Review Article

Idiopathic Pulmonary Fibrosis

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Interstitial lung diseases are a clinically challenging and diverse group of over 150 disorders characterized by varying degrees of fibrosis and inflammation of the lung parenchyma or interstitium. Idiopathic interstitial pneumonias (IIP) are a subset of diffuse interstitial lung diseases of unknown etiology. Idiopathic pulmonary fibrosis (IPF) is the most common disorder of idiopathic interstitial pneumonias. IPF is defined by the Official ATS/ERS/JRS/ ALAT Statement 2011 as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, and limited to the lungs and associated with the histopathologic and/or radiologic pattern of Usual Interstitial Pneumonia (UIP). [1]

Epidemiology

World wide, the incidence of idiopathic pulmonary fibrosis is estimated to be 10.7 cases per 100,000 person-years for males and 7.4 cases per 100,000 person years for females. The prevalence of idiopathic pulmonary fibrosis is estimated to be 20 cases per 100,000 persons for males and 13 cases per 100,000 persons for females [2]. In India, this was earlier considered to be a rare disease. In 1979, Jindal *et al* published their data on 61 cases of Diffuse Parenchymal Lung Disease (DPLD) seen over a period of five years. However, the scenario is different now and the disease is no longer rare or uncommon. Recently the same center published data on 76 patients with IPF diagnosed over a 16-month period showing a definite increase in the frequency of diagnosis.[3,4,5]

Risk factors

Cigarette smoking increases the risk of developing IPF several-fold, as do other exposures such as metal-fume and wood-dust exposure. Occupations that increase the risk of IPF are agricultural work, hairdressing, and stone polishing, supporting the role of environmental exposure in disease pathogenesis.[1] Viruses like Human Herpes Virus, Epstein Barr Virus and Hepatitis C Virus have been linked to the aetiology of IPF [6]

Various comorbid conditions including gastro-esophageal reflux disease(GERD), venous thromboembolism, coronary artery disease, sleep-disordered breathing, depression, emphysema, pulmonary hypertension, lung cancer, diabetes mellitus and hypothyroidism contribute to the morbidity and mortality of fibrotic lung disease[7]. There is mounting evidence that abnormal reflux (GERD) and aspiration of gastric contents may play a role in the pathogenesis of this disease [8].

Genetic Factors

Mutations in surfactant protein C (SP-C) gene lead to abnormal cleaving and accumulation of surfactant in endoplasmic reticulum leading to endoplasmic reticulum stress. Various other pathways leading to endoplasmic reticulum stress like viral infections have also been identified. The endoplasmic reticulum stress can contribute to the epithelial mesenchymal transition which is supposed to be the basis of fibrosis in IPF [10].

It has been described that mutant telomerase is associated with familial idiopathic pulmonary fibrosis [11]. Telomerase is a specialized polymerase that adds telomere repeats to the ends of chromosomes. This helps to prevent shortening that occurs during DNA replication. TGF-β negatively regulates telomerase activity. This telomere shortening may lead to the loss of alveolar epithelial cells,

resulting in aberrant epithelial cell repair.

A common variant in the putative promoter of the gene that encodes mucin 5B *(MUC5B)* has been associated with the development of both familial interstitial pneumonia and sporadic pulmonary fibrosis. *MUC5B* expression in the lung was reported to be 14.1 times as high in subjects who had idiopathic pulmonary fibrosis as in those who did not[12].

Pathogenesis

It was previously thought that the fibrosis in IPFwas the result of persistent or recurrent inflammation. However, anti-inflammatory agents and immune modulators have proved to be minimally effective in modifying the natural course of the disease. It is currently believed that IPF is an epithelial-fibroblastic disease, in which unknown endogenous or environmental stimuli disrupt the homeostasis of alveolar epithelial cells, resulting in diffuse epithelial cell activation and aberrant epithelial cell repair.

The major cell types involved in the pathogenesis are

Type II alveolar epithelial cells (AECs): These cells residing in the 'corners' of alveoli produce surfactant proteins. They also serve as progenitors of type I AECs, which make up the respiratory gas exchange surface.

