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Recent Progress in Treatment of Pulmonary Fibrosis

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Abstract. Idiopathic pulmonary fibrosis (IPF) is the most common fatal interstitial lung disease.There is no known cause. Its pathogenesis is still unclear, which increases the difficulty of anti-fibrosis drug development. Only two drugs, pirfenidone and Nidanib, are approved for the treatment of IPF, and pharmacological treatments for IPF remain urgently needed.At present, researchers are still working on new drugs to treat idiopathic pulmonary fibrosis.There is an urgent need for drugs to combat pulmonary fibrosis, so researchers are constantly working on new drugs to combat it. This review describes current potential drugs for the treatment of pulmonary fibrosis. The researchers conducted clinical trials to determine the safety and effectiveness of these drugs in patients with pulmonary fibrosis. However, before the trial of some marketed drugs for new indications, the data on adverse reactions, tolerability, physical and chemical parameters, pharmacokinetics and safety have been relatively complete, and researchers have studied the mechanism of action of old drugs, so as to use them for other diseases, the strategy is a useful complement to traditional drug development efforts, offering hope to old, dormant drugs and those on the verge of failure.

Keywords: approved drugs; idiopathic pulmonary fibrosis; treatment.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a lung disease that is currently incurable a highly fatal lung disease mainly caused by oxidative stress, which eventually leads to severe impairment of lung function and even death. However, there is currently no effective antioxidant treatment.The reason is that developing an effective antioxidant material is very difficult. Treatment options that have been developed include the use of pirfenidone and nidanib, oxygen therapy, lung transplantation and pulmonary rehabilitation [1].

2. Medical treatment

2.1. Pirfenidone

Pirfenidone (**Figure 2**.) is a novel small molecule compound with anti-fibrotic, anti-inflammatory and antioxidant effects. It can reduce oxidative stress by scavenging free radicals and inhibiting lipid peroxidation (**Figure 1**.).

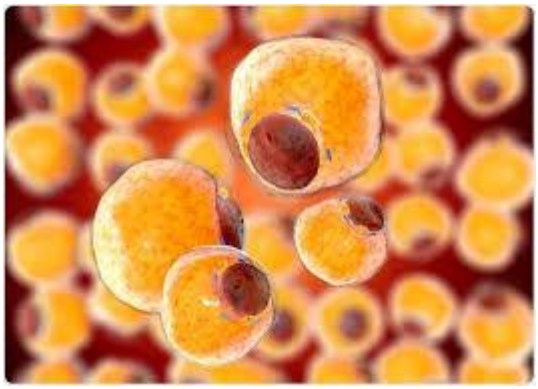

Figure 1. lipid peroxidation[2]

In two of the three Phase 3 trials, investigators reduced disease progression in patients with idiopathic pulmonary fibrosis through forced vital capacity (FVC), or decreased vital capacity; Unfortunately, this was not achieved in the third trial. In this Phase 3 trial, researchers randomly assigned 555 patients with idiopathic pulmonary fibrosis to receive oral pirfenidone (2,403 mg/day) or placebo for 52 weeks. The primary endpoint was, at week 52, whether FVC change or death[3].

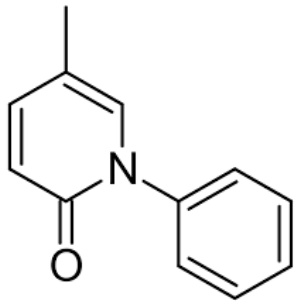

Figure 2. Pirfenidone[3]

As a result, pirfenidone slowed disease progression even more than placebo.Treatment was related to acceptable side effects and fewer deaths [4].

2.2. Nintedanib

Nintedanib **(Figure 3.**) is a triple angiokinase inhibitor that simultaneously targets three major receptors responsible for vascular regeneration and tumor growth, including vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and fibroblastic growth factor receptor.

Nintedanib targets platelet-derived growth factor receptors, fibroblast growth factor receptors, and vascular endothelial growth factor receptors, competitively binds to the adenosine triphosphate (ATP) binding sites of these receptors, blocking the signaling pathway of fibrosis process. Inhibit the spread, metastasis and transformation of fibroblasts, thereby slowing the progression of IPF disease

The researchers conducted two replicated double-blind, phase 3 trials for 52 weeks.To detect the efficacy and safety of 150mg Nintedanib versus placebo in patients with IPF. The primary endpoint was the annual rate of decreasing in forced vital capacity (FVC).

