

**EFFECT OF HIGH-DOSE IBUPROFEN IN PATIENTS WITH CYSTIC FIBROSIS**

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**Abstract Background.** Since the inflammatory response to chronic infection contributes to lung destruction in patients with cystic fibrosis, we hypothesized that anti-inflammatory therapy might slow the progression of lung disease.

**Methods.** In a double-blind trial, 85 patients, 5 to 39 years of age, with mild lung disease (forced expiratory volume in one second [FEV<sub>1</sub>],  $\geq 60$  percent of the predicted value) were randomly assigned to receive ibuprofen or placebo orally twice daily for four years. Doses were adjusted individually to achieve peak plasma concentrations of 50 to 100  $\mu\text{g}$  per milliliter. Changes in pulmonary function, the percentage of ideal body weight, the chest-radiograph score, and the frequency of hospitalization were assessed.

**Results.** Patients randomly assigned to ibuprofen had a slower annual rate of change in FEV<sub>1</sub> than the patients assigned to placebo (mean [ $\pm$ SE] slope,  $-2.17 \pm 0.57$  percent vs.  $-3.60 \pm 0.55$  percent in the placebo group;

$P=0.02$ ), and weight (as a percentage of ideal body weight) was better maintained in the former group ( $P=0.02$ ). Among the patients who took ibuprofen for four years and had at least a 70 percent rate of compliance, the annual rate of change in FEV<sub>1</sub> was even slower ( $-1.48 \pm 0.69$  percent vs.  $-3.57 \pm 0.65$  percent in the placebo group,  $P=0.03$ ), and this group of patients also had a significantly slower rate of decline in forced vital capacity, the percentage of ideal body weight, and the chest-radiograph score. There was no significant difference between the ibuprofen and placebo groups in the frequency of hospitalization. One patient was withdrawn from the study because of conjunctivitis, and one because of epistaxis related to ibuprofen.

**Conclusions.** In patients with cystic fibrosis and mild lung disease, high-dose ibuprofen, taken consistently for four years, significantly slows the progression of the lung disease without serious adverse effects. (N Engl J Med 1995;332:848-54.)

**L**UNG disease in patients with cystic fibrosis is characterized by persistent bacterial infection leading to bronchitis and bronchiectasis. The airways are plugged with thick mucopurulent secretions containing abundant bacteria and neutrophils, and death results from progressive destruction of the lungs.<sup>1</sup> Patients with pancreatic insufficiency or a lower-than-normal weight for their height have shorter lives.<sup>2,3</sup> Vigorous antibiotic therapy, clearance of mucus, and nutritional repletion have been the pillars of conventional therapy.<sup>4</sup> Recently, attention has been focused on the inflammatory response in the lungs, which not only damages the lungs directly but impairs local host defenses, preventing the clearance of infection. Blunting the inflammatory response might preserve lung function.<sup>1</sup>

In a pilot study, the administration of high doses of corticosteroids on alternate days in patients with cystic fibrosis and mild lung disease slowed the progression of the lung disease.<sup>5</sup> A subsequent, larger trial was terminated, however, because of growth retardation and glucose intolerance in the group of patients receiving the high doses of corticosteroids.<sup>6</sup> Nonsteroidal antiinflammatory drugs should be considered as an alternative treatment.

In high doses, ibuprofen inhibits the migration, adherence, swelling, and aggregation of neutrophils, as well as the release of lysosomal enzymes.<sup>7-16</sup> The safety record for ibuprofen has made it acceptable for over-the-counter sale, and there is more experience with this drug than with other nonsteroidal antiinflammatory

drugs in children. In a rat model that mimics the infection and inflammation seen in cystic fibrosis, high-dose ibuprofen significantly reduced lung inflammation without increasing the burden of pseudomonas.<sup>17</sup> Suitable blood levels of ibuprofen can be obtained in patients with cystic fibrosis, but the appropriate dose can be determined only by pharmacokinetic analysis.<sup>18</sup> The present trial was designed to determine whether high-dose ibuprofen, taken consistently, slows the decline of pulmonary function in patients with cystic fibrosis and mild lung disease.

## METHODS

### Study Subjects

From 1988 to 1989, 85 patients with cystic fibrosis, ranging from 5 to 39 years of age, were recruited for the study; 74 were from the Cystic Fibrosis Center at Rainbow Babies and Children's Hospital, Cleveland, and 11 were from the Cystic Fibrosis Center at Children's Hospital Medical Center, Akron, Ohio. Patients were eligible for enrollment if they had cystic fibrosis that had been diagnosed according to the conventional criteria<sup>19</sup> and a forced expiratory volume in one second (FEV<sub>1</sub>) that was at least 60 percent of the predicted value, with no use of intravenous antibiotics during the previous two months. Patients were excluded if they had used corticosteroids (systemic or inhaled) or nonsteroidal antiinflammatory drugs for more than two weeks within the previous two years or had inhaled cromolyn sodium during the six-month period before enrollment. Other criteria for exclusion were hypersensitivity to nonsteroidal antiinflammatory drugs, allergic bronchopulmonary aspergillosis, a respiratory tract culture containing *Burkholderia cepacia*, and hepatic, cardiovascular, renal, neurologic, hematologic, or peptic ulcer disease. Informed consent was obtained from all the patients, and the protocols for the study were approved by the institutional review boards at both hospitals.

