

Therapeutic Update in Idiopathic Pulmonary Fibrosis

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Abstract Idiopathic pulmonary fibrosis (IPF) is a disease of the elderly with a mean age at presentation of 66 years. It is the most common type of idiopathic lung fibrosis, and the most lethal, with a median survival of 3 to 5 years after diagnosis. Abnormalities in fibroblast and humoral response mechanisms may play a role in the pathogenesis of fibrosis in IPF. Clinical trials suggest that pirfenidone, an oral antifibrotic agent, N-acetylcysteine, an antioxidant and perhaps anticoagulation, may have some beneficial effect; however, large-scale studies are necessary for confirmation. Immunosuppression with corticosteroids likely does not confer benefit. Lung transplantation has been shown to improve survival in selected IPF patients. Comorbidities accompanying IPF include gastroesophageal reflux, sleep disturbance, pulmonary arterial hypertension, and coronary artery disease amongst others, and ought to be promptly recognized and managed appropriately. While the US Food and Drug Administration has not currently approved any treatments for IPF, patients with IPF should continue to be

strongly encouraged to enroll in ongoing clinical trials for this devastating disease.

Keywords IPF · Pirfenidone · N-acetylcysteine · Apnea · Reflux · Transplantation

Abbreviations

IPF	Idiopathic pulmonary fibrosis
TLC	Total lung capacity
FVC	Forced vital capacity
DLco	Carbon monoxide diffusing capacity
UIP	Usual interstitial pneumonitis
HRCT	High-resolution computed tomographic
FDA	Food and drug administration
CT	Computed tomography
BUILD	Bosentan use in interstitial lung disease
FEV ₁	Forced expiratory volume in one second
NAC	N-acetylcysteine
GERD	Gastroesophageal reflux disease
OSA	Obstructive sleep apnea
BMI	Body mass index
SLT	Single-lung transplant
BLT	Bilateral-lung transplant
US	United States

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Case Illustration

A 65-year-old Caucasian female homemaker, former smoker (35 pack-years), is seen in your clinic complaining of an insidious onset of breathlessness, particularly with exercise. Her dyspnea has progressively worsened the past 2 years. She denies any fevers, night sweats, or cough. Her weight is steady. There are no pets at home, especially

birds, and there has been no asbestos exposure in the past. Her previous medical and surgical history reveals that she had a myocardial infarction 5 years ago, but has been asymptomatic since.

Physical examination reveals bilateral finger clubbing and post-tussive “Velcro” crackles at both lung bases posteriorly. Serological testing for autoantibodies including anti-nuclear antibodies, anti-cyclic citrullinated peptide, anti-scl-70, anti-centromere antibody, and anti-ribonucleoprotein antibodies were within normal limits. Pulmonary function tests reveal a restrictive pattern with a total lung capacity (TLC) of 3.0 l (68% of predicted), a forced vital capacity (FVC) of 1.5 l (65% of predicted), an FEV₁/FVC ratio of 0.83, and a carbon monoxide diffusion capacity (DLco) of 10.1 ml/min/mmHg (60% of predicted). A high-resolution computed tomographic scan (HRCT) of the chest shows increased peripheral reticular markings especially at the lung bases, with honeycombing and traction bronchiectasis and no ground-glass infiltrates, consistent with a usual interstitial pneumonitis (UIP) pattern, the histopathological correlate of idiopathic pulmonary fibrosis (IPF) (Fig. 1). Right-heart catheterization reveals an elevated mean pulmonary artery pressure of 29 mmHg at rest and a normal pulmonary capillary wedge pressure of 11 mmHg. Left-heart catheterization reveals non-significant coronary artery disease and a normal left ventricular ejection fraction of 65%.

This patient fulfills three of four major and all four minor diagnostic criteria for a diagnosis of IPF [1, 2]. These criteria for IPF diagnosis in the initial absence of a surgical lung biopsy are outlined in Table 1. In light of the classical presentation of this 65-year-old patient with an insidious onset of breathlessness lasting more than 3 months, a UIP pattern on the HRCT chest, restrictive pattern on pulmonary



Fig. 1 HRCT chest consistent with a classic UIP pattern consisting of peripheral increased reticular markings especially at both lung bases asymmetrically, honeycombing (arrowhead) and traction bronchiectasis (arrow) without ground-glass infiltrates