Fibroblasts: Mesenchymal cells that reside in the pulmonary interstitium and produce collagen and extracellular matrix (ECM).

Myofibroblasts: These are contractile mesenchymal cells expressing alpha-smooth muscle actin. It is thought that these cells have an activated phenotype, and contribute to exuberant collagen and ECM production inIPF[9].

It seems likely that progression to lung fibrosis involves both genetic background and environmental exposures (analogous to carcinogenesis), and that 'multiple hits' might be required to induce overt fibrotic lung disease. Based on the current evidence, it has been proposed that genetic

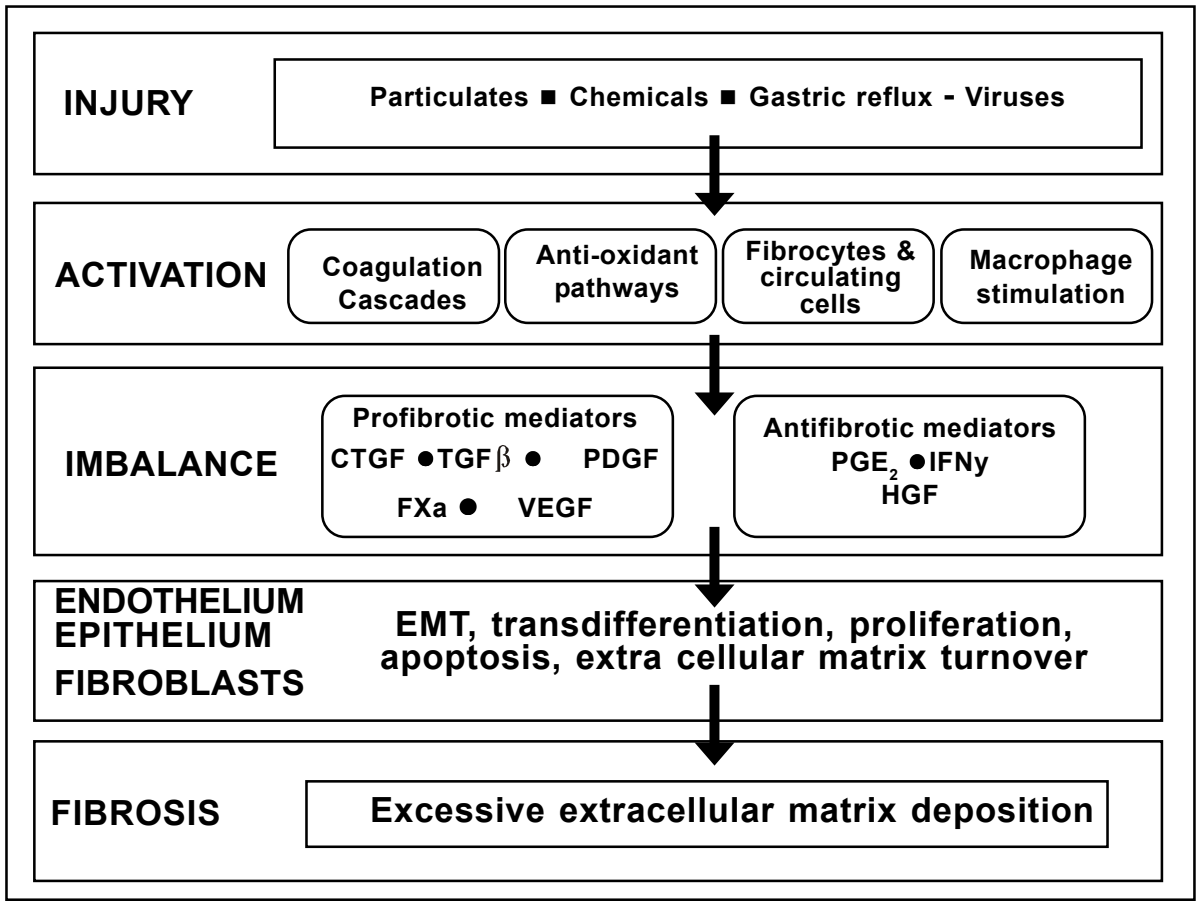

Figure 1. Proposed pathogenetic events in development of IPF
EMT-Epithelialmesenchymal transition

