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Review Article

Idiopathic Pulmonary Fibrosis: Integrating Molecular Pathways, Clinical Management, and Drug Development

Nandeeni Punase[1]*, Shivam Chaudhari

Shri Aurobindo Insitute of Pharmacy, Indore

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) can be defined as an advancing, debilitating interstitial lung disease (ILD) marked by lung scarring and high extracellular matrix (ECM) deposition. This review examines the current understanding of IPF etiology, prevalence, cost to the economy, and treatment modalities. The genesis of IPF is a complicated interplay of aging-related cellular malfunction, environmental variables, and genetic predisposition. TGF-β signaling, integrin-mediated interactions, matrix metalloproteinase activity, and fibroblast growth factor signaling are important molecular pathways linked to the advancement of IPF. The disease mainly affects elderly people, with a three to five-year median survival rate after diagnosis and a substantial financial burden. The two currently licensed therapies, pirfenidone and nintedanib, have demonstrated effectiveness in delaying the course of the disease. However, the need for more effective therapies persists. Novel medicines that target different molecular pathways, such as autotaxin inhibitors, LPA1 antagonists, and PDE4B inhibitors, are being studied in ongoing clinical trials. The role of oxidative stress and inflammation in IPF progression highlights potential avenues for therapeutic intervention. Gene therapy approaches are also being considered for targeting previously "undruggable" molecular targets. As research advances, a multidisciplinary approach combining early detection, personalized treatment strategies, and novel therapeutic modalities may improve IPF patient outcomes. This review underscores the complexity of IPF and the ongoing efforts to develop more effective treatment paradigms. Continued investigation into the intricate cellular and molecular mechanisms driving IPF is essential for improving patient prognosis and quality of life.

INTRODUCTION

Fibrosis is a degenerative illness that damages tissue and negatively impacts the heart, lungs, liver, kidneys, and skin, among other organs. It develops when there is an overabundance of fibrous connective tissue in the extracellular matrix (ECM) region of injured tissues (Antar et

***Corresponding Author:** Nandeeni Punase
Address: *Shri Aurobindo Insitute of Pharmacy, Indore*
Email ✉: nandini2002punase@gmail.com

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al., 2023). Idiopathic pulmonary fibrosis (IPF) is a long-standing, cumulative fibrotic lung disease marked by lung disfeaturing that develops over time in the lung's interstitium (Raghu et al., 2022). Hippocrates wrote about fibrous diseases of the lungs as early as the 5th century BC. Still, reports of four patients with rapidly progressing scatter lung fibrosis by Hamman and Rich in the early 20th century are the source of more recent descriptions of IPF (Todd, Luzina, and Atamas, 2012). This debilitating illness is characterized by a persistent cough (Van Manen et al., 2016), and dyspnea (Kim, Perlman, and Tomic, 2015; Raghu et al., 2022). IPF is a long-term, worsening lung disease with an unclear cause and a grim outlook. (Mei et al., 2022). The CT scan image displays typical interstitial pneumonia symptoms, such as honeycombing zones, fibroblastic foci, architectural distortion, and interstitial patchy patches. Granulomas or indications of inflammation are absent (Sauleda et al., 2018). Diffuse fibrosing alveolitis, diffuse interstitial fibrosis, and IPF are words used to characterize an illness that is more subtle but quite debilitating (Todd, Luzina, and Atamas, 2012). There are now more options for treating IPF. Pirfenidone and nintedanib are two drugs that have been approved for the treatment of IPF for people. While nintedanib works by inhibiting tyrosine kinase, an oral pyridine, pirfenidone has anti-inflammatory, antioxidant, and anti-fibrotic qualities. Both drugs have proven to be efficacious in decelerating the passage of the disease and minimizing the diminishing lung function (Tourin, Swigris, and Olson, 2014).

