Review Article

Sotatercept: A New Treatment of Pulmonary Arterial Hypertension for Adults, A Drug Review

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a dangerous and progressive condition characterized by high pressure in the pulmonary arteries, leading to right heart failure and, ultimately, death if left untreated. Despite breakthroughs in therapeutics targeting nitric oxide, endothelin-1, and prostacyclin pathways, PAH remains a life-threatening illness requiring continued research for novel treatments. To restore pulmonary vascular balance, sotatercept a new fusion protein, targets ligands belonging to the TGF-β superfamily. Clinical trials have demonstrated promising outcomes, including notable enhancements in pulmonary vascular resistance, exercise capacity, and right ventricular function. The effectiveness of sotatercept in lowering pulmonary vascular resistance, enhancing exercise capacity, and improving hemodynamics in patients with PAH was demonstrated by the PULSAR, SPECTRA, and STELLAR studies. Beyond PAH, sotatercept's therapeutic benefits are flexible as it can potentially treat β-thalassemia, myelodysplastic syndromes, pulmonary hypertension linked to idiopathic pulmonary fibrosis, cancer-related anemia, and malignant bone disease. These encouraging outcomes suggest that sotatercept is a useful complement to the PAH therapy options, calling for more investigation and advancement.

Keywords: Sotatercept, pulmonary hypertension, therapy.

INTRODUCTION

Increased pressure in the pulmonary arteries is the hallmark of pulmonary arterial hypertension (PAH), a chronic and progressive illness that, if left untreated, can result in right heart failure and death. The illness is currently separated into five subgroups after being first classified in 1973 and undergoing numerous revisions. Idiopathic or familial PAH is included in group 1 and is frequently linked to gene mutations in BMPR2, ACVRL1, ENG, and Smad8.[1] To diagnose, right cardiac catheterization is necessary for invasive hemodynamic testing, which measures capillary wedge pressure and pulmonary artery pressure. Additionally essential for detecting and assessing the presence of PAH is echocardiography.[2] Over the past few decades, treatment has progressed by focusing on three key pathways: prostacyclin, endothelin-1, and nitric oxide. Prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase type-5 inhibitors are examples of approved treatments. Even with these developments, PAH is still a potentially fatal illness that requires multidisciplinary care and continuous research into novel therapies. To effectively manage the illness, supportive therapy such as oxygen, diuretics, rehabilitation, and anticoagulation are essential.[3] Lung transplantation can be an option for people who do not respond to conventional medical care. To restore pulmonary vascular balance, sotatercept is a fusion protein that binds to particular ligands of the TGF-β superfamily. It improves vessel patency in animal models of pulmonary hypertension by reducing vessel wall inflammation, promoting apoptosis, inhibiting cell proliferation, and reversing vascular remodelling.[4]

SCIENTIFIC SUMMARY

Mechanism of Action

The extracellular domain of the human activin receptor type IIA is fused to the Fc domain of human IgG1 to form the unique, first-in-class fusion protein known as sotatercept. By serving as a ligand trap for TGF-β superfamily members, sotatercept helps to rebalance the growth-inhibiting BMP route and the growth-promoting activin growth differentiation factor pathway[5] (fig 1).

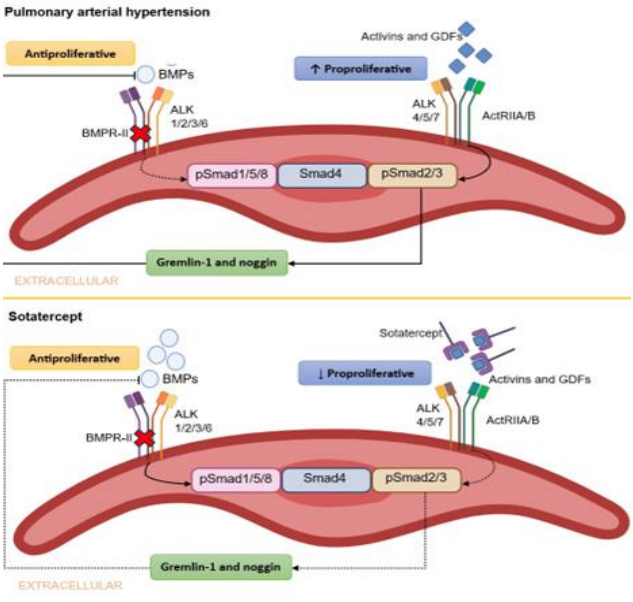

Figure 1

Test subjects for sotatercept included healthy individuals, patients with hematologic disorders, and patients with conditions such as bone loss, chemotherapy-induced anemia, multiple myeloma, myelodysplastic syndromes, β-thalassemia, and end-stage kidney disease that are associated with a dysfunctional TGF-β superfamily signaling pathway[6].

