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Idiopathic Pulmonary Fibrosis, Etiology and its Treatment

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Abstract: *Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive disease characterized by the aberrant accumulation of fibrotic tissue in the lungs parenchyma, associated with significant morbidity and poor prognosis. Lung parenchyma and architecture is destroyed, compliance is lost, and gas exchange is compromised in this debilitating condition that leads inexorably to respiratory failure and death within 3–5 years of diagnosis. The etiology of pulmonary fibrotic diseases is varied, with an array of triggers including allergens, chemicals, radiation and environmental particles. However, the cause of one of the most common pulmonary fibrotic conditions, idiopathic pulmonary fibrosis (IPF), is still unclear. Idiopathic pulmonary fibrosis (IPF) is a fatal age-associated disease that is characterized by progressive and irreversible scarring of the lung. Despite several advances in treatment, idiopathic pulmonary fibrosis (IPF) remains a progressive, symptomatic, and terminal disease in patients not suitable for lung transplantation. With disease progression, IPF often leads to a constellation of symptoms, including dyspnea, cough, anxiety, and depression. Palliative care is appropriate to support these patients. It is reported that pulmonary fibrosis has become one of the major long-term complications of COVID-19, even in asymptomatic individuals. Currently, despite the best efforts of the global medical community, there are no treatments for COVID-induced pulmonary fibrosis.*

Keywords: Fibrosis, Pulmonary fibrosis, pirfenidone, nintedanib, Lung cancer.

I. INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease. It is the most common idiopathic interstitial pneumonia, with a prevalence of 7-20 cases per 100,000 people, up to 175 cases per 100,000 people aged 75 and over. Progressive dyspnea is the main symptom, and the disease often leads to respiratory failure and death. Medical treatment of IPF has not been shown to improve morbidity, physical or electronic markers of disease severity, or survival. The most important thing after an injury is to repair the tissue to restore the body's function. The inflammatory response to infection or injury disrupts epithelial and endothelial integrity, causing edema, leukocyte recruitment, and angiogenesis. Resolution of inflammation via apoptotic and phagocytic pathways often results in minimal damage and normal tissue repair. Therefore, strict treatment after tissue injury is very important. A well-coordinated network of cells replaces the tissue, provides essential nutrients, and repairs the tissue during regeneration. In some cases, a period of fibroproliferation occurs with excessive accumulation of cellular matrix and connective tissue. These conditions are often associated with vascular diseases and can lead to a variety of medical conditions, such as atherosclerosis, cirrhosis, scleroderma, asthma, and various types of pulmonary fibrosis. This review will focus on pulmonary fibrotic conditions and present regulatory mechanisms in the disease, if known. Initial symptoms in IPF are often suspicious, but all of these diseases are unpredictable and some patients experience severe pain after treatment. A period of apparent stability. Older age at presentation, smoking history, low body mass index, and evidence of physical and radiographic disease are associated with more severe disease. Respiratory complications of IPF requiring hospitalization are rare in mild disease but are more common in patients with more severe disease and are associated with severe symptoms and death. Two antifibrotic drugs (pirfenidone and nintedanib) reduce lung function and may reduce the risk of exacerbations and hospitalization, but have no effect on symptoms, daily functioning, or quality of life (HRQL). Many people with IPF develop diseases or complications such as chronic obstructive pulmonary disease (COPD), heart disease, lung cancer or obstructive sleep apnea (OSA). 30-50% of advanced IPF patients have pulmonary hypertension (PH). These comorbidities can lead to disease progression,burden, and decreased quality of

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care, resulting in increased healthcare utilization and healthcare costs. A US population-based study found that healthcare utilization and costs were almost twice as high in uncontrolled IPF compared to uncontrolled IPF. It has therefore been suggested that involvement in symptom management in hospital would help reduce some of the medical costs. Clinical symptoms of IPF are respiratory failure and impaired lung function (Schafer et al., 2020). Over the past few years, significant advances have been made in our understanding of the mechanisms of this disease. The incidence of IPF is believed to be related to genetic and environmental factors. Repeated microinjury of alveolar epithelial cells has been shown to lead to abnormal epithelial-fibroblast communication, ultimately leading to abnormal ECM and pathological lung repair (Heukels et al., 2019; Martinez et al., 2017; 21., Richeldi). . The number of treatment options for IPF continues to increase. Two drugs, nintedanib and pirfenidone, are approved to treat patients with IPF. Nintedanib is a tyrosine kinase inhibitor and pirfenidone is an oral pyridine with anti-inflammatory, anti-inflammatory and anti-inflammatory properties. Both drugs have been shown to reduce lung function and slow disease progression but are also associated with some side effects and tolerability issues (Liu et al., 2017). Lung transplantation is the main treatment for IPF. The average survival time after transplantation is 4-5 years. However, due to limited organs and chronic allograft rejection, only some patients can receive this intervention (Kumar et al., 2018). Currently, the goals of IPF management are to improve symptoms, improve health, and preserve lung function (Glassberg, 2019).A better understanding of the pathogenesis of IPF will facilitate the development of better and safer treatments for IPF. This review will highlight recent advances in the pathogenesis of IPF (Figure 1) and suggest promising new treatment strategies for fibrotic lung disease.

Pathogenesis

FIGURE 1. Pathogenesis of idiopathic pulmonary fibrosis. Genetic factors affect the integrity of epithelial cells, environmental factors and aging-related changes will trigger epigenetic reprogramming. The combined action of the three factors will cause epithelial cell damage and trigger the abnormal activation of epithelial cells. Activated epithelial cells secretes a large number of cytokines such as TGF-β which consequently promotes fibroblast migration and proliferation, and also promote fibroblasts to differentiate into myofibroblasts. Myofibroblasts secrete large amounts of ECM, leading to ECM deposition. In addition, epithelial cell damage, disfunction and exhaustion of stem cells, abnormal deposition of extracellular matrix and matrix stiffness play a vital role in progression of abnormal lung fibrosis and remodeling of lung structure.