Table 1 Current criteria for IPF diagnosis^{ab}

Major criteria

- Exclusion of other known causes of ILD such as certain drug toxicities, environmental exposures, and connective tissue diseases
- Abnormal pulmonary function studies that include evidence of restriction (reduced VC, often with an increased FEV₁/FVC ratio) and impaired gas exchange [increased $P(A - a)O_2$, decreased PaO_2 with rest or exercise or decreased DLCO]
- Bibasilar reticular abnormalities with minimal ground-glass opacities on HRCT scans
- Transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis

Minor criteria

- Age > 50 years
- Insidious onset of otherwise unexplained dyspnea on exertion
- Duration of illness ≥ 3 months
- Bibasilar, inspiratory crackles (dry or “Velcro” type in quality)

BAL bronchoalveolar lavage, DLCO diffusing capacity of the lung for CO, HRCT high resolution computerized tomography, ILD interstitial lung disease, $P(A - a)O_2$ alveolar–arterial pressure difference for O₂, VC vital capacity, and FEV₁ forced exhaled volume in one second

^a In the immunocompetent adult, the presence of all of the major diagnostic criteria as well as at least three of the four minor criteria increases the likelihood of a correct clinical diagnosis of IPF

^b Reprinted by permission from ATS/ERS International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias, Am J Respir Crit Care Med. 2002;165:277–304

function testing, and the absence of other likely etiologies, a confirmatory surgical lung biopsy was deemed unnecessary. She then asks “What can you do for me now doctor?”

Discussion

The management of a patient with IPF begins with both an early and correct diagnosis of a disease that has only recently been precisely defined [1, 2]. It is nevertheless a disease of the elderly [3] that is now recognized as the most common [4, 5] and most lethal of the idiopathic lung fibroses in the United States (US) [5]. Two-thirds of patients present after the age of 60 years, with a mean age at presentation of 66 years [6]. Raghu et al. [7] found an actual prevalence in the US of 4.0 per 100,000 persons aged 18 to 34 years to 227.2 per 100,000 amongst those aged 75 years or older using broad-based criteria. The annual incidence using the same criteria was 1.2 per 100,000 persons aged 18 to 34 years to 76.4 per 100,000 persons aged 75 years or older. With both prevalence and incidence generally higher in males than females, the authors also estimated that there were approximately 89,000 persons aged 18 years and older with diagnosed IPF in the US, and that annually, 34,000 persons in this age

group were newly diagnosed with this disease. In contrast, worldwide prevalence of IPF is quite variable, with a range of three to six per 100,000 in the UK to 16–18 per 100,000 in Finland [8]. This variability may be real or a consequence of different diagnostic criteria and identification and reporting methods. The index of suspicion for IPF may be variable in different countries as well. It is estimated that approximately five million persons worldwide are affected [9]. An international registry for IPF has therefore been suggested that may help standardize diagnostic data collection and reporting [10].

Patients with IPF demonstrate a median survival of 3 to 5 years from the time of diagnosis; [11, 12] a mortality that is worse than that for many cancers, including acute myeloid leukemia [5, 13, 14]. Olson et al. [13] found an average age- and sex-adjusted mortality rate for pulmonary fibrosis of 50.8 per 1,000,000 persons in the US from 1992 to 2003. Of concern however was the age-adjusted pulmonary fibrosis mortality increase in men of 28.4% from 1992 to 2003 (from 40.2 deaths per 1,000,000 in 1992 to 61.9 deaths per 1,000,000 in 2003), and 41.3% in women, from 39.0 deaths per 1,000,000 in 1992 to 55.1 deaths per 1,000,000 in 2003. These significant increases in both genders ($p < 0.0001$) was higher in women ($p < 0.0001$), with the most common cause of death due to the disease itself. In light of these disappointing statistics, especially with regard to mortality, much effort has been expended towards finding an effective therapy for IPF. There are currently no US Food and Drug Administration (FDA) approved treatments for IPF.

Nevertheless, major advances in our understanding of the pathogenesis and classification of interstitial lung disease and specifically IPF, a precise definition of UIP, the histopathological correlate of IPF, and the recent development of more uniform drug trial design with standardized outcome measures should engender significant advances towards finding useful therapies in IPF [5, 15]. The epidemiology and pathogenesis of IPF is well summarized in a recent article by Borchers et al. where aberrations in fibroblast differentiation, activation and proliferation, epithelial–mesenchymal transition, and abnormalities in T and B cells and dendritic cells may all play a role in the stimulation of the fibrosis that is found in IPF [16]. In addition, there is no clear evidence to indicate that a lung-specific autoimmune mechanism leads to IPF or its progression [17].

