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ORIGINAL ARTICLE

High-Dose Acetylcysteine in Idiopathic Pulmonary Fibrosis

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ABSTRACT

BACKGROUND

Idiopathic pulmonary fibrosis is a chronic progressive disorder with a poor prognosis.

METHODS

We conducted a double-blind, randomized, placebo-controlled multicenter study that assessed the effectiveness over one year of a high oral dose of acetylcysteine (600 mg three times daily) added to standard therapy with prednisone plus azathioprine. The primary end points were changes between baseline and month 12 in vital capacity and in single-breath carbon monoxide diffusing capacity (DL_{CO}).

RESULTS

A total of 182 patients were randomly assigned to treatment (92 to acetylcysteine and 90 to placebo). Of these patients, 155 (80 assigned to acetylcysteine and 75 to placebo) had usual interstitial pneumonia, as confirmed by high-resolution computed tomography and histologic findings reviewed by expert committees, and did not withdraw consent before the start of treatment. Fifty-seven of the 80 patients taking acetylcysteine (71 percent) and 51 of the 75 patients taking placebo (68 percent) completed one year of treatment. Acetylcysteine slowed the deterioration of vital capacity and DL_{CO}: at 12 months, the absolute differences in the change from baseline between patients taking acetylcysteine and those taking placebo were 0.18 liter (95 percent confidence interval, 0.03 to 0.32), or a relative difference of 9 percent, for vital capacity (P=0.02), and 0.75 mmol per minute per kilopascal (95 percent confidence interval, 0.27 to 1.23), or 24 percent, for DL_{CO} (P=0.003). Mortality during the study was 9 percent among patients taking acetylcysteine and 11 percent among those taking placebo (P=0.69). There were no significant differences in the type or severity of adverse events between patients taking acetylcysteine and those taking placebo, except for a significantly lower rate of myelotoxic effects in the group taking acetylcysteine (P=0.03).

CONCLUSIONS

Therapy with acetylcysteine at a dose of 600 mg three times daily, added to prednisone and azathioprine, preserves vital capacity and DL_{CO} in patients with idiopathic pulmonary fibrosis better than does standard therapy alone.

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IDIOPATHIC PULMONARY FIBROSIS IS A chronic progressive interstitial pneumonia with a poor prognosis.¹⁻⁴ It has been proposed that a pathogenetic mechanism of idiopathic pulmonary fibrosis is repeated lung injury, with aberrant progressive fibrotic reaction.⁵⁻⁹ If this is the case, it may explain why treatment with corticosteroids and immunosuppressive agents results in only slight therapeutic benefit.^{3,10-12}

An oxidant-antioxidant imbalance may contribute to the disease process in idiopathic pulmonary fibrosis.¹³⁻²⁰ Acetylcysteine, a precursor of the major antioxidant glutathione, given at a daily dose of 1800 mg, has been shown to restore depleted pulmonary glutathione levels¹⁶⁻¹⁹ and to result in a statistically significant improvement in lung function in patients with fibrosing alveolitis after 12 weeks¹⁸ of treatment.

We conducted the IFIGENIA (Idiopathic Pulmonary Fibrosis International Group Exploring N-Acetylcysteine I Annual) trial to test the hypothesis that a high dose of acetylcysteine, administered over a period of one year in addition to prednisone and azathioprine, would slow the functional deterioration in patients with idiopathic pulmonary fibrosis.²¹

METHODS

STUDY DESIGN

This study was a multinational, double-blind, randomized, placebo-controlled, parallel-group trial. The study treatment consisted of oral administration of *N*-acetylcysteine (Fluimucil, Zambon Group) in 600-mg effervescent tablets three times daily or matched placebo. In addition, the patients were given prednisone (starting dose, 0.5 mg per kilogram of body weight per day; 0.4 mg per kilogram per day at month 2; and 0.3 mg per kilogram per day at month 3; the dose was progressively reduced to 10 mg per day in months 4, 5, and 6, and this dose was maintained until month 12) and azathioprine (2 mg per kilogram per day), in addition to the usual care, as recommended by the American Thoracic Society/European Respiratory Society International Consensus.^{21,22}

INCLUSION AND EXCLUSION CRITERIA

Patients 18 through 75 years of age with a histologic or radiologic pattern typical of usual interstitial pneumonia²¹⁻²⁷ were included after other causes of usual interstitial pneumonia had been ruled out.

The inclusion criteria were as follows. A high-resolution computed tomographic (CT) scan was very suggestive or consistent with a probable diagnosis of usual interstitial pneumonia.²¹⁻²⁵ In patients younger than 50 years, open or thoracoscopic lung biopsy was mandatory and showed a pattern of usual interstitial pneumonia^{21,22,26,27}; lung biopsy was optional for older patients. In the absence of lung biopsy, a transbronchial biopsy was strongly advocated to exclude alternative diagnoses. Bronchoalveolar lavage must have been performed at any time before inclusion and must have failed to show features supporting alternative diagnoses. The duration of the disease was more than three months, and bibasilar inspiratory crackles were present. In addition, the following functional abnormalities were present: a dyspnea score of at least 2 on a scale of 0 (minimum) to 20 (maximum),²⁸ vital capacity of no more than 80 percent of the predicted value or total lung capacity less than 90 percent of the predicted value, and single-breath carbon monoxide diffusing capacity (DL_{CO}) less than 80 percent of the predicted value.^{29,30}

Patients were excluded if the standard regimen with prednisone and azathioprine was contraindicated or not justified for them or if they presented with a known intolerance to acetylcysteine. Further exclusion criteria were treatment with prednisone at a dose of at least 0.5 mg per kilogram per day or with azathioprine at a dose of at least 2 mg per kilogram per day during the month before inclusion in the study, or treatment with acetylcysteine at a dose of more than 600 mg per day for more than three months in the previous three years. Other reasons for exclusion were concomitant or preexisting diseases, abnormalities, or treatment at study entry or in the past with drugs (such as antioxidants and antifibrotic drugs) that interfere with the diagnosis, severity, therapy, or prognosis of idiopathic pulmonary fibrosis.

