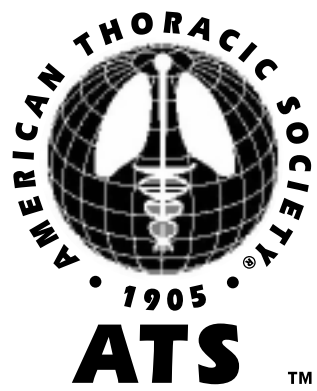

CONTINUING EDUCATION MONOGRAPH SERIES

New Approaches to Managing Idiopathic Pulmonary Fibrosis

Program and Monograph Editor
Talmadge E. King, Jr., MD

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Introduction

This monograph, which is part of the American Thoracic Society's Continuing Education Monograph Series, focuses on idiopathic pulmonary fibrosis (IPF). This progressive and often fatal lung disease is characterized by the presence of a histologic pattern of usual interstitial pneumonia (UIP) on surgical lung biopsy. The key histologic features of UIP include a patchy subpleural and heterogeneous pattern of mild inflammation, dense fibrosis, scattered foci of fibroblast proliferation, and extracellular-matrix remodeling, which result in irreversible distortion of the lungs' architecture. Successful management of this progressive fibroproliferative disorder is hampered by not only its typically late presentation but also the lack of interventions that improve patient survival.

The clinical features of IPF are nonspecific and mimic those of a number of other pulmonary diseases. Consequently, the clinical workup of patients with suggestive symptoms and signs is expensive and time consuming. In addition, the absence of reliable markers of therapeutic efficacy—appearance on chest x-ray and high-resolution computed tomography, results of pulmonary function tests or measurements of gas exchange at rest and after exercise, and bronchoalveolar lavage fluid analysis—makes it difficult to assess the clinical utility of treatment. In an effort to improve our understanding of IPF, the American Thoracic Society and the European Respiratory Society, in collaboration with the American College of Chest Physicians, published an International Consensus Statement in February 2000 that addresses current diagnosis and management of IPF.[1]

The current hypothesis is that UIP represents a model of abnormal wound healing in the lung. Exciting new findings have identified abnormalities in cell migration and proliferation, synthesis and secretion of extracellular-matrix proteins and cytokines, and remodeling of the injured matrix. Increased activity of fibrogenic cytokines (eg, transforming growth factor beta-1 [TGF-β1], tumor necrosis factor [TNF] alpha, basic fibroblast growth factor, platelet-derived growth factor, and insulin-like growth factor) and exaggerated responses to these cytokines have also been reported. Furthermore, abnormal epithelial–mesenchymal interactions and mutations in regulatory genes (such as p53 and p21) have been proposed to help explain the abnormal repair process.

These advances in our understanding of the cellular and molecular biology of pulmonary diseases that are distinguished by inflammation and fibrosis, such as IPF, are leading to more-targeted interventions that should improve patients' quality of life and survival. Examination of the recent studies of IPF pathogenesis and discussion of how this new information might guide future therapeutic trials in IPF were the focus of a one-day conference held in Phoenix, Arizona, in April 2000. This monograph comprises the information presented at that conference.

In "Epidemiology, Morbidity, Mortality, and Familial Distribution of Idiopathic Pulmonary Fibrosis," David Schwartz reviews prevalence data, possible etiologic factors, prognostic factors, and risk factors for IPF.

Kevin Leslie reports in "The Pathology of Idiopathic Pulmonary Fibrosis" that UIP is now considered the pathologic corollary of clinical IPF. Best characterized as a smoldering fibroproliferative disease, UIP begins at the periphery of the lung lobule and tends to leave dense fibrosis and end-stage honeycomb cystic lung remodeling in its wake.

In "Evolving Definition and Approach to Diagnosis of Idiopathic Pulmonary Fibrosis," Ganesh Raghu observes that the differential diagnosis of IPF spans the entire spectrum of lung disease. A complete history, careful physical examination, pulmonary function tests, and chest radiographs are necessary to make the diagnosis clinically.

Kevin Brown observes in "Current Management of Idiopathic Pulmonary Fibrosis and Predictors of Outcome" that treatment of IPF remains relatively ineffective, and he discusses factors that appear to affect disease progression and surrogate end points that can be used for disease staging and to assess prognosis.

Robert Strieter and Michael Keane address "Cytokine Biology and the Pathogenesis of Interstitial Lung Disease." In contrast to the normal repair process, chronic inflammation in interstitial lung disease promotes fibroproliferation and deposition of extracellular matrix, reflecting dysregulated and exaggerated tissue repair.

In "Interferon Gamma-1b: Mechanisms of Action, Preclinical Studies, and Clinical Experience," Rolf Ziesche and Lutz-Henning Block broaden our understand-

ing of the immunomodulatory effects of TGF-β1 in IPF, which include suppression of interferon gamma (IFN-γ) immune reactions. IFN-γ reduces expression of TGF-β1, resulting in a reduction in fibrosis, and IFN-γ1b has been studied in patients as a potential treatment for IPF.

Ganesh Raghu, Kevin Brown, Paul Noble, and Thomas Colby reexamine the results of a published clinical trial of IFN-γ1b in "Interferon Gamma-1b in Idiopathic Pulmonary Fibrosis: Reanalysis of a Published Study." The original study showed that lung function improved in patients treated with IFN-γ1b plus prednisolone and worsened in patients treated with prednisolone only, and their reanalysis confirmed these findings.

Finally, Roland du Bois addresses "Potential Future Approaches to the Treatment of Idiopathic Pulmonary Fibrosis." The most promising approaches at present include antioxidants, IFN-γ, and blockade of TNF-α and TGF-β.

This monograph summarizes our present state of knowledge of IPF and indicates directions future research might take to improve the diagnosis and therapeutic outcomes of IPF. It should provide a focus for continuing discussion among pulmonologists and others involved in the diagnosis and management of this chronic interstitial lung disease.

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Epidemiology, Morbidity, Mortality, and Familial Distribution of Idiopathic Pulmonary Fibrosis

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In a recent study, the prevalence of idiopathic pulmonary fibrosis (IPF) was found to be 20.2 per 100,000 among men and 13.2 per 100,000 among women, which is 5 to 10 times higher than previous figures. Although possible etiologic factors have been identified, including cigarette smoking and heredity, IPF remains a clinical diagnosis of exclusion. Prognostic factors must be evaluated with consideration given to time from onset of symptoms to diagnosis, since many patients, particularly men, tend to present later in the disease with more objective findings. Risk stratification based on a scoring system of prognostically relevant features is feasible. These include age; gender; severity of symptoms; radiographic, spirometric, arterial blood gas, and bronchoalveolar lavage fluid findings; response to corticosteroids; and degree of fibrosis on open-lung biopsy.

Idiopathic pulmonary fibrosis (IPF) is a progressive disorder associated with very poor survival and characterized by disabling dyspnea, extensive interstitial fibrosis, and poor gas exchange.[1] When evaluating novel therapies for IPF, one should consider how the epidemiology of this disease may alter end points that might be considered relevant to a clinical trial. To address this issue, this review is divided into three sections—demographic features, etiologic factors, and prognostic considerations.

DEMOGRAPHIC FEATURES

The prevalence and incidence of pulmonary fibrosis were investigated most definitively in a population-based study conducted by Coultas and colleagues in Bernalillo County, New Mexico.[2] These investigators found that the prevalence of interstitial lung disease (ILD) was 20% higher among men (80.9 per 100,000) than among women (67.2 per 100,000), largely owing to the higher prevalence of occupational and environmental forms of ILD. In contrast, the incidence of ILD among men (31.5 per 100,000/year) and the incidence among women (26.1 per 100,000/year) were nearly equivalent. Among men, IPF accounted for 34% of the prevalent cases of ILD and 36% of the incident cases; among women, IPF accounted for 24% of the prevalent cases and 27% of the incident cases. Among both men and women, IPF was the most common cause of incident cases of ILD. In addition, for both sexes, there was a striking relationship between these diseases and age, with very high rates of ILD and IPF in the older age groups.

A potential limitation of this study is the fact that only 6.9% of those with ILD and 11.1% of those with IPF had an open-lung biopsy. In addition, the demographics of the study population—55.9% non-Hispanic white, 36.2% Hispanic, 3.4% Native American, 2.7% black, and 1.8% other non-whites—do not reflect those of the population at large. Despite these concerns, this study clearly demonstrated that the prevalence and incidence of pulmonary fibrosis are 5 to 10 times higher than previously published figures.[3] Idiopathic pulmonary fibrosis occurs more often among men than among women; two thirds of patients are >60 years old; the disease develops more frequently among

The prevalence and incidence of pulmonary fibrosis are approximately 5 to 10 times higher than suggested by earlier studies.

whites than among blacks; and nationally, several studies have shown no geographic factors in the distribution of IPF, especially with regard to urban vs rural areas.

ETIOLOGIC FACTORS

Etiologically, IPF is a clinical diagnosis of exclusion.[4] Patients with IPF do not have collagen vascular diseases, have not had extensive occupational or environmental exposure to causes of pulmonary fibrosis, and have taken no medications associated with the development of pulmonary fibrosis. Although several surveys raise the possibility that many agents could cause pulmonary fibrosis, two hypothesis-testing case-control studies provide some insight into etiologic factors associated with IPF. A study that focused on cigarette smoking found that smoking was associated with a 1.6- to 2.3-fold excess risk of pulmonary fibrosis.[5] The second investigation found an excess risk of pulmonary fibrosis among individuals who had occupational exposure to metal dust or wood dust.[6]

> *Cigarette smoking is associated with a 1.6- to 2.3-fold excess risk of pulmonary fibrosis.*

The primary concern with both of these investigations applies to all case-control studies: people with disease recall details of their past very differently from people without disease. However, both of these studies were pursuing hypotheses that had been raised by previous independent investigations.

Viruses are always mentioned as a likely cause of IPF. Although much investigative attention has been directed toward this hypothesis, it currently remains unclear whether viruses or small intracellular bacteria play a role in the development of IPF. Epidemiologic studies focusing on a possible viral or intracellular bacterial cause of IPF are still at the hypothesis-generating stage. Despite many interesting leads (Epstein–Barr virus, influenza, cytomegalovirus, hepatitis C virus, parainfluenza 1 and 3 viruses, human immunodeficiency virus 1, measles virus, herpesvirus 6, Mycoplasma, and Legionella), there are few conclusive data that these agents play a role in the development of pulmonary fibrosis.[4,7]

The following lines of evidence support the role of genetic factors in the development of pulmonary fibrosis:

- Clustering of pulmonary fibrosis (a relatively rare disease) is seen in families.
- Inheritance patterns in reported families with two or more cases of pulmonary fibrosis suggest that familial pulmonary fibrosis (FPF) is inherited either as an autosomal recessive trait or as a dominant trait with reduced penetrance.
- Familial pulmonary fibrosis has been reported in separately raised monozygotic twins,[8-10] in closely related members of several families,[10-14] in more than two generations in several case studies,[10] in several father–son pairs,[12,13,15] and in family members separated from an early age.[13]
- Pulmonary fibrosis is associated with pleiotropic genetic disorders such as Hermansky–Pudlak syndrome, neurofibromatosis, tuberous sclerosis, Niemann–Pick disease, Gaucher's disease, and familial hypocalciuric hypercalcemia.
- Pulmonary fibrosis is frequently observed in autoimmune diseases, including rheumatoid arthritis and systemic sclerosis.
- Variable susceptibility is evident among workers who are reported to be exposed occupationally to similar concentrations of fibrogenic dusts.
- Inbred strains of mice differ in their susceptibility to fibrogenic agents.
- Genetic studies suggest that FPF may possibly be associated with genes inherited on chromosome 14, coding for either immunoglobulin allotypes[16] or α-1 protease inhibitor phenotypes.[17,18] However, these specific genes are not thought to be responsible for the development of pulmonary fibrosis, since the lod score at small recombinant distances was low,[16] indicating that the linkage to these specific genes is relatively weak.

Although FPF may prove to be a complex genetic disorder with multiple genes and/or gene–environment interactions responsible for the development of pulmonary fibrosis, a comprehensive linkage analysis remains the most direct and definitive approach to define the genetics of this disorder.

PROGNOSTIC CONSIDERATIONS

Before the relevant prognostic factors in IPF can be evaluated, two issues that might have an impact on prognosis must be considered. First, the time from onset of symptoms to diagnosis varies considerably among patients with pulmonary fibrosis. In the IPF patient population studied at the University of Iowa,

the time between the onset of symptoms and the diagnosis of IPF varied from 0 months to almost 60 months.[19] Second, gender clearly affects the way patients present with pulmonary fibrosis.[20] Men tend to present at later stages of the disease with objective findings such as chest x-ray abnormalities and finger clubbing, whereas women tend to present at earlier stages of the disease with the more-subjective complaint of dyspnea. In general, women present when the disease process may be reversible; in contrast, men tend to present with end-stage disease.

> *It remains unclear whether viruses or small intracellular bacteria play a role in the development of IPF.*

When considering changes in lung function over time, one must recognize that many patients with IPF present in the terminal stages of their disease, and although their dyspnea worsens, objective changes in lung function are not always observed.[19] In fact, in a population of patients with IPF observed for 4 years, we found that, although there was a tendency for the total lung capacity (TLC) and diffusing capacity of the lung for carbon monoxide (D_{LCO}) to decrease, the decrease in lung function was not at all dramatic.[19] Although these patients were very sick, they were at the end stages of their disease and did not have much lung function to lose. In fact, any further loss of lung function was often associated with severe, life-threatening complications.

Several studies have identified features of IPF that are associated with disease progression.[19,21-27] However, among patients with IPF who were observed over a period of 2 years, <30% experienced a decline in either TLC or D_{LCO}.[19] These findings suggest that patients with IPF generally present late in the course of their disease. This point is particularly important, since many of the features of IPF found to be associated with disease progression may be relevant only to the terminal phase of the disease process. Moreover, these findings clearly indicate that efforts should be made to identify patients with IPF earlier in the course of their disease. Severe dyspnea and treatment with immunosuppressive agents (proxy measure of the extent of disease) were found to be independently associated with progressive declines in both lung volumes and gas

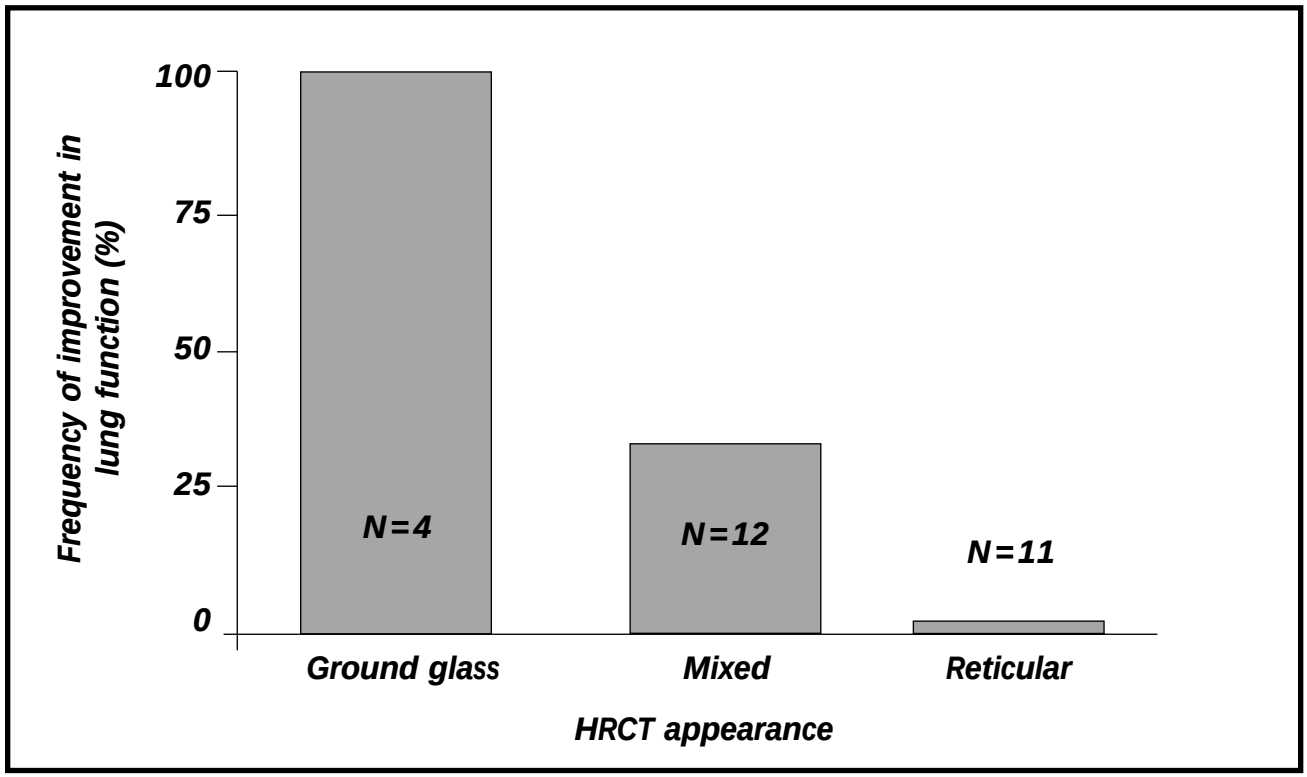

Figure 1. Predictive value of ground-glass abnormalities on high-resolution computed tomographic (HRCT) scans. A predominantly ground-glass appearance is associated with greater improvement in lung function and a better prognosis than a predominantly reticular pattern.[28]

exchange, whereas cigarette smoking was associated with progressive declines in only gas exchange.[19] Among patients with IPF, excess neutrophils[21-24] and eosinophils[19,21,24,25] in bronchoalveolar lavage (BAL) fluid have been associated with a higher likelihood of disease progression and a failure to respond to immunosuppression. In contrast, the concentration of lymphocytes[22,24] and type III procollagen peptide[26] in BAL fluid appears to be directly related to an improved response to immunosuppression. Interestingly, the degree and type of chest radiographic abnormalities do not appear to be predictive in patients with IPF,[27] although a ground-glass appearance on high-resolution computed tomographic scans is associated with improved lung function[28] (Figure 1).

Risk stratification among patients with IPF appears to be feasible and could provide the basis for a clinical staging system. Currently, there is no standard approach to staging IPF either clinically or histopathologically. Although IPF is a progressive form of ILD, the extent and rate of progression vary markedly among patients. Therefore, a system to reliably stage the physiologic and histopathologic components of IPF and quantitatively assess the rate of progression of this

> *Gender clearly affects the way patients present with pulmonary fibrosis: Men tend to present later in the disease, whereas women tend to present earlier.*

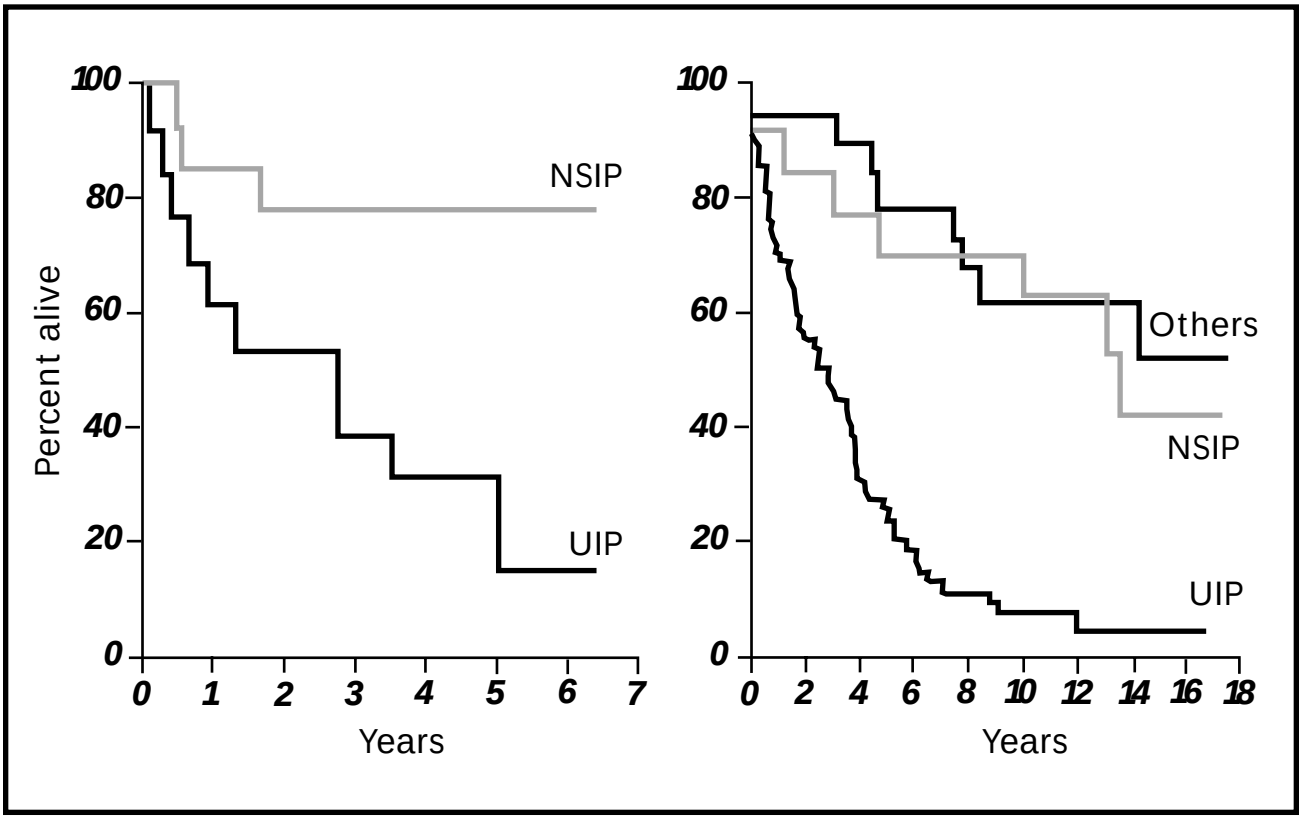

Figure 2. Survival for usual interstitial pneumonia (UIP) vs nonspecific interstitial pneumonia (NSIP). In the study represented in the left panel, the NSIP group had 4 deaths (29%) and the UIP group had 13 (93%) ($p<0.001$). In the study represented in the right panel, survival was significantly worse ($p<0.001$) among those with UIP compared with those with NSIP/fibrosis and others (includes those with desquamative interstitial pneumonia, bronchiolitis, bronchiolitis obliterans organizing pneumonia, respiratory bronchiolitis-associated interstitial lung disease, chronic eosinophilic pneumonia, and hypersensitivity pneumonitis). (Figure on left reprinted with permission from Daniil ZD, Gilchrist FC, Nicholson AG, et al. 1999. A histologic pattern of nonspecific interstitial pneumonia is associated with a better prognosis than usual interstitial pneumonia in patients with cryptogenic fibrosing alveolitis. American Journal of Respiratory and Critical Care Medicine, vol. 160, pp 899-905. Official Journal of the American Thoracic Society. © American Lung Association. Figure on right reprinted with permission from Bjoraker JA, Ryu JH, Edwin MK. 1998. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. American Journal of Respiratory and Critical Care Medicine, vol. 157, pp 199-203. Official Journal of the American Thoracic Society. © American Lung Association.)

