

Role of Low Dose Pirfenidone in Primary and Secondary Lung Fibrosis: An Observational Study.

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Abstract: Pulmonary fibrosis is associated with a number of specific forms of interstitial lung disease (ILD) and can lead to progressive decline in lung function, poor quality of life, and, ultimately, early death. Idiopathic pulmonary fibrosis (IPF), the most common fibrotic ILD, affects up to 1 in 200 elderly individuals and has a median survival that ranges from 3 to 5 years following initial diagnosis. IPF has not been shown to respond to immunomodulatory therapies, but recent trials with novel antifibrotic agents have demonstrated lessening of lung function decline over time. Pirfenidone has been shown to significantly slow decline in forced vital capacity (FVC) over time and prolong progression-free survival, which led to its licensing by the United States Food and Drug Administration (FDA) in 2014 for the treatment of patients with IPF. However, pirfenidone has been associated with significant side effects, and patients treated with pirfenidone must be carefully monitored. We review recent and ongoing clinical research and experience with pirfenidone as a pharmacologic therapy for patients with IPF, provide a suggested approach to incorporate pirfenidone into a treatment algorithm for patients with IPF, and examine the potential of pirfenidone as a treatment for non-IPF forms of ILD accompanied by progressive pulmonary fibrosis. In our study we have used low dose pirfenidone (to reduce side effects) not only in case of IPF but also in other causes of progressive lung fibrosis, in which we have seen remarkable results.

Keywords: idiopathic pulmonary fibrosis, treatments, pirfenidone, interstitial lung disease

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I. Introduction

Many forms of interstitial lung disease (ILD) lead to pulmonary fibrosis that can distort and obliterate terminal airways, alveoli, and the vascular structures that comprise gas exchange units as abnormal injury-response lung tissue remodeling occurs.¹⁻³ Idiopathic pulmonary fibrosis (IPF) is the most frequently diagnosed type of idiopathic interstitial pneumonia (IIP) and the most commonly encountered form of progressive pulmonary fibrosis (Figure 1). Although IPF is characterized by a usual interstitial pneumonia (UIP) pattern on lung histopathologic specimens,^{2,4} a UIP or UIP-like pattern can be seen with other forms of ILD such as lung disease associated with connective tissue disease (CTD-ILD) or chronic fibrosing hypersensitivity pneumonitis (HP).⁵⁻⁷ Therefore, alternative causes of UIP must be ruled out before a confident diagnosis of IPF is established.⁴ Non-IPF forms of fibrotic ILD (Table 1) can also progress to end-stage disease,^{5,7} and some of these entities may be difficult to discern from IPF, despite a comprehensive clinical evaluation, high-resolution computed tomographic (HRCT) imaging of the thorax, invasive surgical procedures to obtain diagnostic lung tissue, and a multidisciplinary team.

Making a correct diagnosis of IPF by carefully excluding non-IPF forms of ILD^{29,30} is a critical step to ensure that appropriate principles of disease management will be followed, and the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association consensus statement provides an algorithm for evaluating patients with a potential diagnosis of IPF.⁴ Most patients present with new onset of dyspnea on exertion, cough, and/or fatigue, but asymptomatic or relatively asymptomatic patients with earlier stages of IPF may be identified when interstitial abnormalities are an incidental finding on thoracic imaging. A careful and comprehensive interview helps to exclude potential alternative causes of pulmonary fibrosis that can have a UIP pattern, such as the presence of a CTD, chronic fibrotic HP, occupational/environmental exposures, or drug-induced fibrosis.³⁰ Chest auscultation usually reveals basilar “Velcro-like” crackles on lung auscultation, and digital clubbing may be present. Pulmonary function testing usually shows a restrictive pattern of lung dysfunction with reduced FVC, total lung capacity

(TLC), and DLCO, although patients with early disease may have values for FVC and TLC that are still in the range of normal predicted values, and patients with CPFE may also lack a restrictive pattern due to the opposing forces of emphysematous hyperinflation and restrictive fibrosis.