DETERMINATION OF SAMPLE SIZE

The sample size was calculated to provide a power of 80 percent ($\alpha=0.05$ by two-sided test) to detect a treatment difference between the two groups of 15 percent for vital capacity and 20 percent for DL_{CO} after one year. On the basis of previous data^{18,31} and with an expected withdrawal rate of 25 percent, including patients who died, a total of 150 patients with confirmed idiopathic pulmonary fibrosis were to be enrolled.

RADIOLOGIC AND HISTOLOGIC COMMITTEES

Independent committees of radiologic and histologic experts, who were blinded to the patients' baseline data, confirmed or rejected each diagnosis on the basis of published criteria²¹⁻²⁷ for the diagnosis of usual interstitial pneumonia by high-resolution CT and surgical lung biopsy, respectively. The committees either confirmed the diagnosis with a "yes" (very suggestive or probable diagnosis) or rejected it with a "no" (diagnosis unlikely). In addition, the severity scores according to high-resolution CT were assessed,^{23,24} and chest radiographic scores were estimated for the clinical, radiologic, and physiological (CRP) score.²⁸

PRIMARY AND SECONDARY END POINTS

The primary end points were the absolute changes in vital capacity and DL_{CO} between baseline and month 12, measured according to the European Respiratory Society guidelines.^{29,30} Post hoc, we evaluated changes in vital capacity of more than 10 percent or 0.2 liter and changes in DL_{CO} of more than 15 percent or 1 mmol per minute per kilopascal as categorical variables, because these were recently shown to be related to the risk of death.³²⁻³⁴

The following prespecified secondary end points were assessed for changes between baseline and 12 months: vital capacity and DL_{CO} as percentages of the predicted value and DL_{CO} :alveolar volume as absolute change and percentage of the predicted value; CRP score²⁸; dyspnea score²⁸; maximum exercise indexes (load [W'_{max}], oxygen uptake [$V'O_{2max}$], and ventilation [$V'E_{max}$])³⁵; scores of ground-glass opacities and of fibrosis on high-resolution CT²⁴ (ranging from 0 [minimum] to 5 [maximum]); health status according to the St. George's Respiratory Questionnaire (total scores range from 0 to 100, with higher scores indicating a worse quality of life)³⁶; number of adverse effects and withdrawals; and mortality during the study and up to one month after withdrawal.

RANDOMIZATION AND EVALUATION

At the screening visit, the patients were checked to determine whether they met the inclusion or exclusion criteria, potentially eligible patients were randomly assigned to treatment with study medication, and treatment was started. High-resolution CT images and histologic slides, if available, were sent to the members of the expert committees, without any additional patient information, and patients for whom the diagnosis of usual interstitial pneumo-

nia was not confirmed were excluded from the study. This process generally took four to six weeks.

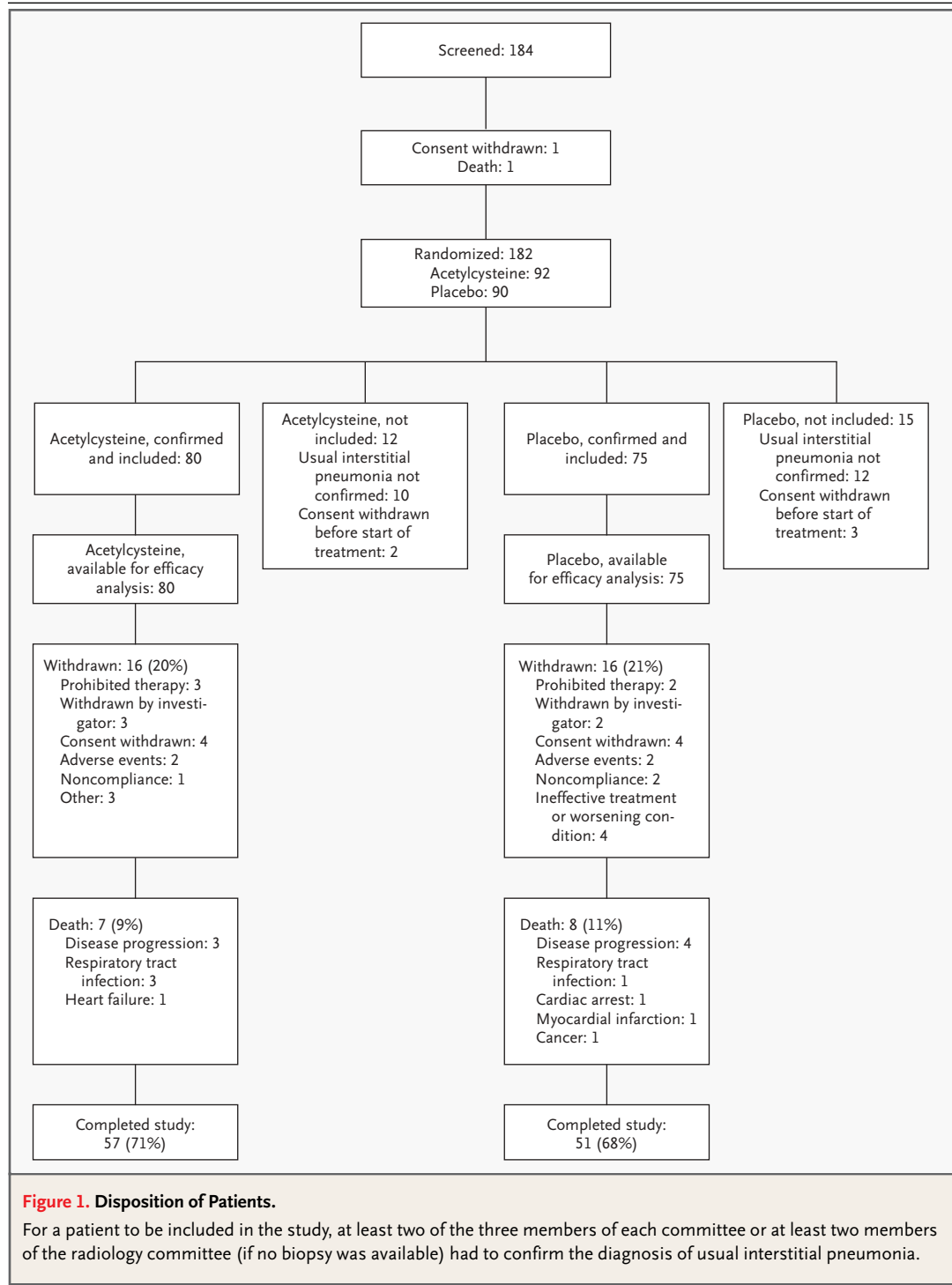
Randomization of treatment (with a 1:1 ratio of acetylcysteine to placebo) was performed centrally with the use of a computer-generated randomization list stratified (in blocks of four) according to country and whether the vital capacity was 60 percent or less of the predicted value or more than 60 percent of the predicted value. The patients underwent clinical examination, laboratory tests, lung-function tests, chest radiography, and assessment of adverse events and drug compliance every three months. Drug noncompliance (defined by an intake of less than 50 percent of the study medication) was determined by counting the returned tablets. The findings from high-resolution CT, the maximum exercise test, and the St. George's Respiratory Questionnaire were evaluated every six months.