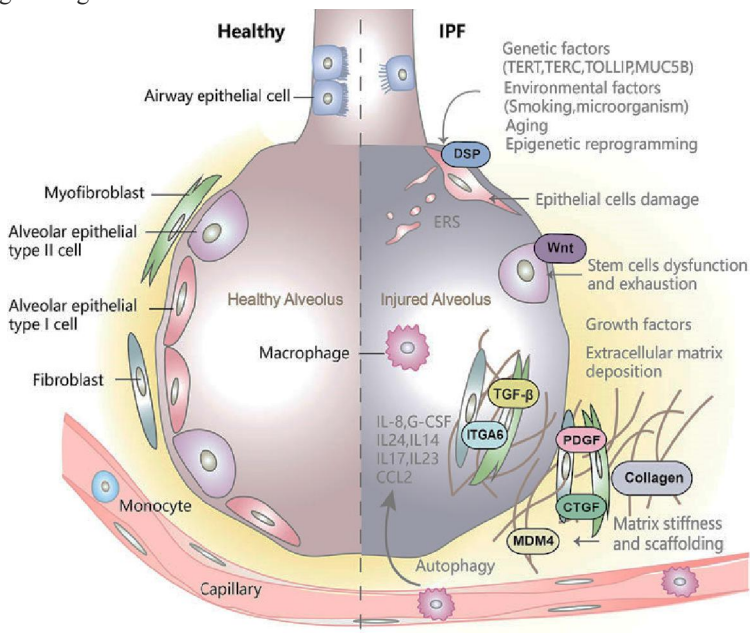

Fig No: 1

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Despite the comprehensive understanding of IPF pathogenesis remains elusive, research efforts in the last few years have reached important milestones. Several environmental and microbial exposures have been proposed as playing roles in IPF pathobiology that might be far from collateral, making the concept of "idiopathic" less compelling. Individual genetic and epigenetic factors remain the most important for the development of the fibrotic process, although the contribution of the variants so far identified, or their interaction with the putative external factors has yet to be clarified. In this context of genetic susceptibility, the repeated micro-injury of the alveolar epithelium has been recognized as the first driver of an altered repair process where several lung cells develop aberrant behaviours, leading to the development and sustainment of the fibrotic process. This section will cover in detail the current evidence on the contribution of these factors to IPF pathogenesis and the main goals of research for the years to come. The main pathogenetic actors in IPF are also illustrated in Fig. 2

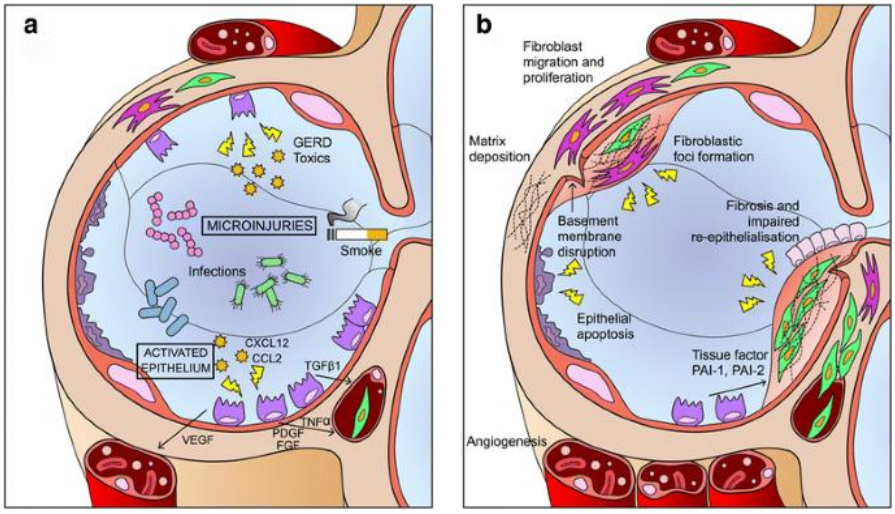

Fig No :2

Schematic view of IPF pathogenesis. Repeated injuries over time lead to maladaptive repair process, characterized by AEC2s apoptosis, proliferation and epithelium-mesenchymal cross-talk (**a**) and following fibroblasts, myofibroblasts proliferation and accumulation of extracellular matrix (**b**).CCL2: chemokine C-C motif ligand 2; CXCL12: C-X-C motif chemokine 12; FGF: fibroblast growth factor; PAI-1: plasminogen activator inhibitor 1; PAI-2: plasminogen activator inhibitor 2; PDGF: platelet-derived growth factor; TGF-β1: Transforming Growth Factor-Beta 1; TNF-α: tumor necrosis factor-alpha; VEGF: vascular endothelial growth factor

Risk Factor

Genetic

Susceptibility to IPF may be associated with a variety of genetic factors through a combination of genetic and genetic factors that contribute to loss of epithelial integrity. Familial interstitial pneumonia (FIP) occurs when two or more members of the same biological family are affected. FIP is inherited in an autosomal dominant manner with variable penetrance and accounts for 2% to 20% of all cases of idiopathic interstitial pneumonia. Different studies have been conducted in which many FIPs have been reported to have a rare genetic cause. These changes are associated with the maintenance of telomere length (telomerase reverse transcriptase-TERT, telomerase RNA component-TERC, poly(A) specific ribonuclease-PARN, and regulatory process), telomere elongating helicase (RTEL), and surfactant protein (and surfactant). A2-SFTPC, SFTPA2) has been recognized even in patients with comorbidities. In addition, two large genome-wide association studies (GWAS) have identified genetic alterations important for epithelial integrity as risk factors for IPF. These studies analyzed telomere biology (TERT, TERC, OBFC1), host defense (MUC5B, ATPase phospholipid transporter 11A-ATP11A, Toll-interfering protein-TOLLIP), and cellular barrier functions (desmoplakin-DSP, dipeptide peptidase 9-DPP).) for the development of the disease. Both GWAS identified the role of the MUC5B gene promoter as a risk factor for the disease and found other mutations associated with IPF, such as TOLLIP and Toll-

