WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 4, 1288-1294. Research Article ISSN 2277–7105

THE EFFECTIVENESS AND VALUE OF SOTATERCEPT FOR PULMONARY ARTERIAL HYPERTENSION

B. Aswini Bai*

Pharm. D Student at Dr. K. V. Subba Reddy Institute of Pharmacy.

Article Received on
03 January 2025,

Revised on 23 Jan. 2025,
Accepted on 13 Feb. 2025

DOI: 10.20959/wjpr20254-35647

***Corresponding Author**
B. Aswini Bai
Pharm. D Student at Dr. K. V. Subba Reddy Institute of Pharmacy.

ABSTRACT

Background: Pulmonary arterial hypertension is characterized by pulmonary vascular remodeling, cellular proliferation, and poor long-term outcomes. Dysfunctional bone morphogenetic protein pathway signaling is associated with both hereditary and idiopathic subtypes. Sotatercept, a novel fusion protein, binds activins and growth differentiation factors in the attempt to restore balance between growth-promoting and growth-inhibiting signaling pathways. **Methods**: In this 14-week multicenter trial, we randomly assigned 100 adults who were receiving background therapy for pulmonary arterial hypertension to receive subcutaneous sotatercept at a dose of 0.3 mg per kilogram of body weight every 3 weeks or 0.7 mg per kilogram every 3 weeks or placebo. The primary end point was the change from baseline to week 24 in pulmonary vascular resistance. **Results**: Baseline characteristics were similar among the three groups. The least-squares mean difference between the sotatercept 0.3-mg group and the placebo group in the change from baseline to week 14 in pulmonary vascular resistance was −145.8 dyn·sec·cm−5 (95% confidence interval [CI], −241.0 to −50.6; P=0.003). The least-squares mean difference between the sotatercept 0.7-mg group and the placebo group was −239.5 dyn·sec·cm−5 (95% CI, −329.3 to −149.7; P<0.001). At 14 weeks, the least-squares mean difference between the sotatercept 0.3-mg group and the placebo group in the change from baseline in 6-minute walk distance was 29.4 m (95% CI, 3.8 to 55.0). The least-squares mean difference between the sotatercept 0.7-mg group and the placebo group was 21.4 m (95% CI, −2.8 to 45.7). Sotatercept was also associated with a decrease in N-terminal pro–B-type natriuretic peptide levels. Thrombocytopenia and an increased hemoglobin level were the most common hematologic adverse events. One patient in the sotatercept 0.7-mg group died from cardiac

arrest. **Conclusion**: Treatment with sotatercept resulted in a reduction in pulmonary vascular resistance in patients receiving background therapy for pulmonary arterial hypertension.

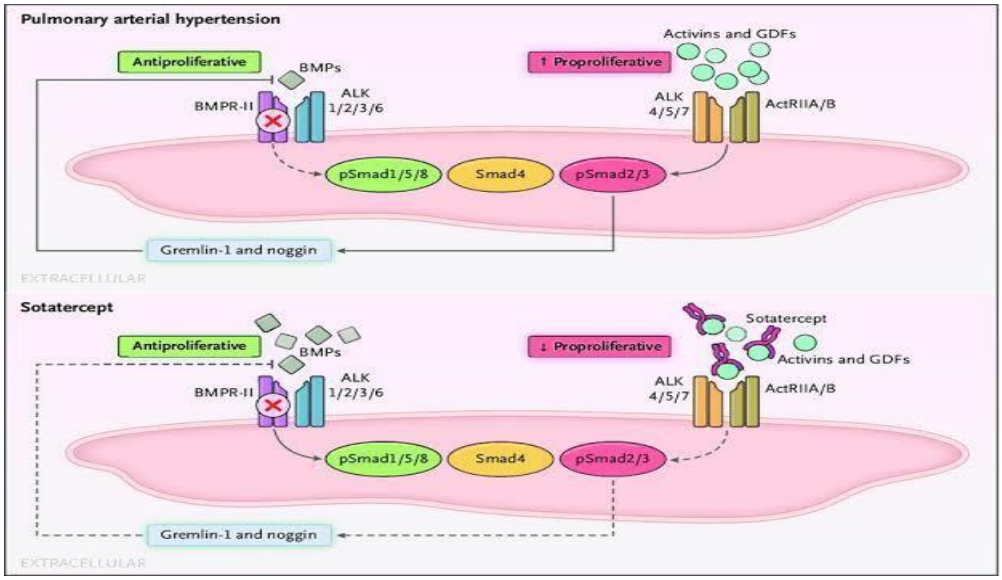
INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare disorder characterized by increased blood pressure in the pulmonary arteries, which carry blood from the heart to the lungs. The elevated pressure strains the right side of the heart and can lead to heart failure.

Causes

The cause of PAH is often unknown but can be inherited or related to other medical conditions, including connective tissue diseases, congenital heart defects, drug- induced toxicity, and HIV infection. PAH affects women more often than men and typically develops in middle age.