If standard therapy had to be adapted (for example, because of adverse effects, poor compliance, or clinical worsening), the patient was treated according to the preference of each center, with the drug-exclusion criteria, especially concerning antioxidants and antifibrotic drugs, taken into consideration. Continuation of treatment with acetylcysteine or placebo and regular follow-up visits was recommended if it was compatible with the medical condition.

Safety was continuously monitored by central collection of records of all serious adverse events. All adverse events, including mortality, were recorded by the investigator until one month after the patient completed or withdrew from the study. Patients were considered to have withdrawn from the study if they discontinued the follow-up visits for any reason.

The study was conducted according to the current standards of Good Clinical Practice of the International Conference on Harmonisation³⁷ and national regulations. The protocol was approved by local ethics committees. All patients gave written informed consent and were free to withdraw at any time. Regular monitoring and sample audits were performed at the centers throughout the study.

The study was designed and analyzed by a committee composed of 19 academic physicians experienced in idiopathic pulmonary fibrosis, 1 independent statistician, and 3 representatives of the sponsor. The sponsor held the data but placed no limitations on study design, data analysis, or the content of the manuscript. The statistical analysis was performed by an independent statistical com-



pany (Innopharma, Milan). All authors participated in the preparation of the manuscript and had full and unfettered access to the raw data and analyses.

STATISTICAL ANALYSIS

The analyses were based on data from all patients who underwent randomization, met the inclusion criteria for the study, received the trial medication

Table 1. Baseline Characteristics of the Study Population.*

Characteristic*	Patients Included in the Study		Patients Excluded from the Study (N=27)
	Acetylcysteine (N=80)	Placebo (N=75)	
Sex — %			
Male	69	75	87
Female	31	25	13
Age — yr	62±9	64±9	58±11
Smoking status — %†			
Current smoker	3.8	6.7	7.7
Former smoker	57.5	62.7	61.5
Never smoked	38.8	30.7	30.8
Months since diagnosis			
Mean	19.9±28.3	18.9±33.1	14.0±26.5
Median	5.0	3.0	5.5
Diagnosed within previous 6 mo — no. (%)	39 (49)	42 (56)	13 (48)
Underwent surgical lung biopsy — no. (%)	38 (48)	35 (47)	24 (89)
Vital capacity — no. of patients‡			
>60%	49	53	17
≤60%	31	22	8
Total lung capacity			
Volume — liters	3.72±1.00	3.72±0.94	4.11±1.37
% of predicted value	62.1±13.9	61.6±11.5	64.4±15.1
PAO ₂ –PaO ₂ at rest — mm Hg	31.6±13.8	30.1±11.8	28.9±13.9
PaO ₂ at rest — mm Hg	70.1±12.7	72.0±11.2	73.8±13.7
Bronchoalveolar lavage			
Fluid instilled — ml	141.4±50.9	146.6±52.8	132.7±64.8
Lymphocytes — %	10.8±11.8	10.6±9.5	19.5±22.8
Neutrophils — %	13.2±16.3	17.4±21.0	9.5±10.6
Eosinophils — %	6.1±9.6	4.3±5.5	4.3±4.8
CD4:CD8 cell ratio	1.6±1.3	2.1±2.4	1.2±0.7
Total SGRQ score	50±18	52±16	—

* The baseline values for the primary and secondary end points are given in Tables 2 and 3. PAO₂ denotes partial pressure of alveolar oxygen, PaO₂ partial pressure of arterial oxygen, and SGRQ the St. George's Respiratory Questionnaire (for which total scores can range from 0 to 100, with higher scores indicating a worse quality of life). Plus-minus values are means ±SD. The distribution of patients randomly assigned to treatment according to country was as follows: Germany: 63 total — 33 acetylcysteine, 30 placebo; France: 41 total — 20 acetylcysteine, 21 placebo; Spain: 21 total — 10 acetylcysteine, 11 placebo; Belgium: 20 total — 10 acetylcysteine, 10 placebo; the Netherlands: 19 total — 9 acetylcysteine, 10 placebo; and Italy: 18 total — 10 acetylcysteine, 8 placebo.

† Current smokers were defined as those actively smoking, irrespective of the number of cigarettes smoked per day. Former smokers were defined as those who had stopped smoking at least three months previously.

‡ Baseline results for vital capacity were not available for two patients who were excluded from the study.

at least once, and underwent at least baseline observation. Missing data were replaced by the last-observation-carried-forward (LOCF) method for all patients who underwent at least one lung-function measurement after baseline.

