

Pulmonary Fibrosis

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Summary

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing lung disease limited to the lungs and associated with the histologic appearance of usual interstitial pneumonia (UIP) on surgical lung biopsy. The estimated prevalence in the United States is between 35,000 and 55,000 cases, and evidence suggests that the prevalence is increasing for IPF. Risk factors associated with pulmonary fibrosis include smoking, environmental exposures, gastroesophageal reflux disease, commonly prescribed drugs, diabetes mellitus, infectious agents, and genetic factors. The diagnosis requires a careful history and physical examination, characteristic physiological and radiological studies, and, in some cases, a surgical lung biopsy. The natural history of IPF is not known, but evidence supports the concept of a continuum of idiopathic interstitial pneumonias that may overlap in time. Most patients with IPF succumb to respiratory failure, cardiovascular disease, lung cancer, pulmonary embolism, infection, and other health problems. The median survival time for patients with IPF is less than 3 yr. Factors that predict poor outcome include older age, male gender, severe dyspnea, history of cigarette smoking, severe loss of lung function, appearance and severity of fibrosis on radiological studies, lack of response to therapy, and prominent fibroblastic foci on histopathologic evaluation. Conventional therapy (corticosteroids, azathioprine, cyclophosphamide) provides only marginal benefit. Lung transplantation should be considered for patients with IPF refractory to medical therapy. In light of the poor prognosis and lack of response to available anti-inflammatory therapy, alternative approaches to therapy are being pursued. Emerging strategies to treat patients with IPF include agents that inhibit epithelial injury or enhance repair, anticytokine approaches, agents that inhibit fibroblast proliferation or induce fibroblast apoptosis, and other novel approaches.

Key Words: Idiopathic pulmonary fibrosis; pulmonary fibrosis; interstitial lung disorders; idiopathic interstitial pneumonias; diffuse interstitial pneumonia; occupational lung disease; hypersensitivity pneumonitis; cryptogenic fibrosing alveolitis; connective tissue disorders and lung involvement.

1. Introduction

The diagnosis and management of idiopathic interstitial pneumonias (IIPs) remains a challenge to the clinician. Recently, there have been substantial

From: Methods in Molecular Medicine, Vol. 117: Fibrosis Research: Methods and Protocols
Edited by: J. Varga, D. A. Brenner, and S. H. Phan © Humana Press Inc., Totowa, NJ

changes in our understanding and approach to these diseases. With greater comprehension of the clinical relevance of the different histopathological subgroups that make up the idiopathic interstitial pneumonias, the term idiopathic pulmonary fibrosis (IPF) is now reserved to patients with idiopathic usual interstitial pneumonia (UIP) on surgical lung biopsy. The following review will provide an updated discussion of the epidemiology, risk factors, diagnosis, natural history, morbidity and mortality, prognosis, and conventional therapy of IPF, as well as emerging strategies for the treatment of patients with this disease.

2. Epidemiology

The true prevalence of IPF, also known as cryptogenic fibrosing alveolitis (CFA), is unknown. Despite the poor quality of the data and the changes in diagnostic criteria and classification, there is evidence suggesting that IPF is increasing (1). There are approx 3 to 20.2 cases of IPF per 100,000 in the general population (1–5). The prevalence increases with older age, history of smoking, and male gender (3,4,6). In a population-based study in Bernalillo County, New Mexico, the prevalence for adults from age 35 to 44 yr was 2.7 per 100,000, but surpassed 175 per 100,000 for individuals older than 75 yr (3). The prevalence of IPF is higher in men (20.2 cases per 100,000) than in women (13.2 cases per 100,000) (3). The estimated prevalence in the United States is between 35,000 and 55,000 cases (3).

The incidence of IPF is estimated at 10.7 cases per 100,000 per year for males and 7.4 cases per 100,000 per year for females (3).

Vital statistics figures are limited and incomplete. In 1988, there were 30,000 hospitalizations and 4851 deaths in the United States owing to pulmonary fibrosis (compared with 665,000 hospitalizations owing to chronic obstructive pulmonary disease and asthma). In Japan, the mortality rate for IPF per 100,000 population was estimated to be 3.3 in men and 2.5 in women, with an overall rate of 3.0 in both sexes (4). In the United Kingdom, the annual number of deaths from IPF increased twofold between 1979 and 1988. The age-adjusted rate of pulmonary fibrosis among deceased in the United States increased from 48.6 per 100,000 in 1979 to 50.9 per 100,000 in 1991 in males, and from 21.4 per 100,000 in 1979 to 27.2 per 100,000 in 1991 in females (7). Pulmonary fibrosis listed as a cause of death increased from 40% in 1979 to 56% in 1991. In the United States, the age-adjusted mortality rates are highest in the western and southwestern states and lowest in the midwest and northeast. In the United Kingdom, highest mortality rates are found in industrialized areas of England and Wales (7,8).

3. Risk Factors

3.1. Smoking

In case-control studies, smoking has been identified as a possible risk factor for IPF with an odds ratio (OR) of 1.6 (95% confidence interval [CI] 1.1–2.4) for ever-smoking, and 1.9 (95% CI 1.3–2.9) for former-smokers (4,9,10). Smokers of 21 to 40 pack-years have an OR of 2.3 (95% CI 1.3–3.8) for pulmonary fibrosis (9). In a recent study in Japan, the adjusted odds ratio for cigarette smoking was estimated at 5.40 (95% CI 2.30–12.66) (11). Interestingly, three studies reported improved survival among current or former smokers with UIP compared to never-smokers (12–14). However, others found no such effect (15–17). It is possible that the apparent protective effect of cigarette smoking may relate to the following: lead time bias; alterations in the balance of proteinases and antiproteinases that would influence net deposition of extracellular matrix in the lung; or inhibitory effects of cigarette smoke on lung fibroblast proliferation and chemotaxis (12,18).

3.2. Gastroesophageal Reflux

Instillation of acid in several animal models results in aspiration-induced lung injury and pulmonary fibrosis (19). Clinical data suggest that a high percentage of patients with IPF have clinically silent gastroesophageal reflux disease (GERD) (19,20). Small tracheobronchial aspirations of gastric acid may play a role in the pathogenesis of IPF; however, a causal relationship has not been established (19,20). Investigators at the University of Washington Medical Center are conducting an ongoing prospective study of 65 patients with IPF. Interim results indicate that the prevalence of IPF patients with GERD is 95%, with only 40% of patients reporting symptoms (19). However, the peripheral pattern of UIP in the lung would be unusual if GERD was truly the cause, as compared with an association.

3.3. Commonly Prescribed Drugs

In one case-control study, IPF was associated with exposure to antidepressants with an OR of 1.79 (95% CI 1.09–2.95), and specifically to imipramine (OR of 4.79 [95% CI 1.50–15.3]), dothiepin OR of 2.37 [95% CI 0.99–5.69], and mianserin OR of 3.27 [95% CI 1.11–9.61]. These associations were independent of smoking and occupational dust exposure. The authors concluded that exposure to antidepressants may be responsible for approx 10% of cases of IPF seen in their population. No significant association was noted between IPF

and the other drug groups tested (anticonvulsants, β -blockers, antibiotics, and nonsteroidal anti-inflammatory drugs [NSAIDs]) (21).

3.4. Diabetes Mellitus

In a recent study, clinical and demographic data were extracted from medical records of 65 consecutive patients with IPF admitted to a Japanese hospital. IPF was associated with diabetes mellitus (DM) with an OR of 4.06 (95% CI 1.80–9.15). The authors concluded that DM might be a risk factor for IPF (11).

3.5. Environmental Exposures

The etiology of IPF is unknown, but environmental factors may play a causative role. Metal and wood dust environments may be important risk factors for pulmonary fibrosis. In one study, metal dust exposure was identified as a risk factor with an odds ratio (OR) of 1.11 (95% CI 1.06–1.16), and wood dust exposure with an OR of 1.12 (95% CI 1.02–1.24). In that study, metal and wood dust exposure may have caused up to 13% and 10% of pulmonary fibrosis cases, respectively. Dust containing brass, lead, cobalt, aluminum, zinc, cadmium, mercury, and pine dusts were associated with pulmonary fibrosis (10).

Certain occupations may predispose to pulmonary fibrosis. In one study, farming was identified as a potential risk factor with an OR of 1.6 (95% CI 1.0–2.5) and exposure to livestock was associated with an OR of 2.7 (95% CI 1.3–5.5). Hairdressing was linked to pulmonary fibrosis with an OR of 4.4 (95% CI 1.2–16.3), metal dust exposure with an OR of 2.0 (95% CI 1.0–4.0), raising birds with an OR of 4.5 (95% CI 1.6–14.1), stone cutting/polishing with an OR of 3.9 (95% CI 1.2–12.7), and vegetable/animal dust exposure with an OR of 4.7 (95% CI 2.1–10.4) (22).

