Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial

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Lancet 2009; 374: 222–28

Published Online June 30, 2009 DOI:10.1016/S0140-6736(09)60551-1

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Summary

Background Idiopathic pulmonary fibrosis is a fatal disease for which no effective treatment exists. We assessed whether treatment with interferon gamma-1b improved survival compared with placebo in patients with idiopathic pulmonary fibrosis and mild-to-moderate impairment of pulmonary function.

Methods 826 patients with idiopathic pulmonary fibrosis were enrolled from 81 centres in seven European countries, the USA, and Canada. Patients were randomly assigned (double-blind) in a 2:1 ratio to receive 200 μg interferon gamma-1b (n=551) or equivalent placebo (n=275) subcutaneously, three times per week. Eligible patients were aged 40–79 years, had been diagnosed in the past 48 months, had a forced vital capacity of 55–90% of the predicted value, and a haemoglobin-corrected carbon monoxide diffusing capacity of 35–90% of the predicted value. The primary endpoint was overall survival time from randomisation measured at the second interim analysis, when the proportion of deaths had reached 75% of those expected by the study conclusion. This study is registered with ClinicalTrials.gov, number NCT00075998.

Findings At the second interim analysis, the hazard ratio for mortality in patients on interferon gamma-1b showed absence of minimum benefit compared with placebo (1·15, 95% CI 0·77–1·71, p=0·497), and indicated that the study should be stopped. After a median duration of 64 weeks (IQR 41–84) on treatment, 80 (15%) patients on interferon gamma-1b and 35 (13%) on placebo had died. Almost all patients reported at least one adverse event, and more patients on interferon gamma-1b group had constitutional signs and symptoms (influenza-like illness, fatigue, fever, and chills) than did those on placebo. Occurrence of serious adverse events (eg, pneumonia, respiratory failure) was similar for both treatment groups. Treatment adherence was good and few patients discontinued treatment prematurely in either group.

Interpretation We cannot recommend treatment with interferon gamma-1b since the drug did not improve survival for patients with idiopathic pulmonary fibrosis, which refutes previous findings from subgroup analyses of survival in studies of patients with mild-to-moderate physiological impairment of pulmonary function.

Funding InterMune.

Introduction

Idiopathic pulmonary fibrosis is a diffuse parenchymal lung disease of unknown origin that is characterised by worsening dyspnoea, reduced lung volume, and impaired gas exchange.[1,2] The outlook is poor; median survival is about 2–5 years from diagnosis.[1–5] The clinical course is characterised by an insidious decline in pulmonary function and progressive worsening of other symptoms (dyspnoea, cough, or fatigue) that limit and eventually preclude routine physical activities. Results of some studies suggest that the disease follows a variable course in which periods of relative stability are punctuated by episodes of accelerated decline, possibly resulting in respiratory failure and death.[6,7] These findings, coupled with the absence of proven effective treatments, provide a strong rationale for the development of drugs to improve survival.

Interferon gamma-1b is a purified protein that is manufactured in *Escherichia coli* from recombinant DNA encoding human interferon γ.[8] The drug is approved to reduce the frequency and severity of infections in patients with chronic granulomatous disease, and to delay time to disease progression in patients with severe malignant osteopetrosis.[9,10] A large, randomised trial[11] did not show improved progression-free survival for patients with idiopathic pulmonary fibrosis given interferon gamma-1b compared with placebo. However, analysis of the intention-to-treat population did show improved survival in patients given interferon gamma-1b (p=0·08), and exploratory subgroup analyses indicated that those with mild-to-moderate severity of disease had the best improvement.[11] A meta-analysis[12] of 390 patients from the previous study[11] and two smaller studies,[13–15] suggested that treatment with interferon gamma-1b was associated with a reduction in mortality for all severities of disease compared with the control group (placebo[11,13,15] or colchicine[12]). The aim of INSPIRE (INternational study of Survival outcomes in idiopathic Pulmonary fibrosis with InteRfEron gamma-1b) was to assess the effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis and mild-to-moderate impairment of baseline pulmonary function.