### Study Design and Tests

The study was a randomized, double-blind, placebo-controlled trial. Randomization was carried out with permuted blocks of four patients each stratified by age (<13, 13 to 18, and  $\geq 19$  years). Two patients in each block were randomly assigned to receive ibuprofen orally twice daily for four years, and two were assigned to receive placebo. The randomization code was known only by the pharmacolo-

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gist, who made the treatment assignments, and the pharmacist, who dispensed the ibuprofen and placebo.

The initial evaluation included a medical-history taking, physical examination, pulmonary-function testing, chest radiography, sputum or throat culture, blood chemical measurements, a complete blood count, analysis of bleeding time, urinalysis, and a stool test for occult blood. Concomitant therapies were documented. The pharmacokinetics of ibuprofen were measured, and adverse effects were determined with a questionnaire.

Follow-up evaluations were scheduled every three months during year 1 and every six months thereafter. All base-line evaluations were repeated at every visit except pulmonary-function tests (performed every six months), chest radiography (performed yearly), and pharmacokinetic studies of ibuprofen (performed during year 3 or if body weight changed by at least 25 percent). All measurements were performed in Cleveland.

Pulmonary-function testing was performed in patients with clinically stable disease with the use of the MedGraphics Pulmonary Function System 1070-1085 (Medical Graphics, St. Paul, Minn.), according to published standards.<sup>20</sup> Bronchodilators were withheld for at least 12 hours before testing. FEV<sub>1</sub>, forced vital capacity (FVC), and forced expiratory flow at 25 to 75 percent of vital capacity (FEF<sub>25-75%</sub>) were each expressed as a percentage of the predicted normal value for the patient's age, sex, and height.<sup>21</sup> Residual volume as a proportion of total lung capacity (RV/TLC) was determined by plethysmography.

The patients' physicians prescribed medications for clinical care (antibiotics, bronchodilators, pancreatic enzymes, and so forth). The use of corticosteroids, nonsteroidal antiinflammatory drugs, salicylates, and cromolyn sodium was specifically limited. None of the patients received other experimental drugs. The study drug was discontinued for any of the following reasons: the development of an illness affecting the response to the study drug or assessment of clinical status, especially an illness requiring prolonged treatment with corticosteroids, nonsteroidal antiinflammatory drugs, or cromolyn sodium; the occurrence of severe adverse effects or hypersensitivity to the study drug; or noncompliance with the protocol.

#### Pharmacokinetics of Ibuprofen and Dose Determinations

The study drugs consisted of ibuprofen tablets (200 mg) and placebo tablets that were identical in appearance (Upjohn, Kalamazoo, Mich.). Pharmacokinetic analysis was used to determine the dose for each patient that would result in a peak plasma concentration of 50 to 100  $\mu\text{g}$  per milliliter. The dose was determined at base line, during year 3, and if there was a weight gain of 25 percent or more. Dose determinations were performed for all patients, whether they were assigned to placebo or ibuprofen, to keep the treatment assignment concealed. Plasma was obtained before and every 30 minutes after the administration of ibuprofen (20 to 30 mg per kilogram of body weight, to a maximum of 1600 mg) for 3 hours. The patients did not eat or take pancreatic enzymes for two hours after the dose had been administered. The ibuprofen concentration was measured by high-performance liquid chromatography.<sup>22</sup> If the peak concentration of 50 to 100  $\mu\text{g}$  per milliliter was achieved at a particular dose, that was the dose given to the patient. If the peak concentration was not achieved, the dose was altered by the pharmacologist, and the pharmacokinetic studies were repeated. The number of pills to be taken was calculated on the basis of these studies.

#### Assessment of Compliance

Compliance was determined by pill counts and blood monitoring. Tablets were dispensed every three months. At each visit, the patients returned all containers received since the previous visit so that unused pills could be counted. Overall compliance was calculated as the mean compliance during each interval between visits, weighted by the length of the interval. Plasma was obtained at each visit for measurements of ibuprofen and salicylate concentrations, and the history was taken to monitor the use of other restricted medications.

#### Analysis of Outcome Measures

The primary outcome measure was the annual rate of change (as assessed by the slope) of FEV<sub>1</sub>. Secondary outcome measures were the annual rate of change in FVC, FEF<sub>25-75%</sub>, and RV/TLC; the annu-

al rate of change in the percentage of ideal body weight; the change in the chest-radiograph score at four years; and the number of hospital admissions and days of care, including the number of days on which intravenous antibiotics were administered at home.

For changes in pulmonary-function measures and the percentage of ideal body weight, a mixed-model analysis of variance (SAS Institute, Cary, N.C.) was used to fit a model that included time, treatment group, and the interaction between time and treatment simultaneously, with the results weighted for each patient according to the number of missing data and the variability of the outcome measures. The coefficient of time (the slope, or rate of change) estimated for each treatment group and the interaction between time and treatment were used to test for differences between the groups. Base-line pulmonary function and age were included as covariates if their contribution to the fit of the model was significant according to likelihood-ratio tests.