Causes of IPF:

IPF's etiology is uncertain, however, several risk factors, including male sex, aging, and cigarette smoking, have been found (Sauleda et al., 2018). Idiopathic interstitial pneumonia (IIP), a subset of interstitial lung disease (ILD) with an unknown etiology that is defined by variegation of patterns of stinging and fibrosis, is the most widespread and intense form of IPF, making up around 5th of all cases of ILD. (Sgalla, Biffi and Richeldi, 2016).

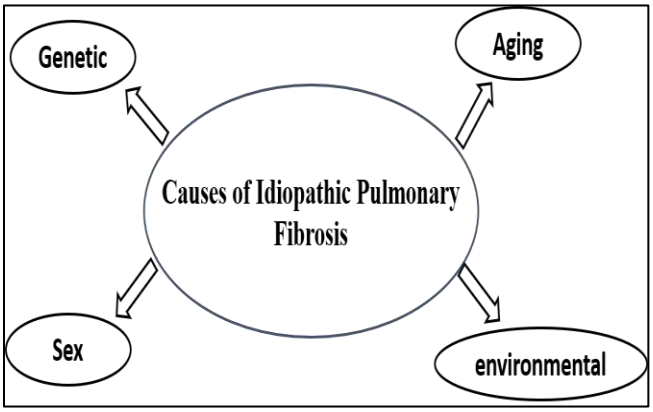

Fig no 1 Causes of Idiopathic Pulmonary Fibrosis

Genetic-

In the last few years, prominent advancements have been established in comprehending the genetic component of IPF. The identification of infrequent gene variations (Individuals carrying a minor allele with a frequency of 0.1% in both coding and noncoding regions) that significantly impact lung cells (mostly epithelial cells) and tissue functions has been made possible in large part by genetic investigations of familial pulmonary fibrosis (FPF). When these family cases manifest after the age of fifty, they are nearly identical to sporadic IPF. The majority of the mutations found in FPF thus far have been associated with telomere biology and surfactant-protein processing (Gandhi et al., 2023).

Environmental-

Numerous environmental and occupational exposures, such as breathing dust in the construction, mining, and manufacturing industries, are connected to greater probabillity of IPF, especially in low- and middle-income countries where safety regulations may be inadequate and among populations of racial and ethnic minorities. Given that reducing exposures during the initial phases of the illness potentially improves outcomes, this emphasizes the significance of obtaining a complete exposure history from all patients for whom IPF is suspected. In addition to other lifestyle factors like food and smoking, air pollution may potentially raise the posibility of IPF, most likely in combination with hereditary factors. However, more study is required to identify and validate circulating biomarkers, establish standardized questionnaires, and conduct studies by industrial hygienists to describe pertinent exposures in IPF patients (Gandhi et al., 2023).

Aging-

The Main Driver of IPF is Aging the primary likelihood risk factor for IPF is aging; however, the potential connecting mechanisms have only recently come to light. In IPF, almost every hallmark of aging that has been proposed occurs prematurely or exaggeratedly. These hallmarks include stem-cell exhaustion, telomere attrition, proteostasis, nutrient sensing, mitochondrial dysfunction, genomic instability, and changes in intracellular communications. The proteostasis network, cell senescence, telomere attrition, epigenetic modifications, and mitochondrial failure have all provided the strongest evidence. Unusual DNA repair and genomic instability resulting from telomere failure constitute a major pathogenic mechanism of cellular aging. As previously stated, there is much proof that individuals with IPF typically have aberrant telomere shortening, which is associated with common or uncommon gene mutations, or excessive proliferation, primarily in epithelial cells (Raghu et al., 2022).

