

ORIGINAL ARTICLE

# A Placebo-Controlled Trial of Interferon Gamma-1b in Patients with Idiopathic Pulmonary Fibrosis

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## ABSTRACT

### BACKGROUND

Idiopathic pulmonary fibrosis is a progressive, fatal disease with no known efficacious therapy.

### METHODS

In a double-blind, multinational trial, we randomly assigned 330 patients with idiopathic pulmonary fibrosis that was unresponsive to corticosteroid therapy to receive subcutaneous interferon gamma-1b or placebo.

### RESULTS

Over a median of 58 weeks, interferon gamma-1b therapy did not significantly affect the primary end point of progression-free survival, defined as the time to disease progression or death, and no significant treatment effect was observed on measures of lung function, gas exchange, or the quality of life. Ten percent of patients in the interferon gamma-1b group died, as compared with 17 percent of patients in the placebo group ( $P=0.08$ ). Treatment with interferon gamma-1b was associated with more frequent constitutional symptoms. However, the rates of treatment adherence and premature discontinuation of treatment were similar in the two groups. More pneumonias were reported among patients in the interferon gamma-1b group, but the incidence of severe or life-threatening respiratory tract infections was similar in the two groups.

### CONCLUSIONS

In a well-defined population of patients with idiopathic pulmonary fibrosis, interferon gamma-1b did not affect progression-free survival, pulmonary function, or the quality of life. Owing to the size and duration of the trial, a clinically significant survival benefit could not be ruled out.

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**I**DIOPATHIC PULMONARY FIBROSIS IS A fatal lung disease of unknown cause characterized by worsening dyspnea, progressive loss of lung volumes, and abnormal gas exchange. The outcome is dismal, with a median survival of only two to three years.<sup>1-3</sup> Although no therapy has been demonstrated to be efficacious, a recent consensus statement recommends treatment of idiopathic pulmonary fibrosis with antiinflammatory and immunosuppressive therapies such as prednisone in combination with azathioprine or cyclophosphamide.<sup>4</sup> However, the only two randomized, controlled trials of these therapies failed to demonstrate significant clinical benefit.<sup>5,6</sup> Moreover, both corticosteroids and cytotoxic agents may have serious side effects.<sup>7-9</sup>

Interferon- $\gamma$  is an endogenously produced cytokine with diverse properties, including antifibrotic, antiinfective, antiproliferative, and immunomodulatory effects.<sup>10</sup> Its dose-dependent inhibition of fibroblast proliferation, collagen-matrix deposition, and collagen synthesis has been demonstrated *in vitro* and in rodent models.<sup>11-13</sup> In idiopathic pulmonary fibrosis, inflammation and widespread fibrosis are believed to result from repeated occult episodes of focal parenchymal injury. The condition is also characterized by an excess of profibrotic cytokines<sup>14-17</sup> and a relative deficiency of interferon- $\gamma$ .<sup>18,19</sup> Exogenous interferon gamma therapy inhibits the expression of these profibrotic cytokines,<sup>20</sup> enhances the activation of macrophages and killing of ingested bacteria,<sup>21</sup> shifts the T-cell response toward a macrophage-dominated inflammatory response,<sup>22-24</sup> and up-regulates the *in vitro* expression of antimicrobial peptides by alveolar macrophages and monocytes.<sup>25</sup> Therefore, interferon gamma-1b may influence the course of idiopathic pulmonary fibrosis through antifibrotic, antiinflammatory, or antiinfective effects.

In a previous randomized, controlled study,<sup>20</sup> 18 patients with corticosteroid-refractory idiopathic pulmonary fibrosis were treated with interferon gamma-1b (200  $\mu$ g three times weekly) plus daily prednisolone or prednisolone alone over a 12-month period. Treatment with interferon gamma-1b was associated with significant improvements in total lung capacity and the partial pressure of arterial oxygen (PaO<sub>2</sub>).<sup>20</sup> Other studies have suggested that interferon gamma-1b therapy may reverse or slow the fibrotic process in cutaneous systemic sclerosis<sup>26,27</sup> and chronic hepatitis C.<sup>28</sup> Given the poor prognosis of patients with idiopathic pulmonary fibrosis, the inadequacy and toxic effects of current

treatment options, and encouraging preliminary data, we performed a randomized, double-blind, placebo-controlled clinical trial of therapy with interferon gamma-1b in patients with this condition.

