Supplementary Material

Riociguat and the right ventricle in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension

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SUPPLEMENTARY TABLE S1. Overview of the effects of riociguat on the RV in preclinical models.

Preclinical model	Riociguat treatment	Changes to the RV following riociguat treatment compared with controls	Reference
Rat model of PH—monocrotaline induced	Daily, oral administration of riociguat (10 mg/kg/day) or vehicle from Day 21 to Day 35 following monocrotaline injection	**Size** • Decreased RV hypertrophy ($p<0.05$) **Other remodelling** • Improved vascular remodelling (as measured by a reduction of fully muscularised PAs [$p<0.05$])	[1]
Mouse model of PH—hypoxia induced	Daily, oral administration of riociguat (10 mg/kg/day) or vehicle from Day 21 to Day 35 following hypoxic gas exposure	**Size** • Decreased RV hypertrophy ($p<0.05$) **Other remodelling** • Decreased transforming growth factor beta ($p<0.05$) and atrial natriuretic factor ($p<0.05$) hypoxia-induced RV gene expression • Improved vascular remodelling (as measured by a reduction of fully muscularised PAs [$p<0.05$])	[1]
Rat model of severe angioproliferative	Daily, oral administration of riociguat (10 mg/kg/day),	**Function** • Decreased PA flow mid-systolic “notch” duration ($p\leq0.05$) and	[2]

PAH—induced by endothelial growth factor receptor antagonist SU5416 in combination with hypoxic exposure	sildenafil (50 mg/kg/day), or vehicle for 2 weeks following induction with SU5416 and chronic hypoxia	increased PA acceleration time (p≤0.05) • Increased CO (p<0.05) • Decreased total pulmonary resistance (p<0.05) • Improved RV function (decrease in tissue Doppler imaging [myocardial performance index] [p<0.05]) • Attenuated RV dilation (increased M-mode TAPSE [p<0.05]) **Size** • Decreased RV hypertrophy (p<0.05) **Other remodelling** • Reduced RV fibrosis (decreased collagen content [p<0.05]) • Improved vascular remodelling (as measured by a reduction of fully muscularised PAs [p<0.01], reduced medial wall thickness of small PAs [p<0.05], and lower proportion of fully closed PAs [p<0.05])	
Mouse model of chronic obstructive pulmonary disease	Daily, oral administration of riociguat (3 or 10 mg/kg/day) or placebo after 6 months of	**Size** • Decreased RV hypertrophy (p<0.001) **Other remodelling**	[3]

and PH—induced by chronic cigarette smoke exposure	cigarette smoke exposure	• Improved vascular remodelling (as measured by reduced vascular muscularisation [various measurements] and decreased medial wall thickness of small PAs [p<0.001])	
Mouse model of left heart failure and secondary PH—induced by transverse aortic constriction	Daily, oral administration of riociguat (10 mg/kg/day), sildenafil (100 mg/kg/day), or vehicle for 2 weeks following transverse aortic constriction	**Function** • Decreased PVR (p<0.05) **Size** • Trend of decreased RV hypertrophy (non-significant) **Other remodelling** • Improved vascular remodelling (as measured by reduced vascular muscularisation [various measurements] and decreased medial wall thickness of PAs [p<0.05]) • Trend of decreased RV collagen deposition (non-significant)	[4]
Mouse model of pressure overload RV hypertrophy—induced by PA banding	Daily, oral administration of riociguat (30 mg/kg/day), sildenafil (100 mg/kg/day), or vehicle for 2 weeks, 1 week following PA banding	**Function** • Decrease in RV end-diastolic volume (p<0.001) and RV end-systolic volume (p<0.01) • Trend of increased RV stroke volume (non-significant) • Increased RV ejection fraction (p<0.001)	[5]

Other remodelling • Decreased RV fibrosis (as measured by decreased collagen content [p<0.001])

CO: cardiac output; PA: pulmonary artery; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion.

References

1 Schermuly RT, Stasch JP, Pullamsetti SS, *et al.* Expression and function of soluble guanylate cyclase in pulmonary arterial hypertension. *Eur Respir J* 2008; 32: 881–891.

2 Lang M, Kojonazarov B, Tian X, *et al.* The soluble guanylate cyclase stimulator riociguat ameliorates pulmonary hypertension induced by hypoxia and SU5416 in rats. *PLoS One* 2012; 7: 1–9.

3 Weissmann N, Lobo B, Pichl A, *et al.* Stimulation of soluble guanylate cyclase prevents cigarette smoke-induced pulmonary hypertension and emphysema. *Am J Respir Crit Care Med* 2014; 189: 1359–1373.

4 Pradhan K, Sydykov A, Tian X, *et al.* Soluble guanylate cyclase stimulator riociguat and phosphodiesterase 5 inhibitor sildenafil ameliorate pulmonary hypertension due to left heart disease in mice. *Int J Cardiol* 2016; 216: 85–91.

5 Rai N, Veeroju S, Schymura Y, *et al.* Effect of riociguat and sildenafil on right heart remodeling and function in pressure overload induced model of pulmonary arterial banding. *Biomed Res Int* 2018; 2018: 3293584.