Courtesy :Clinics in Chest Medicine, Interstitial lung Disease, March 2012, Volume 33, Number 1

and acquired or environmental insults converge to render AECs vulnerable to subsequent injury. When subjected to repeat or persistent injurious stimuli (such as aspiration, inhaled particulates, tobacco smoke and respiratory viruses), normal alveolar repair mechanisms fail and culminate instead in persistent collagen deposition, scar formation and progressive distortion of lung architecture. Over time, clinically evident pulmonary fibrosis develops[9].

Clinical features and diagnosis

IPF is a disease of elderly. Median age of presentation is 66 years with a male predominance. IPF should be considered as a diagnostic possibility in all patients above 50years presenting with unexplained chronic exertional dyspnea, dry cough, bibasilar inspiratory crackles, and finger clubbing. It is usually progressive with a 5 year survival rate of 20% , though variant forms with a much faster decline in lung function and some stable chronic forms of the disease have been recognized recently[1].

Clinical phenotypes of IPF

It has been proposed that the disease has a long (months to years) asymptomatic period. Patients consult physician when the severity of the lung lesions reaches a threshold that is enough to provoke symptoms. Most patients follow a relatively slow clinical and functional decline (slowly progressive) after diagnosis. About 10% of these patients present with episodes of acute clinical deterioration (acute exacerbations) that precede and possibly initiate the terminal phase of their disease. A few patients have a short duration of illness with a rapidly progressive clinical course. Heavy smokers might develop pulmonary fibrosis combined with emphysema, with shorter survival compared with patients with IPF alone.[13] So 3 distinct phenotypes have been proposed.

1. Combined pulmonary fibrosis and emphysema (CPFE)
2. Disproportionate pulmonary hypertension in IPF
3. Rapidly progressive IPF [14]

The major and minor criteria for diagnosis of IPF in the absence of a lung biopsy which was proposed in 2000 by ATS/ERS has been done away with. The diagnosis requires a joint effort between clinician, pathologist and radiologist. Lung biopsy may be excluded in cases with conclusive radiology and clinical features. Since a similar radiological pattern may be seen in other ILDs also, exclusion of connective tissue disorders, drugs and toxin exposures are a prerequisite for the diagnosis of IPF.

Diagnostic Criteria

The diagnosis of IPF requires the following:

1. Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).

2. The presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy.

3. Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy[1].

HIGH-RESOLUTION COMPUTED TOMOGRAPHY CRITERIA FOR UIP PATTERN[1]

UIP Pattern (All Four Features)	Possible UIP Pattern (All Three Features)	Inconsistent with UIP Pattern (Any of the Seven Features)
o Subpleural, basal predominance o Reticular abnormality o Honeycombing with or without traction bronchiectasis o Absence of features listed as inconsistent with UIP pattern (see third column)	o Subpleural, basal predominance o Reticular abnormality o Absence of features listed as inconsistent with UIP pattern (see third column)	o Upper or mid-lung predominance o Peribronchovascular predominance o Extensive ground glass abnormality (extent > reticular abnormality) o Profuse micronodules (bilateral, predominantly upper lobes) o Discrete cysts (multiple, bilateral, away from areas of honeycombing) o Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes) o Consolidation in bronchopulmonary segment(s)/lobe(s)

The major differential diagnostic considerations include UIP in other clinical settings such as connective tissue diseases, chronic hypersensitivity pneumonitis (extrinsic allergic alveolitis), and pneumoconiosis (especially asbestosis).

HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN[1]

UIP Pattern (All Four Criteria)	Probable UIP Pattern (First three or four Criteria)	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution Presence of patchy involvement of lung parenchyma by fibrosis Presence of fibroblast foci Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	Evidence of marked fibrosis / architectural distortion, ± honeycombing Absence of either patchy involvement or fibroblastic foci, but not both Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column) OR Honeycomb changes only	Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation Absence of other criteria for UIP (*see*UIP Pattern column) Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column)	Hyaline membranes* Organizing pneumonia*† Granulomas† Marked interstitial inflammatory cell infiltrate away from honeycombing Predominant airway centered changes Other features suggestive of an alternate diagnosis

Scoring system and predictors of prognosis

6 minute walk Test (6MWT): Distance covered in 6MWT of less than 200 - 250 mtrs predict a 2 to 4 fold increase in mortality risk. But due to difficulty in performing and lack of reproducibility of 6MWT, it is not widely recommended as a prognostic tool[15]. Hypoxemia with rest or exertion has also predicted a worse prognosis. Comorbidities like associated emphysema, cardiovascular disease, lung cancer may affect the morbidity and mortality. Red Cell Distribution Width has also been described as a prognostic marker in IPF.

GAP Index[1]

Predictor	Points
Gender	
Female	0
Male	1
Age	
<60	0
61 - 65	1
>65	2
FVC % predicted	
>75	0
50 - 75	1
<50	2
DLCO % Predicted	
>55	0
36 - 55	1
</= 35	2
Cannot perform	3

% Mortality	Stage I 0-3	Stage II 4- 5	Stage III 6 - 8
1 year	6	16	39
2 years	11	30	62
3 years	16	42	77

Composite Physiologic Index [17]

Wells et al devised Composite Physiologic Index (CPI) which correlated better with extent of diseases on CT than the pulmonary function test alone. The formula for the CPI was as follows: extent of disease on CT = 91.0 – (0.65 × percent predicted diffusing capacity for carbon monoxide [DL_{CO}])–(0.53 × percent predicted FVC) + (0.34 × percent predicted FEV_1).

A Clinical Radiological and Physiological (CRP) prediction model by King et al [18] correlated with pathological derangement in IPF

Treatment options

The various completed trials in IPF have yielded the following results

Trial	Drugs	End points	Outcome	
IFIGENIA [19]	NAC vs Prednisone Azathioprine	Change in vital capacity (VC) and diffusing capacity of the lung	Significant reduction in the decline of both VC and D_{LCO} was shown, whereas there was no effect on the survival between the two groups	
PANTHER-IPF [20]	1)prednisone, azathioprine and NAC; 2) NAC alone; and 3) placebo.	The primary outcome was the change in forced vital capacity (FVC) at 60 weeks.	Triple therapy arm had been discontinued due to an excess number of deaths (11% *versus* 1%), hospitalisations (29% versus 8%) and higher prevalence of adverse effects (31% *versus* 9%)	The other two arms are ongoing
CAPACITY 1 and 2 TANIGUCHI[21,22,]	Pirfenidone		A recent Cochrane review, including the four studies mentioned above, has shown that treatment with pirfenidone reduced the risk for disease progression by 30% (HR 0.70, 95% CI 0.56-0.88) [39].	Based on the results of these studies, pirfenidone was licensed in Europe in 2011, for patients with mild-to-moderate disease.

Trial	Drugs	End points	Outcome	
ACE - IPF[23]	Warfarin vsplacebo		The study was prematurely terminated, due to an increase in mortality and low evidence of benefit in the warfarin group compared with placebo.	
TOMORROW[24]	BIBF 1120 is a triple inhibitor of tyrosine kinases receptors, such as platelet derived growth factor (PDGF), vascular endothelial growth factor and fibroblast growth factor receptors,	Annual rate of decline in FVC, and the secondary end-points included acute exacerbations, quality of life measures and total lung capacity (TLC).	Lesser rate of decline of FVC, fewer acute exacerbations, a preserved quality of life, moderate gastrointestinal symptoms and liver toxicity were also observed in the high dose arm compared with placebo.	
DANIELS [25]	Imatinib mesylate		Not effective	
STEP - IPF[26]	Sildenafil	Improvement in 6MWT	Primary outcome not met , but many secondary objectives were achieved	
BUILD-1 [27] BUILD-3 [28] ARTEMIS-IPF MUSIC-IPF [30]	Bosentan Ambrisentan Macitentan Vs placebo		Not effective	
INSPIRE [31]	IFN-γ		Not effective	
R RAGHU [32]	Subcutaneous IFN- for 58 weeks in 330 patients with IPF compared with placebo,		Not effective	

