IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A COMPREHENSIVE REVIEW ON DIAGNOSIS AND TREATMENT OF PULMONARY FIBROSIS

Shubham Jadhav, Het Bhandari, Rishikesh Bachhav

Department of Pharmaceutical Quality Assurance, R. G. Sapkal College of Pharmacy, Anjaneri, Nashik-422213

Department of Pharmaceutical Quality Assurance, R. G. Sapkal College of Pharmacy, Anjaneri, Nashik-422213

Department of Pharmacology, R. G. Sapkal College of Pharmacy, Anjaneri, Nashik-422213

ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a common and deadly fibrotic lung disease with a median survival time of 2 to 3 years. It is characterized by chronic, progressive fibrosis that worsens over time and is linked to high mortality, progressive respiratory failure, and loss of lung function. Diagnosing IPF requires clinicians to integrate clinical, laboratory, radiologic, and pathologic data. Epidemiologically, IPF primarily affects older adults, with prevalence increasing with age, especially in those over 60. Gender and race differences exist, and risk factors include smoking, environmental exposures, and genetics. IPF is often associated with comorbidities, and its prognosis varies, with a median survival of 3 to 5 years. Early detection of pulmonary fibrosis is crucial for better outcomes, relying on clinical history, physical examination, pulmonary function tests, imaging, biomarkers, and, in some cases, genetic testing. Early intervention may slow disease progression. Currently, no established therapy exists for IPF, but new approaches aim to minimize acute lung injury consequences. Medications such as azathioprine and cyclophosphamide, and interventions like lung transplantation, have been explored with varying success. IPF poses a significant threat to society, necessitating ongoing research efforts for effective therapeutic targets. Understanding the molecular mechanisms underlying IPF development is crucial for future investigations and the development of successful treatments.

KEYWORDS

Pulmonary Fibrosis, Diagnosis, Treatment, Idiopathic, Pathogenesis

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is perhaps the most common and deadly of the idiopathic interstitial pneumonias, with a median survival time of only 2 to 3 years. While probable risk factors such as smoking and other environmental exposures have been reported, the (aetiology) of this incurable and growing fibrotic lung disease remains unknown [1]. One of the most severe types of IIP is idiopathic pulmonary fibrosis (IPF), which is characterized by a chronic, progressive fibrosis that worsens over time and is linked to high mortality, progressive respiratory failure, and an unstoppable loss of lung function.

While the diagnosis of IPF is still a diagnosis of exclusion, approaches to its definition and identification have evolved over the past decade [2]. This approach has evolved over the last decade past 10 years. Understanding the pathophysiology of IPF from chronic inflammatory conditions to rapid changes in wound healing. Unusual increase of fibroblasts and aggregation of extracellular collagen matrix (ECM) proteins have been the focal point of daily IPF therapy studies. This review focuses on the day to day understanding of IPF and newly completed or in progress clinical trials for this fatal disease [3].

EPIDERMOLOGY [4,5,6]

The disease known as pulmonary fibrosis is characterized by lung tissue scarring. The exact cause of pulmonary fibrosis is often unknown, and it can be classified into different types, including idiopathic pulmonary fibrosis (IPF) and secondary pulmonary fibrosis, where the cause is identifiable.

Here are some key points regarding the epidemiology of pulmonary fibrosis:

Prevalence:

- The prevalence of pulmonary fibrosis varies globally.
- Idiopathic pulmonary fibrosis (IPF) is considered the most common form of idiopathic interstitial pneumonia and is primarily a disease of older adults.
- The prevalence increases with age, and it is more common in individuals over the age of 60.

Gender and Race:

- Pulmonary fibrosis affects both men and women, but some studies suggest a slightly higher prevalence in men.
- There may be differences in the prevalence of pulmonary fibrosis among various racial and ethnic groups.

Risk Factors:

- Smoking: Cigarette smoking is a significant risk factor for the development of pulmonary fibrosis.
- Occupational and Environmental Exposures: Exposure to certain occupational and environmental pollutants, such as asbestos, silica, and metal dust, can contribute to the development of pulmonary fibrosis.
- Genetics: Some forms of pulmonary fibrosis have a genetic component, and a family history of the disease may increase the risk.

Comorbidities:

- Pulmonary fibrosis may be associated with other medical conditions, such as gastroesophageal reflux disease (GERD), connective tissue diseases, and certain viral infections.

