A Review of Sitaxsentan Sodium in Patients with Pulmonary Arterial Hypertension

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A review of sitaxsentan sodium in patients with pulmonary arterial hypertension

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Abstract: Pulmonary arterial hypertension (PAH) is a life threatening, progressive condition which eventually leads to fatal right heart failure. Endothelin-1 (ET-1), a potent vasoconstrictor peptide, is increased in the pulmonary arteries of patients with pulmonary hypertension. Endothelin-1 acts through the stimulation of 2 subtypes of receptors (endothelin receptor subtypes A [ETA] and B [ETB]). In PAH patients, ETRAs block the deleterious vasoconstrictor effects of ET-1, and ETRA treatment in PAH patients has been shown to be safe and efficacious. Sitaxsentan is an orally active, highly ETA selective ETRA that, in clinical trials, has demonstrated improvements in exercise capacity, functional class and hemodynamics in PAH patients. Sitaxsentan has been shown to be safe, well tolerated, and associated with a lower incidence of liver toxicity than other approved ETRAs.

Keywords: endothelin receptor antagonist, endothelin receptor inhibitor, endothelin A, sitaxsentan, pulmonary hypertension, endothelin

Introduction
Pulmonary arterial hypertension (PAH) is a life threatening, progressive condition characterized by vascular remodeling and vasoconstriction within small pulmonary arteries, resulting in progressive increases in mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR), leading to fatal right-heart failure (Rich et al 1987; Rich 1998). While the pathogenesis of idiopathic pulmonary arterial hypertension (IPAH) is not fully understood, there is a decreased production of mediators with anti-remodeling, platelet disaggregating, and vasodilator properties, including prostacyclin and nitric oxide. Additionally, there is an excess production of mediators with profibrotic and/or prothrombotic effects, smooth muscle cell mitogenic, and vasoconstrictor properties, such as angiotensin II, endothelin-1 (ET-1), serotonin, and thromboxane A2. These are believed to facilitate narrowing of the pulmonary vascular lumen and to increase vascular resistance as the result of vasoconstriction, vascular wall remodeling, and thrombosis in situ (Barst 2001).

Endothelin-1, a potent vasoconstrictor peptide, is increased in the pulmonary arteries of patients with pulmonary hypertension(Giaid et al 1993); endothelin levels are also increased and correlate with the severity of disease in adults with idiopathic primary pulmonary arterial hypertension (IPAH) (Rubens et al 2001). A strong correlation was found between increased plasma concentrations of ET-1 and increased pulmonary vascular resistance, as well as increased mean pulmonary arterial pressure, in a small cohort of subjects with primary pulmonary hypertension (PPH). In addition, a decreased 6-minute walk distance (6MWD) was also observed (Rubens et al 2001).

Two distinct endothelin (ET) receptor isoforms have been identified; Type A (ETA) and Type B (ETB) (Benigni and Remuzzi 1999). The known pathobiologic effects of ET-1 are believed to be principally mediated through the ETA receptor, which is found primarily on vascular smooth muscle cells and cardiac myocytes. Activation of ETA receptors facilitates sustained vasoconstriction of vascular smooth muscle,
stimulation of cell proliferation or hypertrophy of vascular smooth muscle cells of myocardium. In contrast, ET$_B$ receptors are found primarily on endothelial cells, kidney, and central nervous tissue and may be involved in the clearance of ET-1, particularly in the vascular beds of the lung and kidney. Endothelial ET$_B$ receptors facilitate vasodilation due to the release of smooth muscle relaxants such as nitric oxide and prostacyclin. A recently published study of patients with PAH demonstrated that the elevated levels of ET-1 are predominantly due to excess synthesis, not decreased clearance, and that the clearance function of the ET$_B$ receptor is largely maintained (Langleben et al 2006). This may ultimately play a role in the relative effectiveness of selective or nonselective agents.

Pulmonary hypertension was a consistently fatal condition with no effective medical treatment options before 1996; however, the past decade has witnessed an upsurge in the development of novel therapeutic agents for PAH. There are several approved agents for PAH including endothelin receptor antagonists that have improved the outlook dramatically. Treatment of PAH with endothelin receptor antagonists has been shown to be safe and efficacious.

Endothelin antagonists are often identified as being “selective” (usually for the ET$_A$ type receptor) or “non-selective” (binding to either ET$_A$ or ET$_B$ receptors with similar affinity). A compound is considered selective if its selectivity is greater than 100-fold for the ET$_A$ receptor subtype (Davenport and Battistini 2002). Antagonizing the ET$_A$ receptors, in theory, should prevent the deleterious effects mediated by the ET$_A$ receptors and allow for the favorable effects of ET$_B$ receptors.