TABLE 2. ONGOING CLINICAL TRIALS IN IDIOPATHIC PULMONARY FIBROSIS [33]

Trial#	Drug	Mechanism of action
ASCEND (NCT01366209)	Pirfenidone	Antifibrotic
RECAP	Pirfenidone	
NCT01335477	BIBF 1120	Tyrosine-kinase inhibitor
NCT01335464	BIBF 1120	Tyrosine-kinase inhibitor
NCT01266135	QAX576	Anti-IL-13 monoclonal antibody
NCT00786201	CNTO 888	Anti-CCL-2 monoclonal antibody
NCT01262001	FG-3019	Anti-CTGF antibody
NCT01362231	AB0024	Anti-LOXL2 monoclonal antibody
NCT01385644	MSCs	Epithelial tissue repair

Pirfenidone

Of all medications studied for the treatment of IPF so far, Pirfenidone currently has the highest grade of evidence to support its efficacy and is the only medication approved for the treatment of IPF. Pirfenidone has been evaluated in four randomised, double-blind, placebo-controlled clinical trials conducted in Japan, North America and Europe. The totality of the data from these trials indicate that Pirfenidone is able to reduce the rate of decline in lung function, measured as change in per cent predicted forced vital capacity (FVC) or vital capacity. In vitro studies have demonstrated that pirfenidone inhibits transforming growth factor (TGF)-β-stimulated collagen synthesis, decreases extracellular matrix deposition and blocks the mitogenic effects of platelet-derived growth factor in lung fibroblasts derived from patients with IPF[34,35,36]

Pirfenedone Trials

Following an open-label phase II pilot study[37] and an open-label 1-yr study,[38] a double-blind, placebo-controlled clinical trial of Pirfenidone was conducted in 107 Japanese patients with IPF [39]. This study was terminated early due to a higher number of acute exacerbations in the placebo group than in the Pirfenidone group.

Based on the positive results from this trial, which demonstrated a reduced decline in VC at 9 months in patients receiving Pirfenidone, a phase III trial was conducted in Japanese patients with well-defined IPF and mild-to-moderate impairment in lung function. This three-armed phase III, multicentre, double-blind, placebo-controlled study randomised patients to either high-dose pirfenidone (600 mg three times per day; n = 108), low-dose pirfenidone (400 mg three times per day; n = 55) or placebo (n = 104) in the ratio 2:1:2. The pirfenidone dose was increased in a stepwise manner up to the full dose over 4 weeks [22]. A 44% reduction in VC decline in the high dose Pirfenidone group compared to placebo was observed as the primary end point. A significant difference was also seen between the low-dose pirfenidone and placebo groups (p = 0.0394).

Two concurrent, multinational, randomised, double-blind placebo controlled trials with Pirfenidone in IPF patients have been conducted in Europe and North America. In the study 004 (CAPACITY 1) patients were randomized 2:2:1 to receive Pirfenidone in the dose of 2403mg, placebo or 1197mg Pirfenidone. It was found that pirfenidone was statistically significantly superior compared to placebo in the primary end-point (FVC % pred) at week 72 (p = 0.001). Secondary end-points (defined as death or decline 10% of FVC or ≥15% in $D_{L,CO}$; p = 0.023) were also statistically significant.[15]

In the second study patients were randomized to receive 2403mg of Pirfenidone or placebo in 1:1 ratio. However, in this study Pirfenidone was not found to be statistically significantly superior compared to placebo for the primary end-point (p = 0.501), although the results were generally consistent with and supportive of the results from CAPACITY 1 trial. In CAPACITY 2, Pirfenidone treatment was associated with a significant beneficial effect on the secondary end-point of the 6MWT distance when compared to placebo[21].