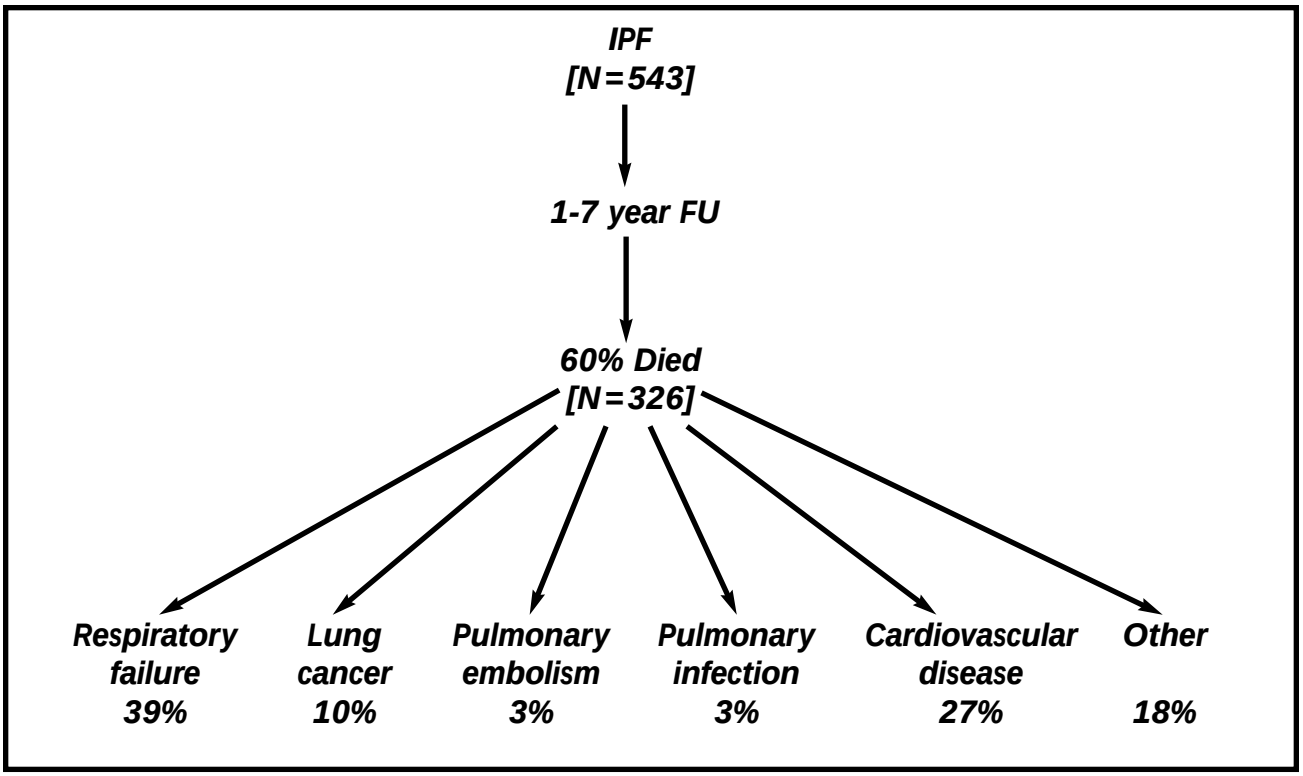

Figure 3. Cause of death among 326 patients with idiopathic pulmonary fibrosis. (Reprinted from The American Journal of Medicine, vol. 88; Panos RJ, Mortenson RL, Niccoli SA, King TE Jr. Clinical deterioration in patients with idiopathic pulmonary fibrosis: causes and assessment, pp 396-404, copyright 1990, with permission from Excerpta Medica, Inc.)

disease is essential. Such a staging system would provide clinicians with the necessary tools to objectively evaluate the effect of medical intervention. Moreover, investigators could use a staging system to identify the features of IPF that are functionally and prognostically relevant and improve the reliability of clinical trials.

To date, only one group of investigators has attempted to develop a clinical staging system for IPF.[29] Their proposed scoring system rates patients from 0 (no impairment) to 100 (total impairment).[29] This scoring system was derived from 26 patients with IPF and includes seven variables (dyspnea, chest radiograph, spirometry, lung volume, diffusion capacity, resting alveolar–arterial pressure difference for oxygen, and exercise oxygen saturation). Importantly, results from the clinical, radiographic, and physiologic (CRP) scoring system were significantly related to the degree of fibrosis seen on open-lung biopsy, and the change in CRP score was related to the cellular component of the open-lung biopsy specimen.[29] This suggests that the CRP scoring system could stage the extent of ILD and may prove helpful in predicting prognosis. Although these results are encouraging, further internal and external validation testing is needed to develop a reliable staging system for IPF.

Median survival among patients with IPF has been reported to be approximately 5 years.[1,30-36] Interestingly, the open-lung biopsy findings appear to be particularly predictive of survival.[30,31] Patients with a desquamative or cellular histology have a mean survival of 12.2 years, whereas those with an interstitial or fibrotic histology have a mean survival of 5.6 years.[30] Recently, nonspecific interstitial pneumonia on lung biopsy has been shown to provide a clear survival advantage compared with usual interstitial pneumonia[37] (Figure 2). Other favorable prognostic factors include younger age, female gender, earlier stage of disease (less dyspnea, less advanced restrictive lung function, and less parenchymal disease on the chest radiograph), and a

Mortality among both men and women with IPF has increased over the past 10 years.

response to corticosteroids.[1,31-36] In contrast, mucous hypersecretion and increased concentrations of neutrophils and eosinophils in the BAL fluid have been found to be associated with shorter survival.[36]

Although respiratory failure is the most frequent cause of death among patients with IPF, accounting for approximately 40% of deaths, heart failure, bronchogenic carcinoma, ischemic heart disease, infection, and pulmonary emboli also represent common causes of death among these patients (Figure 3).[38] Bronchogenic carcinoma has been identified with increased frequency (10% to 15% of patients) in patients with advanced IPF. Two studies, one conducted in the United States[39] and one conducted in the United Kingdom,[40] have investigated trends in IPF mortality during the past decade and have shown increased mortality among both men and women over the past 10 years. Mortality rates are higher for the older age groups and for men. There also appears to be a higher mortality rate among whites than among blacks,[39] and there are interesting regional differences in both the US and the UK study.

concluding points

- **A number of clinical factors are important to consider in patients with IPF, including gender, cigarette smoking, duration of disease, and histologic interpretation of the open-lung biopsy specimen. When populations are randomized to two arms of a controlled clinical trial, it will be important to consider these factors.**
- **A system to reliably stage the physiologic and histopathologic components of IPF and quantitatively assess the rate of progression is essential.**

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The Pathology of Idiopathic Pulmonary Fibrosis

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Usual interstitial pneumonia is now recognized as the pathologic corollary of clinical idiopathic pulmonary fibrosis. The diagnostic features of this chronic interstitial lung disease have remained essentially unchanged since first described by Liebow. Usual interstitial pneumonia is best characterized as a smoldering fibroproliferative disorder of unknown cause, attended by microscopic foci of airspace fibroplasia. The disease begins at the periphery of the pulmonary lobule and has a clear tendency to leave lung fibrosis and honeycomb cystic lung remodeling in its wake. The individual components of the process are not specific, but their physical arrangement in the surgical lung biopsy can be relatively compelling in the right clinical and radiologic context. Accurate diagnosis requires experience with the identification of interstitial lung disease, familiarity with appropriate terminology, and use of a multidisciplinary approach.

Idiopathic pulmonary fibrosis (IPF) is a chronic slowly progressive lung disease with no identifiable cause. It is now generally accepted that the lung pathology of IPF is so-called usual interstitial pneumonia (UIP), which was defined by Liebow more than 30 years ago as the most common and least "differentiated" form of interstitial pneumonia (Table 1).[1] Liebow considered UIP to be a form of the acute lung fibrosis syndrome described by Hamman and Rich first in 1935[2] and subsequently in 1944.[3] For Liebow, UIP described a pattern of diffuse lung fibrosis that was idiopathic in about half of the patients originally studied and "heterogeneous in terms of structure and causation" in the other half.[1] Katzenstein recently proposed modifications to the Liebow classification based on modifications from data that have come forward over the ensuing years (Table 2).[4]

In the years that followed, British and European investigators also were attempting to characterize the

Table 1. Liebow's Original Classification of the Interstitial Pneumonias[1]

- *Usual or "classical" interstitial pneumonia (UIP)*
- *Desquamative interstitial pneumonia (DIP)*
- *Bronchiolitis obliterans with classical interstitial pneumonia (BIP)*
- *Lymphoid interstitial pneumonia (LIP)*
- *Giant cell interstitial pneumonia (GIP)*

Table 2. Proposed Modification of Liebow's Classification (Katzenstein)[4]

- *Usual interstitial pneumonia (UIP)*
- *Desquamative interstitial pneumonia/ respiratory bronchiolitis-associated interstitial lung disease (DIP/RBILD)*
- *Acute interstitial pneumonia (AIP)*
- *Nonspecific interstitial pneumonia/ fibrosis (NSIP/F)*

chronic interstitial pneumonias and had applied the term "cryptogenic fibrosing alveolitis" to fibrosing lung diseases similar to those encompassed by UIP.[5,6] This term is still widely used today, and some believe it to be more descriptive of the pathologic process involved than the rather opaque terminology employed by Liebow. For the first three decades of its use, the term "UIP" was applied liberally to lung diseases with fibrosis, more descriptive of the pattern of fibrosis than of any specific etiologic entity (eg, UIP caused by asbestos and UIP caused by drug toxicity). After the series reported by Carrington and colleagues in 1978,[7] UIP came to be recognized pathologically as a relatively specific form of idiopathic chronic progressive interstitial pneumonia. This relationship was solidified further in a consensus statement published jointly by the American Thoracic Society and the European Respiratory Society, in collaboration with the American College of Chest Physicians, in February 2000.[8] Our task now is to hold clinicians to the accurate clinical assessment of IPF and pathologists to the accurate histologic assessment of UIP.

MECHANISMS OF LUNG INJURY AND REPAIR

The acute lung disease in a small group of patients described by Hamman and Rich[2,3] was probably a number of different disease processes caused by several different mechanisms, and it would likely not be considered UIP as the term is used today. Nevertheless, Liebow recognized important underlying mechanisms involved in the lung's response to injury and its limited repertoire for repair. To Liebow, the acute process that culminated rapidly in fibrosis, as described by Hamman and Rich, was the initial step in a disease that might also be more chronic, with recurrent acute injury superimposed on the lung ("chronic Hamman–Rich syndrome").

The acute lung injury or diffuse alveolar damage that occurs in the adult respiratory distress syndrome (ARDS) is a useful starting point for understanding the lung's stereotypic responses to injury to its various cellular and matrix components. The lung has a limited capacity for repair after significant cell injury and death. Moreover, like most mammalian organs, the lung has a tendency to replace lost or severely damaged tissue with fibrosis or scar.[9,10]

The events involved in the pulmonary response to matrix injury and cell death are complex, and our knowledge of these events is growing at a rapid rate. It is clear, however, that the final resolution of any injury depends on the nature and severity of the injury and the duration of the injurious event. (An excellent review of the potential mechanisms involved in lung repair can be found in a publication by Kuhn.[11]) A large number of soluble factors (cytokines) have been implicated in the orchestration of these events. One question that remains is why some forms of lung injury result in permanent fibrosis, whereas others of seemingly equal severity may be reversible, leaving the lung parenchyma relatively intact. A comparison of the long-term effects of the diffuse alveolar damage that occurs in ARDS and those of the diffuse alveolar damage that occurs in UIP nicely illustrates these divergent outcomes. Survivors of ARDS may have little residual lung damage despite the apparently catastrophic nature of the acute events, both clinically and pathologically. In individuals with UIP, the subtle ongoing lung injury identifiable histopathologically belies the ultimate outcome of end-stage lung fibrosis.

Usual interstitial pneumonia is now recognized as the pathologic corollary of clinical IPF.

HISTOPATHOLOGY OF UIP

At low magnification, the histopathologic findings mimic the radiographic findings (Figure 1), with peripheral accentuation of fibrosis, usually accompanied by gross (Figure 2) and microscopic (Figure 3) "honeycomb" fibrosis. Fibrotic remodeling of the lung in UIP is best seen subpleurally;

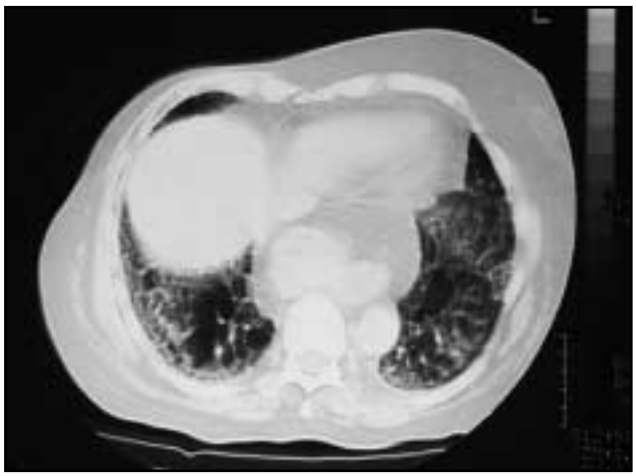

Figure 1. Computed tomographic image of lung bases in idiopathic pulmonary fibrosis. Note the peripheral "rind" of subpleural density, with relative central sparing.

Figure 2. Advanced honeycomb lung in idiopathic pulmonary fibrosis.

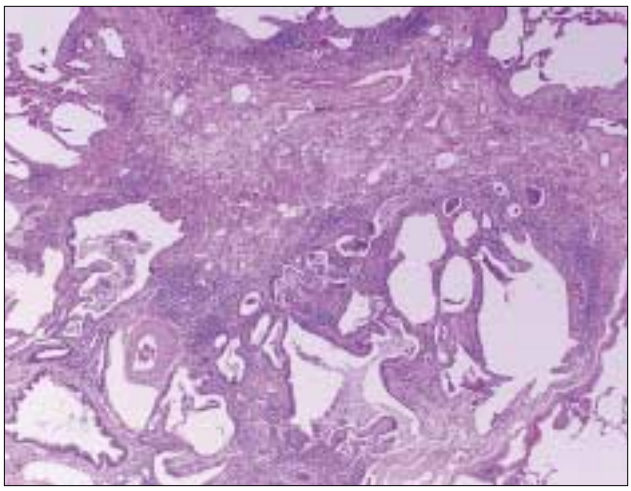

Figure 3. Microscopic honeycombing in idiopathic pulmonary fibrosis. This is the pathologic corollary of gross and radiologic honeycombing, but orders of magnitude smaller. Microscopic changes such as these would not be visible radiographically.

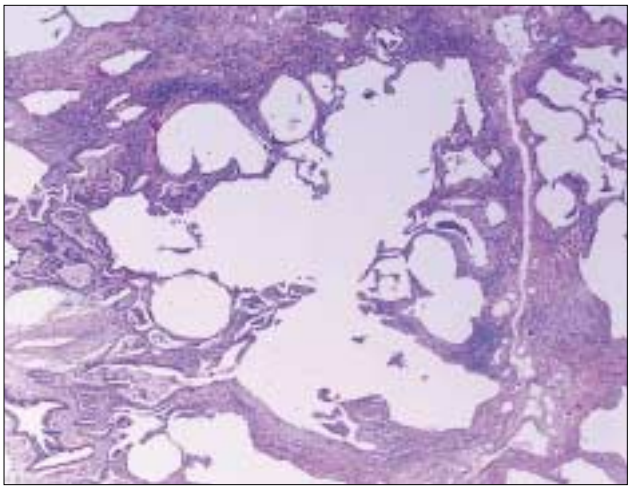

Figure 4. Peripheral accentuation of idiopathic pulmonary fibrosis. This secondary lobule is outlined by fibrosis. Note a few normal-appearing, delicate alveolar walls centrally.

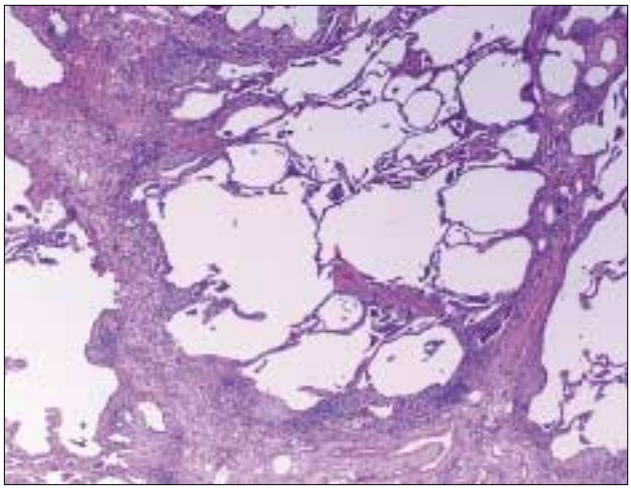

Figure 5. Transition from fibrosis to normal lung tissue. Temporal heterogeneity requires such transitions from fibrotic lung to nearly normal alveolar walls. The leading edge of disease is represented by mild chronic inflammation and delicate fibroblastic foci.

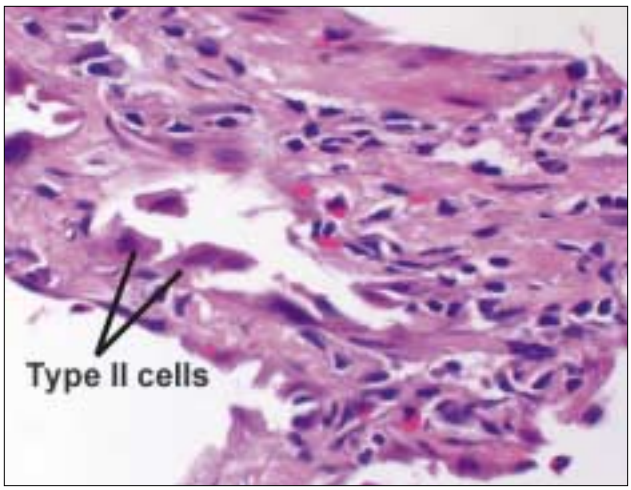

Figure 6. Inflammation in idiopathic pulmonary fibrosis. In the absence of supervening infection or exacerbation, the inflammatory infiltrates in UIP tend to be unimpressive. Mildly reactive type II cells may be present, attesting to ongoing lung injury.

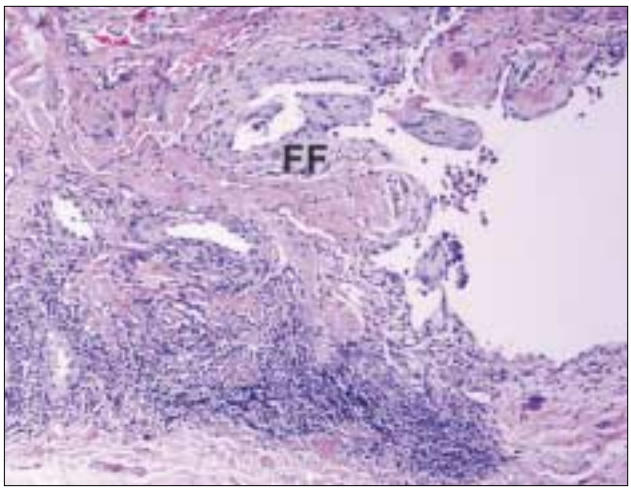

Figure 7. Fibroblastic foci (FF) in usual interstitial pneumonia. These differ from the pattern of bronchioloitis obliterans organizing pneumonia in that the foci tend to be less confluent and are broadly attached to stroma, often forming small crescents that bulge slightly into the airspace.

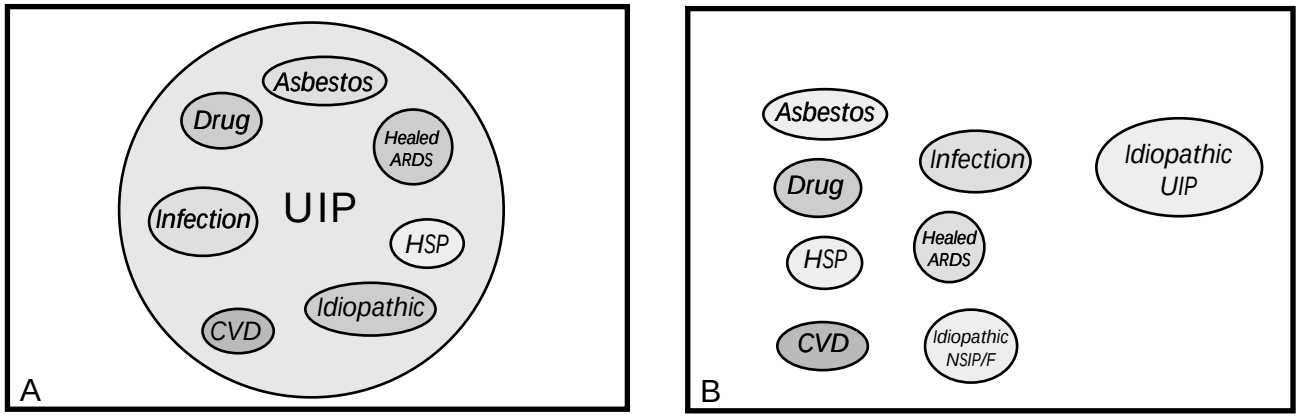

Figure 8. Venn diagrams for idiopathic pulmonary fibrosis/usual interstitial pneumonia (UIP). (A) In the past, the pathologic diagnosis of UIP included many disease processes related only by the presence of fibrosis. (B) Today, UIP stands in juxtaposition to its prior "inclusions," on the basis of histopathology, response to therapy, and prognosis. (ARDS = adult respiratory distress syndrome; CVD = collagen vascular disease; HSP = hypersensitivity pneumonitis; NSIP/F = nonspecific interstitial pneumonia/fibrosis.)

secondary pulmonary lobules also become outlined by the process and serve as an excellent morphologic landmark (Figure 4). At the interface between fibrosis and more normal lung, there is alveolitis with variable numbers of lymphocytes and plasma cells in the alveolar interstitium, and focal airspace organization ("fibroblastic foci") (Figures 5 to 7). Although airspace organization is present to some degree, it is usually not a prominent feature unless infection or other superimposed injury is present (see "Acute Exacerbation of UIP," next page). Within the biopsy specimen, the transitions from end-stage dense fibrosis, with or without honeycombing, to nearly normal lung, with an intermediate stage of alveolar organization and inflammation, are the histologic hallmarks of so-called temporal heterogeneity.

A number of disease states can produce fibrosis that may simulate UIP histopathologically. For example, collagen vascular diseases (and also other autoimmune processes) figure prominently in this category. Asbestosis can produce fibrosis and a heterogeneous inflammatory appearance similar to that seen in classic UIP. Chronic hypersensitivity pneumonitis, chronic eosinophilic pneumonia, certain drug toxicities, and collagen vascular diseases can also produce end-stage fibrosis indistinguishable from that seen in UIP. In contrast to these UIP mimics, UIP is fatal in >90% of patients, and the designation should not be used as a default or "wastebasket" diagnosis for any ill-defined lung disease with inflammation and fibrosis on biopsy. Today, "UIP" has evolved from a broad and inclusive rubric to a term defining a more-specific idiopathic form of lung disease (Figure 8).

Careful analysis of the clinical and radiologic findings, serologic data, and well-processed open-lung biopsy specimens (preferably representing upper and lower lung) is a prerequisite for the accurate diagnosis of UIP. Table 3 outlines an approach to diagnostic terminology for UIP that emphasizes the relationship between the biopsy findings and the completeness of the clinical and radiologic data available.

Table 3. Approach to the Diagnosis of Usual Interstitial Pneumonia

Definite UIP

- *Chronic fibrosing interstitial pneumonia with patchy involvement, architectural loss, zones of chronic scarring with honeycomb change or marked smooth muscle metaplasia/hyperplasia, and frequent subpleural or paraseptal accentuation*
- *Fibroblastic foci present at the junction of fibrosis with normal lung. Interstitial inflammation usually mild*
- *Compatible clinical and radiologic correlation*

Probable UIP

- *As above, but biopsy, clinical, or radiologic issues (number, size, location, only end-stage lung, unilateral disease, etc.) preclude definite diagnosis*

Chronic fibrosing interstitial pneumonia, not otherwise specified

- *Fibrosis as above, but additional loss of specific features (bronchiolocentric fibrosis, granulomas, giant cells, prominent foam cells)*

Not a fibrosing interstitial pneumonia

- *Predominantly inflammatory interstitial disease (nonspecific interstitial pneumonia, eosinophilic pneumonia, hypersensitivity pneumonitis)*

Table courtesy of Thomas V. Colby, MD.

ACUTE EXACERBATION OF UIP

The most common cause of death in patients with IPF is respiratory failure,[12] and acute respiratory failure is the cause of death in a small subset of this group of patients.[12-14] The typical history is that of a patient who, while being treated for interstitial lung disease, develops acute, fulminant respiratory failure, often accompanied by fever, elevation of the erythrocyte sedimentation rate, marked increase in dyspnea, and new opacities that often have an "alveolar" character radiologically. For many years, this manifestation was thought to be an infectious pneumonia, superimposed on a fibrotic lung with marginal reserve. However, because causative organisms are rarely identified (and a small percentage of patients may actually respond to pulse systemic corticosteroid therapy), a number of investigators now consider many such exacerbations to be a form of fulminant progression of the disease process itself.[12-14] This condition has a very poor prognosis, and death within 1 week is not unusual.

