10.1161/CIRCULATIONAHA.126.080191

Stepping into a New Era – Sotatercept for the Treatment of Cpc-PH from HFpEF

Running title: *Sarma and Chin; Sotatercept and HFpEF*

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Pulmonary hypertension associated with left heart disease (group 2 PH) accounts for up to 80% of pulmonary hypertension diagnoses and can occur in all forms of left heart disease when elevated left heart filling pressures are present. When the pulmonary vascular resistance is also elevated, combined pre- and post-capillary pulmonary hypertension (Cpc-PH) is diagnosed. Because the risk of adverse outcomes rises in proportion to pulmonary vascular resistance (PVR)[1], medications that lower PVR in other forms of PH have been appealing as potential therapies for Cpc-PH. However, prior studies evaluating pulmonary arterial hypertension (PAH) therapies in patients with group 2 PH have been disappointing, including studies in heart failure with reduced ejection fraction (HFrEF)[2], HF with preserved ejection fraction (HFpEF)[3,4] and valvular heart disease[5] where there were no improvements in clinical outcomes and often trends towards harm.

To date, treatment of Cpc-PH has focused on treating the underlying left heart disease. For patients with HFpEF, treatment options have expanded in recent years to include sodium glucose co-transporter 2 inhibitors (SGLT2i), mineralocorticoid receptor antagonists (MRA) and angiotensin receptor/neprilysin inhibitors (ARNi). SGLT2i and ARNi modestly reduce pulmonary artery pressures in patients with HFrEF [6,7], while MRAs have not shown benefit in pulmonary arterial hypertension.[8] These drug classes have not been tested in patients with Cpc-PH from HFpEF.

Sotatercept is a novel activin signaling inhibitor first approved by the United States' Food and Drug Administration in March 2024 for the treatment of group 1 PAH. Sotatercept is a ligand trap for activins and growth differentiating factors and has effects that extend beyond reductions in PVR, including reducing vascular smooth muscle cell proliferation and fibrosis and improving pulmonary endothelial cell function – all characteristic pathologic features in PAH.

Vascular changes in Cpc-PH share some similarities with PAH, including proliferation of pulmonary vascular endothelial and smooth muscle cells, increases in inflammatory cells, and elevated cytokines and growth factors[9].

In the pivotal STELLAR trial in PAH, 24 weeks of sotatercept improved 6 minute walk distance by an average of 34 meters and reduced the composite of death or non-fatal clinical worsening events by 84%, with a number needed to treat of 5 patients.[10] Whether sotatercept is effective in Cpc-PH, where mechanisms for exertional intolerance, impaired functional capacity and clinical progression are less well defined, is unknown.

In this issue of Circulation, Gomberg-Maitland and colleagues report findings from the CADENCE trial[11], a phase 2 trial studying sotatercept for the treatment of Cpc-PH secondary to HFpEF. Key selection criteria included PVR ≥4 Wood units, ejection fraction ≥50%, and ability to walk ≥100 meters during a 6-minute walk test. Patients were randomized to either placebo, 0.3 mg/kg or 0.7 mg/kg sotatercept given every 3 weeks for 24 weeks. The primary endpoint was change in PVR with secondary endpoints of functional capacity (6-minute walk test) and time to clinical worsening defined by death, hospitalization for heart failure or cardiopulmonary event, and decline in 6-minute walk distance of ≥15%.

At baseline, patients had severe pulmonary hypertension, with a baseline PVR of 5.2 Wood units, a mean pulmonary artery pressure (mPAP) of 43 mmHg and pulmonary arterial wedge pressure (PAWP) of 21 mmHg. Relative to PAH trials of sotatercept, mean age of participants was older (75 years, versus 40s-50s), and with a higher BMI. After 24 weeks, PVR, MPAP and PAWP all improved, with significant decreases versus placebo for both the 0.3mg/kg and 0.7 mg/kg doses. Cardiac output was also nominally lower in both groups, but importantly oxygen delivery remained stable, with the decline in cardiac output offset by increases in

hemoglobin. On treatment blood pressure did not differ between groups, but systemic vascular resistance increased in both sotatercept groups.