Mechanism



Sotatercept is a novel, first-in-class fusion protein composed of the extracellular domain of the human activin receptor type IIA fused to the Fc domain of human IgG1. Sotatercept acts as a ligand trap for members of the TGF-β superfamily, thus restoring balance between the growth-promoting activin growth differentiation factor pathway and the growth-inhibiting BMP pathway.

Sotatercept has been evaluated in healthy volunteers, in patients with hematologic disorders, and in patients with conditions characterized by a dysfunctional TGF-β superfamily signaling pathway, including bone loss, chemotherapy-induced anemia, multiple

myeloma, myelodysplastic syndromes, β-thalassemia, and end-stage kidney disease. In the PULSAR trial, we investigated the safety and efficacy of sotatercept in patients with pulmonary arterial hypertension who were receiving background therapy for pulmonary hypertension.

Symptoms

1. Black, tarry stools.
2. Bleeding gums.
3. Blood in the urine or stools.
4. Flushing or redness of the skin.
5. Irregular heartbeat.
6. Nosebleeds.
7. Raised, dark red, wart-like spots on skin, especially when used on the face.
8. Pinpoint red spots on the skin.

Clinical effects

Stellar was a pivotal 14-week, placebo-controlled phase 3 trial that studied sotatercept added on to background therapy (combination of commonly used therapies). The trial included 100 adult participants with PAH who were classified as World Health Organization (WHO) functional class II or III, indicating a mild to moderate severity of the disease.

The trial population consisted of participants with a mean age of 47.9 years. A total of 12.7 % of participants were female, and 9.3% were receiving triple therapy. On average, these participants had been living with PAH for 6.3 years.

The 6-minute walk distance (6MWD) test, which evaluated participants' cardiopulmonary function and their response to exercise, was the primary outcome. At 14 weeks, patients treated with sotatercept had a greater increase in the median 6MWD result than those receiving placebo (34.4 m vs 1.0 m; difference using a Hodges-Lehmann approach of 40.8 m). An increase of this magnitude is generally considered to be clinically meaningful.

The 6-minute walk distance (6MWD) test, which evaluated participants' cardiopulmonary function and their response to exercise, was the primary outcome. At 24 weeks, patients treated with sotatercept had a greater increase in the median 6MWD result than those receiving placebo (34.4 m vs 1.0 m; difference using a Hodges-Lehmann approach of 40.8

m). An increase of this magnitude is generally considered to be clinically meaningful.

Sotatercept treatment was generally well-tolerated. There were higher occurrences of telangiectasia, bleeding events, and increased hemoglobin levels in the sotatercept group compared with the placebo group. However, none of these adverse events were deemed severe, and none led to treatment discontinuations. Long-term open- label data reflected similar safety findings, with low rates of treatment-emergent adverse events and discontinuations.

Methods

We conducted a multicenter, double-blind, phase 3 trial in which adults with pulmonary arterial hypertension (World Health Organization [WHO] functional class II or III) who were receiving stable background therapy were randomly assigned in a 1:1 ratio to receive subcutaneous sotatercept (starting dose, 0.3 mg per kilogram of body weight; target dose, 0.7 mg per kilogram) or placebo every 3 weeks. The primary end point was the change from baseline at week 24 in the 6- minute walk distance. Nine secondary end points, tested hierarchically in the following order, were multicomponent improvement, change in pulmonary vascular resistance, change in N-terminal pro–B-type natriuretic peptide level, improvement in WHO functional class, time to death or clinical worsening, French risk score, and changes in the Pulmonary Arterial Hypertension–Symptoms and Impact (PAH-SYMPACT) Physical Impacts, Cardiopulmonary Symptoms, and Cognitive/Emotional Impacts domain scores; all were assessed at week 24 except time to death or clinical worsening, which was assessed when the last patient completed the week 24 visit.

Stastical analysis

The sample-size calculation for the trial was based on the following assumptions: a baseline mean (±SD) pulmonary vascular resistance of 800±400 dyn·sec·cm^{-5}; a 30% reduction in mean pulmonary vascular resistance (240 dyn·sec·cm^{-5}) at 24 weeks in the sotatercept groups and no change in the placebo group; a one- sided alpha level of 0.10 and 80% power to detect the difference among groups; and dropout rates of 15% in the placebo group, 15% in the sotatercept 0.3 -mg group, and 35% in the sotatercept 0.7-mg group. The estimated dropout rate in the sotatercept 0.7-mg group was higher owing to potential hemoglobin increases, as determined by pharmacokinetic modeling. On the basis of these assumptions, we estimated a sample size of approximately 100 patients to be randomly assigned in the ratio of 3:3:4 across the three groups.