Pathologically, acute lung injury, resembling diffuse alveolar damage and/or organizing pneumonia, is superimposed on a background of UIP with honeycombing and fibrosis. This latter finding can be highlighted with the Masson's trichrome stain for collagen.

SUMMARY

Idiopathic pulmonary fibrosis/usual interstitial pneumonia is a chronic fibrotic process characterized by recurrent, often silent, episodes of acute lung injury resulting in lung remodeling and end-stage lung disease. Pathologists must be cognizant of the critical importance of a multidisciplinary approach to the diagnosis. Guidelines for the use of diagnostic terminology may be helpful to pathologists as they manage uncertainty in this regard (Table 3). Through such an approach, histopathologic mimics of UIP that may result from diverse injury and repair mechanisms can be excluded.

concluding points

- **The pathologic corollary of IPF is UIP.**
- **Usual interstitial pneumonia is a diffuse lung disease with a clear tendency to produce lung fibrosis, consistently in a peripheral lobular and subpleural distribution. Grossly visible honeycomb cysts characterize late fibrosis in UIP.**
- **There is peripherally distributed cellular injury occurring throughout the course of the disease, with repair by fibrosis. The microscopic hallmark of the cellular injury episode is the fibroblastic focus.**
- **Massive acute clinical exacerbation, often characterized by diffuse alveolar damage histopathologically, can occur in UIP. In a percentage of patients, exacerbation represents the terminal event.**
- **A multidisciplinary approach is an absolute requirement for an accurate diagnosis of UIP.**
- **Therapeutic advances are beginning to target more-specific control pathways. Such targeted therapies may benefit patients with UIP in the short term while further clarifying the requisite next steps to better elucidate the pathogenesis of this disease.**

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Suggested Reading

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Evolving Definition and Approach to Diagnosis of Idiopathic Pulmonary Fibrosis

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The differential diagnosis of pulmonary fibrosis spans the entire spectrum of lung disease. Idiopathic pulmonary fibrosis (IPF) is a distinct clinical entity with the specific histopathologic features of usual interstitial pneumonia (UIP). A complete history, careful physical examination, pulmonary function tests, and chest imaging studies are necessary to achieve a correct diagnosis. However, in the absence of surgical lung biopsy results consistent with the pattern of UIP, the diagnosis of new-onset IPF remains uncertain in patients with atypical clinical features. Histopathologic features on surgical biopsy distinguish UIP from other subsets of idiopathic interstitial pneumonias; this distinction is important, since UIP in the clinical setting of IPF is associated with a fatal outcome despite the use of corticosteroid therapy. Following a very thorough clinical assessment, and with the recent development of specific guidelines for the clinical diagnosis of IPF, the prudent clinician's ability to make a confident diagnosis in the absence of tissue examination will likely improve.

The differential diagnosis of diffuse interstitial lung disease (ILD) includes a heterogeneous group of perhaps 200 disorders. The diseases due to occupational and environmental causes represent the predominant category. The diseases due to systemic connective tissue diseases, many drugs, inherited diseases, granulomatous diseases, unique clinical entities (for example, pulmonary hemorrhage syndromes, lymphangioleiomyomatosis), and familial idiopathic pulmonary fibrosis are other important subgroups of ILD. In fact, the differential diagnosis of pulmonary fibrosis can span the entire spectrum of lung disease, and clinicians must carefully consider all the clinical features before concluding that a patient has one of the chronic idiopathic interstitial pneumonias. This is particularly important because of the widely different prognoses among subgroups of ILD. Most important, clinicians must not equate the diagnosis of chronic interstitial pneumonia of unknown etiology accompanied by nonspecific histologic findings with the diagnosis of idiopathic pulmonary fibrosis (IPF) (synonym: cryptogenic fibrosing alveolitis).

DEFINITION OF IPF

Idiopathic pulmonary fibrosis is a specific form of chronic fibrosing interstitial pneumonia limited to the lung with the histopathologic characteristics of usual interstitial pneumonia (UIP) on lung biopsy. The prognosis is poor, and the median survival is about 3 years with or without corticosteroid monotherapy. As defined in the recently published joint American Thoracic Society/European Respiratory Society/American College of Chest Physicians (ATS/ERS/ACCP) international consensus statement on diagnosis and treatment,[1] IPF is a distinct clinical entity. In the immunocompetent adult, the presence of all four major diagnostic criteria and at least three of the four minor criteria increases the likelihood of a correct diagnosis of IPF (Table 1). To determine their presence, and to exclude other diseases that mimic IPF, clinicians must take a complete history, carefully perform a physical

IPF is a specific form of chronic interstitial pneumonia of unknown etiology limited to the lung with the histopathologic features of UIP.

Table 1. Criteria for a Diagnosis of Idiopathic Pulmonary Fibrosis[1]

Major Criteria

- Exclusion of other known causes of interstitial lung disease, such as drug toxicities, environmental exposures, and connective tissue diseases
- Abnormal pulmonary function studies that include evidence of restriction (reduced VC, often with an increased FEV_1/FVC ratio) and impaired gas exchange (increased $AaPO_2$ with rest or exercise or decreased D_{LCO})
- Bibasilar reticular abnormalities with minimal ground-glass opacities on HRCT scans
- Transbronchial lung biopsy specimen or BAL fluid 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)

$AaPO_2$ = alveolar-arterial pressure difference for oxygen; BAL = bronchoalveolar lavage; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FEV_1/FVC = forced expiratory volume in 1 second/forced vital capacity; HRCT = high-resolution computed tomography; VC = vital capacity.

examination, assess pulmonary function, scrutinize all available chest radiographs and high-resolution computed tomographic (HRCT) images, and rule out alternative diagnoses with routine use of transbronchial biopsy or bronchoalveolar lavage. A diagnostic algorithm for ILD is shown in Figure 1.[2]

DIAGNOSTIC FEATURES

Patient History and Physical Examination

Idiopathic pulmonary fibrosis presents insidiously, with the gradual onset of a nonproductive cough and progressive, disabling dyspnea.[1] An accurate diagnosis of IPF requires the physician to take a detailed history, despite the time constraints of managed care, and to have a high index of suspicion for the disease. For example, the physician must ask the patient about potential etiologic factors such as drug history, family medical history, hobbies, bird exposures, and environmental exposures. A history of arthritis is an important clue that points away from a diagnosis of IPF. Idiopathic pulmonary fibrosis is not typically associated with arthritis, in contrast to collagen vascular diseases, which are often accompanied by arthritis and may present as ILD. However, some patients with IPF may have mild and nonspecific arthralgia, and a subgroup of patients may have hypertrophic osteoarthropathy.

Hemoptysis is rarely a feature in the history of a patient with IPF, so its presence should suggest a superimposed problem such as lung cancer, pulmonary embolism, or a different diagnosis entirely. Interstitial lung diseases accompanied by pulmonary hemorrhage include Goodpasture's syndrome, Wegener's granulomatosis, lymphangioleiomyomatosis, pulmonary veno-occlusive disease, idiopathic pulmonary capillaritis, and pulmonary hypertension secondary to mitral stenosis.

In more than 60% of patients with IPF, "Velcro" crackles are heard on auscultation of the chest; they are characteristically end-inspiratory and most prevalent at the bases. Clubbing is observed in 25% to 50% of patients with IPF. Although crackles on auscultation and clubbing on inspection are key components of the clinical diagnosis of IPF, it is also important to examine the skin for cutaneous signs of other possible causes of ILD. These other causes include sarcoidosis, Langerhans cell granulomatosis (primary pulmonary histiocytosis X), Churg-Strauss syndrome, neurofibromatosis, tuberous sclerosis, and, more important, the collagen vascular diseases, especially dermatomyositis and systemic sclerosis.

Pulmonary Function Testing

The typical findings on lung function tests are consistent with a restrictive ventilatory defect. Other findings include an increased alveolar-arterial pressure difference for oxygen (at rest or with exertion) and a decreased diffusing capacity of the lung for carbon monoxide (corrected for hemoglobin).

The diagnosis of IPF requires a high index of suspicion, and a thorough and exhaustive history is essential for ruling out diseases that mimic IPF.

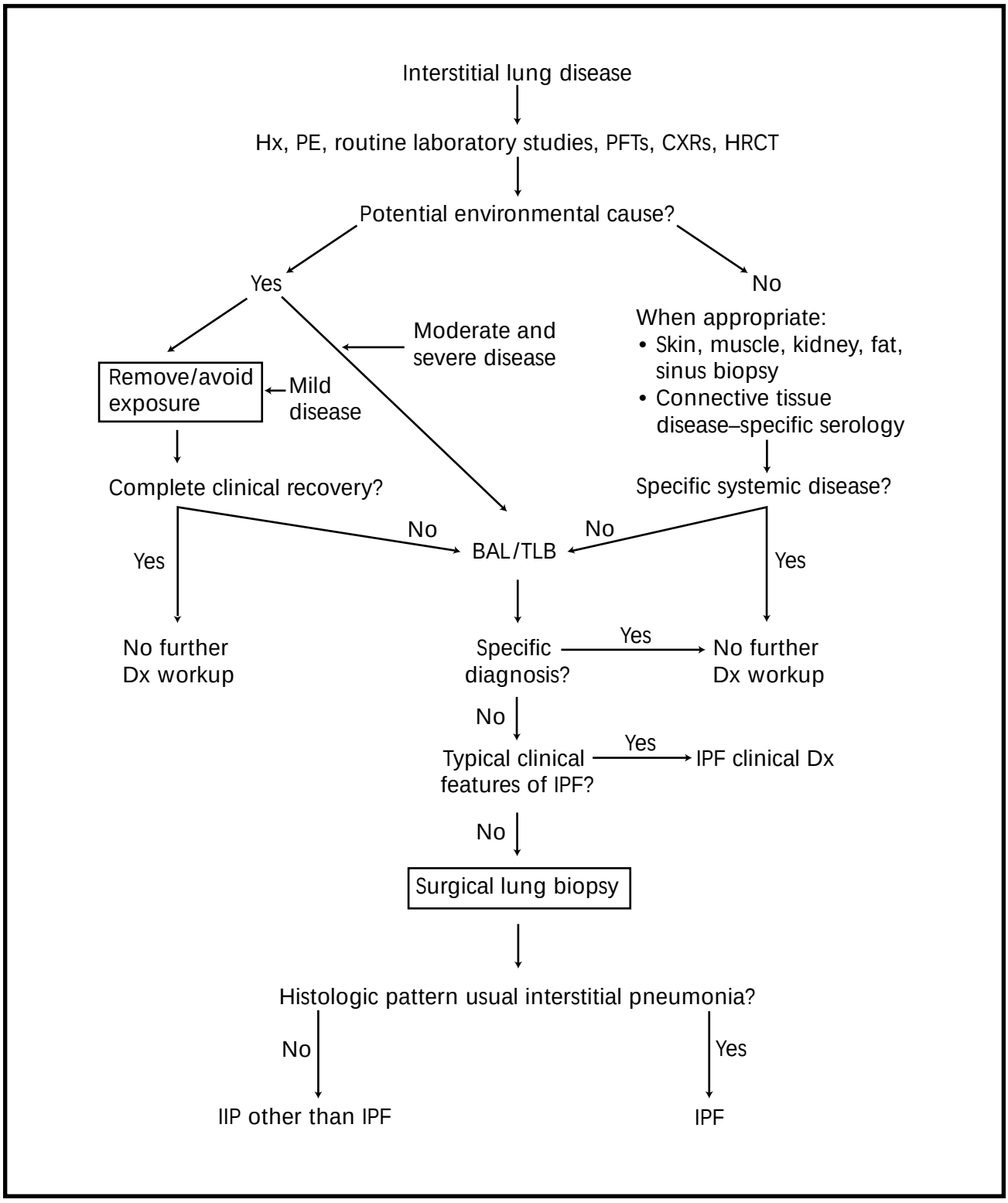

Figure 1. Diagnostic approach to interstitial lung disease. (BAL = bronchoalveolar lavage; CXRs = chest x-rays; Dx = diagnosis; HRCT = high-resolution computed tomography; Hx = history; IIP = idiopathic interstitial pneumonia; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; PE = physical exam; PFTs = pulmonary function tests; TLB = transbronchial lung biopsy.) (Modified from Raghu G. 1995. Interstitial lung disease: a diagnostic approach. Are CT scan and lung biopsy indicated in every patient? American Journal of Respiratory and Critical Care Medicine, vol. 151, pp 909-914. Official Journal of the American Thoracic Society. © American Lung Association.)

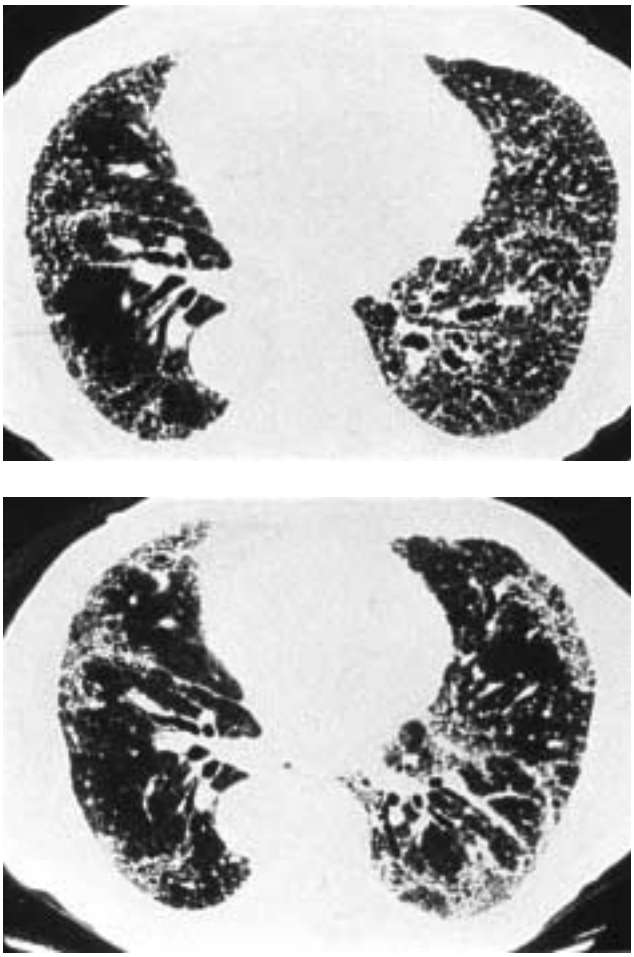

Figure 2. These high-resolution computed tomographic scans show a reticular pattern with a predominantly subpleural distribution in a patient with mid- to late-stage idiopathic pulmonary fibrosis. Septal thickening and honeycombing are also seen.

Radiography

It is important to distinguish ILD patients with preserved or increased lung volumes from those with decreased lung volumes. Virtually every patient with IPF has an abnormal chest x-ray at presentation. The characteristic findings include peripheral reticular opacities that are usually bilateral and often asymmetric.[1] Serial chest x-rays reveal a progressive increase in reticular markings without cardiomegaly, pleural abnormality, or hilar adenopathy. These findings are typically most prevalent in the lower lobes and associated with decreased lung volumes in patients with a histopathologic pattern of UIP. It should be noted, however, that several other disorders are associated with lower-lobe–preponderant disease and low lung volumes. These include disorders with a histopathologic pattern of nonspecific interstitial pneumonia, a subgroup of idiopathic bronchiolitis obliterans organizing pneumonia (BOOP), chronic hypersensitivity pneumonitis, and disorders with a histopathologic pattern similar to that of UIP that occurs in other diseases such as collagen vascular diseases and asbestosis.

Unless there is comorbidity with emphysema, IPF is unlikely in a patient who has radiographic evidence of ILD and preserved or increased lung volumes. Respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, or Langerhans cell granulomatosis is more likely to be the diagnosis of ILD in the setting of preserved or increased lung volumes. Inherited disorders associated with ILD and preserved or increased lung volumes include neurofibromatosis and tuberous sclerosis. Women of child-bearing age who present with clinical evidence of ILD and preserved or increased lung volumes are likely to have lymphangioleiomyomatosis. Finally, idiopathic BOOP, acute hypersensitivity pneumonitis (either drug induced or avian antigen), and some occupational or environmental exposures may also be associated with preserved or increased lung volumes.

Upper-lobe rather than lower-lobe predominance also points to a diagnosis other than IPF. Chest radiography showing predominantly upper-lobe involvement in a patient with clinical evidence of ILD should suggest a diagnosis of sarcoidosis, berylliosis, Langerhans cell granulomatosis, or pneumoconiosis.

Compared with standard chest radiography, HRCT helps narrow the differential diagnosis of ILD, allows earlier diagnosis of ILD, and can increase the level of confidence in a diagnosis of IPF. Characteristic HRCT findings in IPF patients include bibasilar interstitial and intralobular reticular opacities, interlobular septal thickening, subpleural honeycomb changes, and traction bronchiectasis in the lower lobes, without significant ground-glass or pleural abnormalities (Figure 2).

IMPORTANCE OF SURGICAL LUNG BIOPSY

Histopathology

The idiopathic interstitial pneumonias have been divided into subsets according to the predominant histopathologic pattern (Table 2). Histologic examination helps

> *Despite clinical expertise and HRCT scans, a specific, accurate diagnosis of all new-onset ILD and IPF can be made only by histology.*

Table 2. Histologic Classification of Idiopathic Interstitial Pneumonia

Pathologic Pattern	Clinical Syndrome
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis Collagen vascular disease–associated
Desquamative interstitial pneumonia	Respiratory bronchiolitis-associated interstitial lung disease
Nonspecific interstitial pneumonia	Unknown Collagen vascular disease–associated
Diffuse alveolar damage	Acute interstitial pneumonia of unknown etiology
Bronchiolitis obliterans organizing pneumonia	Cryptogenic organizing pneumonia
Eosinophilic pneumonia	Acute eosinophilic pneumonia Chronic eosinophilic pneumonia

distinguish UIP from the other histologic subsets of idiopathic interstitial pneumonias and excludes other processes that may mimic IPF clinically (Table 3). A surgical lung biopsy is recommended in patients with new-onset ILD, suspected IPF whose diagnosis is uncertain if there are no contraindications to surgery and the potential benefits outweigh the risks, especially those with clinical or radiographic features that are not typical of IPF.[1] Without a surgical lung biopsy, the diagnosis of new-onset IPF (<2 years' duration) cannot be made with certainty in all cases, despite a careful, thorough clinical assessment that has included HRCT and nondiagnostic bronchoscopy. Although UIP is the histopathologic pattern seen in IPF, it must be remembered that IPF is an overall clinical diagnosis rather than a pathologic diagnosis. Usual interstitial pneumonia is the histologic pattern that correlates with IPF, but it is also seen in conjunction with other disorders such as collagen vascular diseases.

Confirmation of Clinical Diagnosis

Raghu and colleagues conducted a prospective evaluation of the accuracy and validity of a clinical diagnosis of new-onset IPF or of ILD other than IPF by comparing clinical data and chest radiographic and HRCT features with histologic features on surgical lung biopsy.[3] A total of 59 consecutive community-based patients referred to a tertiary university medical center for evaluation of new-onset ILD underwent surgical lung biopsy within 1 month of the "clinical" diagnosis. An accurate diagnosis of new-onset IPF was made on the basis of clinical features alone in 62% of cases and on the basis of chest x-ray and HRCT alone in 76% of cases. The sensitivity and specificity of the diagnosis of IPF were 62% and 97%, respectively, when made on clinical grounds and 78.5% and 90%, respectively, when made on the basis of radiographic and HRCT findings. The results from another study that gathered data from 81 patients evaluated in eight other tertiary centers are similar.[4] Although these results show that not all patients with new-onset IPF require a surgical lung biopsy for diagnosis, they also show that the diagnosis will be missed in nearly one of three cases of new-onset IPF despite evaluation by experts. Therefore, in patients with new-onset ILD and aberrant features of IPF, a specific, accurate diagnosis of IPF can be made only in the presence of UIP, despite the availability of clinical expertise and state-of-the-art tools such as HRCT.

Assessment of Prognosis

Bjoraker and associates conducted a retrospective analysis of 104 patients with histologically confirmed IPF; these patients had undergone open-lung biopsies between 1976 and 1985 to confirm the histopathologic diagnosis.[5] On the basis of evolving knowledge of different histologic characteristics, they reclassified the histopathology into subsets of idiopathic interstitial pneumonia and determined the prognostic significance of such subsets. The histopathology of these patients previously diagnosed with IPF in fact

Table 3. Contrasting Pathologic Features of Idiopathic Interstitial Pneumonia

Feature	UIP	DIP/RBILD	AIP	NSIP
Temporal appearance	Variegated	Uniform	Uniform	Uniform
Interstitial inflammation	Scant	Scant	Scant	Usually prominent
Collagen fibrosis	Patchy	Variable, diffuse in DIP; focal, mild in RBILD	No	Variable, diffuse
Fibroblast proliferation	Fibroblastic foci	No	Diffuse	Occasional, diffuse, or rare fibroblastic foci
Organizing pneumonia	No	No	No	Occasional, focal
Honeycomb changes	Yes	No	No	Rare
Intraalveolar macrophage accumulation	Occasional, focal	Diffuse in DIP; peribronchiolar in RBILD	No	Occasional, patchy
Hyaline membranes	No	No	Occasional, focal	No

AIP = acute interstitial pneumonia; DIP = desquamative interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; RBILD = respiratory bronchiolitis-associated interstitial lung disease; UIP = usual interstitial pneumonia.

Reprinted with permission from Katzenstein ALA, Myers JL. 1998. Idiopathic pulmonary fibrosis. Clinical relevance of pathologic classification. American Journal of Respiratory and Critical Care Medicine, vol. 157, pp 1301-1315. Official Journal of the American Thoracic Society. © American Lung Association.

reflected a heterogeneous group including UIP, desquamative interstitial pneumonia, acute interstitial pneumonia, nonspecific interstitial pneumonia, BOOP, and other conditions. The median survival of all patients after the original diagnosis made on the basis of lung biopsy findings was 3.8 years. Reevaluation based on findings of the current histopathologic review revealed that the median survival of the UIP group was 2.8 years, which was significantly worse than that of the other subsets ($p < 0.001$). (See "Epidemiology, Morbidity, Mortality, and Familial Distribution of Idiopathic Pulmonary Fibrosis," Figure 2, page 4.) These investigators concluded that accurate histopathologic diagnosis is essential for accurately assessing the prognosis of patients with presumed IPF.

concluding points

- **Until now, in clinical practice and studies, pulmonary patients with several different histopathologic patterns of unknown etiology were considered to have IPF. With increasing knowledge and emerging consensus among experts, IPF is now recognized as a specific pulmonary disorder with distinct clinical features and the histologic pattern of UIP on surgical lung biopsy.**

- **Clearly defined patient populations and well-designed, long-term clinical studies are needed to better define the natural history and treatment outcome of patients with IPF/UIP. This, in turn, requires increased awareness and cooperation among community and academic clinicians to initiate prompt diagnostic and therapeutic interventions worldwide.**

- **The diagnosis of IPF in patients with long-standing, advanced IPF and in a subgroup of patients manifesting all typical features of IPF early in the course of the disease can be made with a relatively high degree of certainty by a prudent clinician after a thorough clinical evaluation without a surgical lung biopsy. However, the same clinician will be uncertain of the diagnosis of IPF in nearly a third of patients with new-onset disease when diagnosis is based on clinical grounds alone.**

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Current Management of Idiopathic Pulmonary Fibrosis and Predictors of Outcome

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Corticosteroids and cytotoxic agents used to treat the inflammatory component of idiopathic pulmonary fibrosis (IPF) have had little impact on long-term survival, although they remain recommended therapy because of the lack of a more-effective alternative. A recently published international consensus statement has outlined a recommended approach to treatment and follow-up. A number of patient-related and disease-related variables, including histologic subtype on open-lung biopsy, age, radiographic features, and pulmonary physiology, have a significant impact on prognosis and the rate of progression of IPF, and they can be used to determine the appropriateness of therapy in an individual patient. Changes in pulmonary physiology over time have prognostic significance and can serve as a surrogate end point to assess the effectiveness of treatment.