Sitaxsentan is a once daily, oral, highly selective (Davenport and Battistini 2002) ET$_A$ receptor antagonist that has a long duration of action and high specificity for ET$_A$ receptors (Wu et al 1999; Wu et al 1997; Tilton et al 2000). Sitaxsentan is approximately 6500-fold more selective as an antagonist for ET$_A$ compared with ET$_B$ receptors (Wu et al 1997), Selective ET$_A$ receptor antagonism may be advantageous to block the harmful vasoconstrictor effects of ET-1 on the pulmonary vasculature, while maintaining the vasodilator and clearance functions of the ET$_B$ receptor. Sitaxsentan has been shown to improve exercise capacity and cardiopulmonary hemodynamics in patients with PAH. In addition, it has been shown to reverse and prevent vascular remodeling in animal models (Barst et al 2004).

In clinical trials, sitaxsentan, at a dose of 100 mg orally, once-daily has been shown to have the greatest risk/benefit in patients with PAH and will be the focus of this review. Higher doses (300 mg and higher) of sitaxsentan have been shown to cause an increased incidence of adverse events without an improvement in efficacy (Barst et al 2004). Similarly, lower doses (50 mg) have been shown to have limited efficacy with no safety benefit (Barst et al 2006).

**Sitaxsentan sodium in PAH STRIDE-1**

Sitaxsentan To Relieve Impaired Exercise (STRIDE)-1 (Barst et al 2004) was a randomized, double-blind, placebo-controlled 12-week trial that enrolled 178 patients with NYHA functional class II-IV PAH at 23 centers in the United States and Canada. These included patients with idiopathic PAH (IPAH), PAH associated with connective tissue disease (PAH-CTD), and patients with PAH associated with congenital heart defects (PAH-CHD). Patients were randomized to receive placebo, sitaxsentan 100 mg, or sitaxsentan 300 mg orally, once daily for 12 weeks. In this study, the primary endpoint was change in peak oxygen consumption per unit time (VO$_2$) at Week 12 while the secondary endpoints included 6MWD, New York Heart Association (NYHA) functional class, VO$_2$ at anaerobic threshold, ventilation per carbon dioxide production (VE/VCO$_2$) at anaerobic threshold, hemodynamics, quality of life using a Short Form 36 (SF-36) questionnaire, and time to clinical worsening. Unlike previous studies at the time, this study included patients with less severe PAH (functional class II) and, moreover, allowed patients to be enrolled without regard to baseline 6MWD (79.2–657.3 m).

Treatment with sitaxsentan 100 mg resulted in statistically significant improvements in 6MWD (35 m placebo corrected improvement, p<0.01). NYHA functional class also significantly improved compared with placebo (p<0.02). With treatment, 29% of the sitaxsentan 100-mg patients improved by at least one functional class without any deteriorations. These functional benefits were accompanied by significant improvements (p<0.01) in pulmonary vascular resistance (PVR) and cardiac index (CI) both of which are predictors of long-term outcome (Rubens et al 2001; McLaughlin et al 2002; Sitbon et al 2002; McLaughlin et al 2005). Clinical worsening events (defined as death, the need for epoprostenol, atrial septostomy, or transplantation) occurred in 3 (5%) placebo patients compared with no events in patients receiving sitaxsentan 100 mg.
While liver abnormalities (increases in liver transaminases) have been recognized as a class effect associated with ETRAs (Channick et al 2001; Barst et al 2002; Rubin et al 2002) the 100-mg dose was not associated with an increased incidence of aminotransferase abnormalities (0%) compared with 3% for placebo. Higher doses (≥300 mg) of sitaxsentan have demonstrated increased rates of liver aminotransferases elevations (11%) suggesting a dose response for safety and tolerability.

The most frequently reported adverse events with sitaxsentan treatment (and more frequent than with placebo) were headache, dizziness, nasal congestion, nausea, and peripheral edema. No patient discontinued prematurely from treatment with sitaxsentan.

While the safety results were promising as well as the improvements in 6MWD and functional class, the discrepancy between the improvement in 6MWD and peak VO$_2$ during CPET was unexpected. The lack of congruence between the tests generated considerable speculation regarding the use of the two modalities as endpoints in future clinical trials. Subsequently, an analysis by Oudiz et al (2006b) determined that while intra-center correlation of change in cardiopulmonary exercise testing (CPET) and 6MWD was fairly reliable, when conducted in a large, multicenter clinical trial, the inter-center results were not necessarily comparable. It was determined that there was too much inter-center variability with regard to CPET. Thus, in multicenter trials without CPET expertise validation at all sites before subject enrollment, this parameter could not be considered a reliable endpoint. The lack of prior CPET expertise validation at all STRIDE-1 sites likely contributed to the discord of the results and thus, CPET was not considered an endpoint in any of the future STRIDE clinical trials.