Arriving at a confident diagnosis of IPF includes the exclusion of non-IPF forms of ILD (eg, chronic HP, non-IPF forms of IIP, CTD-ILD, or drug-induced pulmonary fibrosis) plus having either a definite UIP pattern on thoracic HRCT scanning or a combination of specific HRCT patterns (possible/probable UIP) combined with a lung biopsy that has adequately sampled lung tissue and shows a UIP histopathologic pattern.⁴ A multidisciplinary discussion (clinicians, radiologists, and pathologists with adequate experience with ILD and IPF) provides an optimal opportunity to reach a consensus diagnosis of IPF versus other forms of fibrosing ILD.^{31,32}

Many other forms of fibrosing ILD, such as chronic HP, CTD-ILD, non-IPF IIP, or drug-induced PF, can progress despite immunomodulatory/anti-inflammatory therapies. Although these patients are often younger and may have less comorbidities than older patients with IPF and be more eligible for possible lung transplantation, antifibrotic agents may have a significant impact on disease progression. RCTs that are generally early phase have recently been initiated for some forms of CTD-ILD (scleroderma and rheumatoid arthritis and HP, [Table 5](#)), and the possibility of synergy when pirfenidone is combined with nintedanib for the treatment of IPF is also being explored. The open-label Phase II study of pirfenidone in patients with scleroderma-associated ILD (LOTUSS) showed an acceptable tolerability and safety profile, even when coadministered with mycophenolate mofetil.⁶¹ Because some of these forms of PF may respond to immunomodulatory therapies, an approach that combines traditional therapies with an antifibrotic agent may prove to have enhanced potential to have a significant impact on disease progression. Pirfenidone may also have an significant impact on disorders other than fibrotic ILD, such as progressive airway or parenchymal fibrosis that characterizes chronic lung allograft dysfunction following lung transplantation or obliterative bronchiolitis complicating hematopoietic stem cell transplantation.⁶²

Although mechanisms involved in the development of IPF are not fully understood, a complex and interconnected process occurs, which includes damage to alveolar epithelium and disruption of alveolar basement membranes, release of proinflammatory and profibrotic cytokines, myofibroblast activation and proliferation, and deposition of extracellular matrix proteins by mesenchymal cells that leads to progressive destruction of normal lung architecture and irreversible fibrosis with loss of functional lung units as aberrant lung remodeling occurs.^{11,12} Transforming growth factor-beta (TGF- β) and other profibrotic growth factors have been implicated as playing a key role,^{33,34} and biomechanical characteristics of the matrix environment that lead to increased lung stiffness may also promote fibroblast responses and progression of fibrosis.³⁵ Pirfenidone is an orally bioavailable pyridone derivative that exhibits both anti-inflammatory and anti-fibrotic activities. It has been shown to ameliorate bleomycin-induced lung injury in hamsters,^{36,37} and pirfenidone suppresses TGF- β -induced myofibroblast differentiation and fibrogenic activity of human lung fibroblasts.

II. Materials and Methods

Patient 1

A patient who completed her treatment of pulmonary tuberculosis presented with severe respiratory distress ,spo2 =78%in room air.

Sputum for AFB and CBNAAT done..both were negative.

Other causes of bacterial and viral exacerbations were ruled out.HRCT thorax was done which showed diffuse pulmonary fibrosis.Treatment was initiated with low disepirfenidone and antifibroticagents.On a course of 3 months she had an condiderable clinical and radiological improvement.

HRCT was repeated which showed remarkably reduced fibrosis.The dyspnoea decreased considerably and the saturation was 93% in room air.

Patient 2

A patient who was a known case of rheumatoid artheritis presented with severe respiratory distress and cyanosis.

On examination the patient had grade 3 clubbing,spo2 was 81% in room air and on auscultation there was velcro crepitation on both lung bases .

HRCT scan of chest was done which showed features of ILD.

She was started on antifibrotic therapy and low dose pirfenidone.

She was follwed up after 3months ,and she was clinically better.

The crepitations at the lung bases reduced.

HRCT also showed features of reduced fibrosis.

HRCT Thorax of Post Tubercular Fibrosis before Treatment With Pirfenidone



HRCT Thorax of Post Tubercular Pulmonary Fibrosis Post Treatment with Pirfeninex



HRCT Thorax of RA With ILD Before Treatment



HRCT of RA with ILD Post Treatment with Pirfenidone



III. Conclusion

Pirfenidone was introduced primarily for treatment of Idiopathic interstitial fibrosis, and it showed promising result. But its use was limited, and was not used in any other form of lung fibrosis.

In our study we used low dose pirfenidone (to reduce side effects) in a patient who was suffering from ILD(UIP) secondary to rheumatoid arthritis and the patient improved considerably, clinically and radiologically.

It was also used in a patient of fibrosis secondary to tuberculosis, which showed remarkable improvement. Though more extensive study is needed to provide concrete evidence of its use beyond idiopathic interstitial fibrosis, but this study may open new horizon on treating lung fibrosis secondary to systemic disease.

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