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EFFECT OF INHALED TRIAMCINOLONE ON THE DECLINE IN PULMONARY FUNCTION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

THE LUNG HEALTH STUDY RESEARCH GROUP*

ABSTRACT

Background Chronic obstructive pulmonary disease (COPD) results from a progressive decline in lung function, which is thought to be the consequence of airway inflammation. We hypothesized that antiinflammatory therapy with inhaled corticosteroids would slow this decline.

Methods We enrolled 1116 persons with COPD whose forced expiratory volume in one second (FEV₁) was 30 to 90 percent of the predicted value in a 10-center, placebo-controlled, randomized trial of inhaled triamcinolone acetone administered at a dose of 600 µg twice daily. The primary outcome measure was the rate of decline in FEV₁ after the administration of a bronchodilator. The secondary outcome measures included respiratory symptoms, use of health care services, and airway reactivity. In a substudy of 412 participants, we measured bone density in the lumbar spine and femur at base line and one and three years after the beginning of treatment.

Results The mean duration of follow-up was 40 months. The rate of decline in the FEV₁ after bronchodilator use was similar in the 559 participants in the triamcinolone group and the 557 participants in the placebo group (mean [±SE], 44.2±2.9 vs. 47.0±3.0 ml per year, P=0.50). Members of the triamcinolone group had fewer respiratory symptoms during the course of the study (21.1 per 100 person-years vs. 28.2 per 100 person-years, P=0.005) and had fewer visits to a physician because of a respiratory illness (1.2 per 100 person-years vs. 2.1 per 100 person-years, P=0.03). Those taking triamcinolone also had lower airway reactivity in response to methacholine challenge at 9 months and 33 months (P=0.02 for both comparisons). After three years, the bone density of the lumbar spine (P=0.007) and the femur (P<0.001) was significantly lower in the triamcinolone group.

Conclusions Inhaled triamcinolone does not slow the rate of decline in lung function in people with COPD, but it improves airway reactivity and respiratory symptoms and decreases the use of health care services for respiratory problems. These benefits should be weighed against the potential long-term adverse effects of triamcinolone on bone mineral density. (N Engl J Med 2000;343:1902-9.)

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CHRONIC obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States.¹ COPD results mainly from cigarette smoking by susceptible persons and develops over years, with a progressive decline in lung function. Smoking cessation is the only intervention that effectively slows the decline in pulmonary function, but only 20 to 40 percent of patients succeed in quitting smoking.² Because airway inflammation is thought to cause COPD, it has been hypothesized that antiinflammatory agents might slow progression of the disease.³⁻⁶

In persons with asthma, inhaled corticosteroids reduce airway inflammation, improve lung function, and reduce airway reactivity.⁷ In persons with COPD, there is some evidence that inhaled corticosteroids reduce airway inflammation,^{8,9} but the evidence is not consistent.¹⁰ Inhaled corticosteroids are recommended for symptomatic patients whose disease has responded to oral corticosteroids¹¹ and are widely prescribed for patients with COPD.^{12,13} Three large European clinical trials of inhaled corticosteroids, given for three years to patients with COPD, have had inconsistent results; the first showed no benefit, the second showed an initial improvement in lung function with inhaled corticosteroids, and the third showed a nonsignificant trend toward benefit.¹⁴⁻¹⁶

We conducted a randomized, placebo-controlled clinical trial of inhaled corticosteroids in patients with COPD. The primary hypothesis was that inhaled corticosteroids would decrease the rate of decline of pulmonary function. The secondary hypothesis was that inhaled corticosteroids would reduce symptoms, morbidity, and airway reactivity without systemic adverse effects.

The writing group (Robert Wise, M.D., John Connett, Ph.D., Gail Weimann, M.D., Paul Scanlon, M.D., and Melissa Skeans, M.S.) assumes responsibility for the overall content and integrity of the manuscript. Address reprint requests to Dr. Connett at the Lung Health Study Coordinating Center, 2221 University Ave. SE, Suite 200, Minneapolis, MN 55414, or at john-c@biostat.umn.edu.

*The members of the Lung Health Study Research Group are listed in the Appendix.