The statistical analysis was based on a stepwise, fixed-effects analysis of covariance (ANCOVA) (Proc GLM; SAS, version 8.0), which included country and treatment group in its general design as main fixed factors, country-by-treatment as an

Table 2. Effects of Acetylcysteine on Vital Capacity (VC) and Single-Breath Carbon Monoxide Diffusing Capacity (DL_{CO}) at 12 Months.*

Measurement	No. of Patients		Value for Patients Taking Acetylcysteine	Value for Patients Taking Placebo	Absolute Difference (95% CI)	P Value†	Relative Difference‡
	Acetylcysteine	Placebo					
VC							
			<i>liters</i>				<i>percent</i>
Baseline	80	75	2.29±0.68	2.36±0.74			
12 mo	55§	51	2.31±0.79	2.26±0.72			
12 mo LOCF	71	68	2.22±0.77	2.17±0.71			
Mean difference between baseline value and 12 mo LOCF (95% CI)			-0.06 (-0.14 to 0.02)	-0.19 (-0.29 to -0.09)			
LS-LOCF¶	71	68	2.27±0.05	2.10±0.05	0.18 (0.03 to 0.32)	0.02	9
<i>mmol/min/kPa</i>							
DL_{CO}							
Baseline	79	74	3.85±1.41	3.90±1.39			
12 mo	48	47	4.20±2.07	3.46±1.22			
12 mo LOCF	68	63	3.74±1.99	3.20±1.26			
Mean difference between baseline value and 12 mo LOCF (95% CI)			-0.11 (-0.47 to 0.25)	-0.70 (-0.95 to -0.45)			
LS-LOCF¶	68	63	3.85±0.17	3.10±0.18	0.75 (0.27 to 1.23)	0.003	24

* CI denotes confidence interval, LOCF the last observation carried forward, and LS least squares. Plus-minus values are means ±SD except for LS-LOCF, for which the mean ±SE is given.

† The nominal P value after correction for multiple tests (statistically significant at P<0.025) is given.

‡ The relative difference is the difference between the LS means for the acetylcysteine group and the placebo group, according to the following equation: [(LS-LOCF_{acetylcysteine} - LS-LOCF_{placebo}) ÷ LS-LOCF_{placebo}] × 100.

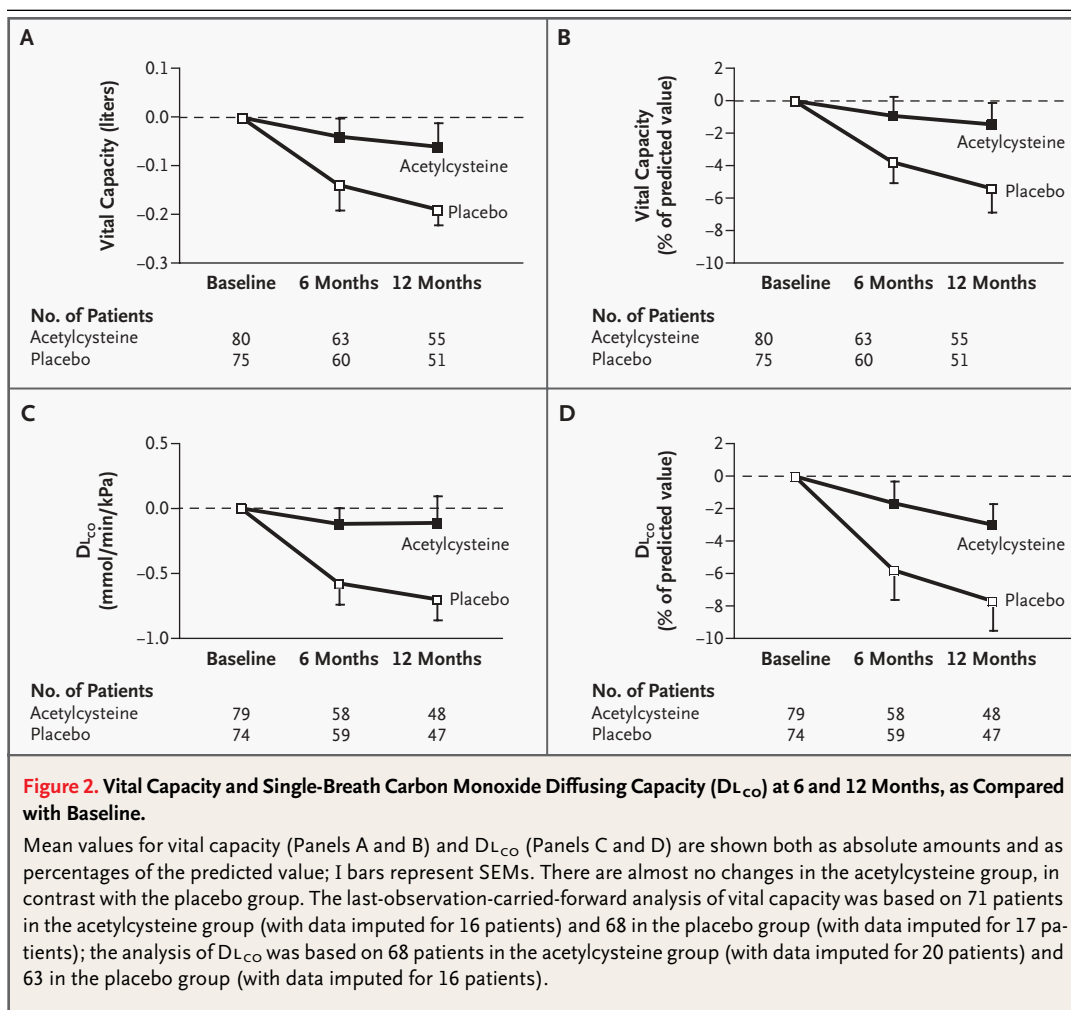
§ Data were not available for two patients.

¶ LS-LOCF is the LS (or adjusted) mean from the LOCF analysis of variance.

interaction, and baseline values as covariates. The following potential cofactors were assessed: smoking history (current or former smokers vs. those who had never smoked), age (<65 years vs. ≥65 years), duration of disease since diagnosis (≤6 months vs. >6 months), DL_{CO} (≤40 percent vs. >40 percent of the predicted value), vital capacity (≤60 percent vs. >60 percent of the predicted value), sex (male vs. female), and whether a biopsy had been performed.

