ORIGINAL ARTICLE

Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

ABSTRACT

BACKGROUND

Acetylcysteine has been suggested as a beneficial treatment for idiopathic pulmonary fibrosis, although data from placebo-controlled studies are lacking.

METHODS

In our initial double-blind, placebo-controlled trial, we randomly assigned patients who had idiopathic pulmonary fibrosis with mild-to-moderate impairment in pulmonary function to receive a three-drug regimen of prednisone, azathioprine, and acetylcysteine; acetylcysteine alone; or placebo. The study was interrupted owing to safety concerns associated with the three-drug regimen. The trial continued as a two-group study (acetylcysteine vs. placebo) without other changes; 133 and 131 patients were enrolled in the acetylcysteine and placebo groups, respectively. The primary outcome was the change in forced vital capacity (FVC) over a 60-week period.

RESULTS

At 60 weeks, there was no significant difference in the change in FVC between the acetylcysteine group and the placebo group (−0.18 liters and −0.19 liters, respectively; P=0.77). In addition, there were no significant differences between the acetylcysteine group and the placebo group in the rates of death (4.9% vs. 2.5%, P=0.30 by the log-rank test) or acute exacerbation (2.3% in each group, P>0.99).

CONCLUSIONS

As compared with placebo, acetylcysteine offered no significant benefit with respect to the preservation of FVC in patients with idiopathic pulmonary fibrosis with mild-to-moderate impairment in lung function. (Funded by the National Heart, Lung, and Blood Institute and others; ClinicalTrials.gov number, NCT00650091.)

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This article was published on May 18, 2014, at NEJM.org.

DOI: 10.1056/NEJMoa1401739

Idiopathic pulmonary fibrosis is a chronic, progressive lung disease of unknown cause that is characterized by the histopathological or radiologic patterns of usual interstitial pneumonia in a typical clinical setting.[1,2] To date, no pharmacologic therapies have been shown to improve survival.[1]

In the IFIGENIA study (Idiopathic Pulmonary Fibrosis International Group Exploring *N*-Acetylcysteine I Annual), investigators found that a three-drug regimen (prednisone, azathioprine, and acetylcysteine) preserved pulmonary function better than a two-drug regimen consisting of azathioprine plus prednisone.[3] In PANTHER-IPF (Prednisone, Azathioprine, and *N*-Acetylcysteine: A Study That Evaluates Response in Idiopathic Pulmonary Fibrosis), patients with mild-to-moderate impairment in pulmonary function were randomly assigned to receive the above-mentioned three-drug regimen, acetylcysteine alone (plus matched placebos for prednisone and azathioprine), or matched placebos for each of the active therapies.[4] After safety concerns were identified by the data and safety monitoring board, the three-drug regimen was stopped by the National Heart, Lung, and Blood Institute (NHLBI) on October 14, 2011, and a clinical alert was issued. After a brief period of interruption for modification of the protocol and approval by the institutional review boards, patients continued to be recruited for the acetylcysteine group and the placebo group and were followed for the prespecified duration of 60 weeks. Here, we report the results of the two-group study.

Methods

Study Oversight

The study was designed and conducted by the steering committee of the Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet) and was carried out at 25 clinical centers in the United States. (A complete listing of IPFnet sites is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org; the original research protocol with all subsequent amendments and the statistical analysis plan can also be found at NEJM.org.) An independent protocol review committee, appointed by the NHLBI, reviewed and approved the protocol for scientific merit. An NHLBI-appointed data and safety monitoring board and all local institutional review boards approved the protocol and all amendments. The data and safety monitoring board met multiple times per year to review data for safety and overall trial progress.

The Duke Clinical Research Institute served as the data coordinating center, and the IPFnet steering committee oversaw all aspects of the conduct of the study. The PANTHER-IPF protocol committee (a subcommittee of the IPFnet steering committee) developed the design and concept of the study and approved the statistical analysis plan; the IPFnet steering committee had full access to all the data. The writing committee wrote the first draft of the manuscript, and the steering committee made subsequent revisions. Zambon, which provided the acetylcysteine and matching placebo used in the study, reviewed and provided comments on a draft of the manuscript before submission for publication; minor changes were made as a result. All the authors assume responsibility for the overall content and integrity of the article.