Chest radiographs obtained at base line and year 4 were scored with the method of Brasfield et al.<sup>23</sup> by a radiologist and another trained observer; identifying information and dates on the radiographs were concealed. The mean differences between the scores at base line and year 4 in the treatment groups were determined with a t-test. Hospital admissions and days of care were compared with the Mann-Whitney U test. For all statistical tests, two-tailed P values less than 0.05 were considered to indicate statistical significance.

#### Use of Concomitant Therapies

Differences in the frequency of concomitant therapies in the year before enrollment in the study were compared with a chi-square test. Changes in the frequency of concomitant therapy from the year before enrollment to year 4 were assessed by categorical-data modeling (SAS Institute), which is similar to a two-way analysis of variance for qualitative data.

#### Analysis of Adverse Effects

A comprehensive questionnaire, based on the table of adverse effects of ibuprofen,<sup>24</sup> was administered by the same research nurse at all visits. A base-line profile of the frequency and severity of symptoms that might be attributable to ibuprofen was established for each patient and compared with symptoms reported during the trial. Differences in the frequency of adverse effects between the ibuprofen and placebo groups were compared with a chi-square test.

## RESULTS

#### Assignment of Subjects

Forty-two patients were randomly assigned to ibuprofen, and 43 to placebo. A 13-year-old girl assigned to ibuprofen withdrew at month 3 because of abdominal pain and poor compliance with the protocol; all other patients returned for follow-up and were included in the intention-to-treat analysis. Fifty-seven patients (67 percent) met the prospective criteria for completion of the trial and were included in the completed-treatment analysis. The ibuprofen and placebo groups were similar at base line for both the intention-to-treat analysis (Table 1) and the completed-treatment analysis (data not shown). Reasons for failure to complete the study did not differ between the two groups (Table 1). There were no deaths.

#### Pharmacokinetics and Doses of Ibuprofen

The peak plasma ibuprofen concentration of 50 to 100  $\mu\text{g}$  per milliliter was achieved in all patients at doses of 16.2 to 31.6 mg per kilogram of body weight (Fig. 1). In 11 patients, the values fell outside this range during the first study; the peak concentrations were less than 50  $\mu\text{g}$  per milliliter at doses of 20.4 to 26.5 mg per

kilogram in 8 patients and more than 100  $\mu\text{g}$  per milliliter at doses of 24.4 to 28.6 mg per kilogram in 3 patients. During the four years of the study, 37 patients required a dose adjustment because of a weight gain of 25 percent or more. Follow-up pharmacokinetic studies during year 3 confirmed that the peak plasma ibuprofen concentrations remained within the target range in all the other patients.

### Compliance

In the intention-to-treat analysis, the mean ( $\pm\text{SE}$ ) compliance was  $68\pm 5$  percent for the ibuprofen group and  $72\pm 4$  percent for the placebo group. Compliance did not vary with age. Salicylate was detected once in each of four patients (one in the ibuprofen group and three in the placebo group). None of the patients in the placebo group had detectable plasma concentrations of ibuprofen on routine monitoring that could not be accounted for by the history. The use of ibuprofen (aside from the study drug) and other restricted medications was within the protocol guidelines in both treatment groups. For four patients, the use of corticosteroids exceeded the protocol guidelines, and these patients were therefore excluded from the completed-treatment analysis.

### Outcome Measures

#### Pulmonary Function

The primary outcome measure,  $\text{FEV}_1$ , declined significantly more slowly in the patients assigned to ibu-

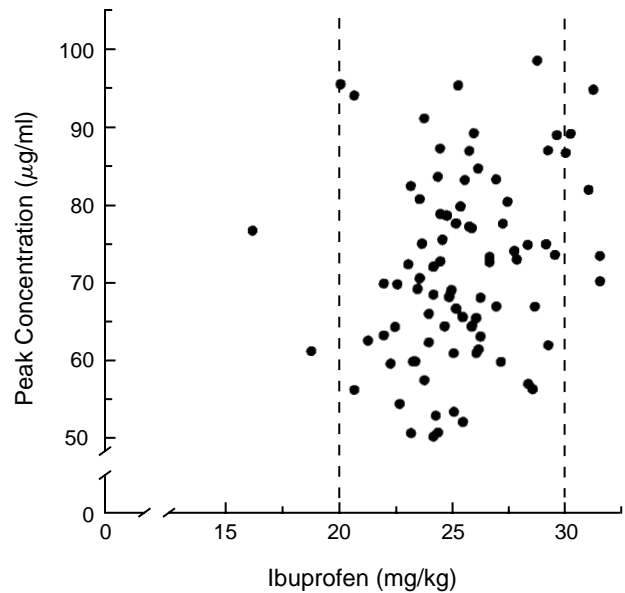


Figure 1. Relation between the Dose and Peak Plasma Concentration of Ibuprofen in 84 Patients with Cystic Fibrosis and Mild Lung Disease.

