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RAP-011 Improves Right Ventricular Remodeling and Hemodynamics in Experimental Pulmonary Arterial Hypertension

Amanda O'Brien, Kimberly Doherty, Michelle Johnson, Melissa Zammit, Peter Senese, Michael Gralinski

CorDynamics, Inc., Chicago, IL

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PRECLINICAL MODELS
TRANSLATIONAL INSIGHTS
BETTER MEDICINES

BACKGROUND / OBJECTIVE

Background

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by increased pulmonary vascular resistance and, consequently, right ventricular remodeling, hypertrophy and failure. Understanding the multifactorial pathophysiology of the disease is needed in preclinical models and the therapeutic modalities being studied. RAP-011, a sotatercept analog, appears to improve preclinical models of PAH. In this study we used echocardiography, hemodynamics, pressure-volume (PV) loops and terminal tissue weights to elucidate the effect of RAP-011 on PAH endpoints.

Objective

To evaluate RAP-011 (sotatercept analog) in a rat hypoxia/SU5416 model of PAH using high-resolution echocardiography along with right ventricle (RV) pressure-volume (PV) loops to examine RV function, structure and hemodynamics.

METHODS

PAH Model and Dosing

Sprague-Dawley rats (0.206–0.293 kg) were administered DMSO or SU5416 (60 mg/kg, SC) on Day 1 and placed in normoxia or hypoxia (approximately 13–15% O_2) until Day 22, with all rats then moved to normoxia from Day 22 until terminal procedures. Rats received either vehicle (PO) or RAP-011 (SC) at 1.5 mg/kg/dose or 5 mg/kg/dose twice weekly beginning on Day 22. Echocardiography was performed on Day 42 or 43, followed by RV PV loop analysis or hemodynamic analysis as well as organ weight collection on Day 43 or 44.

Echocardiography

On Days 42–43, transthoracic RV echocardiography was performed under 1.5–2% isoflurane anesthesia delivered by nose cone using a Vevo F2 imaging system (FUJIFILM VisualSonics, Toronto, Canada) equipped with a UHF29x transducer. Heart rate (HR) was monitored; body temperature was monitored and maintained throughout the procedure. Images were acquired from modified parasternal long-axis views using M-mode and pulsed-wave Doppler and from an apical four-chamber view using B-mode. TAPSE was measured by M-mode at the lateral tricuspid annulus, and peak systolic annular velocity (S') was measured using tissue Doppler imaging. Echocardiographic measurements and calculations followed American Society of Echocardiography recommendations, with adaptations for rat echocardiography. Data were analyzed offline using Vevo LAB version 5.7.1.

Hemodynamics

Following echocardiography, animals underwent either pulmonary artery catheterization for pulmonary arterial pressure measurements or right ventricle (RV) catheterization using a pressure-volume catheter.

Pulmonary Arterial Pressure Measurements

On Day 43 or Day 44, animals undergoing pulmonary arterial pressure (PAP) measurements were anesthetized with ketamine (40-80 mg/kg, IP) and xylazine (10 mg/kg, IP) and maintained with ketamine as necessary. Body temperature and depth of anesthesia were monitored and maintained throughout the procedure. Systemic arterial pressure was measured using a 1.4F solid-state pressure catheter (SPR-671, Millar) inserted into the femoral artery. A fluid-filled catheter was advanced to the pulmonary artery through the right jugular vein. Signals were recorded with NOTOCORD-hem 4.3 acquisition system (NOTOCORD Inc, Philadelphia, PA).

RV PV Loop Procedure

On Day 43 or Day 44, invasive hemodynamic measurements were obtained under a surgical plane of anesthesia. Following induction and initial isoflurane delivery by nose cone, animals were intubated and maintained with 1–2% isoflurane delivered through an endotracheal tube during the PV loop procedure. Positive-pressure ventilation was provided using a PhysioSuite® RoVent ventilator (Kent Scientific, Torrington, CT), with settings based on body weight. Body temperature and depth of anesthesia were monitored and maintained throughout the procedure. Systemic arterial pressure was measured using a 1.4F solid-state pressure catheter (SPR-671, Millar) inserted into the femoral artery. A 2F pressure-volume catheter (SPR-869, Millar) was introduced into the RV through a puncture in the apical free wall. Signals were recorded and analyzed using LabChart Pro version 8.1.28 (ADInstruments).