3.6. Infectious Agents

A number of viruses have been associated with pulmonary fibrosis, but true cause-effect relationships remain unproven. A serological survey found an association between active Epstein-Barr virus (EBV) infection and IPF (23). Egan and colleagues reported immunohistochemical evidence of EBV-productive cycle antigens in type II alveolar epithelial cells in IPF (24). Subsequently, these investigators detected EBV DNA by polymerase chain reaction (PCR) in the lung tissue of patients with IPF (25). Further study demonstrated that productive EBV replication is common in IPF and it is not associated with immunosuppressive therapy (26). Tang and co-workers detected one or more of four herpesviruses (cytomegalovirus [CMV], EBV, human herpesvirus 7 [HHV-7], and human herpesvirus 8 [HHV-8]) in 97% of patients with IPF and 36% of controls, suggesting that a herpesvirus could be a source of chronic antigenic

stimulation in IPF (27). Relatively high prevalence of serum antibodies to hepatitis C was demonstrated in patients with pulmonary fibrosis, but this finding was not confirmed in other studies (28–30). Adenovirus DNA was found in transbronchial lung biopsies (TBBx) from patients with IPF, and it was more prevalent in IPF patients treated with corticosteroids (67%) than in those who were not (10%), suggesting that this virus may newly infect or reactivate following corticosteroid therapy (31). A higher incidence of influenza (32–34), parainfluenza (35,36), CMV (37), human immunodeficiency virus (HIV)-1 (38), measles (39), herpes simplex virus-6, Mycoplasma, and Legionella has been reported in IPF (23,24,30,40).

In a recent study, human T-lymphotropic virus type I (HTLV-I) positive IPF patients had more affected lung parenchyma, demonstrated traction bronchiectasis with honeycomb change, and exhibited increased levels of specific cytokines that correlated with activated T-cells in the bronchoalveolar lavage fluid (BALF). These findings suggested that HTLV-I infection might contribute to the development of IPF via activation of T-cells (41). The latent nature together with episodic reactivation of many of these viruses may provide a scenario for the concept of “multiple hits” host defense followed by repair that these patients may experience during the course of their disease.

3.7. Genetic Factors

The genetics of familial IPF have not been elucidated. An autosomal dominant trait with variable penetrance may account for approx 70% of cases; there is no clear mode of transmission in the remaining 30% (2,42). Investigators have linked IPF to an increase in MZ phenotype for α 1-antitrypsin inhibition on chromosome 14 (43–45). Using a candidate gene approach, researchers identified surfactant protein C gene mutations in large familial pulmonary fibrosis kindred, including adults with UIP and children with nonspecific interstitial pneumonia (NSIP) (46). In a separate study, Selman and co-workers demonstrated that Surfactant protein A and B genetic variants predispose to IPF (47). Genetic polymorphisms for interleukin-1 receptor antagonist (IL-1ra) and tumor necrosis factor (TFN)- α appear to be important in determining risk (48). In contrast, transforming growth factor (TGF)- β polymorphisms do not predispose to IPF, but these polymorphisms may affect the course of the disease (49).

It is unknown what proportion of IPF is familial, but it is estimated that 0.5 to 2.2% of cases have a genetic basis (42). Thirty-eight families affected by pulmonary fibrosis have been identified and are currently under active investigation. The familial aggregation in those families is consistent with a genetic basis in at least a subset of patients with IPF (50).

4. Diagnosis

IPF is a specific form of chronic fibrosing interstitial pneumonia limited to the lungs and associated with the histological pattern of UIP on surgical lung biopsy (2). Many earlier studies included various other idiopathic interstitial pneumonias under the term idiopathic pulmonary fibrosis, but the clinical term IPF is now reserved to patients with idiopathic UIP.

4.1. History and Physical Examination

The diagnostic approach to any patient with diffuse lung disease must include a thorough history and physical examination with attention to symptoms or signs suggestive of a connective tissue disease, occupational or environmental exposures, use of fibrogenic drugs, and family history of pulmonary fibrosis. Patient age at disease onset is generally between 50 and 70 yr of age and IPF is more common in males than females. IPF typically presents insidiously, with gradual onset of a nonproductive cough and dyspnea (2). Patients are often treated for other conditions such as congestive heart failure, “walking pneumonia,” bronchitis, or asthma before the diagnosis is made. The physical examination in most patients (>80%) reveals fine bibasilar inspiratory crackles (“Velcro rales”), and clubbing is noted in up to 50% of patients (51,52). Signs of right heart failure are evident in advanced cases (2).

4.2. Laboratory and Serological Tests

Laboratory abnormalities are mild and nonspecific. One early study described “autoimmune factors” in blood of 8 patients (4 of whom had autoimmune-associated diseases) among 17 patients with diffuse fibrosing alveolitis (53). A positive rheumatoid factor occurred in 3 of 20 patients with unexplained pulmonary fibrosis and positive antinuclear factor in the serum (ANA) (54). A later study examined serum specimens from 122 patients with IPF and compared them with specimens from age- and sex-matched controls; ANAs were present in 21% of patients with IPF and in 6% of the control subjects (55). Positive circulating ANAs or rheumatoid factor occur in 10% to 20% of patients with IPF, but titers are rarely high (2,53,54,56). An elevated erythrocyte sedimentation rate, lactate dehydrogenase, or hypergammaglobulinemia may be found in patients with IPF, but are nondiagnostic (2). Serological findings do not correlate with extent or severity of disease, and have no prognostic value (2,57). In the absence of symptoms of connective tissue disease, the presence of autoantibodies does not imply an underlying systemic disorder. Recently, investigators reported the occurrence of low fasting triglyceride and high free fatty acid levels in patients with pulmonary fibrosis. Because insulin-like growth factor (IGF)-I is known to lower triglycerides and increase free fatty

acids, the authors hypothesized that the reported increased production of IGF-I in patients with IPF may explain such findings (58).

4.3. Radiological Studies

4.3.1. Chest Radiograph

Classic chest radiographic findings in IPF include a basal predominant reticular, or reticulonodular, pattern associated with decreased lung volumes, and in later stages, cystic areas representing honeycomb (HC) lung (2,59–61). When a “confident” diagnosis of IPF is made on the basis of the chest radiograph, it is correct in 48 to 87% of cases (60,62,63). Most patients with IPF will have an abnormal chest radiograph but, rarely, patients may present with a normal plain film (2). It is important to review all previous chest films to assess the rate of change in disease activity. In addition, radiographs are indicated if clinical deterioration occurs in order to identify superimposed infection or malignancy (2,64). Pleural effusions, upper lobe predominant disease, air-bronchograms, or prominent lymphadenopathy should suggest an alternative diagnosis.

4.3.2. High-Resolution Chest Computed Tomography

Typical high-resolution chest computed tomography (HRCT) features of IPF/UIP include patchy, predominantly peripheral, subpleural, and symmetrical bibasilar honeycombing, reticular abnormalities, and limited “ground-glass” opacities (GGO) (65–68). Several studies have shown that experienced radiologists can make a “confident” diagnosis of UIP with specificity greater than 95%, provided CT features are typical (65,69–72). Although a characteristic HRCT is highly specific for IPF/UIP, “typical” HRCT identifies only 37 to 67% of patients with histological UIP; therefore, a surgical lung biopsy (SLB) is recommended when clinical and radiological information result in an uncertain diagnosis (14,65,70,73). One study evaluated the proficiency of physicians with expertise in interstitial lung diseases to identify accurately the HRCT scans from patients with biopsy-proven IPF/UIP. When these investigators made a “confident” diagnosis of IPF based on HRCT scan and clinical data, they were right in more than 80% of the cases. However, more than half of the patients with IPF had an uncertain diagnosis on the basis of HRCT and clinical assessment (70). In a subsequent analysis of these data, investigators identified HRCT features associated with a pathological diagnosis of UIP. On multivariate analysis, lower lobe honeycombing (OR, 5.36), and upper-lung irregular lines (OR, 6.28) were the only independent predictors of UIP. When they combined those two factors, a diagnosis of UIP was established with a sensitivity of 74%, a specificity of 81%, and a positive predictive value of 85%

(65). Interestingly, in that study, adenopathy was observed in 55% and 21% of patients with UIP and without UIP, respectively. This finding suggests that patients with IPF generate a marked lymphoproliferative response to an unknown antigen or antigens; we believe that this observation requires further investigation as it may provide important clues to further our understanding of the pathogenesis the disease. In a separate study, two radiologists independently assessed CT scans from a cohort of patients with either UIP. CT features were “typical” for UIP in only 37% patients, and all of them had histological UIP on SLB. Typical CT features of UIP are associated with advanced, late-stage disease. Among patients with earlier phases of UIP, CT features may be atypical (74) or indeterminate (69).

