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## Term of Approval

October 1, 2004 through September 30, 2006

## Idiopathic Pulmonary Fibrosis: Current approach to diagnosis and therapy

### LEARNING OBJECTIVES

1. Summarize the rationale for categorizing interstitial lung disease (ILD).
2. Specify diagnostic testing recommended for patients with ILD.
3. Describe the recommended diagnostic work-up for idiopathic pulmonary fibrosis (IPF).
4. Review the advantages and disadvantages of the ATS recommendations for treating IPF.
5. Explain the rationale behind new targets for treating IPF and their corresponding treatment options.



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### INTRODUCTION

The interstitial lung diseases (ILD) are a heterogeneous collection of more than 150 acute and chronic pulmonary disorders. While individually rare, as a group they account for 15% or more of cases seen by the practicing pulmonologist. Though classified together, large differences in the risk factors for their development, pathobiologic mechanisms of disease, potential therapies, and prognosis exist among them, making an accurate diagnosis critical for appropriate management.

A complete clinical evaluation should be obtained when evaluating a patient with ILD. This should include a thorough history with a comprehensive review of systems; complete past medical, social, and family histories as well as a focused review of all medications or drugs (both prescription and over-the-counter); and occupational, avocational, and environmental histories focusing on potential exposures.<sup>1</sup> Common clinical features are listed in **Table 1**.<sup>2</sup> Physical exam typically reveals dry, end-inspiratory, basilar crackles on auscultation.

To aid the diagnosis of ILD, the disorders have been categorized as those secondary to a known cause, those of unknown cause, and the idiopathic interstitial pneumonias (**Table 2**).<sup>1,2</sup> To determine whether a known etiology can be identified, laboratory testing should include a complete blood count with differential (CBC),

**Table 1**  
**Common clinical and pathologic features of interstitial lung diseases (ILDs)<sup>1,2</sup>**

Clinical Features
Exertional dyspnea and/or cough
Abnormal breath sounds on auscultation
Bilateral diffuse interstitial infiltrates on chest radiographs
Restrictive physiologic and gas exchange abnormalities, including decreased vital capacity, decreased DL <sub>CO</sub> , abnormal P(A-a)O <sub>2</sub> at rest or with exertion

DL<sub>CO</sub>, pulmonary carbon dioxide diffusion

chemistry profile, and, as indicated, tests that may indicate or rule out the presence of a collagen vascular disease, pulmonary vasculitis, and immune deficiency, among other conditions (Table 3).<sup>1</sup>

Chest x-rays, particularly if previous radiographs can be obtained, may be extremely helpful in determining both the onset and rate of progression of disease. High-resolution computerized tomography (HRCT) should be obtained during the initial evaluation of virtually all patients with ILD; it is more sensitive than a chest x-ray, may suggest a specific diagnosis and, at a minimum, limits the differential to a handful of possibilities. Pulmonary function tests (PFTs) that should be performed at initial evaluation include spirometry with and without a bronchodilator, plethysmographic lung volumes, and carbon dioxide diffusion (DL<sub>CO</sub>). In addition, formal evaluation of gas exchange is important for both therapeutic and prognostic purposes. Both formal 6-minute walk testing and cardiopulmonary exercise testing (CPET) may be useful in determining whether gas exchange abnormalities are present and whether the patient might benefit from the use of supplemental oxygen. Additional testing may include bronchoscopy with bronchoalveolar lavage (BAL) and endobronchial and/or transbronchial lung biopsy (TLB). Surgical lung biopsy via an open or thorascopic technique may ultimately be required for a confirmed diagnosis.

