Sotatercept Analog RAP-011 Inhibits Right Ventricular Remodeling and Restores Function in a Mouse Model of Pressure Overload

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Disclosures

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Pulmonary Arterial Hypertension and RV Failure

• Pulmonary arterial hypertension (PAH) is a life-threatening disease
  o Elevated pulmonary arterial pressures
  o Progressive right heart failure
  o Premature death

• Mechanisms underlying cardiopulmonary remodeling are not well understood

• There are currently no disease-modifying therapies for PAH
Sotatercept analog RAP-011 (ActRIIA-Fc)

Activin/GDF ligand trap

- Homodimeric fusion protein
- Extracellular domain of human ActRIIA linked to murine IgG2a Fc domain
- Proposed to act by rebalancing activin and BMP signaling

Activin Pathway

1. Activins/GDFs → ActRIIA/IIb → ALK4, ALK5, ALK7
2. Smad2/3
3. Nucleus: Target gene expression, e.g., PAI-1

BMP Pathway

1. BMPs → ActRIIA/IIb → ALK1, ALK2, ALK3
2. Smad1/5/8
3. Nucleus: Cell proliferation, differentiation, survival/apoptosis

Overactive in PAH

Activin/GDF

Homeostasis

BMP

Overactive in PAH
Aim and Approach

Aim
To determine whether RAP-011 exerts a direct cardioprotective effect in a mouse model of pressure overload-induced RV failure

Approach

[Diagram showing timeline with labeled points for Pulmonary Artery Banding (PAB), C57BL/6, Echo, S.C Treatment, BIW, 0, 1, 7, 14, 21 days, Echo, Right Heart Cath, RV Histology]
Results: RV Hypertrophy and Function

**Fulton Index**
- PAB caused RV hypertrophy and increased RV wall thickness in comparison to sham surgery ($P < 0.0001$).
- RAP-011 markedly attenuated these PAB-induced changes ($P < 0.0001$).

**TAPSE**
- PAB significantly reduced tricuspid annular plane systolic excursion ($0.68 \pm 0.03$ vs. $0.98 \pm 0.03$ mm; $P < 0.0001$)
- RAP-011 partially restored TAPSE ($0.84 \pm 0.04$ mm; $P < 0.01$).
Results: RV Functional Parameters

Myocardial Performance Index

- PAB-induced increase in myocardial performance index (P < 0.0001).
- RAP-011 markedly attenuated these PAB-induced changes (P < 0.0001).

RV Pressure Changes

- RAP-011 attenuated PAB-induced RV developed pressure (by 82%, P < 0.0001)
- RAP-011 partially normalized peak rates of RV pressure change (+dP/dtmax and -dP/dtmin, P < 0.05).
Results: RV Histological Analysis

RV Fibrosis

RAP-011 also reduced the extent of PAB-induced RV fibrosis (19.5% vs. 10.5%, P < 0.001).

Stain: Masson’s trichrome
Conclusions

• Treatment with sotatercept analog RAP-011 reduces RV remodeling and improves function in a PAB model of pressure overload-induced RV failure.

• Cardioprotective effects of RAP-011 are thus implicated as an important component of its therapeutic effects in severe experimental PAH.
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