While the STRIDE-1 results were promising, demonstrating improvements in 6MWD and functional class, there were limitations to the study beyond the unreliable endpoint of peak VO$_2$ that may have obscured the impact of the efficacy results. Clinical trials in PAH traditionally limit enrolment to class III/IV patients with idiopathic PAH or PAH-CTD, that have a baseline 6MWD of <450 m; however, STRIDE-1, as previously stated, included milder cases (ie, functional class II PAH patients), included PAH-CHD patients, and lacked a customary baseline 6MWD upper limit cut-off.

Langleben et al (2004a) performed a post-hoc analysis of the STRIDE-1 subset of patients that would have qualified for traditional PAH study inclusion criteria (ie, patients with functional class III/IV PAH or PAH-CTD and a baseline 6MWD of <450 m) to elucidate the impact the generous STRIDE-1 inclusion criteria may have had on the efficacy results. This post-hoc analysis compared the change from baseline to endpoint in 6MWD, hemodynamics, functional class and safety for the placebo and sitaxsentan treated groups; and also contrasted the difference of the placebo and sitaxsentan treated groups to discern the placebo-corrected treatment effect. Hence, statistically significant changes were achieved in all parameters from baseline (Table 1), including a 45% improvement in functional class in sitaxsentan-treated patients (p=0.0005). Nonetheless, these findings should be considered with regard to the limitations of the study. This study was a post-hoc analysis, not a prospective design, therefore the data should be considered more cautiously than the overall study.

The results of the analysis revealed in the STRIDE-1 subset of patients that would have qualified for traditional PAH study inclusion criteria improvement in efficacy parameters with sitaxsentan therapy was even greater than seen in the entire STRIDE-1 population, indicating the liberal STRIDE-1 inclusion criteria may have diminished the magnitude of change in efficacy parameters.

Langleben’s conclusions were supported by a subsequent study by Frost et al (2005) that confirmed the six-minute walk test is limited by “floor effect” and “ceiling effect” (ie, a point at which the performance is so good or so bad that further clinically and/or statistically significant deterioration or improvement becomes hard to detect). Thus, lack of a 6MWD upper limit cut-off masks the impact of efficacy measures. In addition, the authors determined that comparison between PAH trials requires recognition of the impact that exercise and functional differences create and trials that do not adjust for the effects of differing enrollment criteria should be considered with caution.

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<td>CI (L/min per m$^2$)</td>
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Abbreviations: CI, cardiac index; mRAP, mean pulmonary arterial pressure; mPAP, mean right atrial pressure; 6MWD, 6-minute walk test distance; PVR, pulmonary vascular resistance.
STRIDE-1X
The STRIDE-1 extension trial (STRIDE-1X) was a blinded (sitaxsentan 100 or 300 mg/day) extension study offered to patients completing STRIDE-1. Patients that had received placebo treatment during STRIDE-1 were randomized to orally receive sitaxsentan 100 mg, or sitaxsentan 300 mg once daily for this long-term, extension trial. In this study, all patients treated with active study drug during STRIDE-1 and 1X, with exposure of ≤58 weeks (mean treatment duration of 26 weeks), demonstrated a one class improvement in NYHA functional class in the sitaxsentan 100-mg group (n=42/79, 53%). Most of the patients improved within the first 12 weeks of active sitaxsentan treatment; however improvement was also noted between Weeks 12–24 in 29% of the 100-mg sitaxsentan-treated patients. Similarly, a small number of patients first improved during Weeks 26–55 (Horn et al 2004). While 5% of patients taking 100 mg sitaxsentan deteriorated from baseline during the entire exposure period, none of the patients who deteriorated had previously improved.

The group treated with 100 mg sitaxsentan demonstrated a significantly lower incidence of elevated hepatic transaminases (8%) than the group treated with 300 mg sitaxsentan (19%) due to nonlinear drug kinetics. Thus, the 100-mg dosage was considered to have the best efficacy/tolerability profile.

