Changes in Pulmonary Function Test Results After 1 Year of Therapy as Predictors of Survival in Patients With Idiopathic Pulmonary Fibrosis*

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The study group consisted of 58 patients with idiopathic pulmonary fibrosis (IPF) recognized between 1970 and 1991 who were treated for their pulmonary disease, survived for at least 1 year from the time of initiation of treatment, and had forced vital capacity (FVC) measurements at the time of diagnosis and 9 to 15 months later. Forty-four of the patients also had a single-breath diffusing capacity (Dsb) measured initially and after 9 to 15 months of treatment and 33 patients had an arterial blood gas, breathing room air at the time of diagnosis and 9 to 15 months into therapy. Patients’ conditions were classified as improved, unchanged, or worse after the year of treatment based on each of the three pulmonary function tests. A >10% increase in FVC, ≥20% increase in Dsb, and ≥5 mm Hg decrease in alveolar-arterial difference in oxygen partial pressure [P(A-a)O2] defined improved function. A ≥10% decrease in FVC, ≥20% decrease in Dsb, and ≥5 mm Hg increase in P(A-a)O2 defined worse function. Patients with <10% change in FVC, <20% change in Dsb, and <5 mm Hg change in P(A-a)O2 were regarded as having unchanged conditions. Kaplan-Meier survival plots and the Cox proportional hazard regression model were used to analyze survival time in relation to change in pulmonary function after 1 year of therapy. Patients with an improved or unchanged FVC at 1 year had no difference in survival (p=0.75), but both showed enhanced survival compared with patients with a ≥10% reduction in FVC with 1 year of treatment (p<0.001). Patients with an improved or unchanged Dsb at 1 year also had no difference in survival (p=0.21) but again, both showed enhanced survival compared with patients with ≥20% decrease in Dsb with 1 year of treatment (p<0.001). Changes in gas exchange after 1 year of treatment did not correlate with survival in the three groups. There was a trend for longer survival in improved patients compared with those with worsening gas exchange, but the p value was not significant at 0.17. We conclude that changes in the FVC and Dsb after 1 year of treatment are strongly predictive of duration of survival in patients with IPF.  

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Key words: change in pulmonary function; prediction of survival; pulmonary fibrosis; therapy

Idiopathic pulmonary fibrosis (IPF) remains a therapeutic enigma. Since the original description of Hamman and Rich1 in 1944, there have been just two randomized trials of treatment for IPF. In 1989, Johnson and colleagues2 compared low-dose prednisolone plus cyclophosphamide with high-dose prednisolone alone and found the two regimens equally effective. In 1991, we reported a trial comparing prednisone alone with prednisone plus azathioprine.3 In this study, the pulmonary services of the Virginia Mason Clinic and the University of Washington required 5 years to enroll 27 evaluable patients. There was no separation of the survival curves of the two groups through the first 4 years of follow-up; however, at 9 years of follow-up, a Cox model analysis showed a survival advantage in the prednisone/azathioprine group. Our experience with this study crystallized two issues that are potential stumbling blocks for future therapeutic trials in IPF. The first was the very slow rate of accrual of a group of patients who met strict diagnostic criteria, had not been previously treated, and were available for close follow-up. The timely accumulation of such a patient group will require multi-institutional involvement. The second was that the use of survival as the criterion to compare therapeutic regimens may require years of follow-up to detect differences. Idiopathic
pulmonary fibrosis is usually a slowly progressive disease and the treatments thus far available have not shown dramatic benefit. Thus, significant differences may take years to recognize. The current study was undertaken to see if changes in pulmonary function after 1 year of treatment are predictive of survival.

**Methods**

**Study Population**

All patients 18 years of age or greater seen at Virginia Mason Medical Center (VMMC), Seattle, between 1970 and 1991 with a diagnosis of pulmonary fibrosis by diagnostic computer ICD-9 code and/or pathology report were reviewed. A diagnosis of IPF was established if the following three criteria were met: (1) the chest radiograph showed a diffuse reticulonodular infiltrate; (2) a lung biopsy (either open or transbronchial) specimen demonstrated interstitial fibrosis in the absence of granuloma, tumor, or infection; and (3) the patient had no known causes of pulmonary fibrosis such as collagen vascular disease, hypersensitivity pneumonitis, drug-induced diffuse lung injury, radiation pneumonitis, etc.

Patients were excluded from the study if the patient was not followed up at VMMC, the patient never received treatment, the patient survived less than 1 year from the time of initiation of treatment, or the patient did not have a forced vital capacity (FVC) performed at the time of diagnosis and repeated in the interval 9 to 15 months after initiation of treatment.