The plotted points represent the doses of ibuprofen necessary to achieve a peak plasma concentration between 50 and 100  $\mu\text{g}$  per milliliter in all subjects before enrollment. The dashed lines at doses of 20 and 30 mg of ibuprofen per kilogram indicate this dose range. With a mean dose ( $\pm\text{SE}$ ) of  $25.4\pm 0.3$  mg per kilogram, the mean peak plasma concentration of ibuprofen was  $71.8\pm 1.3$   $\mu\text{g}$  per milliliter.

Table 1. Characteristics of 84 Subjects with Cystic Fibrosis and Mild Lung Disease Who Were Randomly Assigned to Receive Ibuprofen or Placebo.\*

CHARACTERISTIC	IBUPROFEN (N = 41)	PLACEBO (N = 43)
Age at enrollment (yr)	14.8 $\pm$ 1.3	13.4 $\pm$ 1.0
<13 yr (no. of patients)	24	25
$\geq$ 13 yr (no. of patients)	17	18
Sex (M/F)	26/15	24/19
Pulmonary function at enrollment		
FEV <sub>1</sub> (% of predicted value)	85.9 $\pm$ 2.3	89.0 $\pm$ 2.7
FVC (% of predicted value)	101.6 $\pm$ 2.0	103.1 $\pm$ 2.3
FEF <sub>25-75%</sub> (% of predicted value)	59.0 $\pm$ 3.8	64.3 $\pm$ 3.9
RV/TLC (%)	35 $\pm$ 1	34 $\pm$ 1
Chest-radiograph score at enrollment†	17.8 $\pm$ 0.4	17.9 $\pm$ 0.3
Weight at enrollment (% of ideal body weight)	93.5 $\pm$ 1.8	94.5 $\pm$ 2.1
Genotype for cystic fibrosis (no. of patients)		
$\Delta\text{F}_{508}/\Delta\text{F}_{508}$	21	25
$\Delta\text{F}_{508}/\text{other}$	18	16
Other/other	2	2
Respiratory tract infected with <i>Pseudomonas aeruginosa</i> at enrollment (no. of patients)	31	29
Reason for not completing the trial (no. of patients)		
Adverse effect		
Abdominal pain	2‡	4
Conjunctivitis	1	0
Epistaxis	1	0
Protocol violation		
Use of prednisone	2	1
Pregnancy	0	1
Intercurrent illness	0	1
Compliance with regimen <70%	1	3
Subject's preference		
Fear of adverse effect	4	0
Insufficient commitment	3	3

\*Plus-minus values are means  $\pm$ SE.

†On the 25-point scale developed by Brasfield et al.<sup>23</sup>

‡A third patient was lost to follow-up after three months of study.

profen than in those assigned to placebo (Table 2). Among the patients in the placebo group, the rate of change in  $\text{FEV}_1$  was similar in the intention-to-treat and completed-treatment analyses. Among the patients in the ibuprofen group, however, those who completed treatment had a slower decline in  $\text{FEV}_1$  than those who did not complete treatment; in the completed-treatment analysis,  $\text{FEV}_1$  declined 59 percent more slowly in the ibuprofen group than in the placebo group.

The other pulmonary-function measures, FVC,  $\text{FEF}_{25-75\%}$ , and RV/TLC, showed a concordant trend in the intention-to-treat analysis (Table 2). In the completed-treatment analysis, FVC declined significantly more slowly in the ibuprofen group than in the placebo group, and  $\text{FEF}_{25-75\%}$  and RV/TLC showed similar trends.

For patients who were less than 13 years old at the time of enrollment, the effect of ibuprofen was even greater, slowing the rate of decline in  $\text{FEV}_1$  by 65 percent in the intention-to-treat analysis and by 88 percent in the completed-treatment analysis (Table 3). The results of other pulmonary-function measures were similar. Among the older patients, there were no differences in pulmonary function between the treatment groups (Table 4).

#### Other Outcome Measures

The percentage of ideal body weight declined in the placebo group, but not in the ibuprofen group. This difference was most pronounced in the completed-treat-

Table 2. Results of Outcome Measures for All Patients and for Those Who Completed Treatment.

OUTCOME MEASURE	INTENTION-TO-TREAT ANALYSIS			COMPLETED-TREATMENT ANALYSIS		
	IBUPROFEN (N=41)	PLACEBO (N=43)	P VALUE	IBUPROFEN (N=27)	PLACEBO (N=30)	P VALUE
	<i>mean ±SE</i>			<i>mean ±SE</i>		
Annual rate of change (slope)*						
FEV <sub>1</sub> (% of predicted value)	-2.17±0.57	-3.60±0.55	0.02†	-1.48±0.69	-3.57±0.65	0.03
FVC (% of predicted value)	-2.01±0.51	-3.00±0.50	0.06†	-1.25±0.60	-2.92±0.52	0.03
FEF <sub>25-75%</sub> (% of predicted value)	-1.75±0.74	-3.67±0.72	0.06	-1.23±0.83	-3.45±1.03	0.09
RV/TLC (%)	-0.43±0.36	0.27±0.35	0.16	-0.91±0.47	0.14±0.45	0.1
Weight (% of ideal body weight)	0.05±0.30	-0.94±0.29	0.02	0.38±0.33	-1.06±0.31	0.002
Chest-radiograph score‡	-0.63±0.19	-1.16±0.21	0.06	-0.41±0.22	-1.13±0.26	0.04
Hospital admissions (no.)§	1.63±0.40	2.56±0.62	0.26	0.67±0.19	2.07±0.66	0.12
Hospital days (no.)§	23.80±7.81	32.23±9.69	0.36	6.22±2.10	22.77±7.57	0.12

\*Calculated for each patient on the basis of actual time (in years) between enrollment date and date of pulmonary-function tests. Groups were compared by mixed-model analysis of variance.

