FC with no increase in incidence of peripheral edema.

Keywords: right heart failure, 6-minute walk distance, endothelial receptor antagonist, echocardiogram

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease resulting from pulmonary vascular remodeling leading to right heart failure.¹ Endothelin 1 (ET-1), a modulator of pulmonary vascular remodeling, has an important role in the pathophysiology of this disease. ET-1 binds to 2 receptors, ET_A and ET_B. Endothelin receptor antagonists (ETRAs) block either A or A and B receptors are used to treat PAH. Two Food and Drug Administration (FDA) -approved ETRAs are available to treat PAH in the US. Sitaxsentan, a predominantly ET_A receptor antagonist, was studied

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in the US, Europe, and Canada; sitaxsentan was approved in Europe and Canada but did not receive FDA approval in the US. Thus patients enrolled in open label sitaxsentan extension studies were transitioned to ambrisentan at the time of sitaxsentan study closure. We report our single-center experience of patients transitioning from sitaxsentan to ambrisentan after study closure.

To date indications for changing from one ETRA to another ETRA are anecdotal. Side effect profiles such as liver toxicity and drug interactions differ between these ETAs.² Due to the predominant blockade of endothelin A receptor with sitaxsentan we decided to switch our patients from sitaxsentan to ambrisentan (both predominantly ET_A receptor antagonists). We present the available long-term clinical data for 18 patients switched to ambrisentan at the time of sitaxsentan study closure.

Method

Eighteen PAH patients were enrolled in the open-label extension phase of the original sitaxsentan studies (Sitaxsentan To Relieve Impaired Exercise [STRIDE] -2, -3 and -6) at Baylor Pulmonary Hypertension Center. All patients were on 100 mg oral daily of sitaxsentan. Patients were enrolled in the open label extension phase of clinical studies, which permitted addition of other PAH medications as clinically indicated. These patients were changed to ambrisentan (5 mg oral daily) (between July 2007 and September 2007) at the time of study closure. This transition was necessary because sitaxsentan did not gain FDA approval in US and hence this drug was unavailable to patients after sitaxsentan study was closed.

Data was collected for each patient at pre-transition (PreT), 1 month (1Mth) (48 ± 28 days, range 19–123), and 1 year (1Yr) post transition (401 ± 73 days, range 252–489). Collected data included 6-minute walk distance (6MWD), brain natriuretic peptide (BNP) plasma concentrations, WHO functional class (WHO FC), Borg dyspnea score (BDS), presence of peripheral edema, changes in diuretic dose, and liver function tests. Patient 2 was hospitalized at the time of transition for acute gastroenteritis and remained in the hospital till he died from worsening right heart failure. Hence limited data were available for patient 2. Patient 17 had only laboratory testing done at 1Mth and was unable to do the walk test at 1Yr due to severe hip pain. Patient 3 was taken off ambrisentan and started on intravenous treprostinil due to worsening pulmonary hypertension 9 month post transition and died 13 months post transition. This patient did not have a walk test done at 1Yr because of severe back pain,

which was considered a treprostinil related side-effect by the treating physician. Patient 18 progressed to WHO FC IV at 1Mth from WHO FC III at baseline and subsequently underwent lung transplantation 5.5 months post transition. Patient 9 relocated 5 months post transition. Hence, 1Yr data available for 13 patients was included in this analysis.

Statistical analysis

All data are reported as mean \pm standard deviation (SD) unless stated otherwise. Differences between groups were determined by using paired Student's *t*-test. A chi-square test was used to evaluate the significance of change of WHO FC over 3 time points. We also used a chi-square test to examine the difference in proportions of patients who experienced edema at 3 time points. Analyses were conducted using SAS (v. 9.2; SAS Institute Inc., Cary, NC). Significance was accepted at $P < 0.05$ and all hypothesis testing was two-sided.