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## METHODS

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### PATIENTS

Between September 2000 and October 2001, 330 patients from 58 centers in the United States, Europe, Canada, and South Africa underwent randomization. The diagnosis of idiopathic pulmonary fibrosis was established according to previously described clinical, radiologic, and histologic criteria.<sup>4</sup> Eligible patients were 20 to 79 years of age, had had clinical symptoms of idiopathic pulmonary fibrosis for at least three months, and had a forced vital capacity (FVC) that was 50 to 90 percent of the predicted value, a carbon monoxide diffusing capacity that was at least 25 percent of the predicted value, and a PaO<sub>2</sub> of more than 55 mm Hg while they were breathing ambient air at rest.

High-resolution computed tomography (CT) had to show definite or probable idiopathic pulmonary fibrosis. Definite idiopathic pulmonary fibrosis was defined by all of the following: the presence of a reticular abnormality, traction bronchiectasis, or both, with a basal and peripheral predominance; the presence of honeycombing with a basal and peripheral predominance; and the absence of atypical features of usual interstitial pneumonia — micronodules, peribronchovascular nodules, consolidation, isolated (nonhoneycomb) cysts, ground-glass attenuation (or if present, it had to be less extensive than the reticular opacity), and mediastinal adenopathy (or if present, it had to be too limited to be visible on a chest radiograph). Probable idiopathic pulmonary fibrosis was defined by the presence of a bilateral, predominantly basal and subpleural reticular pattern with subpleural cysts (honeycombing), traction bronchiectasis, or both in the absence of atypical features of usual interstitial pneumonia.<sup>29</sup> The diagnosis of idiopathic pulmonary fibrosis was confirmed by either the finding of usual interstitial pneumonia on surgical lung biopsy or findings on transbronchial biopsy that were not diagnostic of an alternative condition.

Additional criteria for eligibility were a decrease in the predicted FVC of at least 10 percent, evidence of worsening disease on a chest radiograph, or evidence of worsening dyspnea at rest or on exertion within one year before enrollment, as well as a lack

of improvement despite the receipt of prednisone therapy (a total dose of at least 1800 mg) within the preceding two years. Patients were permitted to continue taking prednisone (15 mg or less per day) if the dose remained stable.

Criteria for exclusion were clinically significant exposure to known fibrogenic agents (e.g., exposure to birds, asbestos, and iatrogenic drugs known to cause pulmonary fibrosis), an alternative cause of interstitial lung disease, a ratio of the forced expiratory volume in one second (FEV<sub>1</sub>) to FVC of less than 0.6 after the use of a bronchodilator, a residual volume that was more than 120 percent of the predicted value, active infection within one week before enrollment, unstable cardiovascular or neurologic disease, uncontrolled diabetes, pregnancy, lactation, or a likelihood of death, as predicted by the investigator, within the next year. Laboratory results mandating exclusion were a total bilirubin level that was at least 1.5 times the upper limit of the normal range; an aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase level that was more than 3 times the upper limit of the normal range; a creatinine level that was more than 1.5 times the upper limit of the normal range; an albumin level of less than 3.0 mg per deciliter; a white-cell count of less than 2500 per cubic millimeter; a hematocrit value of less than 30 percent or more than 59 percent; and a platelet count that was less than 100,000 per cubic millimeter. Prior treatment with any interferon was prohibited, as was treatment for idiopathic pulmonary fibrosis other than corticosteroids within the six weeks preceding enrollment or the use of investigational agents within six months before enrollment.