STRIDE-1XC
In a Canadian population, an 11-patient cohort took part in STRIDE-1X and continued to receive open-label 100 mg sitaxsentan. The condition of 1 patient deteriorated at 7 months of therapy. The patient was transferred to epoprostenol therapy, and subsequently died from progressive PAH. The remaining patients completed the evaluation after 1 year of active therapy (mean treatment duration of 374±20 days). Evaluated patients demonstrated sustained significant improvements in 6MWD, functional class, and hemodynamics, compared with baseline (Langleben et al 2004b). 6MWD improved from 386 m at baseline to 436 m at 1 year (p=0.04). Cardiac output increased from 4.3 L/min to 5.4 L/min (p<0.01) and PVR fell from 742 dyn·s·cm$^{-5}$ (9 Wood units) to 585 dyn·s·cm$^{-5}$ (7 Wood units). Mean PAP and PCWP did not significantly change and systemic blood pressure was not affected. At baseline one patient was functional class II and 9 patients class III, at endpoint all 10 patients were functional class II (p<0.01).

There were no serious adverse events during the year of therapy in the remaining 10 patients. Likewise, there were no occurrences of liver function abnormalities. Moreover, there were no complications, or management difficulties, related to the interaction between sitaxsentan and warfarin. The most frequently reported adverse events included headache, peripheral edema, nasal congestion, and nausea. The occurrences of these events were consistent in rate to those of other published reports (Barst et al 2002, 2004; Rubin et al 2002). After 2 years of therapy, this population continued to demonstrate sustained efficacy in 6MWD, functional class. One patient developed multiple myeloma during year 2, and therapy was stopped. At the end of year 2, the remaining 9 patients were all in WHO functional class II and 6MWD improved to 440±86 m (Langleben et al 2005).

STRIDE-2
Sitaxsentan To Relieve Impaired Exercise (STRIDE)-2 (Barst et al 2006) was a randomized, multicenter, international, double-blind, placebo-controlled 18-week trial, that enrolled 247 PAH patients. Two hundred forty-five patients were randomized to receive placebo, sitaxsentan 50 mg, sitaxsentan 100 mg, or bosentan. Patients with WHO functional class II-IV were enrolled and included patients with IPAH, PAH-CTD and PAH-CHD. The primary endpoint was the change in 6MWD from baseline to Week 18, while the secondary endpoints included change in WHO functional class, time to clinical worsening, and change in Borg dyspnea index score.

Subjects treated with sitaxsentan 100 mg showed statistically significant improvement in exercise capacity compared with placebo (31 m placebo corrected improvement, p=0.03). The bosentan active control treatment arm, as expected, also showed improvement over placebo at Week 18 (29 m placebo corrected improvement, p=0.05). Subjects in the sitaxsentan 100-mg group also had statistically significant improvement in WHO functional class compared with placebo (p=0.04), with 98.3% of the subjects in the sitaxsentan 100-mg group improved or remained unchanged. Clinical worsening was seen least often in subjects treated with sitaxsentan 100 mg. The difference in time to clinical worsening between the sitaxsentan 100 mg and placebo treatment groups was not significant.

Overall, sitaxsentan at a dose of 100 mg achieved statistical significance on the primary efficacy parameter of 6MWD and the secondary parameter, change in WHO
functional class. This dose was also numerically superior in time to clinical worsening and Borg score. The 100-mg dose of sitaxsentan performed in a similar manner to the approved non-selective ET receptor antagonist, bosentan, which was included in the study to allow a qualitative comparison in a similarly randomized population.

Treatment-related AEs were reported most frequently in subjects randomized to open-label bosentan, followed by subjects in the sitaxsentan 100-mg group. The majority of AEs were mild or moderate; severe AEs were experienced more often by subjects in the placebo group, and did not occur in a treatment-related pattern in the other groups. Among the treatment-related AEs, the sitaxsentan subjects more frequently reported peripheral edema, nasal congestion, fatigue, and insomnia than placebo subjects and with a frequency that appeared to be dose related. Bleeding adverse events, most commonly epistaxis, were reported in 3 placebo patients, 6 sitaxsentan 100-mg patients, and 4 bosentan patients. None of the bleeding events were considered serious or required hospitalization, transfusion, or treatment. The incidence of liver function abnormalities (elevated liver aminotransferases) was 6% for placebo, 3% for sitaxsentan 100 mg and 11% for bosentan. All events were reversible.

