Current Trends in Pharmacology and Clinical Trials
ISSN: 2642-0848

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Review Article *Volume 5 Issue 1*

Idiopathic Pulmonary Fibrosis: A Panoramic Review

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Received Date: February 18, 2022; **Published Date:** March 15, 2022

Abstract

Idiopathic pulmonary fibrosis is a life-threatening, age-related lung condition with few therapy options. Healthy tissue is replaced by an altered extracellular matrix, and alveolar architecture is damaged, resulting in decreased lung compliance, disturbed gas exchange, respiratory failure, and death. Understanding of the pathophysiology and management of this condition has improved dramatically in less than a decade, and two disease-modifying medicines have been licenced globally. The presentation, pathophysiology, diagnosis, and therapy options for patients with idiopathic pulmonary fibrosis are summarized in this study. This condition has increased our understanding of lung fibrosis mechanisms, and it gives us optimism that comparable treatments can revolutionize the treatment of patients with other progressive fibrotic lung diseases.

This condition was originally assumed to be caused by a persistent inflammatory process, but new data suggests that abnormally activated alveolar epithelial cells are to blame for the fibrotic response (AECs). These cells release mediators that cause fibroblast and myofibroblast foci to develop as a result of their proliferation. Excessive extracellular matrix, primarily collagens, is secreted by the fibroblast and myofibroblast foci, leading in scarring and damage of the lung architecture. The mechanisms that link idiopathic pulmonary fibrosis to ageing and inappropriate epithelial activation are unknown; however, evidence shows that improper recapitulation of developmental pathways and epigenetic alterations may play a role. Recent data on the clinical course, treatment choices, and underlying mechanisms suspected to be involved in the pathophysiology of idiopathic pulmonary fibrosis are reviewed.

Keywords: Epidemiology; Idiopathic Pulmonary Fibrosis; Diagnosis; Clinical Management

Introduction

Idiopathic pulmonary fibrosis (IPF) is an age-related, damaging, chronic, irreversible, progressive lung disease with unknown causes. IPF is a deadly condition in which uncontrolled extracellular matrix deposition results in progressive loss of lung function [1]. Current IPF treatments have a high death rate and a low rate of recovery due to phototoxicity. This condition was originally assumed to be caused by a persistent inflammatory process, but new data suggests that abnormally activated alveolar epithelial cells are to blame for the fibrotic response (AECs). Extracellular matrix, primarily collagens, is secreted in excess by the fibroblast and myofibroblast foci, leading in scarring and damage of the lung structure [2]. IPF is thought to be more dangerous than many malignancies. IPF is more common in middle-aged and older men (range 55–75 years) who have smoked cigarettes in the past, and it affects only the lungs. Shortness of breath and a persistent cough are the most common initial symptoms [3].

IPF patients typically seek medical help because they have chronic and progressive exertional dyspnoea and cough. The natural history of IPF has been described as a slow or constant progression of lung disease, and most individuals follow this pattern. Recent studies, however, suggest that IPF is a heterogeneous disease, with new clinical characteristics and survival patterns being documented [4]. The pathogenic processes are unknown, but a growing body of evidence suggests that the condition is caused by aberrant alveolar epithelial cell behavior that causes mesenchymal cell migration, proliferation, and activation, resulting in the creation of fibroblast and myofibroblast foci. Activated myofibroblasts secrete excessive amounts of extracellular matrix molecules, causing the lung architecture to be destroyed [5].

Idiopathic pulmonary fibrosis (IPF) has a natural history that has been described as a consistent, predictable deterioration in lung function over time. Recent evidence suggests that certain patients may have a more rapid progression, with periods of relative stability followed by sudden respiratory impairment. Many of these acute deteriorations have no recognized cause and are referred to be IPF acute exacerbations [6]. This viewpoint is the product of an international effort to compile the most up-to-date information on acute exacerbations of IPF. Acute exacerbations of IPF are defined as sudden, clinically substantial deteriorations in people with underlying IPF for no apparent reason. Reported aggravation over 30 days or less, new bilateral radiographic opacities, and the lack of infection or another identifiable etiology are among the proposed diagnostic criteria. Infection, disordered cell biology, coagulation, and genetics all have possible pathobiological involvement, and future study approaches are suggested [5,7].