Methods

Patients

1373 patients with idiopathic pulmonary fibrosis were enrolled from 81 centres in seven European countries (Belgium, France, Germany, Ireland, Italy, Spain, and UK), the USA, and Canada and screened for eligibility between Dec 15, 2003, and April 12, 2006. The study took place in teaching and community hospitals and clinics. The trial was discontinued on March 5, 2007, and the last patient visit was on May 2, 2009.

Eligible patients were 40–79 years of age, had been diagnosed with idiopathic pulmonary fibrosis in the past 48 months, had had clinical symptoms for at least 3 months, and had had disease progression in the past 12 months. Additional enrolment criteria were a forced vital capacity (FVC) of 55–90% of the predicted value, a haemoglobin-corrected carbon monoxide diffusing capacity (DL_{co}) of 35–90% of the predicted value, and a distance of at least 150 m covered during a 6-min walk.

Disease was diagnosed according to clinical, radiological, and histological criteria.[1,2] Positive radiological diagnosis by high-resolution CT scan showed features consistent with definite or probable idiopathic pulmonary fibrosis (webappendix p 1). Diagnosis was confirmed by the presence of usual interstitial pneumonia in surgical lung biopsy samples, or from transbronchial biopsy samples or bronchoalveolar lavage that did not suggest an alternative diagnosis. Surgical lung biopsy samples were required for all patients with a clinical and radiological diagnosis of probable idiopathic pulmonary fibrosis, and patients younger than 50 years, irrespective of the certainty with which the clinical and radiological diagnoses were made.

Patients were excluded if they had: a ratio of less than 0·60 for forced expiratory volume in 1 s to FVC, after use of a bronchodilator; residual volume exceeding 140% of the predicted value before use of a bronchodilator; history of clinically significant environmental exposure that was known to cause pulmonary fibrosis; diagnosis of any connective tissue disease; clinical evidence of active infection; or any alternative explanation for interstitial lung disease. Additionally, eligible patients could not be on a waiting list for lung transplantation at randomisation. Previous treatment with interferon gamma-1b, treatment with investigational drugs within 28 days of screening, and prednisolone treatment exceeding 0·125 mg/kg per day or 0·25 mg/kg every other day at randomisation were prohibited. Further exclusion criteria are on webappendix p 2.

Written informed consent was obtained from every patient or legal guardian before screening. US Department of Health and Human Services guidelines on human experimentation, or those of the relevant authors' institutions, or both, were followed. The study protocol was approved by the institutional review board or ethics committee at each study centre.

Study design

Patients were randomly assigned in a 2:1 ratio (double-blind) to receive 200 μg interferon gamma-1b or equivalent volume of placebo subcutaneously, three times per week. The randomisation code was generated by an independent third party statistician (United Biosource Corporation, Bethesda, MD, USA), and every study centre randomised patients according to a permuted block design (six patients per block) with an interactive voice response system. Patients were assigned a number for a drug kit by the independent third party statistician, dependent on their randomised treatment group. The independent statistician had no role beyond assignation of the randomisation code and drug kit numbers. Masking was achieved by use of identically packaged vials containing clear liquid for both the study drug and placebo. In an effort to attenuate the occurrence and severity of adverse events associated with interferon gamma-1b, patients followed a dose-escalation schedule[11] in which half the dose (100 μg as a 0·5 mL injection) was given thrice per week for the first 2 weeks, and the full dose (200 μg as a 1·0 mL injection) was given thrice per week thereafter; patients allocated to placebo were given injections of equivalent volume to the study drug. Patient diaries were used to record injections, supplemental oxygen use, concomitant medications, and adverse events. Compliance was assessed by review of patient diaries and recording of the number of drug vials that were returned. Concomitant treatment for idiopathic pulmonary fibrosis was allowed for patients who met the criteria for progression of disease, acute respiratory decompensation, or acute exacerbation (webappendix p 3).