METHODS

Enrollment of Participants

Participants were recruited from among those who had previously participated in or been screened for the Lung Health Study. The Lung Health Study was a trial of smoking cessation and the use of inhaled bronchodilators in 5887 smokers with airflow obstruction, conducted at 10 centers between November 1986 and May 1994.^{2,17} The enrollment period for the current study was from November 1994 to November 1995. The participants were 40 to 69 years of age and had airflow obstruction, with a ratio of forced expiratory volume in one second (FEV₁) to forced vital capacity (FVC) of less than 0.70 and a value for FEV₁ that was 30 to 90 percent of the predicted value.¹⁸ All were current smokers or had quit within the previous two years. Candidates were excluded if they had medical conditions such as cancer, recent myocardial infarction, alcoholism, heart failure, insulin-dependent diabetes mellitus, and neuropsychiatric disorders, or if they had used bronchodilators or oral or inhaled corticosteroids in the previous year. The participants provided written informed consent, and the protocol was approved by the institutional review board at each of the 10 clinical centers. A data and safety monitoring board approved the protocol and reviewed trial data every six months to monitor performance, safety, and treatment effects.

Treatment Groups

Randomization occurred during the second base-line visit, after eligibility was established and consent had been given. The participants were randomly assigned to one of two treatment groups with stratification according to clinical center and smoking status (participants were current smokers or had recently quit). Those assigned to receive an inhaled corticosteroid were given metered-dose inhalers containing triamcinolone acetonide (Azmacort, Rhône-Poulenc Rorer) and delivering a dose of 100 μ g per inhalation. Those in the placebo group were given identical inhalers containing only vehicle. For each group, six inhalations twice daily were prescribed, resulting in a dose of 1200 μ g per day for the triamcinolone group. The participants and clinical center staff were unaware of the study-drug assignments.

Outcome Measures

The primary outcome measure was the rate of decline in the FEV₁ after the administration of a bronchodilator, an indicator of the progression of COPD. Secondary outcome measures included respiratory symptoms, cause-specific morbidity and mortality, airway reactivity in response to methacholine, and health-related quality of life.

We performed spirometric measurements before and after two inhalations of isoproterenol.¹⁹ The participants underwent methacholine bronchial provocation with use of a dosimeter technique, beginning with the inhalation of five breaths of diluent and then breaths at increasing methacholine concentrations (1, 5, 10, and 25 mg per milliliter).²⁰ The procedure ended when the FEV₁ reached a value 20 percent below the FEV₁ after the inhalation of diluent or when the maximal concentration had been reached. For safety, we performed the methacholine challenge only if the base-line FEV₁ was at least 50 percent of the participant's predicted value.

We assessed respiratory symptoms with the American Thoracic Society–Division of Lung Diseases questionnaire.²¹ This questionnaire asks about smoking status and the presence and severity of cough, phlegm, wheezing, and breathlessness — symptoms associated with a higher risk of a rapid decline in lung function.²² Every three months, clinic staff asked the participants about new or worsening respiratory symptoms and potential side effects of corticosteroids, which were graded as mild, moderate, or severe.

Use of medical care during the previous interval was recorded every six months. Records of hospitalizations, emergency department visits, and nonroutine visits to a physician were obtained so that the reason for the care could be coded by a medical-records expert who was unaware of the participants' treatment assignments. Most records were subsequently classified by a morbidity and mortality re-

view board, a panel of three physicians who were also unaware of treatment assignments. The board reviewed the medical records of participants who died to determine the causes of death. Eight aspects of health-related quality of life (physical function, social function, pain, physical and emotional role limitation, vitality, personal perceptions of health, and emotional well-being) were measured every year with use of the 36-item Medical Outcomes Study Short-Form General Health Survey (SF-36).²³ The scale for each aspect ranges from 0 to 100, with a higher score indicating better health.

Screening Visits and Randomization

During the initial screening visit, we ascertained the patients' eligibility, administered questionnaires about health status and medication use, and conducted spirometry and bronchial provocation testing with methacholine. The second base-line visit included spirometry, the administration of questionnaires, and randomization. Clinic staff distributed an initial supply of inhalers with instructions on their use.