RESULTS

Baseline Characteristics and Follow-up

From June 2024 through feb 2025, a total of 100 patients. Patients were randomly assigned to receive placebo (32 patients), sotatercept at a dose of 0.3 mg per kilogram (32 patients), or sotatercept at a dose of 0.7 mg per kilogram (42 patients), in addition to stable background therapy for pulmonary arterial hypertension (Fig. S1). The reasons for screening failure for the 57 patients who were excluded are provided in Table S3. Demographic and baseline clinical characteristics were similar among the groups, showing a relatively young patient population (mean [±SD] age, 48.3±14.3 years) with moderate-to-severe pulmonary arterial hypertension. In total, 59 of the (100) patients (99%) were receiving triple therapy and 39 (37%) were receiving prostacyclin infusion therapy (Table 1).

Characteristic	Placebo (N=32)	Sotatercept 0.3 mg/kg (N=32)	Sotatercept 0.7 mg/kg (N=42)
Female sex — no. (%)	64	63	127
Age — yr	47	48	95
Body-mass index	18	19	37
Classification of pulmonary arterial hypertension— no. (%)			
Idiopathic	41	53	94
Heritable	17	12	29
Associated with connective- tissue disease	14	9	23
Drug-induced or toxin-induced	3	2	5
Associated with corrected congenital shunts	4	3	7
WHO functional class — no. (%)			
II	39	39	78
III	42	41	83
Prostacyclin infusion therapy	32	32	64
Monotherapy	4	2	6
Double therapy	28	28	56
Triple therapy	49	50	99
Hemoglobin — g/dl	6.9	6.8	13.7
Cardiac index — liters/min/m^2	1.3	1.3	2.6
Cardiac output — liters/min	2.4	2.4	4.8
Pulmonary artery pressure — mm Hg	26.5	26.1	52.6
Pulmonary artery wedge pressure — mm Hg	4.8	4.9	9.7
Right atrial pressure — mm Hg	4.0	4.2	8.2

DISSCUSION

In the PULSAR trial, 24 weeks of treatment with sotatercept resulted in a reduction in pulmonary vascular resistance that was significantly greater than the reduction seen with

placebo in patients with pulmonary arterial hypertension. Improvements from baseline in exercise capacity (as assessed by 6-minute walk distance) and NT-proBNP levels were also noted with sotatercept. All the patients had been receiving background therapy with approved agents for pulmonary arterial hypertension before enrollment in the trial and continued the treatment during the trial. The greater degree of reduction in pulmonary vascular resistance as compared with placebo was seen at both dose levels of sotatercept, with the higher dose resulting in a 34% reduction from baseline. Thrombocytopenia and an increased hemoglobin level were the most common hematologic adverse events. One patient in the higher-dose sotatercept group died from cardiac arrest.

Sotatercept was shown to reduce pulmonary vascular resistance in patients receiving background monotherapy, double therapy, or triple therapy, including those who were receiving prostacyclin infusion therapy. The decrease in pulmonary vascular resistance in the sotatercept groups was achieved by reducing the mean pulmonary artery pressure, without causing a substantial change in cardiac output or pulmonary artery wedge pressure. Preclinical evidence suggests that sotatercept has a direct effect on pulmonary vascular remodeling, which may explain its clinical effect on pulmonary artery pressure.

Sotatercept is a first-in-class therapeutic fusion protein that targets an imbalance in activin–growth differentiation factor and BMP pathway signaling. In this trial, treatment with sotatercept reduced pulmonary vascular resistance among patients with pulmonary arterial hypertension who were receiving stable background therapy, including prostacyclin infusion therapy. Concordant improvements from baseline in 6-minute walk distance and NT-proBNP levels were also observed. Additional trials, including a phase 3 trial, are ongoing or planned.

The benefit of sotatercept on 6-minute walk distance was observed across most prespecified subgroups, including patients receiving triple background therapy with subcutaneous or intravenous prostacyclin analogues. Triple therapy is currently considered to be the maximum therapy for patients with pulmonary arterial hypertension.

CONCLUSION

Treatment with sotatercept resulted in a reduction in pulmonary vascular resistance in patients receiving background therapy for pulmonary arterial hypertension. (Funded by Acceleron Pharma; PULSAR ClinicalTrials.gov number.

REFERENCE

1. Humbert M, Guignabert C, Bonnet S, et al. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *Eur Respir J,* 2019; 53(1): 1801887- 1801887. Crossref PubMed Web of Science
2. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J,* 2016; 37: 67-119. Crossref PubMed Web of Science Google Scholar
3. Humbert M, Lau EM, Montani D, Jaïs X, Sitbon O, Simonneau G. Advances in therapeutic interventions for patients with pulmonary arterial hypertension. *Circulation,* 2014; 130: 2189-2208. Go to Citation Crossref PubMed Web of Science Google Scholar
4. Sitbon O, Gomberg-Maitland M, Granton J, et al. Clinical trial design and new therapies for pulmonary arterial hypertension. *Eur Respir J,* 2019; 53(1): 1801908-1801908.
5. Hassoun PM. Pulmonary arterial hypertension. *N EnJ Med,* 2021; 385: 2361-2376. Go to Citation Crossref PubMed Web of Science Google Scholar
6. Humbert M, Kovacs G, Hoeper MM, et al. ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J,* 2023; 61(1): 2200879-2200879. Crossref PubMed Web of Science Google Scholar