See Online for webappendix

A directed history and review of the patient diary was done at 6-week intervals, and clinical laboratory assessments were done every 12 weeks. Every 24 weeks, patients underwent a complete physical examination and assessment of distance of a 6-min walk, pulmonary function (from FVC and DL_{co}), dyspnoea (University of California San Diego shortness of breath questionnaire[16]), and quality of life (St George's respiratory questionnaire[17]). The total score of the shortness of breath questionnaire ranges from 0 to 120, and the score increases with extent of dyspnoea. The St George's respiratory questionnaire is comprised of three respiratory-specific domains—symptoms, activity, and impacts—and each domain of the questionnaire ranges from 0 to 100, with an increasing score indicating worsening health-related quality of life. Safety was continuously monitored for the occurrence of adverse events and abnormalities in laboratory blood tests. Patients returned 4 weeks (±5 days) after the last dose of study drug for review of the patient diary and follow-up of adverse events. Information about adverse events was gathered from when the patient gave signed consent for enrolment to 28 days after the last dose. Serious adverse events were assessed at regular, prescheduled intervals (after enrolment of 25%, 50%, and 100% of patients, and at two interim analyses) by an independent data monitoring committee.

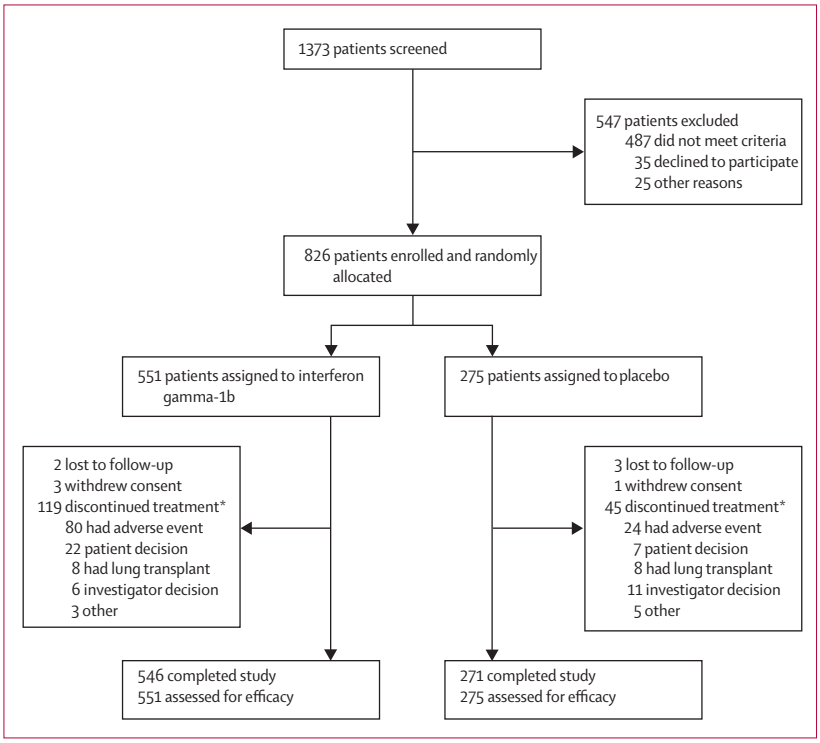

Figure 1: **Trial profile**
*Does not include patients who died.

Ad-hoc data review meetings could have been called by the chairman of the data monitoring committee of the study sponsor at any time in case of a safety concern. The severity of adverse events was categorised according to the Common Terminology Criteria for Adverse Events.

For the **Common Terminology Criteria for Adverse Events** see http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

The primary endpoint was overall survival time from randomisation, which should have been measured 90–96 weeks after enrolment of the 600th patient, but was actually measured at the second interim analysis because the study was stopped early. Secondary endpoints were survival time without lung transplantation, survival days without hospital admission due to a respiratory diagnosis, and change in dyspnoea and distance of a 6-min walk from baseline. Additional exploratory efficacy outcome measures included disease progression, acute respiratory decompensation, and acute exacerbation of disease, and change from baseline in FVC and DL_{co}. Secondary endpoints should have been measured at week 96, after enrolment of the 600th patient, but were actually measured at completion of the study (median duration of 77 weeks on treatment) because the study was stopped early. However, change in dyspnoea and distance of a 6-min walk were measured to week 96, and for those patients who had not reached the week 96 visit, data were inputed as per the statistical anaylsis.