Data recorded from the charts of patients meeting these criteria included the time of onset of symptoms, the type and duration of therapy for IPF, and FVC, single-breath diffusing capacity (Dsb), and arterial blood gas results at rest, breathing room air with calculation of the alveolar-arterial difference in oxygen partial pressure (P(A-a)O2). The FVC was measured with a spirometer (Collin’s Water Spirometer; Warren E. Collins, Inc.; Braintree, Mass) before 1975 and with a different spirometer (Ohio 540; Ohio Medical Products; Madison, Wis; or Wedge Med-Science Spirometer; Med-Science; St. Louis, Mo) from 1975 to 1992. The FVC was performed with a forced expiratory maneuver from maximal inflation and analyzed according to the predicted normal values of Schoenberg et al. The Dsb was measured by an analyzer (Beckman Infrared Analyzer Model 865-11-3 Nondispersive; Beckman Instruments, Inc., Schiller Park, Ill) from 1970 to 1983, and a different analyzer (Med-Science Model 572 Diffusion; Med-Science, St. Louis, Mo) from 1983 to present. The Dsb was corrected for hemoglobin concentrations and analyzed according to Ogilvie et al. The P(A-a)O2 was calculated assuming atmospheric pressure of 760 mm Hg and a gas exchange ratio of 0.8.

A significant change in pulmonary function at 1 year of treatment was defined as ≥10% increase or decrease in FVC, ≥20% increase or decrease in Dsb, or ≥5 mm Hg increase or decrease in P(A-a)O2. Changes in pulmonary function were evaluated by comparing values at diagnosis to those at approximately 1 year of treatment. A follow-up range of 9 to 15 months was allowed as some patients did not have pulmonary function tests performed at exactly 1 year. If multiple pulmonary function tests were performed between 9 and 15 months, the results measured closest to 1 year after initiation of therapy were selected. Patients’ conditions were classified as improved, unchanged, or deteriorated, according to the changes occurring with treatment in each of the three pulmonary function tests.

**Statistical Methods**

Data are expressed as means±SD or range. Kaplan-Meier survival plots and the Cox proportional hazards regression model were used to analyze survival time. The Cox model measures the importance of a variable in terms of the hazard ratio that expresses relative chance of death between groups compared. The p values were calculated by the Cox model and a value ≤0.05 was considered significant.

**Results**

The records of 905 patients with ICD-9 code and/or pathology reports of “pulmonary fibrosis” were re-
viewed. Five hundred three patients had focal radiographic change rather than diffuse parenchymal disease. Two hundred forty-two patients with diffuse pulmonary fibrosis had identifiable causes of the pulmonary scarring, including 102 patients with collagen vascular disease, 52 patients with postinfectious pulmonary fibrosis, 30 patients with sarcoidosis, 20 patients with postirradiation change, and 14 patients with asbestosis. One hundred sixty patients met the diagnostic criteria for IPF. Of these 160 patients, 61 did not have follow-up through VMMC, an additional 32 patients survived less than 1 year, 4 did not have a FVC between 9 and 15 months of treatments, and 5 received no therapy, leaving a study group of 58 patients.

The study group included 27 men and 31 women. The mean age at time of diagnosis was 59.9 years with a range of 27 to 84 years. All 58 patients had a FVC at the time of diagnosis and after 9 to 15 months of treatment. Forty-four patients had an initial Dsb and follow-up Dsb after 9 to 15 months of treatment and 33 patients had an initial arterial blood gas, breathing room air with a follow-up arterial blood gas after 9 to 15 months of treatment. The mean interval between initial and follow-up pulmonary function testing was 11.9 months.

The mean FVC of the entire group at time of diagnosis was 2.27 L (61% predicted normal) with a range from 0.98 to 4.04 L; the mean Dsb was 9.22 mL/min/mm Hg (42% predicted normal) with a range from 2.53 to 23.5; and the mean P(A-a)O2 was 33 mm Hg with a range from 1 to 71 mm Hg. Thirty-one patients (53.4%) were alive at the end of the study period, while 27 patients (47%) had died. The range of survival was from 13 to 246 months with a mean of 88.9 months. Seven patients died from causes other than respiratory failure; one patient with congestive heart failure, one patient with cholangiocarcinoma, one patient with bronchogenic carcinoma, one patient with a cardiac arrhythmia, one patient with disseminated coccidiodymycosis, and two patients committed suicide.