After evaluation of the assumptions underlying the ANCOVA model, the first goal was to obtain the model that best described the data (with treatment excluded); the second goal was then to apply that model to compare the effects of acetylcysteine and placebo. To obtain the best model, we iteratively tested all possible combinations of the cofactors, with the aim of selecting the model in which the smallest variability (P<0.001) and the highest R² value (>0.5) were reached. The relevant combinations of cofactors were then included as fixed factors in the model.

To assess the robustness of the LOCF-ANCOVA primary analysis, a likelihood-based method was applied; this method used a mixed-effect model and was developed under the MAR (missing at random) framework by the MAR method.^{38,39} With the mixed-effect approach, information from the observed data is not explicitly imputed, and no additional data manipulation or analysis is required to accommodate the missing data. Two sensitivity analyses were performed with the mixed-effect model repeated-measure approach (MMRM) on different data sets (but without replacing missing data). The mixed procedure of the SAS package was used, with treatment and time as fixed effects, patients as random effects, and the observed values as the response variable. The first analysis was performed on the LOCF data set, which was based on all patients with confirmed usual interstitial pneumonia who had been randomly assigned to treatment, had taken at least one dose of the study drug, and had undergone at least one lung-function eval-



uation after baseline. The second analysis was performed on the baseline data set, which was the same as the LOCF data set, except that it included data from patients whose lung function had been evaluated only at baseline. The two sensitivity analyses performed to test the robustness of the LOCF-ANCOVA analysis confirmed the results for the primary end points.

There were no interim analyses of efficacy. All reported P values are two-sided and were not adjusted for multiplicity. Because two statistical tests were performed for the analysis of the primary end points, the nominal P value for defining statistical significance was reduced from $P < 0.05$ to $P < 0.025$. Fisher's exact test was used to evaluate categorical variables, such as adverse events. All of the variables are expressed as means \pm SD, unless otherwise specified, and also as medians, quartiles, and minimum-maximum ranges where appropriate.

RESULTS

ENROLLMENT, PATIENT CHARACTERISTICS, AND FOLLOW-UP

Between March 2000 and July 2002, 184 patients were screened in 36 centers in six countries, and 182 were randomly assigned to treatment (Fig. 1). Of these 182 patients, 155 (85 percent) were included in the analysis. In 82 patients (53 percent), the diagnosis was based on high-resolution CT only; in 73 patients (47 percent), the diagnosis was based on both high-resolution CT and histologic findings. Twenty-seven patients were not included in the analysis: 5 withdrew consent before starting treatment, and 22 (12 percent) were excluded because the diagnosis of usual interstitial pneumonia was rejected (by histologic findings in 10, by high-resolution CT in 8, and by both diagnostic methods in 4).

Measurement	Value for Patients Taking Acetylcysteine	Value for Patients Taking Placebo	Absolute Difference (95% CI)	P Value	Relative Difference† percent
Lung function					
VC (% of predicted)					
Baseline	64.76±15.41	66.57±14.42			
12 mo	63.14±19.98	61.59±15.17			
LS mean‡	65.13±1.85	60.34±1.85	4.79 (0.80 to 8.77)	0.02	8
DL _{CO} (% of predicted)					
Baseline	43.04±13.10	44.79±15.15			
12 mo	40.85±14.85	38.75±14.75			
LS mean	41.60±1.35	36.52±1.45	5.08 (1.17 to 8.99)	0.01	14
DL _{CO} :VA (mmol/min/kPa/liter)					
Baseline	1.14±0.45	1.11±0.35			
12 mo	1.21±0.81	0.99±0.31			
LS mean	1.19±0.81	1.00±0.31	0.19 (0.01 to 0.37)	0.04	19
DL _{CO} :VA (% of predicted)					
Baseline	72.09±24.31	72.80±20.44			
12 mo	70.92±25.43	66.71±21.44			
LS mean	72.09±25.43	65.49±21.44	6.60 (1.05 to 12.15)	0.02	10
Exercise§					
W _{max} (W)					
Baseline	86.02±41.60	82.38±36.46			
12 mo	88.76±38.53	73.61±30.86			
LS mean	84.71±3.53	77.27±3.38	7.44 (-2.34 to 17.23)	0.13	10
V'O _{2max} (liters/min)					
Baseline	1.20±0.40	1.31±0.46			
12 mo	1.26±0.52	1.16±0.43			
LS mean	1.28±0.05	1.15±0.05	0.13 (-0.01 to 0.26)	0.08	11
V'E _{max} (liters/min)					
Baseline	56.75±19.44	59.03±17.09			
12 mo	60.70±19.48	57.83±15.17			
LS mean	61.13±1.85	57.10±1.77	4.03 (-1.07 to 9.26)	0.12	7

No significant differences in baseline characteristics were found between the 80 patients assigned to acetylcysteine and the 75 assigned to placebo (Table 1). At the beginning of the study, eight patients assigned to acetylcysteine and two assigned to placebo were receiving continuous oxygen therapy. Forty-seven patients (30 percent) had been treated with prednisone (16 patients assigned to acetylcysteine and 13 to placebo), azathioprine (8 assigned to acetylcysteine and 5 to placebo), or both (2 assigned to acetylcysteine and 3 to placebo).

Of the 155 patients for whom the data were analyzed, 108 (70 percent, 57 assigned to acetylcysteine and 51 to placebo) completed the one-year study (Fig. 1). However, the standard therapy had been changed for 24 of these 155 patients (15 percent, 13 assigned to acetylcysteine and 11 to placebo) during the study. Three patients receiving acetylcysteine and 11 receiving placebo started continuous oxygen therapy. Thirty-two patients (16 receiving acetylcysteine [20 percent] and 16 receiving placebo [21 percent]) withdrew from the study, for

Table 3. (Continued.)