Prognosis:

- The prognosis of pulmonary fibrosis varies widely and depends on factors such as the underlying cause, the extent of lung involvement, and the individual's overall health.
- IPF, in particular, has a generally poor prognosis, with a median survival of 3 to 5 years from the time of diagnosis.

DIAGNOSE

Obtaining a thorough patient history is crucial, encompassing details such as medication and drug use, social factors, occupational and recreational activities, environmental respiratory exposure, risks for HIV, and a comprehensive review of systems. This comprehensive approach ensures the exclusion of alternative causes of interstitial lung disease. Diagnosing idiopathic pulmonary fibrosis (IPF) relies on clinicians integrating clinical, laboratory, radiologic, and/or pathologic data. In IPF, inflammation and scar tissue accumulate in the lungs, leading to thickening and hardening. This fibrosis reduces lung elasticity, making it difficult for the lungs to extract oxygen from the air. Common symptoms include breathlessness during routine activities like walking, and a persistent, non-productive cough [7].

Physical Findings:

Fine bibasilar inspiratory crackles, also known as Velcro crackles, are dry or coarse crackles heard predominantly at the lung bases. Symptoms may include resting tachypnea, cyanosis, and clubbing of the fingers and toes (present in 25-50% of cases), typically without hypertrophic osteoarthropathy. In advanced stages, cor pulmonale becomes apparent, characterized by pulmonary hypertension indicators such as an accentuated pulmonic second sound or a right-sided lift. Eventually, signs of right-sided heart failure emerge. Radionuclide ventriculography often reveals a depressed right ventricular ejection fraction despite normal left ventricular performance [8].

Laboratory testing:

Antinuclear antibodies or rheumatoid factor titers are positive in approximately 30% of individuals with idiopathic pulmonary fibrosis (IPF), but the titers are generally low. Elevated titers may indicate a possible connective tissue disease [9].

C-reactive protein levels and erythrocyte sedimentation rates are raised but lack diagnostic specificity for IPF. Increased circulating immune-complex titers and serum immunoglobulin levels, as well as the presence of cry immunoglobulins, may be observed.

A complete blood cell count may rarely reveal polycythaemia. Arterial blood gas analysis commonly shows chronic hypoxemia.

Pulmonary function studies typically demonstrate nonspecific findings indicative of a restrictive ventilatory defect and reduced diffusion capacity for carbon monoxide (DLCO) [10].

Imaging studies:

Chest radiography reveals abnormal findings, but its diagnostic specificity is limited. Notable features include peripheral reticular opacities (netlike linear and curvilinear densities) primarily at the lung bases, honeycombing (coarse reticular pattern), and lower lobe volume loss [11].

High-Resolution Computed Tomography (HRCT) significantly improves the assessment of interstitial lung diseases by enhancing spatial resolution, allowing detailed visualization of lung parenchyma down to the level of the pulmonary lobule. The HRCT protocol for suspected idiopathic pulmonary fibrosis (IPF) typically involves a section thickness of 1-1.5 mm collimation and an interval size between sections of 1-2 cm. The characteristic HRCT pattern of IPF often exhibits patchy, predominantly peripheral, subpleural, bibasal reticular abnormalities, along with areas of traction bronchiectasis and a limited amount of ground glass opacity [12].

Transthoracic echocardiography is effective in detecting pulmonary hypertension but may show variable performance in individuals with Idiopathic Pulmonary Hypertension and other Chronic Lung Diseases [13].

Procedures/Techniques:

Bronchoscopy can be informative for diagnosing when bronchoalveolar lavage fluid lacks lymphocytosis; instead, an increased presence of neutrophils (70-90% of patients) and eosinophils (40-60% of all patients) may be indicative [14].

Surgical lung biopsy for distinguishing usual interstitial pneumonia from other idiopathic interstitial pneumonias, the most effective sample is obtained through surgical lung biopsy, either via open lung biopsy or the preferred method of video-assisted thoracoscopic surgery (VATS) [15].