CURRENT MANAGEMENT

The management of idiopathic pulmonary fibrosis (IPF) has evolved only slowly; the fundamental approach of aggressive antiinflammatory therapy has remained essentially unchanged for the past 30 years. In centers where IPF is frequently encountered, the therapy that patients receive today is probably no different from the therapy they would have received 15 years ago. This remains true despite an extremely poor prognosis, with outcomes similar to those for many aggressive cancers.[1]

In 1953, Silverman and Talbot wrote, "Unfortunately, the rarity of diffuse interstitial pulmonary fibrosis, the extreme difficulty in establishing an early diagnosis and, finally, the complete ignorance as to its etiology present almost insurmountable obstacles in evaluating any form of therapy in this bizarre condition."[2] The past four decades have proved them essentially correct, as few well-designed prospective treatment trials have been performed. Interpretation of the currently available trials is limited by an unclear natural history of the untreated disease, the lack of placebo controls, the inclusion of heterogeneous patient groups with limited diagnostic certainty, variability in study duration, and inconsistent and nonvalidated criteria for assessment of response to therapy. In fact, after recently reviewing the relevant world literature on IPF, a panel of experts came to the following conclusions: 1) no data adequately document that any of the current treatment approaches improves survival or the quality of life for patients with IPF, and 2) we lack sufficient clinical evidence that any treatment improves survival or the quality of life for patients with IPF.[3] Any discussion of current therapy must acknowledge these limitations.

> *The prevalence and incidence of pulmonary fibrosis are approximately 5 to 10 times higher than suggested by earlier studies.*

Current treatment employs antiinflammatory therapy, including corticosteroids and cytotoxic agents (eg, azathioprine and cyclophosphamide). The rationale for this approach presumes that the progressive fibrosis that characterizes IPF results from chronic persistent inflammation, that this chronic inflammation precedes and ultimately leads to fibrosis, and that aggressive suppression of this inflammation will block subsequent scar formation.

The disappointing results of treatment with antiinflammatory agents have led to the study of alternative approaches. Antifibrotic therapy such as colchicine,[4-6] D-penicillamine,[6-8] interferon gamma (IFN-γ),[9] IFN-γ1b,[10] and pirfenidone[11] focuses on decreasing the excessive matrix (collagen) deposition in the lung or increasing

collagen breakdown. The usefulness, if any, of this approach in general and these agents in particular in IPF remains unproved.

By the early 1950s, a response to corticosteroids by the diffuse lung diseases berylliosis and sarcoidosis had been reported.[12] In 1957, Rubin and Lubliner reported on 63 patients with what was then called Hamman–Rich syndrome but was certainly a heterogeneous group of patients with lung fibrosis.[13] Nineteen patients had been treated with steroids, three (16%) of whom had sustained improvement for at least 1 year. From these limited beginnings, at least 15 studies with evaluable data have been performed since 1960, with objective response rates ranging from 11% to 32%. Despite these unimpressive results, corticosteroids have become a standard part of current therapy because of the lack of any effective alternative.

Cytotoxic therapy (cyclophosphamide and azathioprine) had previously been used primarily in patients with IPF who did not respond to corticosteroids, those with severe steroid complications, and those at high risk for steroid complications. However, results of studies conducted by Johnson and co-workers[14] and Raghu and colleagues[15] suggest that the addition of either cyclophosphamide or azathioprine to modest doses of corticosteroids may offer a benefit beyond that noted with steroids alone. It is on these data that the current treatment approach is based.

The current recommendations for therapy in patients with IPF are summarized in Table 1. The combination of corticosteroids with a cytotoxic agent, either cyclophosphamide or azathioprine, is used for a minimum of 6 months if no intolerable side effects occur. Both corticosteroids and cytotoxic agents can have serious, disabling side effects, some of which can be confused with progression of the underlying IPF. This makes close monitoring for adverse effects of treatment mandatory if this regimen is to be used.

Identifying a response to therapy can be challenging; at this time, no single clinically measurable variable has been proved to correlate well with outcome. For this reason, a combination of clinical, radiographic, and physiologic (CRP) features has been proposed as a means of determining improvement or deterioration after initiation of therapy (Table 2).[3]

Corticosteroids have become standard therapy for IPF mainly because of the lack of any effective alternative.

Table 1. Current Treatment Recommendations for Idiopathic Pulmonary Fibrosis[3]

Corticosteroid (prednisone or equivalent)

0.5 mg/kg lean body weight (LBW)/day orally for 4 weeks

0.25 mg/kg/day for 8 weeks

Taper to 0.125 mg/kg/day or 0.25 mg/kg on alternate days

PLUS

Azathioprine

2–3 mg/kg LBW/day

Maximum dose 150 mg daily

Dosing should begin at 25–50 mg/day, increasing by 25-mg increments every 1–2 weeks until the maximum dose is achieved.

OR

Cyclophosphamide

2 mg/kg LBW/day

Maximum dose 150 mg/day

Dosing should begin at 25–50 mg/day, increasing by 25-mg increments every 1–2 weeks until the maximum dose is achieved.

Therapy should be continued for a minimum of 6 months. Response is determined by symptoms, radiologic findings, and physiologic findings.

Close monitoring for adverse effects of treatment is mandatory.

PREDICTORS OF OUTCOME

In contrast to the relatively poorly characterized effect of treatment on the natural history of IPF, there are a number of patient- and disease-related variables that have a significant impact on prognosis and the rate of disease progression (Table 3). Patients with features suggestive of a more favorable outcome may be more likely to benefit from therapy, and it is for these patients that treatment is most strongly recommended. Patients with late-stage disease and poor prognostic indicators are unlikely to respond to therapy, so consideration should be given to forgoing treatment for these patients, particularly if the risk of adverse effects of therapy is high.

Table 2. Assessing Response to Therapy[3]

- *Clinically improved*

Two or more of the following on two consecutive visits over a 3- to 6-month period:

Symptoms: *Decreased level of dyspnea or severity of cough*

Radiology: *Reduced parenchymal abnormalities on chest x-ray or HRCT scan*

Physiology: *Improvement defined by two or more of the following:*

- *≥ 10% increase in TLC or FVC (minimum 200 mL)*
- *≥ 15% increase in $D_{L_{CO}}$ (minimum 3 mL/min/mm Hg)*
- *Significant improvement (≥ 4 percentage points, ≥ 4 mm Hg) or normalization of O_2 saturation or Pa_{O_2} during formal exercise testing*

- *Clinically stable*

Two or more of the following on two consecutive visits over a 3- to 6-month period:

Symptoms: *No significant changes*

Radiology: *No significant changes*

Physiology: *Stable defined by two or more of the following:*

- *<10% change in TLC or FVC*
- *<15% change in $D_{L_{CO}}$*
- *No significant change in O_2 saturation or Pa_{O_2} during formal exercise testing*

- *Failure (after 6 months of therapy)*

Symptoms: *Otherwise unexplained increase in dyspnea or severity of cough*

Radiology: *Increased parenchymal abnormalities, or development of honeycombing or signs of pulmonary hypertension, on chest x-ray or HRCT scan*

Physiology: *Deterioration defined by two or more of the following:*

- *≥ 10% decrease in TLC or FVC*
- *≥ 15% decrease in $D_{L_{CO}}$*
- *Significant worsening (drop of ≥ 4 percentage points, ≥ 4 mm Hg) of O_2 saturation or Pa_{O_2} during formal exercise testing*

$D_{L_{CO}}$ = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; HRCT = high-resolution computed tomography; Pa_{O_2} = partial pressure of oxygen in arterial blood; TLC = total lung capacity.

Histologic Features

Historically, the histopathologic features of an open-lung biopsy specimen have been the strongest predictor of clinical outcome among patients with interstitial lung disease (ILD). In large part, this may be explained by the previous failure to distinguish between what are now considered distinct idiopathic interstitial pneumonias (desquamative interstitial pneumonia, acute interstitial pneumonia, bronchiolitis-associated interstitial lung disease, nonspecific interstitial pneumonia, and IPF). These defined ILDs have well-characterized and distinctive histologic features[16] and significantly different prognoses.[17] Idiopathic pulmonary fibrosis is characterized and pathologically defined by the usual interstitial pneumonia (UIP) lesion; once alternative histologic diagnoses are excluded, it is unclear if there are particular histologic features, such as degree of fibrosis, inflammatory cell infiltration, or honeycombing, that corre-

A number of patient-related and disease-related features affect the rate of progression of IPF.

Table 3. Factors That Affect Prognosis and Progression of Idiopathic Pulmonary Fibrosis

- Histologic features
- Age
- Gender
- Smoking status
- Duration of symptoms
- Radiographic features
- Lung function
- Bronchoalveolar lavage fluid findings
- Response to therapy

late with either prognosis or response to therapy. Early information suggests that the larger the number of fibroblastic foci (geographically defined regions of fibroblasts, myofibroblasts, and young connective tissue) seen, the poorer the prognosis.

Age

Idiopathic pulmonary fibrosis is a disorder of adults; diagnosed disease in individuals <50 years old is uncommon. There is a clear relationship between age and prognosis, and the older the patient at diagnosis, the poorer the prognosis.[18] The median survival of a 70-year-old diagnosed with IPF is <2 years, whereas that of a 50-year-old diagnosed with IPF is >5 years.

Gender

In a 1980 study of the effect of clinical features of IPF on survival, male gender was associated with a poorer prognosis.[18] Although this early study included patients with autoimmune disease and clinical diagnoses of IPF, other studies with clearer diagnostic criteria seem to support this finding.[19] Recent information suggests, however, that there may be no significant differences in survival between men and women who have UIP confirmed by open-lung biopsy (King TE Jr et al, unpublished data). Overall, if gender affects prognosis, the effect seems to be small.

Smoking Status

Although cigarette smoking has been identified as a potential risk factor for the development of IPF, currently available data suggest that active cigarette smoking by patients who have IPF has an unexplained protective effect (King TE Jr et al, unpublished data). Confirmation and explanation of this finding must await further studies.

Degree and Duration of Dyspnea

Dyspnea ultimately develops in all patients with IPF. Both the severity and the duration of the dyspnea appear to be associated with outcome, with greater degrees of breathlessness and a longer duration of symptoms associated with a poorer prognosis.

Radiographic Features

Radiographic features on both a plain chest x-ray and a high-resolution computed tomographic (HRCT) scan appear to have prognostic significance. More severe pulmonary involvement as quantified by the International Labor Organization classification system on chest x-ray is associated with a worse prognosis. On HRCT scan, the presence of a predominantly ground-glass opacity is associated with longer survival, whereas a predominance of reticular abnormality or the presence of honeycombing both predict a poorer survival. Daniil and coworkers showed that patients whose HRCT scans showed a pattern typical of IPF had reduced survival compared with patients whose scans had an atypical appearance (Figure).[20]

Pulmonary Physiology

In patients with IPF, progressive restrictive changes in pulmonary physiology develop. It is not surprising, then, that in the absence of concomitant chronic obstructive lung disease, the severity of the restriction correlates with prognosis. A severe decrease in total lung capacity (TLC) or forced vital capacity (FVC) and an increase in the ratio of forced expiratory volume in 1 second to FVC have been associated with a poorer prognosis. The impact of a decreased diffusing capacity of the lung for carbon monoxide (D_{LCO}) is less clear, but a severely impaired D_{LCO} is probably a poor prognostic sign.[21]

The data on measures of gas exchange, either at rest or with exercise, are more difficult to interpret, although it is clear that IPF patients with resting hypoxemia at the time of presentation have a decreased survival time.[18]

Bronchoalveolar Lavage Findings

Various abnormalities in the bronchoalveolar lavage (BAL) fluid of patients with IPF have been described, including

Changes in pulmonary physiology over time can serve as surrogate end points for predicting survival.

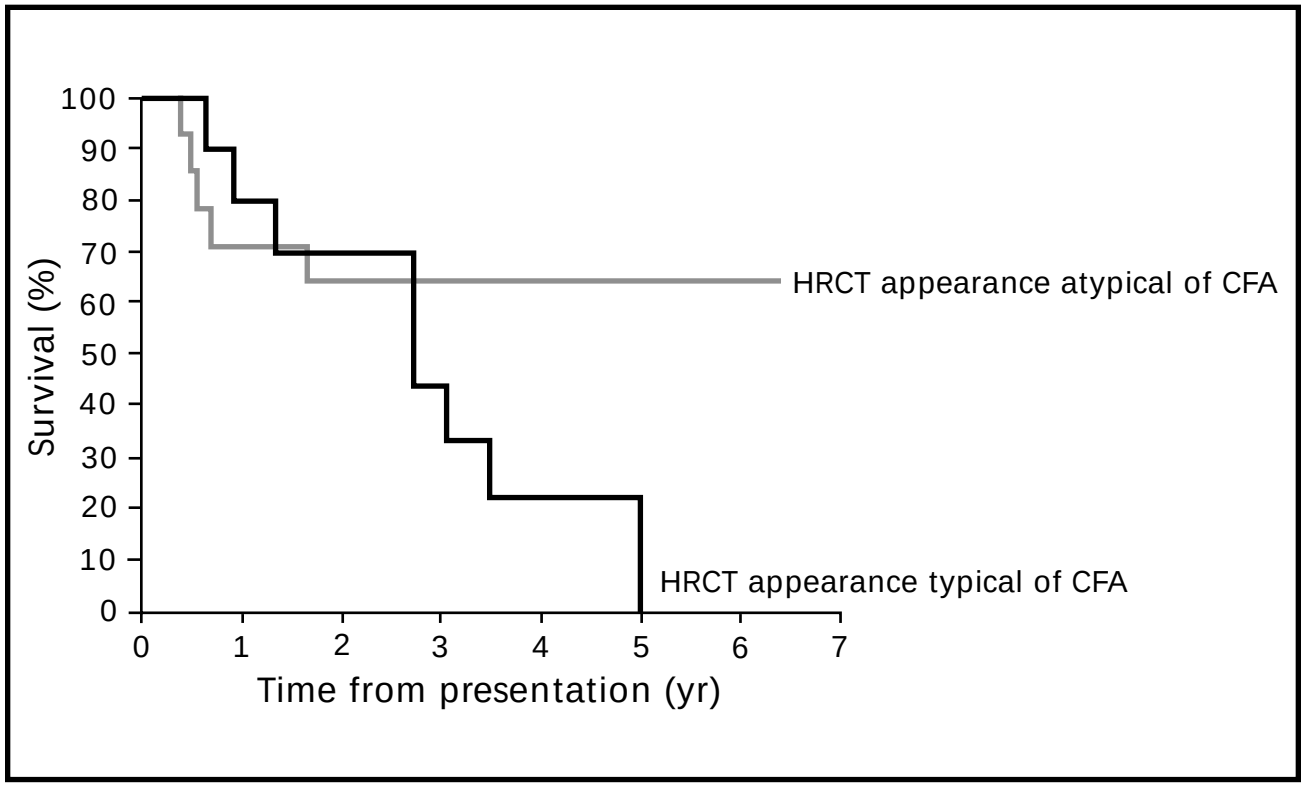

Figure. Survival among patients with idiopathic pulmonary fibrosis (IPF) according to the global assessment of their high-resolution computed tomographic (HRCT) scans at the time of presentation. The 10 patients whose HRCT scans showed the typical appearance of cryptogenic fibrosing alveolitis (CFA), which is the European term for IPF, had reduced survival compared with the 14 patients whose scans had an atypical appearance. (Reprinted with permission from Daniil ZD, Gilchrist FC, Nicholson AG, et al. 1999. A histologic pattern of nonspecific interstitial pneumonia is associated with a better prognosis than usual interstitial pneumonia in patients with cryptogenic fibrosing alveolitis. American Journal of Respiratory and Critical Care Medicine, vol. 160, pp 899-905. Official Journal of the American Thoracic Society. © American Lung Association.)

changes in the cellular differential, level of cellular activation, and cytokine and growth factor levels. Lymphocytosis (≥20%) on initial BAL occurs in <20% of patients but appears to be associated with longer survival and a better response to therapy, whereas an increased percentage of neutrophils or eosinophils (>5%) has generally been associated with a worse prognosis. However, the variability in these findings combined with issues such as BAL technique and laboratory methods limits the usefulness of BAL findings as a reliable predictor of outcome for any individual patient.

Response to Initial Therapy

Although mortality remains the critical end point to be modified, other outcome variables can serve as surrogate end points in assessing the effectiveness of treatment. A response to therapy with corticosteroids either alone or in combination with cytotoxic therapy, as measured by an improvement in pulmonary function test abnormalities (FVC) or the composite CRP score, is associated with a better prognosis.[22] For example, changes in FVC over time correlate with survival. A >10% improvement in FVC during a 6- to 12-month period is associated with substantially prolonged survival. In contrast, a >10% decrease in FVC over the same period reflects rapid disease progression and substantially decreased survival.

concluding points

- **Current treatment options for patients with IPF do not substantially improve survival.**
- **Although the prognosis for patients with IPF remains poor, physicians can assess a variety of features to determine the risk of disease progression and assess the effectiveness of treatment.**

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Cytokine Biology and the Pathogenesis of Interstitial Lung Disease

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Normal repair following lung injury results in rapid restoration of tissue integrity and function. In contrast to normal repair, chronic inflammation in interstitial lung disease (ILD) promotes fibroproliferation and deposition of extracellular matrix (ECM), reflecting dysregulated and exaggerated tissue repair. Although the mechanism(s) by which cellular injury occurs in idiopathic pulmonary fibrosis (IPF) remains unclear, activated alveolar macrophages and neutrophils undoubtedly play a role in the pathogenesis of the inflammatory lung lesion of IPF. The inflammatory response is characterized by recognition, recruitment, removal, and resolution (repair). During the recognition phase, there is increased expression of adhesion molecules for leukocyte trafficking. The recruitment phase is characterized by trafficking of neutrophils, lymphocytes, dendritic cells, and natural killer cells in the presence of chemokines. During the removal phase, T-helper (Th) cell subsets express Th1 and Th2 cytokines. Th1 cytokines, including interleukin (IL)-2 and interferon gamma (IFN-γ), promote cell-mediated immunity and remove cellular antigens; decrease fibroblast procollagen mRNA, fibroblast proliferation, and fibroblast-mediated angiogenesis; and downregulate the growth mediator transforming growth factor beta (TGF-β). Th2 cytokines, including IL-4 and IL-13, promote humoral immunity and produce antibody responses that can lead to fibroblast activation and fibrosis. Normally, the resolution phase restores lung architecture through homeostatic mechanisms. During the resolution phase in IPF, however, there is an imbalance between Th1 and Th2 responses in favor of Th2, leading to high levels of TGF-β, which leads to the accumulation of collagen. Dysregulated angiogenesis may be important in the support of fibroplasia and the deposition of ECM that occurs during chronic fibroproliferative disorders such as IPF. The persistent imbalance in the expression of Th2 vs Th1 cytokines in the lung is a mechanism for the progression of pulmonary fibrosis. Administration of IFN-γ1b may help shift cytokine expression toward a more normal Th1/Th2 balance.

Normal repair following lung injury results in rapid restoration of tissue integrity and function through a series of sequential yet overlapping processes consisting of coagulation, inflammation, granulation tissue formation, and reestablishment of normal parenchymal-stromal cell interrelationships. In contrast to normal repair, chronic inflammation in interstitial lung disease (ILD) promotes fibroproliferation and deposition of extracellular matrix (ECM), reflecting dysregulated and exaggerated tissue repair. The inflammatory

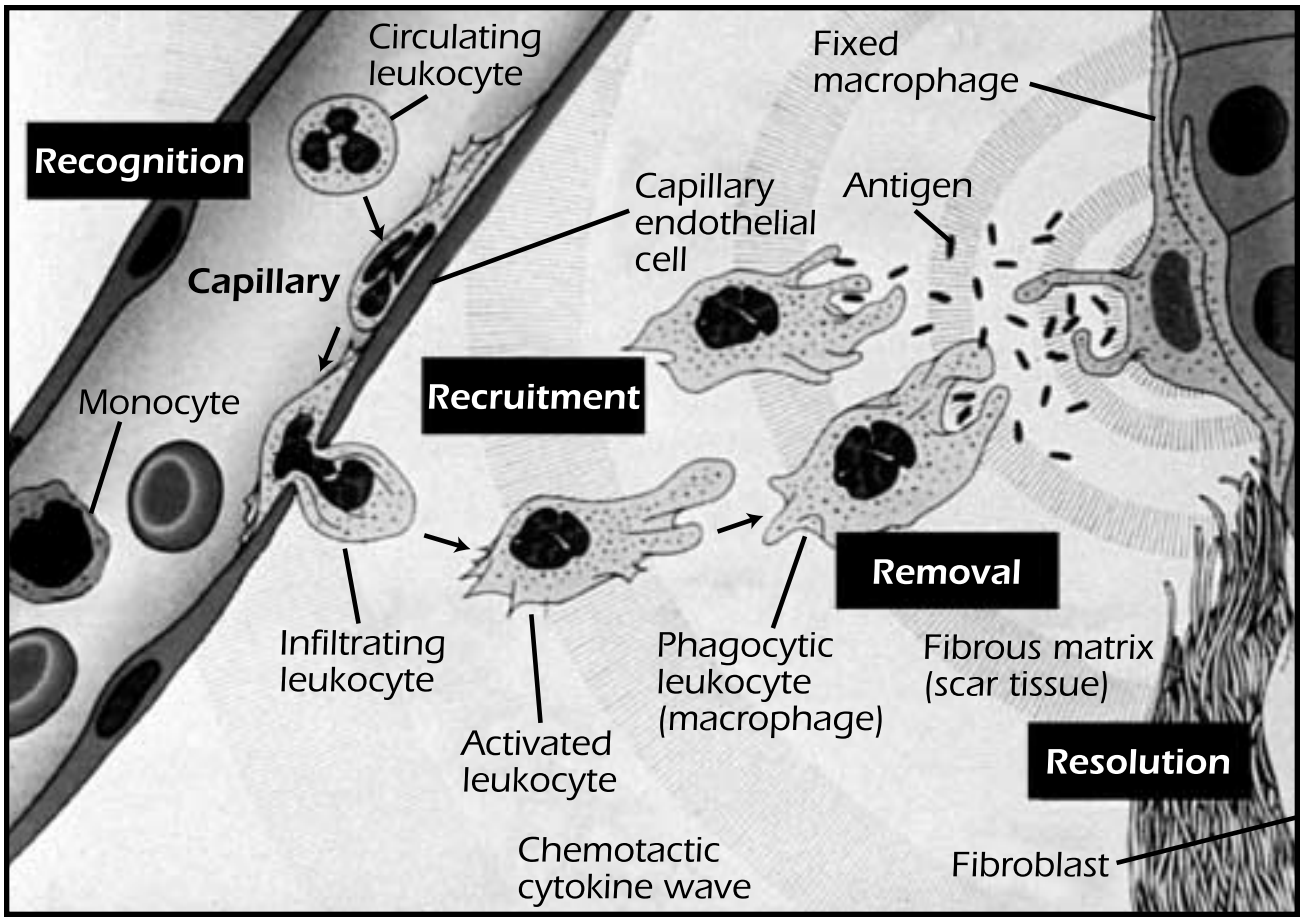

Figure 1. Inflammatory response of the lung. During the recognition phase, there is increased expression of adhesion molecules for leukocyte trafficking, which leads to fibroblast proliferation and migration. During the recruitment phase, there is trafficking of neutrophils, lymphocytes, dendritic cells, and natural killer cells in the presence of chemokines. During the removal phase, T-helper (Th) cell subsets express Th1 cytokines and Th2 cytokines, which have opposing effects on collagen deposition. Normally, the resolution phase restores lung architecture through homeostatic mechanisms. In patients with idiopathic pulmonary fibrosis, however, Th2 responses outweigh Th1 responses, promoting fibroplasia and the accumulation of collagen.

response is characterized by recognition, recruitment, removal, and resolution (repair) (Figure 1). During the recognition phase, there is generation of the early-response cytokines (eg, interleukin [IL]-1 and tumor necrosis factor [TNF]) and increased expression of adhesion molecules for leukocyte trafficking. The pathogenesis of ILD is presumably related to initial loss of alveolar type I epithelial cells and endothelial cells, followed by persistence of inflammation, proliferation of type II cells, recruitment and proliferation of endothelial cells and fibroblasts, and deposition of ECM, leading to end-stage alveolar and interstitial fibrosis. These events involve a complex interplay among diverse immune effector cells, cellular constituents of the alveolar-capillary membrane and interstitium of the lung, and specific cytokines, culminating in chronic inflammation and exaggerated angiogenesis, fibroproliferation, and ECM deposition.

