The Clinical Course of Patients with Idiopathic Pulmonary Fibrosis

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Background: **Prospective data defining the clinical course in idiopathic pulmonary fibrosis (IPF) are sparse.**

Objective: **To analyze the clinical course of patients with mild to moderate IPF.**

Design: **Analysis of data from the placebo group of a randomized, controlled trial evaluating interferon-γ1b.**

Setting: **Academic and community medical centers.**

Patients: **168 patients in the placebo group of a trial evaluating interferon-γ1b.**

Measurements: **Measures of physiology and dyspnea assessed at 12-week intervals; hospitalizations; and the pace of deterioration and cause of death over a median period of 76 weeks.**

Results: **Physiologic variables changed minimally during the study. However, 23% of patients required hospitalization for a respiratory disorder and 21% died. Idiopathic pulmonary fibrosis was the primary cause of death in 89% of patients who died, and an apparent acute clinical deterioration preceded death in 47% of these patients.**

Limitations: **The instrument used to define the pace of deterioration and cause of death was applied retrospectively.**

Conclusions: **Recognition of the common occurrence of acute fatal deterioration in patients with mild to moderate IPF has important implications for monitoring patients and supports early referral for lung transplantation.**

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*A complete list of the IPF Study Group is available from reference 3: Raghu G, Brown KK, Bradford WZ, Starko K, Noble PW, Schwartz DA, et al. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2004;350:125-33.

Idiopathic pulmonary fibrosis (IPF), the most frequent of the idiopathic interstitial pneumonias, is associated with the worst prognosis (1, 2). However, data on the natural history of IPF are sparse. To clearly describe the pace of progression and the cause of death in a well-characterized cohort with mild to moderate IPF, we analyzed data from the placebo group of a randomized, double-blind, controlled clinical trial evaluating therapy with interferon-γ1b in patients with IPF (3). These data provide important insight into the natural history of IPF and events preceding death in patients with IPF. The data suggest that a gradual, progressive decline does not occur in many patients, thereby supporting the need for early referral for lung transplantation.

METHODS

Overview

Using data from a recently completed clinical trial (3), we performed a series of exploratory analyses of physiologic variables, dyspnea measures, hospitalizations, and characteristics of mortality in patients randomly assigned to receive placebo.

The prespecified primary end point analysis for the phase III study was to occur after the 306th randomly assigned patient was scheduled to complete 48 weeks of therapy. Patients were enrolled over an approximately 1-year period. Thus, follow-up times for the patients varied, and the numbers of patients available for visits beyond 48 weeks diminished over time. In the published report of the primary analysis of the trial, the median length of observation was 58 weeks (3). In the current report, we summarize data from randomization through the completion of blinded study therapy (the observation period); the median for this period was 76 weeks.

Study Participants

Study participants were all patients randomly assigned to the placebo group ($n = 168$) in the trial (3). Criteria for enrollment included a diagnosis of IPF according to American Thoracic Society criteria (4), an FVC of 50% to 90%, diffusing capacity of carbon monoxide (DLCO) of 25% or greater, definite or probable IPF on high-resolution computed tomography according to prespecified criteria, and worsening of disease during the preceding year despite a total corticosteroid dose of 1800 mg or greater within the preceding 2 years (3). Patients were permitted to continue taking prednisone (≤15 mg/d) if the dosage remained stable.

Data Collection

Data were collected at 12-week intervals and recorded on standardized case report forms by trained research associates at each institution. Information derived from interview and examination of the patient included demographic

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Context

The natural history of idiopathic pulmonary fibrosis (IPF) is unclear.

Contribution

A total of 168 participants with mild to moderate IPF assigned to placebo in a randomized trial were followed at 12-week intervals for about 76 weeks. For 32 of 36 patients who died, IPF was a related or main cause of death. Although physiologic variables such as FVC changed little, acute clinical deterioration preceded death in half of the patients who died of IPF.

Implications

Clinicians may need to rethink referral timing for lung transplantation because many patients with IPF may experience precipitous clinical declines rather than gradual progression of disease.