PATHOGENESIS

Great progress is been made in understanding of the disease's pathophysiology, which has given rise to the possibility of a more tailored therapeutic strategy. Borchers et al. explain the efforts to better understand the causes behind the higher presence of fibroblasts in the lungs of patients with IPF. UIP histology is thought to be caused by recurrent epithelial damage, which causes alveolar epithelial cells (AECs) to become activated. These AECs subsequently attract and stimulate fibroblasts, causing proliferation and differentiation of fibroblasts into myofibroblasts. Myofibroblasts continue to accumulate and produce an excess of extracellular matrix as a result of improper re-epithelialization. Humoral immunity and autoimmune reactions, as well as genetic influences obtained from persons with familial IPF, have all been mentioned [16].

As a result of these advancements, IPF is no longer considered a solely inflammatory disease. "Progressive extracellular matrix formation, decreased fibroblast-myofibroblast cell death, continuing epithelial cell apoptosis, and abnormal re-epithelialization" are the characteristics of UIP. It's likely because of this that broad anti-inflammatory and immunosuppressive medications haven't been able to change the course of the disease, which is becoming increasingly lethal. Future treatments for IPF, according to Selman and colleagues, should focus on crippling the fibroproliferative response and supporting normal alveolar re-epithelialization [17].

However, the role of inflammatory feedback in the aetiology of IPF remains unknown, as evidenced by recent research using mouse lung damage models. These findings suggest the harmful involvement of an early inflammatory response involving danger signals in the form of uric acid generation, as evidenced by a decrease in observed fibrosis following the administration of uric acid-lowering medications [18]. Human IPF lungs have also been found to have higher uric acid levels than non-fibrotic lungs [19]. While genes involved in acute inflammatory pathways have not been identified to be raised in IPF, several genes encoding chemokines and cytokines have been found to be upregulated [20]. As a result, it's been suggested that more finely tuned anti-inflammatory medicines, such as specific manipulation of key inflammatory pathways, be considered [21].

THE DETECTION OF EARLY DISEASE [22-28]

Early detection of pulmonary fibrosis is crucial for better outcomes, as interventions may be more effective when the disease is identified in its early stages. Early detection relies on a combination of these methods, often guided by clinical suspicion based on symptoms, risk factors, and imaging findings. Regular monitoring and follow-up are essential for individuals at risk of pulmonary fibrosis to detect any progression or complications early on. Early intervention, including lifestyle modifications and pharmacological treatments, may help slow the progression of the disease and improve quality of life.

Here are some common methods used for the detection and diagnosis of early pulmonary fibrosis:

Clinical History and Physical Examination:

- A detailed patient history, including any relevant occupational or environmental exposures, can provide valuable information.
- Physical examination may reveal signs such as crackles in the lungs, clubbing of the fingers, and evidence of respiratory distress.

Pulmonary Function Tests:

- Spirometry and lung volume tests can assess lung function and detect restrictive patterns associated with pulmonary fibrosis.
- Reduced forced vital capacity (FVC) and total lung capacity (TLC) may be indicative of early lung involvement.

High -Resolution Computed Tomography (HRCT):

- HRCT is a key imaging modality for diagnosing pulmonary fibrosis. It provides detailed images of the lungs, allowing for the detection of subtle abnormalities and fibrotic changes.
- Ground-glass opacities, reticular patterns, and honeycombing on HRCT are characteristic findings of pulmonary fibrosis.

Chest X-rays:

- While not as sensitive as HRCT, chest X-rays may reveal abnormalities such as reticular opacities and honeycombing.
- X-rays can be used for initial screening and monitoring disease progression.

Biomarkers:

- Blood tests may be used to measure certain biomarkers associated with pulmonary fibrosis. These can include markers of inflammation, fibrosis, and autoimmunity.
- Examples include serum levels of Krebs von den Lungen-6 (KL-6), surfactant protein-D (SP-D), and C-reactive protein (CRP).

Bronchoscopy:

- Bronchoscopy may be performed to collect samples from the airways and lungs. Analyzing these samples can help rule out other lung conditions and provide additional information about the extent of inflammation and fibrosis.

Lung Biopsy:

- In some cases, a surgical lung biopsy may be recommended, especially when other diagnostic methods are inconclusive.
- A biopsy allows for a direct examination of lung tissue to confirm the presence of fibrosis and identify its underlying cause.

Quantitative Imaging Analysis:

- Advanced imaging techniques, such as quantitative analysis of lung texture and density, may be used to assess subtle changes in lung tissue that are not easily visible on standard imaging.