Extensive GGO is not a major feature of UIP, and suggests an alternative diagnosis such as desquamative interstitial pneumonia (DIP), NSIP, lymphocytic interstitial pneumonia (LIP), cryptogenic organizing pneumonia (COP), hypersensitivity pneumonia (HP), or pulmonary alveolar proteinosis (PAP) (75). In contrast, honeycomb change is a cardinal feature of UIP, and is rare in other IIPs (71,76).

4.4. Physiological Studies

4.4.1. Pulmonary Function Testing

Pulmonary function tests (PFTs) characteristically reveal a restrictive ventilatory defect with impaired gas exchange; however, smokers may have preserved lung volumes or airflow obstruction in the initial stages of the disease (2,77,78). Impairments in gas exchange (i.e., carbon monoxide diffusing capacity [DL_{CO}]) and oxygenation may be evident early in the course of the disease, even when spirometry and lung volumes are normal (79). The most appropriate and simple tests are vital capacity and DL_{CO} ; these are most useful for assessing the extent and monitoring the progression of the disease (80).

4.4.2. Exercise Testing

Cardiopulmonary exercise testing (CPET) demonstrates hypoxemia, widened A-a O_2 gradient, submaximal exercise endurance, reduced oxygen consumption (VO_2), high respiratory frequency, low tidal volume (V_T) breathing pattern, increased dead space (V_D/V_T), increased minute ventilation for the level of VO_2 , and a low O_2 pulse (80–82). Arterial desaturation and abnormal widening of A-a O_2 gradient with exercise may be elicited with relatively simple tests, such as the 6-min walk test (83,84).

4.5. Bronchoalveolar Lavage Fluid

BALF may play a role in the diagnosis of inorganic dust diseases, suspected malignancy, infections, some hematological disorders, drug-induced diseases,

pulmonary alveolar proteinosis, Langerhans' cell histiocytosis, and alveolar hemorrhage (85). BALF is useful in research studies but of limited clinical application when evaluating IIPs (85). Increases in polymorphonuclear leukocytes, eosinophils, mast cells, alveolar macrophages, and countless cytokines are noted in BALF from patients with IPF/UIP; lymphocyte numbers are usually normal (2). BALF neutrophilia is present in 67 to 90% of patients with IPF/CFA (86,87), but does not predict prognosis or therapeutic responsiveness. Elevations in BALF eosinophils were associated with more severe clinical impairment (86,87), but BALF eosinophil counts do not correlate consistently with prognosis (86,87). By contrast, the presence of BALF lymphocytosis, found in fewer than 15% of cases, was associated with a greater responsiveness to corticosteroid therapy, a more cellular biopsy, and less honeycombing (86,87). Data compiled from two studies documented favorable responses to corticosteroids in 12 of 13 patients exhibiting BALF lymphocytosis, but in only 4 of 37 without lymphocytosis (86,87). Because the studies citing BALF lymphocytosis in steroid-responsive patients with IPF (87) or CFA (86) antedated the description of NSIP, it is possible that BALF lymphocytosis reflects disorders distinct from UIP (such as cellular NSIP). Nevertheless, in a recent study, researchers hypothesized that BALF findings may distinguish between UIP and NSIP; BALF total and differential cell counts were not different between the two groups, and in neither group, were BALF findings predictive of survival or changes in lung function (88).

4.6. Biopsy

The American Thoracic Society (ATS) and the European Respiratory Society (ERS) in collaboration with American College of Chest Physicians (ACCP) published an international consensus statement on the diagnosis and treatment of IPF. This statement stated that the definite diagnosis of IPF requires an SLB showing the UIP pattern. However, an SLB is not recommended in patients with suspected IPF in whom the clinical or radiographic information are stereotypical of IPF/UIP. It has been suggested that, in the absence of an SLB, the presence of all four major diagnostic criteria and at least three minor criteria increases the likelihood of an accurate diagnosis of IPF/UIP (2). However, these criteria have not been prospectively validated.

An SLB, preferably by video-assisted thoracoscopy (VATS), is recommended in patients with suspected IPF in whom the clinical or radiographic information are not typical of IPF/UIP (2). Given the patchy and heterogeneous nature of the UIP lesion, a large piece of lung tissue is required and TBBx are used mainly to rule out other disorders that mimic IPF. However, emerging data suggest that TBBx findings may be more useful in diagnosing UIP than previously recognized; characteristic histological features of UIP (interstitial fibrosis with fibroblastic foci [FF] and/or HC change) can be

appreciated even in a small sample obtained by TBBx; these findings in a patient with characteristic clinical and radiographic features may indicate a diagnosis of UIP. However, these findings require prospective validation (89).

Significant advances have been made in our understanding of the idiopathic interstitial pneumonias (IIPs). The most important advancement has been the greater appreciation of the clinical relevance of the different histopathological subgroups that make up the IIPs. Until recently, inflammatory or fibrotic lung disorders of unknown etiology were “lumped” under the term IPF (2,75,90). However, with the advent of VATS lung biopsies and the greater availability and quality of surgical specimens, pathologists have recognized the heterogeneous nature of these disorders and described specific histopathological patterns that predict response to therapy and survival (74,91,92). IPF/UIP is the most common of the IIPs, comprised of 47 to 71% of the cases (76,91,93,94). The UIP lesion is characterized by temporal and geographic heterogeneity, with areas of old scar and HC change, admixed with granulation tissue and normal lung; the lesion has predilection for the subpleural and basilar regions of the lung, there is scant inflammation, and prominent aggregates of fibroblast and myofibroblasts, so-called “fibroblastic foci,” which actively secreting extracellular matrix (75,92,95). Additional features include smooth muscle hypertrophy, metaplasia and hyperplasia of type II pneumocytes, destroyed and disrupted alveolar architecture, traction bronchiectasis and bronchiolectasis, and secondary pulmonary hypertension changes (75,92,95).

Other categories of IIP that must be distinguished from IPF/UIP include NSIP, DIP, respiratory bronchiolitis-associated interstitial lung disease (RBILD), acute interstitial pneumonia (AIP), COP, and LIP (75). NSIP is observed in approx 25% of patients with IIP (75). This provisional category is used to describe a temporally homogeneous lesion with varying degrees of inflammation and fibrosis with favorable response to therapy and prognosis. NSIP can be subdivided into NSIP-cellular and NSIP-fibrotic varieties depending on the degree of inflammation and fibrosis present in the surgical specimen (93). This subclassification provides important prognostic information; patients with idiopathic NSIP, cellular pattern have a better 5- and 10-yr survival than those with idiopathic NSIP, fibrosing pattern (100% vs 90% and 100% vs 35%, respectively) (93).

In many patients, however, histological overlap between UIP and NSIP is evident. Flaherty and co-workers reviewed SLBs from 109 patients with IIP who had multiple lobes biopsied and reported histopathological variability between lobes in 26% of patients. Importantly, in that study, UIP in at least one lobe defined prognosis (94). In a later study, the pathological findings in biopsy and subsequent explant specimens from 20 patients with UIP were reviewed to

refine histological criteria and to assess the relationship between UIP and NSIP. The important new finding was that NSIP-like areas were present in the majority of UIP patients (80%) in both biopsy and explants specimens, and in some, these areas were extensive, making accurate diagnosis of UIP difficult (cases were misdiagnosed as NSIP). The most useful feature for diagnosing UIP in difficult cases is the presence of a distinct “patchwork” or variegated pattern of parenchymal involvement (95).

RBILD and DIP comprise approx 15% of IIPs (75). These entities are thought to be smoking-related diseases and, like NSIP, tend to be responsive to anti-inflammatory therapy. This is not surprising, as pathologically, these lesions are characterized by varying degrees of intra-alveolar and/or peribronchial pigmented macrophage infiltration with scant or no fibrosis. AIP is characterized by active fibrosis consisting of proliferating fibroblasts and myofibroblasts with minimal collagen deposition resembling the organizing stage of diffuse alveolar damage (DAD) (92). Finally within the IIPs, some include COP (previously termed bronchiolitis obliterans organizing pneumonia, or BOOP), and LIP. Both are relatively steroid-responsive lesions; pathologically, COP is characterized by the presence of intra-alveolar plugs of granulation tissue, and LIP by lymphocytic infiltration of the alveolar walls. It should be noted, however, that many experts argue that LIP should not be included within the IIPs because it is considered as lymphoproliferative disorder which, in turn, is rarely idiopathic and is mostly observed in association with infections (e.g., HIV) or collagen vascular diseases (CVDs) (75).