The Cochrane Collaboration recently published the results of a meta-analysis to assess the efficacy of nonsteroid agents in adults with IPF, including Pirfenidone. Four trials involving 1,155 patients were reviewed comparing Pirfenidone with placebo, including the three phase III Pirfenidone trials that reported progression free survival (PFS) as an outcome. The result of the meta-analysis suggested that Pirfenidone significantly reduced the risk of disease progression by 30%. In this Cochrane review the effect of Pirfenidone on pulmonary function in IPF patients revealed a significantly reduced decline in VC from baseline [21, 40, 41].

Adverse reactions

The summary of product characteristics lists the following adverse reactions for Pirfenidone as the most commonly reported (10% or higher): nausea, rash, fatigue, diarrhoea, dyspepsia and photosensitivity reaction. The adverse effects were generally transient and usually resolved if the dose of Pirfenidone was reduced or temporarily discontinued.

NAcetyl Cysteine (NAC), Prednisone and Azathioprine

Data from the IFIGENIA Study[19] provided support for the use of NAC plus prednisone and azathioprine to treat IPF patients. Patients were treated with high-dose NAC (600 mg TID) plus prednisone and azathioprine. The primary endpoint of the study was change in vital capacity. The NAC-based triple-therapy was found to significantly reduce decline in VC after one year of treatment. However, this study had several limitations. There was no direct comparison with placebo group. In view of the drop-out rate from this study of approximately 30% (including deaths), questions were raised regarding the clinical relevance and robustness of the treatment effect. Subgroup analyses from the study confirmed the favourable effects of NAC on lung function, and patients with less advanced disease at baseline appeared to be more responsive to NAC treatment. [42]

The PANTHER-IPF[20] Study was designed to determine whether NAC-based triple-therapy could slow disease progression and improve lung function in patients with moderate IPF. In addition, this study compared the triple-therapy regimen with NAC monotherapy and placebo alone. In 2011, the NIH announced that the triple-therapy arm of the trial had been stopped due to increased mortality observed in this treatment group [43]. Increased risks of death and hospitalization were observed in patients with idiopathic pulmonary fibrosis who were treated with a combination of prednisone, azathioprine, and NAC, as compared with placebo. These findings provide evidence against the use of this combination in patients with IPF.[44]

Currently major international guidelines give the following recommendations for treatment of IPF[1,15]

Strong NO

- Ambrisentan
- Azathioprine
- Bosentan
- Co-Trimoxazole
- MycophenolateMofetil
- Corticosteroid Monotherapy
- Colchicines
- Cyclosporine A
- Combine Steroid Plus Immunomodulator
- Interferon Gamma 1b
- Etanercept

Weak NO- the well informed patient may make a choice of treatment from this group

- Pirfenidone
- Combined acetyl cysteine plus azathioprine and prednisolone
- Acetylcysteine monotherapy
- Anticoagulation
- Mechanical ventilation in advanced cases

Strong YES

- Lung transplantation
- Supplemental oxygen

Weak YES

- Treatment of pulmonary hypertension
- Corticosteroids in exacerbation
- Pulmonary rehabilitation
- Treatment of asymptomatic GERD

Idiopathic pulmonary fibrosis is a disease, having a prognosis similar to, or even worse than, many cancers. So far lung transplantation is the only therapeutic intervention that has offered definite prospect of improved survival for individuals with IPF. The past decade has, however, witnessed an explosion of interest in IPF and Pirfenidone appears to be a promising drug.

Regarding the relation between the IPF patient and the doctor, an interesting observation was made by Craig Conoscenti, et al [34] that pulmonologists with a 'sustained optimism' typology spent longer explaining the prognosis and treatment options to the patient and actively considered clinical trials and lung transplants. Pulmonologists with a 'pragmatic acceptance' typology lacked faith in trials and transplants and focused on managing symptoms. Pulmonologists with this typology may fail to build an appropriate relationship with the patient, leaving them unprepared for the end of life journey.

References

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 RespirCrit Care Med 2011; 183

2 Kim DS, Collard HR, King TE Jr. Classification and natural history of the idiopathic interstitial pneumonias. Proc Am Thorac Soc. Jun 2006;3(4):285-92.

3 Hubbard R, Johnston I, Coultas DB, Britton J. Mortality rates from cryptogenic fibrosingalveolitis in seven countries. Thorax 1996;51:711-6.