Although not all inflammatory disorders result in fibrosis, fibrotic responses are always preceded and potentially perpetuated by chronic inflammation. A salient feature of chronic inflammation is infiltration by

> *Activated alveolar macrophages and neutrophils undoubtedly play a role in the pathogenesis of the inflammatory lung lesion of IPF.*

mononuclear cells. These extravasating leukocytes contribute to the pathogenesis of chronic inflammation and promote fibrosis via the elaboration of a variety of cytokines.

RECRUITMENT/CHEMOTACTIC CYTOKINES

The maintenance of leukocyte recruitment during inflammation requires intercellular communication between infiltrating leukocytes on the one hand and the endothelium and resident stromal and parenchymal cells on the other hand. These events are mediated via the generation of early-response cytokines such as IL-1 and TNF, the expression of cell-surface adhesion molecules, and the production of chemotactic molecules such as chemokines.

The CXC, CC, C, and CX_3C group of human chemotactic cytokines consists of four closely related polypeptide families that behave, in general, as potent chemotactic factors for neutrophils, eosinophils, basophils, monocytes, mast cells, dendritic cells, natural killer cells, and T and B lymphocytes.[1] The chemokines display highly conserved cysteine amino acid residues. The CXC chemokine family has the first two NH_2-terminal cysteines separated by one nonconserved amino acid residue, the CXC cysteine motif; the CC chemokine family has the first two NH_2-terminal cysteines in juxtaposition, the CC cysteine motif; the C chemokine has a lone NH_2-terminal cysteine amino acid, the C cysteine motif; and the CX_3C chemokine has the first two NH_2-terminal cysteines separated by three nonconserved amino acid residues.

> *The initiation, maintenance, and resolution of an immune response appear to be governed by a complex network of specific cytokines.*

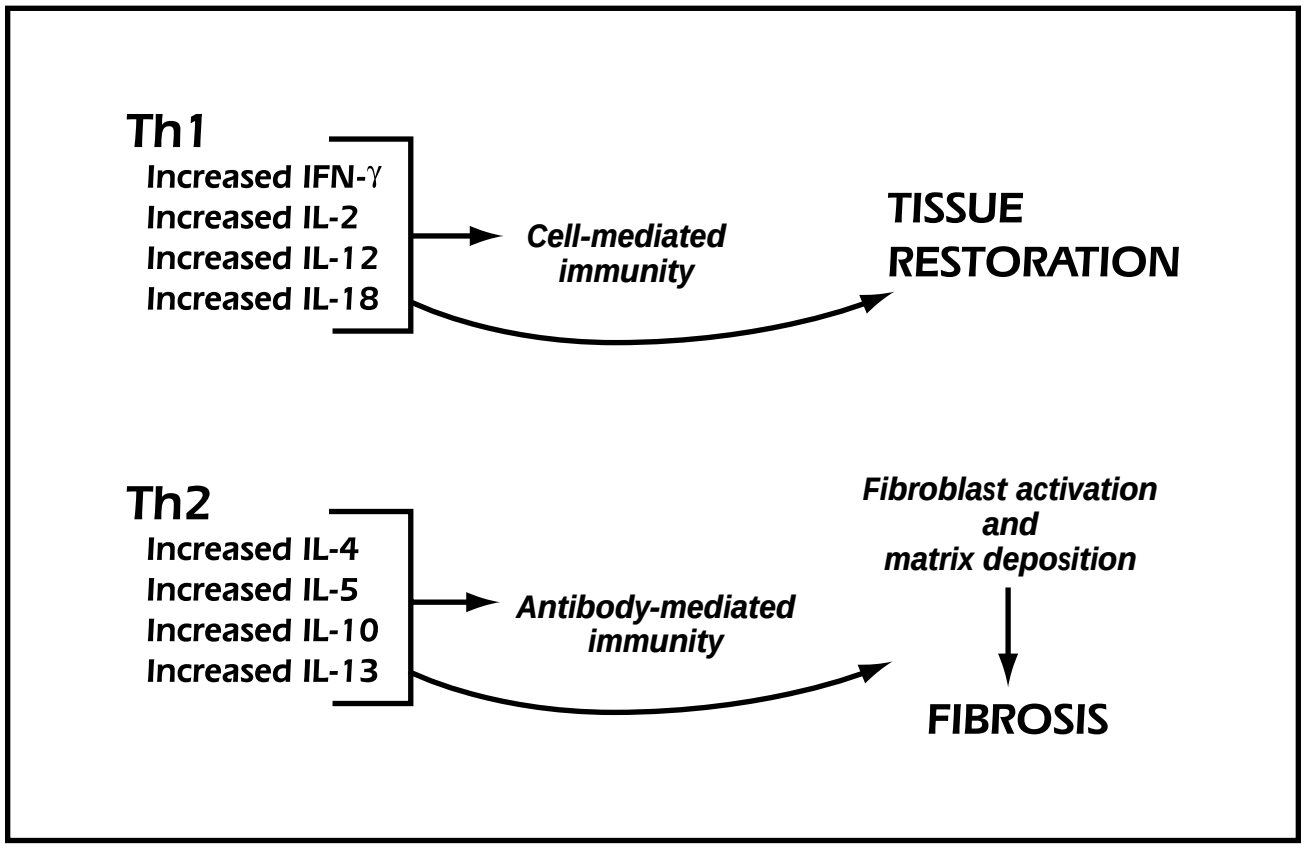

Figure 2. Cytokine components of the Th1 and Th2 responses. The net effect of a predominantly Th1 response is tissue restoration. The net effect of a predominantly Th2 response, as in patients with idiopathic pulmonary fibrosis, is fibroblast activation and extracellular matrix deposition, which lead to fibrosis. (IFN-γ=interferon gamma; IL=interleukin.)

An imbalance in the expression of Th1:Th2 cytokines may be important in dictating different immunopathologic responses.

CXC Chemokines in Pulmonary Fibrosis

Although the mechanism(s) by which cellular injury occurs in IPF remains unclear, activated alveolar macrophages and neutrophils undoubtedly play a role in the pathogenesis of the inflammatory lung lesion of IPF.[2,3] Evidence supports the importance of the neutrophil in the pathogenesis of IPF. Bronchoalveolar lavage (BAL) fluid neutrophilia and evidence of neutrophils in lung tissue have been demonstrated in patients with IPF.[4] Although the number or proportion of neutrophils in BAL fluid does not correlate with activity of alveolitis and has limited prognostic value, declines in the proportion of BAL fluid neutrophils typically occur among patients exhibiting favorable responses to therapy. Neutrophilic alveolitis has been described in humans with IPF as well as in diverse animal models of pulmonary fibrosis. The neutrophil represents a potent immune effector cell and has the capacity to release oxygen radicals, complement fragments, arachidonic acid metabolites, proteolytic enzymes, and various cytokines, which may inflict lung injury. The signals responsible for the recruitment of neutrophils to the lung and the perpetuation of neutrophilic alveolitis have not been fully characterized. The level of the CXC chemokine IL-8 is elevated in patients with IPF compared with healthy persons and patients with sarcoidosis, and elevated IL-8 levels correlate with the presence of neutrophils in BAL fluid.[5,6] The alveolar macrophage and pulmonary fibroblast appear to be important cellular sources of IL-8 in IPF,[5] and levels of IL-8 in IPF may correlate with prognosis.[6]

CC Chemokines in Pulmonary Fibrosis

Animal models such as bleomycin-induced pulmonary fibrosis have demonstrated the presence and contribution of CC chemokines in the early pathogenesis (< 3 weeks) of fibrosis. Time-dependent expression of monocyte chemoattractant protein-1 (MCP-1) has been reported in response to bleomycin challenge in rodents.[7] The expression of both MCP-1 and murine macrophage inflammatory protein-1α (MIP-1α) during the first week after bleomycin challenge temporally correlates with accumulation of lung mononuclear cells.[8] In the second week after bleomycin challenge, increased MIP-1α expression coincides with increases in macrophages, while an elevated MCP-1 level is not observed. The predominant cellular source of either MCP-1 or MIP-1α by in situ hybridization or immunolocalization is the alveolar macrophage; eosinophils are also significant cellular sources of MCP-1, and epithelial cells and interstitial macrophages are significant sources of MIP-1α. Depletion of MCP-1 or MIP-1α results in a reduction of infiltrating cells in the lungs of bleomycin-treated animals by 30% and 35%, respectively. Depletion of MCP-1 had the greatest effect on mononuclear cells, whereas neutralization of MIP-1α reduced B-cell, macrophage, and neutrophil infiltration. Furthermore, bleomycin-challenged mice passively immunized with neutralizing anti-MIP-1α antibodies demonstrated a 49% decrease in total lung collagen, as determined by lung hydroxyproline content. This suggests the existence of other mediators with similar or overlapping activities.

REMOVAL CYTOKINES

There is evidence supporting the paradigm that the initiation, maintenance, and resolution of an immune response are governed by a complex network of specific cytokines.[9] However, our knowledge of the potential mechanisms whereby cytokines function in the various phases of an immune response comes from in vitro studies that are often difficult to translate into in vivo inflammatory events. This difficulty is further compounded by the heterogeneity of cytokines and inflammatory responses that can be observed under different clinical conditions. The discovery that T-helper (Th) cell subsets could be classified on the basis of cytokine profiles (Table) has provided a degree of clarification to chronic cell-mediated immune responses (Figure 2). The type-1 (Th1) and type- 2 (Th2) cytokine patterns in mice were originally identified from a panel of T-helper cell clones. The Th1 cytokines include interferon gamma (IFN-γ) and IL-2, and the Th2 cytokines include IL-4, IL-5, IL-10, and IL-13.[10,11]

The realization that Th1 and Th2 cytokines are expressed by a variety of cells and that the functions of

IFN-γ is a major Th1 cytokine and possesses profound regulatory activity for collagen deposition during chronic inflammation.

Table. Type 1 and Type 2 Cytokines

- Type 1 (Th1) cytokines promote cell-mediated immunity
  - IFN-γ
  - IL-2
  - IL-12
  - IL-18
- Type 2 (Th2) cytokines promote humoral immunity
  - IL-4
  - IL-5
  - IL-10
  - IL-13

IFN-γ = interferon gamma; IL = interleukin; Th = T-helper cell.

these cytokines differ suggests that an imbalance in the expression of Th1:Th2 cytokines may be important in dictating different immunopathologic responses.[9] For example, Th1 cytokines appear to be involved in cell-mediated immunity associated with autoimmune disorders and allograft rejection, whereas Th2 cytokines are involved predominantly in mediating allergic inflammation and chronic fibroproliferative disorders such as asthma, atopic dermatitis, IPF, and systemic sclerosis. Thus, it is more appropriate to define certain diseases in terms of the predominant cytokine profile rather than the predominant T-helper cell subset.

The strict definition of Th1 and Th2 responses may break down in a scenario where the initial inciting agent triggers an unsuccessful Th1 response. The subsequent host reaction to the antigen or the chronicity of the disorder may induce a switch to a response dominated by Th2 cytokines. The manifestation of this latter response is the scenario of stromal cell/fibroblast proliferation and deposition of ECM and, ultimately, fibrosis. Thus, the cytokine pattern in certain diseases is often predictable and appropriate, whereas severe pathologic consequences may result if an inappropriate cytokine phenotype is expressed. This latter situation may play a role in certain chronic inflammatory diseases, such as idiopathic lung disease (ILD), in which unknown factors lead to dysregulated repair with exaggerated chronic inflammation, fibroblast proliferation, deposition of ECM, angiogenesis, and, finally, fibrosis that accompanies end-stage pulmonary fibrosis.

The predominant cytokine profile may determine the disease phenotype responsible for either resolution or progression to end-stage fibrosis. Supporting evidence comes from studies demonstrating that interferons, especially IFN-γ, have profound suppressive effects on the production of ECM proteins such as collagen and fibronectin.[12-14] Investigators have demonstrated that IFN-γ can inhibit both fibroblast and chondrocyte collagen production in vitro as well as decrease the expression of steady-state type I and III procollagen mRNA.[15-21] IFN-γ reduces the lung fibroblast growth induced by platelet-derived growth factor (PDGF) but stimulates PDGF production by alveolar macrophages.[22] IFN-γ upregulates gene expression of the major matrix-degrading metalloproteinase stromelysin-1 by fibroblasts.[23,24] IFN-γ is a potent inhibitor of the eosinophil chemotactic CC chemokine eotaxin from fibroblasts.[25] IFN-γ differentially regulates the expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 on fibroblasts.[26] The administration of IFN-γ in vivo can reduce ECM in animal models of fibrosis.[12-16,27,28] Moreover, IFN-γ treatment of patients with either systemic sclerosis or IPF for 1 year improved pulmonary function and gas exchange, with improved resting and exercise arterial partial pressure of oxygen (Pa_{O2}).[29,30] These findings support the concept that IFN-γ is one of the major Th1 cytokines, possessing profound regulatory activity for collagen deposition during chronic inflammation.

Lung tissue of patients with IPF has been examined for the presence of a Th1 vs Th2 pattern of cytokine expression by in situ hybridization and immunolocalization of cytokine protein.[31] Although there is a pattern for the existence of both Th1 cytokines (characterized by the expression of IFN-γ) and Th2 cytokines (characterized by the expression of IL-4 and IL-5) in IPF lung tissue, the presence of Th2 cytokines predominated over the expression of IFN-γ. This pattern of cytokine expression may be related to either the potential role of the humoral response in the pathogenesis of IPF or the inability of IFN-γ to tip the balance away from an IL-4/IL-13–dependent profibrotic environment. Further supporting an imbalance between Th2 cytokines and IFN-γ is the finding that IFN-γ levels are inversely related to the levels of type III procollagen in the BAL fluid of IPF patients.[32] The levels of IFN-γ, in particular, were inversely correlated with progression of pulmonary

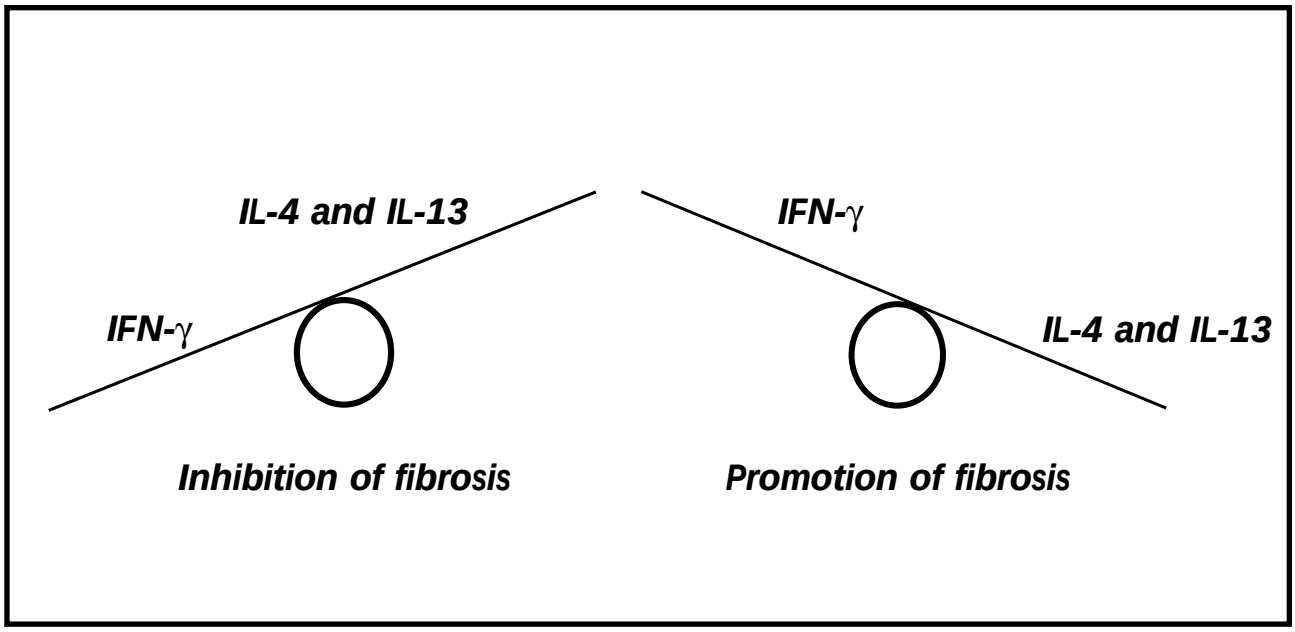

Figure 3. An imbalance between IFN-γ and IL-4 and IL-13 that favors IFN-γ is potentially beneficial in inhibiting fibrosis. In contrast, an imbalance with the interleukins predominating is important in the pathogenesis of fibrosis. (IFN-γ=interferon gamma; IL=interleukin.)

fibrosis as shown by further deterioration of pulmonary function. These findings have been further substantiated by the recent demonstration that IFN-γ1b treatment of IPF patients who had failed to respond to glucocorticoid therapy for 1 year improved total lung capacity and resting and exertional Pa_{O_2}.[30] The predominance of Th2 cytokines, compared with Th1 cytokines, in the chronic inflammation/fibroproliferation of IPF supports the notion that these removal cytokines are probably inadequate to fully eliminate the inciting "antigen," and the promotion of fibrosis by Th2 cytokines may be an attempt to contain or "wall off" the "antigen." These findings suggest that the persistent imbalance in the expression of Th2 vs Th1 cytokines in the lung is a mechanism for the progression of pulmonary fibrosis (Figure 3).

REPAIR CYTOKINES/GROWTH FACTORS

Repair/growth factor cytokines include the PDGFs, basic fibroblast growth factor, insulin-like growth factor-1, and transforming growth factor beta (TGF-β).

TGF-β exists as three closely homologous (72% to 80%) dimeric isoforms: TGF-β1, TGFβ2, and TGF-β3.[33] Although all three isoforms can stimulate fibroblast procollagen production in vitro, they are differentially expressed during bleomycin-induced lung fibrosis.[34] In bleomycin-induced pulmonary fibrosis, maximal expression of TGF-β1 predominates, and this isoform is produced primarily by macrophages.[33] These findings suggest that various isoforms of TGF-β are differentially regulated during bleomycin-induced pulmonary fibrosis. In subsequent studies, the passive immunization of bleomycin-treated mice with neutralizing antibodies to both TGF-β1 and TGF-β2 significantly reduced total lung collagen content, as determined by the level of hydroxyproline.[35]

In IPF, increased expression of TGF-β has been found by immunohistochemistry and is localized to bronchiolar epithelial cells, epithelial cells of honeycomb cysts, and hyperplastic type II pneumocytes.[36] In addition, TGF-β has been found in IPF in association with constituents of the ECM. The predominant isoform in IPF is TGF-β1, as it is in bleomycin-induced pulmonary fibrosis. These and other findings suggest that TGF-β is a critical cytokine for the promotion of pulmonary fibrosis.

TGF-β is a critical cytokine for the promotion of pulmonary fibrosis.

ANGIOGENESIS AND PULMONARY FIBROSIS

Angiogenesis is a fundamental component of inflammation and wound repair. The existence of neovascularization in IPF was originally identified by Turner-Warwick.[37] Subsequently, lung tissue from patients with IPF was demonstrated to have markedly increased angiogenic activity that is almost entirely attributable to the imbalance in the overexpression of the angiogenic CXC chemokine IL-8 compared with the relative down-regulation of the angiostatic interferon-inducible CXC chemokine IP-10.[38] Similarly, during bleomycin-induced pulmonary fibrosis, MIP-2 (murine functional homologue of IL-8) and IP-10, measured in lung tissue, were found to be directly and inversely correlated, respectively, with fibrosis.[39,40] Moreover, when either endogenous MIP-2 was depleted with neutralizing antibodies or exogenous IP-10 was administered to the animals during bleomycin exposure, both treatment strategies resulted in marked attenuation of pulmonary fibrosis that was entirely attributable to a reduction in angiogenesis in the lung.[39,40] These findings support the notion that angiogenesis is a critical biological event that supports fibroplasia and deposition of ECM in the lung during pulmonary fibrosis. Furthermore, IFN-γ1b treatment of IPF may exert its effect in part by shifting the imbalance of the expression of cytokines to favor an angiostatic environment, leading to inhibition of dysregulated neovascularization/vascular remodeling, fibroproliferation, and deposition of ECM.

> *IFN-γ1b treatment of IPF may exert its effect in part by altering the profile of cytokines that are expressed.*

concluding points

- **A variety of cytokines may contribute to pulmonary fibrosis.**
- **Cytokines can be categorized on the basis of their ability to function in recognition, recruitment, removal, and repair in the context of the chronic inflammatory/fibroproliferative nature of ILD.**
- **Many of these proteins are detectable in BAL fluid or lung tissue of ILD patients and may serve as useful laboratory markers of disease activity or novel targets for therapeutic intervention.**
- **Given the limited efficacy of current therapy for ILD/IPF, it seems prudent to consider alternative therapeutic regimens, such as ablation of multiple cytokines, to prevent pulmonary fibrosis and the associated pathophysiology.**
- **The recent discovery that IFN-γ1b treatment of IPF patients results in improved lung function is exciting and suggests that the administration of this pivotal cytokine may have a dramatic impact on a variety of other cytokines that ultimately reduce pulmonary fibrosis.**
- **Future directions in cytokine research may include systemic or local intrapulmonary cytokine, gene, or protein therapy, which may either attenuate or augment the expression of specific cytokines and, in turn, prevent endstage pulmonary fibrosis, leading to reduced morbidity and mortality.**

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Interferon Gamma-1b: Mechanisms of Action, Preclinical Studies, and Clinical Experience

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Pulmonary fibrosis is orchestrated by a complex network of interrelated pathways, which represent the simultaneous control of tissue reorganization, growth, and chronic inflammation. We are just beginning to fully understand the pathogenetic mechanisms involved in these complex processes. Importantly, the ultimate requirement for successful treatment of this devastating disease will be a more complete understanding of the sequence of events that eventually lead to end-stage fibrosis. Thus, further investigations are needed that permit the search for new pharmacologic targets by detailed biological assessment at a clinically defined stage of the disease. We believe that the controlled use of interferon gamma in pulmonary fibrosis provides a useful tool for improving our understanding of the pathogenesis of pulmonary fibrosis.

Progressive pulmonary fibrosis is characterized by a combination of injury and an exaggerated yet futile attempt to repair the damaged lung. This response appears to transform the regular maintenance of organ cell growth into the progressive development of a virtually cell-free scar. Characteristic features of this relentless induction of mesenchymal growth are intensified proteolytic activity, a change in the composition of extracellular matrix (ECM) components, and a shifted cellular immune reaction of low intensity.

IMPORTANCE OF CYTOKINES IN THE FIBROTIC PROCESS

Cytokines such as tumor necrosis factor alpha and the growth mediator transforming growth factor beta-1 (TGF-β1) have long been implicated in the process underlying progressive pulmonary fibrosis. Of these mediators, TGF-β1 has probably become the most important, owing to its strong activation of mesenchymal growth and its ability to modulate cellular immunity. The immunomodulatory action of TGF-β1 is well known.[1-3] It includes the inhibition of interferon gamma (IFN-γ) release[4] and the suppression of IFN-γ–dependent immune reactions,[5] and the induction of immunosuppressive CD8+ lymphocytes.[6] Indeed, a modulation of cellular immunity in patients with progressive fibrosis has been observed for years, even in forms that clearly represent different mechanisms of initial damage.[7]

TGF-β1 has probably become the most important cytokine underlying progressive pulmonary fibrosis, owing to its strong activation of mesenchymal growth and its ability to modulate cellular immunity.

TGF-β1 is known to cause severe pulmonary fibrosis when overexpressed in animal models,[8] and a signifi-

cant overexpression of the mediator is found in human pulmonary fibrosis.[9] More important, if the overexpression of TGF-β1 in fibrosing tissue is reduced by concomitant upregulation of the ECM proteoglycan decorin, organ fibrosis is significantly reduced.[10] Decorin is known to inactivate TGF-β1 by binding to the glycosaminoglycan (GAG) structures of the ECM. In the bleomycin model of lung fibrosis, which in many ways resembles human pulmonary fibrosis, expression of TGF-β1 is increased within hours after stimulation with the drug and maintained for >10 days.[11] This process is accompanied by an increased production of interstitial collagens and of proteoglycans such as perlecan and biglycan, which are frequently observed in fibrosing tissue. At the same time, expression of decorin is reduced.[11] These profound changes in the composition of the ECM occur when inflammatory cells are about to enter the site of damage. This is consistent with a growth-dependent modulation of the ECM that likely precedes the development of the accompanying immune reaction during early stages of fibrosis. In accordance with this view, activation of the gene for connective-tissue growth factor (CTGF), the major mediator of TGF-β1–dependent regulation of wound healing and fibrosis, precedes the changes in the immune reaction by several days (Figure 1).