#### STUDY DESIGN

At each study center, patients were randomly assigned in a 1:1 ratio to receive interferon gamma-1b or placebo subcutaneously three times weekly. The randomization code was generated by an external statistician before the trial was initiated, and eligible patients were randomly assigned to the treatment groups in equal proportions. Randomization was performed at each center with the use of a permuted-block design and stratified according to smoking status, with nonsmokers defined as patients who had never smoked cigarettes or who had stopped smoking more than one year before enrollment, and smokers as those who had smoked within the previous year.<sup>30</sup> Written informed consent was obtained from each patient or guardian, and the study

was approved by the institutional review board at each center.

The dose of the study drug was increased from 100 µg to 200 µg three times a week after two weeks. Bedtime administration of the study drug was recommended, and pretreatment with acetaminophen or ibuprofen was required. Patients, their caregivers, or both were trained at enrollment to administer an accurate volume of the study drug using aseptic techniques. Patients kept diaries to provide a record of injections and oxygen use; compliance was monitored by reviewing the diaries and by counting the number of used medication vials.

After base-line measurements had been obtained and arterial blood gases measured while the patient was breathing ambient air at rest, pulmonary-function tests (FVC, FEV<sub>1</sub>, lung volumes, and carbon monoxide diffusing capacity) were performed, and St. George's Respiratory Questionnaire<sup>31</sup> and the Transition Dyspnea Index<sup>32</sup> were administered and repeated at three-month intervals. Total lung capacity was measured by means of body box plethysmography and chest radiography and high-resolution CT were performed at base line and again at week 48. The difference between alveolar and arterial oxygen tension (P(A-a)O<sub>2</sub>) was calculated with use of a simplified form of the alveolar gas equation and the known barometric pressure for that day and site: partial pressure of alveolar oxygen = partial pressure of inspired oxygen - (partial pressure of arterial carbon dioxide ÷ R), where R, the respiratory quotient, was assumed to be 0.8. Two expert chest radiologists performed central and independent scoring of the extent of lung fibrosis on high-resolution CT scans obtained from each patient at base line and week 48. In the event of discrepant interpretations, a third radiologist evaluated the scans. Worsening disease on high-resolution CT was defined as progression in the extent of reticular opacities or subpleural cysts (honeycombing) as compared with the base-line findings. The radiologists were unaware of the patients' identification, the patients' treatment assignments, and the temporal sequence of the studies.

#### STATISTICAL ANALYSIS

The primary efficacy end point was progression-free survival, measured from randomization to either disease progression or death. Comparison of the study groups and estimation of the hazard ratio, with 95 percent confidence intervals, were performed with the likelihood score test from the Cox

proportional-hazards model, stratified according to smoking status. Progression of disease was defined by either of the following changes from base line, confirmed on a visit 4 to 14 weeks later: a decrease of at least 10 percent in the predicted FVC or an increase of at least 5 mm Hg in the  $P(A-a)O_2$  at rest.

Secondary end points were the change from base line to week 48 in the carbon monoxide diffusing capacity, FVC,  $P(A-a)O_2$  at rest, the score on the St. George's Respiratory Questionnaire, the score on the Transition Dyspnea Index, and the extent of lung fibrosis on high-resolution CT; the most severe monthly requirement for supplemental oxygen; and progression-free survival. The secondary end point of progression-free survival was estimated with the use of an alternative definition of disease progression, which was any two of the following: a decrease from base line in the FVC of at least 10 percent, an increase from base line in  $P(A-a)O_2$  of at

least 5 mm Hg, or a decrease from base line in the carbon monoxide diffusing capacity of at least 15 percent. Survival was compared in two prespecified populations with the use of the log-rank test stratified according to smoking status: all randomized patients according to the intention-to-treat principle and patients who received at least 80 percent of the scheduled doses of study drug (the treatment-adherent cohort). Exploratory subgroup analyses of survival divided the population at median base-line values for FVC and carbon monoxide diffusing capacity. Cox regression models that included variables for treatment, smoking status, and base-line FVC were used to test for an interaction between treatment effect and base-line FVC with respect to survival.