5. Natural History

The natural history of the pathogenesis of IPF is not known. The description of temporal heterogeneity for the histopathological entity of UIP would suggest that this process occurs over a significant period of time within the same low-power microscopic field of the lung. Moreover, the description supports the notion that the lesions are not homogeneous for both the timing of the original injury and the subsequent response to the injury and repair. In addition, the histopathological entity of UIP is not unique to IPF, and can be found in patients with connective tissue diseases, end-stage asbestosis, and end-stage hypersensitivity pneumonia. Therefore, UIP may represent an end-stage of a “process,” not the beginning, intermediate, and end-stage of a disease. The only insight into the natural history of this process comes from two recent studies that suggest the potential concept of a continuum of IIPs that may overlap in time.

In a study of 109 patients whom had multiple lobes biopsied, histological variability was evident in 26% of the patients. Patients concordant for UIP

were older (63 ± 9 yr) than those discordant for UIP (57 ± 12 yr) or with fibrotic NSIP (56 ± 11 yr) or cellular NSIP (50 ± 9 yr), suggesting that NSIP may be an early lesion that progresses with time to UIP (94). In a separate study, investigators found discordant histological diagnoses between lobes in 20% of the patients. NSIP-like reactions were evident in 80% of patients with UIP, suggesting that NSIP may evolve into UIP (95). In a genetic study, two different histopathological patterns of interstitial pneumonia were found to exist in members of a family who shared protein C gene mutations: adults with UIP and children with NSIP; this supports the notion that NSIP may be a precursor lesion to UIP (46).

It has been suggested that most patients with IPF progress in a relentless and insidious manner with a median survival of less than 3 yr (91). This concept was challenged in a recent study of subcutaneous interferon (IFN)- γ 1b (200 μ g thrice weekly) in 330 patients with mild to moderate IPF (forced vital capacity [FVC] > 50% and DL_{CO} > 30%), where a trend toward lower mortality was seen in IFN- γ 1b-treated patients compared with placebo-treated patients (96). Interestingly, there were no significant differences in lung function or gas exchange between IFN- γ 1b-treated and placebo-treated patients at 48 wk of follow-up. In both study groups, 70% of patients remained stable, 25% deteriorated, and the rest improved, suggesting that most patients with mild to moderate IPF remain stable for at least 1 yr on no specific therapy. The so-called “IPF exacerbations” may explain the trend toward lower mortality seen in this study, but this requires further study. IPF exacerbations may be defined as an accelerated deterioration of IPF in the absence of apparent infectious agents and heart failure (97,98). It is often a terminal event, with features of DAD or organizing pneumonia on lung biopsy or autopsy (99,100). This syndrome is indistinguishable from idiopathic AIP (101), and is similar to acute respiratory distress syndrome (ARDS). The factors responsible for this accelerated phase of IPF are unknown, but viral infections, high concentrations of oxygen, or drug reactions are plausible etiological factors (101).

6. Morbidity and Mortality

Only one study has addressed mechanism of mortality of patients with IPF. Panos and colleagues (102) found that most patients with IPF succumb to respiratory failure (39%), cardiovascular disease (27%), lung cancer (6–13%), pulmonary embolism (3%), infection (3%), or other health problems (18%) (102). Although infection would appear unlikely as a cause of mortality in IPF patients, clinically we can only determine the micro-organism cause of community acquired pneumonia in 30% of all patients. Therefore, we do not know the true incidence and prevalence of infection as a cause of mortality in patients

with IPF, and perhaps a significant portion of the respiratory failure mortalities had infectious etiologies. With regard to cardiovascular disease, congestive heart failure and coronary artery disease (CAD) account for 30% of deaths (102). Patients with IPF appear to be at increased risk of developing CAD. In a cross-sectional study of 630 patients referred for lung transplantation, fibrotic lung diseases were associated with an increased prevalence of CAD compared with nonfibrotic diseases after adjustment for traditional risk factors (OR 2.18; 95% CI, 1.17–4.06); the authors theorized that the fibroproliferative process may influence cells beyond the pulmonary compartment, and that mediator molecules produced in these disorders might promote atherogenesis (67).

Pulmonary arterial hypertension occurs in 70% of patients with advanced IPF and its presence correlates with a vital capacity (VC) below 50% of predicted or a DL_{CO} under 45% of predicted (102). Left ventricular (LV) dysfunction occurs in less than 10% of patients and it is mostly (66%) a result of coexisting right heart failure. Other causes of LV dysfunction include ischemic and hypertensive heart disease (5,102). Six to 13% of patients with IPF develop bronchogenic carcinoma. Lung cancer in patients with IPF typically presents as a peripheral squamous cell carcinoma in older male smokers (103). Predisposing factors include squamous metaplasia, atypical epithelial cells, or occupational exposures (13,57,102). Hubbard and colleagues, in a population-based cohort in the United Kingdom, studied 890 patients with IPF and 5884 controls. The risk ratio for IPF and lung cancer was 7.31 (95% CI 4.5–11.9). Importantly, adjusting for previous smoking had little effect on this ratio, suggesting that IPF is an independent risk factor for lung cancer (104).

Pulmonary embolism occurs in approx 3 to 7% of patients; inactivity, heart failure, bronchogenic carcinoma, and possibly corticosteroid therapy predispose patients to thrombosis (102). Pulmonary infection causes 2 to 4% of deaths in patients with IPF; immunosuppressive therapy, traction bronchiectasis, and possibly GERD are predisposing factors (102). Pneumothorax occurs in up to 10% of patients with IPF and tends to be less responsive to tube thoracostomy, often necessitating surgical intervention (102).

6.1. Complications of Therapy

Corticosteroids (CS) can cause a myriad of side effects including myopathy, peptic ulcer disease, cataracts, osteoporosis, compression fractures, fluid and electrolyte abnormalities, adrenal insufficiency, and infection (105,106). In a cross-sectional study in patients with asthma, chronic obstructive pulmonary disease, or “alveolitis” taking oral corticosteroids ($n = 367$) vs controls ($n = 734$), the OR for bone fractures was 1.8 (95% CI 1.3–2.6 [vertebral fracture OR 10, hip fracture OR 6, and ribs or sternum fracture OR 3.2]). Patients tak-

ing corticosteroids experienced more cataracts, used more antacids, had more muscle weakness, back pain, bruising, and oral candidiasis, and had fewer teeth compared with controls (**106**). One prospective study included 41 patients with IPF; 24 received 100 mg/d of prednisone for 3 mo and 17 received 60 mg/d for 1 mo followed by 40 mg/d for 2 mo. Patients were monitored monthly for steroid-related side effects. All patients experienced at least one side effect. Common side effects included insomnia (76%), cushingoid change (73%), weight gain (71%), irritability (61%), infection (49%), blurred vision (41%), abdominal bloating (34%), glucose intolerance (24%), and fractures or avascular necrosis (10%) (**105**).

Cytotoxic agents (cyclophosphamide [CP], azathioprine [AZA]) can cause infections, bone marrow suppression, hepatitis, hemorrhagic cystitis (CP) and/or malignancies (**107,108**). In a prospective uncontrolled study, 19 patients with biopsy-proven UIP who were unresponsive or intolerant to CS therapy were treated with oral CP (1–2 mg/kg/d) for 6 mo. Nearly two-thirds of patients reported adverse effects, and 50% of patients discontinued therapy because of intolerable side effects. Common side effects related to CP include nausea/vomiting (26%), anorexia (26%), cytopenias (21%), weight loss (21%), alopecia (10%), infection (Herpes zoster) (10%), and ovarian failure (5%) (**108**).

7. Prognosis

Several factors have been shown to predict poor outcome in IPF. These include older age at presentation, male gender, severe dyspnea at presentation, history of cigarette smoking, severe loss of lung function, severity of reticular opacities or honeycomb change on HRCT, characteristic HRCT appearance, lack of response to conventional therapy, and histopathological findings showing prominent FF (**2,17,69,74,109**). Investigators from the University of Michigan evaluated the impact of histological diagnosis, baseline clinical, physiological, and radiographical factors on survival in 168 patients with suspected IIP. The presence of histological UIP was the most important risk factor for mortality (risk ratio [RR] of 28.46 [95% CI 5.5–148]), followed by the presence of honeycombing on HRCT, a radiographic feature that was shown to be a good surrogate for histological UIP (sensitivity of 90%, and a specificity of 86%) (**14**). The same group evaluated the impact of HRCT appearance on survival in patients with IIP. Patients with histological UIP and stereotypical HRCT appearance of UIP had a shorter survival (median survival 2.08 yr) when compared with patients with histological UIP and indeterminate HRCT scans (median survival 5.76 yr) (**69**).