**Table 2**  
**Broad classifications of interstitial lung diseases (ILDs)<sup>1,2</sup>**

ILDs of Known Cause
Infections
Occupational/environmental/avocational exposures, such as inorganic dusts (silica, hard metals), organic dusts (bacterial, animal proteins), gases, and fumes
Drugs or toxic exposures; eg, radiation therapy, chemotherapy, nonsteroidal anti-inflammatory agents, antiarrhythmics, antibiotics, tricyclic antidepressants, methotrexate, and penicillamine
Collagen vascular disorders
ILD of Unknown Cause
Sarcoidosis
Other rare disorders; eg, eosinophilic granuloma (pulmonary Langerhans cell histiocytosis), lymphangioleiomyomatosis, pulmonary alveolar proteinosis
Idiopathic Interstitial Pneumonias
Idiopathic pulmonary fibrosis (IPF)
Idiopathic nonspecific interstitial pneumonia (INSIP)
Cryptogenic organizing pneumonia (COP) or bronchiolitis obliterans with organizing pneumonia (BOOP)
Desquamative interstitial pneumonia (DIP)
Respiratory bronchiolitis-interstitial lung disease (RB-ILD)
Acute interstitial pneumonia (AIP)

**Table 3**  
**Recommended diagnostic testing in**  
**patients with interstitial lung disease (ILD)**  
 (adapted from Raghu, 2004)<sup>1</sup>

Diagnostic Testing	
Laboratory testing	<ul style="list-style-type: none"> <li>• CBC with differential</li> <li>• Routine chemistry panel and creatine kinase (CK)</li> <li>• Serologic testing for autoimmune disorders (eg, antinuclear antibody [ANA], ANA profile, rheumatoid factor)</li> <li>• Serum precipitins based on known specific environmental exposures</li> <li>• Immunoglobulins and HIV (to evaluate for immunodeficiencies)</li> </ul>
Chest radiograph	Obtain all previous chest radiographs for review to determine disease onset and rate of progression
HRCT	In most patients, obtain at initial evaluation; HRCT is more sensitive than chest radiograph and may suggest certain diagnoses
Pulmonary function tests	<ul style="list-style-type: none"> <li>• Spirometry with and without a bronchodilatory agent</li> <li>• Plethysmographic lung volumes</li> <li>• DL<sub>CO</sub></li> </ul>
Gas exchange	<ul style="list-style-type: none"> <li>• 6-minute walk test</li> <li>• Consider cardiopulmonary exercise testing in appropriate clinical settings</li> </ul>

CBC, complete blood count; HIV, human immunodeficiency virus; HRCT, high resolution computed tomography; DL<sub>CO</sub>, pulmonary carbon dioxide diffusion

## IDIOPATHIC PULMONARY FIBROSIS: DEFINITION, DIAGNOSIS, AND PROGNOSIS

Approximately two-thirds of ILDs are of unknown cause and fall within the category of idiopathic interstitial pneumonia. The most common form is idiopathic pulmonary fibrosis (IPF), which accounts for up to 45% of ILD diagnoses.<sup>2</sup> IPF has been the focus of renewed investigation in recent years in the areas of genetics, lung fibrosis, lung injury and repair, and potential therapies;<sup>3</sup> this newsletter briefly summarizes what is known about IPF and explores the broad range of emerging potential therapies.

### Definition

The American Thoracic Society has defined IPF as “a specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with the histologic appearance of usual interstitial pneumonia on surgical (thorascopic or open) lung biopsy.”<sup>4</sup>

### Epidemiology

The prevalence of IPF is currently estimated to be 13 cases per 100,000 (females) or 20 per 100,000 (males) in the US, significantly higher than previous estimates.<sup>4</sup> Mean age at diagnosis is 66 years, and prevalence increases sharply with age, reaching 175 per 100,000 for those over the age of 75. While no discernible pattern of geographic distribution for the development of IPF has been identified, there is considerable geographic variation in age-adjusted mortality rates that may reflect differences in types of occupations or environmental exposures.<sup>4</sup>

### Risk factors

Risk factors for IPF are listed in **Table 4**.<sup>4</sup> Cigarette smoking increases risk (odds ratios, 1.6-2.9), as may chronic aspiration secondary to gastroesophageal reflux. Environmental factors include exposure to dusts (brass, steel, lead, pine) and solvents. While no clear evidence of a specific viral etiology exists, infectious agents potentially associated with IPF include Epstein-Barr virus, cytomegalovirus, certain herpes viruses, and hepatitis C. A genetic link has been identified, as well. The familial form of IPF is clinically and histologically indistinguishable from sporadic IPF<sup>5</sup> and appears to be inherited in an autosomal dominant trait with variable penetrance.<sup>4</sup> While it has been estimated to account for 2% of IPF cases,