–The Editors

and clinical data, physiologic assessments, measures of dyspnea, vital status, number of all-cause hospitalizations, and number of hospitalizations for which the primary reason was specified as respiratory. Physiologic measures included FVC, plethysmography, DlCO, and arterial blood gas at room-air ambient temperatures. The transition dyspnea score is derived from an instrument in which the patient assesses the extent of dyspnea in reference to his or her baseline at study entry (5). The transitions or changes in the patient's dyspnea in 3 categories (function impairment, magnitude of task needed to evoke dyspnea, and magnitude of effort needed to evoke dyspnea) are rated in 7 grades from −3 (major deterioration) to 0 (unchanged) to 3 (major improvement); the final score ranged from −9 to 9. The lower the total score, the more severe the dyspnea. The validated University of California, San Diego, Shortness of Breath Questionnaire (6) has 24 items: Patients are asked to rate severity of shortness of breath using a 6-point scale (0 = not at all; 5 = maximal severity) during 21 different activities of daily living associated with varying levels of exertion; they are also asked to rate how their daily lives are limited by shortness of breath, fear of harm from overexertion, and fear of shortness of breath. Scores range from 0 to 120, with increasing score indicating worsening quality of life.

The physician responsible for any patient who died during the study period completed a retrospective supplemental questionnaire. The investigator-physician, who had full access to all measurements obtained as a part of the study, specified the primary cause of death, whether the cause was respiratory, and whether death was related to IPF. Investigator-physicians were to cite IPF as the primary cause of death only in the absence of a known alternative cause and only if the event was witnessed. For deaths considered to be IPF-related, 1 of 4 categories was assigned on the basis of the interval from the onset of new or worsening symptoms or signs until death: abrupt (occurring within minutes to hours), acute (≤4 weeks), subacute (progressing over weeks or months), or unknown. In the current report, we combine the abrupt- and acute-onset events within a single category.

Statistical Analysis

Physiologic variables and measures of dyspnea were compared between baseline and week 72. The frequency of hospitalizations (all-cause and respiratory-related), number of hospital days in patients hospitalized, and mortality were assessed over the entire observation period. Mean values are followed by SDs. The relationships between baseline percentage predicted FVC and the incidence and length of hospitalization were examined by using the Fisher exact test or independent-sample *t*-test, as appropriate. Missing values were not imputed. The reasons for missing values are as follows: 1) To optimize data integrity, data obtained at visits outside a window of 7 days were not included in the analysis, 2) because trial enrollment was staggered, fewer patients were available for analysis at the latter time points, and 3) the value for a particular variable for a particular patient may be missing, even though all other values for that time point and patient are available. On the basis of the nature of the variations leading to the differences in available data over time, no apparent evidence indicated that the variations are not random. Data analyses were conducted by using SAS software, version 8.02 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

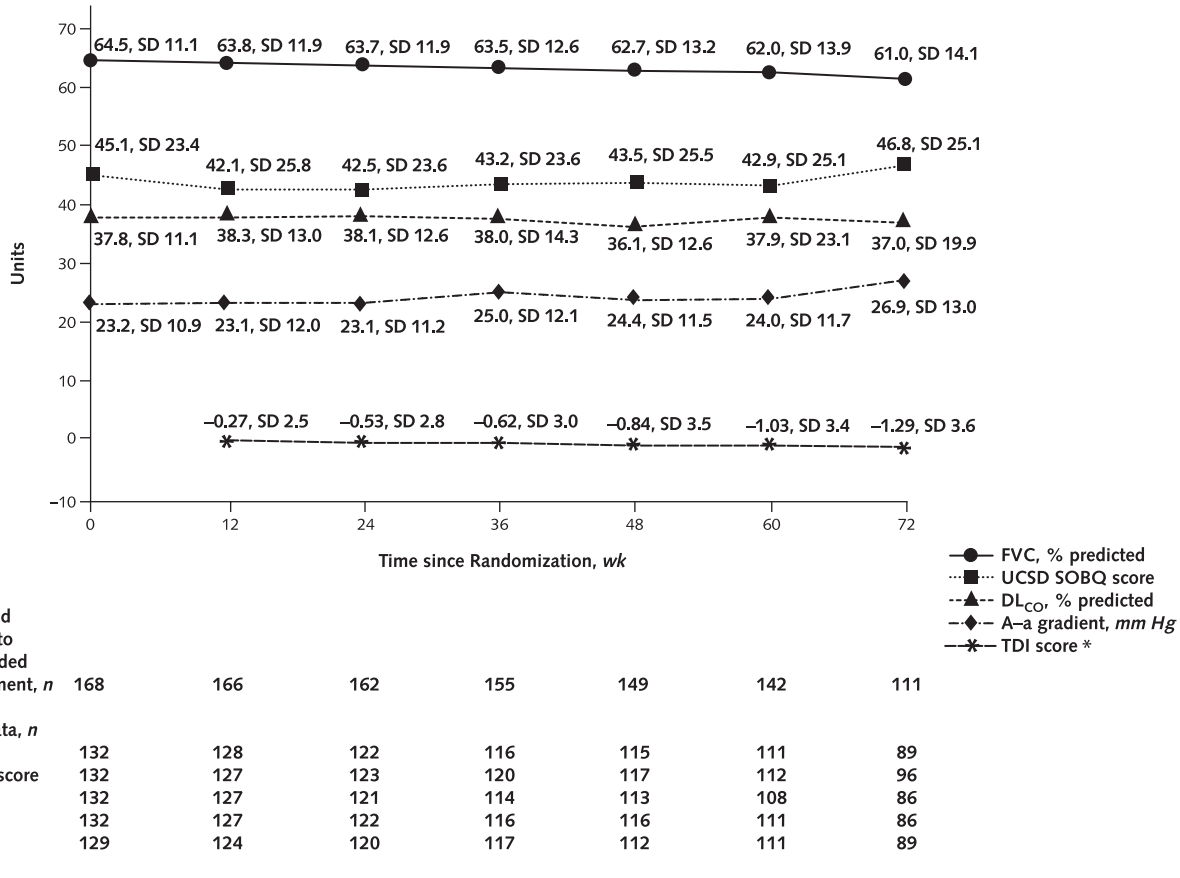
InterMune, Inc., funded this study. Authors from InterMune (Drs. Safrin, Starko, and Bradford) participated in the design and analysis of the study, as did the other authors. All authors had full access to the data. The funding source had no role in the decision to publish the results.

