

PILOT™

Pulmonary Fibrosis Identification: Lessons for Optimizing Treatment

WINTER 2004

PILOT™ MISSION STATEMENT

PILOT™ is a national education initiative designed to provide physicians with a comprehensive continuing medical education program that focuses on the early and accurate diagnosis of idiopathic pulmonary fibrosis (IPF), while addressing educational objectives critical to optimizing disease intervention and management.



PAUL W. NOBLE, MD

WHAT IS PILOT™?

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IPF is an exceptionally debilitating disease for which no known cure exists. Significantly, the accurate diagnosis of IPF can be quite elusive and is often delayed until signs and symptoms are far advanced. In fact, the median survival from the time of diagnosis has been measured at only 2–5 years. With a prevalence currently estimated at 80,000 cases in the United States alone, IPF represents a vital challenge to the medical community involved in caring for patients with this devastating disease.

Patients inflicted with IPF almost always present with very common symptomatology, namely exertional dyspnea and a chronic dry cough. As health care providers are well aware, these symptoms can embody a virtual plethora of conditions ranging from primary pulmonary processes to connective tissue diseases and various cardiac etiologies. As is the case with IPF, sorting out this vast differential diagnosis can be time consuming and challenging, thus delaying appropriate therapeutic intervention and, in certain instances, leading to devastating patient outcomes.

Emerging evidence, as discussed in the American Thoracic Society's consensus statement on IPF, suggests that early diagnosis and intervention may improve outcomes in patients with IPF. Educating practitioners to have a high index of suspicion for IPF and recognizing the early signs of this disease should facilitate the identification of patients earlier in the course of their illness. Thus, a critical need for medical education has been identified with the objective of increasing diagnostic and therapeutic knowledge in the area of IPF.

In order to fulfill this desperate need for increased physician awareness and ultimately improved patient outcomes, an educational program entitled PILOT™ (Pulmonary Fibrosis Identification: Lessons for Optimizing Treatment) has been implemented through the support of an unrestricted educational grant from InterMune. The

objectives of this initiative are to:

- Develop a series of educational tools designed to increase knowledge of the early and accurate diagnosis of IPF
- Identify the evolving treatments available for the management of IPF with the overall intention of improving patient care
- Disseminate the core educational messages to a targeted audience, including pulmonologists, radiologists, pathologists, and primary care physicians
- Measure the impact of PILOT™ activities on physician knowledge through the gathering and analysis of objective, measurable outcome data by pre- and posttesting

With these goals in mind, a multidisciplinary steering committee comprised of six pulmonologists, a radiologist, and a pathologist, all with extensive experience in the field of IPF, has been assembled to direct the development of a program of educational materials. The steering committee will function under the direction of predefined roles and responsibilities, with the ultimate goal of developing educational content and materials that support the PILOT™ initiative.

The principal educational tool in the PILOT™ program will be a four-section slide kit, with each section developed by a separate multidisciplinary work group of experts. The slide kit will include an overview of IPF with a focus on pathophysiology and pathogenesis, a treatise on the early and accurate diagnosis of IPF, the latest clinical information and future treatment options for IPF, as well as clinical tools for the primary care physician and resources for IPF patient management and education.

Interactive cases, quarterly newsletters, and a monograph addressing the early and accurate diagnosis of IPF comprise the remaining key elements of this initiative. Furthermore, a

Web site (www.PILOTforIPF.org) will be created to help in the dissemination of the educational materials to the overall medical community involved in the diagnosis and management of IPF. The Web site will host content developed for the PILOT™ educational programs.

The PILOT™ initiative will play a vital role in providing the medical community with an assemblage of highly effective educational materials that will support the overall goal of increasing knowledge of this extremely debilitating disease and improving the care of patients with IPF.

PILOT™ STEERING COMMITTEE

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PILOT™ RESOURCE HUB

A PLACEBO-CONTROLLED TRIAL OF INTERFERON GAMMA-1B IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS¹

SAMANTHA MATTIUCCI, PHARM.D • THE FRANCE FOUNDATION

The investigators in this double-blind, placebo-controlled trial conducted between September 2000 and October 2001 sought to ascertain the clinical benefit of interferon gamma-1b (IFN γ -1b) in 330 patients with idiopathic pulmonary fibrosis (IPF).¹

In 1999, a report of a randomized, controlled trial, including 18 patients, described a clinical benefit in terms of improvement in total lung capacity and the partial pressure of arterial oxygen among steroid-refractory IPF patients treated with IFN γ -1b.² The encouraging results of this study set the stage for this recent larger investigation to further elucidate the potential benefit of IFN γ -1b.