Results

Demographic and baseline characteristics are outlined in Table 1. There were 15 females and 3 males with a mean age of 52 ± 14 (mean \pm SD). At 1Mth, the ambrisentan dose was increased in 7 patients to 10 mg and 10 patients were continued on 5 mg dose. Patient 2 was on ambrisentan 5 mg when he died in the hospital. At 1Yr, 8 patients were on 10 mg dose, 5 patients remained on 5 mg, and 1 patient was taken off ambrisentan for worsening disease and started on intravenous prostacyclin therapy (patient 3). Patient 11 had sildenafil added to ambrisentan 4 months prior to 1Yr. None of the patients discontinued ambrisentan due to liver function abnormalities (Table 2). Patient 15 had increased aspartate aminotransferase at 1Mth ($3.5 \times$ upper limit of normal) which returned to normal on repeat testing in 1 week without interruption in therapy.

6MWD was 356 ± 126 m at PreT, 361 ± 125 m at 1Mth, and 394 ± 114 m at 1Yr. There was no difference in the 6MWD at 1Mth and at 1Yr compared with PreT ($P = 0.92$ and $P = 0.41$ respectively) (Figure 1). BNP was not significantly different at 1Mth and at 1Yr compared with PreT ($P = 0.50$ and $P = 0.83$ respectively) (Figure 2). BDS was 2.5 ± 1.2 (range 0 to 4) at PreT in 17 patients, 2.4 ± 1.4 (range 0 to 4) at 1Mth in 16 patients and 2.6 ± 1.3 (range 0.5 to 5) at 1Yr in 12 patients (Figure 3). These values was not significantly different ($P = 0.88$ and 0.81 respectively).

Eleven of the 18 patients were idiopathic PAH (IPAH) patients. Patients were divided into 2 groups – IPAH, and PAH associated with other conditions, and data was analyzed to

Table 1 Demographics and baseline patient characteristics of transitioned patients

Patient number	Age, yr	Gender	Race	BMI, kg/m ²	PAH etiology	PAH medications*	Duration of illness at transition, yrs
1	50	F	C	19.31	IPAH	None	6.3
2	44	M	C	21.89	CHD associated PAH	Treprostinil, sildenafil	5.4
3	72	M	C	20.48	IPAH	Iloprost, sildenafil	3.9
4	54	F	C	28.03	CTD associated PAH	Sildenafil	4.3
5	42	F	C	34.37	IPAH	Sildenafil	7.9
6	60	F	H	25.24	IPAH	Sildenafil	7.4
7	53	F	C	36.39	IPAH	Sildenafil	3.6
8	32	M	C	43.45	IPAH	Sildenafil, iloprost	3.3
9	33	F	Asian	21.4	CHD associated PAH	Iloprost	4.8
10	49	F	C	26.73	CTD associated PAH	Sildenafil	3.8
11	56	F	H	31.17	IPAH	None	3.0
12	68	F	H	31.95	IPAH	Sildenafil	3.4
13	59	F	C	24.58	CTD associated PAH	None	7.2
14	67	F	Asian	23.04	IPAH	Sildenafil, Iloprost	4.6
15	45	F	Asian	25.56	CHD associated PAH	None	37
16	25	F	C	24.85	IPAH	Sildenafil	1.2
17	73	F	C	25.68	IPAH	Sildenafil	6.8
18	61	F	C	23.4	IPAH	Epoprostenol	7.7

Note: *In addition to sitaxsentan.

Abbreviations: PAH, pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; CTD, collagen tissue disease; CHD, congenital heart disease; C, Caucasian; H, Hispanic; BMI, body mass index.

determine whether our findings would differ in patients with different PAH etiologies. There was no significant difference between the 2 groups at PreT, 1Mth, and 1Yr in 6MWD ($P = 0.42, 0.34, 0.27$ respectively), BNP levels ($P = 0.63, 0.90, 0.55$ respectively), oxygen saturation ($P = 0.35, 0.47, 0.06$ respectively), and BDS (0.55, 0.45, 0.39 respectively).