Host Risk Factors

Sex-

Epidemiological research has consistently indicated that men are more expected to develop IPF than women, although the underlying reasons remain unclear. Studies have revealed that ERβ plays a role in initiating estrogen's protective effects against various conditions, such as hypertension, cardiac remodeling, apoptosis, and epithelial-mesenchymal transition. The steadiness between ERα and ERβ is essential for proper epithelial cell function. A recent study found that lungs affected by IPF in males and an aging male mouse model of lung fibrosis exhibit higher protein and ERα mRNA levels, resulting in increased ER activity and activation of profibrotic pathways. These microRNAs (miRNAs) target estrogen receptors, and when fibroblasts were transfected with let-7a or let-7d mimics, the production of ERα protein decreased, while the opposite effect was seen with certain inhibitors. Additionally, recent findings have shown that, even after accounting for age and pulmonary function test results, being male is independently associated with a higher risk of death or the need for lung transplantation.

Epidemiology:

IPF is the cause of twenty to fifty percent of ILD patients. IPF is an uncommon disease with a substantial burden; less than five cases occur in 10,000 person-years. Only in Europe, almost 40,000 new cases were identified annually. IPF typically has a poor outlook, with a median survival rate of 3 to 5 years, though the disease can follow a clinically unpredictable course. Taking everything into consideration, it's important to emphasize that IPF incurs direct treatment costs of approximately 25,000 USD per patient annually, making it a more costly disease than breast cancer

and many other severe conditions. IPF, the commonest fibrosing lung disease, accounts for 17% to 86% of all cases of interstitial lung illnesses, the frequency of which has increased over the past 20 years (Pergolizzi Jr et al., 2023). Based on information from a recent interstitial lung disease (ILD) India registry report, which comprised 1084 patients, the prevalence of IPF was calculated to be 13.7% (Singh et al., 2017).

Economic burden:

IPF primarily affects the elderly, and the median survival time following diagnosis is three years due to the disease's progressive nature. Almost one-third of patients needed hospitalization, and 30% had at least one emergency department visit per year. The total direct costs for IPF patients were around $26,000 per person annually (Raimundo et al., 2016). The yearly value of pirfenidone in the United Kingdom (UK) is USD 36,070.80, while the yearly cost of both drugs in the US is above $100,000. For each person with IPF, the average annual direct costs were $31,655, with a 95% confidence interval ranging from $27,723 to $35,757. Using prevalence data and cost projections, the estimated annual expenses in Australia amount to $299 million (Cox et al., 2023).

Pathogenesis of Idiopathic Pulmonary Fibrosis- Whenever tissue is injured, the fibrogenesis process is triggered under normal physiological conditions. This is an essential step in the process of repairing wounds so that homeostasis can be restored. Epithelial damage usually starts the wound healing process by igniting the coagulation and inflammatory cascades. The ECM components are released by fibroblasts, which are activated, recruited, and proliferate as a result. The wound area is healed and the normal tissue structure and structural integrity are restored during the last remodeling stage. (Strieter, 2008)