Measurement	Value for Patients Taking Acetylcysteine	Value for Patients Taking Placebo	Absolute Difference (95% CI)	P Value	Relative Difference†
					percent
CRP score¶					
CRP total					
Baseline	39.73±15.01	37.06±15.88			
12 mo	36.80±14.50	38.68±13.85			
LS mean	37.62±1.75	39.33±1.70	-1.71 (-8.72 to 5.30)	0.70	5
CRP without exercise					
Baseline	32.88±9.81	31.69±9.04			
12 mo	32.54±10.75	33.18±9.78			
LS mean	30.91±0.84	32.50±0.87	-1.59 (-4.37 to 1.19)	0.17	5
Dyspnea					
Baseline	8.35±4.44	7.92±3.99			
12 mo	8.96±5.53	9.12±4.88			
LS mean	8.88±0.49	9.20±0.51	-0.32 (-1.72 to 1.09)	0.65	4
HRCT score¶					
Fibrosis					
Baseline	2.03±0.70	2.05±0.64			
12 mo	2.27±0.74	2.22±0.65			
LS mean	2.29±0.04	2.19±0.04	0.10 (-0.02 to 0.21)	0.09	5
Ground-glass opacities					
Baseline	1.76±0.63	1.79±0.65			
12 mo	1.94±0.62	1.96±0.60			
LS mean	1.95±0.05	1.96±0.05	-0.01 (-0.15 to 0.14)	0.95	1

* CI denotes confidence interval; VC vital capacity; LS least squares; DL_{CO} single-breath carbon monoxide diffusing capacity; VA alveolar volume; W'_{max} maximum exercise load; V'O_{2max} maximum oxygen uptake; V'E_{max} maximum exercise ventilation; CRP clinical, radiologic, and physiological; and HRCT high-resolution computed tomography. Plus-minus values are means ±SD except for LS mean, for which the mean ±SE is given.

† The relative difference is the difference between the LS means for the acetylcysteine group and the placebo group, according to the following equation: $([LS-LOCF_{acetylcysteine} - LS-LOCF_{placebo}] \div LS-LOCF_{placebo}) \times 100$.

‡ The LS mean is the least-squares (or adjusted) mean from the last-observation-carried-forward (LOCF) analysis of variance.

§ Only 61 patients in the acetylcysteine group and 67 in the placebo group were able to perform exercise.

¶ Total CRP scores range from 0 to 100, CRP scores without exercise from 0 to 70, dyspnea scores from 0 to 20, and HRCT scores from 0 to 5. In all cases, higher scores indicate more severe symptoms or findings.

various reasons. In addition, 15 patients (10 percent) died during the study: 7 of these (9 percent) were receiving acetylcysteine, and 8 (11 percent) were receiving placebo ($P < 0.69$).

EFFECTS ON PRIMARY END POINTS

The LOCF analysis included 139 patients (71 receiving acetylcysteine and 68 receiving placebo, with data imputed for 16 and 17 patients, respectively) for the vital capacity analysis and 131 patients (68 receiving acetylcysteine and 63 receiving placebo,

with data imputed for 20 and 16 patients, respectively) for the DL_{CO} analysis (Table 2). There was a slower rate of loss of vital capacity in the group receiving acetylcysteine; the absolute value of vital capacity was 0.18 liter, or 9 percent, greater ($P = 0.02$) and the value of DL_{CO} was 0.75 mmol per minute per kilopascal, or 24 percent, greater ($P = 0.003$) in those receiving acetylcysteine than in those receiving placebo. The analysis of DL_{CO} after correction for hemoglobin levels yielded similar results: the value was 0.81 mmol per minute per kilopascal or

25 percent greater in patients receiving acetylcysteine ($P=0.001$). None of the combinations of cofactors included in the fixed-effects LOCF-ANCOVA analysis were statistically significant, and therefore the treatment comparisons are unadjusted. The changes in vital capacity and DL_{CO} over the 12-month period are illustrated in Figure 2.

POST HOC ANALYSIS OF CATEGORICAL CHANGES

When the vital capacity data were dichotomized so that a change in vital capacity from baseline to 12 months of more than 10 percent or 0.2 liter versus a smaller change was treated as a categorical variable, then the condition of 63 percent of patients receiving acetylcysteine (45 of 71) and 49 percent of those receiving placebo (33 of 68) was considered stable or improved, and the condition of 37 percent of those receiving acetylcysteine (26 of 71) and 51 percent of those receiving placebo (35 of 68) was considered to have deteriorated ($P=0.22$). Similarly, when the DL_{CO} data were dichotomized so that a change in DL_{CO} of more than 15 percent or 1 mmol per minute per kilopascal from baseline to 12 months versus a smaller change was treated as a categorical variable, the condition of 57 percent of patients receiving acetylcysteine (39 of 68) and 49 percent of those receiving placebo (31 of 63) was considered stable or improved, and the condition of 43 percent of those receiving acetylcysteine (29 of 68) and 51 percent of those receiving placebo (32 of 63) was considered to have deteriorated ($P=0.17$).

EFFECTS ON SECONDARY END POINTS

For vital capacity and DL_{CO} expressed as percentages of the predicted values, the relative differences between the study groups at 12 months were 8 percent ($P=0.02$) and 14 percent ($P=0.01$), respectively (Table 3), with values higher in the group receiving acetylcysteine. The changes in other secondary end points did not differ significantly between the two study groups (Table 3).

COMPLIANCE AND SAFETY

More than 85 percent of the patients in both groups took on average more than 80 percent of the prescribed daily dose of the study drug. The overall incidence of adverse events is presented in Table 4, and the incidence of fatal adverse events in Figure 1. None of the differences between the study groups were significant except for adverse events related to bone marrow toxicity, which occurred in 4 percent of patients receiving acetylcysteine (3 of 80) and in

13 percent of those receiving placebo (10 of 75) ($P=0.03$).

DISCUSSION

Our results show that the addition of acetylcysteine to standard therapy with prednisone and azathioprine in patients with idiopathic pulmonary fibrosis significantly slows the rate of deterioration of the primary pulmonary surrogate end points vital capacity and DL_{CO} . A relative difference of 24 percent was observed for DL_{CO} and of 9 percent for vital capacity, differences that are in agreement with the assumed differences in the sample-size power calculation. Although we could not establish that the acetylcysteine-related reduction in the decline of vital capacity and DL_{CO} translates into a survival benefit, our data suggest that the effects of acetylcysteine on the primary end points may slow disease progression.