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like receptor (TLR) 3. However, the MUC5B promoter region rs35705950 is a loss. The -function variant has been found to be the most likely risk factor for the development of familial interstitial pneumonia and sporadic IPF. IPF-affected subjects with the rs35705950 variant showed improved survival compared to patients without this variant. EnvironmentalEnvironmental exposure and genetic susceptibility may play a synergistic role in the development of IPF (Figure 1). In sporadic and familial pulmonary fibrosis, environmental exposure of the lung epithelium increases the risk of IPF. Among these, smoking and metal dust are the most dangerous. Smoke can cause various cellular changes through epigenetic processes. It also promotes lung injury and differentiation of fibroblasts into myofibroblasts by causing miRNA imbalance and ER stress. Pollutants and ultrafine particles in cigarette smoke contain carbon black (CB) and cadmium (Cd). In IPF lung tissue, Cd and CB contents increase significantly and are proportional to the amount of citrulline vimentin (Cit-Vim). Based on Akt1 and peptidyl arginine deiminase 2 (PAD2) activity, Cd/CB can induce Vim citrullination and Cit-Vim secretion, thereby causing fibroblast infiltration of lung microspheres and promoting the expression of collagen and α-Smooth muscle actin (α-SMA increases). and causes pulmonary fibrosis. Microorganisms (bacteria, fungi and viruses) play an important role in the pathogenesis of IPF. The composition of the lung microbiota in patients with IPF is unbalanced compared to normal people, and this may serve as a constant stimulus for recurrent alveolar damage. Inflammatory and fibrotic mediators and immune responses in the lungs of patients with IPF are associated with the disease. In animal models of pulmonary fibrosis, pulmonary dysbiosis occurs before the peak of lung damage and persists throughou fibrosis. Lung disease predicts disease progression in patients with IPF after adjustment for chemotherapy and physical therapy. In addition, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus have been detected in alveolar epithelial cells of patients with IPF; This indicates an association between infection and the risk of IPF. Although the IPF-associated mechanism of infection is unclear, studies have shown that it may be associated with activation of the epithelial-mesenchymal transition, promotion of TGF-β expression, and induction of epigenetic reprogramming. Interestingly, IPF patients expressing the MUC5B risk allele had reduced disease compared to patients without the risk allele. NEDD4-2 regulates epithelial Na + channels (ENaC) through ubiquitination, which are important for mucociliary clearance of inhaled irritants and bacteria. Recent studies have shown that NEDD4-2 expression is reduced in IPF tissues. NEDD4-2 promotes fibrotic remodeling by regulating the expression of proSP-C, Smad2/3 and TGF-β signaling pathway

Epigenetic changes

Any processes that alter the activity of genes without changing the underlying genetic code are defined as epigenetic changes. Traditionally, epigenetic modifications refer to DNA methylation and histone modifications. Additionally, dysregulation of non-coding RNAs, particularly microRNAs, has recently been implicated as part of the epigenome. The important processes of DNA methylation and histone modification appear to mediate the genetic and environmental influences of genetics and disease traits, especially as age increases. Additional evidence supports the important role of epigenetic changes in IPF. DNA methylation changes include hypermethylation and hypomethylation of cytosine residues in various genes, as well as unexpected errors in methylation. Genome-wide DNA methylation analysis of lung tissue from 94 IPF patients and 67 controls identified 2130 differentially methylated regions genome-wide; approximately one-third of these were shown to be associated with significant genetic alterations, including genes associated with IPF. MicroRNA silences approximately 90% of human genes by degrading target mRNA or inhibiting protein translation. There is evidence that regulatory miRNA levels are significantly altered in IPF patients compared to healthy controls. Smoking and aging are important epigenetic changes, given their association with IPF and their association with DNA methylation. Genome-wide studies in aging cells and tissues show that changes in DNA methylation lead to epigenetic mosaicism in aging stem cells. Theoretically, this genetic mutation could limit cellular plasticity and thus contribute to the development of age-related diseases such as IPF.

Aging

Aging is a pathological feature of human IPF and experimental pulmonary fibrosis in animals. Key features of lung aging include telomere changes, epigenetic changes, loss of proteostasis, mitochondrial dysfunction, and cellular senescence (Figure 1). Telomere mutations often cause abnormal DNA repair and genomic instability, leading to cellular senescence. In addition to DNA damage, telomere shortening or damage can promote fibrosis by repairing

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tissue damage, activating p53, reducing mitochondrial biogenesis, and causing cellular senescence. Old way There is evidence that most changes in IPF, including telomere shortening that occurs primarily in alveolar epithelial type II cells (AT2), are associated with aging. F-box and WD repeat domain-containing protein 7 (FBW7) was identified as a driver of lung prematurity and fibrosis. It is an E3 ubiquitin ligase that catalyzes multisite polyubiquitination of telomere protection protein 1 (TPP1) and accelerates it by binding to TPP1, thereby causing telomere decapping and leading to cell senescence and tissue fibrosis. Studies have shown that the expression of important markers of aging is greatly affected in IPF AT2 cells. These markers include CDKN1A/p21, CDKN2A/p16, TP53, MDM2, CCND1. Additionally, aging can lead to impaired stem/progenitor cell function, resulting in the inability of alveolar epithelial cells to repair and regenerate damaged lungs. Senescent epithelial cells can produce a variety of pro-inflammatory and pro-fibrotic mediators, such as interleukin-6 (IL-6), IL-1, and TGF-β, which are part of the senescence-associated secretory phenotype (SASP). . In contrast, older fibroblasts are more resistant to apoptosis against environmental stress and may induce a different cellular matrix. Metabolic changes such as glycolytic reprogramming also play an important role in the development of pulmonary fibrosis. Human metabolomics studies have shown increased glycolysis in IPF lung tissue compared to healthy controls. In particular, old fibroblasts become resistant to apoptosis by increasing glucose utilization. Studies have shown that plasminogen activator inhibitor 1 (PAI-1) protects (muscle) fibroblasts from apoptosis in aged mice. PAI-1 is an effector molecule of TGF-β and can cause senescence by inducing p21. Old mice develop irreversible pulmonary fibrosis after lung injury. Interestingly, p53 signaling is abnormally activated at age AT2, and silencing p53 expression can inhibit the development of fibrosis, Changfu Y et al. Identification of aging, and not AT2 cell death, as the key driver of cancer susceptibility leads to future therapeutic targets of genetic perturbation targeting p53 activation and aging for pulmonary fibrosis. These findings suggest that targeting senescent cells may be effective in treating fibrotic lung disease. Aging is an important risk factor for IPF, and many of the major cellular defects described in senescent cells have been found in epithelial and interstitial lung cells of patients with IPF. It is unknown how these mechanisms influence and contribute to the pathogenesis of this disease, but the identification of specific pathways that may help as new treatments is interesting and has begun to be investigated.(FIG. 3).