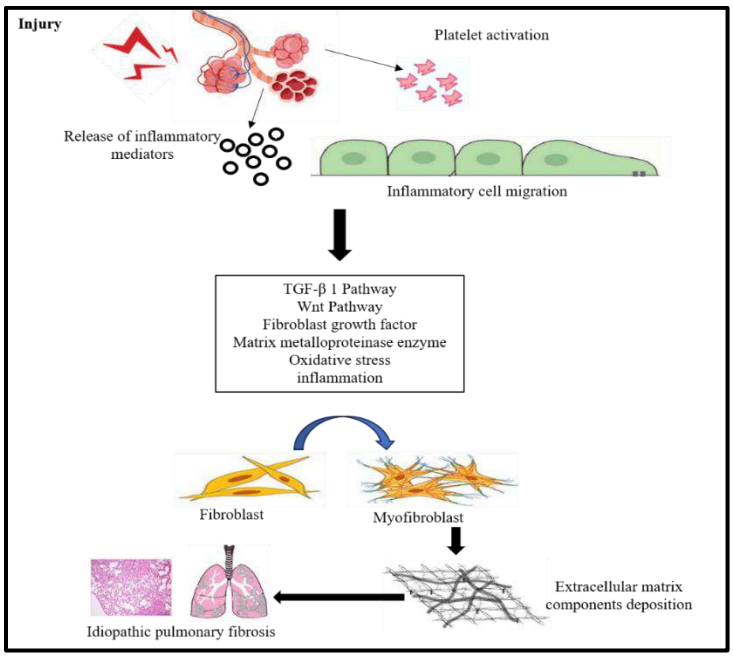

Fig no 2 Development of Lung Fibrosis

We characterized the progress of fibrosis in three phases

1. Alveolar Epithelial Injury
2. Inflammatory phase
3. The Fibrotic Response and ECM Remodeling Phase.

Molecular Mechanism of Pulmonary Fibrosis:

a. TGF-beta pathway:

TGF-β is involved in several biological activities, including immune surveillance, tissue repair, embryonic development, and preserving adult homeostasis. TGF-β plays a complex role in cancer and fibrosis, depending on the stage of the disease, exhibiting either promoting or inhibiting actions. Overexpression of TGF-β can cause cancer-associated fibroblast (CAF) production, ECM accumulation, and epithelial-to-mesenchymal transition (EMT), both of which can contribute to fibrotic conditions and cancer. The preceding article discusses the basic mechanisms of TGF-β, its dual involvement in cancer and fibrosis, and the therapeutic uses of TGF-β-targeting treatments. The SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 receptor-regulated SMAD proteins (R-SMADs) (Peng et al., 2022).

1. The single member of the common SMAD (Co-SMAD), SMAD4.
2. SMAD6 and SMAD7 are among the inhibitory SMADs (I-SMADs). The kinase activity of the membrane-bound serine/threonine receptors activates the R-SMADs upon binding to them. The activated R-SMADs and the co-SMAD combine as co-factors to generate a complex that translocates into the nucleus. Through a variety of ways, I-SMADs neutralize the effects of R-SMADs and hence suppress TGF-β superfamily signaling (Xu et al., 2016).

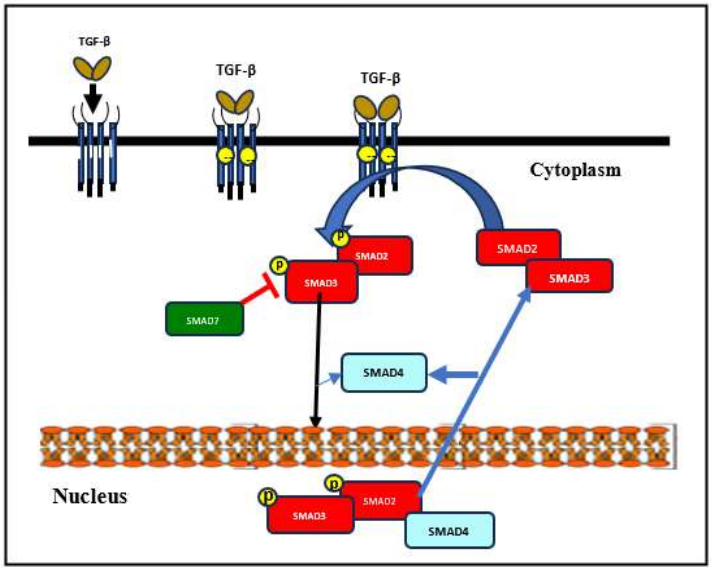

Fig no 3 TGF-β Pathway (Yu et al., 2015)

b. Integrins:

The integrin family of cell adhesion molecules, transmembrane proteins, mediates numerous crucial cell-matrix and cell-cell interactions during fibrosis. Integrins are closely implicated in developing, maintaining, and resolving tissue fibrosis. They serve as a crucial point of interaction among the ECM, inflammatory cells, fibroblasts, and parenchymal cells (Sheppard, 2008).

c. Matrix Metalloproteinase (MMP):