Study Patients

The inclusion criteria have been described previously.[4] Patients between the ages of 35 and 85 years who had idiopathic pulmonary fibrosis were eligible to participate in the study if they had mild-to-moderate impairment in pulmonary function, which was defined as a forced vital capacity (FVC) of 50% or more of the predicted value and a carbon monoxide diffusing capacity of 30% or more of the predicted value. All patients were required to meet the modified criteria of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association for a diagnosis of idiopathic pulmonary fibrosis,[1,5] which was determined on the basis of high-resolution computed tomography (HRCT) or biopsy. All patients had received a diagnosis of idiopathic pulmonary fibrosis within 48 months before enrollment.

Patients were excluded if they had nonidiopathic fibrotic lung disease; an extent of emphysema that was greater than the extent of fibrotic change on HRCT; physiological evidence of airflow obstruction, which was defined as a ratio of the forced expiratory volume in 1 second (FEV_1) to FVC of less than 0.65 or a residual volume of more than 120%; or any current signs or symp-

toms of severe, progressive, or uncontrolled coexisting illnesses, as determined by the site investigator; if they were on an active waiting list for lung transplantation; or if they had received combination therapy with azathioprine, prednisone, and acetylcysteine for more than 12 weeks in the previous 4 years. Patients who were originally randomly assigned to the discontinued three-drug regimen were not allowed to participate in the two-group study. All patients provided written informed consent. (Details of the inclusion and exclusion criteria are provided in the PANTHER-IPF protocol.)

STUDY DESIGN

A permuted, block-randomization plan was created with varying block sizes, with stratification according to clinical center. Once the screening process was completed, patients were randomly assigned to receive the available treatment regimens with equal probability (1:1:1 before the clinical alert and 1:1 after the clinical alert) by means of telephone contact with a central interactive voice-response system.

After the termination of the three-drug regimen, an additional 105 patients were randomly assigned to receive either 600 mg of acetylcysteine or matching placebo three times daily, with a planned follow-up period of 60 weeks. This report details the comparison between the acetylcysteine group and the placebo group.

OUTCOME MEASURES

The primary outcome measure was the change in FVC over 60 weeks. Secondary outcome measures included the rate of and time until death; the frequency of acute exacerbations; the frequency of maintained FVC; the time to disease progression; the change in the carbon monoxide diffusing capacity; a composite physiological index[6]; the alveolar–arterial oxygen gradient; data from the 6-minute walk test, including the distance walked, the area under the curve for oxygen saturation, the distance walked until desaturation to less than 80% occurred, and the number of minutes walked; health status and well-being, as measured on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), the EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D), and St. George's Respiratory Questionnaire; dyspnea, as measured with the use of the University of California at San Diego Shortness of Breath Questionnaire; general capability, as measured with the use of the Investigating Choice Experiments for the Preferences of Older People Capability Instrument (ICECAP); the frequency and types of adverse events, along with infectious and noninfectious respiratory complications; and the frequency of all-cause and respiratory-related hospitalizations. (The range and sign for each evaluation are provided in Table 1.)

ADJUDICATION

The IPFnet adjudication committee was tasked with reviewing all deaths and hospitalizations, as well as all cases of suspected acute exacerbation, to determine the cause. The prespecified definition of acute exacerbation was in accordance with published criteria.[9]

STATISTICAL ANALYSIS

After accounting for a potential dropout rate of 20% and a 2% rate of nonadherence,[10] we calculated that a sample size of 130 patients per study group would provide a power of 93% to determine a significant between-group difference of 0.15 liters in the FVC over a 60-week period.[11] All the analyses were based on the intention-to-treat principle and included all patients who underwent randomization. Patients who prematurely discontinued a study medication but did not withdraw consent were followed for 60 weeks. For continuous baseline factors, summary measures are presented with the use of means plus standard deviations. For categorical variables, counts and percentages are presented.

For the primary analysis, we fitted a linear model for longitudinal data (PROC MIXED in SAS software) to compare differences between the study groups in the slope of FVC measurements over the 60-week study period, with planned measurements at baseline and at weeks 15, 30, 45, and 60. This model assumes that data were missing at random, and no data were imputed. Variables in the regression model included treatment, time, the interaction between time and treatment, age, sex, race, and height. The slope estimates capture the change in FVC over time. We used estimates of between-group differences in the slopes of the interaction between treatment and time (along with 95% confidence intervals) to estimate the treatment effect. A similar approach was used to analyze the secondary end points.