**Table 4**  
**Potential risk factors for idiopathic pulmonary fibrosis (IPF)**  
 (adapted from ATS, 2000)<sup>4</sup>

Potential Risk Factors
Cigarette smoking
Exposure to antidepressants
Chronic aspiration
Environmental factors
Infectious agents
Genetic predisposition

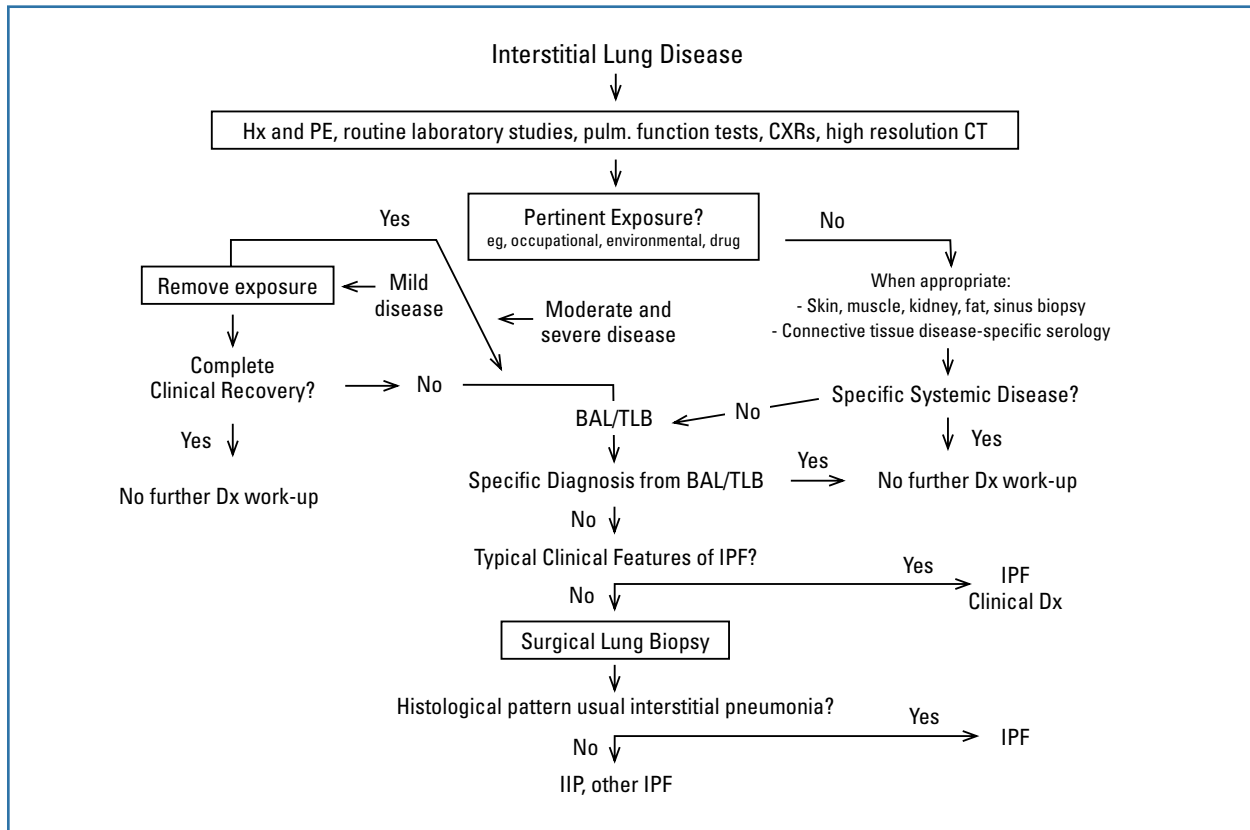
**Table 5**  
**Criteria for diagnosing idiopathic pulmonary fibrosis (IPF) in the absence of a surgical lung biopsy**  
 (adapted from ATS, 2000)<sup>4</sup>