MMPs are important players in the processes of tissue modifying and healing because they are enzymes that break down components of the ECM. Furthermore, in influencing ECM turnover, MMPs also have an impact on gene expression, cellular survival, accumulation, and inflammation. By influencing the activation of myofibroblasts, which are essential components of the fibrotic process, these enzymes can modify fibrosis (Giannandrea and Parks, 2014). Diverse studies have suggested an escalation in MMPs, rather than

a decrease of MMPs, in IPF (McKeown et al., 2009). Agumented levels of MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, and MMP-9 have been subjected. MMP-12 and MMP-13 have also been implicated in experimental fibrosis. According to reports, fibroblast foci in the mesenchymal cells and hyperplastic epithelial cells covering intra-alveolar fibrosis, both express MMP-2 (gelatinase A) extensively in fibrotic lungs (Selman et al., 2000). MMP-2 degrades matrix substrates, including type IV collagen, and is often overexpressed in lung fibrosis models. It, adjacent to MMP-9, is linked to lamina densa rupture (Ruiz et al., 2003). The basement membrane is crucial for alveolar wall integrity; When it breaks down, it can enable interstitial cells and fluid accumulations to penetrate, which may result in tissue damage and advancing fibrosis (O'Kane et al., 2009). Although resident cells do not manufacture MMP-9, fibroblasts, smooth muscle cells, endothelial cells, bronchial epithelial cells, alveolar type II cells, and, Clara cells can all make MMP-9 when stimulated in different ways (Atkinson and Senior, 2003). In both human and experimental-induced lung fibrosis, there is an increase in MMP-9 gene expression and protein. (Lemjabbar et al., 1999).

d. Fibroblast growth factor (FGF):

The pathophysiology of IPF may be influenced by FGF signaling, according to mounting data (Chanda et al., 2019). It is well-established that the FGF family plays a role in tissue repair and the migration of fibroblasts. Interestingly enough, pulmonary fibrosis has been discovered to be significantly attenuated by members of the FGF family. While the present investigation does not tackle the role of endogenous FGFs in the advancement of IPF, a wealth of data suggests that the FGF genealogy could serve as a viable beneficial target for the treatment of IPF. It has been demonstrated that FGF1 inhibits the development of myofibroblasts, promotes the growth of airway epithelial cells (AECs), controls TGFR1 expression and mortification to regulate TGF-β1 signaling, and controls the expression of FGFR1. These results declairs that FGF1 may be a target for treatment and prevention of TGF-1-driven lung fibrosis. (Shimbori et al., 2016). Meanwhile, research has demonstrated that FGF-2 acts as an antifibrotic agent by counteracting TGFβ1-induced collagen and alpha-smooth muscle actin (αSMA) expression, and by decreasing fibroblast differentiation and stress fiber formation in the lung (Koo et al., 2018). In the bone marrow, hematopoietic stem cells that exhibited elevated levels of FGF7 suppressed BLM-induced lung fibrosis. Administering an adenovirus vector with overexpressed FGF7 via intratracheal infusion yielded similar results (Aguilar et al., 2009). FGF9 and FGF18, which are largely regulated by FGFR3, influence the interactions between epithelial and mesenchymal tissue by encouraging migration and survival while preventing lung myofibroblast differentiation.

Inflammation in IPF-

Histologic examination of lung specimens from pulmonary fibrosis patients reveals signs of fibrosis, inflammation, and a disordering of the lung parenchymal cells. These findings suggested that pulmonary fibrosis and lung damage are caused by the inflammatory process. More recent advancement has shown that the first injury produces intra-alveolar fibrosis and the collapse of alveolar capillary units, contrary to earlier findings that claimed the fibrosis happened in the lung's interstitial space (Ward and Hunninghake, 1998; Kuhn III et al., 2012). These more recent findings have raised the possibility that pulmonary fibrosis is a persistent type of acute lung damage that develops gradually at different locations throughout the lung. The mechanisms that lead to the advancement of lung illness in particular lung regions remain unknown, even in cases when the

underlying etiology of the disease is recognized, such as asbestosis. The observations highlight the necessity of administering efficacious therapy for these illnesses early in the disease's natural course before significant lung damage and fibrosis emerge (Mack, 2018).