The treatment received varied among the 58 patients of the study group. Twenty patients received prednisone alone, 26 patients received prednisone and azathioprine, 5 patients received prednisone and cyclophosphamide, and 7 patients were switched from an initial prednisone/azathioprine combination to prednisone/cyclophosphamide during the first year of treatment. Only 9 patients received medication for less than 1 year; none received less than 6 months of treatment. The average length of treatment for these 9 patients was 8 months.

Relation of Survival to Change in FVC After 1 Year of Treatment

Twenty-four of 58 patients had a 10% or greater increase in vital capacity over the first year of treatment (Table 1). The mean increase was 33.6% with a range of 13 to 76%. Fourteen patients had a 10% or greater decrease in FVC with a mean loss of 25.4% and a range from 10.5 to 55%. Twenty patients had <10% change in FVC after 1 year of treatment. Patients with a ≥10% increase in FVC had a mean survival of 103.8±65.6 months and patients with unchanged conditions had a mean survival of 106.7±58.2 months that compared with 37.9±38.4 months for patients with a decrease in FVC after 1 year of treatment. Figure 1 shows the Kaplan-Meier survival curves for these three groups. Table 2 lists the hazard ratios obtained comparing the frequency of death of patients with an improved FVC with treatment vs those unchanged, unchanged vs worse FVC, and finally, the improved vs worse groups. Patients with improved or unchanged conditions at 1 year had no difference in survival but both showed enhanced survival compared with the patients with ≥10% reduction in FVC after 1 year of treatment (p<0.001).

Relation of Change in Dsb at 1 Year of Treatment

A Dsb at the time of initiation of therapy and 9 to 15 months later was available for 44 patients. Ten patients had a ≥20% increase, 24 patients had <20% change, and 10 patients had a ≥20% decrease through 1 year of treatment. Patients with an improved Dsb had a mean survival of 113.2±60.8 months and patients with an unchanged Dsb had a mean survival of 102.5±69 months that compared with 27.3±12.4 months for those with a ≥20% decrease at 1 year of treatment. Figure 2 shows the Kaplan-Meier survival curves for the three groups. Table 2 lists the hazard ratios obtained comparing the frequency of death of patients with an improved Dsb with the other two
groups. Similar to the FVC results, patients with an improved or unchanged Dsb at 1 year had no difference in survival but both showed enhanced survival compared with patients with ≥20% decrease in Dsb after 1 year of treatment (p<0.001).

Relation of Survival to Change in Gas Exchange After 1 Year of Treatment

An arterial blood gas at rest and breathing room air was available at the time of initiation of therapy and after 1 year of treatment in 33 patients. Thirteen patients had improved gas exchange with therapy with a 5 mm Hg or greater decrease in P(A-a)O₂. Six patients were unchanged and 14 patients showed deterioration of gas exchange with P(A-a)O₂ increasing ≥5 mm Hg with treatment. Patients with improved gas exchange had a mean survival of 107.5±69.6 months and patients with unchanged P(A-a)O₂ had a mean survival of 94.8±66.1 months that compared with 60.4±48.6 months for the patients with a ≥5 mm Hg increase after 1 year of treatment. Figure 3 shows the Kaplan-Meier survival curves for the three groups. Table 2 lists the hazard ratios obtained comparing the frequency of death in the three patient groups. Change in gas exchange after 1 year did not correlate with survival in the three groups. There was a trend for longer survival in patients with improved conditions compared with those with worsening exchange, but the p value was not significant at 0.17.

Table 1—Frequency of Change in FVC, Dsb, and P(A-a)O₂ After 1 Year of Treatment in Patients With IPF

<table>
<thead>
<tr>
<th>Pulmonary Function Test</th>
<th>a=Improved</th>
<th>b=Unchanged</th>
<th>c=Worse</th>
<th>No. of Patients (%)</th>
<th>Mean Change (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (n=58)</td>
<td>a ≥10% increase</td>
<td>b &lt;10% change</td>
<td>c ≥10% decrease</td>
<td>24 (41)</td>
<td>+33.6% (+13 to +76)</td>
</tr>
<tr>
<td></td>
<td>20 (34)</td>
<td>-0.4% (-8 to +9)</td>
<td>14 (24)</td>
<td>-25.4% (-10.5 to -55)</td>
<td></td>
</tr>
<tr>
<td>Dsb (n=44)</td>
<td>a ≥20% increase</td>
<td>b &lt;20% change</td>
<td>c ≥20% decrease</td>
<td>10 (23)</td>
<td>+91.3% (+25 to +223)</td>
</tr>
<tr>
<td></td>
<td>24 (55)</td>
<td>-3.3% (-19.2 to +18.9)</td>
<td>10 (23)</td>
<td>-33.8% (-20 to -53)</td>
<td></td>
</tr>
<tr>
<td>P(A-a)O₂ (n=33)</td>
<td>a Decrease of ≥5 mm Hg</td>
<td>b &lt;4 mm Hg change</td>
<td>c Increase of ≥5 mm Hg</td>
<td>13 (39)</td>
<td>-16.5 (-5 to -30)</td>
</tr>
<tr>
<td></td>
<td>6 (18)</td>
<td>+0.1 (+2.3 to -2)</td>
<td>14 (43)</td>
<td>+13.7 (+5 to +23)</td>
<td></td>
</tr>
</tbody>
</table>