It is important to note that UIP per se is not pathognomonic for IPF, as it can be found in other interstitial lung diseases such as hypersensitivity pneumonitis, asbestosis, and collagen vascular disease. This distinction is relevant as UIP associated with IPF has a dramatically worse mortality than UIP associated with collagen vascular disease for example. In one study, Flaherty et al. found that

patients with UIP on surgical lung biopsy due to collagen vascular disease showed fewer fibroblastic foci histologically, and no deaths during a median follow-up of 3.5 years. In contrast, 52 patients (53%) died in the idiopathic UIP or IPF group with a median survival of 2.7 years [18]. This inexorable progression to death in IPF suggests that the current management of IPF must not only include involvement in clinical trials, but also much earlier and correct diagnosis, and subsequent management of the patient as a whole.

Previous Treatment Strategies

The use of long-term pharmacologic immunosuppression in IPF was likely based on the hypothesis that IPF emanates from a persistent inflammatory alveolitis that may be amenable to immunomodulation [5, 15]. In 2000, the joint American Thoracic Society/European Respiratory Society international consensus statement on IPF suggested low dose prednisone and azathioprine or cyclophosphamide as a treatment regimen for IPF based on expert opinion rather than grade-A evidence [2, 7]. Since then, a systematic review by Richeldi et al. of 17 randomized controlled trials and controlled clinical trials found that none were suitable for meta-analysis due to inadequate methodologies. The authors therefore concluded that there was no evidence to support the routine use of corticosteroids alone in the management of IPF [19].

A combination of low-dose prednisone and azathioprine vs. low-dose prednisone alone suggested a survival effect in a prospective double-blind, randomized, placebo-controlled study of 27 newly diagnosed IPF patients [20]. Unfortunately, the diagnostic criteria for IPF were not as precisely defined at that time, and some of the cases may have been cases of nonspecific interstitial pneumonia instead [9]. A subsequent Cochrane review to determine the effects of non-corticosteroid immunosuppressive, anti-fibrotic, and immunomodulatory agents in the treatment of IPF [21] identified 59 studies of generally poor quality, of which only three were suitable for meta-analysis. Of these three studies, different agents were used in the form of azathioprine, interferon gamma-1 β , and colchicine; thus making meaningful direct comparisons difficult. No high quality studies were available utilizing cyclophosphamide. The authors and others [9, 15] concluded that there was little to justify the routine use of any immunomodulatory agent in the treatment of IPF.

Interferon gamma-1 β is a cytokine that downregulates transforming growth factor- β and has other antifibrotic and immunomodulatory effects. In a large, randomized, double-blind placebo-controlled trial of 330 patients, the use of interferon gamma-1 β did not meet the primary endpoint of

progression-free survival (defined as death or a categorical change in pre-defined pulmonary function values) over a 58-week period [22]. A second and larger trial investigating interferon gamma-1 β was conducted at least in part because of a trend towards improved survival ($p=0.08$) in the intent-to-treat with interferon gamma-1 β population of patients [5, 9]. Despite the enrollment of 886 patients, this trial also failed to reach its primary endpoint and was subsequently discontinued [23]. Under these circumstances, interferon gamma-1 β administered subcutaneously has not been shown to prolong survival or to improve the pulmonary function of IPF patients.

Treatment Strategies Currently Under Evaluation

The poor or lack of response in IPF to conventional anti-inflammatory therapies in terms of delaying disease worsening, or death, or reducing the rate of lung function decline may be explained by an alternative hypothesis for the pathogenesis of this disease. This alternative hypothesis suggests disordered fibroproliferation after recurrent alveolar epithelial injury [11]. Epithelial cell injury with aberrant repair may lead to inappropriate fibrosis, with aberrant protein processing through the endoplasmic reticulum that can induce cell stress and apoptosis [5]. More patients with sporadic IPF have short telomeres that limit tissue renewal capacity in the lung rather than identified telomerase mutations. This pattern therefore suggests currently unidentified genetic abnormalities in a higher proportion of patients [24, 25]. These recent findings may translate into novel, anti-fibroproliferative treatment strategies, rather than broadly targeting inflammatory mechanisms.