Sitaxsentan inhibits warfarin metabolism via inhibition of CYP2C9 (the principal hepatic enzyme involved in warfarin metabolism) and bosentan induces CYP2C9 (Dingemanse and van Giersbergen 2004). Due to the effect of sitaxsentan on inhibition of the CYP2C9, an 80% reduction in the warfarin dose for sitaxsentan patients was recommended at baseline for sitaxsentan-treated patients, with adjustment made as needed to maintain international normalized ratio (INR). Dosage adjustments occurred with similar frequencies for the four groups. Compared with placebo, the mean daily warfarin doses were lower for patients treated with sitaxsentan and higher for patients treated with bosentan. In all groups in this study, concomitant therapy with warfarin was well tolerated, and bleeding events were rare, non-serious, and did not require treatment.

Consistent with the STRIDE-1 study, durability of therapy with sitaxsentan 100 mg was maintained in STRIDE-2 with fewer premature discontinuations compared with the placebo and bosentan groups. Only 3% of patients in the sitaxsentan group discontinued due to adverse events compared with 10% for placebo and 10% for bosentan.

The authors concluded “treatment with the selective ET\(_A\) receptor antagonist sitaxsentan, orally once daily at a dose of 100 mg, improves exercise capacity and WHO functional class in PAH patients, with a low incidence of hepatic toxicity”.

**Safety**

Liver function abnormalities appear to be a class effect of ETRA therapy (Channick et al 2001; Barst et al 2002; Rubin et al 2002). All ET\(R\)As have been associated, to date, with varying rates of elevated liver aminotransferases (AST and/ or ALT >3 × ULN). In a combined analysis of 4 clinical trials with ET\(R\)As compared with placebo, the background incidence of abnormal liver function in a PAH patient population over a 12- to 28-week study period is estimated to be 4% (Abbott et al 2006). In clinical trials, the ETRA bosentan causes elevation of liver aminotransferases (ALT and AST) >3 × ULN in about 11% of patients, accompanied by elevated bilirubin in a small number of cases (Actellion 2004). The combined pivotal studies discussed here, STRIDE-1 and -2, have demonstrated an abnormal liver function rate of approximately 2% for sitaxsentan 100 mg compared with a placebo rate of 5% over 12–18 weeks of therapy. Longer studies have shown the one-year risk of developing abnormal liver function with sitaxsentan therapy, as measured by Kaplan-Meier analysis, is lower at 4% than that of bosentan at 14%–15% (Girgis et al 2005; McLaughlin et al 2005).

When prescribing any ETRA, it is important to be aware of potential interactions with concomitant medications. Patients with PAH frequently require anticoagulant therapy and both sitaxsentan and bosentan affect warfarin metabolism (Dingemanse and van Giersbergen 2004). Bosentan induces CYP2C9, the principal hepatic enzyme involved in the metabolism of S-warfarin, and has been shown to reduce INR in patients receiving warfarin. Increases in warfarin dose may be necessary to maintain a therapeutic INR. Conversely, sitaxsentan inhibits CYP2C9 (Barst et al 2002) and can increase INR in patients being given warfarin or similar anticoagulants. While warfarin management is similar between bosentan, sitaxsentan, and placebo, monitoring of coagulation status is warranted when ET\(R\)As are prescribed (Coyne and Dixon 2005).

A recent analysis of data from STRIDE-2 and the STRIDE-2 extension study (STRIDE-2X) compared bleeding rates of PAH patients treated with either sitaxsentan or bosentan. It was concluded that bleeding rates were similar between patients treated with bosentan and sitaxsentan (Coyne et al 2006). This analysis also examined the incidence of bleeding events in patients that were anticoagulated versus those not anticoagulated. The results
revealed that bleeding rates were similar for those who were anticoagulated and those who were not anticoagulated. Teratogenicity appears to be a class effect of ETARs. Therapy with an ETAR requires a monthly pregnancy test and the use of reliable contraception. Moreover, pregnancy must be excluded prior to the initiation of therapy.

Conclusions
Pulmonary arterial hypertension is a progressive, life threatening condition. Sitaxsentan may become a preferred first-line oral endothelin receptor antagonist agent given its once daily dosing and decreased frequency of liver function test abnormalities. In multicenter, randomized, placebo-controlled clinical trials in PAH patients, sitaxsentan has been shown to improve exercise capacity (i.e., 6MWD), functional classification, and hemodynamics in PAH subjects (Barst et al 1996, 2004; Miyamoto et al 2000; Langleben et al 2004a; Behr et al 2005; Oudiz et al 2006a). Sitaxsentan has also been shown to be safe and well tolerated, and the incidence of liver function abnormalities is low with sitaxsentan therapy. Data out to 1 and 2 years now suggests that sitaxsentan has a durable response with a low incidence of adverse events.

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Disclosures
Dr Waxman was an investigator in the STRIDE-1, -2, and -3 clinical trials.

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Waxman