RESULTS

Patients

We analyzed 168 patients (mean age, 64 years, SD 9). Most patients were male (66%), white (86%), and nonsmokers (that is, never-smokers or ex-smokers) (91%). Mean time since the diagnosis of IPF was 378 days, SD, 295. The diagnosis of IPF was confirmed by surgical lung biopsy in 58% of patients; in 83%, findings on high-resolution computed tomography met prespecified criteria for definite IPF. At study entry, 31% of patients used supplemental oxygen and 82% were receiving systemic corticosteroids. During the observation period, 2 patients (1.2%) used azathioprine and 1 patient (0.6%) used cyclophosphamide.

Figure 1. **Measures of physiology and dyspnea from study entry through week 72 for patients who survived throughout trial.**



Patients alive and continuing to receive blinded study treatment, *n*	168	166	162	155	149	142	111
Patients with available data, *n*							
FVC	132	128	122	116	115	111	89
UCSD SOBQ score	132	127	123	120	117	112	96
DLCO	132	127	121	114	113	108	86
A–a gradient	132	127	122	116	116	111	86
TDI score	129	124	120	117	112	111	89

Values are the means and SDs. A–a = alveolar–arterial gradient; DLCO = diffusing lung capacity for carbon monoxide; TDI = Transition Dyspnea Index Questionnaire Score; UCSD SOBQ = score on the University of California, San Diego, Shortness of Breath Questionnaire. *The TDI score denotes change from baseline.

