Sotatercept analog RAP-011 is more effective than sildenafil in improving pulmonary hypertension and reducing right ventricular hypertrophy in a ZSF1 rat model of heart failure with preserved ejection fraction

Sachindra R. Joshi, PhD[1], Jun Liu, MS[1], Patrick Andre, PhD[1], Ravindra Kumar, PhD[1], Gang Li, PhD[1].
[1]Acceleron Pharma, Cambridge MA

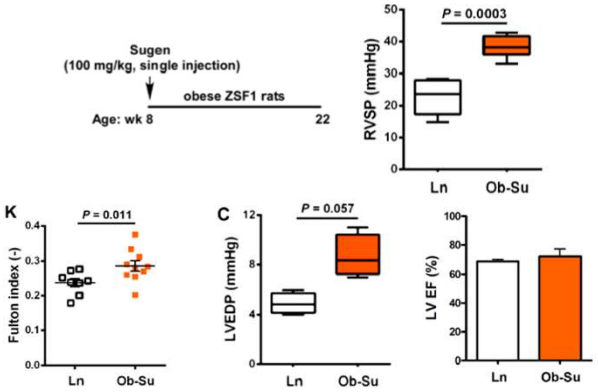
Background

Introduction:

Group 2 pulmonary hypertension involves post-capillary hypertension secondary to left heart disease. PH due to heart failure with preserved ejection fraction (PH-HFpEF) is the most prevalent form of WHO Group 2 PH but lacks effective treatment options. We previously found that sequestration of activins and growth differentiation factors with the sotatercept analog RAP-011, an activin receptor type IIA-Fc fusion protein, reverses pathological remodeling of pulmonary arteries and the right ventricle (RV) in experimental models of pulmonary arterial hypertension (PAH, Group 1 PH). This strategy of selective multi-ligand neutralization offers a promising new approach for treating patients with PAH and is under active clinical evaluation (PULSAR, SPECTRA, and STELLAR).

Rat Model of PH-HFpEF: (Lai et al., Circulation 2016)

A "two-hit" model with multiple features of metabolic syndrome due to (1) double leptin receptor defect (obese ZSF1 rat) and (2) VEGF receptor blockade with the small-molecule inhibitor SU5416.



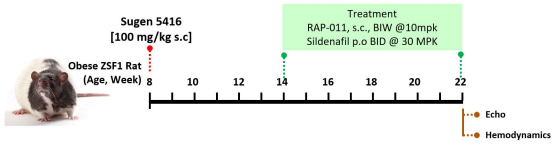
Objective

To compare the cardiopulmonary effects of therapeutic treatment with RAP-011 to those of sildenafil in a rat model of PH-HFpEF.

Methods

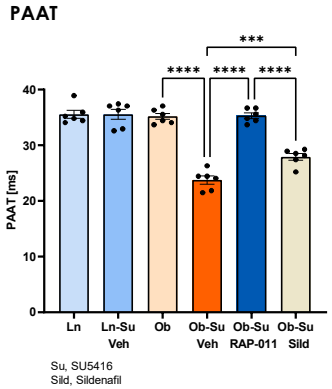
PH was induced in adult male obese ZSF1 rats by a single subcutaneous injection of SU5416 (100 mg/kg). To model the timeline of diagnosis and treatment for Group 2 PH patients, we initiated treatment with RAP-011 and sildenafil 6 weeks post SU5416 administration—at which point RV dysfunction is prominent—and continued treatment for 8 weeks. RV systolic pressure (RVSP), pulmonary artery acceleration time (PAAT), RV hypertrophy, and tricuspid annular plane systolic excursion (TAPSE) were evaluated by right heart catheterization and echocardiography following the 8-week treatment regimen.

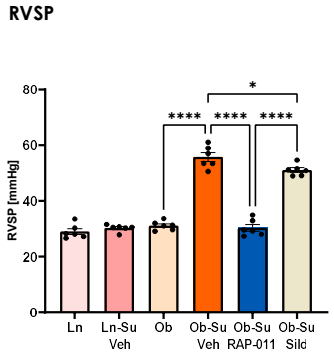
Study Design



Results

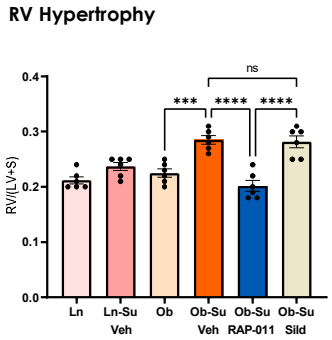
1. Obese ZSF1 rats treated with SU5416 exhibited decreased pulmonary artery acceleration time (PAAT) and increased RV systolic pressure (RVSP), which were fully reversed by RAP-011 treatment (P<0.001). Sildenafil treatment improved RVSP by 19% (P < 0.05) and PAAT by 36% (P < 0.001).

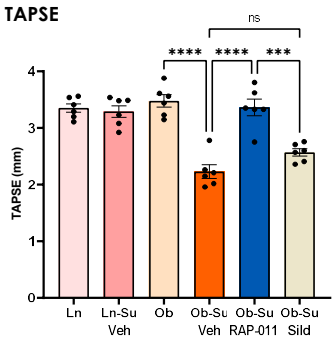




Results

2. Obese ZSF1 rats treated with SU5416 exhibited RV hypertrophy and RV dysfunction as indicated by decreased tricuspid annular plane systolic excursion (TAPSE), which were normalized by RAP-011 (P<0.001) but not with sildenafil treatment.





Conclusions

- Therapeutic treatment with the sotatercept analog RAP-011 exerted beneficial cardiopulmonary effects in a ZSF1 rat model of PH-HFpEF that were significantly greater than those produced by sildenafil, fully normalizing PH and RV hypertrophy and improving RV function.
- These results implicate activins and GDF ligands in the etiology of experimental PH-HFpEF.
- These findings support evaluation of sotatercept in patients with PH-HFpEF (Group 2 PH).

Citation

Lai YC, Tabima DM, Dube JJ, et al. SIRT3-AMP-Activated Protein Kinase Activation by Nitrite and Metformin Improves Hyperglycemia and Normalizes Pulmonary Hypertension Associated With Heart Failure With Preserved Ejection Fraction. Circulation 2016;133(8):717-31. DOI: 10.1161/CIRCULATIONAHA.115.018935.

Financial disclosure: Funding by Acceleron Pharma. All authors are employees of Acceleron Pharma.