Morphometric analysis

After hemodynamic measurements, animals were euthanized by exsanguination. The heart-lung block was perfused with ice-cold saline until clear, and the heart was weighed. Atria were removed; RV and left ventricle (LV) + septum were separated and weighed. Lungs were weighed.

Monitoring and statistical analysis

Daily cageside observations and weekly body weights were recorded. Data are mean ± SD. Statistics were run on full-precision individual animal values in GraphPad Prism: ordinary one-way ANOVA with Tukey's multi-comparisons test; adjusted p<.05 was significant.

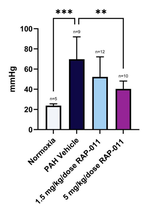
SURVIVAL, CLINICAL OBSERVATIONS AND BODY WEIGHT

- Survival rates were as follows: 100% in the normoxia group, 83% in the PAH vehicle control group, 100% in the RAP-011 at 1.5 mg/kg/dose group and 85% in the 5 mg/kg/dose group.
- An adverse clinical observation of swollen limbs was noted in a total of 4 animals administered 5 mg/kg/dose RAP-011 twice a week; 2 of these animals were euthanized prior to terminal study day due to clinical signs. One additional animal administered the 5 mg/kg/dose RAP-011 was found dead without any preceding clinical observations. No other adverse clinical observations were noted for either dose of RAP-011.
- For the animals that survived to terminal study day, body weight gains were as follows:
  Normoxia animals gained an average of 0.196 kg (+76%) over the 43-day study duration; PAH vehicle control animals gained an average of 0.160 kg (-11 percentage points vs normoxia). Body weight gain was similar in both RAP-011 dose groups compared to PAH vehicle control (1.5 mg/kg/dose: +5 percentage points; 5 mg/kg/dose: -5 percentage points).

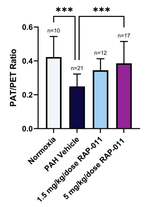
RESULTS

Figure 1. RAP-011 Reduces Right Ventricular Pressure Load

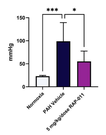
RV end-systolic pressure (RV Pes)



Pulmonary acceleration / ejection time (PAT/PET ratio)



Systolic Pulmonary Arterial Pressure (sPAP)
PAH vehicle: +328% versus normoxia (p=.0006).
RAP-011 at 5 mg/kg/dose: −44% versus PAH vehicle (p=.0233).
RAP-011 at 1.5 mg/kg/dose: no data (ND).



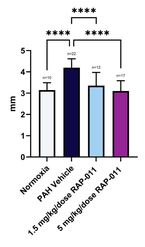
PAH vehicle versus normoxia: RV Pes +194% (p=.0001) and PAT/PET −41% (p=.0002). Versus PAH vehicle, RAP-011 at 1.5 mg/kg/dose changed RV Pes −25% (p=.0980) and PAT/PET +38% (p=.0504); RAP-011 at 5 mg/kg/dose changed RV Pes −42% (p=.0027) and PAT/PET +55% (p=.0006).

- **Key pulmonary pressure load parameters RV Pes and PAT/PET ratio indicate dosing twice weekly with RAP-011 at 5 mg/kg/dose lowered pulmonary pressure load; this was reinforced by the reduction in sPAP in the subset data.**

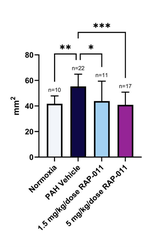
Group	RV Pes (mmHg) mean ± SD (n)	PAT/PET (ratio) mean ± SD (n)	sPAP (mmHg) mean ± SD (n)
Normoxia	23.8 ± 1.8 (n=5)	0.423 ± 0.122 (n=10)	23.1 ± 1.7 (n=5)
PAH vehicle	69.8 ± 22.1 (n=9)	0.249 ± 0.073 (n=21)	98.8 ± 40.6 (n=11)
RAP-011 at 1.5 mg/kg/dose	52.3 ± 19.8 (n=12)	0.345 ± 0.068 (n=12)	ND
RAP-011 at 5 mg/kg/dose	40.3 ± 7.8 (n=10)	0.386 ± 0.129 (n=17)	55.0 ± 22.6 (n=7)