TGF-β1 is secreted as an inactive, "latent" molecule, noncovalently bound to the latency-associated peptide (LAP).[12,13] Only when TGF-β1 is released from LAP can it exert its biological function. Thus, dissociation of the LAP–TGF-β1 complex, which is otherwise inactively bound to the ECM, becomes an important way to regulate the biological effectiveness of TGF-β1. LAP contains several binding sites for ECM proteins, including arginine-glycine-aspartic acid (RGD) sequences,[14] that allow for binding to integrins of the alphav-type.[15] Proteolytic enzymes such as plasmin or matrix metalloproteinases activate latent TGF-β1 by cleaving the LAP.[16,17] Thrombospondin-1 activates TGF-β1 by changing the conformation of the LAP–TGF-β1 complex.[18] However, knockout systems for these proteins indicate the existence of further activators of TGF-β1. It has been demonstrated that cells that can bind the LAP–TGF-β1 complex by expressing integrin alphavbeta6 on their surface cause spatially restricted activation of TGF-β1.[14] Moreover, mesenchymal cells, which express the alphavbeta3 integrin, may escape apoptosis by binding to ECM products such as osteopontin or

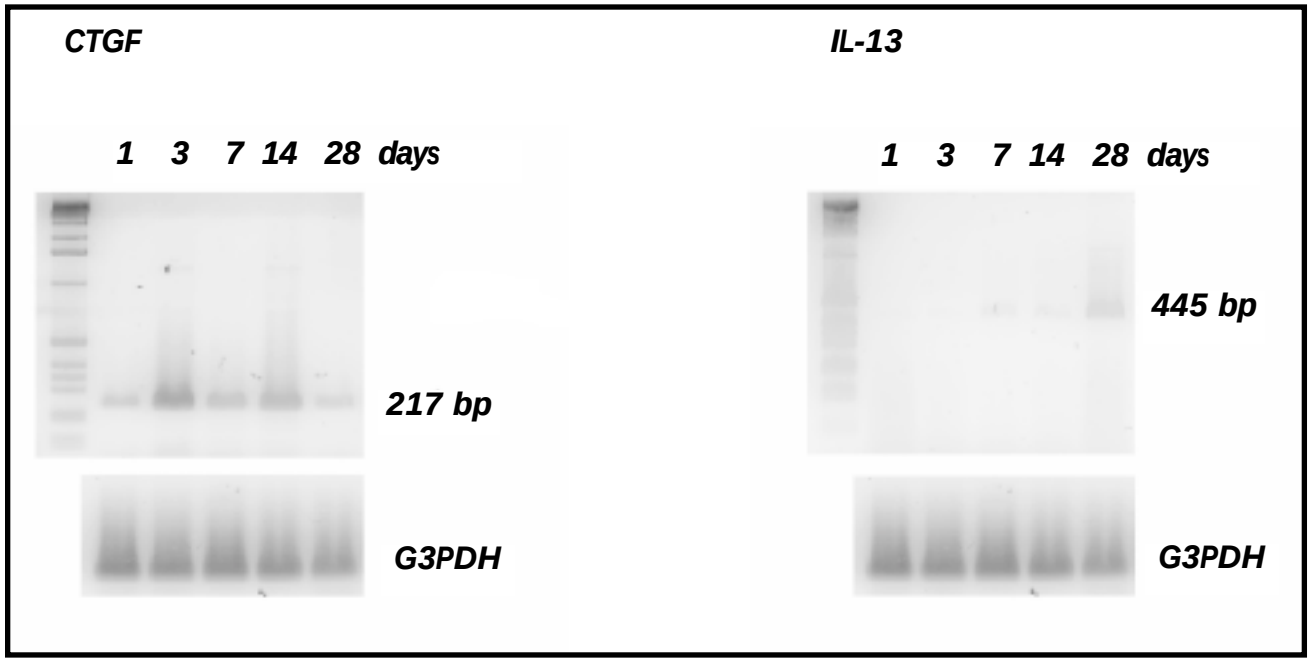

Figure 1. Reverse transcriptase-polymerase chain reaction (RT-PCR)–based analysis of transcription of connective-tissue growth factor (CTGF) and interleukin (IL)-13 genes in bleomycin-induced pulmonary fibrosis. Analysis was performed before and after 1, 3, 7, 14, and 28 days of intratracheal challenge with the drug. One microgram of cDNA was used for semiquantitative RT-PCR. The specific amplification products for CTGF and IL-13 were 217 base-pairs (bp) and 445 bp in length, respectively. Constitutive control was glyceraldehyde-3-phosphate dehydrogenase (G3PDH). Specificity of the amplification products was controlled by Southern hybridization. PCR was performed in a total volume of 50 µL. Thirty cycles of a hot-start PCR were performed on a Stratagene RoboCycler®. Aliquots were electrophoretically separated on a NuSieve GTG/agarose gel and visualized with Vistragreen.

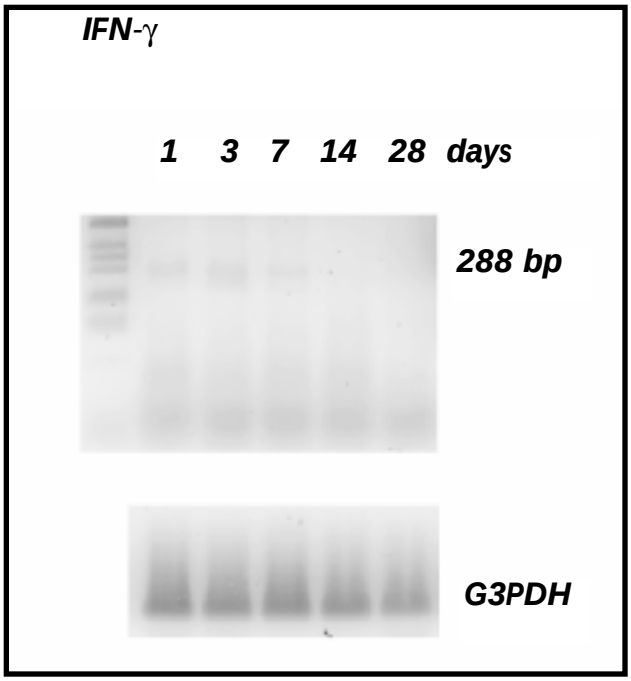

Figure 2. Reverse transcriptase-polymerase chain reaction (RT-PCR)–based analysis of transcription of the interferon gamma (IFN-γ) gene in bleomycin-induced pulmonary fibrosis. The specific amplification product for IFN-γ was 288 base-pairs (bp) in length. Constitutive control was glyceraldehyde-3-phosphate dehydrogenase (G3PDH).

tenascin, which, in turn, are expressed as a result of intensified repair.[19] Thus, specific cell types or subtypes may respond to intensified growth and at the same time escape growth control by interaction with an ECM milieu that represents intensified repair. The frequent observation of fibroblastic foci accompanying sites of epithelial repair in idiopathic pulmonary fibrosis (IPF)[20] emphasizes this possibility.

CELLULAR EVENTS IN THE PATHOGENESIS OF IPF

Recent investigations have demonstrated that progressive scarring in IPF is accompanied by a shift in the balance of T lymphocytes that favors the formation of the so-called T-helper type-2 (Th2) reaction.[21,22] This reaction is characterized by increased production of Th2 cytokines such as interleukin (IL)-4, IL-10, and IL-13 and a reduction in, or even complete loss of, transcription of IFN-γ, the main mediator of the T-helper type-1 (Th1) reaction.[23] In bleomycin-induced lung fibrosis, transcription of the IFN-γ gene decreases from day 7 onward and is no longer detectable by day 28 (Figure 2). Reciprocally, transcription of IL-13, which also has fibrogenic activity,[24,25] starts on day 7 and increases until day 28 (Figure 1). In contrast to the chronic inflammatory reaction accompanying fibrosis, acute inflammation of

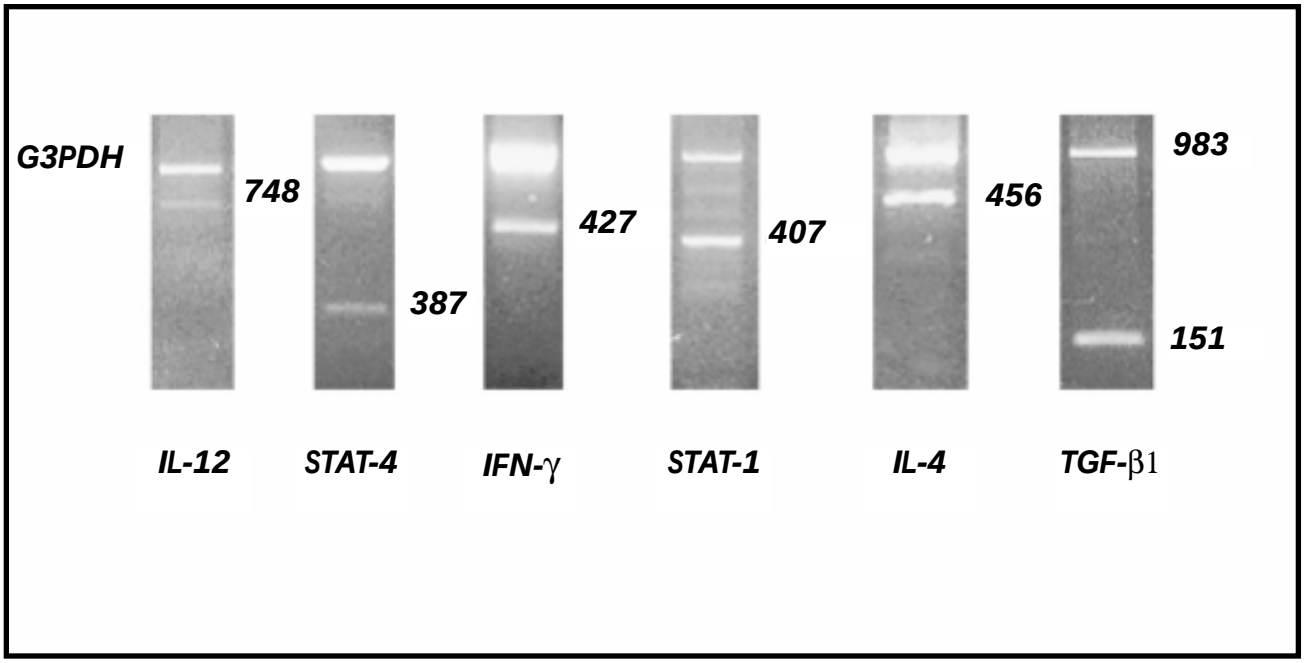

Figure 3. Reverse transcriptase-polymerase chain reaction (RT-PCR)–based assessment of transcription of interleukin (IL)-12, signal transducer and activator of transcription (STAT)-4, interferon gamma (INF-γ), STAT-1, IL-4, and transforming growth factor beta-1 (TGF-β1) genes in transbronchial lung biopsy specimens from a patient with acute interstitial pneumonia due to infection with Mycoplasma pneumoniae. For assessment of gene transcription, three transbronchial specimens were taken from the same lung segment. One microgram of cDNA was used for semiquantitative RT-PCR. Constitutive control was glyceraldehyde-3-phosphate dehydrogenase (G3PDH). During acute interstitial pneumonia, transcription of TGF-β1 and that of both T-helper type-1 and type-2 cytokines are activated concomitantly.

the pulmonary interstitium due to infection with Mycoplasma pneumoniae (Figure 3) is characterized by simultaneous transcription of both Th1 and Th2 cytokine genes (ie, IL-12 and IFN-γ, and IL-4, respectively). In addition, this reaction includes increased transcription of TGF-β1, probably reflecting activated tissue repair.

Unfortunately, as a result of the usually late diagnosis of IPF, the early cellular events in this disease are virtually impossible to assess. However, a PCR-based analysis of IL-4, IFN-γ, and TGF-β1 transcription in a patient with familial IPF who had symptoms of breathlessness for <1 year demonstrated that the immune balance had already shifted and the transcription of TGF-β1 was already intensely activated by this time (Figure 4). We found that the degree of transcription of the TGF-β1 gene was seven times greater in a group of patients with IPF than in individuals with normal lungs. In summary, our observations demonstrate features of pathologically intensified repair mechanisms.

The ECM contains considerable amounts of negatively charged GAG structures, mainly heparan sulfate, dermatan sulfate, and chondroitin sulfate. During fibrogenesis, the composition of GAGs is profoundly changed. In bleomycin-induced fibrosis, the concentration of highly sulfated heparan and dermatan sulfates increases over time, and the amount of chondroitin sulfates simultaneously decreases (Figure 5). This is also true for IPF. As IFN-γ strongly binds to highly sulfated heparan sulfate,[26-28] it is very likely that the composition of GAGs will have an impact on the bioavailability of IFN-γ. Notably, in bleomycin-induced fibrosis, these changes occur at the same time that the transcription of IFN-γ decreases.

> *IFN-γ causes reduced expression of TGF-β1 together with a reduction in the amount of fibrosis.*

ANTIFIBROTIC PROPERTIES OF INTERFERON GAMMA

The antifibrotic properties of IFN-γ are well documented.[29-32] It has already been suggested that reduced expression of TGF-β1 may account for this effect.[33] TGF-

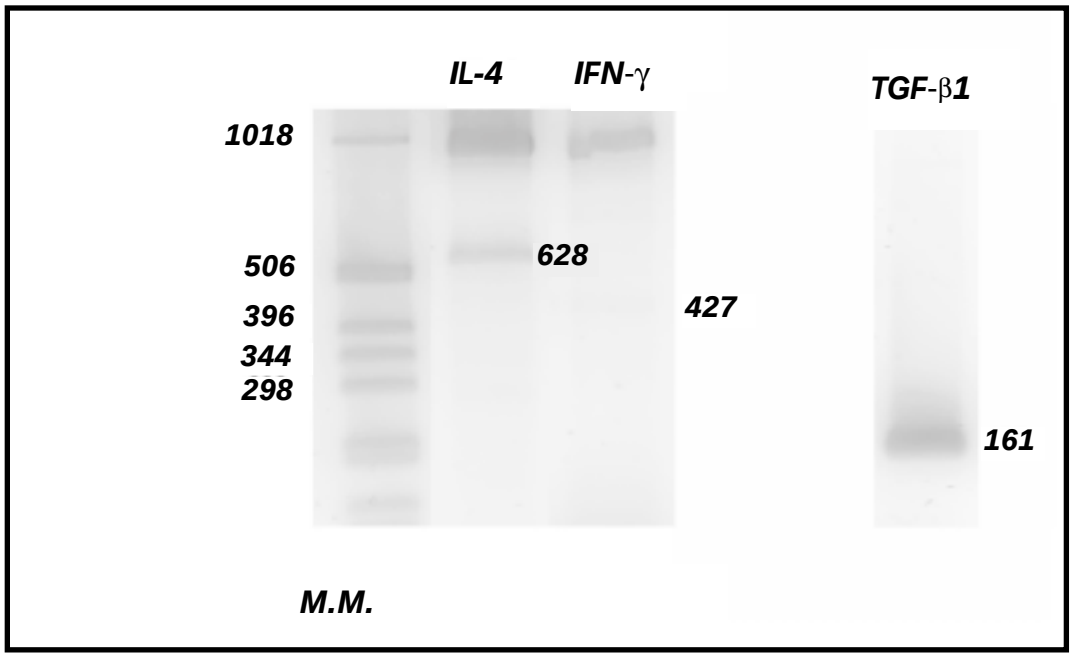

Figure 4. Analysis of transcription of interleukin (IL)-4, interferon gamma (IFN-γ), and transforming growth factor beta-1 (TGF-β1) genes in a patient (M.M.) with idiopathic pulmonary fibrosis. For assessment of gene transcription, three transbronchial specimens were taken from each lobe of the right lung and subsequently pooled for reverse transcriptase-polymerase chain reaction (RT-PCR) analysis. One microgram of cDNA was used for semiquantitative RT-PCR. Constitutive control was glyceraldehyde-3-phosphate dehydrogenase. The left lane depicts the molecular size marker. Specific amplification products were 628 base-pairs (bp) for IL-4, 427 bp for IFN-γ, and 161 bp for TGF-β1.

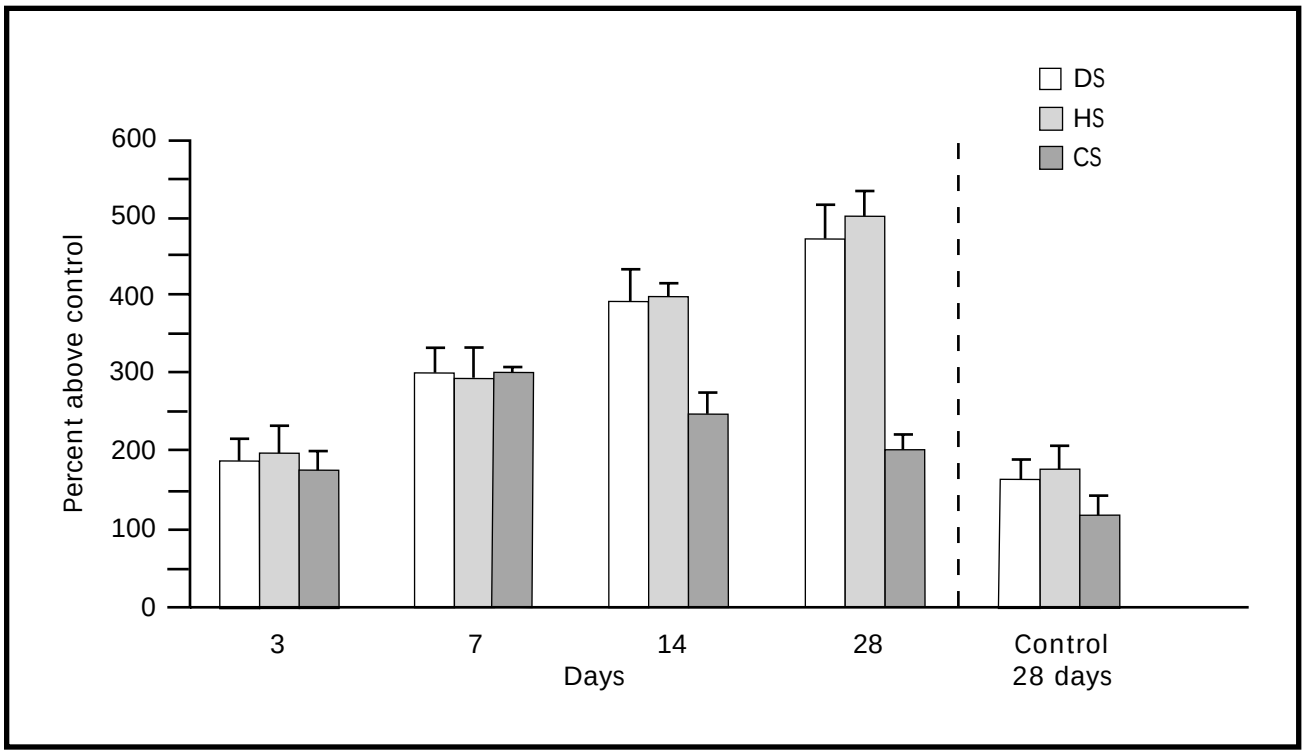

Figure 5. Assessment of glycosaminoglycan content of the extracellular matrix in bleomycin-induced pulmonary fibrosis. Lung sections were harvested before stimulation and after 3, 7, 14, and 28 days (n=6). Frozen sections were enzymatically digested and subjected to high-performance liquid chromatography analysis for identification of the different glycosaminoglycans. Values are given as percent above control. Compared with the control, a significant increase in both dermatan sulfate (DS) and heparan sulfate (HS) was observed in the lungs of bleomycin-treated animals. (CS=chondroitin sulfate.)

β1 signals through a receptor serine kinase that phosphorylates and activates the transcription factors Smad2, Smad3, and Smad4. As a result of this activation, a complex between Smad3 and Smad4 is formed, which then translocates to the nucleus, causing activation of TGF-β1–dependent genes. This signaling pathway is negatively controlled by the expression and activation of Smad7, an antagonistic SMAD that prevents the interaction of the Smad3/Smad4 complex with the TGF-β receptor. It was recently demonstrated that IFN-γ inhibits the promotion of TGF-β1–responsive genes by preventing phosphorylation and subsequent association of Smad3 with Smad4, and by inducing and activating Smad7 via specific activation of the IFN-γ–dependent Jak1 and Stat1 signaling pathways.[34]

Clinically, after 6 months of therapy with IFN-γ1b, the transcription of TGF-β1 and CTGF is significantly diminished. The simultaneous improvement in lung function of patients receiving IFN-γ1b[35] provides additional support for the hypothesis that the mesenchymal activation in patients with lung fibrosis depends, at least in part, on the continuous overexpression of TGF-β1 and CTGF. Moreover, these results suggest that an acquired deficiency of IFN-γ may be necessary for the exaggerated wound-healing process characteristic of progressive organ fibrosis.

POTENTIAL EFFECTIVENESS OF IFN-γ1b THERAPY

The effectiveness of IFN-γ1b therapy depends on two

In our experience, a history of breathlessness for >3 years before the start of IFN-γ1b therapy reduces the possibility that treatment will significantly improve lung function and clinical symptoms, although disease stability may well be achieved.

conditions: the extent of completed scarring, as reflected by the duration of disease-related symptoms, and the control of infection, either preexisting or acquired during therapy. In our currently limited experience, a history of breathlessness for >3 years before the start of IFN-γ1b therapy reduces the possibility that treatment will significantly improve lung function and clinical symptoms, although disease stability may well be achieved. Optimum results with IFN-γ1b require a dosage of 180 to 200 μg three times per week for a period of 9 to 12 months; some patients will require treatment for up to 15 months. The typical side effects of IFN-γ1b (mainly fever and chills) ideally decline within the first 6 to 9 weeks of treatment. If these symptoms reappear, infection is the most common cause. Our current experience with long-term IFN-γ1b therapy indicates that treatment cannot be stopped without risking the slow reappearance of fibrosis, although in several of our patients, the amount of IFN-γ1b required to maintain improvement gradually decreased. To confirm these results and extend the experience with this new treatment, a controlled study in a larger population is now required.

Our current experience with long-term IFN-γ1b therapy indicates that treatment cannot be stopped without risking the slow reappearance of fibrosis, although in several patients, the amount of IFN-γ1b required to maintain improvement gradually decreased.

concluding points

- **Cytokines such as tumor necrosis factor alpha and growth mediators such as TGF-β1 appear to play key roles in the fibrotic process of IPF.**
- **Several studies suggest that there may be a general impairment of the production of IFN-γ in patients with pulmonary fibrosis.**
- **The early cellular events in IPF have been difficult to assess. However, PCR-based analysis of IL-4, IFN-γ, and TGF-β1 transcription in a mildly symptomatic patient with familial IPF showed that a shifted immune balance and intense activation of TGF-β1 transcription were present at a presumably early stage of the disease process.**
- **Mesenchymal cell activation in patients with IPF corresponds with a low level of IFN-γ transcription, which is consistent with an acquired IFN-γ deficiency. Thus, the potential exists for IFN-γ1b therapy to have a counterbalancing effect, especially on TGF-β1–dependent activation of mesenchymal tissues, that suppresses or reverses the fibroproliferative response.**

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Interferon Gamma-1b in Idiopathic Pulmonary Fibrosis: Reanalysis of a Published Study

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The authors would like to acknowledge Rolf Ziesche, MD, for providing the clinical data for each patient and answering all questions raised by the expert panel.

Interferon gamma (IFN-γ) has been implicated in the pathogenesis of idiopathic pulmonary fibrosis (IPF); it inhibits proliferation of fibroblasts and reduces synthesis of connective-tissue matrix proteins. Patients with IPF may have deficits in IFN-γ production. Ziesche et al conducted a 12-month study of IFN-γ1b in 18 patients with pulmonary fibrosis of unknown etiology who were unresponsive to corticosteroid therapy. Nine patients received IFN-γ1b plus prednisolone and nine received prednisolone alone. The results showed that lung function improved in the patients treated with IFN-γ1b and worsened in those treated with prednisolone only. The differences were statistically significant. A number of questions were raised about the study because it was unclear that all the patients studied had IPF, as their length of survival was atypical, and the difference in outcome between the treated patients and the control group did not appear to be clinically significant. Therefore, an independent expert panel reanalyzed the data on a case-by-case basis with Dr. Ziesche, using the recently published criteria developed by the American Thoracic Society, the European Respiratory Society, and the American College of Chest Physicians to reassess the diagnosis and response to therapy. The reanalyzed data revealed that 15 patients had definite or probable IPF and confirmed the improvement in gas exchange and lung volumes among those treated with IFN-γ1b.