†The comparison includes age as a covariate.

‡Base-line value subtracted from the value at year 4. Groups were compared by t-test.

§Mean number per patient for four years. Groups were compared by the Mann-Whitney U test.

ment analysis and among the patients who were less than 13 years old. The chest-radiograph score tended to decline less in the ibuprofen group than in the placebo group ( $P=0.06$ ) and declined significantly less among those who completed treatment with ibuprofen. These changes did not differ significantly among the three age subgroups.

Forty-nine percent of the patients in the ibuprofen group and 40 percent of those in the placebo group were not hospitalized during the trial, but a few patients spent considerable time in the hospital. Although the patients in the ibuprofen group tended to have fewer hospital admissions and days of care than the patients in the placebo group, the differences were not significant, even when only hospitalizations for respiratory symptoms were considered.

### Concomitant Therapies

The use of concomitant therapies was similar in the two treatment groups during the one-year period before enrollment. At year 4 there was a greater increase in the use of bronchodilators and intravenous antibiotics among the patients in the placebo group (Table 5).

### Adverse Effects

Nine patients (five in the ibuprofen group and four in the placebo group) discontinued the study drug because of adverse effects (Table 1). However, there was a high prevalence of these symptoms at base line (Table 6). Adverse effects were clearly related to the use of ibuprofen in one patient with conjunctivitis and in one with epistaxis. These pre-existing problems worsened with the administration of the study drug, improved with the withdrawal of the drug, and worsened on repeated challenge.

Of the seven patients with ab-

dominal pain (including epigastric pain and heartburn) severe enough to discontinue the study drug, one patient in the placebo group had severe esophagitis on endoscopy. However, abdominal pain, which is nearly universal in patients with cystic fibrosis, decreased in many cases. The proportion of patients in whom abdominal pain increased was similar in the two treatment groups (Table 6). The use of antacids or H<sub>2</sub>-receptor antagonists increased no more in the ibuprofen group than in the placebo group (Table 5). The frequency or severity of other possible adverse effects did not differ between the two groups.

## DISCUSSION

A regimen of high-dose ibuprofen for four years significantly slowed the progression of lung disease in patients with cystic fibrosis who were over five years of age and whose disease was mild at the outset. The effect was particularly evident in patients who completed treatment and in those who were initially less than 13 years old. In addition, weight (expressed as a percent-

Table 3. Results of Outcome Measures for Patients Who Were Initially Less Than 13 Years of Age.

OUTCOME MEASURE	INTENTION-TO-TREAT ANALYSIS			COMPLETED-TREATMENT ANALYSIS		
	IBUPROFEN (N=24)	PLACEBO (N=25)	P VALUE	IBUPROFEN (N=17)	PLACEBO (N=19)	P VALUE
	<i>mean ±SE</i>			<i>mean ±SE</i>		
Annual rate of change (slope)*						
FEV <sub>1</sub> (% of predicted value)	-1.49±0.77	-4.20±0.75	0.01	-0.44±0.86	-3.82±0.82	0.005
FVC (% of predicted value)	-1.83±0.70	-3.86±0.69	0.04	-0.53±0.68	-3.68±0.64	0.001
FEF <sub>25-75%</sub> (% of predicted value)	-0.51±0.99	-3.41±0.96	0.04	0.07±1.24	-2.97±1.17	0.08
RV/TLC (%)	-1.09±0.51	0.03±0.50	0.12	-1.50±0.63	0.29±0.60	0.17
Weight (% of ideal body weight)	-0.05±0.41	-1.50±0.40	0.01	0.23±0.46	-1.42±0.43	0.01
Chest-radiograph score†	-0.67±0.24	-1.12±0.26	0.21	-0.35±0.23	-1.00±0.29	0.09
Hospital admissions (no.)‡	1.25±0.49	2.28±0.74	0.16	0.53±0.19	2.21±0.94	0.12
Hospital days (no.)‡	19.17±10.34	25.00±8.73	0.28	5.12±2.16	22.16±10.39	0.18

\*Calculated for each patient on the basis of actual time (in years) between enrollment date and date of pulmonary-function tests. Groups were compared by mixed-model analysis of variance.

†Base-line value subtracted from the value at year 4. Groups were compared by t-test.