Counseling of Participants and Monitoring of Adherence

We measured adherence to treatment at each three-month visit by questioning the participants and by weighing returned canisters. We observed how the participants used their inhalers at each six-month visit and provided counseling to improve their technique or adherence as necessary. The participants were informed that they had abnormal pulmonary function resulting from cigarette smoking and were advised to quit. Those who requested assistance were referred to smoking-cessation programs. We provided transdermal nicotine patches for those who had a prescription from their physician. No other medications were provided as part of the study.

Data-Collection Schedule

The participants returned every three months to obtain new inhalers and to report respiratory symptoms or potential side effects. Every six months, the participants underwent spirometry and were interviewed about medical care during the preceding interval. At the first six-month visit, and annually thereafter, participants completed questionnaires on respiratory symptoms. Methacholine testing was repeated at the 9-month and 33-month visits. The participants were followed from randomization until a common ending date (April 30, 1999) 4½ years after the initiation of the trial.

An ancillary study of bone mineral density was performed in a convenience sample of 412 participants at seven clinical centers. Bone scans were obtained with Hologic dual-energy x-ray absorptiometry scanners (model QDR 1000, 1000w, or 2000, Hologic, Bedford, Mass.). Scans of the lumbar spine and the femoral neck were obtained at base line and at the one-year and three-year visits. The scanners were cross-calibrated against a standard bone model that was circulated among the centers. The technical quality of digitized images was evaluated and bone density was determined at a central reading facility at the Mayo Clinic. No instructions were given to participants regarding the use of calcium or vitamin D supplements.

Statistical Analysis

The target enrollment of 1100 participants was designed to enable the study to detect a mean difference of 12.5 ml per year between the treatment groups in the degree of change in the FEV₁, with a two-sided P value of 0.05 and a power of 85 percent, on the assumption that follow-up would be 90 percent complete and that the rate of adherence to the treatment protocol would be 50 percent. We defined satisfactory adherence as the use of six or more puffs per day, averaged over all study visits.

The primary study outcome was analyzed according to the intention-to-treat principle. Preliminary examination of the data indicated that the decline in FEV₁ was approximately linear. The data were fitted to a linear longitudinal random-effects model²⁴ to determine whether the treatment assignment altered the rate of decline in FEV₁. Secondary analyses with adjustment for base-line covariates,

including sex, age, smoking status, base-line lung function, and base-line bronchodilator response, were performed with use of a similar model with additional terms. The statistical analysis was performed with the SAS Proc Mixed procedure (SAS Institute).²⁵ Similar analyses were conducted for the FEV₁ before the use of a bronchodilator and the FVC before and after the use of a bronchodilator. Prespecified subgroup analyses performed with use of similar methods explored treatment effects according to sex and according to initial lung function, bronchodilator response, presence or absence of asthma diagnosed by a physician, airway reactivity, and presence or absence of wheezing at base line. We also examined the effect of treatment on the decline in FEV₁ within subgroups of participants with similar rates of adherence to the use of inhalers.

Interim analyses of outcome measures were presented to the monitoring board six times during the final three years of the trial.²⁶ No formal rules for stopping were adopted by the monitoring board, although the board did suggest consideration of halting the trial if the power of the study, conditional on the results of the interim analysis, fell below 15 percent, an event that did not occur.

The rates of health care use and of new or worsening respiratory symptoms were compared according to treatment group with use of the Wilcoxon rank-sum test. The dyspnea and wheezing scales and airway reactivity in response to methacholine were treated as ordered categorical variables. These variables were also compared by means of the Wilcoxon rank-sum test. Comparisons of overall and cause-specific mortality were performed with use of life-table methods and the log-rank test. Other quantitative variables were compared with use of the t-test.

We report quantitative base-line characteristics as means ±SD and outcome measures as means ±SE or as percentages within groups. The reported P values are two-sided, and the P values for comparisons of treatment groups have not been adjusted for multiple comparisons or interim analyses.