Since we assumed that data were missing at

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Overall		Before Clinical Alert		After Clinical Alert	
	Acetylcysteine (N=133)	Placebo (N=131)	Acetylcysteine (N=81)	Placebo (N=78)	Acetylcysteine (N=52)	Placebo (N=53)
Age — yr	68.3±8.4	67.2±8.2	68.7±7.7	67.9±8.1	67.5±9.4	66.1±8.3
Female sex — no. (%)	26 (19.5)	33 (25.2)	17 (21.0)	21 (26.9)	9 (17.3)	12 (22.6)
White race — no. (%)†	126 (94.7)	126 (96.2)	78 (96.3)	75 (96.2)	48 (92.3)	51 (96.2)
Never smoked — no./total no. (%)	36/132 (27.3)	33/131 (25.2)	20/80 (25.0)	20/78 (25.6)	16/52 (30.8)	13/53 (24.5)
Time since diagnosis — yr	1.0±1.0	1.1±1.0	1.0±1.1	1.1±1.0	1.0±0.9	1.3±1.1
Concomitant illness — no./total no. (%)						
Coronary artery disease	32/133 (24.1)	28/130 (21.5)	21/81 (25.9)	18/78 (23.1)	11/52 (21.2)	10/52 (19.2)
Diabetes	28/132 (21.2)	23/130 (17.7)	14/81 (17.3)	14/78 (17.9)	14/51 (27.5)	9/52 (17.3)
Gastroesophageal reflux disease	79/132 (59.8)	82/131 (62.6)	50/81 (61.7)	46/78 (59.0)	29/51 (56.9)	36/53 (67.9)
Forced vital capacity						
Value — liters	2.9±0.8	2.9±0.8	2.9±0.9	2.8±0.7	3.0±0.8	3.1±0.8
Percent of predicted value	72.2±15.9	73.4±14.3	71.9±15.4	72.1±14.5	72.7±16.6	75.2±13.8
Carbon monoxide diffusing capacity corrected for hemoglobin						
Value — ml/min/mm Hg	13.2±3.7	13.5±3.8	12.8±3.8	13.1±3.6	13.8±3.5	14.1±4.0
Percent of predicted value	44.7±10.8	46.0±12.2	43.9±10.3	45.3±12.2	46.0±11.5	47.1±12.2
Partial pressure of arterial oxygen while breathing ambient air — mm Hg	80.7±10.5	81.5±11.8	79.7±11.0	79.3±11.4	82.1±9.6	84.7±11.8
6-minute walk distance — m	371±116	375±105	371±116	369±117	373±116	385±83
Score on UCSD Shortness of Breath Questionnaire‡	26.1±17.1	27.1±18.7	26.7±17.6	28.8±19.2	25.2±16.4	24.5±17.8
Score on St. George's Respiratory Questionnaire§	40.2±16.5	38.0±17.2	40.1±15.8	39.2±17.2	40.4±17.9	36.3±17.2
Score on SF-36¶						
Aggregate physical score	41.4±8.8	40.7±9.3	41.2±7.9	40.7±9.2	41.7±10.1	40.7±9.5
Aggregate mental score	53.2±9.1	55.3±7.5	53.0±9.9	55.9±7.4	53.7±7.8	54.3±7.6
ICECAP summary score‖	0.87±0.09	0.88±0.09	0.88±0.09	0.89±0.08	0.86±0.09	0.87±0.09
Score on EuroQoL visual-analogue scale**	78.3±15.0	77.7±14.3	78.5±13.6	78.4±15.1	78.1±17.0	76.7±13.3

* Plus–minus values are means ±SD. No significant between-group differences in baseline characteristics were observed.
† Race was self-reported.
‡ Scores on the University of California at San Diego (UCSD) Shortness of Breath Questionnaire range from 0 to 120, with higher scores indicating worse function. The minimally important difference is 5 points.[7]
§ Scores on St. George's Respiratory Questionnaire range from 0 to 100, with higher scores indicating more limitations. The suggested minimally important difference for patients with idiopathic pulmonary fibrosis has been estimated at 5 to 8 points.[8]
¶ Scores on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) range from 0 to 100, with higher scores indicating better function. The suggested minimally important difference for patients with idiopathic pulmonary fibrosis has been estimated at 2 to 4 points.
‖ Scores on the Investigating Choice Experiments for the Preferences of Older People Capability Instrument (ICECAP) range from 0 to 1, with higher scores indicating more capability. The minimally important difference for the ICECAP survey among patients with idiopathic pulmonary fibrosis has not been established.
** Scores on the EuroQoL Group 5-Dimension visual-analogue scale range from 0 to 100, with higher scores indicating a better quality of life. The minimally important difference for the EuroQoL among patients with idiopathic pulmonary fibrosis has not been established.

