Incremental efficacy of an inhaled PDGFR inhibitor in combination with tadalafil and ambrisentan for the treatment of pulmonary arterial hypertension

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Many patients with pulmonary arterial hypertension (PAH) fail to respond to combination therapy with PDE5 inhibitors and endothelin receptor antagonists. We tested the hypothesis that a novel inhaled PDGFR kinase inhibitor, PK10571, in combination with Ambrisentan and Tadalafil would provide incremental benefit in an animal model of severe PAH. AAVS/6.2CMV PDGF B was administered by pulmonary insufflation to male SD rats in order to overexpress PDGFBB in the lung. Four weeks later, SU5416 was given and rats housed in a hypoxia chamber at FiO₂ 10% for 3 weeks. After PAH had developed, PK10571 was administered either alone (0.25mg/kg twice daily via inhalation route) or in combination with Ambrisentan and Tadalafil (10mg/kg, oral gavage; once daily) for 28 days. AAV-PDGF alone did not result in PAH. Overexpression of PDGF B resulted in a decrease in total PDGFRβ. However, subjecting these animals to SU5416/hypoxia dramatically increased pPDGFR β/PDGFR. Right ventricular systolic pressure (RVSP) was significantly decreased in rats treated with Ambrisentan+Tadalafil (TA-V) or PK10571 (V-PK) alone compared to vehicle (V-V). Combination treatment (TA-PK) provided additional benefit (V-V, 62.64±4.07; TA-V, 42.89±2.23; V-PK, 44.30±1.88; TA-PK, 33.24±1.15, mm Hg, p<0.01 TA-V, V-PK, or TA-PK vs V-V; p<0.01 TA-PK vs TA-V or V-PK). RV hypertrophy (RV/(LV+IVS)) was significantly decreased in rats treated with TA-V, V-PK or TA-PK compared to V-V, and TA-PK provided additional reduction in RVH (V-V, 0.505±0.03; TA-V, 0.376±0.02; V-PK, 0.36±0.01; TA-PK, 0.277±0.01, p<0.01 TA-V, V-PK, or TA-PK vs V-V; p<0.05 TA-PK vs TA-V or V-PK). The incremental efficacy of combination therapy (TA-PK) was associated with a decrease in pPDGFR β/PDGFRβ. These data show that Inhaled PK10571 was as effective as treatment with Tadalafil plus Ambrisentan in the AAV-PDGF SU5416/Hypoxia rat model of PAH. Combination treatment of inhaled PK10571 plus Tadalafil and Ambrisentan provided additional benefit compared to Tadalafil plus Ambrisentan.