4 Jindal SK, Malik SK, Deodhar SD, Sharma BK. Fibrosingalveolitis; A report of 61 cases seen over the past five years. IndJ Chest Dis All Sc 1979;19:174-9.

5 Maheshwari U, Gupta D, Aggarwal AN, Jindal SK. Spectrum and Diagnosis of Idiopathic Pulmonary Fibrosis. Indian J ChestDis Allied Sci2004;46:23-6.

6 Philip L. Molyneaux andToby M. Maher.The role of infection in the pathogenesis of idiopathic pulmonary fibrosis:EurRespir Rev 2013 22:376-381

7 Nations JA, Nathan SD. Co-morbidities of advanced lung disease.Mt Sinai J Med.2009 Feb;76(1):53-62.

8 Allaix ME, Fisichella PM, Noth I, Herbella FA, Borraez Segura B, Patti MGIdiopathic Pulmonary Fibrosis and Gastroesophageal Reflux. Implications for Treatment.J Gastrointest Surg. 2013 Sep 4. [Epub ahead of print

9 Jonathan A. Kropski, William E. Lawson, Lisa R. Young and Timothy S. Blackwell. Genetic studies provide clues on the pathogenesis of idiopathic pulmonary fibrosis. Dis. Model. Mech. January 2013, doi: 10.1242/dmm.010736 vol. 6no. 1 9-17

10 Chapman, H. A.Epithelial-mesenchymal interactions in pulmonary fibrosis. Annu. Rev. Physiol. (2011). 73, 413-435.

11 Armanios MY, Chen JJ, Cogan JD, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. N Engl J Med; Mar 29 2007:356(13):1317-26.

12 Seibold MA, Wise AL, Speer MC, Steele MP, Brown KK, Loyd JE. A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med; Apr 21 2011;364(16):1503-12

13 Talmadge E King Jr, Annie Pardo, Moisés Selman. Idiopathic pulmonary ?brosis. Lancet 2011; 378: 1949–61

14 Fell CD. Idiopathic pulmonary fibrosis: phenotypes and comorbidities. Clin Chest Med. 2012 Mar;33(1):51-7. doi: 10.1016/j.ccm.2011.12.005.

15 U. Costabel. Emerging potential treatments: new hope for idiopathic pulmonary fibrosis patients?Eur Respir Rev September 1, 2011 vol. 20 no. 121, 201-207

16 Brett Ley, MD; Christopher J. Ryerson, MD, MAS; Eric Vittinghoff, PhD; Jay H. Ryu, MD; Sara Tomassetti, MD; Joyce S. Lee, MD, MAS. A Multidimensional Index and Staging System for Idiopathic Pulmonary Fibrosis .Ann Intern Med. 2012;156(10):684-691. doi:10.7326/0003-4819-156-10-201205150-00004

17 Athol U. Wells, Sujal R. Desai, Michael B. Rubens, Nicole S. L. Goh, Derek Cramer, Andrew G. Nicholson, Thomas V. Colby, Roland M. du Bois, and David M. Hansell. Idiopathic Pulmonary Fibrosis - A Composite Physiologic Index Derived from Disease Extent Observed by Computed Tomography.American. Journal of Respiratory and Critical Care Medicine;Vol. 167, No. 7 (2003), pp. 962-969.

18 King TE Jr, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J RespirCrit Care Me;. 2001 Oct 1;164(7):1171-81.

19 Demedts M, Behr J, Buhl R, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med 2005; 353: 2229-2242.

20 Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G,Anstrom KJ, et al. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012; 366: 1968-1977.

21 Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet2011; 377: 1760-1769.

22 Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis. EurRespir J 2010; 35: 821-829.

23 Noth I, Anstrom KJ, Calvert SB, et al. A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. Am J RespirCrit Care Med2012; 186: 88-95

24 Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011; 365:1079-1087

25 Daniels CE, Lasky JA, Limper AH, et al. Imatinib treatment for idiopathic pulmonary fibrosis: randomized placebo-controlled trial results. Am J RespirCrit Care Med 2010; 181: 604-610.