random in the primary analysis, we performed a sensitivity analysis for the FVC end point using the worst-rank approach, which assigns the worst possible value to missing data.[12] This analysis was conducted at each of the scheduled follow-up assessments (at 15, 30, 45, and 60 weeks). For binary end points, statistical comparisons were based on two-sided Fisher's exact tests or chi-

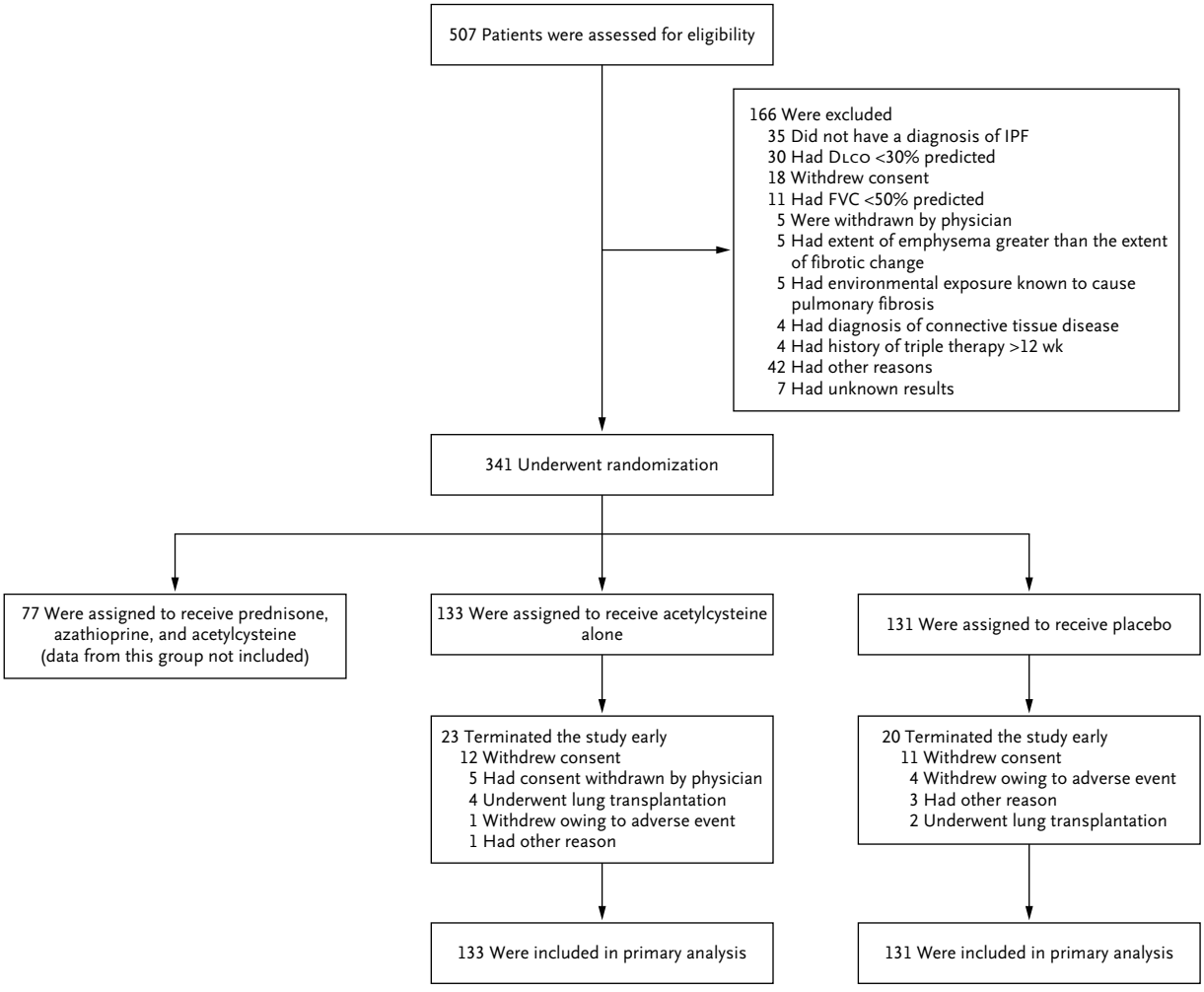

Figure 1. Enrollment and Outcomes.