The recent trial randomized 330 patients with steroid refractory IPF to receive IFN γ -1b or placebo. The majority of patients were Caucasian, non-smoking males between the ages of 61 and 80 years, having a diagnosis of IPF for more than one year prior to study enrollment.

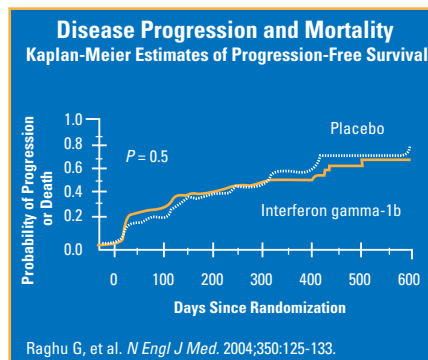
The diagnosis of IPF was established in the study population according to the strict clinical, radiologic, and histologic criteria as described by the American Thoracic Society / European Respiratory Society in its 2002 consensus classification of idiopathic interstitial pneumonias (IIP).³ Over 60% of patients had the diagnosis of IPF confirmed by surgical lung biopsy, while greater than 80% had findings on high-resolution CT interpreted as indicating definite IPF.

The primary endpoint of progression-free survival was defined as the time to disease progression or death. Progression was further defined as either a ≥ 5 mm Hg increase in the A-a gradient or a $\geq 10\%$ decrease in the baseline percent predicted FVC. Secondary endpoints included survival changes in the carbon monoxide diffusing capacity, forced vital capacity, AaO₂ difference, quality of life questionnaires, and the extent of fibrosis on high-resolution CT.

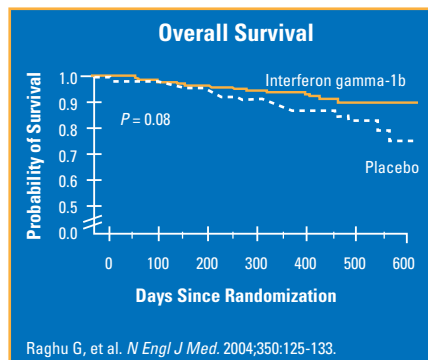
After randomization, comparison of the two groups revealed no statistically significant imbalances in clinically relevant base-line characteristics. Over a median of 58 weeks, the study investigators also found no significant difference in the duration of progres-

sion-free survival between the IFN γ -1b and placebo groups (median time to death or disease progression 439 days and 344 days, respectively [$P = 0.5$]).

The study further revealed no significant differences between the groups in any of the secondary endpoint measures.



Of note, a trend toward increased overall survival was observed in the IFN γ -1b group. Among the patients receiving IFN γ -1b, 10% died, while 17% of patients taking placebo died ($P = 0.08$). Moreover, this trend became significant when the data were analyzed using only treatment-adherent patients (5% and 14% death rate, respectively [$P = 0.02$]) and patients with less severe lung impairment at baseline (4% and 12% death rate, respectively [$P = 0.04$]).



Although the overall occurrence of adverse events in this trial was high, with headache, upper respiratory tract infections (URI), and cough comprising the top three, most categories of side effects demonstrated no significant differences between groups. The IFN γ -1b group exhibited significantly more cases

of headache, URI, fever, rigors, pain, influenza-like illness, and myalgias, while the patients in the placebo group had significantly more instances of nausea and vomiting. While pneumonia was reported more frequently in the IFN γ -1b group, there was no difference between groups in the number of severe or life-threatening pneumonias. Importantly, the criteria for diagnosing pneumonia were not prospectively defined; therefore, the significance of this finding remains unclear.

In their discussion, the investigators noted that their results differed from those reported from the previous trial of IFN γ -1b. Although it is unclear why they achieved different results, the investigators suggested that the patients in the earlier trial might represent a sub-group of treatment-responsive patients because molecular analysis of their lung tissue demonstrated an almost complete absence of IFN γ . This molecular analysis for the presence of IFN γ was not performed in this more recent trial, thus prohibiting this distinction from being made.

In conclusion, the investigators remarked that over a one-year period, IFN γ -1b did not influence conventional measures of disease progression in patients with IPF. They added that the trend toward increased overall survival in patients taking IFN γ -1b is an intriguing finding that warrants further investigation. Accordingly, a second trial powered to assess the impact of IFN γ -1b on survival time has been developed and is currently enrolling patients.

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ACUTE EXACERBATIONS AND COMPLICATIONS OF IDIOPATHIC PULMONARY FIBROSIS

STEVEN A. SAHN, MD

Idiopathic pulmonary fibrosis (IPF) is a chronic form of interstitial lung disease characterized clinically by an insidious onset of dyspnea, which often is accompanied by cough. The incidence of IPF in the United States is on the rise with approximately 30,000 new cases diagnosed each year. Furthermore, a cure for IPF has yet to be identified, but research into the pathogenesis of this disease has provided new and promising options for therapy.