Genetic Testing:

- In cases where there is a suspicion of a hereditary form of pulmonary fibrosis, genetic testing may be considered.

TREATMENT AND THERAPY:

Currently, there is no established therapy for idiopathic pulmonary fibrosis (IPF). In light of recent insights into the disease's origins, new approaches aim to minimize the consequences of repeated episodes of acute lung injury.[29]

Azathioprine: Some patients showed modest improvement and increased survival when treated with a combination of azathioprine and corticosteroids. A prospective, double-blind, randomized, placebo-controlled study involving 27 patients found a marginally significant survival advantage with the combination of azathioprine and prednisolone.[30]

Cyclophosphamide: High-dose intravenous cyclophosphamide, administered every 2 to 4 weeks within a dose range of 500 to 1,800 mg, has been tested in open trials for refractory IPF. However, a recent study suggested that combined corticosteroid and cyclophosphamide therapy did not impact survival in IPF patients.[31]

Colchicine: Colchicine, which inhibits collagen formation and modulates the extracellular environment, has been investigated for its potential benefits. Despite its ability to suppress the release of alveolar macrophage-derived growth factor and fibronectin, subsequent studies failed to demonstrate any advantages of colchicine treatment over no treatment at all.[32]

Lung Transplantation: For certain patients with IPF, lung transplantation has become a viable option. Unfortunately, eligibility for this procedure is limited due to factors such as older age or complicating medical conditions.[33]

CONCLUSION:

Idiopathic pulmonary fibrosis is a rapidly progressive fatal disease of unknown cause characterized by sequential acute lung injury with subsequent scarring and end-stage lung disease. This disease causes a serious threat to the society along with the increased many pulmonary problems. Till today, no drug therapy has clearly been demonstrated to benefit patients with idiopathic pulmonary fibrosis, a number of novel investigational scientists hold promise for future study. The complexity of IPF study and the understanding of molecular mechanisms in the development of IPF are required for future investigation, and we hope these efforts will lead to find effective therapeutic targets for the treatment of IPF.

Reference:

1. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011; 183:788-824.

2. American Thoracic Society, European Respiratory Society. American Thoracic Societ y/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 2002; 165:277-304.

3. King TE Jr, Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet 2011; 378:1949-61.

4. Costabel U, King TE. International consensus statement on idiopathic pulmonary fibrosis. Eur Respir J 2001; 17:163-7.

5. Collard HR. The age of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2010; 181:771-2

6. Olson AL, Swigris JJ, Lezotte DC, et al. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. Am J Respir Crit Care Med 2007;176:277-84

7. Frankel SK, Schwarz MI. Update in idiopathic pulmonary fibrosis. Curr Opin Pulm Med 2009; 15: 463-9

8. Reynold HY. Idiopathic Pulmonary Fibrosis. In: Fauci AS, editor. Principles of Internal Medicine, 14th ed. The McGraw-Hill Companies 1998; 1461-63.

9. Fishman A, Elias J, Fishman J, Grippi M, Senior R, Pack A. Idiopathic Pulmonary Fibrosis. In: Fishman AP,editor. Fishman's Pulmonary Diseases and Disorders. 4th ed. The McGraw-Hill Companies 2008; 1143-60.

10. Martinez FJ, Flaherty K. Pulmonary function testing in idiopathic interstitial pneumonias. Proc Am Thorac Soc 2006; 3:315-21

11. Misumi S, Lynch DA. Idiopathic pulmonary fibrosis/usual interstitial pneumonia: imaging diagnosis, spectrum of abnormalities, and temporal progression. Proc Am Thorac Soc. Jun 2006; 3:307-14.

12. Orens JB, Kazerooni EA, Martinez FJ, Curtis JL, Gross BH, Flint A, Lynch III JP. The sensitivity of highresolution CT in detecting idiopathic pulmonary fibrosis proved by open lung biopsy: a prospective study. Chest 1995; 108:109-15.

13. Patel NM, Lederer DJ, Borczuk AC, Kawut SM. Pulmonary hypertension in idiopathic pulmonary fibrosis. Chest 2007; 132:998-1006.

14. Rudd RM, Haslam PL, Turner-Warwick M. Cryptogenic fibrosing alveolitis relationships of pulmonary physiology and bronchoalveolar lavage to treatment and prognosis. Am Rev Respir Dis 1981; 124:1-8.