Pharmacokinetics (PK)

Metabolism and Excretion

Although the exact metabolic mechanism of sotatercept is unknown, it may entail protease breakdown and Fc receptor-mediated clearance. This suggests that sotatercept may attach to Fc receptors and then be ingested and broken down by immune system cells (reticuloendothelial system) or digested into smaller fragments by proteases. Dialysis tests have demonstrated that sotatercept is difficult to clear by dialysis due to its high molecular weight, which limits the amount of medicine that can pass through renal glomerular filtration. Sotatercept, however, may be broken down into smaller fragments and then metabolized and cleared through the kidneys, with a small portion also possibly excreted directly through the bile duct. Studies have indicated that the glomerulus can filter the Fab fragments of antibodies, and IgG has also been found in bile[7].

Absorption

Human dose proportionate absorption of sotatercept is seen, with comparable pharmacokinetic characteristics for intravenous and subcutaneous administrations. Compared to intravenous injections, which are more expensive and need hospital procedures, subcutaneous injections are more useful for research and clinical practice because of their convenience and capacity to be administered by the patient themselves. Because of its greater solubility, sotatercept can be injected subcutaneously at larger drug concentrations, effectively satisfying patient dose needs. Hyaluronidase treatment can enhance medication dispersion in subcutaneous tissue[7].

Potential Interactions

There are no published data on medication interactions with sotatercept. Its ActRIIA-Fc fusion protein mode of action means it is probably less prone to cause drug interactions than other PAH medicines, which frequently do so because of how the CYP450 system handles its metabolism[8].

Pharmacodynamics (PD)

In clinical trials, sotatercept reduced pulmonary vascular resistance in patients with pah[5]. In pre-clinical models of pah, it reversed pulmonary arterial wall and right ventricular remodeling[9]. An analogue of sotatercept decreased inflammation and prevented smooth muscle and endothelial cell growth in diseased vasculature in rat models of pah. Thicker arterial walls, a partial reversal of right ventricular remodeling, and better hemodynamics were linked to these cellular alterations. The usage of sotatercept was linked to thrombocytopenia and elevated hemoglobin levels.

The bone morphogenetic protein receptor type 2 (BMPRII), activin receptor type IIA (ActRIIA), and the ActRIIA ligands activin A, activin B, growth differentiation factor 8 (GDF8), and GDF11 are some of the members of the transforming growth factor β (TGF-β) superfamily. These TGF-β superfamily ligands control vascular proliferation and preserve endothelial integrity in pulmonary arteries by promoting pro-proliferative (ActRIIA/Smad2/3-mediated) or anti-proliferative (BMPRII/Smad1/5/8-mediated) signaling pathways[5]. The pathophysiology of PAH has been linked to altered signal transduction by TGF-β ligands, where proliferative and antiapoptotic signaling predominate[10]. Consequently, pulmonary vascular remodeling, enhanced cellular proliferation, and endothelial dysfunction occur. Recombinant activin receptor type IIA-Fc, or ActRIIA-Fc, fusion protein, is what is known as sotatercept. By directing binding to and sequestering many activin-class ligands, it functions as a ligand trap, enhancing the equilibrium between the growth-inhibiting BMP route and the growth-promoting activin growth differentiation factor pathway[9,10].

Phase II Trials

Study 1:

The multicenter, randomised, double-blind, phase 2 PULSAR trial consists of a 24-week placebo-controlled phase that is followed by an 18-month extension period using an active medication. It was approved by the appropriate ethics bodies and created in partnership with Acceleron Pharma. Patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II or III were randomized to receive subcutaneous sotatercept injections every 21 days at a dose of 0.3 mg/kg or 0.7 mg/kg, respectively. Every three weeks, safety and effectiveness were evaluated. The main outcome was the change in pulmonary vascular resistance (PVR) between baseline and week 24. The secondary objectives included changes in NT-proBNP levels, the 6-minute walk distance, and other clinical parameters.

The PVR for both sotatercept groups was significantly lower than the placebo group, according to the results. The mean decrease in the 0.3 mg/kg and 0.7 mg/kg groups was 162.2 and 255.9 dyn·sec·cm−5, respectively, whereas the placebo group experienced a decrease of 16.4 dyn·sec·cm−5, as compared to the other groups. The sotatercept groups also showed reductions in NT-proBNP levels and improvements in 6-minute walk distance[5].

Study 2:

Phase 2a, single-arm, open-label SPECTRA trial assessed sotatercept's effects in patients on combination medication for pulmonary arterial hypertension (PAH) in WHO functional class III. Among the 21 patients who finished the treatment, the major endpoint, change in

peak oxygen uptake at 24 weeks, revealed a significant mean improvement of 102.74 mL/min (P=0.0097). Secondary endpoints, including a 6-minute walk distance and hemodynamics during peak activity and rest, both showed improvement. Furthermore, improvements in right ventricular function were shown by cardiac magnetic resonance imaging at 24 weeks. Overall, sotatercept dramatically enhanced a number of clinical and functional assessments in patients with PAH. [11]