Statistical analysis

The primary endpoint was analysed on an intention-to-treat basis with a log-rank test to establish significance and the Cox proportional-hazards model to estimate the treatment effect. Data are summarised as Kaplan-Meier estimates of the probability of survival.

Secondary endpoints were analysed on an intention-to-treat basis. ANCOVA was done to test the effect of treatment on secondary endpoints in which the outcome variable was change from baseline to week 96. Survival without lung transplantation was analysed with a log-rank test for statistical significance and the Cox proportional-hazards model to estimate the magnitude of the treatment effect. Survival days without respiratory-related hospital admission were compared between study groups with the Wilcoxon rank-sum test. For dyspnoea and distance of a 6-min walk, values that were missing for reasons other than death were imputed for post-baseline visits up to week 96 by calculating the average value of the three patients with the smallest sum of squared differences up to the missed visit. Missing values due to death were replaced with the worst possible value for each variable (120 for dyspnoea, 0 m for distance of 6-min walk). Statistical analyses were planned for assessment of quality-of-life scores, disease progression, acute respiratory decompensation, or acute exacerbation of disease, but were not done because the study was stopped early.

We designed the study to have 90% statistical power to detect a treatment effect equivalent to a 50% reduction (ie, from 24% to 12%) in 3-year mortality with a log-rank test (α=0·025, one-sided). About 600 patients were needed to achieve the targeted number of events within the planned duration of the trial. Two assessments of sample size were planned at pre-specified intervals (3–6 months before the projected end of enrolment, and at the second of two interim analyses), with protocol provisions to increase enrolment or extend the study duration; on the basis of events at the first assessment, a further 200 patients were enrolled.

Webappendix p 4 shows the expected timeline of the study. For the primary endpoint, two interim analyses were planned before the start of the study. The total number of deaths expected in the study population was 96—about 48 (12%) on interferon gamma-1b and 48 (24%) on placebo. The first interim analysis was scheduled for after 48 deaths had occurred (α=0·0027), and the second after 72 deaths had occurred (α=0·005825). The final analysis was to be done at a significance level of 0·04861. The two interim analyses were done in confidence by the data monitoring committee and an independent third party using the Lan-Demets alpha-spending principle[18] and the symmetric O'Brien-Fleming sequential stopping boundaries.[19,20] We planned to end the trial early if interim survival data were sufficiently favourable and strongly inconsistent with the hypothesis of no reduction in the mortality rate, or if interim survival data were sufficiently unfavourable and strongly inconsistent with the hypothesis of at least a 33% reduction in the mortality rate. The boundaries of the hazard ratio estimate that would lead to rejection of the null hypotheses were 0·4704–1·4180 (α=0·0024, one-sided)

at the first interim analysis and 0·6307–1·0575 (α=0·0104, one-sided) at the second interim analysis. All secondary endpoint and safety assessments were done on the final dataset for the full duration of the study. No statistical analyses were done for assessment of safety. All statistical analyses were done with SAS software (version 9.1.3).

This study is registered with ClinicalTrials.gov, number NCT00075998.

Role of the funding source

The study sponsor participated in study design, data collection, data analysis, data interpretation, and writing of the report. Following completion of the trial, the data were held and analysed by the sponsor. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Overall 99% (817 patients) of enrolled patients completed the study; five patients were lost to follow-up, and four withdrew consent. Table 1 shows baseline characteristics of participants assigned to interferon gamma-1b or placebo. Most patients were white men and the mean age of the whole group was 66 years (SD 7·8). High-resolution CT findings were sufficient to diagnose definite idiopathic pulmonary fibrosis in 485 (88%) and 235 (85%) patients on interferon gamma-1b and placebo, respectively. Surgical lung biopsy was used to confirm histopathological diagnosis in 305 (55%) and 151 (55%) patients on interferon gamma-1b and placebo, respectively.