15. Web link: http://emedicine.medscape.com/article/301226-overview. Idiopathic Pulmonary Fibrosis. Apr 28, 2014

16. Borchers AT, Chang C, Keen CL, et al. Idiopathic pulmonary fibrosisan epidemiological and pathological review. Clin Rev Allergy Immunol 2011;40:117-34.

17. Selman M, King TE, Pardo A. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. Ann Intern Med 2001;134:136-51.

18. Gasse P, Riteau N, Charron S, et al. Uric acid is a danger signal activating NALP3 inflammasome in lung injury inflammation and fibrosis. Am J Respir Crit Care Med 2009;179:903-13.

19. Markart P, Luboeinski T, Korfei M, et al. Alveolar oxidative stress is associated with elevated levels of nonenzymatic low-molecular-weight antioxidants in patients with different forms of chronic fibrosing interstitial lung diseases. Antioxid Redox Signal 2009;11:227-40.

20. Zuo F, Kaminski N, Eugui E, et al. Gene expression analysis reveals matrilysin as a key regulator of pulmonary fibrosis in mice and humans. Proc Natl Acad Sci U S A 2002;99:6292-7.

21. Datta A, Scotton CJ, Chambers RC. Novel therapeutic approaches for pulmonary fibrosis. Br J Pharmacol 2011;163:141-72.

22. Muller, N. L., Miller, R. R., Webb, W. R., Evans, K. G., Ostrow, D. N. 1986. Fibrosing alveolitis: CT -pathologic correlation. Radiology 160: 585-88.

23. Muller, N. L., Staples, C. A., Miller, R. R., Vedal, S., Thurlbeck, W. M., et al. 1987. Disease activity in idiopathic pulmonary fibrosis: CT and pathologic correlation. Radiology 165: 731-34.

24. Wells, A. U., Hansell, D. M., Corrin, B., Harrison, N. K., Goldstraw, P., et al. 1992. High resolution computed tomography as a predictor of lung histology in systemic sclerosis. Thorax 47: 738-42

25. Jones, G. J., Minty, B. D., Royston, D. 1982. The physiology of leaky lungs. Br. J. Anaesthesia 54: 705-21

26. Chi net, T., Dusser, D., Labrune, S., Collignon, M. A., Chretien, J., et al. 1990. Lung function declines in patients with pulmonary sarcoidosis and increased respiratory epithelial permeability to 99mTc-DTPA. Am. Rev. Respir. Dis. 141: 445-49

27. Schmekel, B., Wollmer, P., Venge, P., Linden, M., Blom-Bulow, B. 1990. Transfer of 99mTc-DTPA and bronchoalveolar lavage findings in patients with asymptomatic extrinsic allergic alveolitis. Thorax 45: 525-29

28. Raghu G, Depaso WJ, Cain K, Hammar SP, Wetzel CE, Dreis DF, Hutchinson J, Pardee NE, and Winterbauer RH. Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective, double-blind randomized, placebo-controlled clinical trial. Am Rev Respir Dis 1991; 144:291-6.

29. Harrison, N. K., Glanville, A. R., Strickland, B., Haslam, P. L., Corrin, B., et al. 1989. Pulmonary involvement in systemic sclerosis: the detection of early changes by thin section CT scan, bronchoalveolar lavage and 99mTcDTPA clearance. Respir. Med. 83: 403- 14

30. Baughman RP, Lower EE. Use of intermittent, intravenous cyclophosphamide for idiopathic pulmonary fibrosis. Chest 1992; 102:1090-4.

31. Collard HR, Ryu JH, Douglas WW, Schwarz MI, Curran-Everett D, King TE Jr, Brown KK. Combined corticosteroid and cyclophosphamide therapy does not alter survival in idiopathic pulmonary fibrosis. Chest 2004; 125:2169-74.

32. Rennard SI, Bitterman PB, Ozaki T, Rom WN, Crystal RG. Colchicine suppresses the release of fibroblast growth factors from alveolar macrophages in vitro: the basis of a possible therapeutic approach to the fibrotic disorders. Am Rev Respir Dis 1988; 137:181-5.

33. Douglas WW, Ryu JH, Schroeder DR. Idiopathic pulmonary fibrosis: impact of oxygen and colchicine, prednisone, or no therapy on survival. Am J Respir Crit Care Med 2000; 161:1172-8.