APD811 (ralinepag), a novel non-prostanoid IP receptor agonist, has potent antiproliferative and vasorelaxant properties in human pulmonary artery

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Introduction: APD811 is an oral, non-prostanoid IP receptor agonist with a long plasma half-life (~ 24 hr) in development for pulmonary arterial hypertension (PAH). Little is known about the pulmonary pharmacology of this agent. The aim was to compare the functional effects of APD811 in distal human pulmonary smooth muscle cells (PASMCs) and arteries (PAs) alongside other prostacyclin mimetics already licensed for PAH.

Methods: PASMCs from PAH patients were grown in 9% serum and treated with IP receptor agonists ± 1 µM RO-1138452 (IP receptor antagonist) for 1hr (cyclic AMP) or 96hr (cell proliferation). Cyclic AMP was assessed using an ELISA and cell proliferation using an MTS assay. Distal PAs from control patients (mean age 66yr) were mounted in a myograph and pre-tensioned to an equivalent of ~22 mmHg (3K Pascal) before being constricted with U46619 (thromboxane mimetic; 100nM). The concentration (EC_{50}) producing the half maximal response (E_{Max}) was determined.

Results: Iloprost, APD811, MRE-269 (selexipag metabolite) and treprostinil increased cyclic AMP (EC_{50} 17, 252, 340, 550 nM, respectively). E_{Max} was lower ($P<0.001$; n=5) for all three agents (64, 45, 25%, respectively) compared with treprostinil. In proliferation assays, APD811 was 10 fold more potent (14 nM) than MRE-269 (145 nM) and E_{Max} were lower for both compared to treprostinil (57% versus 89%). RO-1138452 (1 µM) abolished agonist-induced cAMP generation and the antiproliferative effects of APD811 and MRE-269. In contrast, the antiproliferative effects of treprostinil and iloprost were weakly inhibited by RO-1138452. In PAs, APD811 produced a significantly ($P<0.001$, n=5-8) greater relaxation (E_{Max} 98%) compared to iloprost (E_{Max} 84%), treprostinil (E_{Max} 71%) or MRE-296 (E_{Max} 59%) and was more potent than MRE-269 (EC_{50} 449nM versus 1579 nM) but similar to iloprost (EC_{50} 650 nM) or treprostinil (EC_{50}=320 nM).

Conclusions: APD811 and MRE-269 behave as selective, but partial IP receptor agonists, whereas iloprost and treprostinil can inhibit cell proliferation through IP-receptor independent

pathways. In all assays APD811 produced superior effects to MRE-269 and had a favourable vasodilator profile compared with iloprost and treprostinil.

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