Major Criteria	Minor Criteria
Exclusion of other known causes of ILD	Age >50 yr
Abnormal PFTs that include evidence of restriction and/or impaired gas exchange with rest or exercise, or decreased DL <sub>CO</sub>	Insidious onset of unexplained dyspnea on exertion
HRCT results: bibasilar reticular abnormalities with minimal ground glass opacities	Illness lasting at least 3 months
TLB or BAL with no features that support an alternative diagnosis	Bibasilar, inspiratory crackles (dry)

ILD, interstitial lung disease; PFT, pulmonary function test; DL<sub>CO</sub>, pulmonary carbon dioxide diffusion; HRCT, high resolution computed tomography; TLB, transbronchial lung biopsy; BAL, bronchoalveolar lavage

**Figure 1**

Algorithm for diagnosing idiopathic pulmonary fibrosis (IPF). (Reprinted with permission from Raghu, 2004)<sup>1</sup>



familial IPF accounts for 19% of patients receiving lung transplantation at one US medical center.<sup>5</sup> Specific genetic markers are still being evaluated, but a mutation in the surfactant protein C gene has been demonstrated in 5 generations of one family with IPF.<sup>5</sup>

## Diagnosis

The diagnostic workup for IPF is that of ILD and focuses on the exclusion of other known causes of diffuse lung disease. Clues that point toward IPF rather than other ILD include patient age >50 years, an insidious onset with dyspnea as the most prominent symptom, lack of systemic symptoms, or signs pointing toward connective tissue disease.<sup>4</sup> Laboratory analyses are often only helpful in that they may allow some known causes of parenchymal lung disease to be excluded. For example, elevated erythrocyte sedimentation rate (ESR) is rare in IPF, while elevated gamma globulins or lactate dehydrogenase (LD) may be noted but are nondiagnostic. Positive ANA or rheumatoid factor (RF) occurs in 10% to 20% of patients with IPF, but high titers are suggestive of a connective tissue disease.

An algorithm for the differential diagnosis of IPF is shown in **Figure 1**. The diagnosis includes:

1. Exclusion of other known causes of ILD
2. Abnormal PFTs that include evidence of restriction and/or impaired gas exchange with rest or exercise, or decreased DL<sub>CO</sub>
3. Abnormalities on chest x-ray (peripheral reticular opacities that are most profuse at the lung bases) or HRCT (bibasilar reticular abnormalities with minimal ground glass opacities)

In the absence of a surgical lung biopsy, the presence of the major criteria and 3 of 4 minor criteria listed in **Table 5** are considered presumptive of IPF.

The typical patient with IPF has an abnormal chest radiograph upon initial presentation, but a normal radiograph cannot be used to exclude the diagnosis.<sup>4</sup> Typical findings on the chest radiograph include decreased lung volumes with bilateral basal-predominant, peripheral reticular opacities. Even if the chest x-ray is normal, the HRCT will virtually always demonstrate disease. HRCT will narrow the differential diagnostic possibilities and may provide an earlier diagnosis. The most common pattern seen on HRCT contains patchy, peripheral, subpleural, bi-basal reticular changes with focal areas of honeycombing and limited areas of ground glass opacity. With the appropriate

HRCT pattern, the trained radiologic observer is able to predict the underlying usual interstitial pneumonia (UIP) pathologic pattern with 90% accuracy.<sup>4</sup>

As in other causes of ILD, pulmonary function tests (PFTs) demonstrate reduced vital capacity and total lung capacity, usually with reduced DL<sub>CO</sub>.<sup>4</sup> Resting room air arterial blood gases may be normal or reveal an elevated alveolar-arterial gradient. Pulmonary hypertension at rest is rare in early IPF, but common when the vital capacity drops below 50% of predicted or DL<sub>CO</sub> declines below 30% of normal. Pulmonary hypertension may also be seen during exercise throughout the course of the disorder. Identification and correction of sleep-related hypoxemia with the use of supplemental oxygen may be beneficial.

BAL may be useful in the evaluation of ILD, but there is no pattern of inflammatory cells that is diagnostic for IPF.<sup>4</sup> A surgical lung biopsy is diagnostic for IPF when the clinical scenario is that of an idiopathic interstitial pneumonia (IIP) and the histopathology reveals UIP. When necessary, surgical lung biopsy can be performed safely in the vast majority of patients, though the risk of significant complications increases with age >70 years, extreme obesity, cardiac disease, and severely impaired lung function.

