

Long-Term Results of Sitaxentan Therapy in Pulmonary Arterial Hypertension (PAH) Associated With Connective Tissue Disease (CTD)

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Abstract

Background: PAH is a leading cause of mortality and late disease morbidity in systemic sclerosis (SSc) and other CTDs. Subgroup analyses from short-term (12–18 week) randomized controlled trials (RCTs) in PAH have demonstrated benefit in exercise capacity, functional status, hemodynamics, and quality of life in response to a variety of agents, although all outcome measures appear blunted in PAH-CTD patients in comparison to patients with idiopathic PAH. Long-term controlled data are not available. Important measures such as survival and time to clinical worsening are thus estimated from open-label (OL) observational series.

Objectives: We examined survival in patients with PAH-CTD receiving sitaxentan 100 mg daily (started as monotherapy as part of their chronic medical regimen) in an OL experience of up to 3 years.

Methods: Sitaxentan is an oral bioavailable selective antagonist of the endothelin-A receptor. An 18-week RCT (STRIDE-2) compared sitaxentan 100 mg and 50 mg with placebo; an OL cohort on bosentan (nonselective endothelin antagonist) was also included for observational comparison only. The 18-week RCT was followed by a one year OL comparison of sitaxentan 100 mg with bosentan (both as monotherapy; STRIDE-2X) (*Chest*. 2008;134:775-82). In post-hoc analyses of the CTD subgroup from 2X receiving sitaxentan 100 mg vs bosentan, outcomes raised the possibility of improved outcomes with sitaxentan including survival, time to clinical worsening, and discontinuations for adverse events including liver function test abnormalities (*Ann Rheum Dis*. 2006;65(suppl II):393).

Results: Data are now available on 42 CTD patients treated with sitaxentan 100 mg QD for 3 years including STRIDE-2, -2X, and -3 (OL extension of the one year 2X, early rollover from 2X for patients in whom additional PAH meds were started before completion of the one year OL extension, and bosentan patients stopping bosentan in 2 or 2X to start sitaxentan in 3 (**Table 2**)).

Disclosure of Interest: Drs. Seibold, Benza, Frost, Gaine, Hill, Highland, Langleben, and Naeije have received research funding, speaker fees, and consultancy payment from Pfizer/Encysive (the sponsor of this study). Dr. Davie is a full-time employee of Pfizer.

Conclusion: PAH survival appears to be improving in the modern era with currently available PAH drugs. An analysis similar to that as above of the CTD subgroup receiving bosentan during OL extensions of previously reported RCTs revealed survival rates of 85.9% at one year and 73.4% at 2 years (*Ann Rheum Dis*. 2006;65:1336-40), which was comparable to the 80% survival at one year in STRIDE-2X for those patients on bosentan. Survival with PAH associated with CTD has been reported from the UK PAH Centers as 78% at one year and 47% at three years (*Am J Respir Crit Care Med*. 2009;179:151-7). While protocol-derived cohorts may differ from general community experience, these OL studies suggest improved survival in PAH associated with CTD in the era of modern targeted therapies including endothelin receptor antagonists.

Introduction

- Pulmonary arterial hypertension (PAH) is a leading cause of death and late disease morbidity in patients with systemic sclerosis (SSc, scleroderma).
- PAH occurs in 8%–12% of patients with connective tissue disease (CTD).^{1,2}
- Survival is reduced in PAH associated with CTD in comparison to patients with idiopathic PAH.³
- Factors influencing survival include older patient age, concomitant interstitial lung disease, concomitant left ventricular diastolic dysfunction, other organ comorbidities, and unrecognized right ventricular diastolic dysfunction.^{4,7}
- Long-term controlled trials are not yet available. Open-label observational studies suggest improved survival in patients with CTD-associated PAH in comparison with historical controls.⁸

Background

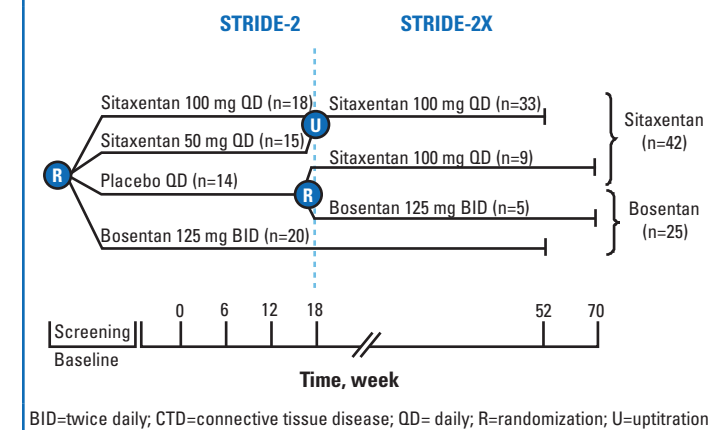
- Sitaxentan sodium (Thelin[®]) is an orally bioavailable, highly selective endothelin receptor antagonist (ET_A, 6500:1 ET_A:ET_B) licensed in the European Union, Canada, and Australia for the treatment of patients with PAH classified as World Health Organization Functional Class III (and Class II in Canada).