Phase III Therapeutic Trials

A phase 3 multicenter, double-blind, randomized, placebo-controlled study called the STELLAR trial examined sotatercept effectiveness in treating individuals with pulmonary arterial hypertension (PAH). In addition to steady background medication, eligible individuals with PAH in WHO functional classes II or III were randomized to receive sotatercept or a placebo. The sotatercept group significantly improved their 6-minute walk distance after 24 weeks, while the placebo group saw a drop of 1.4 meters (P<0.001), according to the primary objective. Sotatercept was also preferred for secondary endpoints such as time to first death or nonfatal clinical deterioration, pulmonary vascular resistance, NT-proBNP levels, WHO functional class, and multi-component improvement. According to quality-of-life measurements, significant improvements in physical effects and cardiovascular symptoms were observed. The study showed that sotatercept considerably enhanced several clinical outcomes and decreased the likelihood that PAH patients' conditions would worsen[9].

Therapeutic Indications

1. Sotatercept's safety and efficacy in treating β-thalassemia patients, as evidenced by improvements in hemoglobin levels and a decrease in the need for transfusion. Moreover, sotatercept showed comparable advantages in anemia patients with myelodysplastic syndromes, suggesting that it could be used as a treatment for erythropoiesis, which isn't working in several situations[12].

2. Sotatercept shows promise in balancing the signaling pathways linked to pulmonary hypertension in patients with coexisting idiopathic pulmonary fibrosis and pulmonary hypertension[13].

3. A first-in-class medication called sotatercept is being developed clinically to treat anemia associated with cancer, particularly those with low erythropoiesis, like those seen in myelodysplastic syndromes. It differs from erythropoietin in that it acts quickly. As shown in preliminary clinical studies, Sotatercept may be a useful treatment for multiple myeloma and malignant bone disease because of its potential anticancer effects and anabolic bone activity[14].

4. Sotatercept improves bone development and raises indicators of bone formation, such as bone-specific alkaline phosphatase (bALP).Moreover, it decouples pathological bone remodeling to shift the balance of that remodeling more in favour of bone creation, possibly offsetting the osteolytic bone lesions linked to myeloma[15].

5. Sotatercept demonstrated benefits in the distance travelled on a 6-minute walk and hemodynamics during peak exertion and rest when compared to baseline measurements. Week 24 cardiac magnetic resonance imaging showed improvements in right ventricular function compared to baseline[11].

Safety

With respect to adverse events, the Sotatercept and placebo groups had similar pooled relative risks (RR) for diarrhoea 1.55 [0.92; 2.61], dizziness 2.70 [0.65; 11.26], fatigue 0.75 [0.32; 1.76], nausea 0.87 [0.51; 1.47], headache 1.31 [0.88; 1.96], thrombocytopenia 3.37 [1.26; 9.02], an adverse event resulting in withdrawal from the trial 0.48 [0.12; 2.00], serious adverse events 0.94 [0.40; 2.25], and lastly any adverse event reported 0.97 [0.90; 1.04]. Furthermore, with an RR of 11.10, the pooled analysis revealed that the Sotatercept group saw a higher frequency of elevated haemoglobin levels[16].

CONCLUSIONS

For the treatment of pulmonary arterial hypertension (PAH), a disorder characterized by increased pulmonary arterial pressure that, if left untreated, can result in right heart failure and possibly death, sotatercept represents a prospective therapeutic development. The results highlight its potential to improve how PAH patients are treated.

The adaptability of sotatercept goes beyond PAH to other disorders marked by disruptions in TGF-β signaling pathways. These comprise malignant bone disorders, cancer-related anemia, myelodysplastic syndromes, idiopathic pulmonary fibrosis-associated pulmonary hypertension, and β-thalassemia. This wide range of therapeutic applications demonstrates sotatercept's capacity to meet various unmet medical requirements.

Future Aspects:

There is much potential for sotatercept's clinical usage in the future. Future and ongoing studies should concentrate on:

1. Long-term effectiveness and Safety: To ensure sotatercept's continued benefits and monitor any potential negative effects over lengthy periods, more research is required to investigate the drug's long-term effectiveness and safety in various patient populations.
2. Combination medications: Researching sotatercept's synergistic effects with currently available PAH medications may offer a more all-encompassing therapeutic approach, improving patient satisfaction.
3. Tailored therapy: By investigating genetic and biomarker-driven methods to pinpoint individuals who would most benefit from sotatercept, treatment plans

might be improved and tailored therapy for PAH and related disorders could be strengthened.

4. Expanded Indications: Further investigation into the use of sotatercept in other illnesses linked to dysregulation of the TGF-β pathway, such as hematologic disorders and malignancies, may uncover new therapeutic indications.
5. Mechanistic Studies: Detailed mechanistic investigations to completely clarify the sotatercept molecular mechanism of action may offer valuable information for maximizing its application and identifying novel therapeutic targets within the TGF-β superfamily pathway.

In conclusion, sotatercept is a promising addition to the PAH treatment arsenal and beyond, with the potential to impact patient outcomes across various conditions significantly. Continued research and development will be crucial to fully realize its therapeutic potential and integrate it effectively into clinical practice.

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