Epidemiology and Risk Factors

The annual incidence of IPF is increasing, with estimates ranging from 4.6 to 16.3 cases per 100,000 and a frequency of 13 to 20 cases per 100,000. Men have a higher prevalence of the condition (1.5 to 1.7:1) than women, and the incidence rises with age [8]. Cigarette smoking and metal and wood dust exposure are the two most significant environmental risk factors. In around 0.5–3.7 % of patients with IPF, genetic transmission occurs, however this number could be greater. Obesity, diabetes, gastric reflux, pulmonary hypertension, obstructive sleep apnea, coronary artery disease, and emphysema are all comorbid conditions [9,10].

Pathophysiology

Idiopathic pulmonary fibrosis was once thought to be a persistent inflammatory condition that developed to established fibrosis [11]. Idiopathic pulmonary fibrosis is now thought to be caused by a combination of hereditary and environmental risk factors, with repeated local micro-injuries to the ageing alveolar epithelium playing a key role. These micro-injuries cause abnormal epithelial–fibroblast communication, matrix-producing myofibroblast induction, and significant extracellular matrix buildup and remodelling of the lung interstitium [9,12].

Environmental Exposures

Particulate inhalation has been linked to idiopathic pulmonary fibrosis development and progression. In most cases, a history of cigarette smoking is linked to the development of idiopathic pulmonary fibrosis. Other environmental exposures, such as metal and wood dusts, agriculture and farming, viruses, and stone and silica, have also been linked [13,14].

Genetic Factors

Genetic predisposition appears to have a role in the development of idiopathic pulmonary fibrosis, according to growing data. Rare genetic variations related with surfactant dysfunction (SFTPC, SFTPA2) and telomere biology have been discovered in studies of familial interstitial pneumonia, which affects two or more members of the same biological family (TERT, TERC, PARN, RTEL) [15].

Maladaptive Repair Process

It's been difficult to pinpoint the pathogenic causes of fibrogenesis in idiopathic pulmonary fibrosis; nonetheless, persistent deregulation of type 2 alveolar epithelial cells (AEC2s) is thought to play a key role. AEC2s are lung stem cells that help type 1 alveolar epithelial cells (AEC1) regenerate during homoeostasis or after lung damage. In idiopathic pulmonary fibrosis tissue, AEC1 loss and aberrant AEC2s are seen, with fibroblastic foci often positioned close to hyperplastic or apoptotic alveolar epithelial cells [16,17]. Although evidence suggests that abnormal extracellular matrix deposition contributes to disease development, the progression from a normal to an abnormal extracellular matrix in idiopathic pulmonary fibrosis is poorly understood.

Clinical Presentations, Signs, and Symptoms

Exertional dyspnoea with or without a dry cough is the most common symptom in patients. To avoid diagnostic delays, primary care clinicians must have clinical suspicion of idiopathic pulmonary fibrosis [4]. This presentation may initially be attributed to age, deconditioning, or other comorbidities (e.g., smoking history, emphysema, cardiovascular disease, or obesity) [18]. Patients may present abruptly, with respiratory symptoms worsening for days to weeks, often accompanied by fever and influenza-like symptoms. Pulmonary function tests detect restrictive

disease (lower total lung capacity) and abnormal gas exchange in those who have already been diagnosed with a disease (reduced capacity for carbon monoxide diffusion) [19,20].

Diagnosis

IPF frequently necessitates a multidisciplinary approach comprising pulmonologists, radiologists, and pathologists with experience in interstitial lung disorders. A pattern on high-resolution CT or lung tissue recovered by surgical lung biopsy that is indicative of typical interstitial pneumonia is critical for the final diagnosis [21]. Fibrotic nonspecific interstitial pneumonia is the most important differential diagnosis, and other types of idiopathic interstitial pneumonias and interstitial lung illnesses caused by occupational or environmental exposure, systemic disease, or medicines must be ruled out. Even if there are no indications or symptoms of connective tissue diseases, a serological examination is suggested [22]. There are few reliable biomarkers derived from blood or bronchoalveolar lavage fluid that could be used for differential diagnosis or outcome prediction.

Clinical Phenotypes and Prognosis

IPF has a wide range of clinical manifestations, with a median survival time of 2.5-3.5 years after diagnosis. Clinical profiles with distinct comorbidity and survival patterns are being identified. Old age (>70 years old), smoking history, a low BMI, substantial physiological impairment, a large radiological extent of disease, and pulmonary hypertension are all linked to a worse prognosis [23].