- Endothelin-1 levels are increased in plasma and tissue of patients with SSc and have been implicated in vasospastic, vasoproliferative, fibrotic, and inflammatory features of illness.⁵
- A 1-year, open-label, observational study suggested that sitaxentan at 100 mg daily may be associated with improved survival, increased time to clinical worsening, and improved tolerance of therapy in comparison with bosentan 125 mg twice daily.⁹

Methods

- Initial findings from the trial have been reported.⁹
- The first phase of the STRIDE-2 trial was double-blinded for the 2 doses of sitaxentan and placebo, whereas the bosentan arm was an open-label observational safety arm (**Figure 1**).
- STRIDE-2X was an open-label study (**Figure 1**).

Figure 1. STRIDE-2/2x Study Design: CTD Subgroup



- At completion of STRIDE-2X, patients continued on open-label sitaxentan at 100 mg daily in STRIDE-3.
- Results are presented from the first date of exposure to sitaxentan 50 mg or 100 mg once daily.
- We ascertained survival status (dead/alive) at annual intervals. We report here the available data at 3 years.

Results

- 42 CTD patients were treated with sitaxentan 100 mg daily for 3 years, including STRIDE-2, -2X, and -3 (OL extension of the one year 2X, early rollover from 2X for patients in whom additional PAH medications were started before completion of the one year OL extension, and bosentan patients stopping bosentan in 2 or 2X to start sitaxentan).
- Patient mean age was 59.8 (range, 22–78) years, and most patients were women (90%) and white (79%) (**Table 1**).

Table 1. Patient Characteristics (n=42)

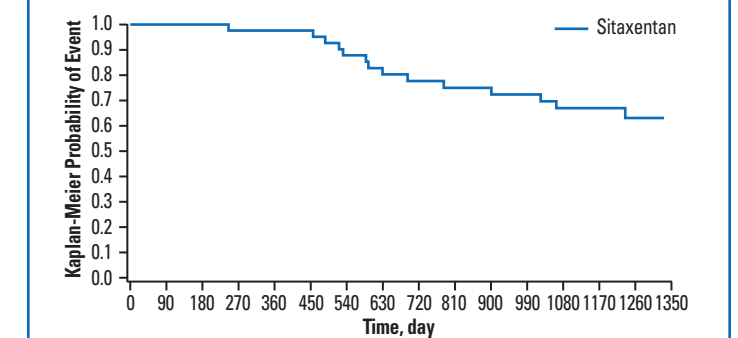
Men/women, n	4/38
Age, mean (range), y	59.8 (22–78)
Race/ethnicity, n	
White	33
Black	8
Hispanic	1
Hemodynamic parameters at baseline, mean (SD)	
Mean pulmonary artery pressure, mmHg	41.4 (10.7)
Pulmonary capillary wedge pressure, mmHg	8.5 (3.7)
Pulmonary vascular resistance, mmHg/L/min	9.7 (6.9)
Mean right atrial pressure, mmHg	8.3 (6.6)
Cardiac index, L/min/m ²	2.5 (0.72)

- Survival (Kaplan-Meier estimates) was 98% at 1 year, 78% at 2 years, and 67% at 3 years for patients receiving sitaxentan 100 mg daily (**Table 2, Figure 2**).

Table 2. Survival Analysis (n=42)

	Year 1 Cut-off	Year 2 Cut-off	Year 3 Cut-off
Total patients at risk, n	41	30	25
Patients died, n	1	9	13
Patients censored before cut-off, n	0	3	4
Kaplan-Meier rate, %	97.6	77.7	67.0

Figure 2. Kaplan-Meier Plot



Discussion

- Firm conclusions may not be made from open-label observational studies.
- Open-label follow-up of protocol-based cohorts may differ from general practice and the experiences of referral centers.⁴
- Ethical considerations present challenges to performing long-term placebo-controlled trials in PAH.
- Sample size requirements of noninferiority trials present challenges to performing long-term comparison trials in PAH.

Conclusion

- Survival in this cohort of patients with PAH associated with CTD (67% survival after 3 years) exceeds the one-year survival rate of 45% reported from the era before modern specific therapies.⁶

References

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