Role of oxidative stress-

A significant early occurrence in disorders such as IPF is the death of alveolar epithelial cells (AECs), which is caused by oxidative stress. To mediate this apoptosis, endoplasmic reticulum (ER) stress and mitochondria are involved in p53-regulated death pathways. Enzymes that repair mitochondrial DNA, such as mitochondrial aconitase (ACO2) and human 8-oxo guanine-DNA glycosylase 1 (hOgg1), are effective in halting oxidant-induced mitochondrial malfunction and apoptosis. Furthermore, the possibility of using NOX4 activation and other ROS-related pathways as targets for pulmonary fibrosis therapeutic approaches (Cheresh et al., 2013).Reactive oxygen species (ROS) contribute to the death of alveolar epithelial cells (AECs) and the initiation of fibrogenic pathways, which are important steps in the pathophysiology of IPF. This involves higher collagen synthesis and overexpression of TGF-β. As potential treatments for IPF, oxidative stress mechanisms such as NOX4 inhibitors and mitochondrial antioxidants may be targeted. Additional studies must be conducted on the molecular pathways of intrinsic apoptosis, p53 activation, and mitochondrial DNA repair to better understand and cure pulmonary fibrosis (Kliment and Oury, 2010).

Drug treatment for IPF:

IPF is a long-term devastating disease with fewer treatment regimens. The available therapies are few and often associated with significant adverse effects. Currently, two drugs that are available to treat IPF nintedanib, and pirfenidone, have been approved by the US FDA. Other drugs are still undergoing clinical trials, with the hope that they will demonstrate beneficial effects against the disease.

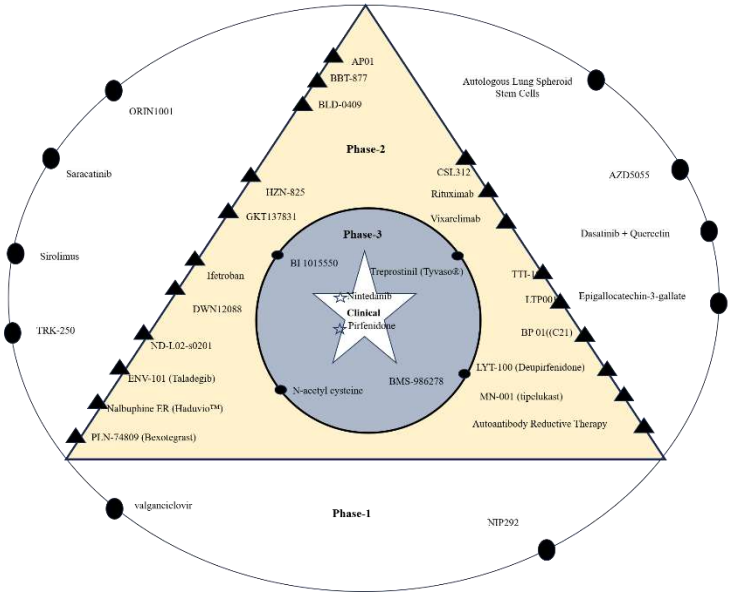

Fig no 4 Development of agents to treat IPF (ClinicalTrials.gov)

Clinical:

a. Nintedanib:

The vascular endothelial growth factor (VEGF) pathway is inhibited by the tyrosine kinase inhibitor nintedanib (BIBF 1120), which has anti-angiogenesis properties. After being developed initially as an anti-tumor medication, nintedanib's antifibrotic qualities were found. It is postulated that nintedanib reduces fibroblast activity by blocking profibrotic mediators such as VEGF,

TGF-β, FGF, and platelet-derived growth factor (PDGF) (Rivera-Ortega et al., 2018).