Three studies have shown that a higher HRCT-fibrosis score identify patients with worse prognosis. Gay and colleagues did not find any measure of pulmo-

nary function to be predictive of survival, but did find both the HRCT-fibrosis score and the pathological fibrosis score to be useful in predicting survival (**109**). Similarly, investigators from the United Kingdom found that baseline percent-predicted DL_{CO} and HRCT-fibrosis score were independent predictors of mortality (**110**). Japanese investigators demonstrated that the baseline HC score and the rate of HC progression were both predictive of worse survival in patients with IPF (**111**).

Histopathological findings showing prominent FF identify patients with poor outcome. Nicholson and associates retrospectively studied (**53**) patients with IPF/UIP and analyzed the prognostic significance of four specific microscopic features of UIP. Multivariate analysis revealed that increasing FF and mononuclear cell infiltrate scores were associated with worsening lung function. Higher profusion of FF and a lower DL_{CO} were independent predictors of mortality (**112**). These results supported the findings by King and co-workers, who also demonstrated that an increase in the number of FF correlated highly with mortality in patients with IPF/UIP (**13**). In a separate study, expert pathologists reviewed SLB from 108 patients with idiopathic or CVD-associated UIP and assigned a score for FF. Patients with idiopathic UIP had more FF and worse survival compared with patients with CVD-associated UIP (**113**).

A number of composite scoring systems have been developed with which to predict survival in IPF. King and co-workers studied 238 patients with IPF/UIP and derived a clinical-radiological-physiological (CRP) scoring system using clinical (age, smoking status, clubbing), radiographical (extent of interstitial opacities, presence of pulmonary hypertension on chest radiographs), and physiological parameters (reduced lung volume, abnormal gas exchange during maximal exercise). These investigators demonstrated that the CRP score correlated with important histopathological findings and was helpful in predicting survival in patients with IPF. A second abbreviated CRP scoring system that excluded Pa_{O₂} during maximal exercise was inferior in predicting survival (**12,114**). Similarly, investigators from the Brompton Hospital devised a composite physiological index (CPI) using radiographical and physiological information that predicted mortality more accurately than individual PFT in patients with IPF (**115**). Even though these composite scoring systems are accurate in their predictive ability, they are expensive and cumbersome to generate in clinical practice. With this in mind, the prognostic value of oxygen desaturation during a 6-min walking test was evaluated in patients with IPF. Desaturation defined as a fall in oxygen saturation to 88% or less during the 6-min walk test identified patients with higher mortality compared with patients who did not desaturate. The 4-yr survival rate of IPF patients who desaturated

to that level was 34.5% compared with 69.1% in patients who did not desaturate (84).

Predicting survival in IPF has been centered on baseline radiographical, pathological, and/or physiological testing. Recently, researchers have focused on the association of serial changes in pulmonary function or radiographical features and prognosis. One study determined that a decrease in FVC (>10% from baseline) during the initial 6 mo of follow-up was associated with increased mortality (hazard ratio 2.06; CI 1.09–3.89) (116). In a separate study, investigators concluded that at 6 and 12 mo of follow-up, serial pulmonary function trends (change in DL_{CO}, FVC, forced expiratory volume in 1 s [FEV₁], and the CPI) provided important prognostic information in IPF (117). A third study showed that assessment of changes in clinical and physiological variables (dyspnea score, total lung capacity, thoracic gas volume, FVC, FEV₁, DL_{CO}, pO₂, oxygen saturation, and alveolar-arterial oxygen gradient) at 6 and 12 mo provide clinicians with more accurate prognostic information than baseline values alone (118).

Serum markers and nuclear medicine testing may have a predictive role in IPF. Greene and colleagues found that serum levels of surfactant protein-A (SP-A) were predictive of survival in patients with IPF (119).

In a prospective study, investigators analyzed the usefulness of inhaled 99m-labeled diethylenetriamine penta-acetic acid ([99m] Tc-DTPA) aerosol clearance and survival in a cohort of 106 patients with UIP. Multiple stepwise Cox regression analysis identified fast clearance as an independent predictor of mortality (120).

8. Therapy

8.1. Conventional Therapy

Conventional therapy (CS, AZA, or CP) for IPF provides only marginal benefit. Unfortunately, in many studies, diagnoses were not based on the findings of lung biopsies or were not classified by current pathological criteria; thus, there is uncertainty as to the nature of the disease being treated. Two recent meta-analyses searched two large databases for randomized controlled trials (RCT) and controlled clinical trials (CCT) using CS or non-CS agents in patients with histological UIP or who fulfilled all ATS criteria for IPF; the authors could not find RCTs or CCTs evaluating CS alone in IPF and concluded that there are scant good-quality data regarding the efficacy of non-CS agents in IPF (121,122). The following is a brief discussion of anti-inflammatory (conventional) therapy in the treatment of IPF.

8.1.1. Corticosteroids

CS were the mainstay of therapy for more than four decades, but are of unproven efficacy, and are associated with significant toxicities (**105,123,124**). Early studies of patients with IPF/CFA cited response rates of 10 to 30% with CS (alone or combined with immunosuppressive agents), but complete or sustained remissions were rare (**105,125–127**). More importantly, many responders likely had IIPs other than UIP (e.g., NSIP or RBILD/DIP).

In recent studies, response rates to CS among patients with histological evidence for UIP are low (0–17%) (**16,57,74,76,123**). Large retrospective studies of patients with IPF showed no survival benefit with CS (**12; 15,123,128**). In one retrospective study from England, survival was worse among IPF patients treated with CS or CP, although this likely reflects a selection bias (**15**). Given the potential severe toxicities associated with CS (**105,124**), recent international consensus statements argue that high-dose CS should not be used to treat IPF (**2,61**). However, because anecdotal responses to CS are occasionally noted in patients with IPF/UIP (**14**), these statements acknowledge that selected patients with clinical or physiological impairment or worsening PFTs should be treated (**2,61**). Both statements (**2,61**) advocate an individualized approach to treating IPF/UIP. Among patients requiring treatment, both statements recommend combining therapy with either oral AZA or CP plus low-dose prednisone or prednisolone (0.5 mg/kg [lean body weight per d] for 4 wk, then 0.25 mg/kg for 8 wk, then 0.125 mg/kg). This represents a substantial departure from earlier regimens advocating high-dose prednisone (e.g., ≥ 1 mg/kg/d for ≥ 6 –12 wk) (**114,125,126**). Combined therapy should be continued for 6 mo in the absence of adverse effects. Treatment should be continued beyond 6 or 12 mo or later time points only if patients improve or remain stable. It should be emphasized that these recommendations (**2,61**) reflect expert opinion, but have *not* been validated in clinical trials. We believe CS should not be given to patients at high risk for adverse effects (e.g., age > 70 yr, osteoporosis, DM, extreme obesity, and so on).

8.1.2. Azathioprine

Two prospective studies evaluated AZA for IPF (**125,126**). In both studies, AZA was combined with prednisone. In the first study, 20 patients with progressive IPF were initially treated with prednisone alone for 3 mo (**125**). At that point, AZA (3 mg/kg/d) was added and both agents were continued for an additional 9 mo or longer. Twelve patients (60%) responded. The independent effect of AZA was difficult to assess, because all patients received prednisone concomitantly. In a second, double-blind trial, Raghu and associates compared the effect of AZA plus prednisone on lung function with that of prednisone

alone in previously untreated patients with IPF (the study population may have included patients with IIP other than UIP). Forty-three percent of patients randomly assigned to AZA plus prednisone died during the 9-yr follow-up period, compared with 77% of patients randomly assigned to prednisone alone. The difference became statistically significant only after adjustment for age ($p = 0.02$) (126).