Figure 2. RAP-011 Attenuates Right Ventricular Structural Remodeling

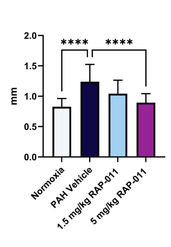
RV internal diameter: diastole (RVIDd)



RV end-systolic area (RVESA)



RV free wall thickness (RVFWT)



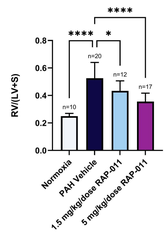
PAH vehicle versus normoxia: RVIDd +34%, RVESA +33%, and RVFWT +50% (all p<.05). Versus PAH vehicle, RAP-011 at 1.5 mg/kg/dose changed RVIDd −20% (p<.0001), RVESA −21% (p=.0245), and RVFWT −16% (not significant [ns]). RAP-011 at 5 mg/kg/dose changed RVIDd −26%, RVESA −26%, and RVFWT −28% (all p<.001).

- **RV chamber size decreased with RAP-011 dosed twice weekly at 1.5 mg/kg/dose and 5 mg/kg/dose. RVFWT decreased significantly at 5 mg/kg/dose. These findings are consistent with reduced RV structural remodeling in this PAH model.**

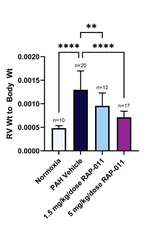
Group	RVIDd (mm) mean ± SD (n)	RVESA (mm²) mean ± SD (n)	RVFWT (mm) mean ± SD (n)
Normoxia	3.14 ± 0.35 (n=10)	41.7 ± 6.2 (n=10)	0.83 ± 0.13 (n=10)
PAH vehicle	4.20 ± 0.41 (n=22)	55.3 ± 9.6 (n=22)	1.24 ± 0.29 (n=22)
RAP-011 at 1.5 mg/kg/dose	3.35 ± 0.62 (n=12)	43.9 ± 15.6 (n=11)	1.04 ± 0.22 (n=12)
RAP-011 at 5 mg/kg/dose	3.10 ± 0.48 (n=17)	40.9 ± 9.9 (n=17)	0.89 ± 0.15 (n=17)

Figure 3. RAP-011 Reduces Right Ventricular Hypertrophy and Lung Weight to Body Weight Ratio

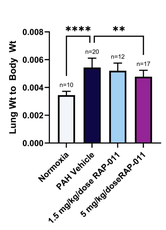
Fulton's index: RV / (LV + septum)



RV weight to body weight ratio



Lung weight to body weight ratio



PAH vehicle versus normoxia: Fulton's index +111%, RV Weight to Body Weight ratio +169%, and Lung Weight to Body Weight ratio +58% (all p<.0001). Versus PAH vehicle, RAP-011 at 1.5 mg/kg/dose changed these endpoints −18%, −26%, and −4%, respectively (Fulton's index p=.0164; RV Weight to Body Weight p=.0071; lung weight to body weight ns). RAP-011 at 5 mg/kg/dose changed them −32%, −45%, and −12%, respectively (all p<.01).

- **Both RAP-011 doses decreased RV hypertrophy as there were reductions in Fulton's index and RV weight to body weight ratio.**
- **Lung weight to body weight ratio reduction further confirmed that the pulmonary pathophysiology of PAH improved with twice weekly RAP-011 administration, reaching statistical significance with the 5 mg/kg twice weekly dose of RAP-011.**