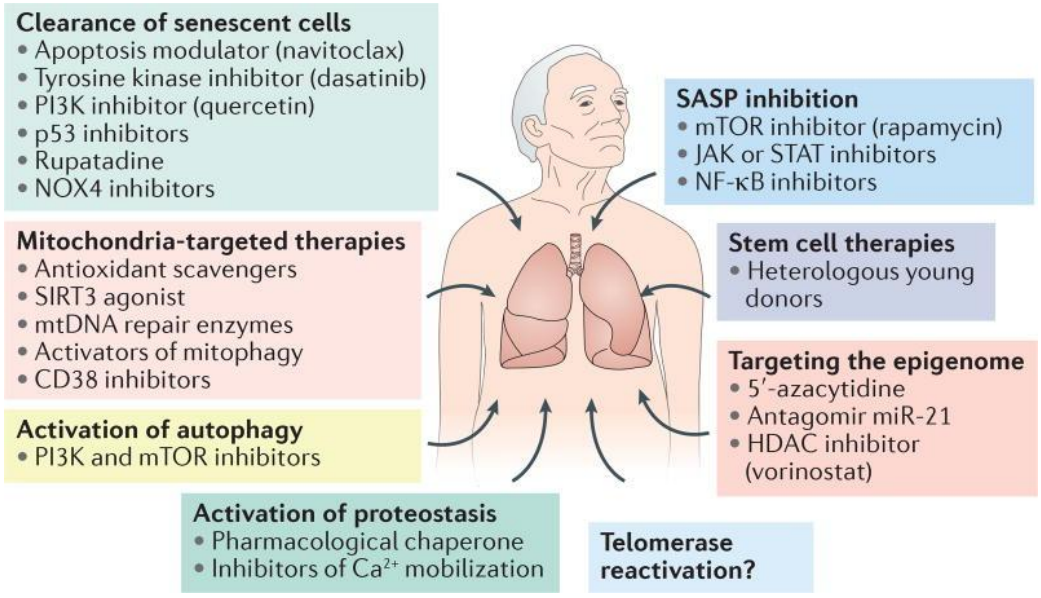

Fig No:3

Selected emerging therapeutic interventions that target age-related cell perturbations in lung fibrosis

New treatments for age-related diseases target key cellular processes in aging cells. Senolytic drugs include dasatinib, quercetin, and navitoclax. Dasatinib and quercetin inhibit tyrosine kinase, and navitoclax inhibits anti-apoptotic members of the B-cell lymphoma 2 (BCL-2) protein family. The secretion-associated senescence phenotype (SASP) is controlled by target of rapamycin (mTOR), and mTOR inhibitors such as rapamycin can reduce the presence of SASP factors in senescent fibroblasts. mTOR inhibitors also promote autophagy and apoptosis in lung fibroblasts of patients

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with idiopathic pulmonary fibrosis (IPF). Rupatadine has also been shown to reduce cellular senescence and can attenuate SASP by preventing activation of the p53-p21 pathway and reducing the expression of CCAAT/enhancer binding protein-β (C/EBPβ), a positive regulator of SASP. Inhibitors of the nuclear factor (NF)-κB signaling pathway inhibit SASP. The pharmacological chaperone, Ca 2+ mobilization inhibitor, and osmotic compound 4-phenylbutyric acid (4-PBA) can increase protein homeostasis. Various therapeutic strategies are being developed to improve mitochondrial function; these include small molecules such as MitoQ and XBJ-5-131, which act as an antioxidant and free radical scavenger. The specific changes observed in IPF lung cells suggest that mechanisms that increase the level of sirtuin 3 (SIRT3) activators, mitochondrial autophagy inducers, and mitochondrial DNA (mtDNA) repair enzymes may be beneficial. Estrogen receptor modulators such as raloxifene and androgens have been used to stimulate telomerase activity and increase telomere length, but more research is needed. HDAC, histone deacetylase; JAK, Janus kinase; miR-21, microRNA-21; NOX4, NADPH oxidase 4; PI3K, phosphoinositide 3-kinase; STAT, signal transducer and activator of transcription.

Mechanism OF Wound Healing And Fabrosis

A wound-healing response is often described as having three distinct phases—injury, inflammation and repair [Figure 4]. Although not all pulmonary fibrotic conditions follow this simple paradigm, it has been a useful model to elucidate the common and divergent mechanisms of pulmonary fibrosis.