1066 patients were randomly asked to receive nidanib or placebo in ratio of 3:2. In group 1, the adjusted annual rate of change in FVC was -114.7 ml in the Nidanib group, -239.9 ml in the placebo group, -113.6 ml in the Nidanib group, and -207.3 ml in the placebo group. In group 2, nidanib had a significant benefit. Diarrhea was the most common adverse event in patients treated with nidanib, occurring at 61.5% and 18.6% in the Nidanib and placebo groups, and 63.2% and 18.3% in the 1 and 2 groups, respectively [5].

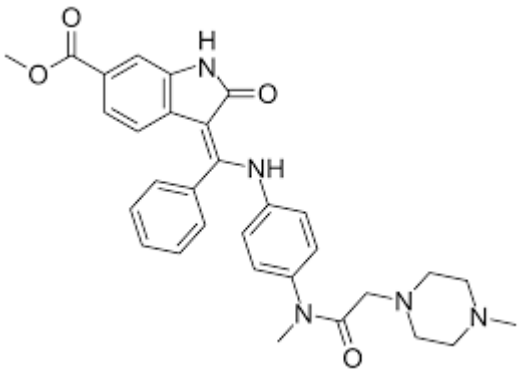

Figure 3. Nintedanib[6]

2.3. PDE4B Inhibitors

Although the direct pathogenic pathway of IPF is still unclear, the formation mechanism of pulmonary fibrosis should be the disorder and remodeling of damage and repair of alveolar epithelial cells. Many pro-fibrotic mediators may be very important in the pathogenesis of IPF. PF-ILD develops through similar mechanisms - self-sustaining dysregulation of cell repair, fibroblast proliferation mechanisms, and alveolar dysfunction. PDE4 can regulate the production of pro-inflammatory and anti-inflammatory cytokines through specific hydrolysis of the second messenger cAMP, thus playing a series of roles. Therefore, PDE4 has also become an important therapeutic target for inflammatory diseases, and the potential of PDE4 inhibitors in anti-fibrosis is waiting to be explored.

In a phase 2 clinical trial, researchers investigated the efficacy and safety of oral priority inhibitors of the PDE4B subtype in idiopathic pulmonary fibrosis. Patients were randomly assigned to receive BI 1015550 **(Figure 4.)** or placebo in a ratio of 2:1. The main endpoint was that, in the twelfth week, baseline changes in forced vital capacity (FVC).

As patients who had not used antifibrotic drugs, the median change in FVC was 5.7 ml in the BI 1015550 group and -81.7 ml in the placebo group. In patients had already treated with antifibrotic drugs, the median change in FVC was 2.7 ml. In the BI 1015550 and placebo groups, the median change in FVC was -59.2 ml. Repeated measurement analysis of the mixed model provided results consistent with Bayesian analysis. The proportion of serious adverse events was similar between the two groups.In this BI 1015550 treatment, antifibrotic agents, either alone or in the background. Compared with placebo, there was prevention of a decline in lung function in patients with pulmonary fibrosis [7].

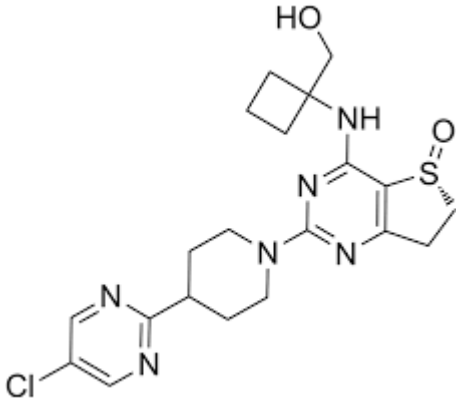

Figure 4. BI 1015550[8]

2.4. TNIK inhibitor

The researchers used predictive artificial intelligence (AI) methods to identify TRAF2- and neck interacting kinases as anti-fibrosis targets.An AI-driven approach was used to generate a small molecule TNIK inhibitor called INS018_055 **(Figure 5.)** that exhibits desirable drug-like properties and anti-fibrotic activity in different organs in the body by oral or inhalation.