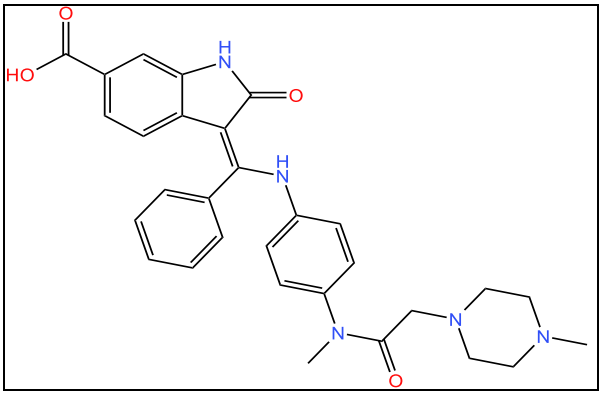

Fig no 5 Structure of Nintadanib

b. Pirfenidone:

Pirfenidone (PFD), an anti-fibrotic drug, is known to reduce lung fibrosis in IPF by acting on many fibrogenic pathways. Growth factor synthesis is hindered by it. In addition, it interferes fibroblast proliferation and affects the TGF-β-mediated differentiation of fibroblasts into myofibroblasts (Shah et al., 2021).

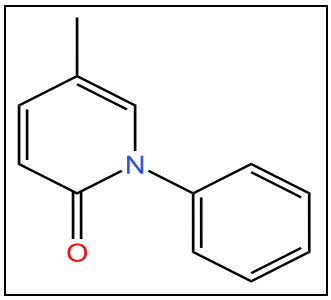

Fig no 6 Structure of Pirfenidone

c. Gene therapy:

Gene therapies represent a promising treatment option for a diversity of illnesses, including IPF. Introducing genetic material into cells has made it possible to modify molecular targets that were previously thought to be "undruggable," a term commonly used to designate targets that cannot be regulated via conventional approaches, such as small-molecule medicines (Ruigrok et al., 2021).

PHASE-3

N- acetylcysteine-

NAC is a reductant of Disulfide bonds that is commonly used as a mucolytic agent (Millea, 2009). On December 17, 2020, Weill Medical College of Cornell University initiated a clinical investigation with NAC under the NCT ID NCT04300920. N-acetylcysteine has been licensed by the FDA to be used as a mucolytic agent and antioxidant in the therapy of persistent obstructive pulmonary disease (COPD), per research. With IPF, a larger dose of 1800 mg per day was employed in the study, indicating its potential function in managing the condition without significantly interfering with current therapy (Demedts et al., 2005). A prospective, single-arm clinical trial on inhaled N-acetylcysteine (NAC) in IPF was carried out at the Saitama Red Cross Hospital in Japan. The findings demonstrated that forced vital capacity (FVC) loss in these individuals could be effectively mitigated by inhaling NAC. The mean FVC changed significantly by 170 mL over the 26 weeks before therapy. The FVC drop was less severe after starting inhaled NAC therapy, suggesting the possible advantages of this treatment (Okuda et al., 2016).

BI 1015550-

According to the research, BI 1015550 is an oral preferred PDE4B inhibitor, which suggests that it has better tolerance than the selective oral PDE4 inhibitors that are currently on the market. According to the preclinical profile, BI 1015550 shows great promise as an oral therapeutic medication choice for the treatment of interstitial lung disorders (ILDs), including IPF. A phase II trial comparing BI 1015550 to a placebo is now being conducted in individuals with IPF (NCT04419506) (Herrmann et al., 2022).

A phase III investigation called the FIBRONEER-ILD trial is assessing PDE4B inhibitor BI 1015550 in individuals with progressive pulmonary fibrosis (PPF). Over a minimum of 52 weeks, this randomized, placebo-controlled study will evaluate the side effects and effectiveness of two different doses of BI 1015550, either in the presence or absence of baseline nintedanib

medication. The variation in FVC at 52 weeks is the main outcome, and the time to exacerbation, hospitalization, or mortality are the secondary outcomes. The motive of this research is to ascertain whether the encouraging outcomes shown with BI 1015550 in the IPF patients can be applied to a larger PPF population, thereby providing these patients with a new course of treatment (Maher et al., 2023).

