Sotatercept: PAH's systemic secret weapon?

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Pulmonary arterial hypertension (PAH) remains a progressive, life-limiting condition despite advances in vasodilatory therapies. These treatments primarily target the pulmonary vasculature, but PAH involves systemic pathology beyond the lungs, including inflammation, metabolic dysfunction, and right ventricular failure. Sotatercept, an activin ligand trap, significantly improves exercise tolerance in patients with PAH. A new analysis published in the Journal of the American College of Cardiology explores the broader mechanisms contributing to this benefit, extending beyond its direct pulmonary effects.1

KEY TAKEAWAYS

- The Pivot: Sotatercept's benefits in PAH extend beyond pulmonary vascular remodeling, influencing systemic hematologic and metabolic pathways.
- The Data: Sotatercept markedly improves exercise tolerance, a key clinical endpoint for PAH patients.
- The Action: Clinicians should consider sotatercept as a therapy that addresses multiple pathogenic mechanisms in PAH, not solely pulmonary vascular disease.

Pulmonary arterial hypertension is characterized by progressive remodeling of the pulmonary arteries, leading to increased pulmonary vascular resistance and right heart failure. Standard therapies, while effective at vasodilation, often fall short in reversing the underlying proliferative and inflammatory processes that drive the disease. This persistent unmet need has spurred the development of novel agents targeting different pathogenic pathways.1

Sotatercept, a first-in-class activin receptor type IIA (ActRIIA) fusion protein, acts as a ligand trap for members of the transforming growth factor-beta (TGF-β) superfamily. These ligands, including activins and growth differentiation factors (GDFs), are implicated in the aberrant cellular proliferation and inflammation central to PAH pathogenesis. By sequestering these ligands, sotatercept aims to rebalance signaling pathways that promote vascular remodeling.1

Beyond Pulmonary Vasodilation: A Broader Mechanism

The study by Reddy, Frantz, and Miranda sought to elucidate the systemic effects of sotatercept, moving beyond its well-established impact on pulmonary vascular resistance. They investigated how the drug influences central hemodynamics, hematologic parameters, and peripheral metabolic and inflammatory markers. This deep dive into the drug's pleiotropic effects provides a more comprehensive understanding of its clinical benefits.1

Patients with PAH often exhibit a range of systemic abnormalities, including iron deficiency, erythrocytosis, and altered metabolic profiles, which contribute to exercise intolerance and overall disease burden. Traditional PAH therapies do not consistently address these systemic issues. Sotatercept's mechanism of action, by modulating TGF-β signaling, suggests a potential to impact these broader pathological processes.1

The investigators analyzed data from patients receiving sotatercept, focusing on changes in right heart catheterization

parameters, complete blood count, iron studies, and various inflammatory and metabolic biomarkers. They aimed to correlate these changes with improvements in exercise capacity, as measured by the 6-minute walk distance (6MWD). The cohort included patients with varying etiologies of PAH, reflecting a real-world population.1

Central Hemodynamic Improvements

Sotatercept demonstrated significant improvements in central hemodynamics, which are the cornerstone of PAH management. The drug reduced mean pulmonary arterial pressure (mPAP) by an average of 14 mmHg (95% CI, 12-16 mmHg; P<.001) and pulmonary vascular resistance (PVR) by 35% (95% CI, 30-40%; P<.001). These reductions are substantial and align with the primary mechanism of reversing pulmonary vascular remodeling.1

But, the benefits extended to right ventricular function. The cardiac index, a measure of cardiac output relative to body surface area, increased by an average of 0.4 L/min/m2 (95% CI, 0.3-0.5 L/min/m2; P<.001). This improvement in cardiac output is critical for enhancing systemic oxygen delivery and reducing symptoms of fatigue and dyspnea. The right ventricle, often the Achilles' heel in PAH, showed clear signs of improved performance.1

The study also noted a decrease in right atrial pressure (RAP) by an average of 3 mmHg (95% CI, 2-4 mmHg; P<.001), indicating reduced right ventricular preload and improved diastolic function. These central hemodynamic shifts are directly linked to the observed improvements in exercise tolerance. Patients with greater reductions in PVR and increases in cardiac index generally experienced more pronounced gains in 6MWD.1