Peripheral edema was present in 7/18 patients at PreT, 8/16 patients at 1Mth, and in 6/13 patients at 1yr (Figure 3). At 1Mth, the diuretic dose was increased in 2 of the 16 patients (patients 4 and 18). At 1Yr, a second diuretic was added for patient 4. Proportions of patients with edema over these 3 time points did not change significantly ($P = 0.803$).

Oxygen saturation was not different at 1Mth compared with PreT ($P = 0.49$). Oxygen requirements remained unchanged except for 1 patient who was on room air PreT and was started on 2 L oxygen at 1Mth and remained on 2 L at 1Yr. 1Yr data

were available for 13 patients and oxygen saturation slightly improved compared with PreT ($P = 0.06$).

Over 3 points (PreT, 1Mth, and 1Yr), there was no significant change in WHO function class ($P = 0.672$) (Figure 4).

Discussion

In this single-center retrospective study switching from sitaxsentan to ambrisentan was safe and efficacy was maintained. At the end of the open label extension phase of STRIDE studies, we switched all of the patients then enrolled to ambrisentan. In the open label extension phase, addition of PAH therapies was allowed. Prior to transitioning, 3 patients enrolled in this extension phase had died. Our data suggest that switching from a selective ETRA to another selective ETRA may be reasonable and safe. However, 3 patients in our cohort developed disease worsening and 2 patients died

Table 2 Serum aminotransferase concentrations in transitioned patients

	Pre transition	1 month post transition	1 year post transition
AST (mU/mL)	19 ± 8	31 ± 35*	26 ± 19
ALT (mU/mL)	16 ± 7	23 ± 23	24 ± 18

Notes: *Patient 15 AST increased to 151 mU/mL at 1 month then decreased to 19 mU/mL in 1 week without any intervention. This patient was subsequently switched to bosentan (3 months post transition) for worsening right heart failure and died 5 months after transition. Normal laboratory values: AST = 10–42 mU/mL; ALT = 10–60 mU/mL.

Abbreviations: AST, aspartate aminotransferase; ALT, alanine transaminase.

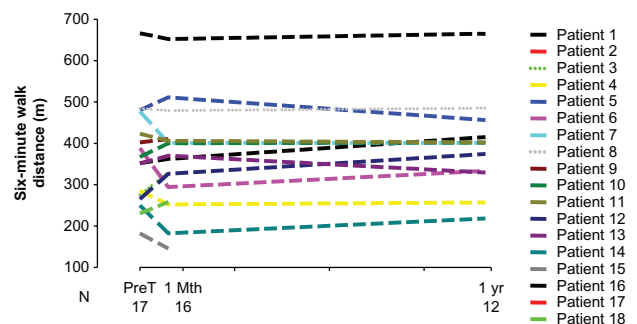


Figure 1 Six-minute walk distance at transition and follow-up in PAH patients. **Abbreviation:** PAH, pulmonary hypertension.

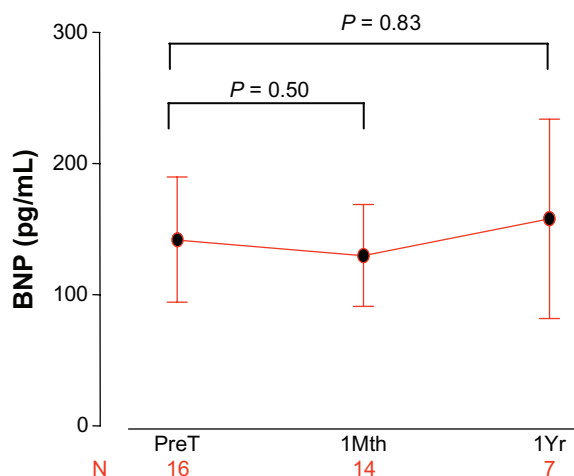


Figure 2 BNP levels at transition and follow-up in PAH patients. Data presented as mean \pm standard error.