8.1.3. Cyclophosphamide

Two randomized trials evaluated CP for IPF (127,129). In one 6-mo trial, 28 patients with “mid-course” IPF were randomized to prednisone alone ($n = 16$); prednisone plus oral CP (1.5 mg/kg/d) ($n = 9$); or CP alone ($n = 5$) (129). Mean BALF neutrophil counts declined in the cohort receiving CP, but PFTs did not change in any group. Johnson and colleagues compared the effect of prednisolone alone with that of prednisolone plus CP on breathlessness, radiographic appearance, and lung function in patients with IPF (the study population included patients with CVD and with IIP other than UIP). Initial improvement occurred in 7 of the 22 patients in the prednisolone-only group and in 5 of the 21 patients in the CP plus prednisolone group. However, at 36 mo, only 2 of the 22 patients in the prednisolone-only group remained improved, and only 1 of the 21 patients in the CP-prednisolone group remained improved. Life-table analysis suggested better survival in patients in the CP-prednisolone group, but this was not statistically significant (127). In a prospective uncontrolled study, Zisman and associates studied the efficacy of CP in 19 patients with biopsy-proven UIP who were unresponsive or intolerant to CS therapy. Only 1 patient improved; 7 remained stable, and 11 deteriorated. Nearly two-thirds of the patients developed drug-related side effects and one half of the patients discontinued therapy due to intolerable side effects (108). Intermittent, intravenous “pulse” CP, administered every 2 to 4 wk, has been tried for IPF refractory to CS in nonrandomized studies, but benefit was not convincing (130–132).

8.2. Lung Transplantation

Lung transplantation should be considered for patients with IPF refractory to medical therapy (133,134). Two-year survival following single lung transplant (SLT) ranges from 60 to 80%; 5-yr survival is 40 to 60% (134–136). In one study, lung transplantation reduced the risk of death by 75% (135). In addition, patients surviving lung transplantation appear to achieve considerable improvement in most dimensions of health-related quality of life (137–139). Unfortunately, owing to a shortage of donor organs, waiting time may be prolonged (up to 2–3 yr) and many patients with IPF die while awaiting transplantation (134,135). One study evaluated baseline PFT and HRCT fibrosis

scores and the relationship to 2-yr survival in patients with IPF younger than 65 yr of age; the optimal points on the receiving operator characteristics (ROC) curves for discriminating between survivors and nonsurvivors corresponded to a combination of DL_{CO} of 39% predicted with HRCT-fibrosis score of 2.25 (110). In a separate study, investigators reviewed all transplant referrals for IIP that were listed for lung transplantation at their center. The aim of the study was to determine a parameter that would discriminate between patients who survived and patients who died awaiting transplantation. The severity of hypoxemia at rest was the only significant difference between both groups (140). Unless contraindications exist, patients with severe functional impairment (e.g., FVC <60% predicted, DL_{CO} <40% predicted), oxygen dependency, and a deteriorating course refractory to medical therapy should be listed promptly for transplantation (133,134).

8.3. Antifibrotic Therapy

Historically, the fibrotic process in IPF has been thought to be preceded by a chronic inflammatory process that injures the lung and modulates fibrogenesis (141). Conventional management of IPF has been primarily based on the notion that suppressing inflammation may prevent progression to fibrosis. Evidence against the notion that inflammation plays an important role in the pathogenesis of IPF comes from the lack of correlation of most markers of inflammation with disease stage or outcome, and the recognition that inflammation is not a prominent histopathological finding in UIP (92,141). Additionally, emerging evidence suggests that inflammation is not required for the development of a fibrotic response (141). In light of the poor prognosis and lack of response to available anti-inflammatory therapy, alternative approaches to the treatment of IPF are being pursued. The following is a brief discussion of antifibrotic therapy and other promising agents in the treatment of IPF.

8.3.1. Colchicine

Colchicine is an alkaloid derivative of the plant *Colchicum autumnale*, which has been used in acute attacks of gout. It is known to bind microtubular proteins necessary for intracellular trafficking and cellular mitosis, thus adversely affecting secretion of proteins from cells and cellular proliferation (142,143). Its antifibrotic activity was described following the discovery that colchicine inhibits secretion of collagen and other important growth factors necessary for fibroblast proliferation (144). However, further studies (145) with or without additional therapeutic agents, such as steroids, failed to document efficacy of colchicine in the treatment of human pulmonary fibrosis. It is thus not currently recommended for use in therapy of IPF.

8.3.2. Penicillamine

The D-isomer of penicillamine has been extensively studied in animal models of fibrosis, in which it has been shown to prevent accumulation of collagen in the lung by interrupting cross-linking of collagen molecules (146). This observation has led to its use in treating fibrotic lung disease associated with systemic sclerosis with good results (147). However, its efficacy in the treatment of IPF has been disappointing (148), and it is known to have toxic and significant adverse effects (2). Thus it is currently not recommended as therapy for IPF.

8.3.3. Pirfenidone

Pirfenidone is a novel agent with broad-spectrum antifibrotic activity. Numerous in vitro and animal model studies have demonstrated its effectiveness as an antifibrotic agent. In vitro studies have shown that pirfenidone significantly reduced mRNA levels of type I and type III collagen, and may act at the transcriptional or translational level of collagen synthesis (149). In vivo, it has been shown to inhibit TGF- β 1-induced collagen synthesis, decrease extracellular matrix deposition, and suppress the overexpression of TGF- β in the bleomycin model of pulmonary fibrosis (150,151). Because IPF is becoming increasingly recognized as primarily a fibrotic process, the potential role of pirfenidone as a therapeutic agent is being explored.

In a prospective open-label study, Raghu and colleagues (152) treated 54 (42 biopsy-proven) consecutive patients with pirfenidone who were either unwilling to receive or unresponsive to conventional therapy. Survival rates of 78% at 1 yr and 63% at 2 yr compared favorably with historical controls. In addition, 83% of patients discontinued prednisone therapy and the remaining 17% were able to reduce their daily dose. All patients treated with immunosuppressive therapy tolerated discontinuation of the drug. Interestingly, patients whose lung function had deteriorated before enrollment appeared to stabilize after beginning pirfenidone. Side effects were relatively common, with patients reporting nausea (44%), fatigue (44%), and photosensitivity (24%). Despite these encouraging observations, the results of this study are difficult to interpret owing to the lack of appropriate controls, incomplete pre-entry and follow-up pulmonary function test data, a small study population, and a bias associated with survivorship effect (pulmonary function data of patients who died were not included in the analysis, and this could have biased the results). Furthermore, the observed steroid- and immunosuppressive-sparing effects of pirfenidone may have simply reflected lack of efficacy of conventional therapy rather than a true effect of pirfenidone. In a second open-label trial, Japanese investigators evaluated oral pirfenidone in eight patients with IPF and two with

diffuse lung disease associated with systemic sclerosis; after 1 yr of therapy, there was no change in chest radiographic scores and arterial oxygen tension; the drug was well tolerated (153). Early treatment with pirfenidone appears to slow the progression of pulmonary fibrosis in patients with Hermansky–Pudlak syndrome (154). A randomized-controlled trial focusing on early treatment is warranted to test the efficacy and safety of this agent in IPF.

8.3.4. Interferon- γ 1b

IFNs play an integral role in the regulation of fibroblast proliferation and collagen synthesis, but the mechanism by which they exert their effect is not clearly understood. Recent observations have shown that IFN- γ has antiproliferative, immunomodulatory, and antifibrotic effects (155), and thus may play a crucial role in the pathogenesis of IPF. IFN- γ decreases collagen content in the bleomycin model of lung fibrosis by inhibiting TGF- β transcription and subsequent procollagen mRNA production (156). In addition, IFN- γ inhibits fibroblast proliferation in cultures derived from normal and fibrotic human lung, making an argument that IFN- γ may have therapeutic applications (157). Lower levels of IFN- γ have been found in patients with IPF compared with patients with less fibrotic diseases such as pulmonary sarcoidosis (158). Kuroki and associates (159) measured levels of type III collagen in patients with progressive pulmonary fibrosis and found an inverse correlation with IFN- γ levels, particularly in patients with IPF. These studies suggest that patients with IPF may have a defect in IFN- γ production or function, which predisposes them to develop fibrosis following injury. However, the potential for developing fibrosis is not likely to be dependent on one factor; rather it is likely the result of a complex interplay of fibrotic mediators, differential gene expression, and feedback mechanisms. A study by Shaw and colleagues (160) showed that alveolar macrophages from patients with interstitial lung disease had increased production of platelet-derived growth factor, which is a potent mitogen for fibroblasts. This increase in platelet-derived growth factor was upregulated following treatment with IFN- γ , suggesting that IFN- γ may act to potentiate fibrosis in certain cellular environments.