## Prognosis

IPF is associated with a poor prognosis, especially in older patients (age >50 years), and median survival time of about 2.5 to 3 years.<sup>6,7</sup> Other risk factors for shortened survival include history of cigarette smoking, severity of dyspnea on presentation, moderate to severe loss of lung function, deteriorating lung function, neutrophilia or eosinophilia in BAL fluid, honeycomb changes on HRCT, and poor response to corticosteroid therapy.

## IDIOPATHIC PULMONARY FIBROSIS: CURRENT AND NOVEL POTENTIAL THERAPIES

No medical therapy has been shown to be useful in the treatment of IPF. Only lung transplantation has been proven to prolong survival or quality of life, and as such, lung transplant evaluation should be considered early rather than late in the course of the disease. Single lung transplantation is the current preferred surgical option and is associated with a 5-year survival of 50 to 60% after transplantation. However, given the extremely poor prognosis of the disease, the associated progressive

**Table 6**  
**International Consensus Conference treatment recommendations**  
**for idiopathic pulmonary fibrosis (IPF)<sup>4</sup>**

Treatment Recommendations	
Medications	Corticosteroids plus azathioprine or cyclophosphamide
Initial treatment	Minimum of 6 months
Re-evaluate for a response to therapy	Every 3 months for first 18 months; at regular intervals thereafter (monitoring for medication-related toxicity must occur more frequently)
Definition of positive response	<p>Two or more of the following, documented on 2 consecutive visits over a 3- to 6-month period:</p> <ul style="list-style-type: none"> <li>• Decrease in symptoms</li> <li>• Reduction in parenchymal abnormalities on chest radiograph or HRCT</li> <li>• Physiologic improvement (2 of the following): <ul style="list-style-type: none"> <li>- at least 10% or 200 mL improvement in total lung capacity (TLC) or vital capacity (VC);</li> <li>- at least 15% or 3 mL/min/mmHg increase in DL<sub>CO</sub>;</li> <li>- improvement or normalization of O<sub>2</sub> saturation [at least 4%] or PaO<sub>2</sub> [at least 4 mm Hg]</li> </ul> </li> </ul>
Definition of stable response	<p>Two or more of the following:</p> <ul style="list-style-type: none"> <li>• 10% or &lt;200 mL change in TLC or VC</li> <li>• &lt;15% or &lt;3 mL/min/mmHg change in DL<sub>CO</sub></li> <li>• No change in O<sub>2</sub> saturation or PaO<sub>2</sub></li> </ul>
Definition of failure to respond	<ul style="list-style-type: none"> <li>• An increase in symptoms</li> <li>• An increase in opacities on chest radiograph or HRCT</li> <li>• Evidence of deterioration in lung function in 2 of the 3 measures listed above</li> </ul>

HRCT, high resolution computed tomography; DL<sub>CO</sub>, pulmonary carbon dioxide diffusion

impairment in quality of life, and the rarity of the availability of lung transplantation in this group of patients, medical therapy is always considered and generally prescribed.

### Pathogenesis

Until recently, medical treatment of IPF has been based on the assumption that chronic persistent inflammation in the lung leads to injury and pulmonary fibrosis; that is, that the inflammation precedes and promotes fibrosis. Medical therapy, therefore, focused on blocking inflammation.<sup>4,8</sup> However, the pathogenesis of IPF is not well understood, and important questions remain to be answered regarding the relative roles of persistent inflammation and abnormal repair and remodeling responses.<sup>2</sup> While conventional treatment has focused on chronic inflammation, more recent therapeutic interventions are targeting fibrosis.