DLCO denotes carbon monoxide diffusing capacity, and FVC forced vital capacity.

square tests. We used Kaplan–Meier curves to display event rates and log-rank tests to test statistical hypotheses. Statistical comparisons were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance unless otherwise specified.

Prespecified groups of interest included patients with an increased baseline FVC, those with a reduced composite physiological index at baseline, those who had received medical therapy for gastroesophageal reflux, and those who had a severity of emphysema of more than 25% on HRCT; additional subgroups were defined according to typical versus atypical results on the baseline HRCT, a recent versus a more remote diagnosis of idiopathic pulmonary fibrosis, race, sex, and smoking history. Continuous subgroup factors were split into two groups with the use of the median as the cutoff value. Given the major protocol modifications related to the termination of the three-drug regimen and the continuation of the two-group study, we compared the cohort of patients who underwent randomization before the clinical alert with the cohort of patients who underwent randomization after the clinical alert. This comparison was not specified in the updated statistical analysis plan. For subgroup analyses, a P value of less than 0.001 was considered to indicate statistical significance.

RESULTS

STUDY PATIENTS

From December 2009 to mid-October 2011 (before the clinical alert) and from January 2012 through July 2012 (after the clinical alert), we enrolled 264 patients, with 133 in the acetylcysteine group and 131 in the placebo group (Fig. 1). From mid-October 2011 to mid-January 2012, enrollment was interrupted while the protocol was amended and approved by the steering committee, the data and safety monitoring board, and the local institutional review boards.

The baseline characteristics of the patients were well matched in the two study groups. The mean age was 67 years, 22% of the patients were women, and 96% were white (Table 1). The mean FVC was 73% of the predicted value, and the mean carbon monoxide diffusing capacity was 45% of the predicted value. The mean distance on the 6-minute walk test was 373 m. HRCT findings were sufficient to diagnose definite usual interstitial pneumonia in 77% of the patients. A total of 139 of 264 patients (52.7%) underwent surgical lung biopsy.

STUDY-DRUG ADHERENCE

A total of 34 of 133 patients (25.6%) in the acetylcysteine group and 29 of 131 patients (22.1%) in the placebo group discontinued the study medication (P = 0.53). At 30 weeks, 93.3% of patients in the acetylcysteine group and 91.7% in the pla-

Table 2. Changes from Baseline in Key Outcome Measures at 60 Weeks.

End Point	Acetylcysteine (N = 133)	Placebo (N = 131)	Treatment Difference (95% CI)	P Value
Forced vital capacity (liters)*	−0.18	−0.19	0.01 (−0.06 to 0.09)	0.77
Before clinical alert	−0.17	−0.22	0.06 (−0.04 to 0.15)	0.27
After clinical alert	−0.19	−0.13	−0.06 (−0.18 to 0.06)	0.32
Carbon monoxide diffusing capacity corrected for hemoglobin (ml/min/mm Hg)*	−1.3	−1.4	0.2 (−0.4 to 0.8)	0.56
Before clinical alert	−1.1	−1.9	0.8 (0.1 to 1.5)	0.03
After clinical alert	−1.4	−0.8	−0.7 (−1.6 to 0.3)	0.18
Distance on 6-minute walk test (m)*	−23.4	−47.5	24.2 (−2.6 to 50.9)	0.08
Before clinical alert	−27.2	−67.7	40.5 (6.1 to 74.8)	0.02
After clinical alert	−14.1	−15.8	1.7 (−38.7 to 42.1)	0.93
Score on UCSD Shortness of Breath Questionnaire†	6.0	5.8	0.2 (−4.1 to 4.4)	0.94
Before clinical alert	5.6	7.6	−2.1 (−8.3 to 4.2)	0.52
After clinical alert	7.4	2.8	4.6 (−0.7 to 9.8)	0.09
Total score on St. George's Respiratory Questionnaire†	4.3	5.5	−1.2 (−4.9 to 2.4)	0.51
Before clinical alert	4.5	7.7	−3.3 (−8.3 to 1.7)	0.20
After clinical alert	4.3	2.7	1.6 (−3.7 to 6.9)	0.55
SF-36 aggregate mental score*	0.0	−2.6	2.6 (0.3 to 5.0)	0.03
Before clinical alert	0.8	−3.5	4.3 (1.3 to 7.3)	0.005
After clinical alert	−1.3	−1.2	−0.1 (−3.8 to 3.6)	0.97
ICECAP summary score*	0.01	−0.02	0.03 (0.01 to 0.05)	0.01
Before clinical alert	−0.00	−0.05	0.04 (0.01 to 0.08)	0.008
After clinical alert	0.02	0.00	0.01 (−0.02 to 0.05)	0.40
Score on EuroQoL visual-analogue scale*	0.9	−3.3	4.2 (−0.3 to 8.8)	0.07
Before clinical alert	−1.7	−7.6	5.9 (−0.1 to 11.9)	0.05
After clinical alert	4.5	1.6	2.8 (−3.8 to 9.4)	0.40