Clearly, there is a complex regulatory mechanism in place with regard to whether fibrosis occurs or not, and conflicting *in vitro* studies must be interpreted with caution. A randomized, prospectively controlled trial was conducted in 18 patients with IPF comparing IFN- γ 1b and low-dose prednisolone with prednisolone alone for 12 mo (161). The results were remarkable in that patients with progressive pulmonary fibrosis treated with IFN- γ 1b plus low-dose prednisolone demonstrated improvement in pulmonary function, whereas those who received prednisolone alone experienced further decline in pulmo-

nary function. The authors showed that all patients treated had almost undetectable levels of IFN- γ mRNA, and increased levels of both TGF- β and connective tissue growth factor mRNA in lung tissue. Furthermore, after treatment with IFN- γ 1b, transcription of TGF- β and connective tissue growth factor were both significantly decreased. Several concerns have been raised regarding the findings reported by Ziesche and co-workers (**162**), particularly the unexpectedly good results with IFN- γ 1b. To address some of the issues raised, an outside panel of experts reanalyzed the study data by reviewing each patient's lung function studies, CT scans, and SLBs to assess the clinical course and diagnosis of IPF according to the International Consensus Statement (**2,163**). Fifteen of 18 patients had either definite ($n = 9$) or probable ($n = 6$) IPF. The panel reanalyzed treatment response using published criteria and eliminated the patients who definitely did not have IPF. Patients treated with IFN- γ 1b plus low-dose prednisolone demonstrated either stability or improvement in pulmonary function and gas exchange after 1 yr of treatment, whereas treatment with prednisolone alone was associated with no improvement in all patients (**163**). The observed benefit of IFN- γ 1b on lung function has not been reproduced in subsequent studies. In one retrospective uncontrolled observation of 21 patients with IPF treated with IFN- γ 1b, only one patient experienced objective improvement, 7 discontinued therapy (owing to lack of perceived benefit), and 11 died after 6 mo of therapy (**164**). In a separate study of five patients with IPF treated with IFN- γ 1b, only one patient improved, two discontinued treatment owing to adverse effects and decline in lung function, and one died after 3 mo of therapy (**165**).

In a recent prospective, randomized, placebo-controlled, double-blind, multicenter phase III clinical trial of subcutaneous IFN- γ 1b (200 μ g thrice weekly) in 330 patients with mild to moderate idiopathic pulmonary fibrosis (FVC $>50\%$ and DL_{CO} $>30\%$), a trend toward lower mortality was seen in IFN- γ 1b-treated patients compared with placebo-treated patients. However, there were no significant differences in lung function or gas exchange between IFN- γ 1-treated and placebo-treated patients after 48 wk of therapy (**96**). A prospective controlled multinational trial is planned to verify the possible survival benefit observed with IFN- γ 1b therapy in IPF.

8.3.5. Interferon β -1a

IFN- β is used for the treatment of chronic hepatitis C and multiple sclerosis. In vitro IFN- β 1a has been shown to reduce fibroblast proliferation (**166**), inhibit collagen production by fibroblasts (**167**), increase collagenase mRNA (**168**), decrease pro-collagen mRNA (**169**), and increase collagenase activity (**167**). Further, IFN- β inhibits irradiation-induced pulmonary fibrosis in mice (**170**).

A multicenter randomized, double-blind clinical trial examining the efficacy of IFN β -1a was recently completed. Patients were randomized into four groups: placebo or IFN β -1a at 15, 30, or 60 μ g intramuscularly twice per week for a minimum of 12 mo and up to 2.5 yr. Preliminary results suggest that IFN β -1a lacks significant efficacy (171).

8.4. Emerging Strategies

With a dismal response to existing therapy and its accompanied toxicity, the search for additional therapies has intensified in the past decade. The following is an overview of other therapeutic approaches, most of which are undergoing investigation and have not been adequately studied in humans.

8.4.1. Agents That Inhibit Epithelial Injury or Enhance Repair

The prior discussion has centered on fibroblast proliferation and collagen deposition as two areas of therapeutic intervention. It is becoming more apparent that the fibrotic process has multiple pathogenetic mechanisms. One of the fundamental hypotheses of pulmonary fibrosis involves an imbalanced response to injury, in which the capacity of the alveolar epithelium to repair itself is compromised, ultimately leading to fibrosis. Some investigators propose that the alveolar epithelium itself has antifibrotic properties, and that chronic loss of alveolar epithelium leads to an environment conducive to the development of fibrosis (172). Support for this notion exists in the fact that induction of apoptosis of alveolar epithelium has been shown to occur following administration of bleomycin (173). Therapies that either inhibit epithelial injury or enhance repair may limit the fibrotic response. In this regard, captopril, an angiotensin-converting enzyme inhibitor widely used in clinical practice, may have a role in the treatment of IPF. In vitro, captopril inhibits fibroblast proliferation, and in models of bleomycin-induced pulmonary fibrosis, it has been shown to reduce alveolar epithelial cell apoptosis and fibroproliferation. In addition, captopril abrogates Fas-induced apoptosis in human alveolar epithelial cells (141,174). There is currently an ongoing clinical trial at the National Institute of Respiratory Diseases in Mexico testing the efficacy of captopril in patients with IPF (141).

Another agent that may protect the alveolar epithelium is keratinocyte growth factor (KGF). This class of growth factor stimulates type II cell proliferation with no direct effects on fibroblasts (175). Keratinocyte growth factor increases surfactant protein gene expression and sodium/potassium adenosine triphosphatase, factors that may protect the alveolar epithelium (175). In vivo, KGF has been shown to protect animals from injury and subsequent development of fibrosis caused by a variety of insults (175).

There is evidence that an exaggerated oxidant stress may play a role in the pathogenesis of pulmonary fibrosis by injuring the alveolar epithelial cells. This oxidant burden is thought to be a consequence of both increased levels of reactive oxygen species and a defective antioxidant response. A major protector of oxidant-induced injury of the alveolar epithelium is glutathione, which has been shown to be deficient in the BALF of patients with IPF (176). Moreover, *in vitro* studies have shown that *N*-acetylcysteine (NAC), a precursor for glutathione synthesis, may augment the antioxidant defense system and protect the alveolar epithelium from free radical-induced injury (177). *In vivo*, Hagiwara and associates (178) reported a significant inhibition of bleomycin-induced lung fibrosis in mice following aerosolized NAC during the early inflammatory phase of injury. Whether this effect was secondary to NAC inhibition of cellular inflammation, or its role as a scavenger of reactive oxygen species, is not clear. German investigators evaluated oral NAC as a strategy to augment lung glutathione levels in 17 patients with biopsy-proven IPF. Following therapy with NAC, glutathione levels in BALF were significantly increased compared with pretreatment levels (177). In a separate study, Behr and colleagues (179) prospectively studied 18 patients with IPF and assessed the redox balance of the lung and changes in lung function following high-dose NAC therapy for 12 wk. They reported an increase in the total and reduced form of glutathione concentration in the BALF, and significant improvement in pulmonary function. The authors suggest that NAC may be considered as an adjunct in the treatment of IPF. Currently, there is a clinical trial in Europe to evaluate the potential benefits of NAC in IPF.

8.4.2. Anticytokine Approaches

As mechanisms of fibrosis at the cellular and molecular level become elucidated, their application to the development of novel therapeutic strategies appears promising. Given the temporal heterogeneity of the UIP lesion, early histopathological abnormalities may be present even in patients with advanced IPF. If early cytokine release is relevant to the initiation of this pathogenic response, then the targeting of early cytokines such as TNF- α should be considered. TNF- α appears to be upregulated soon after bleomycin-induced injury and has been implicated in a variety of inflammatory processes (180). Sime and colleagues (181) showed that transient overexpression of TNF- α in rat lung led to fibrosis associated with concomitant TGF- β expression and proliferation of myofibroblasts (181). Furthermore, upregulation of TNF- α expression has been shown to occur in inbred murine strains that are sensitive to bleomycin-induced lung fibrosis, with similar expression being absent in resistant strains (180). In addition, Ortiz and colleagues (182) showed that TNF

receptor-deficient mice did not develop pulmonary fibrosis following exposure to bleomycin despite increased TNF expression. Studies of human lung biopsy specimens of patients with IPF have shown an upregulation of TNF- α mRNA and protein (183). These observations along with other studies in animal models demonstrating abrogation of pulmonary fibrosis following treatment with soluble TNF receptors suggest that TNF- α may play an important role in the pathogenesis of pulmonary fibrosis (184). Several agents that can block TNF- α are now available for human use (185). There is currently an ongoing clinical trial evaluating the safety and efficacy of etanercept, a TNF- α receptor antagonist, in patients with IPF.