Bosentan is an orally available dual endothelin-receptor antagonist that is approved for the treatment of pulmonary arterial hypertension [5]. Park et al. [26] found that endothelin-1 was involved in the pathogenesis of pulmonary fibrosis in a rat model of bleomycin-induced lung fibrosis. Use of bosentan to block these receptors also reduced collagen deposition in the lung. At least in part on the basis of these pre-clinical discoveries, 158 patients (mean age 65.3 years in the bosentan group, 65.1 years in the placebo group) were enrolled in the Bosentan Use in Interstitial Lung Disease (BUILD)-1 trial. Patients with severe pulmonary hypertension were excluded, defined as those with echocardiographic systolic pulmonary pressures ≥ 50 mmHg or tricuspid regurgitation velocity ≥ 3.2 m/s. This was a randomized, placebo-controlled, double-blind study that did not show any superiority of bosentan to placebo in 6-min walk distance up to month 12, the primary efficacy endpoint [27]. However, a trend in favor of bosentan with respect to a secondary endpoint of death or disease progression in a patient subgroup who had

undergone diagnostic surgical lung biopsy was noted. A subsequent multicenter double-blind, randomized, placebo-controlled, parallel group, event-driven phase 3 clinical trial (BUILD-3), randomized 616 patients at 119 sites. The primary endpoint this time was time to death or deterioration in lung function using pre-specified parameters. However, a corporate communication (Actelion Pharmaceuticals Ltd. Allschwil, Switzerland 3/1/2010) indicates that this primary endpoint was not met ($p=0.21$). This suggests that bosentan for IPF per se cannot be recommended at this time.

Sildenafil, a phosphodiesterase-5 inhibitor, stabilizes cyclic guanosine monophosphate, leading to pulmonary vasodilatation. It may preferentially improve blood flow to well-ventilated lung tissue through vasodilatation, thus improving ventilation-perfusion matching and hence oxygenation in patients with advanced IPF. A double-blind, randomized, placebo-controlled trial of sildenafil involving 180 IPF patients (mean age 69 years) did not however show a significant difference in the primary outcome of a 20% or more improvement in the 6-min walk test distance at 12 weeks (10% in the sildenafil group vs. 7% in the placebo group showed this improvement, $p=0.39$). Small but significant differences in the secondary outcomes of arterial oxygenation, DLco, degree of dyspnea, and quality of life were nevertheless reported, favoring the sildenafil group. No significant difference in serious adverse events was seen between the two groups [28]. In addition, data regarding right-heart catheterization were not available in this study, hence the severity and extent of pulmonary vascular disease is unknown in this patient cohort. Under these circumstances additional and larger clinical trials investigating the use of phosphodiesterase-5 inhibitors in IPF are necessary prior to any recommendation regarding their use in IPF patients.

Pirfenidone is an oral antifibrotic, anti-inflammatory, and antioxidant agent [5] that inhibits transforming growth factor- β in vitro [15] and lessens bleomycin-induced lung fibrosis in the hamster model [29]. It was recently (2008) approved for use in the management of IPF in Japan by the Japanese Ministry of Health, Labour and Welfare [5]. This approval was in large part based on a Japanese Phase III study involving 267 patients who had been randomized to receive placebo (mean age 64.7 years), high dose (1,800 mg daily, mean age 65.4 years) or low dose (1,200 mg daily, mean age 63.9 years) pirfenidone over 52 weeks. The primary endpoint of change in lung vital capacity showed significant preservation of this parameter between the placebo group (-0.16 l) and the high-dose group (-0.09 l, $p=0.0416$). The secondary endpoint of progression-free survival time was also significant between these two groups ($p=0.0280$). The major adverse event in this study was photosensitivity, a well-recognized side effect of pirfeni-

done. While mild in severity in most patients, 37% of subjects in the high-dose pirfenidone group withdrew from the study, likely affecting data interpretation [30].

Pirfenidone was studied in two additional multinational, randomized, double-blind, placebo-controlled phase III trials (CAPACITY 1 and CAPACITY 2) conducted in IPF patients with mild to moderate disease. The CAPACITY 1 trial enrolled 344 patients and involved a daily dose of 2,403 mg of pirfenidone vs. placebo. The CAPACITY 2 trial enrolled 435 patients who were randomized 2:2:1, respectively to pirfenidone 2,403 mg daily, placebo or pirfenidone 1,197 mg daily. After a 72-week treatment period, the primary endpoint of change in FVC was met in CAPACITY 2 ($p=0.001$) but not in CAPACITY 1 ($p=0.501$; Corporate Communication, Intermune, Brisbane, CA 2/3/2009). Their side effect profiles appeared similar to the Japanese study above [5]. In 2010, the FDA decided against approving pirfenidone for the treatment of IPF in the US, citing the necessity for further clinical studies. Until such studies are performed, pirfenidone cannot be recommended for IPF patients.