A theory emerging from this research suggests that IPF results from an imbalance in the inflammatory response to multiple microscopic sites of ongoing alveolar epithelial injury.¹ This theory may explain the temporally heterogeneous pattern of disease seen in patients with IPF, as well as provide an explanation for the fulminant clinical deterioration that sometimes accompanies this disease.

Although IPF is insidious and chronic in nature, some patients present with a sudden onset of an accelerated form of their illness. These rapid deteriorations have been labeled "acute exacerbations" of IPF and were defined by Kondoh and colleagues in 1993 (see table 1).²

Table 1. Definition of Acute Exacerbation of IPF

- Exacerbation of dyspnea within a few weeks
- Newly developing pulmonary infiltrates on chest radiograph
- Deterioration of hypoxemia ($\text{PaO}_2/\text{FiO}_2 < 225$)
- Absence of apparent infectious agents

These investigators reviewed three cases of acute clinical exacerbation in patients with IPF and analyzed their clinical, radiologic, pathologic, and therapeutic findings. They noted that these patients presented with an influenza-like illness or cough with fever as well as leukocytosis, and progressed rapidly to a state of severe lung injury compatible with adult respiratory distress syndrome (ARDS). For these reasons, the investigators concluded that acute exacerbation in their patients represented an accelerated form of IPF.

Although the cause of such rapid clinical deteriorations remains unclear, the medical community recognizes these progressive and rapidly fatal events as a distinct entity, differ-

ing from the complications of IPF, which can also affect a swift clinical decline (see table 2).

Table 2. Factors Causing and Contributing to the Clinical Deterioration of Patients with IPF³

- Acute exacerbation – IPF progression
- Cardiovascular diseases
- Bronchogenic carcinoma
- Pulmonary infections
- Pulmonary thromboembolism
- Complication of therapy
- Pneumothorax

In a meta-analysis examining the clinical course of 543 patients with IPF, Panos and co-workers found that disease progression most commonly accounted for the clinical deterioration of their patients, yet they noted the difficulty in distinguishing disease progression from disease associated complications and adverse effects of therapy.³ In this series, other factors, such as cardiac disease, bronchogenic carcinoma, pulmonary embolism, pulmonary infections, complications of therapy, and pneumothorax were implicated as factors contributing to the clinical deterioration of patients with IPF.

As a result of the clinical similarities between acute exacerbation and complications of IPF, the diagnosis and management of clinically deteriorating patients is problematic. An acute exacerbation of IPF is a diagnosis of exclusion, thus the physician must first eliminate the possibility of a comorbid condition, so that interventions can be appropriately directed.

The process of making this distinction begins with a medical history and physical examination focused upon eliciting information that may direct an appropriate work-up. Unfortunately, many of the previously mentioned complications of IPF that cause clinical deterioration present with the same complex of symptoms and physical findings as an acute exacerbation, further complicating the diagnostic process.

Various tests have been employed to make this distinction. Although not always diagnostic, a 12-lead EKG and echocardiogram can identify a cardiogenic source of a sudden clinical deterioration, but these patients often require invasive procedures to distinguish

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UPCOMING CME EVENTS

PILOT™ CME PRECEPTORSHIPS: (to be scheduled from May through July 2004)

Yale University School of Medicine
hosted by Paul W. Noble, MD,
June 10, 2004

University of Pittsburgh
hosted by James H. Dauber, MD
July 9, 2004

David Geffen School of Medicine at
UCLA hosted by Robert M. Strieter, MD
July 20, 2004

Medical University of South Carolina
hosted by Steven A. Sahn, MD
July 23, 2004

PILOT™ CME DINNER MEETINGS: UPDATE ON IDIOPATHIC PULMONARY FIBROSIS: A Case-Study Approach to Early and Accurate Diagnosis

April 8, 2004: Minneapolis, Minnesota
Ganesh Raghu, MD

May 4, 2004: Denver, Colorado
Steven D. Nathan, MD

May 18, 2004: Beverly Hills, California
David A. Zisman, MD

June 1, 2004: Columbus, Ohio
Paul W. Noble, MD

June 3, 2004: Spokane, Washington
Ganesh Raghu, MD

June 15, 2004: Fort Wayne, Indiana
Steven D. Nathan, MD

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patients often require invasive procedures to distinguish heart disease from acute exacerbation of IPF.

IPF has been further implicated as a significant risk factor for the development of lung cancer, which can also lead to a clinical exacerbation of IPF. A review of 205 patients with IPF, identified 20 patients (9.8%) with bronchogenic carcinoma, which correlated with an odds ratio of 14 when compared to the general population.⁴ Because of underlying chronic changes in the lungs of patients with IPF, a high index of suspicion for underlying malignancy must be maintained when evaluating chest radiographs and HRCT scans in these patients.