Relation of Survival to Changes in Combination of Pulmonary Function Tests

There was good concordance between changes in FVC and Dsb after 1 year of treatment. Fifteen of 24 patients with an increase in FVC at 1 year had Dsb measurements prior to the therapy and 1 year later. Eight of this group had an increased Dsb, seven patients had unchanged conditions, and no patient had a decreased Dsb. In contrast, the 13 patients with an increase in FVC and gas exchange measurements included 7 with improved gas exchange, 1 patient with no change, and five patients with worse gas exchange.

Sixteen patients with unchanged FVC after 1 year of treatment had Dsb measurements and 13 of them had an unchanged Dsb with one patient increasing ≥20% and two patients decreasing. Gas exchange was again discordant. The ten patients with unchanged FVC and paired arterial blood gas measurements included four patients with improved gas exchange, three who had unchanged conditions, and three who were worse.

Thirteen patients with a decrease in FVC had Dsb measurements. Eight patients had a decrease in Dsb, four had unchanged conditions, and a single patient had an increase in Dsb in the face of a reduced FVC. Ten patients with reduced FVC had gas exchange measured; six were worse, two were unchanged, and two were improved.

Simultaneous changes in both FVC and Dsb proved to correlate with the chance of survival better than ei-

Table 2—Survival Analysis by Cox Proportional Hazard Ratios Comparing Patients With IPF Who Measured Improved, Unchanged, or Worse in Each of Three Pulmonary Function Tests After 1 Year of Treatment

<table>
<thead>
<tr>
<th>Pulmonary Function Test</th>
<th>Groups Compared (Improved, Unchanged, Worse)</th>
<th>Hazard Ratio</th>
<th>95% Confidence Index</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (n=58)</td>
<td>Improved vs unchanged</td>
<td>1.189</td>
<td>0.42 to 3.40</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>Unchanged vs worse</td>
<td>7.56</td>
<td>2.84 to 20.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Improved vs worse</td>
<td>8.98</td>
<td>3.35 to 24.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dsb (n=44)</td>
<td>Improved vs unchanged</td>
<td>2.64</td>
<td>0.59 to 11.86</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Unchanged vs worse</td>
<td>12.5</td>
<td>3.96 to 39.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Improved vs worse</td>
<td>32.9</td>
<td>5.99 to 181.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P(A-a)O₂ (n=33)</td>
<td>Improved vs unchanged</td>
<td>1.88</td>
<td>0.49 to 7.20</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>Unchanged vs worse</td>
<td>1.15</td>
<td>0.29 to 4.63</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>Improved vs worse</td>
<td>2.16</td>
<td>0.72 to 6.50</td>
<td>0.17</td>
</tr>
</tbody>
</table>
ther test alone. Eight patients had an increase in both FVC and Dsb after 1 year of treatment, 8 patients had decreases in both measurements, and 13 patients had unchanged values in both. A comparison of those patients with improved conditions on both measures to those with unchanged conditions showed no difference in survival with a hazard ratio of 1.76 (95% confidence interval [CI], 0.34 to 9.17, and p=0.5). However, patients with improvement or no change in both test results after 1 year of treatment had a striking survival advantage when compared with patients who were worse in both tests. Comparison of the group with deteriorating measurements to those unchanged showed a hazard ratio of 37.38 (95% CI, 4.2 to 332, and p=0.001). Patients with deteriorating conditions in both tests had a hazard ratio of 65.66 (95% CI, 5.63 to 65.4, and p<0.001) when compared with patients showing improvement in both tests.

The number of patients with concordant change in both FVC and P(A-a)O_2 or Dsb and P(A-a)O_2 were too small for statistical comparison.

