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Rare Diseases Congress-2018: Serotonergic targets in the treatment of pulmonary arterial hypertension (PAH) and idiopathic pulmonary fibrosis (IPF) - Laxminarayan Bhatt - Reviva Pharmaceuticals, Inc

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Pulmonary arterial hypertension (PAH) and idiopathic pulmonary fibrosis (IPF) are two progressive, debilitating, and fatal lung diseases. Both sicknesses are incomplete in action choices and haven't any therapy. Pulmonary hypertension, inflammation, and structural remodeling, all with varying degrees of severity, are the most common and significant underlying pathophysiologic factors associated with these conditions. Although the pathogenesis is not clearly understood, increased levels of inflammatory cytokines, including growth factors and dysfunctional endothelial vasoactive mediators (e.g., serotonin, 5-HT; endothelia, ET; nitric oxide, NO; and prostacyclin, PGI2), are found in the lungs of PAH and IPF patients. The 5-HT receptor signaling pathway appears to play a central role in the pathobiology of both conditions. RP5063, a new chemical entity, is a potent modulator of 5-HT signaling that involves specifically the 5-HT2A/2B/7 receptors within the lung. The signal transduction pathways involving these 5-HT receptors mediate significant underlying pathophysiology (vasoconstriction, and vascular/alveolar inflammation, fibrosis, and proliferation) for PAH and IPF. RP5063 has demonstrated proof of concept in translational animal models that emulate IPF and PAH in humans. The U.S. FDA has granted an Orphan Drug Designation to RP5063 for the treatment of PAH and IPF, in which clinical phase 2 studies are planned to start soon. This presentation will briefly review approved therapies and unmet medical needs for PAH and IPF. It will segue to the current understanding of 5-HT receptor signaling pathways in the pathobiology of these two diseases, and will then discuss RP5063 pharmacology and preclinical efficacy for PAH and IPF. It will close by delineating the clinical pharmacokinetic/ pharmacodynamics and safety profiles of this compound. Recent Publications. Bhatt L, Hawkinson J, Cantillon M, et al. (2017). RP5063, a novel, multimodal, serotonin receptor modulator, prevents Signe 5416-induced pulmonary arterial hypertension in rats. European J Pharmacology, 810: 83-91. 2. Bhatt L, Hawkinson J, Canutillo M, et al. (2017). RP5063, a novel, multimodal, serotonin receptor modulator, prevents monocrotaline-induced pulmonary arterial hypertension in rats. European J Pharmacology, 810: 92-99. 3. Canutillo M, Ings R, and Bhatt L. (2018) A population pharmacokinetic and pharmacodynamics analysis of phase 2 study data evaluating RP5063 in patients with schizophrenia or schizoaffective disorder. European Journal of Drug Metabolism and Pharmacokinetics, (00) 1-13. 4. Canutillo M, Ins R, Bhatt L. (2018). RP5063 Phase 1 Experience: Evaluation of safety in normal healthy volunteers and of safety, and pharmacodynamics of multiple-doses over 10 days to stable schizophrenia patients. Clinical & Translational Science, (00) 1-10. Pulmonary endothelial serotonin synthesis via tryptophan hydroxylase 1 (TPH1) is increased in patients with PAH and serotonin can act during a paracrine fashion on underlying pulmonary arterial smooth muscle cells Increased synthesis of serotonin and/or activity of serotonin in pulmonary arteries have been implicated in the pathobiology of pulmonary arterial hypertension. “Serotonin hypothesis of pulmonary hypertension” Over the last few decades there has been an accumulation of convincing evidence that targeting serotonin synthesis or signaling may be a novel and promising approach to the development of novel therapies for PAH the observation that there was increased plasma serotonin in some patients with primary PH associated with platelet storage pool defects. Serotonin is a neurotransmitter in the central nervous system and an autacoid in the periphery. It is synthesized from L-tryptophan through the activity of tryptophan hydroxylase. The remaining 10% is taken up by platelets concentration of free serotonin in the blood is therefore normally extremely low. Pathologically, PAH is characterized by vasoconstriction of the small pulmonary arteries and proliferation in all layers of the vessel wall as well as fibrosis and inflammation. Recently, this has been shown to be facilitated by myoendothelial gap junctions Transglutaminase 2 (TG2) is a multifunctional enzyme that cross-links proteins with monoamines such as serotonin via a transglutamidation reaction. Serotonin-induced fibrosis may also play a role in PAH. Serotonin can activate pulmonary arterial fibroblasts and promote adventitia fibrosis through signaling predominate in systemic arterial medial tissue and are expressed in the normal PASM of species such as rats and mice but it is the 5-HT1B receptor that normally mediates pulmonary arterial responses to serotonin in larger animals and man pulmonary artery is that it can amplify the accumulation of [3H] inositol phosphates elicited by a Go-protein coupled receptor and these mediate serotonin-induced proliferation in these cells.

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