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Title: Effect of POL6014, a protein epitope mimetic (PEM) neutrophil elastase inhibitor, in a model of monocrotaline (MCT)-induced pulmonary arterial hypertension in rats

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Body: Rationale: Neutrophil elastase (NE) contributes to the development of pulmonary arterial hypertension (PAH) by enhancing pulmonary arterial smooth muscle cell proliferation which thickens the vessel wall and reduces the lumen. Objective: Evaluate the effect of a NE inhibitor, POL6014, after repeated direct administration in the lungs in a rat PAH model. Methods: After a single injection of MCT Sprague Dawley rats were treated daily with POL6014 at two doses, 0.3 and 3 mg/kg, or its vehicle PBS, and with a reference compound, Tadalafil at 10mg/kg or its vehicle respitose for 21 days. All treatments were given intratracheally (IT). On Day 21 hemodynamic parameters were recorded and right ventricular hypertrophy was assessed by the calculated mass ratio RV/LV+S (right ventricle weight divided by left ventricle and septum weight). Results: POL6014 at both doses induced a statistically significant reduction in mean right ventricular pressure (RVP) when compared to the PBS group (PBS: 50.01±2.35 mmHg vs POL6014, 0.3 mg/kg: 36.52±2.56 mmHg, $p<0.01$ and vs POL6014, 3 mg/kg: 38.42±2.82 mmHg, $p<0.01$). Tadalafil at 10 mg/kg also reduced significantly mean RVP in comparison to respitose (respitose: 49.43±3.15 mmHg vs Tadalafil: 36.68±1.79 mmHg, $p<0.001$). Moreover POL6014 and Tadalafil significantly decreased the ratio RV/LV+S. Conclusion: POL6014 significantly improves RVP and attenuates right ventricular hypertrophy in a rat MCT-induced PAH model after chronic IT administration. POL6014 at 0.3 mg/kg is as efficient as Tadalafil at 10 mg/kg. The PEM NE inhibitor POL6014 may thus provide another therapeutic treatment option for PAH.