Idiopathic pulmonary fibrosis (IPF) appears to be an immune-mediated disorder characterized by inflammation, proliferation of fibroblasts, and deposition of connective-tissue matrix proteins in the lungs. Despite the use of immunosuppressive agents (ie, corticosteroids, azathioprine, and cyclophosphamide) to control the inflammation and thereby halt the progressive fibrogenesis, the prognosis for patients with IPF remains poor.[1] Recent research, therefore, has focused on more-targeted interventions, which block specific components of the proposed immunologic pathways leading to the fibroproliferative response that inevitably supervenes in patients with IPF.

One such approach has been the augmentation of interferon gamma (IFN-γ), a type-1 T-helper cell (Th1) cytokine that has been shown to inhibit the proliferation of fibroblasts and reduce the synthesis of connective-tissue matrix proteins by fibroblasts.[2,3] IFN-γ appears to exert this effect by downregulating the expression of transforming growth factor beta-1 (TGF-β1), a type-2 T-helper cell (Th2) cytokine that provokes fibroblast proliferation and synthesis of connective-tissue matrix proteins.[4] TGF-β1 activates a series of processes that uniformly contribute to accumulation of collagen, and it may be the "master switch" for fibrotic events in the lung.[5] In a reciprocal manner (ie, negative feedback loop), TGF-β1 downregulates the expression of IFN-γ.[6]

IFN-γ inhibits the proliferation of fibroblasts and reduces the synthesis of connective-tissue matrix proteins.

Th1 and Th2 cytokines generally have complementary modulatory effects, and the balance between their expression may be key to the control of immune responses at sites of disease.[7] Studies of lung tissue from patients with IPF have shown deficits in IFN-γ[8,9] and increased levels of TGF-β1[10] Impaired IFN-γ release may be a potentiating factor in the pathogenesis of IPF. A brief summary of a small study reported by Ziesche and colleagues in 1996 suggested that treatment of pulmonary fibrosis with a combination of IFN-γ1b and low-dose prednisolone was helpful in patients who were resistant to therapy with high-dose corticosteroids.[11] This prompted a prospective study, the results of which have been published as a preliminary report.[12] The study is provocative, as this is the first report that suggests that IFN-γ may indeed by a worthwhile antifibrotic agent for patients with IPF. Since other antiinflammatory and/or immunosuppressive agents have not yielded encouraging results in several studies, the published report of IFN-γ[12] has raised appropriate concerns and skepticism. An independent expert panel has reanalyzed the published data directly with the lead investigator. This article summarizes the findings of the original study and those of the reanalysis.

SUMMARY OF PUBLISHED REPORT

Study Patients and Methods

On the basis of the findings of their 1996 study, Ziesche and associates conducted an open, randomized, 12-month phase II study of IFN-γ1b and low-dose prednisolone in patients with IPF (Figure 1).[12] This study was conducted between May 1996 and February 1998, and the results were published in The New England Journal of Medicine in October 1999.

All 18 patients entered in the study were apparently nonsmokers who had not previously responded to corticosteroids or other immunosuppressive agents, had experienced a decrease in lung function of at least 10% during the preceding 12 months, and had histologic evidence of usual interstitial pneumonia (UIP) on open-lung biopsy. All 18 patients had unmeasurable levels of IFN-γ mRNA in tissue samples from transbronchial biopsies.

The main histopathologic feature used to diagnose IPF was the presence of subpleural and periacinar fibrotic lesions. The radiographic criteria were the absence of bilateral patchy infiltrates and the presence of a predominantly peripheral distribution of lesions on high-resolution computed tomography (HRCT).

Over the course of 1 year, the investigators treated nine patients with 200 μg of IFN-γ1b subcutaneously three times per week plus 7.5 mg of prednisolone orally per day, whereas the other nine patients received only prednisolone at a daily dose ranging from 7.5 mg to 50 mg, according to each patient's symptomatic response. Physiologic outcome measures included lung function and arterial blood gases determined at baseline and after 3, 6, 9, and 12 months of treatment.

Impaired release of IFN-γ may be a potentiating factor in the pathogenesis of IPF.

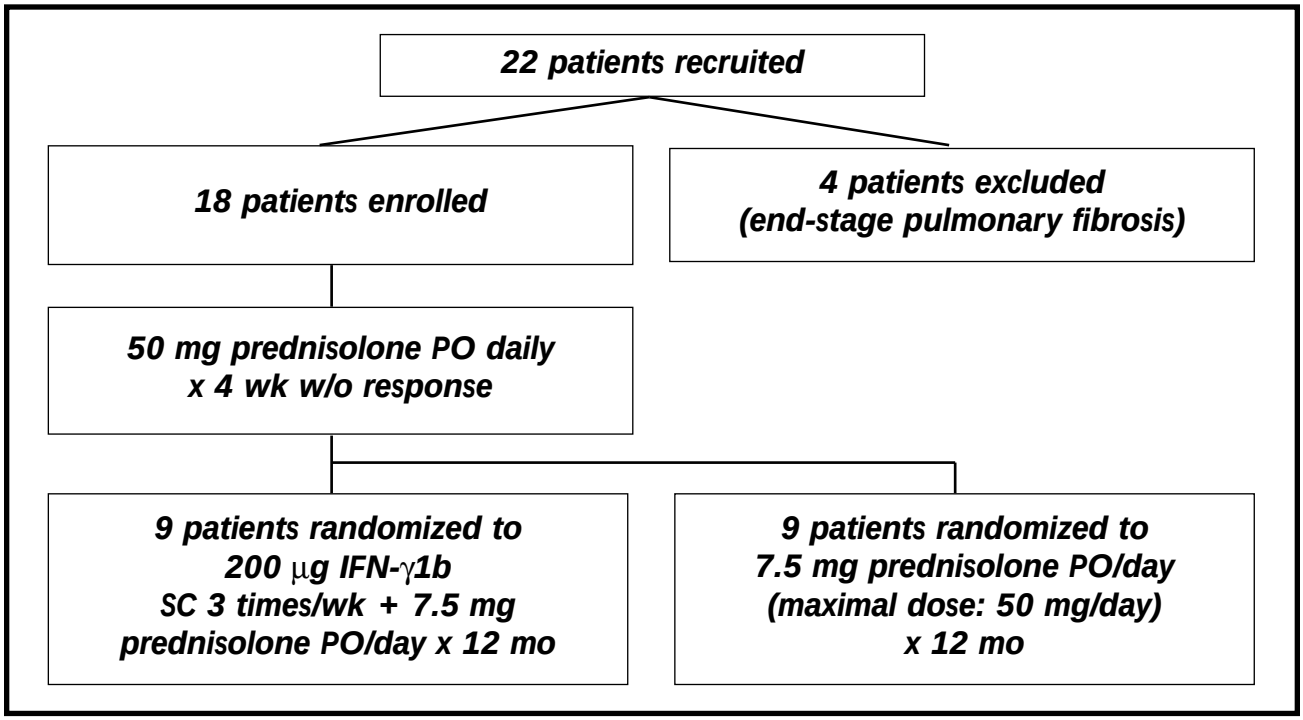

Figure 1. Randomization and treatment of patients in the original study conducted by Ziesche and co-workers.[12]

Study Results

All 18 patients completed the study. Over the 12-month period of the study, the 9 patients receiving only prednisolone had a mean absolute decrease in total lung capacity (TLC) of 4%, whereas the 9 patients treated with IFN-γ1b and prednisolone had a mean absolute increase in TLC of 9%. The results for changes in forced vital capacity (FVC) were similar to those for changes in TLC. Over the same period, the patients receiving only prednisolone had a mean decrease in the arterial partial pressure of oxygen (Pa_{O_2}) of 3 mm Hg at rest, whereas patients treated with IFN-γ1b and prednisolone had a mean increase in Pa_{O_2} of 11 mm Hg at rest. The difference in the change from baseline values between the two groups was statistically significant for each comparison ($p < 0.001$).

CRITICAL REVIEW OF PUBLISHED REPORT

Potential Selection Bias

Because the medical management of patients with IPF has been so unsuccessful, the atypically good results associated with IFN-γ1b in this study raised a number of questions. Egan commented in The Lancet that the rigorous selection criterion of histologic evidence of UIP from tissue acquired by open-lung biopsy may have introduced a selection bias, since IPF patients with a favorable clinical course are more likely to have undergone lung biopsies than those with a poor prognosis.[13]

In a letter to the editor of The New England Journal of Medicine, King observed that some patients enrolled in the study may not have had IPF, noting that the criteria used to make this diagnosis histopathologically and on HRCT scans were unclear and incomplete.[14] *Since patients with IPF invariably have progressive disease, King also expressed surprise at the outcome and duration of survival of the study patients, all of whom were alive in July 1999.*

Ziesche and Block replied to King's comments,[15] *noting that the investigators had carefully considered the diagnostic criteria for IPF during patient enrollment and used the definition published by the pathology department of the Mayo Clinic in 1998.*[16] *However, this was a highly selected study population. Specifically, all 18 patients entered in the study were nonsmokers and had unmeasurable levels of IFN-γ mRNA in tissue samples from transbronchial biopsies.*

All patients in the study by Ziesche et al had unmeasurable levels of IFN-γ mRNA in tissue samples from transbronchial biopsies.

Inadequate Control Group

Egan speculated that the higher dose of corticosteroids received by the prednisolone-only group may have contributed to the decrease in pulmonary function seen in these patients. He speculated that this might have occurred as a result of a steroid-induced increase in body-mass index. Egan also raised the theoretical possibility that the higher doses of glucocorticoids received by the control group might have promoted an exacerbation of the lung injury by activating a latent viral infection, for example, Epstein-Barr virus replication within the pulmonary tissue. This may have conferred a statistical advantage on the group receiving IFN-γ1b. According to Egan, this possibility highlights the need to compare novel therapies for IPF with either placebo or no treatment. Such issues should be considered when new studies of IFN-γ1b are planned.

Clinical Significance of the Treatment Outcome

King noted that the treatment outcome was probably not clinically significant according to the recently defined American Thoracic Society (ATS)/European Respiratory Society (ERS)/American College of Chest Physicians (ACCP) criteria.[1] The investigators responded that the progression, duration, and outcome of IPF vary considerably, and the treatment outcome was significant because the mean absolute increase in TLC for the study population was about 500 mL.

POSTSTUDY REANALYSIS OF DATA

After Ziesche et al had published their results,[12] the ATS and the ERS, in collaboration with the ACCP, published an international consensus statement that included revised diagnostic criteria and outcomes guidelines for IPF.[1] Because of these new criteria and the questions raised by King,[14] the results reported in The New England Journal of Medicine were reanalyzed by an independent panel of experts.*

Statistical Analysis

The Fisher exact test was used to analyze data because of the small sample size. A value of $p < 0.05$ was accepted as statistically significant.

Confirmation of IPF/UIP Diagnosis

The expert panel reviewed each patient's surgical lung biopsy slides and photographs of HRCT chest scans to reconfirm the diagnosis of IPF. On the basis of strict diagnostic criteria for UIP on lung biopsy, correlated with confirmatory radiographic findings on HRCT chest scans, the panelists determined that 15 of the original 18 patients had either definite or probable IPF, whereas the remaining 3 patients definitely did not have IPF (Table 1). Of the 9 patients treated only with prednisolone, 5 had definite IPF and 3 had probable IPF. Of the 9 patients treated with IFN-γ1b and prednisolone, 4 had definite

Table 1. Reanalysis of Diagnoses of Idiopathic Pulmonary Fibrosis

Diagnosis	Treatment	
	Prednisolone Only (n = 9)	IFN-γ1b and Prednisolone (n = 9)
Definite IPF	5	4
Probable IPF*	3	3
Definitely not IPF	1	2

*Usual interstitial pneumonia ± chronic hypersensitivity pneumonitis, nonspecific interstitial pneumonia, or other nonspecific fibrosis.

*The independent review of the original data was conducted in March 2000, led by Ganesh Raghu with the assistance of Kevin Brown, Paul Noble, and Thomas Colby at the Mayo Clinic, Scottsdale, Arizona. Each patient's lung function studies, CT scans, and surgical lung biopsy were reviewed directly with Rolf Ziesche, who provided this panel of experts with the clinical data, including HRCT scans and histology slides of each study patient, to reconfirm the diagnosis of IPF according to the ATS/ERS/ACCP diagnostic criteria and to reassess the clinical course. This work was sponsored by InterMune Pharmaceuticals, Burlingame, California.

Table 2. Reanalysis of Data for Patients with Definite or Probable Idiopathic Pulmonary Fibrosis

Response by Criterion Measured	Prednisolone Only	IFN-γ1b + Prednisolone
*FVC at 12 mo**		
Improved	*0*	*3*
Stable	*5*	*4*
Worse	*3*	*0*
*$AaPO_2$ at 12 mo**		
Improved	*0*	*7*
Stable	*5*	*0*
Worse	*3*	*0*
*TLC at 12 mo**		
Improved	*0*	*4*
Stable	*7*	*3*
Worse	*1*	*0*
*FVC + $AaPO_2$ at 12 mo**		
Improved	*0*	*3*
Stable	*7*	*4*
Worse	*1*	*0*
*FVC on two consecutive measurements 3 mo apart**		
Improved	*0*	*3*
Stable	*6*	*4*
Worse	*2*	*0*
*$AaPO_2$ on two consecutive measurements 3 mo apart**		
Improved	*0*	*7*
Stable	*6*	*0*
Worse	*2*	*0*

**p < 0.05 for patients treated with IFN-γ1b + prednisolone vs prednisolone only.*
$AaPO_2$ = alveolar-arterial pressure difference for oxygen; FVC = forced vital capacity; IFN-γ = interferon gamma; TLC = total lung capacity.

IPF and 3 had probable IPF. The lung biopsy specimens of patients classified as having definite IPF showed histologic evidence of UIP. The lung biopsy specimens of patients classified as having probable IPF showed histologic evidence of UIP and coexisting findings suggestive of chronic hypersensitivity pneumonitis, nonspecific interstitial pneumonia, or other nonspecific parenchymal fibrosis in other areas of the same section.

All 15 cases with open-lung biopsies showed fibrosing interstitial pneumonia with evidence of irreversible interstitial fibrosis, usually including honeycomb change. In 10 of the 15 cases, the histologic pattern was typical of UIP; 3 showed a UIP pattern with relatively prominent cellular interstitial infiltrates or lymphoid hyperplasia in the nonfibrotic lung tissue. Two of these showed a UIP pattern in some regions, with other regions suggesting chronic hypersensitivity pneumonitis. One case was interpreted as fibrotic nonspecific interstitial pneumonia. One case showed marked fibroblastic proliferation, and only frozen sections were available for review.

Reassessment of Treatment Response and Clinical Course

The panel then used the published ATS/ERS/ACCP criteria[1] to reassess the response to IFN-γ1b and the clinical course of IPF. Response was defined according to the change in FVC, TLC, resting alveolar-arterial pressure difference for oxygen ($AaPO_2$), or combinations of these parameters. In the case of FVC and TLC, improvement was defined as an increase of ≥10% of the predicted

When the data from the study by Ziesche et al were reanalyzed, the number of patients whose TLC, FVC, and $AaPO_2$ improved or stabilized was significantly greater in the group treated with IFN-γ1b and prednisolone than in the group receiving prednisolone alone.

percent value (or an absolute increase of ≥200 mL); a stable response was defined as a change in TLC or FVC no greater than ±9% (or a change ≤ 200 mL); and worsening was defined as a decrease in TLC or FVC of ≥10% (or a decrease >200 mL). In the case of $AaPO_2$, improvement was defined as a decrease of ≥5 mm Hg from baseline, a stable response was defined as a change of < ±5 mm Hg, and worsening was defined as an increase of ≥5 mm Hg from baseline.

Using these criteria and eliminating the patients who definitely did not have IPF, the panel reanalyzed the data for these parameters (Table 2). When the change in FVC at 12 months was reanalyzed, it was found that five patients in the prednisolone-only group stabilized and three showed deterioration in lung function, whereas three patients in the IFN-γ1b plus prednisolone group improved and four stabilized; none of the patients treated only with prednisolone improved and none treated with IFN-γ deteriorated (Figure 2). Analysis of the change in $AaPO_2$ at 12 months showed that five patients in the prednisolone-only group stabilized, three deteriorated, and none improved, whereas all seven patients treated with IFN-γ1b and prednisolone improved (Figure 3). When the change in TLC at 12 months was reanalyzed, it was found that none of the patients in the prednisolone-only group improved, seven stabilized, and one deteriorated (Figure 4). In contrast, four patients in the IFN-γ1b plus prednisolone group improved, three stabilized, and none deteriorated. Data were similar for two consecutive measurements of FVC or $AaPO_2$ performed 3 months apart.

When the criteria included both FVC and $AaPO_2$ at 12 months, the panel's analysis found that three patients in

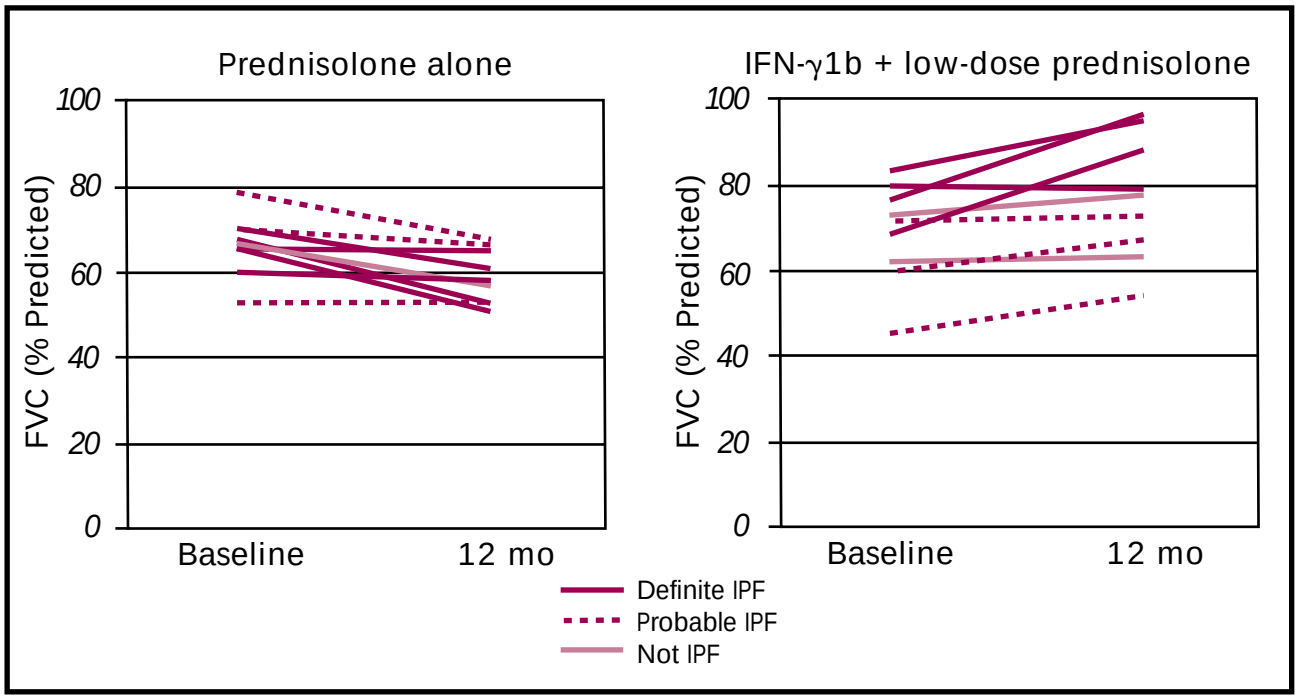

Figure 2. Change in forced vital capacity (FVC) in the reanalysis study conducted by Raghu and co-workers. As the left panel shows, treatment with prednisolone alone was associated with no improvement in FVC in all patients with idiopathic pulmonary fibrosis (IPF). In the patient without IPF, FVC declined. As the right panel shows, among the patients treated with IFN-γ1b and low-dose prednisolone, FVC improved in three of the seven patients with definite or probable IPF and stabilized in four. In the two patients with other forms of idiopathic interstitial pneumonia, FVC remained stable.

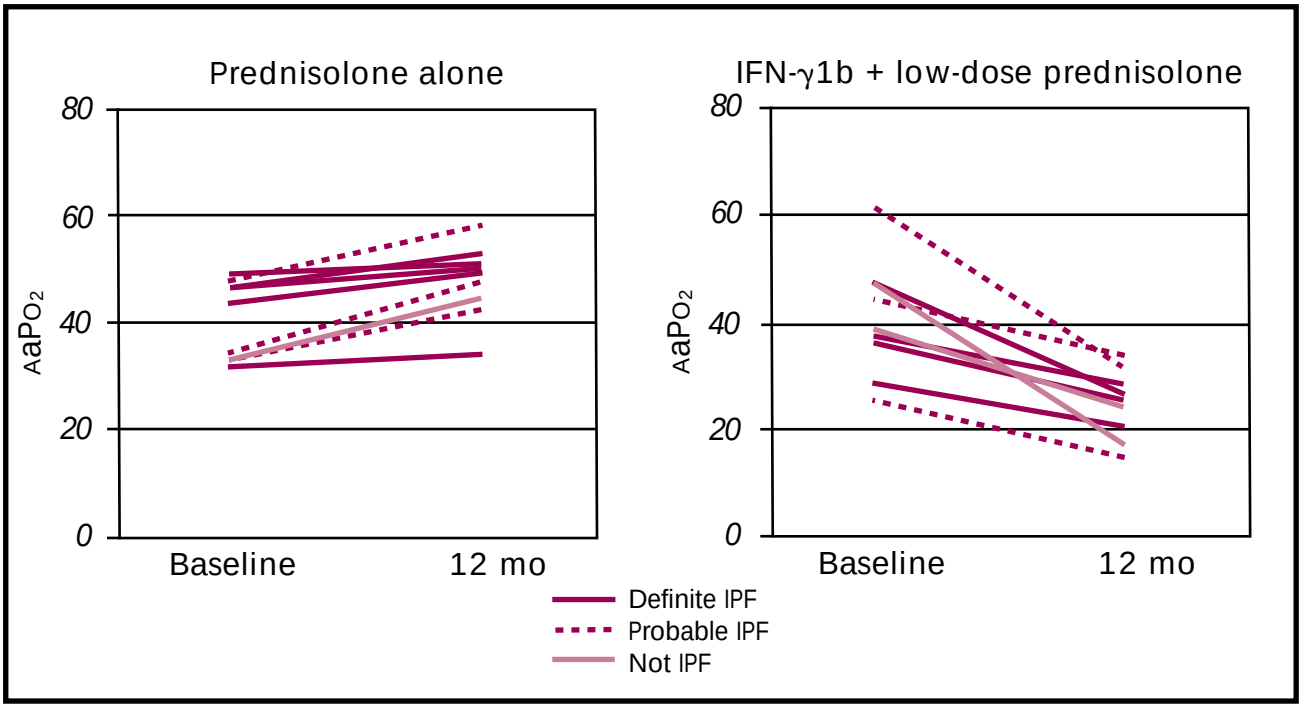

Figure 3. Change in the alveolar-arterial pressure difference for oxygen ($AaPO_2$) in the reanalysis study conducted by Raghu and co-workers. As the left panel shows, treatment with prednisolone alone was associated with no improvement in $AaPO_2$ in all patients. As the right panel shows, $AaPO_2$ improved in all patients treated with IFN-γ1b and low-dose prednisolone.