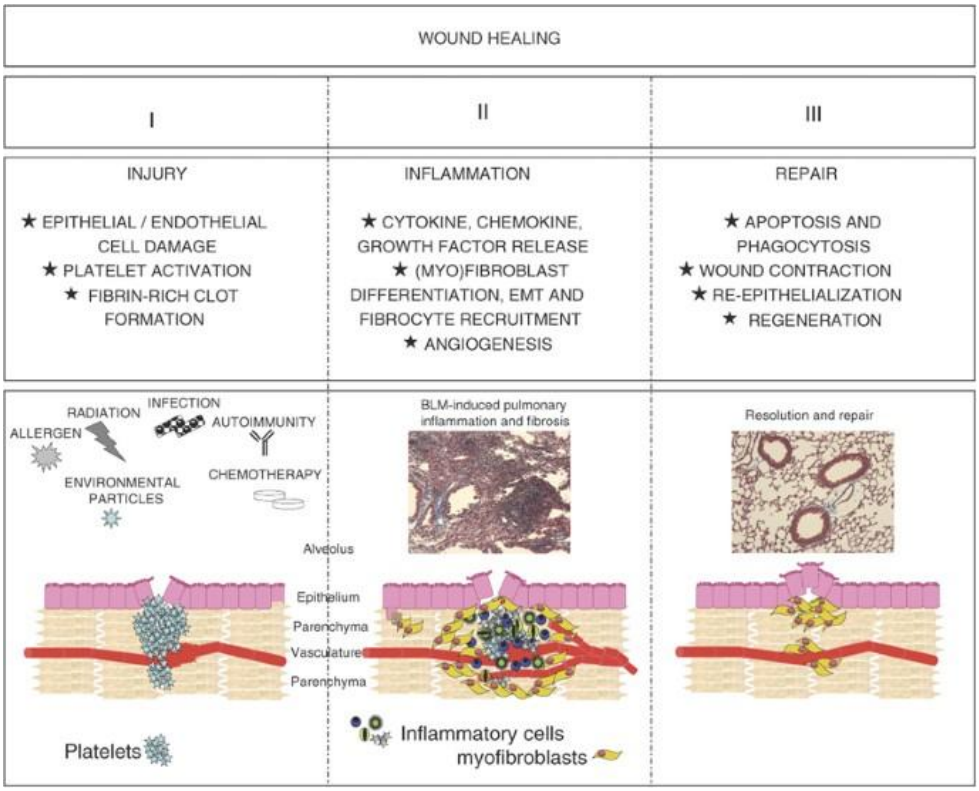

Fig No: 4

Phases of wound healing. A three-phase injury and wound-healing model describes distinct phases of a successful response. (1) Injury; many agents can cause pulmonary injury, including environmental particles, allergens, infectious agents, chemotherapy and radiation. Disruption of epithelial and endothelial cells initiate an anti-fibrinolytic cascade, temporarily plugging the affected tissue. (2) Inflammation; circulating inflammatory cells and fibrocytes are recruited to the injured site through chemokine gradients, supplying fibroblast-activating cytokines and growth factors. Neo-vascularization provides access to damaged areas and a steady stream of inflammatory, anti-inflammatory, and phagocytic cells. (3) Fibroblasts contract and decrease the size of the wound. Inflammatory cells and α-SMA+

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myofibroblasts undergo apoptosis, terminating collagen deposition, and are cleared by phagocytic cells. Epithelial and endothelial cells are replaced and tissue architecture is restored.

Phase 1 Injury

Injuries, environmental issues, diseases, or trauma resulting from autoimmune or allergic reactions all often lead to the destruction of normal tissue that begins to heal the response. Post-inflammatory inflammation can cause cell damage and tissue damage. Epithelial and endothelial cells must be replaced to reflect function and integrity, respectively, and to prevent blood loss. Severe damage to endothelial cells leads to the release of inflammatory mediators and initiates the antifibrinolytic coagulation cascade that disrupts damaged vessels rich in platelets and fibrin7. Lung homogenates, epithelial cells or BAL fluid from IPF patients 8 show that X-box binding protein 1,9 shows greater platelet differentiation and activity to potentiate the thrombotic response compared to COPD and control patients. In addition, thrombin (the serine protease required to convert fibrinogen to fibrin) also entered the lung and alveolar space of many lung fibrosis patients, further confirming the coagulation process. Thrombin can directly activate fibroblasts,13 increasing proliferation and promoting the differentiation of fibroblasts into collagen-producing myofibroblasts. Injury to the airway epithelium (especially alveolar alveolar cells) 16 can cause a similar antifibrinolytic activity and lead to airway obstruction, areas of severe inflammation, and detachment of the epithelium from the basement membrane. Platelet aggregation, degranulation, and clot formation rapidly lead to levels of vasodilation with increased permeability, allowing leukocytes to extravasate and recruit directly to the site of injury. The basement membrane forms the ECM beneath the parenchymal tissue epithelium and endothelium, preventing direct contact with damaged tissue. To neutralize this physical effect, zinc-dependent endopeptidases, also known as matrix metalloproteinases (MMPs), cleave one or more ECM components, allowing entry into the damaged site. In particular, MMP-2 (gelatinase A, type N collagenase) and MMP-9 (gelatinase B, type IV collagenase) break down type N collagen and gelatin, two important basement membrane materials. In most, but not all, studies, 22 MMP-2 and MMP-9 were upregulated, indicating tissue damage and regeneration processes in fibrotic states.

Phase 2 Inflammation

As it enters the area of damaged tissue, a chemokine gradient recruits inflammatory cells. Neutrophils, eosinophils, lymphocytes, and macrophages are present at the injury site, and cellular debris and areas of necrosis are removed by phagocytes. The impact of specific diseases on the lower respiratory tract, particularly in IPF, is controversial (and recently reviewed). One view emerges from the observation that antibiotics are generally less effective in treating patients with IP and pneumonia. Based on these observations, many researchers believe that exercise may not be the cause of fibrosis. However, we believe this discrepancy reflects our limited knowledge and understanding of IPF's personnel and processes. The timing of the inflammatory event may determine the role played by the inflammatory process. Early inflammation, which decreases later in the disease, may promote wound healing and lead to fibrosis. For example, early recruitment of eosinophils, neutrophils, lymphocytes, and macrophages that provide cytokines and chemokines can induce local TGFβ and IL-13. However, after the initial cell damage and wave, subsequent selection of inflammatory cells can assist in phagocytosis, eliminate cell debris, and control excessive cell proliferation, which together can become static. Therefore, late inflammation may have an antifibrotic effect and require resolution of wound healing. For example, a late inflammatory signature enriched in phagocytic macrophages that aid in fibroblast clearance, inhibit local chemokine production, and TGFβ, in addition to regulatory T cells that secrete IL-10, would prevent fibro blastogenesis. It will prevent the cells from being overactive. Therefore, it is only a matter of time before the absence of pain occurs in patients with IPF, and the explanation is not related to pain. In fact, corticosteroids that inhibit endogenous inhibitory and phagocytic pathways can cause complications. However, it should not be forgotten that the mechanisms that lead to lung fibrosis are diverse, including genetic, environmental and immunological factors, and manage the entire process.

Type-2 inflammatory responses: pro-fibrotic IL-4 and IL-13

IL-4 is a classical type 2 cytokine identified as a profibrotic cytokine and is implicated in IPF, cryptogenic fibrosing alveolitis, radiation pneumonitis, and pulmonary fibrosis, as well as liver fibrosis after Schistosoma mansoni infection.