The mean duration of treatment was 537 days (SD 236) for patients on interferon gamma-1b, and 554 days (SD 223) for those on placebo. Overall compliance was high—504 (91%) and 258 (94%) patients on interferon gamma-1b and placebo, respectively, received more than 80% of scheduled doses of study drug. 232 (28%) patients discontinued treatment before the study conclusion (163 [30%] on interferon gamma-1b, including 44 deaths; 69 [25%] on placebo, including 24 deaths). Despite early termination of the trial, assessable data (including vital status) was obtained for 817 patients at completion of the study (546 [99%] on interferon gamma-1b, including 93 deaths; 271 [99%] on placebo, including 39 deaths).

At the second interim analysis, assessment of the primary endpoint from the hazard ratio for mortality in patients on interferon gamma-1b showed absence of minimum benefit compared with placebo (1·15, 95% CI 0·77–1·71, p=0·497), and indicated that the study should be stopped. The treatment phase of the study ended but follow-up of patients continued until complete study close (webappendix p 5). After a median duration of 64 weeks (IQR 41–84) on treatment, 80 (15%) patients on interferon gamma-1b had died, compared with 35 (13%) on placebo. Kaplan-Meier survival distributions showed that probability of survival was not significantly different between patients on interferon gamma-1b and placebo (figure 2).

	Interferon gamma-1b (n=551)	Placebo (n=275)
Age (years)	66·0 (7·7)	65·9 (7·9)
Men	398 (72%)	187 (68%)
Weight (kg)	86·4 (16·2)	86·6 (18·1)
Ethnic origin*		
White	511 (93%)	260 (95%)
Hispanic	22 (4%)	11 (4%)
African	8 (1%)	1 (<1%)
Native North American	3 (1%)	1 (<1%)
Asian	2 (<1%)	0
Other	5 (1%)	2 (1%)
Smoking status		
Never smoked	157 (28%)	84 (31%)
Previous smoker	376 (68%)	177 (64%)
Current smoker	18 (3%)	14 (5%)
Family history of idiopathic pulmonary fibrosis		
Yes	45 (8%)	27 (10%)
Possibly	23 (4%)	12 (4%)
Unknown	10 (2%)	3 (1%)
No	473 (86%)	233 (85%)
History of environmental exposure		
Metal dust		
Yes	86 (16%)	43 (16%)
No	453 (82%)	229 (83%)
Unknown	12 (2%)	3 (1%)
Wood dust		
Yes	92 (17%)	38 (14%)
No	454 (82%)	234 (85%)
Unknown	5 (1%)	3 (1%)
FVC†	72·2% (12·3)	73·1% (13·4)
DL_{co}†	47·4% (9·2)	47·3% (9·3)
Dyspnoea (total score of shortness of breath questionnaire)	35·1 (23·0)	35·0 (22·7)
Quality of life (total score of St George's respiratory questionnaire)	41·6 (17·9)	42·4 (18·2)
Distance of 6-min walk (m)	392·2 (106·5)	392·8 (112·9)
Use of supplemental oxygen	89 (16%)	41 (15%)
Use of prednisolone or equivalent	90 (16%)	47 (17%)

Data are number of patients (%) or mean (SD). FVC=forced vital capacity. DL_{co}=haemoglobin-corrected carbon monoxide diffusing capacity. *Assigned by the investigator from a checklist of six categories. †Percent of predicted value.

Table 1: **Demographic indicators at baseline**

At completion of the study (median duration of 77 weeks on treatment), analysis of secondary endpoints showed that compared with placebo, treatment with interferon gamma-1b did not significantly affect survival without lung transplantation, survival days without respiratory-related hospital admission, or change from baseline in dyspnoea and mean distance of the 6-min walk (table 2). Additionally, the difference was not significant for interferon gamma-1b versus placebo for mean change from baseline in percentage of the predicted value of FVC (–15·3% *vs* –14·5%, p=0·691), or DL_{co} (–13·6% *vs* –11·7%, p=0·107).