Final data analysis was performed at a prespecified point 48 weeks after the 306th patient underwent randomization. Efficacy analyses included all randomized patients. Safety analyses included all patients who received at least one dose of the study drug. Analysis of covariance was used for continuous variables; categorical variables were analyzed with the use of the Cochran–Mantel–Haenszel row mean-scores test, stratified according to smoking status. For end-point evaluations, values were carried forward from the last available observation for all patients.

The planned sample of 306 patients provided the study with 94 percent power to detect a 50 percent reduction in the primary end point, the rate of disease progression or death at one year (i.e., from 40 percent to 20 percent). An independent data monitoring committee regularly reviewed emerging safety and efficacy data. Patients were to continue blinded therapy for up to four months after the primary study analysis. Mortality is being monitored for five years from the date of randomization for all patients.

All the authors participated fully and integrally in the design and conduct of the trial, analysis of the data, and reporting of the results. All were members of the steering committee, which met regularly to devise the protocol and discuss issues regarding study performance, analysis, and interpretation. The data were held and analyzed by the sponsors. All authors had full access to the raw data after the initial analysis, and all authors were encouraged by the study sponsor to suggest and review additional analyses that were performed, with the results reported when relevant. No limits were placed on the analysis or content of the manuscript by the study sponsor.

**Table 1. Characteristics of the Study Population at Entry.\***

| Characteristic  | Interferon Gamma-1b (N=162) | Placebo (N=168) |
|---|-----------------------------|-----------------|
| Age (yr)  | 63.6±8.6                    | 63.4±8.6        |
| Male sex (% of patients)                              | 72                          | 66              |
| Race or ethnic group (% of patients) †                |                             |                 |
| White   | 91                          | 86              |
| Black   | 2                           | 5               |
| Asian   | 0                           | 3               |
| Hispanic  | 5                           | 4               |
| Other   | 2                           | 1               |
| Smoking status (% of patients) ‡                      |                             |                 |
| Nonsmokers  | 95                          | 91              |
| Current smokers                                       | 5                           | 9               |
| Days since diagnosis of idiopathic pulmonary fibrosis | 425.3±368.6                 | 378.2±295.2     |
| PaO <sub>2</sub> at rest (mm Hg)                      | 73.5±10.2                   | 74.1±10.3       |
| Forced vital capacity (% of predicted)                | 63.9±10.7                   | 64.1±11.3       |
| Carbon monoxide diffusing capacity (% of predicted)   | 37.2±11.2                   | 36.8±10.6       |
| Use of prednisone or equivalent (% of patients)       | 75                          | 77              |
| Use of supplemental oxygen (% of patients)            | 41                          | 31              |

\* Plus–minus values are means ±SD. There were no significant differences between the groups with the use of t-tests for continuous data and chi-square tests for categorical data. PaO<sub>2</sub> denotes partial pressure of arterial oxygen. Because of rounding, percentages may not total 100.

† The race or ethnic group was assigned by the investigator, who used a checklist comprising these five categories. In the checklist, “white” was referred to as “Caucasian.”

‡ Current smokers were defined as those who had smoked cigarettes within the year before study entry; nonsmokers were defined as those who had never smoked or who had stopped smoking more than one year before study entry.

## RESULTS

Of the 330 patients who underwent randomization, 162 received interferon gamma-1b and 168 received placebo. No imbalances in clinically relevant baseline characteristics were apparent between the two groups (Table 1). The majority of patients were white men 61 to 80 years of age who were nonsmokers and who had received the diagnosis of idiopathic pulmonary fibrosis more than one year before enrollment. The diagnosis was confirmed by the identification of usual interstitial pneumonia on surgical lung biopsy in 62 percent of patients in the interferon gamma-1b group and 67 percent of patients in the placebo group. Findings on high-resolution CT were interpreted as indicating definite idiopathic pulmonary fibrosis in 84 percent of patients in the interferon gamma-1b group and 83 percent of patients in the placebo group.