* A positive value for the treatment difference favors the acetylcysteine group, and a negative value favors the placebo group.
† A positive value for the treatment difference favors the placebo group, and a negative value favors the acetylcysteine group.

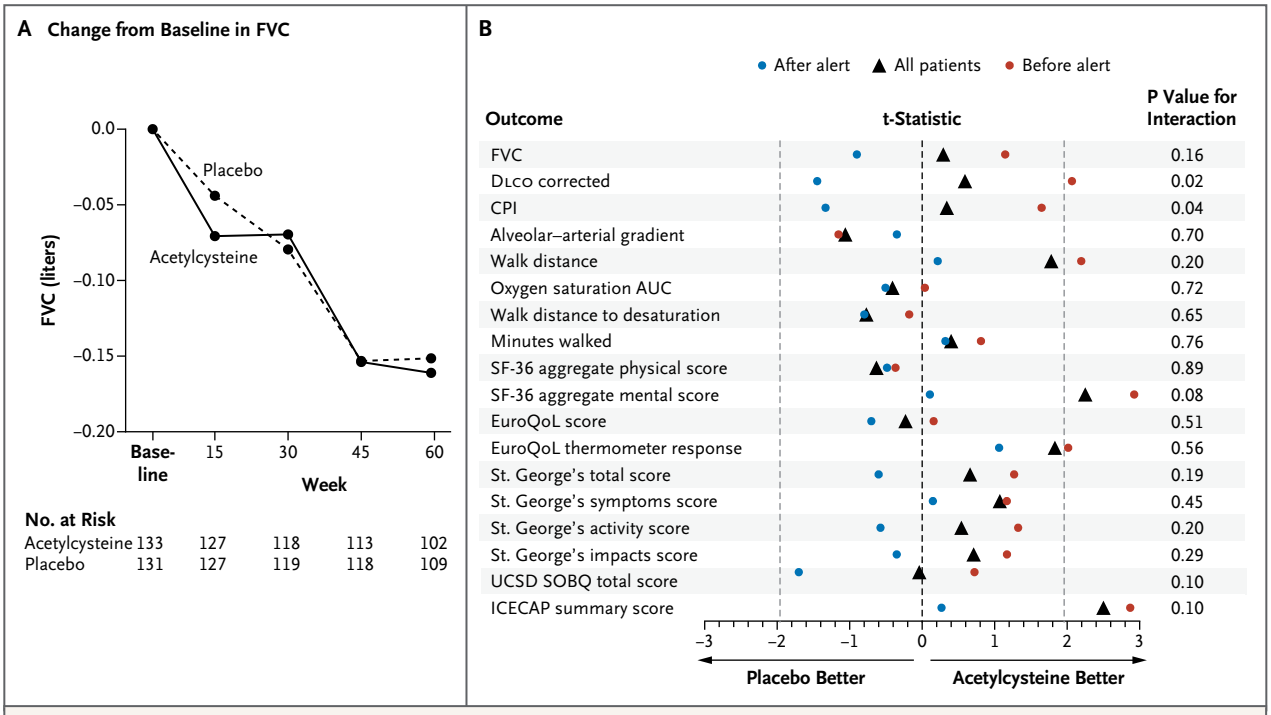

Figure 2. Changes from Baseline in FVC and Subgroup Analyses before and after the Clinical Alert.