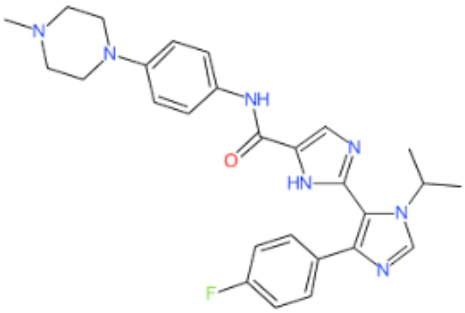

Figure 5. INS018_055[9]

Putative drug targets in pulmonary fibrosis fail to translate into clinically efficient treatments.Researchers at Insilico Medicin used predictive artificial intelligence (AI) methods to recognize TRAF2- and interacting kinase as an anti-fibrosis target. Using an AI-driven approach, the researchers generated INS018_055. The researchers made INS018_055, a small molecule TNIK inhibitor that exhibits desirable drug-like properties and anti-fibrotic activity in various organs of the body by oral or topical administration. Its safety, tolerability and pharmacokinetics were validated in 78 healthy participants in a Phase I clinical trial (NCT05154240). Another Phase I trial, CTR20221542, conducted in China, also showed similar safety and pharmacokinetic profiles. From target discovery to preclinical drug candidate nomination, the experimenter took 18 months to complete the work and demonstrated the ability of generative AI-driven drugs to have a discovery pipeline.

At present, INS018_055 has been found to be safe and tolerated in healthy volunteers. Overall, the results from preclinical and Phase I clinical trials demonstrate the potential for AI-driven drug discovery to streamline drug design for fibrosis and other diseases[10].

2.5. Anlotinib hydrochloride

Anlotinib hydrochloride is a novel multi-target tyrosine kinase inhibitor. The previous study found that anlotinib can inhibit the signal of TCE-B1, Inflammation and oxidative stress in the lungs of mice, inhibit the proliferation of fibroblasts and improve pulmonary fibrosis. Examples of mouse models lacking antioxidant enzymes can be identified as having fetal death, shortened lifespan or no effect. Several antioxidant deficiency models have been reported to be detrimental to healthy longevity. In one case, a reduction in antioxidant defense (Gpx4+/- mice) actually led to a significant 7% longer life. A small number of models looked normal, suggesting that redundancy plays an important role in antioxidant defense components in mice and vertebrates. Most mouse models with enhanced antioxidant defenses showed no effect on lifespan. Many transgenic mice that overexpress important antioxidant defense proteins show significant resistance to acute stressors, demonstrating that antioxidant defense has a role in health.

Therefore, in the future, these deletion-critical enzyme models will be valuable in determining whether these deletions reduce the health of adult animals. Understanding the role of key antioxidant enzymes through condition determination will provide insight into the function of these enzymes in physiological aging[11].

2.6. Metormin

Metformin is a biguanide hypoglycemic drug used in the treatment of type 2 diabetes, which has a pleiotropic effect on cells. Metformin demonstrated good antifibrotic effects in both mouse and rat models of BLM-induced pulmonary fibrosis. The researchers believe that metformin inhibits NOX4 expression through AMPK activation, thereby weakening TGF-B1-mediated cell signaling and myofibroblast differentiation. Rangarajan, a scientist found that metformin can accelerate the rate of regression of pulmonary fibrosis that has already occurred, the researcher showed that metformin plays an anti-fibrotic role by regulating metabolic pathways, inhibiting TGE B1 signaling, activating

peroxisome proliferator activation receptors, inhibiting collagen formation, and inducing adipose differentiation of lung fibroblasts[12].

2.7. Acetylcysteine

Pulmonary fibrosis is a very serious lung disease, and there is a certain relationship between various respiratory diseases, such as acute respiratorydistress syndrome and pulmonary fibrosis. Many ARDS patients survive in the acute phase, usually with obvious signs of pulmonary fibrosis, and severe fibrosis has been proved to be ARDS is a common complication, so the researchers believe that respiratory drugs may have the potential to alleviate pulmonary fibrosis.

The listed drug Acetylcysteine **(Figure 6.)** is suitable for dyspnea caused by a large number of phlegm obstruction, such as postoperative dysparexia, acute and chronic bronchitis, pneumonia, emphysema and other diseases. Some researchers reported that lysyl oxidase is essential for the formation of stable extracellular matrix, while in BLM induced mouse models of pulmonary fibrosis, Acetylcysteine inhibits LOX activity and the progression of pulmonary fibrosis by increasing the expression of glutathione in the lung [13].

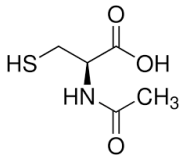

Figure 6. Acetylcysteine [14]

3. Conclusion

Pulmonary fibrosis is a chronic lung disease, the cause of which is still unclear, and there is no specific drug that can significantly prolong the survival of patients. However, before the trial of some marketed drugs for new indications, the data on adverse reactions, tolerability, physical and chemical parameters, pharmacokinetics and safety have been relatively complete, and researchers have studied the mechanism of action of old drugs, so as to use them for other diseases, the strategy is a useful complement to traditional drug development efforts, offering hope to old, dormant drugs and those on the verge of failure.

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