NEW THERAPIES FOR IPF: BREATHING A LITTLE EASIER

Idiopathic pulmonary fibrosis (IPF) is a rare but serious lung disease with an estimated 5,000 new cases each year and over 100,000 patients in the US[1]. IPF is characterized by the development of thick scar tissues in the interstitial spaces in the lungs that results in reduced gas exchange over time. Over time, the air sacs or alveoli in the lungs are replaced with stiff scar tissue. Essentially, IPF is the result of a disbalance between epithelial cells and fibroblasts resulting in increased fibrosis in lung tissues. It has been suggested that IPF develops due to repeated injury by unknown factors to the lung epithelial cells resulting in wound formation. As the name suggest, a definitive disease driver has not been identified for IPF but risk factors have been identified including a family history of interstitial lung disease, smoking, gastroesophageal reflux disease (GERD), age (older than 50 years) and gender (75% of IPF patients are male).

Oxygen therapy and lifestyle management help delay disease progression but if IPF progresses to a severe stage, a lung transplant may be the only available option but there are some pharmaceutical options. Currently, there are 2 drugs on the market for IPF - nintedanib (Ofev®) from Boehringer Ingelheim and pirfenidone (Esbriet®) from Roche. Nintedanib is a broad tyrosine kinase inhibitor that binds to and inhibits activation of tyrosine kinase receptors like FGFR (fibroblast growth factor receptor), VEGFR (vascular endothelial growth factor receptor) and PDGFR (platelet derived growth factor receptor), that are important for fibroblast proliferation and migration as well as the development of the extracellular matrix (ECM)[2]. Pirfenidone is an anti-inflammatory agent that also reduces fibroblast proliferation and inhibits the production of specific collagen forms. While pirfenidone have been shown to extend life span by 2.5 years[3], and nintedanib and pirfenidone have been shown to slow the decline in lung function.

In the past couple of years, promising new therapies for IPF have been moving into the clinic. PRM-151 is currently in phase III clinical trials. This therapy was originally developed by Promedior, which was acquired by Roche in 2019[4]. PRM-151 was shown to delay and reverse pulmonary fibrosis in phase II trials suggesting that this therapy may have disease modifying potential. PRM-151 is a recombinant protein called pentraxin-2 that is associated with normal wound repair that would minimize fibrosis and scar tissue formation. Another new therapy from Galapagos NV is being tested in a proof-of-concept Phase II trial in 68 IPF patients[5]. The novel therapy is GLPG1205 that is an antagonist of a G-protein coupled receptor called GPR84 that has been implicated in chronic inflammatory diseases.

Additionally, there is a new therapy that is going into the clinic – Endeavor Medicines recently raised $62 million series A funding to evaluate taladegib, a small molecule inhibitor of the Hedgehog pathway in IPF patients in phase II trials[6]. The company plans to first evaluate the efficacy and safety of taladegib as a monotherapy and then test in combination with currently available therapies such as nintedanib or pirfenidone. Hedgehog signaling is a well-studied signaling pathways involved in development and the Sonic Hedgehog (SHH) pathway is involved in lung development including lung branching and the survival of the mesenchyme cells. A 2012 study confirmed that the Hedgehog pathway is reactivated in IPF and the downstream transcription factors GLI1 and GLI2 were accumulated in the nuclei of fibrotic cells[7]. Furthermore, when fibroblasts derived from IPF patients were cultured *in vitro* and treated with recombinant SHH, they showed a remarkable resistance to apoptosis, which may play a role in increasing lung fibrosis.

These new therapies that have disease-modifying potential could be the much-needed breakthrough that IPF patients have been waiting for.

References:

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