DISCUSSION

Previous clinical studies have emphasized pretreatment variables that are predictive of a beneficial response to treatment. A duration of disease of less than 1 year, more cellular reaction with less fibrosis on open lung biopsy specimen, and a bronchoalveolar lavage cell population with increased proportions of lymphocytes have each been correlated with better response to treatment.6-11

This study was conducted to assess the ability of changes in pulmonary function testing at 1 year of therapy to predict survival in patients with IPF. The selection of a treatment period of 1 year was not totally arbitrary. In our experience, patients responding to prednisone therapy show rapid improvement that is frequently maximal within the first month. In contrast, the response to cytotoxic treatment is much slower, typically taking 3 months to be appreciable and 6 to 9 months for maximum benefit. Because many of our patients were receiving combinations of prednisone plus azathioprine or cyclophosphamide, we believed that a 1-year period of treatment allowed for maximal effect to have occurred. It is possible that measurements made after 6 months of treatment might also be predictive of survival, but such data were not available in this study.

The data presented should not be misconstrued as typical of the effect of therapy on IPF. The inclusion criteria of survival to 1 year introduces a bias for selection of patients with a favored outcome. This would explain why 44 of our 58 (76%) patients had an increased or unchanged FVC and only 14 patients (24%) had a 10% or greater decrease in FVC. Similarly, 34 of 44 patients (77%) had an increased or unchanged Dsb and only 10 (23%) had decreased values after 1 year's treatment.

Improved survival in responders to corticosteroid therapy has been reported previously.12,13 Turner-Warwick and colleagues12 defined a positive response to treatment as ≥10% increase in FVC maintained for at least 1 year after initiation of treatment. Twenty-eight (31%) of 91 patients had a positive response to treatment and survival was significantly longer in responders than in nonresponders. Although patients with ≥10% increase in FVC and ≥10% increase in Dsb were identified, no analysis relating change in Dsb to survival was done. No gas exchange studies were performed. Stack and colleagues13 defined two levels of improvement in 69 patients with IPF who were treated with corticosteroids. Mild improvement (grade 1) was "slight symptomatic improvement, vital capacity increased up to 10% and/or slight radiological improvement." This group is similar to our patients with an unchanged FVC after treatment. Substantial improvement (grade 2) required "substantiated relief of dyspnea, vital capacity increased by more than 10% and considerable or complete radiological clearing." Twenty-eight (41%) of the 69 patients had either grade 1 or grade 2 improvement. The 5-year survival for these 28 patients was 43% compared with only 20% in the 41 patients uninfluenced by corticosteroid therapy. The 11 patients with grade 2 improvement had a 5-year survival of 67%.

Our study separated patients with unchanged conditions from those with improved or worsened conditions after 1 year of treatment and analyzed the changes in Dsb and P(A-a)O_2 in addition to changes in FVC. Our analysis shows that changes in FVC and Dsb measured at 1 year of treatment are predictive of survival for IPF. Patients with a ≥10% increase in FVC and those with a <10% change in FVC both had a survival advantage over patients with a 10% or greater decrease in FVC. Also patients with improved or unchanged Dsb had increased survival compared with patients with ≥20% decrease after 1 year of treatment. The good outcome of the patients with an unchanged FVC or Dsb after a year of treatment is worthy of emphasis. Most patients with IPF have progressive disease and will demonstrate a steady downhill course. Spontaneous remission in this illness is rare. Thus, stable lung function at the end of a year's time implies a therapeutic benefit and an interruption of the downhill course. This is supported strongly by the current data.

The concordance between changes in FVC and Dsb were notable. No patient with an improved FVC had ≥20% decrease in Dsb and just 2 of 16 patients with an unchanged FVC had ≥20% decrease in Dsb. One of the latter died after 34 months and the other patient is alive after 57 months of follow-up. Favorable results
in both FVC and Dsb after 1 year of treatment correlated with a chance of survival, which is better than predicted by either test alone. Measuring both FVC and Dsb at 1 year may provide better prognostic information than determining only the FVC.

The data presented on gas exchange apply to only 33 patients. Changes in gas exchange at 1 year did not produce a statistically significant correlation with survival. This comes as a surprise and needs to be reevaluated by others with larger groups of patients. Changes in gas exchange were frequently discordant with FVC and Dsb.

The results of this study have significant clinical and research implications. For the individual patient, the current study provides a basis for interpretation of changes in pulmonary function test results after 1 year of treatment and their relation to survival. Our results also provide a rationale for using changes in pulmonary function test results after 1 year of treatment as criteria for comparing therapeutic regimens. Patients with an increased or unchanged FVC and/or increased or unchanged Dsb after 1 year of treatment gain a statistically significant survival benefit over those with a decrease in FVC, Dsb, or both. Thus, change in these pulmonary function test results at 1 year can provide a reasonable basis for comparing effectiveness of therapeutic regimens.

REFERENCES

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