Group	Fulton's index (ratio) mean ± SD (n)	RV Wt to Body Wt (×10⁻³ g/g) mean ± SD (n)	Lung Wt to Body Wt (×10⁻³ g/g) mean ± SD (n)
Normoxia	0.250 ± 0.020 (n=10)	0.482 ± 0.052 (n=10)	3.447 ± 0.279 (n=10)
PAH vehicle	0.526 ± 0.114 (n=20)	1.296 ± 0.401 (n=20)	5.439 ± 0.671 (n=20)
RAP-011 at 1.5 mg/kg/dose	0.434 ± 0.073 (n=12)	0.956 ± 0.273 (n=12)	5.204 ± 0.552 (n=12)
RAP-011 at 5 mg/kg/dose	0.356 ± 0.061 (n=17)	0.712 ± 0.131 (n=17)	4.778 ± 0.459 (n=17)

The body weight ratios are shown as coefficients of ×10⁻³ g/g (e.g., 0.482 represents 0.000482 g/g). Wt, weight.

Table 1. Additional Echocardiography and PV Loop Parameters

Endpoint (unit)	Normoxia mean ± SD (n)	PAH vehicle mean ± SD (n) % change[a]	RAP-011 at 1.5 mg/kg/dose % change[b]	RAP-011 at 5 mg/kg/dose % change[b]
RVPdev (mmHg)	27.7 ± 0.9 (n=5)	**70.0 ± 20.2 (n=9) +153% (p=.0002)**	−21% (p=.1566); n=12	**−38% (p=.0051); n=10**
RVIDs (mm)	1.80 ± 0.21 (n=10)	**2.77 ± 0.46 (n=22) +54% (p<.0001)**	**−26% (p=.0001); n=12**	**−34% (p<.0001); n=17**
RAA (mm²)	19.1 ± 4.6 (n=10)	**29.4 ± 13.0 (n=22) +54% (p=.0308)**	**−41% (p=.0087); n=10**	**−43% (p=.0008); n=17**
PAT (ms)	25.9 ± 5.2 (n=10)	**16.9 ± 4.0 (n=22) −35% (p<.0001)**	+20% (p=.1759); n=12	**+39% (p=.0002); n=17**
TAPSE (mm)	2.62 ± 0.41 (n=10)	2.32 ± 0.39 (n=19) −12% (p=.2771)	−5% (p=.8793); n=12	−11% (p=.3185); n=17
S' (mm/s)	49.1 ± 4.4 (n=10)	40.6 ± 11.8 (n=21) −17% (p=.0904)	−2% (p=.9969); n=12	−8% (p=.6845); n=17

[a] PAH vehicle percent change versus normoxia; [b] RAP-011 percent change versus PAH vehicle. p values are Tukey-adjusted after ordinary one-way ANOVA; bold entries p < .05.

Abbreviations: PAH, pulmonary arterial hypertension; PAT, pulmonary acceleration time; PV, pressure-volume; RAA, right atrial area; RV, right ventricle; RVIDs, RV internal diameter in systole; RVPdev, RV developed pressure; S', peak systolic annular velocity; TAPSE, tricuspid annular plane systolic excursion.

- **Twice weekly RAP-011 at 5 mg/kg/dose reduced RVPdev, RVIDs and RAA and increased PAT versus PAH vehicle (all p<.05), suggesting reduced RV chamber size and RV pressure load.**
- **Twice weekly RAP-011 at 1.5 mg/kg/dose significantly reduced RVIDs and RAA, supporting a reduced chamber size.**
- **TAPSE and S' showed no significant improvement versus PAH vehicle at either dose, so these longitudinal RV systolic measures did not parallel the structural and pressure findings.**

CONCLUSION

Twice weekly dosing with RAP-011 attenuated RV remodeling and reduced pulmonary vascular load. RV remodeling improvements were confirmed as reductions in RVIDd, RVESA, Fulton's index and RV weight to body weight ratio. PAH-associated pulmonary pressure was attenuated, supported by lower RV Pes and sPAP with RAP-011 at 5 mg/kg/dose.

Bars and Figure 1–3 data tables: mean ± SD with endpoint-specific n. Table 1: percent changes and adjusted p values use the comparisons in its footnotes; bold entries p<.05. Brackets: *p<.05, **p<.01, ***p<.001, ****p<.0001. All percentages use full-precision group means; RV/BWT and lung/BWT are scaled to ×10⁻³ g/g.

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