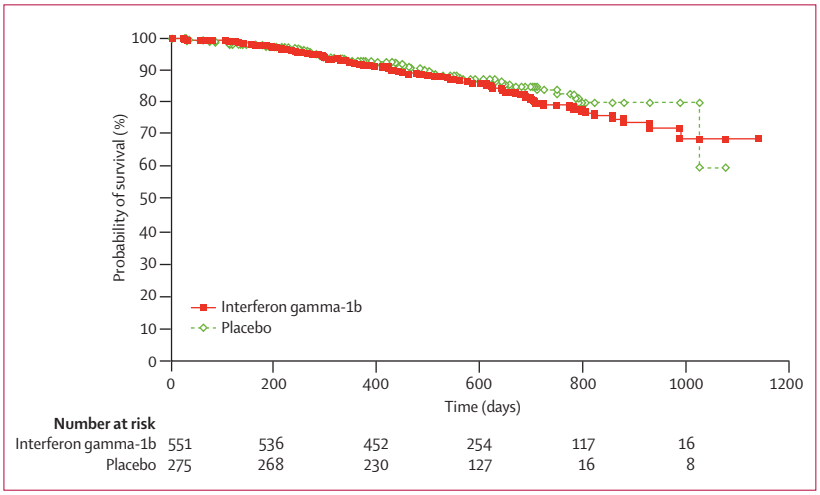

Figure 2: **Kaplan-Meier survival distribution for patients on interferon gamma-1b or placebo (intention-to-treat group)**

	Interferon gamma-1b (n=551)	Placebo (n=275)	p value
Survival time of patients without lung transplantation	451 (82%)	230 (84%)	0·562*
Survival days without respiratory-related hospital admission (SD; % of total days)	590 (218; 91·7%)	590 (216; 92·7%)	0·452
Change from baseline of dyspnoea (total score of shortness of breath questionnaire)	20·6 (31·9)	20·2 (30·4)	0·837
Change from baseline of mean distance of 6-min walk (m)	−106·5 (171·0)	−98·7 (160·4)	0·503

Data are number (%) or mean (SD), unless otherwise indicated. *Hazard ratio 1·11 (95% CI 0·78–1·58) for mortality without lung transplantation between interferon gamma-1b and placebo.

Table 2: **Secondary endpoints**

The interferon gamma-1b and placebo groups had similar results for: mean change from baseline in quality-of-life score (5·7 [SD 13·5] *vs* 6·2 [SD 14·3]), and occurrence of disease progression (46 [8%] *vs* 21 [8%] events), acute respiratory decompensation (49 [9%] *vs* 24 [9%]), and acute exacerbation of disease (25 [5%] *vs* 15 [6%]).

Assessment of safety showed that treatment-related adverse events were common; almost all (810 [98%]) participants reported at least one adverse event (table 3; webappendix pp 6–10). Consistent with previous clinical experience, more patients on interferon gamma-1b had constitutional signs and symptoms (influenza-like illness, fatigue, fever, and chills) than did those on placebo. Adverse events were judged to be related to the study drug in 495 (90%) patients on interferon gamma-1b, compared with 205 (75%) on placebo. Serious adverse events were reported in 215 (39%) patients on interferon gamma-1b and 101 (37%) on placebo (webappendix p 11). The most commonly reported serious adverse events (occurring in ≥2% of either the interferon gamma-1b or placebo group) for patients on interferon gamma-1b were pneumonia (32 [6%] patients), disease progression (18 [3%]), respiratory failure (17 [3%]), and non-cardiac chest pain (12 [2%]). For patients on placebo, the most commonly reported serious adverse events were pneumonia (13 [5%]), disease progression (9 [3%]), respiratory failure (7 [3%]), and acute respiratory failure (5 [2%]). Severe or life-threatening adverse events were reported in 251 (46%) patients on interferon gamma-1b and 107 (39%) on placebo. At completion of the study (median duration of 77 weeks on treatment), 130 (16%) patients had discontinued treatment because of an adverse event (95 [17%] on interferon gamma-1b, 35 [13%] on placebo).

Occurrence of clinically significant (grade 3 and 4) abnormalities in laboratory blood tests was slightly increased for patients on interferon gamma-1b compared with placebo (106 [19%] *vs* 39 [14%]). The most frequently reported clinically significant abnormalities in patients receiving interferon gamma-1b were: hyperglycaemia (38 [7%]), raised serum amylase concentration (30 [5%]), and lymphopenia (27 [5%]). The number of cases of pneumonia, respiratory failure, and thromboembolism did not differ significantly between treatment groups. About 2% of patients in each group (11 [2%] on interferon gamma-1b, 6 [2%] on placebo) met the criteria for clinical diagnosis of pneumonia (webappendix p 12); however, the investigator judged that 77 (9%) patients had 91 events of pneumonia, of which 62 events were in 53 (10%) patients on interferon gamma-1b, compared with 29 events in 24 (9%) patients on placebo (p=0·706).