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IL-4 receptors are found on lung fibroblasts, and IL-4 signaling increases extracellular matrix protein and collagen deposition. Surprisingly, some studies have shown that IL-4 is superior to TGF-β1 in promoting collagen synthesis in fibroblasts. Indirect mechanisms of IL-4 include its ability to promote selective activation of macrophages (AA-Mac) through expression of arginase, Fizz-1, Ym-1, and mannose receptors. 59 Macrophages have long been thought to cause pulmonary fibrosis. However, the exact mechanisms and functions of AA-Macs in pulmonary fibrosis are only now being determined. AA-Mac can produce TGF-β, PDGF, and regulate polyamine and proline biosynthesis, cell growth, and collagen production through arginase regulation. AA-Macs were isolated and obtained from bronchoalveolar lavage fluid (BAL) of patients with IPF, and culture supernatants of these AA-Macs increased collagen production by human fibroblasts in a CCL18-dependent manner. Animal studies have also shown that AA-Macs are involved in a variety of fibrosis models, including mice overexpressing human TGFβ in the lung, human and animal studies of dystrophic muscle fibrosis, and γMultiorgan fibrosis-infected IFNγR-/- mice . Herpes virus. Although macrophages have not been identified as AA-Mac, macrophages have long been recognized in human and animal models of pulmonary fibrosis. Taken together, these data indicate that direct release of TGFβ, PDGF, and proline by AA-Mac are just a few of the many pathways through which AA-Mac influences the development of pulmonary fibrosis.

Phase III: Tissue repair and contraction

The final stage of wound healing involves cellular remodeling led by fibrin-rich scaffold formation, wound contraction, closure, and epithelial renewal. Most of the studies elucidating the mechanisms involved in this phase of wound healing have come from dermal studies and in vitro systems. Therefore, if possible, we will extend these studies to the lungs. Myofibroblast-derived collagen and α-SMA form the temporary extracellular matrix, and macrophages, platelets, and fibroblast-derived fibronectin form the fibrin scaffold. These structures together are called granulation tissue. Primary fibroblasts or alveolar macrophages isolated from IPF patients 147 produced more fibronectin and α-SMA than control fibroblasts; this,indicates greater fibroblast activation. Interestingly, macrophage-derived fibronectin levels in steroid-treated IPF patients were similar to those in untreated IPF patients. Therefore, similar to steroid-resistant IL-13-mediated myofibroblast differentiation, macrophage-derived fibronectin release also appears to be resistant to steroid treatment, providing another reason why treatment steroids may not be effective. . In animal models, fibronectin appears to be required for the development of pulmonary fibrosis, with mice specifically deleted for the type III fibronectin domain (EDA) in addition to wild-type mice administered B. Fibrosis seen after Lemisin 148 decreased. .

Etiology

Alleviating symptoms is a major concern for patients with pulmonary fibrosis. Understanding the causes of pulmonary fibrosis may provide the opportunity to reverse long-term symptoms and disease. Therefore, there are now many positive factors associated with pulmonary fibrosis, as will be discussed below. In general, animal models are ideal for studying the management of pulmonary fibrosis and airway repair.

Cystic Fibrosis and Cystic Lung Disease

Cystic fibrosis (CF) is unique between pulmonary fibrosis and pulmonary fibrosis in its causes. It is caused by a genetic mutation, making it the only disease in Caucasians, affecting 1 in 2,500-4,000 people. CF transmembrane conductance regulator (CFTR) is the genetic “Achilles tendon healer” responsible for this disease. The CFTR product is a chloride channel protein found in cell membranes in the lungs, liver, pancreas, intestine, colon, and skin. However, the leading cause of death in people with CF is lung disease. In addition to the direct effects of CFTR mutations causing inadequate cAMP-mediated chloride secretion in epithelial cells and dysfunction of lymph nodes, CF patients also develop severe lung disease, submucosal inflammation, and increased morbidity. Long-term application of aerosol disinfectants will limit the number of bacteria in the system; However, the consequences of chronic infection are lung damage, chronic inflammation, airway repair, and fibrosis. Chronic inflammatory responses, particularly neutrophil responses, are key factors driving CF pathology. Gajar et al. Neutrophil elastase, an enzyme elevated in the BAL fluid of CF patients, has recently been shown to stimulate MMP9 precursors and inhibit TIMP-1, thereby affecting the protease/antiprotease balance. Additionally, the establishment of epithelial cell renewal and repair may be affected in CF, leading to altered lung physiology. Several cftr -/- mice with varying degrees of lung disease have been generated, and CF-modifying

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genes have been identified in various constructs. The challenge of creating mice with chronic lung disease has been accomplished, allowing the pathophysiology of mouse CF to be studied. cftr −/− mice develop parenchymal interstitial thickening and fibrosis with granulocyte influx, fibroblastic infiltration, and matrix protein deposition. The development of mouse models of CF has enabled studies of the immune response, the involvement of gene mutations, the effects of the disease, and many other issues.