Anticoagulation was found to have a beneficial effect on survival in one open-label study of 56 patients with IPF (mean age 69.4 years) randomized to prednisolone alone or prednisolone with anticoagulation consisting of coumadin as an outpatient and intravenous dalteparin as an inpatient [31]. The 3-year survival in the anticoagulant group was found to be significantly different (63% vs. 35% in the no-anticoagulant group, $p=0.049$). In addition, the mortality associated with acute exacerbation of IPF was significantly reduced in the anticoagulant group vs. the no-anticoagulant group (18% vs. 71% respectively, $p=0.008$). D-dimer levels, a marker of thrombotic disease, were found to be significantly higher in patients who died compared to survivors during acute exacerbation of IPF, leading the authors to suggest an activated hemostasis system in patients with this condition. The unblinded nature of this trial, possible selection bias towards more severe disease requiring hospitalization, and a 26% withdrawal rate in the anticoagulant group after randomization, but prior to treatment, are however of significant concern [15, 31]. Therefore, the AntiCoagulant Effectiveness in Idiopathic Pulmonary Fibrosis trial is being conducted under the auspices of the National Heart, Lung, and Blood Institute (NHLBI) prior to any recommendation regarding use of anticoagulant therapy in IPF.

N-acetylcysteine (NAC) has been investigated as being potentially beneficial in the treatment of IPF, as it is a precursor of the antioxidant glutathione, which is depleted in IPF lungs [9, 32]. The use of NAC may therefore ameliorate a hypothesized oxidant/antioxidant imbalance contributing to progressive fibrosis in IPF [33]. The Idiopathic Pulmonary Fibrosis International Group Explor-

ing N-Acetylcysteine I Annual (IFIGENIA) study randomized 182 IPF patients to NAC (mean age 62 years) or placebo (mean age 64 years), with both groups receiving azathioprine and prednisone. After 12 months of treatment, the rate of decline in the FVC and DLco were significantly lower in the NAC group with a 9% relative reduction of the FVC decline and a 24% relative reduction in the DLco decline [15, 34]. No significant difference in mortality was found (9% NAC arm vs. 11% placebo arm, $p=0.69$). In light of the lack of a true “no-treatment” arm, and the fact that approximately 30% of patients died or were lost to follow-up at 12 months, the NHLBI is currently conducting the PANTHER-IPF trial (Evaluating the Effectiveness of Prednisone, Azathioprine, and N-acetylcysteine in People With Idiopathic Pulmonary Fibrosis). The results of this trial are awaited before further recommendations regarding NAC therapy for IPF patients can be made.

Nevertheless, the current improvement in study design, advances in IPF disease classification, and the results of some of the completed clinical trials above are hopeful. IPF patients should continue to be strongly encouraged to participate in randomized multi-centered, double-blind clinical trials to hopefully determine an effective and safe treatment strategy for this progressive, and lethal lung disease. Table 2 delineates currently active clinical drug trials for IPF that are closed to new recruitment, but Table 3 lists a selection of active clinical trials for IPF that are or will be open to new recruitment.

Lung Transplantation

This is currently the only treatment modality that improves survival in selected patients with IPF, reducing the risk of death by 79% in one study (95% confidence interval, 8–86%; $n=46$, mean age 50.1 years; $p=0.03$) [35]. The institution of the relatively new Lung Allocation Score has resulted in significant reduction in both wait times and mortality on the wait list for IPF patients. It is controversial as to whether single-lung transplant (SLT) or bilateral-lung transplant (BLT) is preferred for IPF patients. However, recent data from the International Society for Heart and Lung Transplantation demonstrated that between January 2000 to June 2005, 1- and 5-year survival rates for SLT in IPF were 76% and 45% ($n=1,084$), and 77% and 52.5% ($n=687$) for BLT [36]. Thus BLT may suggest a survival advantage over SLT in selected IPF patients. Suitable IPF patients should therefore be considered for early lung transplant evaluation. However, a significant number of IPF patients may not be suitable candidates for lung transplantation because of associated comorbidities, and also advanced age if there is a delay in diagnosis.