The median duration of treatment was 383 days in the interferon gamma-1b group (range, 13 to 643) and 374 days in the placebo group (range, 12 to 646). An average of 93 percent of all scheduled doses were received (i.e., 94 percent in the interferon gamma-1b group and 92 percent in the placebo group), and 90 percent of patients complied with the protocol-specified follow-up visits overall, even if they discontinued treatment. Sixty of the 330 randomized patients (18 percent) — 33 in the interferon gamma-1b group and 27 in the placebo group — discontinued treatment prematurely: 16 patients in each group asked to be withdrawn; 8 and 2, respectively, stopped because of an adverse event; 5 and 1, respectively, withdrew because of an expected lung transplantation; 1 and 4, respectively, withdrew for other reasons; 3 in each group were withdrawn by the investigator; and 1 patient in the placebo group used prohibited therapy. Four patients in each group underwent lung transplantation during the study period. Seven patients (one in the interferon gamma-1b group and six in the placebo group) who discontinued blinded treatment received interferon gamma-1b therapy outside the study protocol.

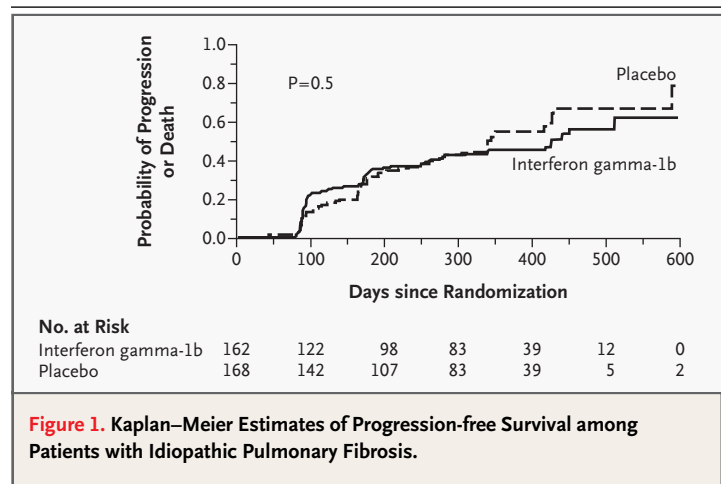
## DISEASE PROGRESSION AND MORTALITY

In the primary efficacy analysis, there was no significant difference in the duration of progression-free survival between the interferon gamma-1b and placebo groups: median time to death or disease progression, 439 and 344 days, respectively ( $P=0.5$ ) (Fig. 1). The hazard ratio for death or disease pro-

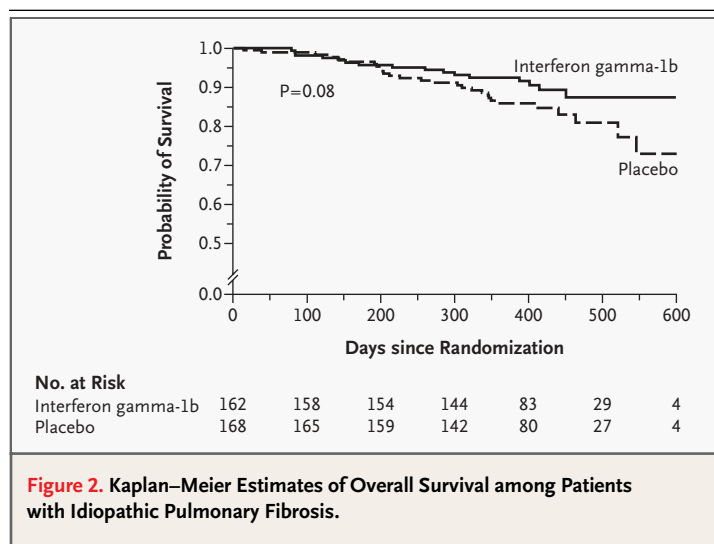
gression in the interferon gamma-1b group, as compared with the placebo group, was 0.9 (95 percent confidence interval, 0.6 to 1.2). Disease progression or death occurred in 46 percent of patients in the interferon gamma-1b group and 52 percent of those in the placebo group. The majority of primary endpoint events (88 percent) were disease-progression events rather than death, and the majority of disease-progression events in both groups (62 percent) were increases in the  $P(A-a)O_2$  at rest.