Asthma and allergic airway inflammation

Over the last 30 years, there has been an unprecedented increase in the number of people with respiratory allergies and asthma in developed and developing countries, especially in urban areas. Allergic asthma is a polygenic disease characterized by hypersensitivity to IgE and IgG1, respiratory and interstitial eosinophilia, mucus secretion, and airway hyperresponsiveness. Asthma is associated with repeated exposure to allergens and irregular inflammation of the mucosal surface; this leads to goblet cell hyperplasia, smooth muscle hypertrophy and proliferation, angiogenesis, and finally subepithelial fibrosis. CD4 + Th2 cells regulate the production of IL-4 and IL-25 derived from many cells or basophils in the allergic dendritic drive. Cytokine-secreting Th2 cells are activated and migrate to the lung interstitium and mucosal surface, spreading local cellular influx. In particular, Th2-derived cytokines IL-5 and IL-9 mobilize, mature, and recruit into tissues and air eosinophils and mast cells, which are frequently found in biopsies of patients with asthma. TGFβ is also elevated in human asthmatic patients, and the effect of subepithelial fibrosis is associated with a decrease in forced expiratory force (FEV1). Flood-page et al. Observations of increased eosinophils, TGFβ, and subepithelial fibrosis by. 271 Investigate cell-specific localization of TGFβ. In fact, 86% of TGFβ mRNA + cells in the bronchial mucosa of asthmatic patients were eosinophils; this suggests that eosinophils are an important source of profibrotic TGFβ in the allergic lung. Additionally, several studies have determined that collagen deposition is associated with greater tissue eosinophilia and myofibroblasts and submucosal expression of MMP9 and MMP12. These observations have led to a variety of clinical trials and treatment options using anti-IL-5 drugs to prevent tissue eosinophilia, with little success. Treatment of patients with allergic asthma and atopic dermatitis with anti-IL-5 antibody (mepolizumab) reduces tissue eosinophilia despite no change in end-stage allergy. Most striking was the decrease in the thickness and density of the extracellular matrix (tenascin, lumican, and procollagen III (COL3A)) after anti-IL-5 treatment; This suggests that IL-5-mediated tissue eosinophilia is actually ECM. However, despite this support, the role and contribution of eosinophils in human asthma remains controversial, and various anti-IL-5 mAb experiments suggest some improvement. Animal studies using IL-5-deficient mice or eosinophil-depleted mice confirm the important role of decreased eosinophils in peribronchial fibrosis and smoothness, as well as several other aspects of allergic asthma after pneumonia. Thick muscles. Similarly, blocking TGFβ or interfering with TGFβ signaling may reduce airway remodeling following allergen exposure. In conclusion, animal models have demonstrated a clear role for eosinophils and eosinophil-derived TGFβ in airway injury and repair. However, human studies have yielded mixed results, and further studies with more definitive data are needed to address the role of IL-5 and eosinophils in the inflammation, growth, and recurrence of subepithelial fibrosis in asthmatic airways. IL-13 may also be a harmful cytokine in allergic individuals. Many pathological conditions in patients with allergic asthma can be traced to IL-13. For example, IL-13 can regulate goblet cell proliferation in the local epithelium and increase mucus production, obstructing small airways. IL-13 may also promote epithelial repair, fibroblast growth, EMT, and collagen deposition. In addition to airway epithelium, IL-13 induces smooth muscle hyperplasia and subepithelial fibrosis. Similar to the mechanism proposed using the bleomycin model, IL-13 can synergize and promote profibrotic TGFβ eotaxin production and TIMP expression. Therefore, in the context of allergic asthma, eosinophils, TGFβ, and IL-13 may all contribute to the recovery of airways and pulmonary fibrosis. The history of long term of the chronic Obstructive Pulmonary Diseases , pneumonia, and tuberculosis then cause the Idopathic Pulmoary Fibrosis.

Diagnosis

Early diagnosis of IPF is difficult because the initial symptoms (usually shortness of breath and cough) are mild and nonspecific and overlap with many other conditions. When symptoms are more severe, diagnosis can be made and treatment of fibrotic diseases can be started. On physical examination, breathing of the lungs, bursting of Velcro, and clubbing of the fingers can be clearly seen. Pulmonary Function Testing (PFT) demonstrates standard limitations

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measured as reduction in vital capacity (FVC), reduction in forced expiratory volume in 1 second (FEV1), and reduction in lung transplant function is estimated by measuring diffusion capacity. Carbon monoxide (DLCO). Normal findings of spirometry are an FEV1/FVC ratio of greater than 0.70 and both FEV1 and FVC above 80% of the predicted value. If lung volumes are performed, TLC above 80% of the predictive value is normal. Diffusion capacity above 75% of the predicted value is also considered normal.The Gender, Age and Physiology (GAP) score includes age and gender as well as FVC and DLCO and is considered a useful and functional index in predicting mortality in IPF. The 6-minute walk test, which is a simple and understandable method of determining exercise capacity by asking patients to walk as much as possible on a flat surface in 6 minutes, has a prognostic value because the lower the decline in walking, the higher the mortality. The histopathological features of IPF are more characteristic of interstitial fibrotic pneumonia (UIP), appearing microscopically as a heterogeneous patchwork of fibrotic focal areas with hyperplasia adjacent to fibroblastic foci. Normal or near-normal lung tissue. The structure of the lungs is disrupted, resulting in impaired gas exchange

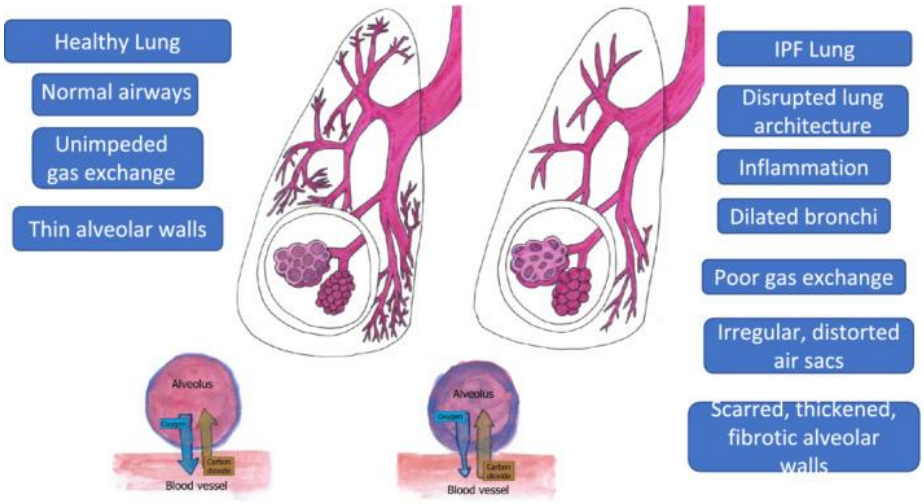

Fig No:5

IPF is usually visualized with computed tomography (CT), but the role of magnetic resonance imaging is emerging. The most common electronic model is UIP. The degree of fibrosis on CT can be assessed visually or using computer algorithms. High-resolution CT often shows honeycombing, traction bronchiectasis, and a reticular pattern often around the lower lobes. In addition to poor health, patients with IPF often suffer from many diseases such as hypertension, chronic obstructive pulmonary disease (COPD), emphysema, diabetes and gastroesophageal reflux (GERD). These can reduce quality of life, complicate treatment, prolong stay, and make patients worse.

Treatment Of IPF

Since the first trial nearly 30 years ago, the field of clinical management of IPF has evolved significantly, reflecting improved understanding of the disease, modeling of pain diagnosis, and the design of large randomized trials. (randomized controlled trial). Substantial evidence regarding the safety and effectiveness of drugs that target pain and prevent infection or interfere with the coagulation system leads to a recommendation against their use in establishing the ultimate treatment for IPF. Both pirfenidone and nintedanib have been shown to reduce FVC in patients with IPF, regardless of disease severity. In the summary analysis of our study, pirfenidone may help reduce mortality, while nintedanib may reduce the risk of exacerbations. However, these two antifibrotic drugs have not been shown to improve respiratory symptoms, HRQL, or patient-reported outcomes.