26 Zisman DA, Schwarz M, Anstrom KJ, et al. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med 2010; 363: 620-628.

27 King TE, Behr J, Brown KK, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J RespirCrit Care Med 2008; 177: 75-81.

28 King TE, Brown KK, Raghu G, et al. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J RespirCrit Care Med2011; 184: 92-99.

29 Raghu G, Behr J, Brown K, et al. Artemis-IPF: a placebo-controlled trial of ambrisentan in idiopathic pulmonary fibrosis. B93. Clinical Trials in Idiopathic Pulmonary Fibrosis and Sarcoidosis.May 1, 2012; A3632.

30 Raghu G, Million-Rousseau R, Morganti A, et al. Efficacy and safety of macitentan in idiopathic pulmonary fibrosis: results of a prospective, randomized, double-blind, placebo-controlled trial. B93. Clinical Trials in Idiopathic Pulmonary Fibrosis and Sarcoidosis.May 1, 2012; A3631.

31 King TE Jr., Albera C, Bradford WZ, et al. Effect of interferon-?-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. Lancet 2009; 374:222-228.

32 Raghu G, Brown KK, Bradford WZ, et al. A placebo-controlled trial of interferon-?-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med2004; 350: 125-133

33 ClinicalTrials.gov available at HYPERLINK "http://www.clinicaltrials.gov

34 Gurujeyalakshmi G, Hollinger MA, Giri SN. Pirfenidone inhibits PDGF isoforms in bleomycin hamster model of lung fibrosis at the translational level. Am J Physiol 1999; 276: L311-L318.

35 Iyer SN, Gurujeyalakshmi G, Giri SN. Effects of pirfenidone on procollagen gene expression at the transcriptional level in bleomycin hamster model of lung fibrosis. J PharmacolExpTher 1999; 289: 211-218.

36 Oku H, Shimizu T, Kawabata T, et al. Antifibrotic action of pirfenidone and prednisolone: different effects on pulmonary cytokines and growth factors in bleomycin-induced murine pulmonary fibrosis. Eur J Pharmacol 2008; 590:400-408.

37 Raghu G, Johnson WC, Lockhart D, et al. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label phase II study. Am J RespirCrit Care Med

1999;159: 1061-1069.

38 Nagai S, Hamada K, Shigematsu M, et al. Open-label compassionate use one year-treatment with pirfenidone to patients with chronic pulmonary fibrosis. Intern Med 2002; 41: 1118-1123

39 Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J RespirCrit Care Med 2005; 171: 1040-1047

40 Noble PW, Albera C, Bradford W, et al. The CAPACITY (CAP) trials: randomized, double?blind, placebo?controlled, phase III trials of pirfenidone (PFD) in patients with idiopathic pulmonary fibrosis (IPF). 2009 American Thoracic Society International Conference (San Diego, CA, USA).Am J RespirCrit Care Med 2009; 179: A1129.

41 Albera C, Bradford W, Costabel U, et al. The magnitude of pirfenidone treatment effect in patients with idiopathic pulmonary fibrosis (IPF): a pooled analysis of outcomes in the CAPACITY (CAP) studies. EurRespir J 2010; 36:Suppl. 54, 41s.

42 Behr J, Demedts M, Buhl R. et al. Lung function in idiopathic pulmonary fibrosis--extended analyses of the IFIGENIA trial. Respir Res. 2009;14:101. doi: 10.1186/1465-9921-10-101.

43 National Heart, Lung, and Blood Institute. Clinical Alert: Commonly Used Three-Drug Regimen for Pulmonary Fibrosis Found Harmful. NIH Stops One Treatment Arm of Trial; Other Two Treatments to Continue. US National Library of Medicine: National Institutes of Health; October 21, 2011.

44 Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012;14(21):1968-77.

45 Craig Conoscenti, MD; Eben Rubin, MD; Nadia Sapiro. Idiopathic Pulmonary Fibrosis (IPF): The Pulmonologist's Journey. Chest. 2013;144 (4_MeetingAbstracts):477A. doi:10.1378/chest.1702731