In our opinion, the effects of acetylcysteine on the primary end points are of clinical relevance. It has recently been shown that decreases in vital capacity of 10 percent or more and in DL_{CO} of 15 percent or more from baseline over a period of 6 to 12 months are associated with an increased risk of death in patients with idiopathic pulmonary fibrosis.³²⁻³⁴ Figure 2 and Table 2 show that, in the present study, acetylcysteine reduced the declines in vital capacity and DL_{CO} after one year of treatment. However, the present study did not document the finding of other studies³²⁻³⁴ that changes in vital capacity and DL_{CO} are associated with survival. Other recent studies indicated that the six-minute walk test may be a predictor of survival as well.^{41,42} Such tests were not performed in this trial.

The post hoc analysis of categorical changes in vital capacity and DL_{CO} did not find a significant difference between the responses to acetylcysteine and placebo; however, the sample-size power calculation indicated that at least 200 patients with idiopathic pulmonary fibrosis would have had to be enrolled to detect a statistically significant difference of 10 percent for vital capacity and 15 percent for DL_{CO} .

The main rationale for the present study was based on previous findings that an oxidant-antioxidant imbalance existed in idiopathic pulmonary fibrosis,¹³⁻²⁰ that depleted glutathione levels were restored by high doses of acetylcysteine,¹⁶⁻¹⁹ and (in a pilot study) that acetylcysteine treatment had concomitant favorable effects on lung function.¹⁸

Table 4. Adverse Events Occurring in at Least 5 Percent of Patients.*

Adverse Event	Acetylcysteine Group		Placebo Group	
	No. of Adverse Events	Patients (N=80) no. (%)	No. of Adverse Events	Patients (N=75) no. (%)
All adverse events	322	72 (90)	303	67 (89)
Respiratory tract infection†	22	20 (25)	27	24 (32)
Dyspnea‡	16	16 (20)	21	19 (25)
Fever	17	15 (19)	10	10 (13)
Liver-function test abnormal§	15	14 (18)	13	11 (15)
Cough	15	13 (16)	17	16 (21)
Abdominal pain¶	12	12 (15)	7	7 (9)
Upper respiratory tract infection	11	11 (14)	15	13 (17)
Blood glucose increased**	9	9 (11)	12	11 (15)
C-reactive protein increased	7	6 (8)	3	3 (4)
Blood alkaline phosphatase increased	6	6 (8)	1	1 (1)
Blood lactate dehydrogenase increased	6	6 (8)	2	2 (3)
Back pain	6	6 (8)	6	5 (7)
Respiratory failure	5	5 (6)	1	1 (1)
Bone marrow toxic effects††	3	3 (4)	10	10 (13)
Edema‡‡	3	3 (4)	5	5 (7)
Headache	4	3 (4)	6	6 (8)
Asthenia§§	3	3 (4)	5	5 (7)
Influenza-like illness	3	3 (4)	5	5 (7)
Muscle cramp	1	1 (1)	4	4 (5)

* All diagnoses were based on the clinical judgment of the investigator and were blindly coded by qualified persons according to the *Medical Dictionary for Regulatory Activities*.⁴⁰

† Lower respiratory tract infections, pneumonia, bronchopneumonia, bronchitis, acute bronchitis, and bronchial infection are included.

‡ Exacerbated dyspnea is included.

§ Increased or abnormal aspartate aminotransferase or alanine aminotransferase and increased or abnormal γ -glutamyltransferase are included.

¶ Gastritis is included.

|| Rhinitis, sinusitis, and nasopharyngitis are included.

** Hyperglycemia is included.

†† Anemia, leukopenia, lymphopenia, neutropenia, thrombocytopenia, decreased lymphocyte count, and decreased red-cell count are included. Bone marrow toxic effects were significantly less frequent with acetylcysteine than with placebo (P=0.03).

‡‡ Peripheral edema is included.

§§ Fatigue is included.

The favorable effects of acetylcysteine on lung function have, indeed, been confirmed by the present trial. It was not our aim to examine whether the therapeutic effect of the activity of acetylcysteine is in accordance with the current hypothesis that persistent lung injury from fibrosis, and not from inflammation, is the primary pathogenetic mechanism in idiopathic pulmonary fibrosis.⁶⁻⁹ On the basis of this hypothesis, there has been particular interest in antifibrotic drugs,⁷ such as pirfeni-

done,^{43,44} and in immune modulators, especially interferon gamma-1b.⁴⁵⁻⁴⁷ In a recent double-blind study, pirfenidone was shown to improve vital capacity and to prevent acute exacerbations of idiopathic pulmonary fibrosis.⁴⁴ Interferon gamma-1b appeared to be effective in a pilot study,⁴⁵ but this was not confirmed in subsequent studies.^{46,47} However, a retrospective analysis of the data of Raghu et al.⁴⁶ found that a decrease of more than 10 percent in forced vital capacity (as a percentage

of the predicted value) is a valid measure of disease progression.⁴⁸ If the pathogenetic mechanism in idiopathic pulmonary fibrosis is, indeed, an aberrant and irreversible fibrosis, then improvement by therapy may be improbable, and at best a slowing down of disease progression may be accomplishable.

In this study, N-acetylcysteine was administered in three 600-mg effervescent tablets, for a total dose of 1800 mg per day. This is three to nine times the usual approved dose of acetylcysteine when it is administered as an antioxidant and mucolytic agent in chronic obstructive pulmonary disease. The acetylcysteine and placebo groups had similar overall rates of side effects, withdrawals, and treatment failures, a result suggesting that it was unlikely that acetylcysteine was interfering with therapy with prednisone plus azathioprine. There was a tendency toward a higher rate of respiratory failure in the group receiving acetylcysteine than in that receiving placebo (6 percent vs. 1 percent, $P=0.24$); however, eight patients in the acetylcysteine group and only two in the placebo group were receiving oxygen continuously at the beginning of the study. Furthermore, compliance with the study drugs and with the standard therapy was generally good. The lower incidence of adverse events related to bone marrow toxicity in the acetylcysteine group might have been due to the augmentation of glutathione biosynthesis induced by acetylcysteine. In recent publications, acetylcysteine has been shown to protect hepatocytes from azathioprine-induced toxicity by replenishing intracellular glutathione concentrations.^{49,50}