The expression of TNF- α is inhibited by certain cytokines such as IL-10, which is produced by a variety of cells including T-helper (Th) cells, monocytes, and alveolar macrophages (186,187). It is conceivable that IL-10 may be useful in blunting the action of increased TNF- α observed following bleomycin-induced lung injury, therefore possibly inhibiting progression to fibrosis. Arai and colleagues (188) investigated the possible inhibitory effects of IL-10 by introducing the IL-10 gene into mice exposed to bleomycin and found that bleomycin-induced pulmonary fibrosis was suppressed. These results suggest that treatment with IL-10 during the early inflammatory phases of lung injury may be promising and requires further investigation. Concerns regarding the role of this agent in treating pulmonary fibrosis exist in that IL-10 is a type-2 Th (Th2) cytokine that could suppress IFN- γ expression and promote fibrogenesis (189). A clinical trial to study the effect of this cytokine is now underway in the United States.

The realization that Th cell subsets could be categorized on the basis of cytokine profiles has helped clarify our understanding of chronic cell-mediated immune responses. The type-1 (Th1) cytokines include IFN- γ , IL-2, IL-12, IL-18, and Th2 cytokines include IL-4, IL-5, IL-10, and IL-13. Analysis of subset populations of Th cells within the interstitium of patients with IPF reveal a predominantly Th2-type pattern of cytokine production, suggesting that alterations in T-cell subpopulations of Th1 and Th2 cells and their associated pattern of cytokine production may contribute to progression of IPF (190). Supporting evidence comes from studies demonstrating that IFN- γ (a Th1 cytokine) has profound antifibrotic effects in IPF possibly because it shifts the balance away from a Th2-dependent profibrotic environment. Thus, it seems reasonable to target therapy to correct the Th imbalance by either favoring a Th1 phenotype or abrogating the predominant Th2 response (e.g., administration of IL-12 to promote IFN- γ expression, or inhibition of IL-4, IL-13, and so on).

TGF- β is a critical cytokine for the promotion of fibrosis. In bleomycin-induced pulmonary fibrosis, passive immunization with neutralizing antibod-

ies against TGF- β reduces collagen deposition (**191**). In addition, the overexpression of TGF- β results in a fibrogenic response resembling UIP (i.e., abundant FF) (**192**). In patients with IPF, increased expression of TGF- β is localized to bronchiolar epithelial cells, epithelial cells of HC cysts, and hyperplastic type II pneumocytes (**193**). It is possible that therapy with neutralizing antibodies against TGF- β 1, or utilization of a TGF- β 1 inhibitor such as decorin, may become useful in the treatment of IPF (**194**).

TGF- β signals through a receptor that activates transcription factors Smad2 and Smad3 promoting TGF- β gene transcription. Interestingly, IFN- γ inhibits the activation of Smad3 and induces the expression of Smad7, an antagonistic molecule that inhibits TGF- β expression. Smad7 can be produced in the laboratory and may become a useful molecule in the treatment of IPF (**195**).

Monocyte chemoattractant protein (MCP)-1 is a member of the C-C subfamily of chemokines involved in monocyte/macrophage mediated inflammation (**196,197**). In addition, MCP-1 has been shown to stimulate pulmonary fibroblasts, TGF- β synthesis, and collagen production (**198**). Analysis of serum, BALF, and lung biopsy specimens from patients with IPF reveal increased levels of this chemokine (**196,197,199**). Furthermore, serum MCP-1 levels correlate with clinical course in patients with interstitial lung disease (**199**). Further investigation into the clinical significance of MCP-1 and its contribution into the pathogenesis of IPF are necessary, and may provide the groundwork for novel therapies.

Another potential mediator of fibrosis produced in a variety of cells in the lung is the vasoactive peptide endothelin (ET)-1 (**200,201**). First thought to be primarily a vasoactive agent, ET-1 has been shown to stimulate fibroblast proliferation, activate monocytes, induce collagen production, and regulate cytokine production (**202**). Mutsaers and colleagues (**203**) revealed that ET-1 levels are augmented following administration of bleomycin with increased localization of the agent in areas of fibrosis. With increases in ET-1 synthesis following TNF- α and TGF- β stimulation, one may speculate that ET-1 may play an important role in the cascade of events leading to pulmonary fibrosis (**204,205**). Additional support for its role in pulmonary fibrosis comes from studies in animals in which fibrosis was attenuated following treatment with bosentan, an ET receptor antagonist (**206**). ET-1 has also been associated with pulmonary fibrosis in humans. In a study examining the expression of ET-1 in patients with interstitial lung fibrosis, Giaid and associates (**200**) found a striking expression of ET-1 in lung tissue that correlated with parameters of disease activity in patients with IPF. There is currently an ongoing clinical trial evaluating the safety and efficacy of bosentan in patients with IPF.

8.4.3. Other Agents That Inhibit Fibroblast Proliferation or Induce Fibroblast Apoptosis

Some have hypothesized that inducing fibroblast apoptosis may curb progression of fibrosis. Lovastatin is a pharmacological agent widely used in the treatment of hypercholesterolemia that inhibits 3-hydroxy-3-methylglutaryl-coenzyme A, therefore affecting many cellular functions essential for normal cell homeostasis including proliferation and cell survival. Tan and associates showed that clinically achievable concentrations of lovastatin induced apoptosis of human lung fibroblasts *in vitro*, and *in vivo* reduced granulation tissue formation and induced fibroblast apoptosis in a guinea pig wound model of fibroproliferation (207). With its known safety profile and potential antifibrotic effect, lovastatin is an attractive candidate in the treatment of IPF.

Suramin is a sulfonated naphthylurea that has been used to treat onchocerciasis, acquired immunodeficiency virus, and prostate cancer. *In vitro*, suramin antagonizes the effects of a number of growth factors that promote fibrogenesis such as TGF- β , insulin-like growth factor-1, platelet-derived growth factor, epidermal-like growth factor, and fibroblast growth factor. *In vivo*, suramin has been shown to delay wound healing (175).

Relaxin is a protein secreted by the gravid uterus responsible for remodeling of the interpubic ligament and cervix during the later phases of pregnancy. Relaxin inhibits the TGF- β -mediated overexpression of extracellular matrix, stimulates the expression of collagenases by lung fibroblasts *in vitro*, and has been shown to block bleomycin-induced fibrosis in mice (141).

The eicosanoids are potential candidates for therapeutic intervention. The prostaglandin PGE₂ is a potent inhibitor of fibroblast proliferation and extracellular matrix deposition and may ameliorate the fibrotic process in IPF (175). Indomethacin, an inhibitor of cyclo-oxygenase, has been shown to decrease bleomycin-induced pulmonary fibrosis in an animal model but to our knowledge, it has not been evaluated in human IPF (175). The profibrotic leukotriene B₄ has been shown to be increased in BALF and lung tissue of patients with IPF (175). Inhibition of leukotriene production may be an effective adjuvant therapy, and drugs are now available to block leukotriene synthesis.

Gene-specific antisense therapy against proteins known to be important in human lung fibroblast proliferation may become an effective approach in treating IPF patients. *In vitro*, Chen and associates showed that gene-specific oligonucleotides (oligos) against c-Ki-RAS substantially inhibited the proliferation of human fibroblasts (141).

Beractan is a natural bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins. *In vitro*, beractan pro-

voked fibroblast apoptosis, induced collagenase-1 expression, and decreased type I collagen (**141**).

8.4.4. Other Novel Strategies

Pulmonary fibrosis can be complicated by pulmonary hypertension limiting exercise tolerance and survival. German investigators performed a randomized-controlled, open-label trial in 16 individuals with pulmonary hypertension secondary to pulmonary fibrosis. They compared oral sildenafil with inhaled nitric oxide and infused epoprostenol. A single dose of sildenafil reduced pulmonary vascular resistance by nearly one-third and increased the mean arterial blood oxygen tension by 14 mmHg. The drug was well tolerated with no adverse effects on ventilation-perfusion matching (**208**). A clinical trial evaluating sildenafil in patients with IPF and pulmonary hypertension will be conducted soon.

9. Conclusions

In recent years, significant advances have been made in our understanding and management of IPF. However, in order to further our knowledge and make significant progress in the care of these patients, it is critical that we improve our understanding of the natural history and pathogenesis of IPF. In addition, we need to pursue novel imaging and diagnostic technologies to improve earlier diagnosis and we must also educate primary care physicians and pulmonologists to refer patients early to an interstitial lung disease specialist or lung transplant center. Therapeutic strategies must target specific aberrant pathways during the natural history of the pathogenesis of pulmonary fibrosis. Only when these issues are in place will we be able to improve the prognosis of disorders associated with progressive pulmonary fibrosis.

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