APD811, a novel and highly selective non-prostanoid IP receptor agonist in smooth muscle cells from patients with pulmonary hypertension.

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Introduction: APD811 is an oral, non-prostanoid IP receptor agonist with a long plasma half-life (~ 24 hr) in development by Arena Pharmaceuticals Inc for pulmonary arterial hypertension (PAH). Little is known about the pulmonary pharmacology of this agent. We assessed the ability of APD811 to generate cyclic AMP (cAMP) and inhibit cell proliferation in pulmonary artery smooth muscle cells (PASMCs) isolated from PAH patients. The role of the IP receptor was investigated alongside prostacyclin mimetics already licensed for PAH.

Methods: Distal PASMCs were stimulated with 9% serum and treated with agonists ± RO-118452 (IP receptor antagonist; IPRA) for 1 hr or 4 days to measure cAMP (ELISA) and cell proliferation (MTS), respectively. The concentration (EC_{50}) producing the half maximal (E_{Max}) response was determined.

Results and conclusions: Iloprost APD811, MRE 269 (selexipeg metabolite) and treprostinil increased cAMP (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 cell proliferation assays, APD811 was 10 fold more potent (14 nM) than MRE-269 (145 nM); both produced a lower E_{Max} compared to treprostinil (57% versus 89%). RO-118452 (1 µM) essentially abolished agonist-induced cAMP generation and the effects of APD811 and MRE-269 in cell proliferation assays. In contrast, the antiproliferative effects of treprostinil and iloprost were weakly inhibited by RO-118452. In combination with other PAH therapies, APD811 produced a greater (range 0.1-10,000 nM) antiproliferative response in the presence of riociguat (100nM) and to a lesser extent with 100nM treprostinil or the phosphodiesterase inhibitor, sildenafil but not when combined with 100nM endothelin receptor antagonists (bosentan and macitentan).

Summary: In human PASMCs, APD811 and MRE-269 both behave as selective, but partial IP receptor agonists in cAMP and cell proliferation assays, with APD811 a more effective agonist than MRE-269. Iloprost and treprostinil inhibit proliferation through IP-receptor independent pathways. Agents stimulating cyclic GMP could work better at inhibiting cell proliferation in combination with APD-811 than endothelin receptor antagonists.

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