Panel A shows changes in the FVC from baseline in the acetylcysteine group and the placebo group. This two-group study was a continuation of the three-group PANTHER-IPF study, which was terminated by the National Heart, Lung, and Blood Institute on October 14, 2011, after safety concerns were identified regarding the three-drug combination of prednisone, azathioprine, and acetylcysteine. At that time, a clinical alert was issued. Panel B shows the t-statistic for outcome variables for patients enrolled before the clinical alert was issued and after the clinical alert was issued. The t-statistic is for the treatment difference in the linear model. A t-statistic of more than 2 favors the acetylcysteine group, and a t-statistic of less than –2 favors the placebo group. AUC denotes area under the curve, CPI composite physiological index, DLCO carbon monoxide diffusing capacity, ICECAP Investigating Choice Experiments for the Preferences of Older People Capability Instrument, St. George's St. George's Respiratory Questionnaire, SF-36 Medical Outcomes Study 36-Item Short-Form Health Survey, and UCSD SOBQ University of California at San Diego Shortness of Breath Questionnaire.

cebo group reported taking more than 80% of the recommended doses of the study drug. Similarly, at 60 weeks, 90.4% in the acetylcysteine group and 94.4% in the placebo group reported taking more than 80% of the recommended doses of the study drug.

PRIMARY OUTCOME

There was no significant difference in the change in FVC at 60 weeks between the acetylcysteine group and the placebo group (–0.18 liters and –0.19 liters, respectively; P = 0.77) (Table 2 and Fig. 2A, and Fig. S1 in the Supplementary Appendix). Similarly, a sensitivity analysis that was performed on the basis of the worst-rank scores showed no evidence of treatment effect when changes in the percentage of the predicted FVC were categorized in various ways and when missing data were assigned to the worst rank (Table S1 in the Supplementary Appendix). There were no significant differences with respect to the primary end point in the prespecified subgroups.

SECONDARY OUTCOME MEASURES

There were no significant differences between the acetylcysteine group and the placebo group with respect to the majority of prespecified secondary end points (Table 2), including the carbon monoxide diffusing capacity (Fig. S2A in the Supplementary Appendix). However, there were trends favoring acetylcysteine in the 6-minute walk distance (P = 0.08) (Fig. S2B in the Supplementary Appendix), the score on the EuroQoL visual-analogue scale (P = 0.07), the SF-36 mental score (P = 0.03), and the ICECAP summary score (P = 0.01) (Table 2).

Over the 60-week study period, in Kaplan–Meier analyses, there were no significant differences between the acetylcysteine group and the placebo group with respect to death (6 patients

[4.9%] vs. 3 patients [2.5%], P=0.30 by log-rank test). Similarly, there were no significant differences with respect to acute exacerbation (3 patients [2.3%] in each study group, P>0.99). Among other measures, there were no significant between-group differences with respect to the rate of death from respiratory causes, hospitalizations for any cause or for respiratory causes, or the proportion of patients with disease progression (which was defined as a 10% decline in the FVC or death) (Table 3, and Fig. S3 in the Supplementary Appendix).

ADVERSE EVENTS

The overall incidence of adverse events and serious adverse events is presented in Table 3. There were no significant between-group differences in the rates of serious adverse events, except for cardiac disorders, which occurred in 9 of 133 patients (6.8%) in the acetylcysteine group and in 2 of 131 patients (1.5%) in the placebo group (P=0.03), and gastrointestinal disorders, which occurred in no patients in the acetylcysteine group and in 6 of 131 patients (4.6%) in the placebo group (P=0.01).

SUBGROUP ANALYSES

None of the comparisons of outcome measures reached the prespecified conservative P value (P<0.001). There were no significant between-group differences with respect to the primary end point either before the clinical alert or after

Table 3. Clinical Events and Safety.