Pirfenidone

Pirfenidone is an oral pyridine that exhibits combined anti-inflammatory, antioxidant and anti-fibrotic effects in vitro and in animal models of pulmonary fibrosis, as well as inhibiting fibroblasts and collagen, including conversion of

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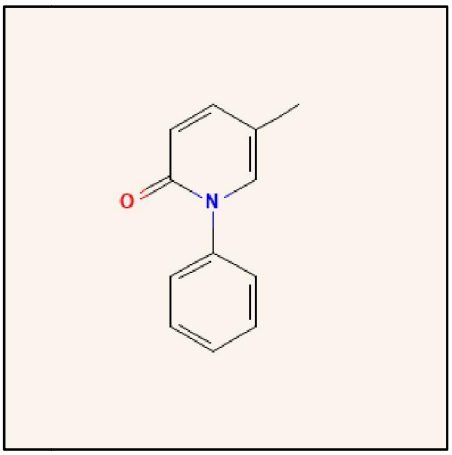
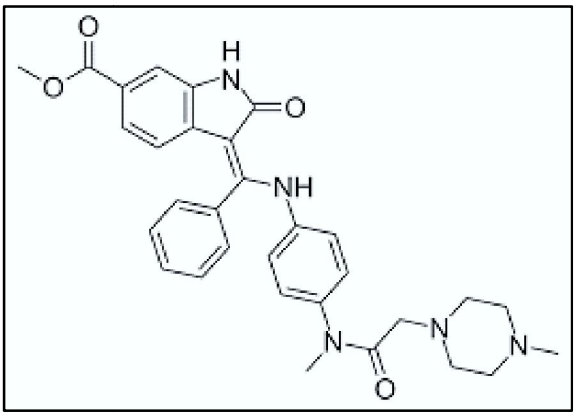
TGF-β expression. synthesis. However, the exact mechanism of action remains unclear. Four randomized placebo-controlled studies investigated and confirmed the beneficial effect of pirfenidone in patients with IPF. Results from pooled data analysis including data from Phase 3 studies supported the effectiveness of pirfenidone in reducing overall and IPF-related mortality; however, mortality rates were not significantly different from prospective studies. Overall, in published studies, pirfenidone use has been associated with mostly mild to moderate use-related adverse events, such as gastrointestinal symptoms (nausea, indigestion), increased work pressure, and photosensitivity. A recent interim report from an international open-label study continues to provide post-authoritative data confirming the safety and tolerability benefits of pirfenidone. Results from several individual studies conducted in Europe and Japan also help confirm long-term and effective performance and sometimes demonstrate diseasestability in the majority of treated patients.



Pirfenidone

Nintedanib

Nintedanib is a multiple tyrosine kinase receptor inhibitor involved in the pathogenesis of pulmonary fibrosis, including PDGF receptors α and β, VEGF receptors 1, 2, and 3, and FGF receptors 1, 2, and 3, and has been shown to prevent the development of pulmonary fibrosis. fibrosis Bleomycin mouse model. In phase 2 and 3 trials, nintedanib 150 mg taken twice daily effectively reduced labor cost, leading to the drug being approved for the treatment of patients with minor to IPF. The most common side effects in the treatment group were gastrointestinal side effects (diarrhea, nausea and vomiting) and elevation of liver enzymes. Evidence from real-life studies on the use of nintedanib is very limited. Data from the German multicenter study of the Humanitarian Use Program of Nintedanib in IPF showed that most patients achieved clinical and functional stability 6 months after initiation of nintedanib therapy, as calculated by the Subgroup of patients previously treated with pirfenidone whose disease progressed to treatment. reported that he had arrived..



Nintedanib

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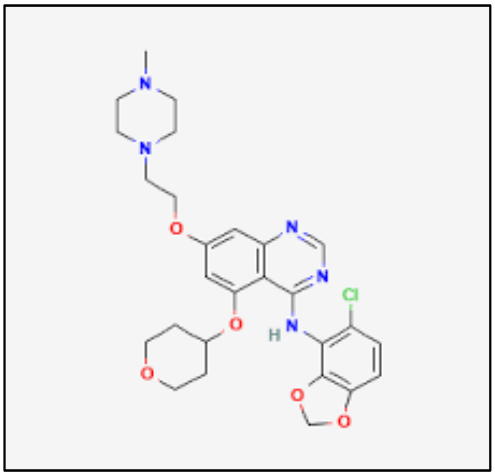
saracatinib

Saracatinib is a dual-specific inhibitor of Src and Abl, protein tyrosine kinases that are overexpressed in chronic myeloid leukemia cells. This agent binds to and inhibits these tyrosine kinases and affects cell motility, cell migration, adhesion, invasion, proliferation, differentiation, and survival.



Saracatinib

Exercise of IPF

Some activities often done in pulmonary fibrosis which includes walking on a treadmill, riding a stationary bike, stretching and light weight training. Use your oxygen. Many patient finds that using oxygen when they exercise is a game changer. They can be more with less worry.

Breathing exercise such as belly breathing and pursed lip breathing can help your lungs be more efficient.

II. CONCLUSION

Today, much progress has been made in understanding the pathogenesis of IPF and in the treatment options available to patients. However, important questions regarding diagnosis and treatment remain unanswered. The process of reliably identifying IPF is never easy. Currently, only morphological data obtained from HRCT or SLB is open to debate, and interpretations may differ between physicians and even experts. Many different genetic markers and biomarkers have been proposed to aid diagnosis and prognosis, but their clinical applications are currently unknown. It is widely believed that in the future, blood or lung-specific molecular biomarkers that indicate disease activity and behavior will be incorporated into the diagnostic process. More care and deeper research are urgently needed to develop treatments that will prolong life and improve quality of life for patients with idiopathic pulmonary fibrosis. Pirfenidone and nintedanib are two types of antibiotics currently available for the treatment of IPF. Only a lung transplant can change his currently unsustainable situation. The discovery of effective drugs has spurred new drug research, and many different molecules are currently being studied in Phase I and II clinical trials. Further studies also aim to test combinations with existing antifibrotic drugs and their use in the treatment of fibrotic pneumonias other than IPF.

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