### Therapies that block inflammation

Corticosteroids have been used since the early 1950s with limited success and significant associated side effects. From 10 to 30% of patients with IPF have been reported to have at least some improvement when treated with corticosteroids.<sup>4,9</sup> However, one of the problems with interpreting results of corticosteroid therapy has been the lack of diagnostic certainty in these historical studies; therefore, earlier studies likely have included other IIPs that are known to respond to corticosteroids.<sup>8</sup>

Cytotoxic therapy (eg, cyclophosphamide or azathioprine) has been added to anti-inflammatory steroidal regimens since the 1960s in an attempt to minimize the morbidity associated with corticosteroid.<sup>8</sup> Some small trials have demonstrated a positive effect of combination therapy, but the results are not consistent, with a number of patients developing significant side effects. For most patients, aggressive anti-inflammatory treatment results in an unsatisfactory response.<sup>4</sup>

The ATS has provided recommendations for therapy in patients with IPF.<sup>4</sup> ***However, it must be emphasized that these recommendations were made with the acknowledgment that this approach has not been proved to be beneficial and should be limited to those patients in whom the potential benefits of therapy clearly outweigh the potential side effects.*** These recommendations are summarized in **Table 6**.

1. A combination of corticosteroids and a cytotoxic agent is used if considered appropriate.<sup>4,8</sup> Patients

who receive corticosteroid and cytotoxic therapy should be advised of the potential risk of side effects and closely monitored. Clinically measurable improvement requires a minimum of 3 months of therapy.

2. At the 6-month time point, patients whose disease is progressing should be considered for an alternate therapy.
3. Patients who do show a response to corticosteroids at the 6-month period, either with stabilization or objective improvement, may be maintained on the existing drug regimen for an additional 6 months, and then re-evaluated.
4. Combined therapy can be continued for a total of 18 months if improvement or stabilization continues. Longer-term therapy should be considered only in those whose condition continues to improve or stabilize using objective evidence.
5. Patients should also be encouraged to enroll in a pulmonary physical rehabilitation program.

### Novel treatment options: targeting fibrosis

Given the general lack of benefit of aggressive anti-inflammatory therapy in treating IPF, new hypotheses have been generated to explain the disease. One current hypothesis suggests that progressive fibrosis rather than chronic persistent inflammation accounts for the progressive nature of the disease.<sup>8</sup> Therapy directed against fibrosis is now considered the future of treatment in this disease, and a number of specifically targeted approaches are now being investigated. Desirable characteristics for an antifibrotic agent to evaluate in the treatment of IPF are outlined in **Table 7**,<sup>8</sup> and a number of potential targets and specific therapies for the next generation of treatment have been identified (**Table 8**). The following sections review a number of these.

#### *Transforming growth factor-beta (TGF-beta)*

Transforming growth factor-beta (TGF-beta) plays a critical role in the process of fibrosis in animal models, and bleomycin-induced lung fibrosis in the rodent is blocked by inhibitors of TGF-beta signaling.<sup>8</sup> High levels of TGF-beta are found in a number of conditions associated with fibrosis, including IPF, and in organs other than the lung that also develop pathologic fibrosis.<sup>8</sup> Therefore, TGF-beta and other growth-factor signaling pathways are the objects of considerable interest for new drug development

**Table 7**

**Desirable attributes for an antifibrotic to treat idiopathic pulmonary fibrosis (IPF)**

(modified from Brown and Schwarz, 2004)<sup>8</sup>

A successful antifibrotic agent:
Decreases lung fibroblast proliferation
Increases lung fibroblast apoptosis
Decreases excessive extracellular matrix synthesis and deposition
Promotes extracellular matrix breakdown and remodeling
Protects against ongoing tissue injury
Promotes restoration of normal tissue architecture

**Table 8**

**Potential targets for therapy and corresponding therapies based on these targets**

Target	Therapy	Outcome of Clinical Trials
TGF-beta	<ol style="list-style-type: none"> <li>1. Interferon-beta</li> <li>2. Interferon-gamma</li> </ol>	<ol style="list-style-type: none"> <li>1. Not beneficial</li> <li>2. Large randomized, double-blind study found no change in progression-free survival, lung function, gas exchange, or quality of life; however, a clinically significant survival benefit could not be ruled out</li> </ol>
TNF	Etanercept, a TNF-alpha blocker	Large randomized, double-blind trial has been fully enrolled. Results are pending. Small open-label study showed some positive results
Endothelin	Endothelin antagonists	Large randomized, double-blind trial is enrolling patients
Reactive oxygen species	N-acetyl cysteine (NAC)	A large, multi-center trial is now underway to test the efficacy of prednisone and azathioprine with and without NAC
Platelet-derived growth factor (PDGF)	Imatinib mesylate (Gleevec)	Large randomized, double-blind trial has been designed and is enrolling patients

and testing. Interferons (IFN) are cytokines with many of the desirable characteristics of the ideal antifibrotic agent. They consist of 2 categories, Type I (IFN-alpha, -beta, -omega, and -tau) and Type II (IFN-gamma); these differ primarily in the cells of origin but also in receptor specificities, signal transduction mechanisms, and ability to stimulate MHC class II antigens.<sup>8</sup>