132 (16%) patients had died by completion of the study: 93 (17%) on interferon gamma-1b and 39 (14%) on placebo (p=0·346, log-rank test; table 4). The immediate cause of death was respiratory-related in most cases. Duration of the clinical course leading to death did not seem to differ between treatment groups.

Discussion

We assessed a well defined population of patients with idiopathic pulmonary fibrosis and mild-to-moderate impairment of pulmonary function, in a study of patients who had high adherence to the protocol and assigned treatment. Treatment with interferon gamma-1b did not improve survival in patients compared with placebo, and consequently the data monitoring committee recommended early termination of the trial after the second interim analysis 152 weeks after enrolment began. Consistent with previous findings,[6,11,19] we noted negligible changes to mean values of pulmonary function and gas exchange for the median duration of 77 weeks on treatment with either interferon gamma-1b or placebo. Additionally, we recorded similar results for both treatment groups for the occurrence of progression of disease, acute respiratory decompensation, or acute exacerbation of disease.

Treatment with interferon gamma-1b was generally safe and well tolerated. The type and frequency of adverse events were generally consistent with the previously described safety profile of interferon gamma-1b;[11,13,21] for patients on interferon gamma-1b, the most frequent adverse events were cough, headache, influenza-like illness, and fatigue.

	Interferon gamma-1b (n=551)	Placebo (n=275)
Any adverse event	540 (98%)	270 (98%)
Cough*	209 (38%)	94 (34%)
Headache†	201 (36%)	61 (22%)
Influenza-like illness	201 (36%)	44 (16%)
Fatigue‡	182 (33%)	69 (25%)
Fever	156 (28%)	25 (9%)
Chills	150 (27%)	17 (6%)
Upper respiratory infection§	140 (25%)	77 (28%)
Nasopharyngitis	119 (22%)	64 (23%)
Bronchitis¶	107 (19%)	63 (23%)
Nausea	93 (17%)	30 (11%)
Back pain	86 (16%)	46 (17%)
Diarrhoea||	86 (16%)	45 (16%)
Insomnia	81 (15%)	30 (11%)
Myalgia	80 (15%)	31 (11%)
Sinusitis	83 (15%)	36 (13%)
Dizziness	84 (15%)	32 (12%)

Data are number of patients (%). *Cough, worsened cough, and productive cough. †Headache, worsened headache, migraine, and sinus headache. ‡Fatigue and worsened fatigue. §Any upper respiratory tract infection (including viral), sinusitis, acute sinusitis, otitis media, ear infection, laryngitis, nasopharyngitis, and streptococcal pharyngitis. ¶Bronchitis, acute bronchitis, acute exacerbation of chronic bronchitis, and tracheobronchitis. ||Diarrhoea and worsened diarrhoea.

Table 3: **Adverse events occurring in at least 15% of patients on either interferon gamma-1b or placebo**

	Interferon gamma-1b (n=93)	Placebo (n=39)
Respiratory-related	75 (81%)	32 (82%)
Non-respiratory-related	15 (16%)	6 (15%)
Cardiac*	3 (3%)	2 (5%)
Sepsis or multiorgan failure†	4 (4%)	2 (5%)
Gastrointestinal	2 (2%)	1 (3%)
Cancer	2 (2%)	1 (3%)
CNS‡	2 (2%)	0
Vascular§	2 (2%)	0
Unknown	3 (3%)	1 (3%)¶

Data are number of patients (%). *Arrhythmia, myocardial infarction, cardiac arrest, and congestive heart failure. †Perforated duodenal ulcer or bleeding, acute pancreatitis, and intestinal obstruction. ‡Cerebrovascular accident, and intracranial haemorrhage. §Pulmonary artery rupture, and haemorrhagic shock. ¶Reported to be non-respiratory-related but no specific cause was defined.