Stable or Slowly Progressive Course: Many patients with IPF have a sluggish clinical history and don't see a doctor for months or years after symptoms first appear (cough and progressive dyspnoea). Patients have decreased lung volumes and capacities at presentation, as well as hypoxemia at rest that increases with exercise. The mean annual rate of loss in forced vital capacity in placebo groups of big therapeutic studies ranged from 0.13 L to 0.21 L [24,25].

Accelerated Variant: Accelerated IPF refers to a subgroup of patients, mostly male cigarette smokers, who have a fast-progressing disease with a shorter life expectancy. The transcriptional signature in these cases suggests the upregulation of various functional pathways, most of which are found in the alveolar epithelial and mesenchymal domains [26]. Despite having similar lung function, chest imaging, and histological abnormalities at the time of diagnosis, accelerated IPF has a different clinical trajectory and transcriptional profile than the conventional slowly progressing variant.

Acute Exacerbation: A subgroup of patients, mainly male cigarette smokers, has a rapidly progressive course with shortened survival, known as accelerated IPF. In these cases, the transcriptional signature indicates the up regulation of several functional pathways, which mostly operate in alveolar epithelial and mesenchymal domains [27]. Accelerated IPF differs in clinical course and transcriptional profile from the typical slowly progressive form, despite having similar lung function, chest imaging, and histological findings at the time of diagnosis. Because the number of circulating fibrocytes increases during an acute exacerbation and returns to pre-exacerbation levels in patients who recover, they could be involved [28].

Biology

Acute exacerbations of IPF have a complicated pathobiology. Disrupted epithelial cell integrity, cellular inflammation, cytokines, matrix metalloproteinases (MMPs), and coagulation components are all likely involved in the pathophysiology of IPF, and rapid alterations in these processes can cause acute exacerbations. Below, we'll go over some of these fundamental mechanisms in greater depth, as well as how they may be involved in IPF acute exacerbations [11,29].

Epithelial Cell Integrity: In acute exacerbations, loss of alveolar epithelial cell integrity and damage may play a key role, resulting to fibrin extrusion onto the alveolar surface and remodelling. BALF neutrophilia and histopathology demonstrating diffuse alveolar damage characterize acute exacerbation morphologically. Both of these findings show that damage and loss of alveolar epithelial cell integrity may play a role [30,31]. Environmental influences are expected to interact with genetic variations in epithelial cell function, which could explain why only a small percentage of IPF patients experience acute exacerbations.

Fibrocyte Function: In both human and animal models of fibrosis, fibrocytes are circulating bone marrow-derived progenitors that move to the lungs. Fibrocytes can be recruited in response to chemokines produced by infection or damage, and they can help to promote fibrogenesis by producing extracellular matrix and secreting profibrotic substances [32]. According to recent research, the percentage of circulating fibrocytes in IPF patients is higher than in healthy controls (6–10 vs. 0.5–2.4 %, respectively). The level rises even more in patients who are suffering an acute exacerbation [33,34]. During an acute exacerbation, the level of fibrocytes in one patient was 23.1 %, but after 6 weeks, it had dropped to 3.7 %. It's unclear whether fibrocyte recruitment and/or function are aberrant during acute exacerbation.

MMP-9 and Transforming Growth Factor-B: MMPs control the turnover of the extracellular matrix. Active MMP-9 levels in the BALF of patients with quickly progressing IPF are higher. Excessive MMP-9 can damage the alveolar–capillary basement membrane's structural and functional integrity, as well as activate latent transforming growth factor (TGF)-, a profibrotic cytokine [35]. TGF- may be further stimulated by lung stretching via an integrin-mediated mechanism. The result that acute exacerbations after video-assisted thoracopic surgery (VATS) were more prevalent in the intraoperatively ventilated lung supports the idea that single-lung ventilation can cause stretch-dependent TGF activation and acute exacerbation. As a result, increased MMP-9 and TGF-activation may encourage the onset of an acute aggravation of IPF [36].

Disordered Coagulation and Fibrinolysis: Acute exacerbations of IPF may be characterized by abnormal coagulation and fibrinolysis. A procoagulant and antifibrinolytic alveolar environment has been observed in individuals with stable IPF, and a similar environment has been described in patients with acute respiratory distress syndrome (ARDS). The prevalence of disrupted coagulation and fibrinolysis in stable IPF, as well as the clinical and pathologic parallels between acute exacerbations and ARDS, suggest that these mechanisms may play a role [37,38].