Table 2 Active clinical drug trials of IPF treatment CLOSED to new recruitment^a

Treatment arm(s)	Mechanism of action	Enrollment goal (<i>n</i>)	Primary outcome measure	Sponsor
Zileuton vs. azathioprine and prednisone phase 2	Leukotriene modifier	140	Change in LTB ₄ levels in bronchoalveolar lavage fluid following six months of treatment	University of Michigan
Bosentan vs. placebo phase 3 (BUILD-1)	Dual endothelin receptor antagonist	158	Change in 6-min walk distance	Actelion
Bosentan vs. placebo phase 3 (BUILD 3)	Dual endothelin receptor antagonist	600	Time to occurrence of disease worsening or death up to End of Study.	Actelion
Bosentan phase 3 (BUILD 3- open label extension)	Dual endothelin receptor antagonist	600	Long term-safety and tolerability	Actelion
Macitentan vs. placebo phase 2 (MUSIC)	endothelin receptor antagonist	178	Change in FVC	Actelion
Minocycline phase 3	Angiogenesis inhibitor	Unknown	Assess the efficacy of minocycline as an anti-angiogenetic agent as an add on therapy for IPF patients through the analysis of clinical data, BALF, and lung tissue specimens	University of California, Los Angeles
Pirfenidone open-label phase 3 (PIPF-012)	Anti-fibrotic, antioxidant, and anti-inflammatory	603	Adverse events, clinical lab tests, early discontinuations, death	InterMune
Pirfenidone safety and efficacy phase 2 (PF/IPF)	Anti-fibrotic, antioxidant, and anti-inflammatory	90	Adverse events, clinical lab tests, directed physical exams	InterMune

^a From <http://clinicaltrials.gov>, accessed 21 Dec 2010

Management Strategies for Potential Comorbidities in IPF

The current absence of an FDA approved treatment for IPF does not, however, preclude good management of IPF comorbidities.

Coronary Artery Disease While the prevalence of coronary artery disease in patients between 55 and 64 years of age in the US is 13.1% for men and 8.4% in women [37, 38], the prevalence of coronary artery disease was 65.8% in IPF patients compared to 46.1% of chronic obstructive pulmonary disease patients in one study based on left-heart catheterization studies [38]. Significant disease was found in 28.8% of IPF patients, and 18% of IPF patients were found to have unsuspected significant coronary artery disease. IPF patients with significant coronary artery disease had a median survival of 572 days from the time of left-heart catheterization, significantly worse than those with no or non-significant coronary artery disease ($p < 0.003$). These findings appeared to be independent of commonly recognized coronary risk factors and suggest that aggressive diagnostic and therapeutic intervention for coronary artery disease in IPF may impact survival.

Pulmonary Hypertension Lettieri et al. [39] found that pulmonary hypertension was common, with 31.6% of their

IPF patients demonstrating this finding. The 1-year mortality rate was significantly higher at 28% in this group compared to 5.5% in IPF patients without pulmonary hypertension ($p=0.002$). A low DLco (<40%), use of supplemental oxygen, or poor 6-min walk performance suggested underlying pulmonary hypertension, whereas FVC and TLC did not. Recommendations for targeted therapy with vasoactive drugs such as phosphodiesterase-5 inhibitors, prostacyclin analogues, and endothelin-1 receptor antagonists will depend on the results of current and future clinical trials using these therapies in IPF patients and also in the subgroup of IPF patients with pulmonary hypertension. Supplemental oxygen should continue to be prescribed according to standard-of-care guidelines based on oxygenation status (oxygen saturation $\leq 88\%$ or chronic stable $PO_2 \leq 55$ mmHg) [40].

Gastroesophageal Reflux Disease (GERD) Raghu et al. showed abnormal esophageal reflux in 87% of 65 IPF patients using 24-h pH monitoring and esophageal manometry. However, only 47% of IPF patients demonstrated classic GERD symptoms. No correlation between IPF severity and GERD severity was found [7]. The authors concluded that repeated micro-aspiration of acid droplets from GERD may at least contribute to the progressive fibrosis in IPF, thus suggesting that optimal therapy of GERD may be of potential benefit in IPF.