‡Mean number per patient for four years. Groups were compared by the Mann-Whitney U test.

age of ideal body weight) was better maintained in the ibuprofen group. The effect of ibuprofen was sustained throughout the four-year trial, and the values for the outcome measures between the treatment groups continued to diverge at the end of the trial.

FEV<sub>1</sub> was selected as the primary outcome measure because multivariate analyses, including those performed in the patient population at our center, indicated that, of the pulmonary-function measures, FEV<sub>1</sub> best predicts mortality.<sup>25,26</sup> In the intention-to-treat analysis, FEV<sub>1</sub> declined significantly more slowly in the ibuprofen group than in the placebo group, and there was a trend toward similar improvement in the other measures. In the completed-treatment analysis, the rate of decline in FEV<sub>1</sub> and FVC differed significantly between the treatment groups.

Consideration of the results of the completed-treatment analysis is appropriate for several reasons. First, this subgroup analysis was specified prospectively on the assumption that the drug would not benefit those who did not take it, particularly during a period of four years. Second, in the completed-treatment analysis, the decline in pulmonary function was slower only in the ibuprofen group, not in the placebo group, suggesting that the drug, not simply compliance, makes the difference. Third, adverse effects, which make an intention-to-treat analysis critical in trials in which adverse effects of drugs are severe, were similar in the two treatment groups. In addition, the results of the intention-to-treat and completed-treatment analyses were similar.

The effect of ibuprofen is clinically important, significantly affecting two characteristics that have been associated with mortality among patients with cystic fibrosis: FEV<sub>1</sub> and the percentage of ideal body weight. In the intention-to-treat analysis, FEV<sub>1</sub> declined 40 percent less among the patients assigned to ibuprofen than among those assigned to placebo. Moreover, the

Table 4. Results of Outcome Measures for Patients Initially 13 Years of Age or Older.\*

OUTCOME MEASURE	INTENTION-TO-TREAT ANALYSIS		
	IBUPROFEN (N = 17)	PLACEBO (N = 18)	P VALUE
	<i>mean ± SE</i>		
Annual rate of change (slope)†			
FEV <sub>1</sub> (% of predicted)	-3.13±0.78	-2.77±0.76	0.75
FVC (% of predicted)	-2.28±0.66	-1.81±0.64	0.61
FEF <sub>25-75%</sub> (% of predicted)	-3.52±1.04	-4.01±1.01	0.74
RV/TLC (%)	0.50±0.44	0.60±0.43	0.88
Weight (% of ideal body weight)	0.19±0.35	-0.15±0.34	0.49
Chest-radiograph score‡	-0.59±0.31	-1.22±0.36	0.19
Hospital admissions (no.)§	2.18±0.68	2.94±1.08	0.84
Hospital days (no.)§	30.35±12.09	42.28±19.87	0.86

\*Since the differences in the intention-to-treat analysis were not significant for any measure, the data from the completed-treatment analysis are not shown.

†Calculated for each patient on the basis of actual time (in years) between enrollment date and date of pulmonary-function tests. Groups were compared by mixed-model analysis of variance.

‡Base-line value subtracted from value at year 4. Groups were compared by t-test.

§Mean number per patient for four years. Groups were compared by the Mann-Whitney U test.

Table 5. Use of Concomitant Therapies at Base Line and Year 4.

THERAPY	IBUPROFEN (N = 41)		PLACEBO (N = 43)		P VALUE‡
	BASE LINE*	YEAR 4†	BASE LINE*	YEAR 4†	
	<i>% of patients</i>				
Mucus clearance	83	76	79	84	0.19
Bronchodilators	49	56	35	70	0.03
Antibiotics					
Oral	95	90	86	91	0.28
Inhaled	54	54	51	56	0.35
Intravenous	27	29	14	37	0.04
Pancreatic enzymes	88	85	93	93	0.15
Antacids or H <sub>2</sub> - antagonists	32	56	21	53	0.51

\*For one year before enrollment.

†For one year from month 37 through month 48.

‡For the comparison of the change over time in the use of therapy between the ibuprofen group and the placebo group.

patients in the ibuprofen group maintained their weight, whereas the patients in the placebo group lost 4 percentage points of ideal body weight during the trial. The effect of ibuprofen was concentrated among the younger patients: there was no significant treatment effect among the older patients. Among the patients in the ibuprofen group who were less than 13 years old initially and who completed treatment, the rate of decline in FEV<sub>1</sub> was reduced by 88 percent, so that by the end of four years, FEV<sub>1</sub> had declined by less than 2 percent of the predicted value, as compared with a decline of over 15 percent of the predicted value in the placebo group. Similarly, whereas the younger patients treated with ibuprofen gained almost 1 percentage point of ideal body weight over a period of four years, the younger patients treated with placebo lost 6 percentage points. If FEV<sub>1</sub> and relative underweight predict mortality among patients with cystic fibrosis<sup>3,25,26</sup> and if ibuprofen slows the decline in these measures, then ibuprofen may prolong survival.

The better results in the ibuprofen group cannot be attributed to more intensive conventional treatment or to a lower frequency of pseudomonas infection, since these variables were similar in the two treatment groups at base line, and the frequency of new cases of pseudomonas infection was similar in the two groups during the trial (data not shown). The use of concomitant therapies was also similar, except that the use of bronchodilators and intravenous antibiotics increased significantly in the placebo group.