Genetic Predisposition: In some IPF patients, a variation in erythrocyte complement receptor 1 and mutations in surfactant protein genes are found. Several families with IPF and one patient with spontaneous IPF have recently been discovered to have heterozygous mutations in the telomerase reverse transcriptase (hTERT) and/or RNA component (hTR) genes, which encode telomerase components [39]. These mutations because shortened telomeres, which may restrict alveolar epithelial cell regeneration potential and contribute to the pathobiology of acute exacerbation.

Clinical Management

Patients with known or suspected idiopathic pulmonary fibrosis should be referred to a centre with competence in idiopathic pulmonary fibrosis care as soon as possible, because delayed access is linked to an increased risk of death. Patients who are referred have access to diagnostic and management skills, such as the commencement of disease-modifying treatment, monitoring, side-effect control, and non-pharmacological care [40]. Non-pharmacological treatments for IPF include oxygen therapy and lung transplants, although they are expensive and have a lower recovery rate. PFD is commonly utilized and preferred for pharmacological medication treatment. Co-morbidities typically linked with idiopathic pulmonary fibrosis, such as emphysema, pulmonary hypertension, gastro-esophageal reflux disease, and obstructive sleep apnea, may be present in addition to idiopathic pulmonary fibrosis focused management [41,42].

Lung Transplantation

Lung transplantation can enhance quality of life and lengthen longevity in selected individuals with idiopathic pulmonary fibrosis, with a 5-year survival rate of roughly 50%. Due to the medical difficulty of the surgery and post-surgical treatment, as well as the limited supply of donor organs, only a few people undergo this treatment [43].

Stem Cell-Based Therapy

Adult organs, including the lungs, can be regenerated and repaired using stem cells obtained from both embryonic and adult tissue. This is most likely caused by the migration and spread of neighbouring and newly recruited circulating progenitor cells, which multiply and undergo phenotypic differentiation to cover the denuded surfaces during normal repair [11]. Mesenchymal stem cells have the potential to regenerate tissue. In animals with bleomycin-injured lungs, these cells move to the lung, assume an epithelium-like phenotype, and decrease fibrosis [44].

Additional Management Factors

Broad-spectrum antibiotics and corticosteroids are commonly used to treat patients with acute exacerbations. Mechanical breathing is frequently required, although it is usually ineffective, resulting in a high hospital death rate. Recurrence is common and usually fatal in people who survive and are discharged from the hospital.

Patients can benefit from pulmonary rehabilitation, education programmes, and joining support groups to help them breathe more efficiently and complete their everyday tasks with less dyspnea. Hypoxemia, which normally worsens with activity, frequently necessitates the use of additional oxygen therapy [42].

Disease-Modifying Therapy

The standardized diagnostic criteria for idiopathic pulmonary fibrosis have allowed for large, multicenter, randomized placebo-controlled trials of potential disease-modifying medicines. Various possible medicines (e.g., prednisolone with azathioprine, acetylcysteine, and warfarin) were found to be ineffective or hazardous in randomized controlled studies. Two big phase 3 development programmes identified the first effective disease-modifying medicines for idiopathic pulmonary fibrosis-nintedanib and pirfenidone-through these randomized controlled trials [42,45]. Both medications are now approved worldwide for the treatment of idiopathic pulmonary fibrosis, which has revolutionized patient care.

Pirfenidone is a pyridine that is taken orally and has anti-inflammatory, antioxidant, and antifibrotic properties, while the exact mechanism of action is uncertain [4,46].

Summary

Cough, exertional dyspneoa, basilar crackles, a restrictive defect on pulmonary function tests, honeycombing on high-resolution, thin-section computed tomographic scans, and the histological diagnosis of usual interstitial pneumonia on lung biopsy characterize idiopathic pulmonary fibrosis (IPF), also known as cryptogenic fibrosing alveolitis. The progression is usually slow but relentless. Within 3-8 years of the onset of symptoms, the majority of patients die of gradual respiratory failure. Current treatments have not been demonstrated to be effective. Although the origin of IPF is unknown, early theories suggested that lung injury triggers a cycle of persistent alveolar inflammation that leads to fibrosis and the deterioration of lung architecture. Corticosteroids, immunosuppressive, and cytotoxic medicines have all been found to be ineffective as anti-inflammatory medications. Although successive alveolar epithelial cell injury is considered to be a critical event in the etiology of IPF, the cardinal event is an abnormal host response to wound repair, according to more recent ideas. The fibrotic process is characterized by aberrant epithelial-mesenchymal interactions, altered fibroblast phenotypes, increased fibroblast proliferation, and excessive collagen and extracellular matrix deposition.

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