Abbreviations: BNP, brain natriuretic peptide; PAH, pulmonary hypertension.

after this change, suggesting that individual responses to selective ET receptor antagonists may vary.

Ambrisentan and sitaxsentan are both ET_A -selective antagonists. Based on in vitro competitive receptor binding assay, ambrisentan has a 77-fold affinity for ET_A compared with ET_B receptors.³ On the other hand, sitaxsentan has a ~6500-fold affinity for ET_A compared with ET_B receptors.^{4,5} Activation of the ET_A receptor on smooth muscle cells causes sustained vasoconstriction and proliferation of these cells. However, activation of ET_B on endothelial cells

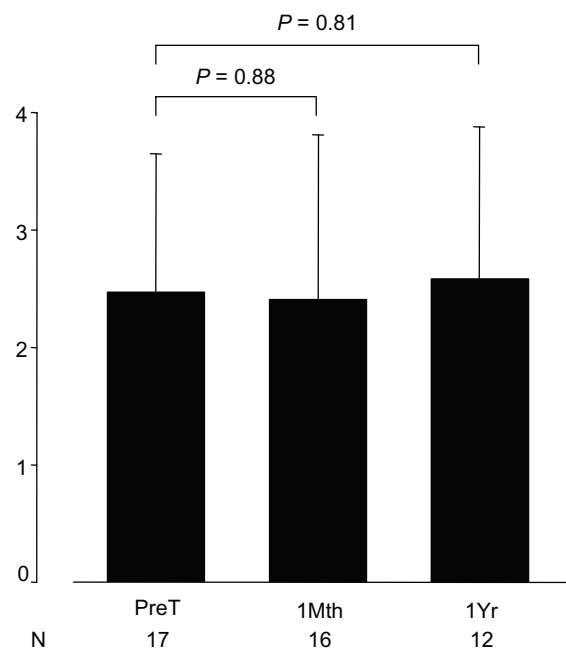


Figure 3 Borg dyspnea score at transition and follow-up in PAH patients. Data presented as mean \pm standard deviation.

Abbreviations: PAH, pulmonary hypertension; SD, standard deviation.

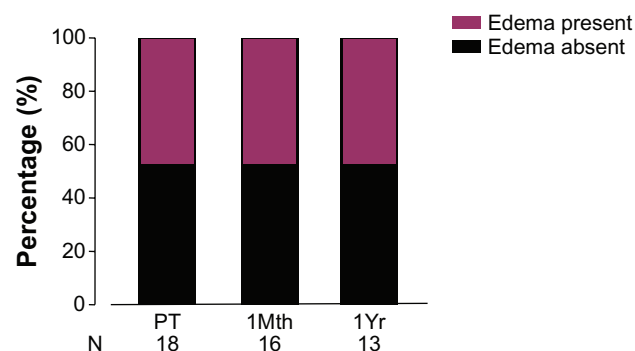


Figure 4 Presence of peripheral edema at transition and follow-up. Data presented as percentage (%). One patient had undergone lung transplantation, 1 patient had relocated, and 2 patients had died at 1 year follow-up.

induces clearance of ET-1 from the circulation and mediates vasodilation through the activation of NO and prostacyclin. This selectivity of ET_A receptor blockages has been proposed to prevent the deleterious effects of ET_A , while allowing the favorable effects of ET_B .² However, this difference in selectivity has not translated into substantial differences in clinical efficacy, as shown by the published clinical studies.⁶⁻¹⁰ Our data show that the walk distance was maintained for up to 1 year after the switch in the ETRA. This suggests that selective ETRA can be used interchangeably as required by the clinical necessity. However, we caution against using this data for the dual receptor ETRA, because we switched our patients to a selective ETRA, ambrisentan, in our cohort.