Physiologic Variables and Measures of Dyspnea

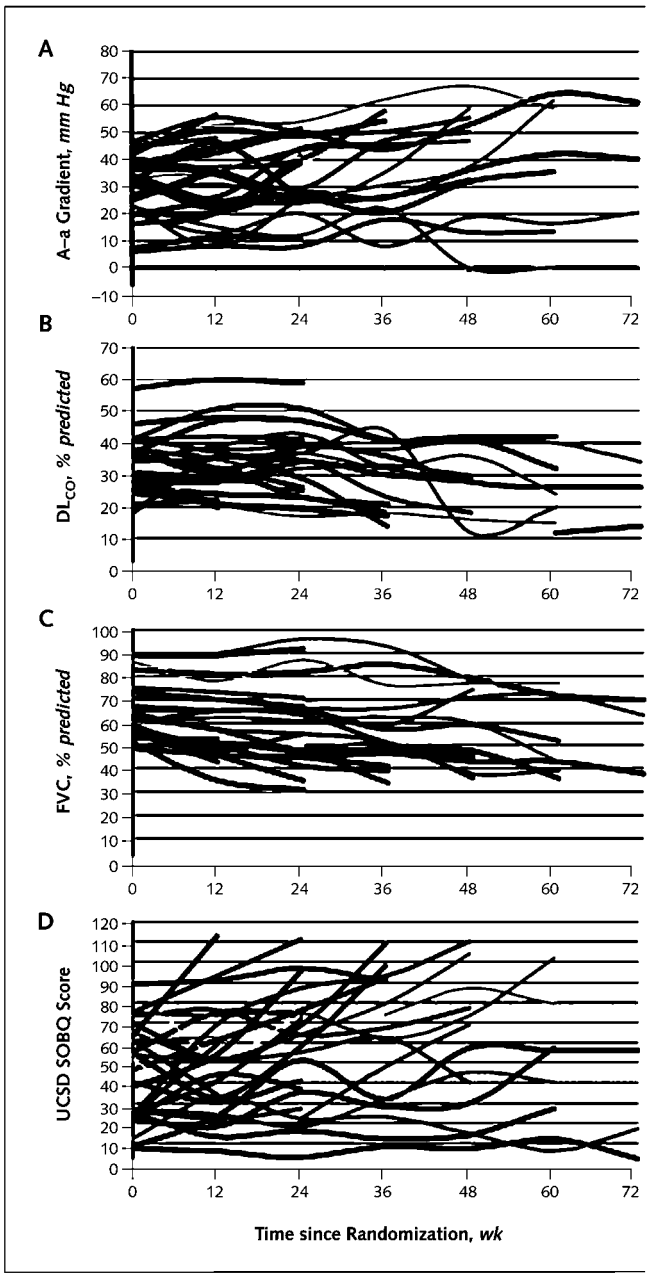
For patients who survived to week 72, the mean percentage predicted FVC decreased from 64.5%, SD 11.1%, to 61.0%, SD 14.1%; the mean percentage predicted DLCO decreased from 37.8%, SD 11.1%, to 37.0%, SD 19.9%; and the mean alveolar–arterial gradient increased from 23.2 mm Hg, SD 10.9, to 26.9 mm Hg, SD 13.0. The mean transition dyspnea index score was −1.29, SD 3.6, at week 72, indicating worsening dyspnea, whereas the mean University of California, San Diego, Shortness of Breath Questionnaire score changed minimally (from 45.1, SD 23.4, to 46.8, SD 25.1) (**Figure 1**). For patients who died during the trial, we observed a general trend toward increases in alveolar–arterial gradient and dyspnea and toward decreases in FVC and DLCO (**Figure 2**). The spaghetti plots (**Figure 2**) highlight the finding that although dyspnea or alveolar–arterial gradient often increased sharply before a patient's death, significant intrapatient variability occurs over time.

Hospitalizations

Fifty-seven (34%) patients had a total of 95 all-cause hospitalizations during the observation period. Among those hospitalized, the mean total number of hospital days was 14.3, SD 13.5. Thirty-eight (23%) patients had 57 hospitalizations for a respiratory disorder, with a mean total number of hospital days of 15.0, SD 14.6. The most commonly reported reason for respiratory hospitalization (33%) was presumed infection.

When stratified by the baseline median percentage predicted FVC, patients with more severely impaired lung function (≤62%) were more likely to be hospitalized for any reason than patients with baseline percentage predicted FVC greater than 62%—35 (42%) versus 22 (26%) patients ($P = 0.05$) and 58 versus 37 hospitalizations overall. Respiratory hospitalizations were similarly more frequent in the subset of patients with baseline FVC of 62% or less: 25 (30%) versus 13 (15%) patients ($P = 0.04$). In hospitalized patients, the total number of hospital days for those with baseline percentage predicted FVC of 62% or less versus greater than 62% did not significantly differ for all-cause hospitalization (11.8 days, SD 9.9, vs. 15.9 days, SD 15.2; $P = 0.2$) or for respiratory hospitalization (11.4 days, SD 9.0, vs. 16.9 days, SD 16.7, respectively; $P = 0.2$).

Figure 2. **Measures of physiology and dyspnea for each of the 36 patients who died during the trial; each line represents a single patient.**



The study continued up to a maximum of week 108; data shown are to week 72. **A.** Alveolar–arterial (*A–a*) gradient. **B.** Percentage predicted diffusing capacity of carbon monoxide (*DLCO*). **C.** Percentage predicted FVC. **D.** Score on the University of California, San Diego, Shortness of Breath Questionnaire (*UCSD SOBQ*). An interruption in a line indicates that no data were available at that time point.