IFN-beta was shown to have no benefit for patients with IPF in a large, randomized, controlled clinical trial.<sup>8</sup> IFN-gamma, a Type II interferon, has garnered much interest as a potential antifibrotic agent, particularly because it has significant antifibrotic activity *in vitro*.<sup>8</sup> A small study undertaken to test its effectiveness in treating IPF in 18 patients who had failed corticosteroid treatment demonstrated improvement in lung function.<sup>10</sup> This was particularly encouraging because those receiving placebo had worse or unchanged lung function. However, when tested in a large (>300 patients) prospective multi-center, double-blind, placebo-controlled trial, therapy with IFN-gamma was no different than treatment with placebo in terms of progression-free survival time, lung function, gas exchange, or quality of life in IPF patients who had been previously shown to be unresponsive to corticosteroid therapy.<sup>11</sup> A clinically significant survival benefit could not be ruled out due to the size and duration of the trial, and additional study of IFN-gamma is warranted to evaluate this potential survival benefit.

#### *Tumor necrosis factor-alpha (TNF-alpha)*

Tumor necrosis factor-alpha (TNF-alpha) may stimulate fibroblast proliferation and collagen gene upregulation, but it has also been shown to suppress collagen gene expression.<sup>8</sup> However, increased amounts of TNF-alpha are produced in lung cells from patients with IPF.<sup>8</sup> In a small open-label pilot study of the TNF-alpha blocker etanercept, some of the 9 patients with IPF (previously diagnosed by biopsy) showed improvements in FVC (n=3), DL<sub>CO</sub> (n=4), or P(a-A) gradient (n=5) over a period of 9 months.<sup>12</sup> These results have led to the design of a large, prospective, multicenter, double-blind, placebo-controlled trial to test the use of etanercept for the treatment of IPF, with initial results anticipated in late 2005.<sup>8</sup>

#### *Endothelin-1*

Endothelins are a family of peptides with several types of activity, including vasoactive, bronchogenic, immunomodulatory, and mitogenic properties.<sup>8,13,14</sup>

Endothelin-1 is the most abundant of 3 distinct isoforms, and its concentration is highest in the lungs.<sup>13</sup> Endothelin-1 is a proinflammatory cytokine,<sup>14</sup> and, among many functions demonstrated to date, it stimulates fibroblast proliferation and collagen synthesis, and induces TGF-beta production.<sup>8</sup> Endothelin-1 may play a role in the initial phases of lung injury, and several types of evidence point to its role in IPF.<sup>13</sup> For example, endothelin-1 levels are increased in plasma and BAL samples from patients with IPF, and lung biopsies from patients with IPF demonstrate evidence of increased endothelin-1 that correlate with disease activity.<sup>13</sup> A large clinical trial has been initiated to test endothelin-1 in the treatment of IPF with initial results anticipated in late 2005 or early 2006.

#### *Reactive Oxygen Species*

Reactive oxygen species are found in large amounts in the lungs of patients with IPF.<sup>8,15</sup> Because these free radicals oxidize proteins and lipids, contributing to cell death and tissue injury, one suggested treatment for IPF is to target the reactive oxygen species with antioxidants. One well-characterized antioxidant is N-acetyl-L-cysteine (NAC), which scavenges hydrogen peroxide with its sulfhydryl group.<sup>15</sup> NAC is also de-acetylated to cysteine, a precursor of the natural antioxidant glutathione; increasing NAC, therefore, increases the cellular glutathione level.<sup>15</sup> Because IPF is characterized by low glutathione in addition to the high levels of reactive oxygen species,<sup>8,15</sup> treatment with NAC is currently under investigation.<sup>8</sup> A small, preliminary study in 20 patients with IPF evaluated the addition of NAC to a standard immunosuppressive regimen for 12 weeks, and improvement in DL<sub>CO</sub> was noted.<sup>16</sup> A large, multi-center trial is now underway to test the efficacy of prednisone and azathioprine with and without NAC.<sup>8</sup>