Table 4: **Immediate cause of death**

By contrast with previous reports,[11,22] we recorded similar occurrence of pneumonia for both treatment groups.

Several research groups have suggested that treatment with interferon gamma-1b is associated with improved survival in patients with idiopathic pulmonary fibrosis.[11,14,15] None of these trials were designed to assess the effect of treatment on overall survival, and the findings were based exclusively on subgroup and exploratory analyses. Other important limitations of these trials included small sample size (330,[11] 42,[14] and 18 patients[13]), short duration, and high rates of premature discontinuation. A meta-analysis[12] of these trials suggested that interferon gamma-1b therapy was associated with a significant reduction in the risk of mortality (hazard ratio 0·418, 95% CI 0·253–0·690, p=0·0003); however, one large trial accounted for 85% of the patients in the analysis,[11] and survival data for an additional 5% of patients was based on unpublished long-term follow-up from a previously reported study.[13] In view of these limitations, the investigators concluded that use of the results should be restricted to guiding the aims and design of subsequent randomised controlled trials.

Our study has several potential limitations. We enrolled a highly selected group of patients with mild-to-moderate impairment of pulmonary function at baseline, and therefore the extent to which our findings are generalisable to patients with more advanced disease is unknown. We designed and powered our study to detect a difference in overall survival largely based on past clinical experience. However, we found that in our study population, survival during the trial period was better than anticipated, and we had to enlarge the trial to achieve adequate numbers of events. Additionally, the inclusion criteria might have excluded individuals who were already progressing rapidly, and therefore an inadvertent bias to more stable disease might have restricted the opportunity to record benefit. Interestingly, the number of cases of pneumonia and acute exacerbation of disease, although common even in mild disease, were lower than those recorded in the previous study of interferon gamma-1b.[6,7,11]

The results of our study, the largest randomised controlled clinical trial in patients with idiopathic pulmonary fibrosis, conclusively refute the findings that interferon gamma-1b improves survival. Furthermore, these findings reaffirm the importance of confirming results of subgroup and exploratory analyses in prospective, well designed, randomised placebo-controlled trials.

Contributors

TEK and RMdB co-chaired the steering committee. TEK, CA, WZB, UC, LL, PWN, SAS, JS, MT, DV, and RMdB participated in study conception and design. The clinical research sites were responsible for data collection. Covance was the clinical research organisation responsible for building the INSPIRE trial database from data collected by the clinical research sites. TEK, CA, WZB, UC, LL, PWN, SAS, JS, MT, DV, and RMdB participated in data analysis, and PH did statistical analyses. All authors participated in data interpretation, wrote and revised the report, and approved the final version.

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Conflicts of interest

TEK has been a consultant for Actelion, AstraZeneca, Genzyme, InterMune, Merck, GlaxoSmithKline, Gilead, and ImmuneWorks; a member of the data and safety monitoring board for GlaxoSmithKline; and a member of an advisory committee for Actelion, InterMune, and ImmuneWorks. CA has been an investigator for InterMune, Centocor, and Actelion. WZB and JS are employees of InterMune, and WZB owns stock in InterMune. UC has been a member of an advisory committee for Boehringer Ingelheim, Centocor, InterMune, Serono, Wyeth, and Zambon; and an investigator for InterMune. PH is an independent statistical consultant under contract with InterMune. LL has been an investigator for InterMune. PWN has been an investigator and member of an advisory committee for InterMune; and has an affiliation or financial relationship with Actelion, Gilead, Boehringer Ingleheim, and Novartis. SAS has been a consultant, investigator, and member of an advisory board for, and received honoraria from InterMune. MT has been a consultant and investigator for InterMune. DV has been a consultant and investigator for InterMune and Actelion. RdB has been a consultant, investigator, or member of a steering committee for InterMune, Actelion, Centocor, Boehringer Ingleheim, Novartis, Genzyme, and MondoBiotech.

Acknowledgments

This study was funded by InterMune (Brisbane, CA, USA). We thank Kenneth Glasscock for editorial support in the writing of this report, and staff members and patients at all study centres.

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