For clinical outcomes, 6-minute walk distance nominally increased in the 0.3 mg/kg but was unchanged in the 0.7 mg/kg group compared with placebo. Time to clinical worsening was 82% lower in the 0.3 mg/kg group but was not significantly reduced in the 0.7 mg/kg group. Safety endpoints were similar between sotatercept and placebo groups. Three patients in the 0.7 mg/kg group discontinued treatment due to adverse events, including 1 directly attributable to sotatercept.

The authors and study investigators are to be congratulated for this pivotal work addressing an area of unmet need in the care of patients with HFpEF. In the spectrum of patients with HFpEF, the presence of Cpc-PH connotes worse prognosis, lower functional capacity and remains challenging to treat. Trends towards improved 6-minute walk time, echocardiographic and hemodynamic markers of both right and left heart function, and lower likelihood of clinical decompensation suggest sotatercept has the potential to become a foundational therapy for patients with Cpc-PH from HFpEF, provided the results are replicated in a larger, confirmatory phase 3 trial. The lack of an increase in cardiac output in an otherwise positive trial is, at first glance, surprising. However, this is consistent with PAH clinical trials of sotatercept, where large clinical improvements were seen without significant increases in cardiac output.[10,12-14]. Importantly increasing oxygen delivery could be particularly beneficial in HFpEF-PH, where low peak $\dot{V}O_2$ arises from low exercise cardiac output and skeletal muscle oxygen diffusion.[15]

There are several unanswered questions regarding the use of sotatercept in Cpc-PH from HFpEF. First, would the magnitude of benefit be muted by more rigid treatment of HFpEF prior to randomization? The average baseline PAWP was 21 mmHg, suggesting further room for

optimization of diuretics, SGLT2i and MRAs. While the hemodynamic benefits of sotatercept extended beyond PAWP reduction, a key driver of improved clinical outcomes with sotatercept was a reduction in urgent diuretic use. Whether this effect would still be present in patients with lower baseline PAWP is unknown. Second, the lack of a dose-response for clinical outcomes and potential for increased hospitalization from cardiopulmonary events in the 0.7 mg/kg dose is puzzling. This is in contrast to a trial in PAH where 0.7 mg/kg was the target dose and provided the greatest benefit[12]. Reductions in PAWP and PVR were similar in both sotatercept groups, arguing against elevations in resting PAWP from lower PVR (i.e. "flooding the left heart") as a cause for increased hospitalization in the 0.7 mg/kg group. Whether higher doses of sotatercept worsen V/Q matching or cause occult intrapulmonary shunt preferentially in group 2 versus group 1 PH is unknown and will require greater scrutiny. Lastly, the enrollment of patients with a relatively high PVR (>4 Wood Units) raises the question of where the biology of group 1 and 2 PH overlaps. Specifically, higher PVR likely enriches for patients with more significant vascular fibrosis and inflammation, similar to patients with group 1 PH. Whether sotatercept is effective in patients with CPc-PH and lower PVR is unknown.

Notably, the CADENCE trial emphasizes the importance of targeting underlying biologic mechanisms responsible for disease, versus focusing solely on improving hemodynamic parameters. Similar to PAH trials, the benefits of sotatercept transcend the relatively modest reductions in resting PVR and highlight the importance of targeting inflammation, cell proliferation and endothelial function in HFpEF. As the biology of ligand traps evolves, sotatercept marks the first step in leveraging the power of signaling networks to reverse fibrosis and cellular hypertrophy.

Disclosures

Satyam Sarma reports no disclosures related to this work.

Kelly Chin has received fees for work on steering, advisory or adjudication committees for Gossamer Bio, Inhibikase, Janssen, Merck and United Therapeutics and her institution has received research support for clinical studies overseen by her from Gossamer Bio, Inhibikase, Janssen, Merck, Novartis, Pulmovant and United Therapeutics.

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