Survival

Thirty-six (21.4%) patients died during the observation period (**Table**). Death was considered to be IPF-related in 32 (89%) patients; progression of IPF was the primary cause of death in 20 (56%) patients. In patients with an IPF-related death, 15 (47%) deaths were categorized as acute or abrupt and 16 (50%) deaths were considered subacute. The pace was unknown in 1 patient.

Progression of IPF was cited as the primary cause of death in 14 (88%) patients with a subacute course. In contrast, 6 (40%) patients with an acute pace of death had progression of IPF listed as the primary cause; pneumonia was listed for an additional 4 patients (27%), and the acute respiratory distress syndrome was listed for 2 (13%) patients.

Discussion

We found that the clinical course of patients with mild to moderate IPF was characterized by 1) minimal physiologic deterioration (as measured by FVC, DLCO, and alveolar–arterial oxygen gradient) or worsening severity of dyspnea over 72 weeks in patients remaining under observation, 2) frequent hospitalizations for respiratory disorders, and 3) an apparently acute and rapid progression of lung disease in almost half of the patients who died of an IPF-related cause. These data provide new insight into the known progressive nature of the disease (7).

Of note, even though patients with severe lung disease were excluded from the study, nearly 23% of all patients were hospitalized for a respiratory-related condition at least once, and 21% of patients died. In addition, 89% of deaths were deemed IPF-related. While the dominance of respiratory failure due to IPF progression as a cause of death has been previously described (7), a novel and clinically relevant finding is that approximately half of the IPF-related deaths in our study occurred after a period of decompensation that lasted up to 4 weeks. In fact, acute decompensation occurred at a frequency equal to that of subacute respiratory deterioration.

Acute exacerbation of IPF, also known as the accelerated form of IPF, has been described previously (8–12). This syndrome is characterized by acute progression of dyspnea over 1 month or less, in concert with new, diffuse opacities on chest radiography, worsening hypoxemia, and rapid development of respiratory failure in the absence of infection or alternative diagnoses (12). Pathologic examination typically shows acute alveolar injury with or without hyaline membrane formation (8–10). While the exact in-

Table. **Primary Causes and Pace of Deaths Related to Idiopathic Pulmonary Fibrosis**

Primary Cause of Death	Acute Deaths* (*n* = 15), *n*	Subacute Deaths* (*n* = 16), *n*
Progression of idiopathic pulmonary fibrosis	6	14
Pneumonia	4	0
Acute respiratory distress syndrome	2	0
Cor pulmonale	1	0
Other	0	1†
Unknown or unwitnessed	2	1

* Acute deaths occurred after a period of decompensation lasting 4 weeks or less; subacute deaths occurred after a period of progressive respiratory deterioration over weeks or months. The pace of death was unknown in 1 patient.
† Complications of lung transplantation.

cidence of this acute syndrome is unknown in patients with IPF, we found that 40% of those who died of an IPF-related cause appeared to fall into this category; an additional 13% died of the acute respiratory distress syndrome. These data suggest that rapid respiratory decompensation in patients with mild to moderate IPF is substantially more common than currently perceived.

The limitations in our analysis should be noted. The retrospective nature of collection of data on pace of disease progression leading to death may have led to miscategorization. The criteria for hospitalization were not prespecified, the specific clinical details of the respiratory decompensation were not documented, and longer periods of follow-up may be required to document deterioration in standard indices (13). Most patients received low doses of corticosteroids during the observation period, and all had previously shown disease progression while receiving this treatment before enrollment. Therefore, the use of prednisone is unlikely to have had any substantive therapeutic effects. Whether our findings apply to patients early in their disease course and in patients previously untreated with steroids or immunosuppressive agents cannot be addressed with our data. Future studies should ensure prospective, detailed collection of such information.

Our results provide novel, compelling, and clinically relevant information that can be used to monitor patients with IPF and to form a basis for treatment decisions. Our finding that a significant majority of patients remains stable by traditional measures, despite their subsequent course, may have important implications for the design of future therapeutic studies in IPF. Given the current absence of medical therapies known to improve survival, this enhanced understanding of the natural history of IPF strongly encourages more frequent patient reevaluations, new approaches to recognition and management of acute exacerbations of IPF, and early referral for lung transplantation. The latter is particularly important given the recent change in organ allocation in the United States, which mandates that a candidate's medical urgency and the transplant benefit be used to determine priority (14). Flexibility in updating clinical status will be crucial to maximize survival in patients with IPF considered for lung transplantation.

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