No treatment effect was discernible with respect to the mean change from base line to week 48 in the FVC ( $-0.20$  liter in the interferon gamma-1b group and  $-0.16$  liter in the placebo group), the  $P(A-a)O_2$  (3.3 and 2.9 mm Hg, respectively), or the carbon monoxide diffusing capacity ( $-1.0$  and  $-0.7$  ml per minute per mm Hg, respectively). There was also no significant difference between the groups in the mean change in lung fibrosis on high-resolution CT or in the prespecified alternative definition of progression-free survival (data not shown).

Vital status was ascertained in all enrolled patients at the time of study completion. There was no statistically significant effect on overall survival. Sixteen of the 162 patients in the interferon gamma-1b group (10 percent) died, as compared with 28 of the 168 patients in the placebo group (17 percent) ( $P=0.08$ ). The hazard ratio for death in the interferon gamma-1b group, as compared with the placebo group, was 0.6 (95 percent confidence interval, 0.3 to 1.1) (Fig. 2). Analysis of the treatment-adherent cohort of patients showed an absolute reduction in the risk of death of 9 percent in the interferon gamma-1b group, as compared with the placebo group, and a relative reduction in the risk of 66 per-



**Figure 1. Kaplan-Meier Estimates of Progression-free Survival among Patients with Idiopathic Pulmonary Fibrosis.**



**Figure 2.** Kaplan–Meier Estimates of Overall Survival among Patients with Idiopathic Pulmonary Fibrosis.

cent (5 percent of 126 patients in the interferon gamma-1b group and 14 percent of 143 patients in the placebo group died,  $P=0.02$ ). The hazard ratio for death in the interferon gamma-1b group, as compared with the placebo group, was 0.3 (95 percent confidence interval, 0.1 to 0.9).

Exploratory analyses suggested that the effect of treatment on the risk of death depended on the FVC at base line ( $P=0.05$  with the use of a test for interaction) and that treatment appeared to have had a greater effect on survival among patients with less severe impairment in lung function than among those with more severe impairment. Among patients with a base-line FVC above the median (at least 62 percent of the predicted value), 4 percent of the 86 patients in the interferon gamma-1b group died, as compared with 12 percent of the 88 patients in the placebo group ( $P=0.04$ ). Conversely, among 156 patients with a base-line FVC that was less than 62 percent of the predicted value, no survival benefit was apparent (mortality rate of 17 percent in the interferon gamma-1b group and 21 percent in the placebo group,  $P=0.6$ ). Among patients with a base-line carbon monoxide diffusing capacity that exceeded the median (at least 35 percent of the predicted value), 5 percent died in the interferon group, as compared with 13 percent in the placebo group ( $P=0.06$ ).

Respiratory events were reported as the cause of death in 81 percent of the patients in the interferon gamma-1b group who died and in 82 percent of those in the placebo group who died. Respiratory insufficiency or progression of idiopathic pulmonary

fibrosis accounted for 62 percent and 71 percent of these events, respectively. The duration of disease, sex, a definite diagnosis of idiopathic pulmonary fibrosis on high-resolution CT, the mode of histopathological diagnosis of idiopathic pulmonary fibrosis, and the use of prednisone during the study period did not affect the differences in survival between the groups (data not shown).

#### DYSPNEA AND THE QUALITY OF LIFE

Neither dyspnea, as assessed by the score on the Transition Dyspnea Index at week 48, nor the quality of life, according to the score on the St. George's Respiratory Questionnaire at week 48, was affected by treatment ( $P=0.9$  and  $P=0.2$ , respectively).

