

Idiopathic Pulmonary Fibrosis and Antagonism of Serotonin Receptor-Subtype 2: Why? When? How?

Samah M Elaidy*

Department of Clinical Pharmacology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

***Corresponding Author:** Samah M Elaidy, Associate Professor, Department of Clinical Pharmacology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.

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Idiopathic pulmonary fibrosis (IPF) represents an important sector about 20 - 50% of interstitial lung diseases. IPF is a severe chronic progressive form of idiopathic interstitial pneumonias (IIPs), which recognized by its unknown notable roots. IPF has a very poor prognosis with a median survival of 2.5 - 3.5 years after diagnosis. IT displayed a global incidence of 2.8 - 9.3 per 100,000 with 5% prevalence increments per year [1,2]. The highlighted importance and burden of IPF are results of unpredictable disease-course, encroachments in acute exacerbations, higher mortality and co-morbidity beyond cancer. IPF patients showed an amplified rates of hospital admission with higher medical care cost, which mostly precedes the actual diagnosis [2-4].

Despite the epidemiological, and health concerns about IPF, just two anti-fibrotic regimens were approved by Food and Drug Administration (FDA), pirfenidone and nintedanib [5]. While safety and efficacy of these two anti-fibrotics are documented in several phase III clinical trials, patients with advanced and comorbid risks have escaped those convenient and efficacious impacts [6-8].

Numerous genetic and clinical IPF phenotypes are evidenced, which showed a great behavioral overlapping with other comorbid diseases. Alongside those phenotypes, various genetic, epigenetic, and molecular cascades are involved [6,9,10]. According to these evidences, the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT) clinical practice guideline subtly recommends the need for holistic approaches in diagnosis of IPF. The holistic approach recommend simultaneous diagnoses by molecular targets and clinical estimations [5].

Of notice, an augmented serotonergic-dependent pathogenic pathway is a preclinical research-provoking issue in pulmonary fibrosis. The signaling between serotonin (5-HT) and its highly expressed metabotropic lung 5-HT₂ receptors is strongly evident in IPF pathogenesis and progression. Tryptophan hydroxylase 1 (TPH 1) is the enzyme responsible for formation of 5-HT in the lung. TPH1 Knockout mice showed less aggravated pulmonary fibrosis than TPH1 wild mice [11].

Widespread allocations of 5-HT₂ receptor subtypes are demonstrated in fibrotic lung tissue and cells as alveolar epithelial cells, fibroblasts, myofibroblasts (5-HT_{2A/B}) and alveolar macrophages (5-HT_{2C}). That permits unique modulations of the fibrogenesis/proliferation/angiogenesis in IPF. It also provides an emphasis on the alternate phenotypes of alveolar macrophages. In various preclinical studies, individual or combined blockade of 5-HT_{2A}, B, and C receptors attenuated the lung fibrosis and dysregulated hemodynamics and remodeling delivered by bleomycin, a reproducible animal model of pulmonary fibrosis. Amelioration in lung edema and collagen deposition, and molecular inflammatory, pro-/fibrotic, and angiogenic growth factors, as transforming growth factor- β 1 (TGF- β 1), tumor necrosis factor- α (TNF- α), vascular endothelial growth factor (VEGF), and plasminogen activator inhibitor-1 (PAI-1) were evidenced [12-18].

In the gastro-esophageal reflux disease (GERD), as a clinical phenotype of IPF and a comorbidity, serotonin evidently increases the gastric and intestinal constitutive motility and contraction through the stomach enteric neuron 5-HT_{2A/B} [19-21].

Overall in IPF, the exploration of intercalated roles of 5-HT on the 5-HT₂ receptors is a promising inspire. The diminution of 5-HT in the serum and lung of IPF patients could be a diagnostic and prognostic marker. The timing of targeting and blocking the lung 5-HT₂ receptors is an important concern, which needs further thorough investigations. In susceptible comorbid patients and patients with prodromal manifestations as unexplained attacks of dyspnea and cough, a blockade of lung 5-HT₂ receptors could halt the inflammatory and fibrogenic cascades. Finally, in a holistic manner, 5-HT₂ receptors antagonism could be targeted in IPF therapy, individually or in combination with other approved regimens.

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