As would be expected, patients with IPF are also at an increased risk of developing pneumonia, which can cause clinical deterioration similar to an acute exacerbation. Often patients are treated empirically with broad-spectrum antibiotics while microbiologic investigations are pending. It is critical to explore all potential causes of pulmonary infection with fluid and tissue cultures as well as serum titers for various bacterial, fungal, and viral agents.

Patients with IPF have several risk factors for pulmonary thromboembolism such as inactivity, heart disease, malignancy, and steroid use. In order to exclude a pulmonary embolus, a CT angiogram is required, for ventilation/perfusion scanning is of little clinical utility in IPF patients because of their baseline defects. Negative venous ultrasonography of the lower extremities and d-dimer make the diagnosis unlikely.

Many patients with IPF are prescribed high doses of corticosteroids and cytotoxic agents (cyclophosphamide and azathioprine) in an effort to slow the progression of their disease. These agents are associated with multiple adverse events, not the least of which is an increased susceptibility to infection. Consequently, the physician must always consider the role of medications in the development of accelerated clinical decline.

Pneumothorax is another complication of IPF that has been found to imitate acute exacerbation. Although it is a relatively unusual occurrence in patients with IPF, pneumothorax in the face of a significantly reduced pulmonary reserve sets these patients up for rapid clinical deterioration. Fortunately, in this instance, radiologic studies often easily identify pneumothorax, and thoracostomy tube drainage becomes the obvious treatment, although persistent air leak may occur requiring pleurodesis.

Other modalities such as bronchoscopy with bronchoalveolar lavage (BAL) and trans-bronchial lung biopsy and surgical lung biopsy have been used to elucidate an accurate diagnosis in clinically deteriorating IPF patients. By excluding other causes of clinical decline, such as pulmonary infection, BAL was helpful in arriving at a presumptive diagnosis of acute exacerbation in five patients reviewed in a recent report.⁵ The study investigators also found that all of their patients had a markedly increased number of neutrophils and type II reactive cells on BAL fluid examination, suggesting that these findings may indicate acute exacerbation.

A few studies have examined the histopathology of lung tissue from patients with acute exacerbation. The consensus is that diffuse alveolar damage (DAD) is superimposed upon the underlying fibroblastic foci and honeycomb cysts of usual interstitial pneumonia (UIP) in this hastened form of IPF.

In the review by Kondoh and colleagues, histopathologic examination of lung biopsy specimens displayed a pattern of acute lung injury without hyaline membranes and chronic interstitial pneumonia, UIP type.² Other reports have confirmed these findings with histologic examination of lung tissue from IPF patients during their acute exacerbations, also demonstrating DAD in the setting of chronic UIP.^{5,6,7}

Once an accurate diagnosis is established treatment can proceed. In general, therapy for an acute exacerbation of IPF encompasses supportive care in combination with controversial interventions. Since these patients frequently have hypoxemic respiratory failure, they may require ICU admission and endotracheal intubation for mechanical ventilation.

A number of studies have reported on steroid treatment for acute exacerbations. All three patients reported by Kondoh² improved in association with methylprednisolone therapy, while in a 2001 report, Nishiyama and colleagues described the successful outcome of an acute exacerbation of IPF when steroids were used.⁸ However, there is no definitive evidence that steroids are effective in these acute exacerbations as in ARDS.

Cyclosporin A has also been investigated as a treatment for acute exacerbations of IPF.⁹ In a retrospective review of 17 patients with acute exacerbation of IPF, four of seven patients who received cyclosporin A had prolonged survival after their acute exacerbation. The authors concluded that cyclosporin A may prevent re-exacerbation of IPF and improve a patient's chances for

long-term survival.

Ultimately, whether aggressively treated or not, patients experiencing acute exacerbations of IPF have a poor prognosis. In a retrospective study of IPF patients admitted to the ICU, 11 of 15 (73%) died during their hospital stay.¹⁰ In addition, another review of 38 patients with exacerbations of IPF revealed 61% in-hospital mortality, with over 90% of the survivors expiring within two months of hospital discharge.¹¹

Only a few retrospective reports in the literature describe acute exacerbation of IPF and the diagnostic strategies and potential therapies for this condition. Although the etiology of this accelerated form of IPF remains unclear, it is certain that other causes of fulminant clinical deterioration must be identified and treated appropriately. Without better options, health care providers have used steroids with variable success, and the prognosis for an acute exacerbation remains extremely grave. More research is needed to further elucidate the clinical information surrounding acute exacerbations of IPF, and in due course, improve the outcome of patients experiencing these events.

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