#### SAFETY

The overall incidence of adverse events during the study period was high, with events occurring in 99 percent of patients in the interferon gamma-1b group and 98 percent of patients in the placebo group (Table 2). The most common adverse events in both groups were headache, cough, and upper respiratory tract infection. The incidence of mild adverse events was 15 percent in the interferon gamma-1b group and 17 percent in the placebo group; the incidence of moderate adverse events, 40 percent and 47 percent, respectively; the incidence of severe adverse events, 36 percent and 26 percent, respectively; and the incidence of life-threatening adverse events, 8 percent in each group. The following severe or life-threatening events occurred in at least 5 percent of patients in each group: hyperglycemia, defined by a serum glucose level of more than 13.9 mmol per liter (250 mg per deciliter) (9 percent of the interferon gamma-1b group and 6 percent of the placebo group); lymphopenia, defined by an absolute lymphocyte count of less than 500 per cubic millimeter (6 percent and 2 percent, respectively); and pneumonia (6 percent and 5 percent, respectively). The respective overall incidence of severe or life-threatening infections was 9 percent in the interferon gamma-1b group and 10 percent in the placebo group.

Constitutional symptoms, such as fever, rigors, an influenza-like illness, headache, and myalgia, were significantly more common among patients who received interferon gamma-1b, whereas nausea and vomiting were significantly more frequent among patients who received placebo (Table 2). Severe constitutional symptoms occurred in 6 percent of patients given interferon gamma-1b, as com-

pared with 1 percent of those given placebo; no constitutional symptom in either group was graded as life-threatening. A time-based analysis of fever and rigors among patients receiving interferon gamma-1b showed that these symptoms diminished greatly after the first several weeks, despite continued therapy. Whereas 14 percent of patients reported fever and 14 percent of patients reported rigors in the first two weeks of interferon gamma-1b therapy, only 8 to 9 percent of patients reported either symptom in the subsequent two weeks; these percentages decreased further to 5 percent or less in any subsequent month during the next six months. Also, no more than 3 of the 33 patients reporting fever or 2 of the 34 patients reporting rigors in the first month of interferon gamma-1b therapy reported these symptoms in any of the subsequent five months of therapy.

Respiratory tract infections, reported by site investigators without the use of predefined criteria, occurred in 68 percent of patients in the interferon gamma-1b group and 56 percent of those in the placebo group. Of these infections, pneumonias (reported without the use of predefined criteria) accounted for 15 percent and 8 percent, respectively, and unspecified respiratory tract infections accounted for 12 percent and 11 percent, respectively. Severe or life-threatening respiratory tract infections were reported in 8 percent of patients in each group. Twenty-nine respiratory tract infections resulted in the hospitalization of 26 patients in the interferon gamma-1b group (16 percent), as did 19 such infections in 16 patients in the placebo group (10 percent). Respiratory tract infections resulted in three deaths in each group. Only one respiratory tract infection — acute bronchitis and pneumonia in a patient in the placebo group — resulted in the withdrawal of treatment.

## DISCUSSION

We conducted a large, randomized, multinational, double-blind, placebo-controlled trial in a well-defined population of patients with idiopathic pulmonary fibrosis who had high rates of adherence to the protocol and treatment regimen. No significant differences were noted in the primary outcome measure of progression-free survival (defined as either disease progression or death) or in conventional measures of lung function and gas exchange at rest, or the quality of life. Our results differ from those of another randomized, controlled trial of in-