Our trial used prednisone and azathioprine as standard therapy for all patients, as proposed by the International Idiopathic Pulmonary Fibrosis Consensus Statement.²¹ The mortality up to one month after completion of the study or withdrawal from the study was rather low (9 percent in the acetylcysteine group and 11 percent in the placebo group). This result suggests that the standard therapy with prednisone and azathioprine may be beneficial, but controlled trials are needed to confirm this. Because our study, unlike previous studies, included patients with both early and late stages of idiopathic pulmonary fibrosis, the results are more likely to be applicable to the majority of patients seen in daily clinical practice. To our surprise, there was no difference in the results between newly and previously diagnosed patients, or between those with a baseline vital capacity of more than 60

percent and those with a baseline vital capacity of 60 percent or less of the predicted value. Finally, our study illustrates the difficulty of conducting clinical trials in patients with idiopathic pulmonary fibrosis: we required 36 sites and 27 months to enroll 155 patients.

Some potential limitations of the study need to be addressed. First, the evidence supporting the better preservation of vital capacity and DL_{CO} in the acetylcysteine group should be interpreted with caution, since about 30 percent of the patients were lost to follow-up at 12 months owing to death or withdrawal. Second, this trial does not permit firm conclusions regarding the effects and side effects of treatment with prednisone plus azathioprine given that there was no placebo group for these drugs. Third, it is unknown whether acetylcysteine would have the same effects when given without standard therapy. Fourth, the study was not powered or designed to detect an effect on survival.

In conclusion, the results of our trial demonstrate that acetylcysteine at a dose of 600 mg three times daily, added to prednisone and azathioprine, in patients with idiopathic pulmonary fibrosis preserves vital capacity and DL_{CO} better than standard therapy alone. High-dose acetylcysteine in addition to standard therapy is, therefore, a rational treatment option for patients with idiopathic pulmonary fibrosis.

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APPENDIX

The following members of the IFIGENIA Study Group participated in the study: Steering Committee: M. Demedts (chair), J. Behr, R. Buhl, U. Costabel, P.N.R. Dekhuijzen, H.M. Jansen, W. MacNee, B. Wallaert, and M. Thomeer. High-Resolution CT Scientific Committee: C.D.R. Flower, F. Laurent, and J. Verschakelen. Histology Scientific Committee: A.G. Nicholson, E.K. Verbeken, and F. Capron. Country Coordinators: J. Behr, J.M.M. van den Bosch, P. De Vuyst, E. Rodriguez-Becerra, S. Petruzzelli, and B. Wallaert. Zambon Group: Clinical Trial Coordinators: G. Corvasce and A. Peviani; Medical Department: I. Lankhorst, E. Makin, L. Licciardello, S. Bellinva, C. Di Padova, M. Sardina, N. Kormoss, P. Boulanger, and A. Esteras; Data Coordination: F. Sirtori; Drug Safety: G. Moroni; Statistics: A. Ardia; Biostatistics: M. Montanari (Innopharma). Active participating centers and clinical investigators: *Belgium*: M. Demedts and M. Thomeer, U.Z. Gasthuisberg, Leuven; H. Slabbynck, Algemeen Ziekenhuis Middelheim, Antwerp; E. Michiels, Z.O.L. Campus St. Jan, Genk; P. De Vuyst, Free University of Brussels, Erasmus Hospital, Brussels. *France*: B. Wallaert and N. Just, C.H.R.U. de Lille, Hôpital Calmette, Lille; J.F. Muir, Hôpital de Bois Guillaume, Rouen; P. Delaval, Hôpital Pontchaillou, Rennes; P. Chanez and A. Bourdin, Hôpital Arnaud de Villeneuve, Montpellier; J. Cadranet, Hôpital Tenon, Paris; P. Camus, C.H.U. Le Bocage, Dijon. *Germany*: U. Costabel and H. Steveling, Medical Faculty Essen, Ruhrlandklinik, Essen-Heidhausen; J. Behr and R. Baumgartner, University of Munich, Klinikum Grosshadern, Munich; A.M. Kirsten, III, Medizinische Klinik, Klinikum der Johannes-Gutenberg-Universität, Mainz; J. Müller-Quernheim, Forschungszentrum Borstel, Medizinische Klinik, Borstel; R. Loddenkemper, Lungenklinik Heckeshorn, Klinikum Zehlendorf, Berlin; T. Welte, Zentrum für Innere Medizin, Universitäts Klinikum Magdeburg, Magdeburg; A. Meyer, Universitäts Krankenhaus Eppendorf, Hamburg; R. Bonnet and I. Mäder, Zentralklinik Bad Berka, Bad Berka. *Italy*: G. Simon, Azienda Ospedaliera Villa Sofia, Palermo; G. Bottino, D.I.M.I.—Università di Genova, Genoa; C. Giuntini, Dipartimento Cardiotoracico, Università degli Studi di Pisa, Pisa; A. Rossi, I.R.C.C.S. Policlinico S. Matteo, Pavia; S. Gasparini, Ospedale Torrette, Torrette di Ancona; M. Dottorini, Ospedale R. Silvestrini, Perugia; G. Anzalone, Ospedale di Prato, Prato; G. Bustacchini, Ospedale S. Maria delle Croci, Ravenna. *Spain*: E. Rodriguez-Becerra, Hospital Universitario Virgen del Rocío, Seville; L. Callol Sanchez, Hospital Universitario Del Aire, Madrid; J. Ancochea Bermudez, Hospital Universitario de la Princesa, Madrid; J.M. Rodriguez-Arias and I. Vigil, Hospital Sant Pau, Barcelona; J.L. Llorente, Hospital De Cruces, Baracaldo-Bilbao. *The Netherlands*: J. van den Bosch, St. Antonius Ziekenhuis, Nieuwegein; F. Beaumont, Bosch Medicentrum, Locatie Grootziekgasthuis, Hertogenbosch; H.M. Jansen, Academic Medical Center, Amsterdam; F.J.J. van den Elshout, Ziekenhuis Rijnstate, Arnhem; M. Drent, University Hospital Maastricht, Maastricht.

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