Table 3 Active clinical trials of IPF treatment OPEN to new recruitment^a

Treatment arm(s)	Mechanism of action	Enrollment goal (n)	Primary outcome measure	Sponsor
Losartan pilot study	Angiotensin II receptor antagonist	25	Stable or improved forced vital capacity (FVC) response at 1 year	H. Lee Moffitt Cancer Center and Research Institute
CNTO 888 vs. placebo phase 2	Anti-CLL2 human monoclonal antibody	120	Pulmonary Function Safety and efficacy	Centocor, Inc.
Sildenafil, losartan or both vs. placebo phase 2/3	Phosphodiesterase type-5 inhibitor/angiotensin II receptor antagonist	40	6 minute walk test and Quality of Life Score	University of Iowa
Warfarin vs. placebo phase 3 (ACE-IPF)	Anticoagulant	256	Time to death, non-bleeding/non-elective hospitalization, or >10% drop in forced vital capacity.	National Heart, Lung, and Blood Institute (NHLBI)
Ambrisentan vs. placebo phase 3 (ARTEMIS-IPF)	Endothelin A receptor antagonist	225	Time to death or disease progression	Gilead Sciences, Inc.
Azathioprine, prednisone, and n-acetylcysteine (NAC) vs. NAC vs. placebo phase 3 (PANTHER-IPF)	Immunosuppressive/antiinflammatory/antioxidant	390	Change in serial forced vital capacity	National Heart, Lung, and Blood Institute (NHLBI)
CC930 vs. placebo phase 2	c-Jun N-terminal kinase (JNK) inhibitor	36	Evaluate the type, frequency, severity, and relationship of adverse events to CC-930	Celgene Corp.
Ambrisentan vs. placebo phase 3 (ARTEMIS-PH)	Endothelin-A receptor antagonist	600	Change in 6-minute walk distance	Gilead Sciences, Inc.
Bosentan phase 4	Dual endothelin receptor antagonist	50	6 minute walk distance in the peri-lung transplant setting in IPF patients with either resting or exercise PAH.	University of California, Los Angeles
Treprostinil phase 3	Prostacyclin analogue	20	6 minute walk distance in IPF patients with severe PAH.	University of California, Los Angeles
Sildenafil vs. placebo pilot study phase 4	Phosphodiesterase type-5 inhibitor	50	6 minute walk distance in patients with PAH secondary to IPF:	University of California, Los Angeles
Interferon-alpha lozenges phase 2	Angiogenesis inhibitor	80	Frequency/severity of cough in patients with COPD or IPF	Amarillo Biosciences, Inc.
Thalidomide phase 3	Immunosuppressive and anti-angiogenic agent	20	Efficacy of thalidomide in suppressing chronic cough in IPF.	Johns Hopkins University
Pomalidomide phase 2	Immunomodulatory agent	20	Cough related QOL as measured by Cough-Specific Quality of Life instrument (CQLQ)	Stanford University

^a From <http://clinicaltrials.gov>, accessed 21 December 2010

Sleep Disorders Recently obstructive sleep apnea (OSA) has been demonstrated to be common in IPF patients and underrecognized by both primary care providers and specialists. Its presence may contribute to the development of pulmonary arterial hypertension in these patients. In a study of 50 IPF patients with a mean age of 64.9 years and a mean body mass index (BMI) of 32.3, nocturnal polysomnography revealed OSA in 88% of subjects, of which 34 patients (68%) had moderate-to-severe OSA (apnea–hypopnea index >15 events per hour) [41]. In comparison, OSA occurs in only about 20% of older adults [42]. The Sleep Apnea Scale of Sleep Disorders Questionnaire showed improved sensitivity and specificity (88% and 50%, respectively) when compared to the Epworth Sleepiness Scale questionnaire (75% and 15%, respectively). The BMI correlation with the apnea–hypopnea index was weak ($r=0.30$; $p=0.05$). It is possible that an inverse relationship between FVC in the supine position and the severity of sleep apnea may exist. Most if not all patients with IPF should therefore be strongly considered for OSA screening using polysomnography.

Pulmonary Rehabilitation Such exercise training helps improve aerobic capacity, peripheral muscle conditioning and flexibility, and together with psychosocial support, can contribute to an improved functional status and desensitization to the sensation of dyspnea. Ferreira et al. [43] found a statistically significant difference in both the Borg score and 6-min walk test after pulmonary rehabilitation ($p<0.0001$) in ILD patients. The baseline 6-min walk test distance also significantly predicted the post-pulmonary rehabilitation change in 6-min walk test distance, with maximal benefit in patients with poorer functional status. Pulmonary rehabilitation is now likely to be of benefit in patients with interstitial lung disease.