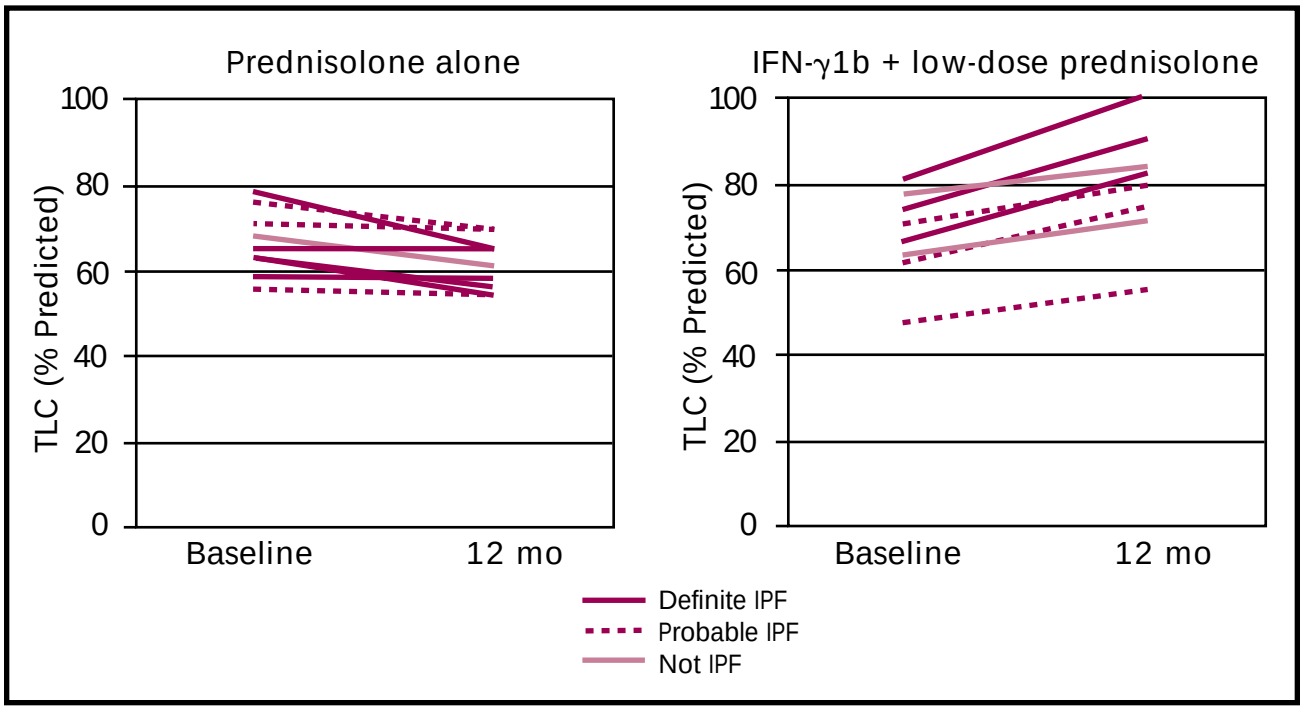

Figure 4. Change in total lung capacity (TLC) in the reanalysis study conducted by Raghu and co-workers. As the left panel shows, treatment with prednisolone alone was associated with no improvement in TLC in all patients. As the right panel shows, among the patients treated with IFN-γ1b and low-dose prednisolone, TLC improved in four of the seven patients with definite or probable idiopathic pulmonary fibrosis (IPF) and remained stable in three. In the two patients without IPF, TLC remained stable. None of the patients treated with IFN-γ1b and low-dose prednisolone showed a deterioration in TLC.

the IFN-γ1b and prednisolone group improved and four stabilized, with none worsening, whereas none in the prednisolone-only group improved, seven stabilized, and one deteriorated.

The independent expert panel concluded that several patients in the published phase II clinical trial indeed had IPF and were previously unresponsive to corticosteroids. A significant improvement in gas exchange and lung volume was attributable to the combination of IFN-γ1b and prednisolone in the patients studied.

The panel reiterated the original investigators' own acknowledgment of the preliminary nature of the study. The panel concluded that the results were provocative and promising, and only a well-designed phase III clinical trial would determine the potential efficacy of IFN-γ in the treatment of IPF.

concluding points

- **After reanalyzing the data from a phase II clinical trial by Ziesche et al, an expert panel independently concluded that patients with pulmonary fibrosis of unknown etiology who are resistant to an adequate trial of corticosteroids do improve with IFN-γ1b and low-dose prednisolone therapy.**
- **A phase III clinical trial with larger numbers of accurately diagnosed patients is needed to confirm the potential benefits of IFN-γ in steroid-resistant IPF.**

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Potential Future Approaches to the Treatment of Idiopathic Pulmonary Fibrosis

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Current attempts to improve the outcome of idiopathic pulmonary fibrosis (IPF) have met with limited success, in part because of poor trial design and nontargeted therapeutic approaches. A better understanding of the pathogenesis of IPF allows us to suggest a number of potential future interventional strategies. Targets of these strategies include the earliest pathologic process that produces lung injury; early proinflammatory cytokines that activate cytokine networks, resulting in further lung injury and fibrosis; cytokines that affect the delicate balance between proinflammatory and antiinflammatory mechanisms; and final common pathways in fibrogenesis. At present, the most promising approaches include antioxidants, interferon gamma, and blockade of tumor necrosis factor alpha and transforming growth factor beta. Future possibilities include blockade of cell signaling transduction elements and, ultimately, gene transfer blocking strategies.

Treatment of idiopathic pulmonary fibrosis (IPF) has been unsuccessful. Many studies of the efficacy of corticosteroids, corticosteroids plus other immunosuppressants such as cyclophosphamide or azathioprine, colchicine, and other agents have shown no more than 30% improvement in objective indices. Review of these studies reveals that none of them was placebo controlled, only some were prospective and comparative, many included patients we would not now diagnose as having IPF, and some included patients with rheumatologic diseases such as systemic sclerosis. Since the histopathologic pattern in lung tissue of patients with systemic sclerosis is predominantly that of nonspecific interstitial pneumonia and not of usual interstitial pneumonia (UIP), inclusion of patients with this and other rheumatologic diseases is inappropriate in an evaluation of therapy for IPF. For all these reasons, a meaningful interpretation of these studies in the context of the tighter definition of IPF recently put forth by the American Thoracic Society and the European Respiratory Society, in collaboration with the American College of Chest Physicians, in their joint International Consensus Statement is extremely difficult.[1]

The study of mixed populations, the use of different end points, and the failure to classify disease stabilization after deterioration as improvement are all errors that must not be reproduced in any future approach used to evaluate targeted therapy for IPF. Therefore, all future studies should be prospective, randomized, double-blind, placebo-controlled evaluations of therapy that is more targeted than that used previously, and all recruited patients should strictly fulfill current diagnostic criteria for IPF.

ESTABLISHED THERAPY

Of all the "traditional" treatments for IPF, azathioprine stands out as the one most likely to have a beneficial effect. The study of azathioprine plus prednisolone conducted by Raghu and co-workers almost certainly consisted of patients with UIP, as confirmed by surgical lung biopsy, and excluded patients with rheumatologic or other associated diseases.[2] Although the number of subjects was small, there appeared to be a survival advantage in the azathioprine group, particularly when controlled for age. This has important implications with respect to the combination of targeted therapies together with more traditional immunosuppressant approaches that are discussed below.

PREVIOUS SUGGESTIONS FOR NOVEL THERAPY

Two workshops conducted by the National Heart, Lung, and Blood Institute reviewed potential future approaches to the treatment of IPF. During the first workshop, in 1994, a broad range of proposed pathophysiologic mechanisms was discussed and a wide variety of potential interventional strategies was outlined.[3] During the second workshop, in 1998, specific growth factors, fibrogenic factors, antifibroblast approaches, upregulation of metalloproteinases, and downregulation of tissue inhibitor of metalloproteinases emerged as the most attractive targets.[4] The range of potential interventions, however, remained quite broad (Table 1).

Table 1. 1998 National Heart, Lung, and Blood Institute Workshop on Potential Therapeutic Interventions for Idiopathic Pulmonary Fibrosis: Suggested Targets

- Pirfenidone
- Interferon gamma
- Interferon beta
- Suramin
- Relaxins
- Eicosanoids (eg, prostaglandin E_2)
- Angiotensin-converting enzyme inhibitors
- Angiotensin II receptor antagonist
- Keratinocyte growth factor
- Cyclosporin
- N-acetylcysteine
- Endothelin receptor antagonists
- Interleukin-10
- Anticoagulants

In addition, some of these approaches had already been only moderately successful (eg, colchicine, pirfenidone [not commercially available]).[5,6]

Anticytokine/antigrowth factor approaches appear to hold the most promise. For example, the efficacy of interferon gamma (IFN-γ) was reported in a recent study.[7] (See "Interferon Gamma-1b in Idiopathic Pulmonary Fibrosis: Reanalysis of a Published Study," page 44.) This agent has a wide range of effects on pathogenetic mechanisms involved in IPF, most notably an antifibroblastic/antifibrogenic effect. However, IFN-γ also modifies the balance between type-1 (Th1) and type-2 (Th2) T-helper cells in the lung, which increasingly is believed to be of importance in the immunopathology of diffuse lung disease. In contrast, IFN-α and IFN-β would appear to be less efficacious.

HOW TO ARRIVE AT NEW TARGETS FOR THERAPEUTIC INTERVENTION

Although we have not intervened in IPF as successfully as we would have wished, sophisticated cellular biological and molecular biological approaches have recently provided substantial insights into the pathogenesis of IPF and have spawned new concepts. The immense range of mediators, including proinflammatory cytokines, regulatory cytokines, chemokines, adhesion molecules, angiogenesis factors, growth factors, and fibrogenic agents, can present a bewildering array of potential interventional targets, particularly as there is marked redundancy in some of the mediator pathways. Because of this redundancy, blockade of one mediator may not affect the outcome, and this makes the selection of appropriate targets quite difficult.

One approach that might be more successful is to target mediators believed to be key. The term "key" is, however, difficult to define in this context. Nevertheless, it might be logical to begin by targeting the earliest pathogenetic events or the final common pathway leading to fibrosis. The initial injurious agent would be an excellent target. Unfortunately, this agent has not yet been identified. Whether the injurious effects of oxidants and proteases are occurring sufficiently "upstream" of the initial pathogenetic process remains to be determined. A second logical target is the proinflammatory cytokines that are released early in the disease process and initiate a cascade of other pathogenetic mechanisms. A third target could be the cytokines that significantly affect the balance between proinflammatory and antiinflammatory factors. Finally, a targeted approach to a growth factor (or factors) that participates in the final common pathway would also be logical. Potential specific target cytokines are listed in Table 2.

Lung Injury

The initial injurious agent in IPF is unknown. However, it is known that with the influx of granulocytes into the lower respiratory tract, there is an increase in oxidant release that is compounded by a relative deficiency of glutathione in the epithelial lining fluid of patients with

It might be logical to target the earliest pathogenetic events or the final common pathway leading to fibrosis.

Table 2. Potential Future Therapy for Idiopathic Pulmonary Fibrosis: Most Attractive Options

- Antioxidants
- Antitumor necrosis factor alpha
- Interferon gamma–inducible protein
- Antitransforming growth factor beta-1

IPF. Together with macrophages, these granulocytes also release proteolytic enzymes, which add to the burden of injury.

Antioxidant strategies might therefore be logical. However, a cautionary note needs to be struck. Granulocytes, particularly neutrophils, are present in greatest numbers in previously damaged lung tissue. It is possible, therefore, that these cells reflect the severity of disease rather than the initial insult or the progression of disease. It could be argued that these injurious mechanisms are activated too far "downstream" from the initial injury to have any significant impact on the global disease process. Notwithstanding this caveat, there remains some logic in further considering antioxidant strategies. First, glutathione levels in lung epithelial lining fluid are reduced in individuals with IPF. Second, there is evidence of increased oxidant release. Third, as a surrogate for this increased release, higher levels of oxidized methionine in the epithelial lining fluid are found in patients with IPF than in normal individuals.

Borok and colleagues found that aerosolized glutathione given twice daily for 3 days to patients with IPF increased glutathione levels in epithelial lining fluid.[8] In a pilot study, Behr and co-workers found that oral N-acetylcysteine, 600 mg three times a day, increased glutathione and decreased oxidized methionine levels in bronchoalveolar lavage fluid from patients with IPF and also produced minor improvements in lung function.[9] These data were sufficiently convincing to promote the concept of a larger study, which is now beginning in Europe.

Targeting Early Proinflammatory Cytokines

It is widely recognized that the majority of patients who present with IPF are already at a late stage in terms of physiologic abnormality. However, it is also widely recognized that early histopathologic abnormalities may be seen even in patients with extensive physiologic disease. If early proinflammatory cytokine release is relevant to the initiation of this pathogenetic response, then the targeting of early proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) may be logical.[10]

A number of studies have demonstrated that TNF-α is synthesized and secreted in excess amounts in the lungs of animals used as models of lung injury and also in humans with IPF.[11-18] The studies conducted by Piguet et al emphasize the significance of anti-TNF-α blockade in fibrogenesis.[11-15,17] These studies demonstrated that in bleomycin and silica models, fibrosis could be abrogated by the administration of anti-TNF-α or its soluble receptor. Furthermore, studies of human lung biopsy specimens have shown an upregulation of TNF-α mRNA and protein.[16]

A second group of studies that reinforce the anti-TNF-α approach comes from the rheumatology literature.[19-22] Rheumatoid arthritis (RA) bears many pathogenetic similarities to IPF. Most notable is the presence at disease sites of increased numbers of lymphoid follicles with secondary germinal centers implying an active immunologic response and the characteristic bursts of acute inflammatory activity with a neutrophil influx mediated by interleukin (IL)-8, on a background of chronic inflammation. The efficacy of an anti-TNF-α strategy in RA has been studied. The logic for exploring this was that blockade of TNF-α inhibited RA in a murine collagen model and in a TNF-α overexpressing transgenic arthritis model. However, studies using human synovium explants show that caution must be used with these new approaches. In these experiments, blockade of TNF-α resulted in the downregulation of both proinflammatory and antiinflammatory factors, emphasizing the concept of balances within the local microenvironment.

On the basis of these preliminary studies, approval was given for the study of chimeric anti-TNF-α in humans. This chimera involved an IgG1κ coupled to the Fv region of the high-affinity neutralizing murine antihuman TNF-α antibody. A pilot study of the infusion of this chimeric antibody into humans with RA conducted in 1993 showed an improvement in joint inflammation scores at 8 weeks.[19]

A larger, multicenter, double-blind, placebo-controlled 26-week study was conducted.[22] The study included 101 patients with active disease, all of whom had had an incomplete response to low-dose methotrexate. Patients were randomized to 1 of 7 groups: 3 groups received 5 infusions of 1, 3, or 10

mg/kg of anti-TNF-α at weeks 0, 2, 6, 10, and 14; 3 groups received the same doses of anti-TNF-α plus methotrexate, 7.5 mg/week; and 1 group received intravenous placebo plus low-dose methotrexate.

At week 26, 60% of the anti-TNF-α groups receiving the highest doses, with or without methotrexate, had improved. Patients who received the lowest dose of anti-TNF-α plus methotrexate improved, but those who received low-dose anti-TNF-α without methotrexate became unresponsive to the therapy and produced antibodies to anti-TNF-α. The placebo group had no response. The study investigators concluded that multiple infusions of anti-TNF-α were well tolerated. They emphasized, however, that antibody production could be a problem and that a combination of this type of specific treatment plus traditional therapy may be more appropriate for future consideration. Several agents that can block TNF-α are now available for human use.

Modulation of Other Cytokines

Issues of redundancy make logical but theoretical targets downstream of the early cytokines difficult to define. However, the recognition of an apparent imbalance between Th2 and Th1 cytokines in IPF (relatively more Th2 than Th1) endorses the value of testing further the efficacy of improving levels of Th1 cytokines such as IFN-γ1b.[23]

A second "balance" approach involves angiogenesis. There is good evidence from studies of models of angiogenesis and also lung tissue from humans that a relative overexpression of angiogenic mediators (eg, IL-8) compared with angiostatic mediators (eg, IFN-γ– inducible protein [IP-10]) may play a role in the ongoing fibrogenetic response in IPF.[24-26] *It may be logical, therefore, to consider as another target the increase in local availability of angiostatic cytokines such as IP-10.*

> *Of all the possible therapeutic approaches to fibrogenesis, the blockade of TGF-β appears the most attractive.*

Antifibrogenic Strategies

Of all of the possible therapeutic approaches to fibrogenesis, the blockade of transforming growth factor beta (TGF-β) appears the most attractive, for many reasons. First, blockade of TGF-β in animal models prevents lung fibrosis.[27] *Second, TGF-β protein co-localizes with mRNA for collagen in human lung.*[28] *Third, TGF-β is the upregulator of connective tissue growth factor, which is arguably the final common pathway of fibrogenesis.*[29] *Finally, the elegant studies from Gauldie's group have demonstrated that the transient overexpression of transfection of an active TGF-β adenovirus construct results in an inflammatory response at day 3, followed rapidly by a fibrogenic response that not only is rapid in onset but also endures long after the transfectant has become inactive.*[30] *This ongoing fibrogenic response has as an important histopathologic characteristic abundant fibroblastic foci, which are a key feature of UIP. It would appear that therapy with chimeric anti-TGF-β1 or, alternatively, the overexpression of a TGF-β1 inhibitor such as decorin*[31] *could be a very attractive approach.*

MORE-DISTANT FUTURE TARGETS

Other, even more-focused target possibilities will emerge as our understanding of the mechanisms involved in cell signaling increases. Among the signaling mechanisms, specific blockers of signal transduction pathways are now emerging. Gene transfection possibilities have also emerged that may allow selective blockade of individual signal transduction elements. The long-term vision of the most-specific targeting strategies would therefore involve gene transfer modulation of signal transduction pathways.

concluding points

- **We are entering a golden era in which our increased understanding of the cellular and molecular mechanisms underlying IPF gives us a great opportunity to target more specifically the pivotal pathogenetic factors.**
- **No treatment for IPF has been properly tested.**
- **Specific targeted therapies for IPF are available and could be employed, most notably IFN-γ and anti-TNF-α.**
- **Any future targeted approach should be evaluated by international, multicenter, prospective, randomized, placebo-controlled, double-blind studies.**
- **The impact on changes in physiologic indices and death should be used as end points in IPF studies, and stabilization of deterioration should not be ignored.**
- **A network of centers needs to be established to provide an ongoing "template" for future evaluative studies.**

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CME Section

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Intended Audience

This monograph is intended for pulmonologists and other physicians with an interest in the management of idiopathic pulmonary fibrosis.

Learning Objectives

After reading this monograph, clinicians should be able to:

- *Use the appropriate terminology to classify the various types of interstitial lung diseases.*
- *Recognize that the prevalence and incidence of pulmonary fibrosis are 5 to 10 times higher than previously estimated.*
- *Understand the role of certain cytokines in the pathogenesis of idiopathic pulmonary fibrosis (IPF) and why they may be logical targets for therapy.*
- *Appreciate the importance of a surgical lung biopsy in the diagnosis of IPF.*
- *Cite the factors that are associated with an increased risk of IPF as well as those that affect survival.*
- *Cite the potential benefits of interferon gamma in patients with steroid-resistant IPF.*

CME Questions

FOR EACH QUESTION, CIRCLE THE ONE BEST ANSWER ON THE ANSWER SHEET (PAGE 63)

1. All of the following are immunomodulatory effects of TGF-β1 except
   a. Inhibition of IFN-γ release
   b. Decreased production of interstitial collagens in extracellular matrix
   c. Suppression of IFN-γ–dependent immune reactions
   d. Induction of immunosuppressive CD8+ lymphocytes

2. Upregulation of the extracellular matrix proteoglycan decorin
   a. Upregulates the expression of TGF-β1
   b. Downregulates the expression of TGF-β1
   c. Increases production of interstitial collagens
   d. Activates the gene for connective-tissue growth factor

3. IPF patients with excess neutrophils in BAL fluid have
   a. A higher likelihood of disease progression
   b. A high probability of intercurrent bacterial pneumonitis
   c. An improved response to immunosuppression
   d. Increased concentrations of type III procollagen in BAL fluid

4. All of the following are components of a proposed scoring system for estimating impairment from IPF except
   a. Resting alveolar-arterial O_2 difference
   b. Lung volume
   c. Degree of fibrosis on open-lung biopsy
   d. Chest radiograph

5. IFN-γ–inducible protein is an example of
   a. An angiostatic cytokine
   b. An antioxidant
   c. A fibrogenic cytokine
   d. A specific blocker of signal transduction pathways

6. The effect of IFN-γ in IPF can best be described as
   a. Stimulatory of extracellular matrix deposition
   b. Antiinflammatory
   c. Tissue metalloproteinase inhibition
   d. Antifibroblastic/antifibrogenic

7. The recently reported study by Ziesche et al showed that in patients with IPF, IFN-γ1b
   a. Improved total lung capacity
   b. Decreased total lung capacity
   c. Did not affect total lung capacity
   d. Decreased arterial partial pressure of oxygen

8. All of the following characterize the relationship between TGF-β1 and IFN-γ1b except
   a. IFN-γ1b downregulates the expression of TGF-β1
   b. TGF-β1 downregulates the expression of IFN-γ1b
   c. TGF-β1 is increased and IFN-γ1b is decreased in lung tissue from patients with IPF
   d. TGF-β1 is a Th1 cytokine and IFN-γ1b is a Th2 cytokine

9. All of the following are typical clinical findings in patients with IPF except
   a. Hemoptysis
   b. Dyspnea
   c. Nonproductive cough
   d. "Velcro" crackles on chest auscultation

10. When based on clinical and radiographic findings alone, the diagnosis of new-onset IPF (<2 years' duration) will be missed in nearly 1 of
    a. 3 patients
    b. 2 patients
    c. 5 patients
    d. 8 patients

11. "Temporal heterogeneity" refers to
    a. The variable time from symptom onset to diagnosis of IPF
    b. Transitions from near-normal lung to alveolar organization and inflammation to dense fibrosis in usual interstitial pneumonia
    c. The coexistence of reticular densities and a ground-glass appearance on chest radiographs in IPF
    d. The decline in lung function over time in patients with IPF

12. All of the following can produce end-stage fibrosis indistinguishable from that of usual interstitial pneumonia except
    a. Sarcoidosis
    b. Chronic hypersensitivity pneumonitis
    c. Chronic eosinophilic pneumonia
    d. Certain drug toxicities

13. An example of a CXC cytokine is
    a. Monocyte chemoattractant protein
    b. Interleukin-8
    c. Murine macrophage inflammatory protein
    d. Eotaxin

14. In bleomycin-induced lung disease, which TGF-β isoform predominates?
    a. TGF-β1
    b. TGF-β2
    c. TGF-β3
    d. All are equally expressed

15. Significantly improved survival in IPF has been shown with
    a. Prednisolone
    b. Azathioprine plus prednisolone
    c. D-penicillamine plus prednisolone
    d. None of the above

16. Prolonged survival is most likely in an IPF patient with
    a. Marked cellular infiltration on lung biopsy and ground-glass appearance on chest CT scan
    b. Reticular appearance on high-resolution chest CT scan
    c. A large number of fibroblastic foci on lung biopsy
    d. No response to corticosteroids

17. A proposed means of determining improvement or deterioration after initiation of IPF therapy focuses on
    a. Clinical features
    b. Radiographic features
    c. Physiologic features
    d. A combination of all the above

18. The median survival of a 50-year-old diagnosed with IPF is
    a. <2 years
    b. 3 years
    c. 5 years
    d. >5 years

New Approaches to Managing Idiopathic Pulmonary Fibrosis

CONTINUING EDUCATION REGISTRATION FORM AND ANSWER SHEET

INSTRUCTIONS

1. *Read the monograph carefully.*
2. *Read each question, choose the correct answer, and record your answer on this form. Retain a copy of your answers so that they can be compared with the correct answers, which will be sent to you at a later date.*
3. *Print or type your full name and address in the spaces below.*
4. *Send the completed form with your check or money order for $15 (US) made payable to the American Thoracic Society, or that amount charged to your credit card, to:*

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5. *Your answers will be graded, and you will be advised that you have passed (or failed). A minimum score of 80% must be obtained in order for a certificate of credit (AMA/PRA category 1; 5 credit hours) to be awarded.*
6. *Credit for this CME posttest is available until September 2002.*

CME POSTTEST ANSWER SHEET

(Circle the one best answer.)

1. a b c d	6. a b c d	11. a b c d	16. a b c d
2. a b c d	7. a b c d	12. a b c d	17. a b c d
3. a b c d	8. a b c d	13. a b c d	18. a b c d
4. a b c d	9. a b c d	14. a b c d	
5. a b c d	10. a b c d	15. a b c d	

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