Hematologic and Peripheral Effects

Beyond the pulmonary vasculature, sotatercept exerted notable effects on hematologic parameters. Patients with PAH frequently develop iron deficiency and erythrocytosis, both of which can impair exercise capacity and quality of life. The drug led to an increase in hemoglobin levels by an average of 0.8 g/dL (95% CI, 0.6-1.0 g/dL; P<.001) and serum ferritin levels by 45 ng/mL (95% CI, 30-60 ng/mL; P<.001).1

This improvement in iron status and hemoglobin suggests a beneficial impact on erythropoiesis and oxygen-carrying capacity. Many PAH patients present with functional iron deficiency, even with normal hemoglobin, which contributes to fatigue. Sotatercept appears to mitigate this, potentially by modulating inflammatory pathways that interfere with iron metabolism.1

The drug also influenced inflammatory markers. High-sensitivity C-reactive protein (hsCRP), a general marker of systemic inflammation, decreased by an average of 1.2 mg/L (95% CI, 0.8-1.6 mg/L; P=.003). This reduction in systemic inflammation could contribute to improved endothelial function and reduced vascular remodeling, complementing its direct effects on TGF-²signaling.1

Metabolic parameters also shifted. There was a modest but statistically significant decrease in fasting glucose levels by 5 mg/dL (95% CI, 3-7 mg/dL; P=.008) and an increase in adiponectin, an anti-inflammatory and insulin-sensitizing adipokine, by 2.5 µg/mL (95% CI, 1.8-3.2 µg/mL; P=.001). These peripheral metabolic changes suggest a broader systemic impact on metabolic health, which is often dysregulated in PAH.1

Clinical Correlates and Limitations

The observed changes in central, hematologic, and peripheral markers correlated with improvements in exercise tolerance. Patients who experienced greater reductions in PVR, increases in hemoglobin, and decreases in hsCRP showed larger gains in 6MWD. This multi-pronged benefit underscores sotatercept's potential to address the complex

pathophysiology of PAH more comprehensively than existing therapies.1

The study was an exploratory analysis of existing trial data, which is an obvious caveat. While it provides valuable insights into the mechanisms of benefit, it was not a prospectively designed mechanistic trial. The observational nature of some correlations means causality cannot be definitively established, though the consistency of the findings is compelling.1

The patient population, while diverse, still represents a subset of PAH patients, primarily those in WHO functional class II or III. Whether these precise mechanisms and magnitudes of benefit extend to patients with more advanced disease or those with different PAH etiologies requires further investigation. The duration of follow-up for some biomarkers was also limited, and long-term effects on these systemic parameters warrant continued study. Clinicians can find more detailed guidance on managing complex cardiovascular conditions in the Oxford Handbook of Cardiology.1

Still, the consistent pattern of improvement across multiple physiological systems provides a strong rationale for sotatercept's efficacy. The drug is not merely a pulmonary vasodilator; it appears to be a systemic modulator of disease processes that contribute to the overall burden of PAH. This broader understanding may inform future treatment strategies and combination therapies.1

CLINICAL IMPLICATIONS

Sotatercept's demonstrated impact beyond the pulmonary vasculature fundamentally shifts how we should view PAH management. For too long, the focus has been almost exclusively on pulmonary hemodynamics, often neglecting the systemic manifestations that cripple patients. This drug forces a re-evaluation, showing that targeting broader pathogenic pathways can yield more comprehensive benefits.

The improvements in hematologic parameters, particularly iron status and hemoglobin, are clinically meaningful. Many PAH patients struggle with fatigue exacerbated by functional iron deficiency, even when their pulmonary pressures are somewhat controlled. Addressing this directly could significantly improve quality of life, a critical but often overlooked endpoint in chronic diseases.

The reduction in systemic inflammation and the subtle shifts in metabolic markers suggest that sotatercept is not just remodeling the pulmonary arteries; it is rebalancing fundamental physiological processes. This pleiotropic effect makes it a compelling addition to the PAH armamentarium, moving beyond symptomatic relief to address underlying disease drivers. It is a more holistic approach to a systemic disease.

While the data on these broader mechanisms are exploratory, they provide a strong mechanistic underpinning for the observed clinical efficacy. Future trials should explicitly incorporate these systemic biomarkers to further characterize the drug's full therapeutic potential and identify patient subgroups most likely to benefit from its multi-faceted action.

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REFERENCES

1. 1. Reddy YNV, Frantz RP, Miranda WR. Sotatercept in Pulmonary Arterial Hypertension: Central, Hematologic, and Peripheral Mechanisms of Benefit. J Am Coll Cardiol 2026.