We evaluated antiinflammatory therapy in patients with mild lung disease because such patients have substantial airway inflammation even when they appear to be clinically stable.<sup>27</sup> Antiinflammatory therapy should have the greatest effect before fixed structural damage develops. Also, FEV<sub>1</sub> declines more rapidly in patients with mild disease than in those with more severe disease, so fewer subjects are required to demonstrate a benefit from an effective intervention.

We chose a peak plasma ibuprofen concentration of

Table 6. Prevalence of Possible Adverse Effects of Ibuprofen Therapy during the Four-Year Study Period.

ADVERSE EFFECT	IBUPROFEN	PLACEBO
	(N = 41)*	(N = 43)
	<i>no. of patients</i>	
Abdominal pain		
Base line†	38	38
New or increased	5	7
Severe enough to discontinue therapy	2	4
Decreased	16	19
Conjunctivitis		
Base line†	11	13
New or increased	4	7
Severe enough to discontinue therapy	1	0
Decreased	2	3
Epistaxis		
Base line†	20	19
New or increased	7	6
Severe enough to discontinue therapy	1	0
Decreased	2	1

\*One additional patient with abdominal pain was lost to follow-up after three months.

†History of symptom.

50 to 100  $\mu\text{g}$  per milliliter as a target on the basis of concentration–response data in the literature and our own previous work. Our goal was to achieve the inhibitory effect of ibuprofen on neutrophil activation and migration, which generally occurs at concentrations over 50  $\mu\text{g}$  per milliliter.<sup>7-16</sup> In pseudomonas-infected rats treated with ibuprofen twice daily, a mean peak plasma concentration of 55  $\mu\text{g}$  per milliliter significantly reduced lung inflammation, as compared with that in controls, and resulted in better weight gain without worse infection.<sup>17</sup> With a dose of 20 to 30 mg of ibuprofen per kilogram, the influx of neutrophils to the alveolar crevices of the oral mucosa was reduced in subjects with cystic fibrosis and in normal controls.<sup>28</sup> However, low doses of ibuprofen (2 to 3 mg per kilogram) increased the influx of neutrophils, arousing concern that inadequate peak concentrations might be detrimental. This dose-related response was also observed in a rat model of endotoxin-induced alveolitis.<sup>12</sup> Because low peak concentrations might be detrimental, we chose 50  $\mu\text{g}$  per milliliter as the lower limit of our dose range. Although the target peak concentration was ultimately achieved with a dose of 20 to 30 mg per kilogram in 90 percent of our patients, it was not possible to predict the dose in an individual patient.

Adverse effects and study dropouts were evenly distributed between the two treatment groups. Abdominal pain is reportedly common with ibuprofen therapy.<sup>24</sup> It also occurs in association with cystic fibrosis. During this trial, as we observed previously,<sup>18</sup> more patients in both treatment groups reported improvement than worsening of abdominal pain. The use of antacids and H<sub>2</sub>-receptor antagonists was evenly distributed between the two groups. Thus, we have no evidence of an ibuprofen-related increase in abdominal pain. However, this study was too small to detect reliably even a common drug-related complication, and negative data should be interpreted with caution.

Two adverse effects, conjunctivitis and epistaxis, appeared to be directly related to ibuprofen. The mechanism underlying conjunctivitis is unknown. Preexisting epistaxis may be exacerbated by ibuprofen, since it interferes with platelet aggregation. Ibuprofen should be used cautiously during episodes of epistaxis and possibly hemoptysis.

In summary, high doses of ibuprofen significantly slowed the progression of lung disease during a period of four years in patients with cystic fibrosis who had initially mild lung disease, without unacceptable adverse effects. These results are clinically important and warrant the evaluation of patients who have cystic fibrosis with an FEV<sub>1</sub> of at least 60 percent of the predicted value, particularly younger patients, for therapy with high-dose ibuprofen. Monitoring by physicians for adverse effects and adequate doses is essential. Ibuprofen therapy will not add much to the cost of care (less than \$200 annually for the highest dose).

Antiinflammatory agents represent a new strategy in the treatment of patients with cystic fibrosis and mild lung disease, augmenting conventional therapy as practiced in the two centers participating in this study. Our results should encourage further research with other dose schedules or other agents directed against lung inflammation in patients with cystic fibrosis.