RESULTS

Base-Line Characteristics

A total of 1116 participants were enrolled, out of 1347 candidates who completed initial in-clinic screening. The most common reason for exclusion was failure to meet the pulmonary-function criteria. The mean age of the participants was 56 years at entry. In general, the two treatment groups were well matched with respect to base-line characteristics (Table 1). They had mild-to-moderate abnormalities of pulmonary function, with an FEV₁ before bronchodilator use of 64.1±13.3 percent of the predicted value. The triamcinolone group had slightly better base-line lung function. About 35 percent of the participants reported having daily cough and phlegm for three or more months during the previous year, and 41 percent reported some breathlessness. Ninety percent of the participants were smokers, with an average daily consumption of 23.5±12.7 cigarettes. Ten percent were former smokers.

Follow-up and Adherence

During follow-up, 90.7 percent of the pulmonary-function tests and 95.0 percent of the questionnaires were completed. The mean duration of follow-up was 40.0 months. At the final visit, we obtained questionnaire data from 96 percent of the participants and performed pulmonary-function tests in 92 percent. The rate of satisfactory adherence to the treatment proto-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 1116 STUDY PARTICIPANTS.*

CHARACTERISTIC	TRIAMCINOLONE (N=559)	PLACEBO (N=557)
Age (yr)	56.2±6.8	56.4±6.8
Female sex (% of participants)	36.0	37.9
Nonwhite race (% of participants)	6.3	4.1
FEV ₁ before bronchodilator use		
Liters	2.16±0.62	2.10±0.64
Percent of predicted value	64.9±13.5	63.4±13.2
FEV ₁ after bronchodilator use		
Liters	2.28±0.62	2.22±0.65
Percent of predicted value	68.5±12.8	67.2±12.7
Response to bronchodilator (% change)	6.5±7.3	6.8±7.7
FVC before bronchodilator use		
Liters	3.77±0.93	3.65±0.96†
Percent of predicted value	88.8±13.5	87.0±13.2‡
FVC after bronchodilator use		
Liters	3.92±0.92	3.79±0.96‡
Percent of predicted value	92.3±12.8	90.3±12.4§
Response to inhalation of methacholine (% of participants)¶		
Diluent alone	0.5	1.2
1 mg/ml	12.0	12.5
5 mg/ml	33.7	37.1
10 mg/ml	23.9	20.2
25 mg/ml	13.0	10.2
No response to any concentration of methacholine	17.0	18.8
Current smoking (% of participants)	90.5	89.8
Cigarettes per day (among current smokers)	22.9±12.2	24.2±13.3
Daily cough and phlegm ≥3 mo/yr (% of participants)	33.6	36.1
Daily cough or phlegm ≥3 mo/yr (% of participants)	56.2	60.7
Highest dyspnea level (% of participants)		
No dyspnea	60.3	58.4
Dyspnea while walking up a slight hill or hurrying	27.4	29.2
Walks more slowly than people of similar age	6.5	7.2
Stops while walking on level	1.1	1.1
Stops after walking 100 yd (91 m)	4.1	3.2
Too breathless to leave house	0.6	0.8
Highest wheezing level (% of participants)		
No wheezing	26.8	22.3
Wheezing with a cold only	19.0	18.9
Wheezing apart from a cold	29.3	31.8
Wheezing most days and nights	24.9	27.1
Illnesses diagnosed by a physician (% of participants)¶¶		
Asthma	9.7	7.7
Emphysema	5.9	9.2†
Chronic bronchitis	10.2	11.1

*Plus-minus values are means ±SD. Results of pulmonary-function tests are expressed at body temperature and standard pressure of saturated gas. Because of rounding, percentages may total more than 100. FEV₁ denotes forced expiratory volume in one second, and FVC forced vital capacity.

†P=0.04.

‡P=0.03.

§P=0.01.

¶Response to methacholine at a specified level is defined as a decrease in FEV₁ of at least 20 percent from the diluent level or, in the case of those with reactivity to the diluent alone, from the base-line level.

¶¶Percentages are based on information provided by patients.

col was 68.9 percent for the placebo group and 69.4 percent for the triamcinolone group, according to the participants' reports; the rates were 58.5 percent for placebo and 53.7 percent for triamcinolone, according to canister weights. Sixty-six participants (38 in the placebo group and 28 in the triamcinolone group) permanently discontinued the study drug. Twelve of these (4 in the placebo group and 8 in the triamcinolone group) stopped because of side effects, and 17 (12 and 5, respectively) stopped because their physicians prescribed an inhaled corticosteroid other than triamcinolone for treatment of their respiratory disease. Other reasons for discontinuation included difficulty in adhering to the regimen, perceived lack of efficacy, and the advice of their personal physician. During the trial, the smoking rates declined to 75.3 percent among those who were current smokers at the beginning of the trial and increased to 23.8 percent among those who were former smokers at the beginning of the trial. At the end of the study, 71.4 percent of all participants were smoking, and the percentage of smokers did not differ significantly between the treatment groups.