#### *Other targets and agents*

Several other targets for therapeutic intervention in IPF have also been identified.<sup>8</sup> These include

- Platelet-derived growth factor (PDGF) isoforms are a family of polypeptides that bind to cell surface receptors. PDGF induces fibroblast proliferation and has been implicated in fibroproliferative lung damage. Imatinib mesylate (Gleevec) is a tyrosine kinase inhibitor with activity against PDGF receptors. A large randomized, double-blind trial designed to test the effects of imatinib mesylate in IPF is now enrolling patients.

- A failure of appropriate fibroblast apoptosis may also play a role in IPF. Agents such as lovastatin that induce apoptosis in isolated normal lung and fibrotic lung fibroblasts are potential therapeutic agents that will require further research.
- The lipoxygenase pathway in the lung increases proinflammatory leukotrienes, which appear to play a role in IPF. Lipoxygenase blockers are under consideration as potential treatments for IPF.
- IPF may involve an imbalance in the plasminogen/plasma renin system. There seems to be an increase in plasminogen activator inhibitor-1 (PAI-1) in IPF that is sensitive to agents that block both angiotensin and aldosterone.
- Extracellular matrix proteases may be responsible for abnormal wound repair or matrix remodeling. This is an area that is under preliminary investigation; no clinical trials are underway at this time.

### SUMMARY

IPF is a progressive fibrosing interstitial lung disease with a poor prognosis that currently has no clearly beneficial treatment options. Because progressive fibrosis rather than chronic persistent inflammation may be responsible for the progression of IPF, a number of new therapeutic agents that specifically target molecules critical to the development of fibrosis are now being investigated.

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|  | 5. Balanced material content?                          |   |

## POST TEST

- Which of the following is not one of the 3 current, main categories of interstitial lung diseases (ILD)?
  - ILD secondary to a known cause
  - Idiopathic pulmonary fibrosis
  - ILD of unknown cause
  - Idiopathic interstitial pneumonias
- Which of the following are risk factors for idiopathic pulmonary fibrosis (IPF)?
  - Cigarette smoking and gastroesophageal reflux
  - Exposure to dusts and solvents
  - A genetic trait that is inherited in an autosomal dominant manner
  - A, B, and C are correct
- Laboratory analyses are often used to identify the diagnosis of IPF with excellent sensitivity and specificity.  
True    False
- Which of the following results of pulmonary function tests is not typically seen in IPF?
  - Reduced vital capacity
  - Reduced total lung capacity
  - Normal  $DL_{CO}$
  - None of the above; answers A, B, and C are all typically seen in IPF
- Risk factors for shortened survival in IPF include all but which of the following?
  - Age <50 years
  - History of cigarette smoking
  - Severity of dyspnea on presentation
  - Poor response to corticosteroid therapy
- Lung transplantation has been proved to prolong survival and quality of life in patients with IPF.  
True    False
- Which of the following statements best describes the use of corticosteroids in patients with IPF?
  - Corticosteroids are very useful in slowing the progression of IPF in most patients.
  - Corticosteroids greatly improve the quality of life in most patients with IPF.
  - Corticosteroids have not been proven beneficial for most patients with IPF.
  - Both A and B are correct.
- Which of the following statements best describes the use of interferon-gamma (IFN-gamma) in the treatment of IPF?
  - A large multi-center double-blind placebo-controlled trial of IFN-gamma demonstrated a statistically significant improvement in progression-free survival time
  - IFN-gamma did not produce statistically significant improvements in lung function in a large clinical trial of patients with IPF.
  - IFN-gamma improves gas exchange in patients who are unresponsive to corticosteroid therapy.
  - Patients with more advanced disease demonstrate the most improvement with IFN-gamma.
- Therapy directed against fibrosis is now considered the future of treatment in IPF.  
True    False

### Answer Key

1. B 2. D 3. D 4. C 5. A 6. True 7. C 8. B 9. True

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