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## REFERENCES

- Konstan MW, Berger M. Infection and inflammation of the lung in cystic fibrosis. In: Davis PB, ed. Cystic fibrosis. New York: Marcel Dekker, 1993:219-76.
- Gaskin K, Gurwitz D, Durie P, Corey M, Levison H, Forstner G. Improved respiratory prognosis in patients with cystic fibrosis with normal fat absorption. *J Pediatr* 1982;100:857-62.
- Kraemer R, Rudeberg A, Hadorn B, Rossi E. Relative underweight in cystic fibrosis and its prognostic value. *Acta Paediatr Scand* 1978;67:33-7.
- Davis PB. Evolution of therapy for cystic fibrosis. *N Engl J Med* 1994;331:672-3.
- Auerbach HS, Williams M, Kirkpatrick JA, Colten HR. Alternate-day prednisone reduces morbidity and improves pulmonary function in cystic fibrosis. *Lancet* 1985;2:686-8.
- Rosenstein BJ, Eigen H. Risks of alternate-day prednisone in patients with cystic fibrosis. *Pediatrics* 1991;87:245-6.
- Brown KA, Collins AJ. Action of nonsteroidal, anti-inflammatory drugs on human and rat peripheral leucocyte migration in vitro. *Ann Rheum Dis* 1977;36:239-43.
- Spisani S, Vanzini G, Traniello S. Inhibition of human leucocytes locomotion by anti-inflammatory drugs. *Experientia* 1979;35:803-4.
- Higgs GA, Eakins KE, Mugridge KG, Moncada S, Vane JR. The effects of non-steroid anti-inflammatory drugs on leucocyte migration in carrageenin-induced inflammation. *Eur J Pharmacol* 1980;66:81-6.

10. Shimanuki T, Nakamura RM, Dizerega GS. Modulation of leukotaxis by ibuprofen: a quantitative determination in vivo. *Inflammation* 1985;9:285-95.
11. Sordelli DO, Cerquetti MC, el-Tawil G, Ramwell PW, Hooke AM, Bellanti JA. Ibuprofen modifies the inflammatory response of the murine lung to *Pseudomonas aeruginosa*. *Eur J Respir Dis* 1985;67:118-27.
12. Rinaldo JE, Pennock B. Effects of ibuprofen on endotoxin-induced alveolitis: biphasic dose response and dissociation between inflammation and hypoxemia. *Am J Med Sci* 1986;291:29-38.
13. Venezio FR, DiVincenzo C, Pearlman F, Phair JP. Effects of the newer non-steroidal anti-inflammatory agents ibuprofen, fenoprofen, and sulindac on neutrophil adherence. *J Infect Dis* 1985;152:690-4.
14. Maderazo EG, Breaux SP, Woronick CL. Inhibition of human polymorphonuclear leukocyte cell responses by ibuprofen. *J Pharmacol Sci* 1984;73:1403-6.
15. Kaplan HB, Edelson HS, Korchak HM, Given WP, Abramson S, Weissmann G. Effects of non-steroidal anti-inflammatory agents on human neutrophil functions in vitro and in vivo. *Biochem Pharmacol* 1984;33:371-8.
16. Flynn PJ, Becker WK, Vercellotti GM, et al. Ibuprofen inhibits granulocyte responses to inflammatory mediators: a proposed mechanism for reduction of experimental myocardial infarct size. *Inflammation* 1984;8:33-44.
17. Konstan MW, Vargo KM, Davis PB. Ibuprofen attenuates the inflammatory response to *Pseudomonas aeruginosa* in a rat model of chronic pulmonary infection: implications for antiinflammatory therapy in cystic fibrosis. *Am Rev Respir Dis* 1990;141:186-92.
18. Konstan MW, Hoppel CL, Chai B, Davis PB. Ibuprofen in children with cystic fibrosis: pharmacokinetics and adverse effects. *J Pediatr* 1991;118:956-64.
19. Cystic Fibrosis Foundation Center Committee and Guidelines Subcommittee. Cystic Fibrosis Foundation guidelines for patient services, evaluation, and monitoring in cystic fibrosis centers. *Am J Dis Child* 1990;144:1311-2.
20. Standardization of spirometry — 1987 update: statement of the American Thoracic Society. *Am Rev Respir Dis* 1987;136:1285-98.
21. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983;127:725-34.
22. Minkler PE, Hoppel CL. Determination of ibuprofen in human plasma by high-performance liquid chromatography. *J Chromatogr* 1988;428:388-94.
23. Brasfield D, Hicks G, Soong S, Tiller RE. The chest roentgenogram in cystic fibrosis: a new scoring system. *Pediatrics* 1979;63:24-9.
24. Physicians' desk reference. 42nd ed. Oradell, N.J.: Medical Economics, 1988:2138-40.
25. Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med* 1992;326:1187-91.
26. Wagener JS, Taussig LM, Burrows B, Hernried L, Boat T. Comparison of lung function and survival patterns between cystic fibrosis and emphysema or chronic bronchitis patients. In: Sturgess JM, ed. *Perspectives in cystic fibrosis: proceedings of the Eighth International Cystic Fibrosis Congress*, Toronto, May 26-30, 1980. Toronto: Canadian Cystic Fibrosis Foundation, 1980:236-45.
27. Konstan MW, Hilliard KA, Norvell TM, Berger M. Bronchoalveolar lavage findings in cystic fibrosis patients with stable, clinically mild lung disease suggest ongoing infection and inflammation. *Am J Respir Crit Care Med* 1994;150:448-54.
28. Konstan MW, Hilliard KA, Davis PB. Effect of ibuprofen on neutrophil (PMN) delivery to mucosal surfaces. *Pediatr Pulmonol Suppl* 1989;4:152-3. abstract.

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