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


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 SSC have demonstrated a benefit in exercise capacity, functional status, hemodynamics, and quality of life in response to a variety of agents, although all outcome measures appear limited 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 110 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 orally 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) (Chesn 2006;134:775-82). In post-BOC analysis of the CTD subgroup from long-term sitaxentan 100 mg in bosentan, outcomes 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):III).

Results: Data are now available on 42 CTD patients treated with sitaxentan 100 mg QD for 3 years including STRIDE-2X, 50 mg QD, and 3 QD of the one year QD, early stay with 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 in 3 (Table 2).

Discussion: Drs. Seibold, Benza, Frost, Gaine, Hill, Highland, Langleben, and Naeije have received research funding, speaker fees, and consultancy payment from Pfizer (co-sponsor of the study). Dr. Davis 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 above of the CTD subgroup receiving bosentan during OL extensions of prospective patients reported RCTs remains survival at 85.0% at year and 73.4% at 2 years (Ann Rheum Dis 2006:65(suppl II):III), which was comparable to the 8% survival at one year in STRIDE-2 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 (Ann Respir Crit Care Med 2009;70:151-7). 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). Survival is reduced in PAH associated with CTD in comparison to patients with idiopathic PAH. Factors influencing survival include older patient age, concomitant interstitial lung disease, concomitant left ventricular dysfunction, other organ comorbidities, and unrecognized right ventricular diastolic dysfunction. Long-term controlled trials are not yet available. Open-label observational studies suggest improved survival in patients with PAH associated with CTD in comparison with historical control.

Background

Sitaxentan (Thalban®) is an orally bioavailable, highly selective endothelin receptor antagonist (ETR A/B, 6500 I ET B/T) licensed in the European Union, Canada, and Australia for the treatment of patients with PAH classified as World Health Organization Functional Class II (and Class II in Canada).

At completion of STRIDE-2X, patients continued on open-label sitaxentan 100 mg daily in one arm of STRIDE-3. Results are presented from the first date of exposure to sitaxentan 50 mg or 100 mg daily for one year.

We accepted survival status (dead/alive) at annual intervals. We report here the available data from 3 years.

Disclosure of Interest:

J. R. Seibold, R. Benza, N. Davies, A. Frost, S. Gaine, N. S. Hill, K. Highland, D. Langleben, R. Naeije have received research funding, speaker fees, and consultancy payment from Pfizer (co-sponsor of the study). Dr. Davis is a full-time employee of Pfizer.


1Scleroderma Program, University of Michigan, Ann Arbor, MI, USA; Cardiovascular Research, Allegheny General Hospital, Pittsburgh, PA, USA; Cardiovascular Research, Pfizer Inc, London, UK; Pulmonary Hypertension, Baylor College of Medicine, Houston, TX, USA; Pulmonary Hypertension. Tufts Medical Center, Boston, MA, USA; Pulmonary, Medical University of South Carolina, Charleston, SC, USA; Cardiology, Montreal Jewish Hospital, Montreal, QC, Canada; Intensive Care, Universite Libre de Bruxelles, Brussels, Belgium

References


Table 1. Patient Characteristics (n=42)

Table 2. Survival Analysis (n=42)

Table 3. Kaplan-Meier Plot

Figure 2. Kaplan-Meier Plot

Discussion

Firma conclusions may not be made from open-label observational data.

Open-label follow-up of protocol cohorts may differ from general practice and the experiences of referral centers.

Ethical considerations present challenges to performing long-term placebo controlled trials in PAH.

Sample size requirements of noninferiority trial present challenges to performing long-term comparison trials in PAH.

Conclusion

Survival in a cohort of patients with PAH associated with CTD (87% survival at 3 years) exceeds the one-year survival rate of 40% reported from the era before modern specific therapies.

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