Treprostinil-

The TETON phase 3 trials are evaluating the use of inhaled Treprostinil, a prostacyclin analog, for treating IPF, a debilitating lung disease. These randomized, double-blind, placebo-controlled trials involve nearly 400 participants and aim to measure changes in lung function, particularly forced vital capacity (FVC), over 52 weeks. Secondary objectives include tracking clinical worsening, safety, and tolerability. If successful, treprostinil could become a significant new treatment option for IPF patients (Nathan et al., 2022).

BMS-986278-

A phase 2 trial is underway to evaluate BMS-986278, a lysophosphatidic acid receptor 1 (LPA1) antagonist, for treating IPF and progressive fibrotic interstitial lung disease (PF-ILD). The trial focuses on the drug's ability to slow lung function decline over 26 weeks while assessing its safety, tolerability, and effects on blood pressure. The conclusion of this trial could result in a new treatment option for patients with these conditions (Corte et al., 2021).

PHASE 2-

There are many compounds ongoing for the phase 2 clinical trial each giving evidence to prove beneficial against idiopathic pulmonary fibrosis AP01 which is an Autotaxin inhibitor showed a promising effect in the phase 2 clinical trial (West et al., 2023). 2nd drug BBT-887 Autotaxin inhibitor testing for IPF (Simonetti et al., 2024). Other drugs BLD-0409 autotoxin inhibitor (Wong et al., 2022), HZN-825, a potent selective antagonist of lysophosphatidic acid receptor 1 (LPAR1) (Luo et al., 2023), GKT137831 is a potent, dual NADPH oxidase NOX1/NOX4 inhibitor (Luo et al., 2023), CSL312 is a humanized anti-FXIIa monoclonal antibody (Wong et al., 2017), Rituximab is a monoclonal antibody (Sgalla et al., 2020), Vixarelimab (Simonetti, Sgalla and Richeldi, 2023), DWN12088 is a PRS (Prolyl-tRNA Synthetase) inhibitor (Lee et al., 2020), ENV-101 (Taladegib) (Lahmar et al., 2022), Nalbuplune ER (Haduvio™) (Harris, 2023), PLN-74809 (Bexotegrast) (Lancaster et al., 2023), LYT-100 (Deupirfenidone), MN-001 (tipelukast) and Autoantibody Reductive Therapy.

CONCLUSION:

IPF remains a complex and challenging ILD characterized by progressive fibrosis and an unfavorable outlook. The pathogenesis of IPF involves a multifaceted interplay of genetic susceptibility, environmental factors, and age-related cellular dysfunction, leading to aberrant wound healing and excessive ECM deposition. Recent advances in understanding the Biochemical process underlying IPF have elucidated key pathways, including TGF-β signaling, integrin-mediated interactions, matrix metalloproteinase activity, and fibroblast growth factor signaling. These perceptions have paved the process for targeted therapeutic approaches. Current treatment options, notably nintedanib, and pirfenidone, have demonstrated efficacy in slowing disease progression. However, the need for more effective therapies persists. Ongoing clinical trials are exploring novel compounds targeting various molecular walkways implicated in IPF pathogenesis, including PDE4B inhibitors, LPA1 antagonists, and autotaxin inhibitors. The financial stress of IPF remains substantial, underscoring the urgency for developing cost-effective treatment strategies. Furthermore, the

part of oxidative stress and inflammation in IPF progression highlights potential avenues for therapeutic intervention. As research progresses, a multidisciplinary approach combining early detection, personalized treatment strategies, and novel therapeutic modalities, including gene therapy, may provide improved outcomes for patients with IPF. Continued investigation into the complex interplay of genetic pathways driving IPF is essential to develop more effective treatment paradigms and ultimately improve patient prognosis.

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