Pulmonary Function

There were no significant effects of treatment assignment on the decline in the FEV₁ or the FVC either before or after bronchodilator use (Table 2 and Fig. 1). The mean decline in the FEV₁ after bronchodilator use in the triamcinolone group was 44.2±2.9 ml per year, as compared with 47.0±3.0 ml per year in the placebo group (95 percent confidence interval for the difference, -11.0 to 5.4 ml per year) (Table 2 and Fig. 1). At base line the triamcinolone and placebo groups had similar airway reactivity in response to methacholine (Table 1). However, at 9 and 33 months, the triamcinolone group had less reactivity in response to methacholine than the placebo group (P=0.02 for both comparisons) (Table 2).

Symptoms and Respiratory Illness and Death

The incidence of respiratory symptoms over the preceding 12 months, as reported on the American Thoracic Society–Division of Lung Diseases questionnaire at the 36-month visit, did not differ significantly between the treatment groups, with the exception of dyspnea, which was more frequent in the placebo group (P=0.02) (Table 2). Unscheduled physicians' visits and hospitalization for respiratory conditions were less frequent in the triamcinolone group. There were no significant differences between the groups in the rate of visits to an emergency department (not resulting in hospitalization) for either respiratory or nonrespiratory conditions, or in the rate of all health care visits (visits to a physician, visits to an emergency department, and hospitalizations) for nonrespiratory conditions. Thirty-four participants (15 taking triamcinolone and 19 taking placebo) died dur-

ing the trial. Cancer was the most common cause of death. There was no significant difference between the treatment groups in overall mortality, but there were more deaths from cancers other than lung cancer in the placebo group (P=0.02). None of the eight quality-of-life aspects showed changes associated with treatment assignment except the score on the mental health subscale, which was slightly worse at 36 months in the triamcinolone group (decrease from base line, 2.3±0.6 vs. 0.1±0.7 on a scale of 100; P=0.03, without adjustment for multiple comparisons).

Side Effects

Thrush developed in five participants taking triamcinolone and in two taking placebo (P=0.26). Those taking placebo were more likely to report moderate or severe mouth irritation than those taking triamcinolone (2.3 percent vs. 1.1 percent per year, P=0.02). Those taking triamcinolone were more likely to report moderate or severe degrees of easy bruising than those taking placebo (0.8 percent vs. 0.4 percent per year, P=0.16). There were no significant differences between the groups in the number of participants reporting cataracts (122 taking triamcinolone and 114 taking placebo), diabetes, or myopathy. Technically satisfactory bone scans of the lumbar spine were obtained at base line, one year, and three years in 328 participants, and satisfactory scans of the femoral neck in 359 participants. After three years, those taking triamcinolone had a higher percentage decrease from base line in the bone density at the lumbar spine and the femoral neck than those taking placebo (Table 3). Increased bone demineralization was evident in both men and women (data not shown).

DISCUSSION

Our main finding is that the inhaled corticosteroid triamcinolone acetonide, given at a dose of 1200 μg per day, has no significant effect on the rate of decline in the FEV₁ in persons with mild-to-moderate COPD. Although we did not exclude those with asthma, we did exclude those who regularly used bronchodilators or corticosteroids. Thus, we effectively excluded people with symptomatic asthma. Other studies of the use of inhaled corticosteroids in patients with COPD have tended to show greater benefit in those whose disease has more asthma-like characteristics.²⁷ Our analyses of subgroups defined according to the degree of airway reactivity, severity of wheezing, and presence or absence of a diagnosis of asthma did not identify any group that benefited in terms of the decline in the FEV₁. Despite counseling to promote adherence to the use of inhalers, only slightly more than half the participants used the inhalers at a satisfactory level — a rate similar to that for patients with asthma for whom inhaled corticosteroids are prescribed.^{28,29} Although nonadherence may have obscured an effect of treatment, there was no clear ben-