The patient illustrated in the case above is admitted via the Emergency Department 3 months later, complaining of semi-acute worsening breathlessness for 3 weeks prior to admission. No fevers, cough, purulent phlegm, or night sweats are noted. She is intubated and mechanically ventilated for refractory respiratory failure. A CT angiogram of the chest shows new bilateral ground-glass infiltrates with an underlying chronic UIP pattern, but no pulmonary emboli. Bronchoscopy is negative for infection and malignancy. An echocardiogram reveals a left ventricular ejection fraction of 68%. She is placed empirically on high-dose corticosteroid therapy together with broad-spectrum antibiotics. The patient's condition stabilizes. She subsequently undergoes lung transplantation.

Acute Exacerbation of IPF This is the most likely diagnosis in the patient illustrated above, after other major causes in the differential diagnosis (infection, malignancy, heart

Table 4 Current diagnostic criteria for an acute exacerbation of IPF^e

Diagnostic criteria
Previous or concurrent diagnosis of idiopathic pulmonary fibrosis ^a
Unexplained worsening or development of dyspnea within 30 days
High-resolution computed tomography with new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with usual interstitial pneumonia pattern ^b
No evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage ^c
Exclusion of alternative causes, including the following: • Left heart failure • Pulmonary embolism • Identifiable cause of acute lung injury^d
Patients with idiopathic clinical worsening who fail to meet all five criteria due to missing data should be termed “suspected acute exacerbations”
^a If the diagnosis of idiopathic pulmonary fibrosis is not previously established according to American Thoracic Society/European Respiratory Society consensus criteria [2], this criterion can be met by the presence of radiologic and/or histopathologic changes consistent with usual interstitial pneumonia pattern on the current evaluation
^b If no previous high-resolution computed tomography is available, the qualifier “new” can be dropped.
^c Evaluation of samples should include studies for routine bacterial organisms, opportunistic pathogens, and common viral pathogens
^d Causes of acute lung injury include sepsis, aspiration, trauma, reperfusion pulmonary edema, pulmonary contusion, fat embolization, inhalational injury, cardiopulmonary bypass, drug toxicity, acute pancreatitis, transfusion of blood products, and stem cell transplantation
^e Reprinted by permission from Collard et al., Am J Respir Crit Care Med, Vol. 176. pp 636–643, 2007

failure, and pulmonary embolism) have been excluded. The current diagnostic criteria for an acute exacerbation of IPF are delineated in Table 4 [44]. Acute exacerbation of IPF appears unrelated to the severity of pulmonary function derangement, and most commonly shows diffuse alveolar damage superimposed on the underlying UIP [44, 45]. Its incidence remains unknown, but is likely approximately 5% to 19% of patients per year [46]. While its etiology remains unknown, Kim et al. found the in-hospital mortality rate to be 78%, and that it commonly recurred, often resulting in death [45]. No data from randomized controlled trials exist regarding effective treatment for acute exacerbation of IPF. In a single study however, pulse corticosteroids followed by cyclosporine A ($n=7$, mean age 64 years) helped to increase survival and prevent re-exacerbation (survival up to 208 weeks) compared to corticosteroids alone ($n=6$, mean age 71 years, survival up to 66 weeks) [47]. However, at this time, no known effective therapies for acute exacerbation of IPF exist. Under these circumstances, IPF patients may proactively consider palliative care in case such a situation arises.

Palliation IPF patients with end-stage disease who decline or are unsuitable to undergo lung transplantation, including the frail and elderly, may benefit from palliative hospice management with low-dose opioids to reduce breathlessness. Such therapy can be successful without a concomitant significant fall in the oxygen saturation level [48].

Conclusion

The pathogenesis of IPF, a disease of the elderly, may be related to abnormal fibroblast response mechanisms. The precipitating factors remain unclear. Despite the current absence of an FDA-approved treatment for IPF, early and accurate diagnosis of IPF often enables effective management of its comorbidities, enhancing quality of life. A high index of suspicion is therefore important for the possible diagnosis of IPF in the appropriate clinical setting. The results of ongoing and new clinical trials in the treatment of this disease suggest a multifactorial approach utilizing combined therapies [5]. Together with recent advances in the understanding of its biochemistry and pathophysiology, it is expected that significant breakthroughs will ensue in the future.

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