Both ambrisentan and sitaxsentan have a long half-life and require once daily dosing.^{7,11,12} Ambrisentan is a propanoic acid-based compound that is metabolized predominately by glucuronidation and transported via the bile. Sitaxsentan is derived from amidothiophenesulphonamides by a series of chemical modifications. It is metabolized by the CYP2C9 and CYP3A4 with 50% to 60% of the dose excreted in the urine and the remaining in feces. The incidence of liver function

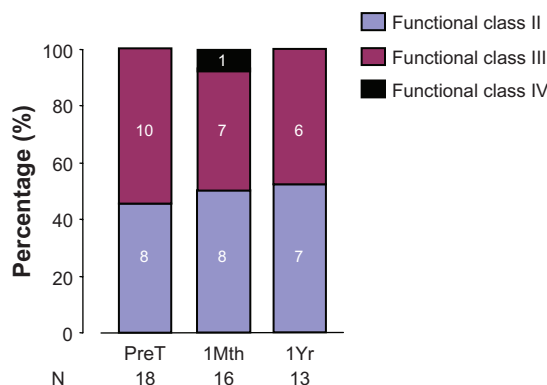


Figure 5 WHO Functional Class at transition and at follow-up in transitioned patients. Data presented as percentage (%).

test abnormalities is similar between the two drugs (3% with both ambrisentan and sitaxsentan).^{7,11,13}

Transitioning from one ETRA to another ETRA may be required in different clinical situations. This may be because of side-effects, liver function abnormalities, or availability of the drug. McGoon et al have previously shown that patients who discontinued bosentan due to liver function test abnormalities tolerated ambrisentan and this change resulted in improvement in walk distance.¹⁴ We have previously shown that carefully selected patients can be safely transitioned from intravenous prostacyclin to oral agents.¹⁵ Our data was obtained from patients with normal liver function who were switched to ambrisentan when the sitaxsentan did not gain FDA approval in US. We included patients who died, were lost to follow-up, or underwent lung transplantation. We did not exclude any patient to prevent an introduction of bias in data collection. Patient 15 in our cohort developed transient elevation in transaminase, which resolved spontaneously without any medical intervention. This patient had a congenital heart defect (ventricular septal defect), Eisenmenger physiology, and Down syndrome. This patient was not on any additional PAH therapy due to significant underlying medical conditions and parents' request. This patient did not develop increased edema at 1Mth and the parents felt that the breathing was unchanged. However, this patient developed an intolerable cough and 3 months post transition the walk distance had significantly deteriorated and therefore the patient was switched to bosentan and subsequently died 5 months post transition. It is conceivable that the clinical condition may have deteriorated when this patient was switched from sitaxsentan to ambrisentan. On the other hand, this patient was 45 years of age at the time of transition and had been diagnosed with PAH for the previous 37 years. Possibly this patient was at the end of the disease spectrum.

Peripheral edema is considered to be a class side-effect of ETRAs,¹⁶ with a greater percentage of older patients (>65 years) experiencing higher rates of peripheral edema.¹⁶ Some ETRAs were thought to be associated with more peripheral edema than others. However, our data suggest that at least in the selective ETRAs there was no significant worsening of peripheral edema. None of the patients required intravenous diuresis or hospitalization for worsening edema. One patient, however, who was already in the hospital at the time of study closure, developed worsening right heart failure and subsequently died. This could have been related to the progression of disease or, on the other hand, may have been related to worsening right heart failure as a consequence of increased fluid retention caused by a switch in the ETRA.

Therefore, switching ETRA in patients with marginal clinical status should be undertaken cautiously. We do not recommend switching between ETRAs without a compelling reason such as when side-effects must be mitigated. Hence, such switches should be undertaken only when they confer a greater clinical benefit to the patient.

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Disclosure

ZS has been on Gilead Science, Actelion, United Therapeutics and Pfizer advisory boards and has provided consultancy for these companies.

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