**Table 2. Adverse Events Occurring in at Least 15 Percent of Patients.**

| Adverse Event                      | Interferon<br>Gamma-1b<br>(N=162) | Placebo<br>(N=168) | P Value* |
|------------------------------------|-----------------------------------|--------------------|----------|
|                                    | <i>no. of patients (%)</i>        |                    |          |
| Any adverse event                  | 161 (99)                          | 165 (98)           | 0.33     |
| Headache†                          | 86 (53)                           | 52 (31)            | <0.001   |
| Upper respiratory tract infection‡ | 82 (51)                           | 63 (38)            | 0.02     |
| Cough§                             | 59 (36)                           | 59 (35)            | 0.81     |
| Fever                              | 53 (33)                           | 16 (10)            | <0.001   |
| Rigors                             | 53 (33)                           | 15 (9)             | <0.001   |
| Fatigue¶                           | 39 (24)                           | 33 (20)            | 0.33     |
| Dyspnea                            | 39 (24)                           | 43 (26)            | 0.74     |
| Pain                               | 37 (23)                           | 23 (14)            | 0.03     |
| Diarrhea**                         | 37 (23)                           | 35 (21)            | 0.66     |
| Arthralgia                         | 33 (20)                           | 23 (14)            | 0.11     |
| Influenza-like illness             | 31 (19)                           | 13 (8)             | 0.002    |
| Myalgia                            | 30 (18)                           | 15 (9)             | 0.01     |
| Nausea, vomiting, or both††        | 29 (18)                           | 49 (29)            | 0.02     |
| Back pain                          | 29 (18)                           | 20 (12)            | 0.13     |
| Chest pain                         | 26 (16)                           | 27 (16)            | 0.10     |
| Nasal congestion                   | 25 (15)                           | 26 (15)            | 0.10     |
| Bronchitis‡‡                       | 25 (15)                           | 29 (17)            | 0.65     |
| Dizziness                          | 18 (11)                           | 29 (17)            | 0.11     |

\* P values were derived from the chi-square test.

† Headache includes headache, aggravated (worsened) headache, migraine, and sinus headache.

‡ Upper respiratory tract infection includes any upper respiratory tract infection, viral upper respiratory tract infection, sinusitis, acute sinusitis, otitis media, ear infection, laryngitis, nasopharyngitis, and streptococcal pharyngitis.

§ Cough includes any cough, aggravated (worsened) cough, and productive cough.

¶ Fatigue includes any fatigue and aggravated (worsened) fatigue.

|| Dyspnea includes any worsening dyspnea, exacerbated dyspnea, and exertional dyspnea.

\*\*Diarrhea includes diarrhea and aggravated (worsened) diarrhea.

††This category includes any nausea, aggravated (worsened) nausea, and vomiting.

‡‡Bronchitis includes any bronchitis, acute bronchitis, acute exacerbation of chronic bronchitis, and tracheobronchitis.

terferon gamma-1b therapy in 18 patients with idiopathic pulmonary fibrosis, which reported a significant improvement in total lung capacity and PaO<sub>2</sub> over a one-year period.<sup>20</sup> The reason for these differences is not apparent. In the previous study, lung tissue from all patients was characterized by a nearly complete lack of expression of interferon- $\gamma$  at entry; we did not perform a similar molecular analysis. Conceivably, therefore, patients in the prior study represent a subgroup of patients with idiopathic

interstitial pneumonia who were not well represented in our study.

Our study was designed and powered to detect a difference in the composite primary outcome, which measured disease progression or death, rather than in overall survival. Nevertheless, we observed a trend toward enhanced survival in all randomized patients who were treated with interferon gamma-1b, as compared with those receiving placebo (an absolute reduction in the risk of death of 7 percent and a relative reduction in the risk of 41 percent), which was more pronounced in patients who adhered to treatment (an absolute reduction in the risk of death of 9 percent and a relative reduction in the risk of 66 percent). This finding in treatment-adherent patients may reflect either a true benefit of treatment or a post-randomization bias somehow related to the administration of the study medication. For example, it is possible that patients with more severe illness found the side effects of the medicine unacceptable and elected to discontinue therapy. Alternatively, exploratory analyses suggest that the survival benefit may have been concentrated in the subgroup

of patients who had less severe impairment in lung function at base line. Our study design and data do not allow us to draw treatment inferences from these analyses.

In summary, our results demonstrate that over a one-year period interferon gamma-1b therapy does not significantly influence conventional markers of disease progression measured at rest in patients with idiopathic pulmonary fibrosis. Longer and larger studies are needed to investigate further whether interferon gamma-1b increases survival among patients with this devastating disease.

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#### APPENDIX

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