Outcome	Acetylcysteine (N=133)	Placebo (N=131)	P Value
Death — no./total no. (%)			
From any cause	6/133 (4.5)	3/131 (2.3)	0.50
Before clinical alert	4/81 (4.9)	3/78 (3.8)	>0.99
After clinical alert	2/52 (3.8)	0	0.24
From respiratory cause	5/133 (3.8)	3/131 (2.3)	0.72
Before clinical alert	3/81 (3.7)	3/78 (3.8)	>0.99
After clinical alert	2/52 (3.8)	0	0.24
Acute exacerbation — no./total no. (%)	3/133 (2.3)	3/131 (2.3)	>0.99
Before clinical alert	2/81 (2.5)	2/78 (2.6)	>0.99
After clinical alert	1/52 (1.9)	1/53 (1.9)	>0.99
Hospitalization — no./total no. (%)			
For any cause	20/133 (15.0)	18/131 (13.7)	0.76
Before clinical alert	14/81 (17.3)	9/78 (11.5)	0.30
After clinical alert	6/52 (11.5)	9/53 (17.0)	0.43
For respiratory cause	11/133 (8.3)	10/131 (7.6)	0.85
Before clinical alert	9/81 (11.1)	5/78 (6.4)	0.30
After clinical alert	2/52 (3.8)	5/53 (9.4)	0.44
Serious adverse events — no. (%)*	25 (18.8)	20 (15.3)	0.45
Respiratory	9 (6.8)	9 (6.9)	0.97
Infectious	6 (4.5)	6 (4.6)	0.98
Cardiac	9 (6.8)	2 (1.5)	0.03
Gastrointestinal	0	6 (4.6)	0.01
Death (95% CI) — %†	4.9 (2.2–10.6)	2.5 (0.8–7.5)	0.30
Disease progression (95% CI) — %†‡	27.1 (20.1–36.0)	26.5 (19.5–35.4)	0.82
Death or hospitalization (95% CI) — %†	17.5 (11.9–25.4)	15.6 (10.2–23.3)	0.59

* Patients could have more than one serious adverse event.
† Percentages are Kaplan–Meier estimates, and P values were calculated with the use of the log-rank test.
‡ Disease progression was defined a reduction of more than 10% in the FVC or death.

the clinical alert (P=0.27 and P=0.32, respectively) (Table 2). For a number of other comparisons, trends toward a favorable response in the acetylcysteine group, as compared with the placebo group, were noted before the clinical alert, as compared with after the clinical alert (Tables 2 and 3 and Fig. 2B).

DISCUSSION

The use of acetylcysteine has been suggested to benefit patients with idiopathic pulmonary fibrosis by favorably altering the oxidative state of the lung.[3] In the IFIGENIA study, a three-drug regimen consisting of azathioprine, prednisone, and acetylcysteine preserved the FVC and carbon monoxide diffusing capacity better than a two-drug regimen consisting of azathioprine and prednisone.[3] In our study, we found that over a 60-week period, acetylcysteine (at a dose of 600 mg three times a day) was not associated with preservation of the FVC, as compared with a matched placebo, in patients with idiopathic pulmonary fibrosis who had mild-to-moderate impairment in pulmonary function. The patients in the acetylcysteine group reported having better mental well-being (on the basis of the SF-36 mental score and ICECAP summary score) than did those in the placebo group. There were no significant between-group differences with respect to all-cause and respiratory mortality, all-cause and respiratory hospitalizations, acute exacerbations, or the proportion of patients with disease progression. Acetylcysteine monotherapy was associated with more cardiac events and fewer gastrointestinal events than was placebo.

The responses in the patients in the acetylcysteine group were similar in the periods before the clinical alert and after the clinical alert. A trend toward improvement in other outcome measures among patients in the placebo group in the period after the clinical alert, as compared with the period before the clinical alert, was noted. An explanation for this finding is not evident.

It must be emphasized that our results are applicable only to patients with idiopathic pulmonary fibrosis who met the inclusion and exclusion criteria of this trial and not to patients with more advanced disease or other forms of idiopathic interstitial pneumonia or interstitial lung disease. In conclusion, treatment with acetylcysteine did not help preserve the FVC in patients with idiopathic pulmonary fibrosis who had mild-to-moderate impairment in pulmonary function at baseline.

The views expressed in this article are those of the authors and do not necessarily represent the official views of the NHLBI or the National Institutes of Health.

Supported by grants (U10HL080413, to the data coordinating center; and U10HL080274, U10HL080370, U10HL080371, U10HL080383, U10HL080411, U10HL080509, U10HL080510, U10HL080513, U10HL080543, U10HL080571, and U10HL080685, to the clinical centers) from the NHLBI and by the Cowlin Family Fund at the Chicago Community Trust. Zambon provided the acetylcysteine and matching placebo that were used in the study.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients who volunteered to participate in this study.

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