TABLE 2. OUTCOME MEASURES.*

MEASURE	TRIAMCINOLONE	PLACEBO	P VALUE
Duration of follow-up (mo)	40.2±0.33	39.8±0.39	0.54
Change in FEV ₁ after bronchodilator use (ml/yr)	-44.2±2.9	-47.0±3.0	0.50
Change in adjusted FEV ₁ after bronchodilator use (ml/yr)†	-43.3±2.9	-47.2±2.9	0.34
Change in FEV ₁ before bronchodilator use (ml/yr)	-48.6±3.2	-49.9±3.2	0.78
Change in FVC after bronchodilator use (ml/yr)	-50.6±4.1	-42.3±4.1	0.16
Change in FVC before bronchodilator use (ml/yr)	-55.8±4.7	-51.0±4.7	0.47
Response to inhalation of methacholine at 9 mo (% of participants)‡			0.02
Diluent alone	0.2	1.5	
1 mg/ml	9.3	10.7	
5 mg/ml	35.4	41.0	
10 mg/ml	21.9	21.1	
25 mg/ml	12.9	10.7	
No response to any concentration of methacholine	20.0	15.0	
Response to inhalation of methacholine at 33 mo (% of participants)			0.02
Diluent alone	0.3	0.3	
1 mg/ml	9.6	12.1	
5 mg/ml	31.7	35.6	
10 mg/ml	22.1	25.2	
25 mg/ml	13.4	11.4	
No response to any concentration of methacholine	22.7	15.4	
Daily cough and phlegm ≥3 mo/yr at 36 mo (% of participants)	30.3	27.1	0.26
Highest dyspnea level at 36 mo (% of participants)			0.02
No dyspnea	68.2	61.5	
Dyspnea while walking up a slight hill or hurrying	20.8	22.7	
Walks more slowly than people of similar age	4.4	6.7	
Stops while walking on level	1.5	2.1	
Stops after walking 100 yd (91 m)	4.0	6.0	
Too breathless to leave house	1.1	1.0	
Highest wheezing level at 36 mo (% of participants)			0.74
No wheezing	33.6	34.8	
Wheezing with a cold only	21.6	19.2	
Wheezing apart from a cold	25.2	23.5	
Wheezing most days and nights	19.7	22.5	
No. of new or increased respiratory symptoms categorized as moderate or severe per 100 person-yr			
Difficulty breathing	11.0	15.4	0.05
Wheezing	5.6	8.6	0.005
Coughing	15.4	18.5	0.04
Chest tightness	5.4	6.4	0.43
Other breathing problems	3.6	5.2	0.06
Any breathing problem	21.1	28.2	0.005
No. of hospitalizations per 100 person-yr			
Respiratory conditions	0.99	2.1	0.07
Nonrespiratory conditions	8.76	9.5	0.54
No. of emergency department visits not resulting in hospitalization per 100 person-yr			
Respiratory conditions	1.3	1.0	0.36
Nonrespiratory conditions	2.8	4.0	0.17
No. of outpatient physician visits per 100 person-yr			
Respiratory conditions	1.2	2.1	0.03
Nonrespiratory conditions	15.7	17.8	0.52
Total no. of health care visits per 100 person-yr			
Respiratory conditions	3.5	5.3	0.09
Nonrespiratory conditions	27.3	31.3	0.29
Deaths (no. of participants)			
Due to cardiovascular disease	6	2	0.16
Due to lung cancer	5	4	0.74
Due to other cancer	2	10	0.02
Due to other or unknown cause	2	3	0.65
Total	15	19	0.49

*Plus-minus values are means ±SE. Because of rounding, not all percentages total 100. FEV₁ denotes forced expiratory volume in one second, and FVC forced vital capacity.

†FEV₁ has been adjusted for sex, age, base-line smoking status, response to bronchodilator, and FEV₁ as a percentage of the predicted value.

‡Response to methacholine at a specified level is defined as a decrease in FEV₁ of at least 20 percent from the diluent level or, in the case of those with reactivity to the diluent alone, from the base-line level.

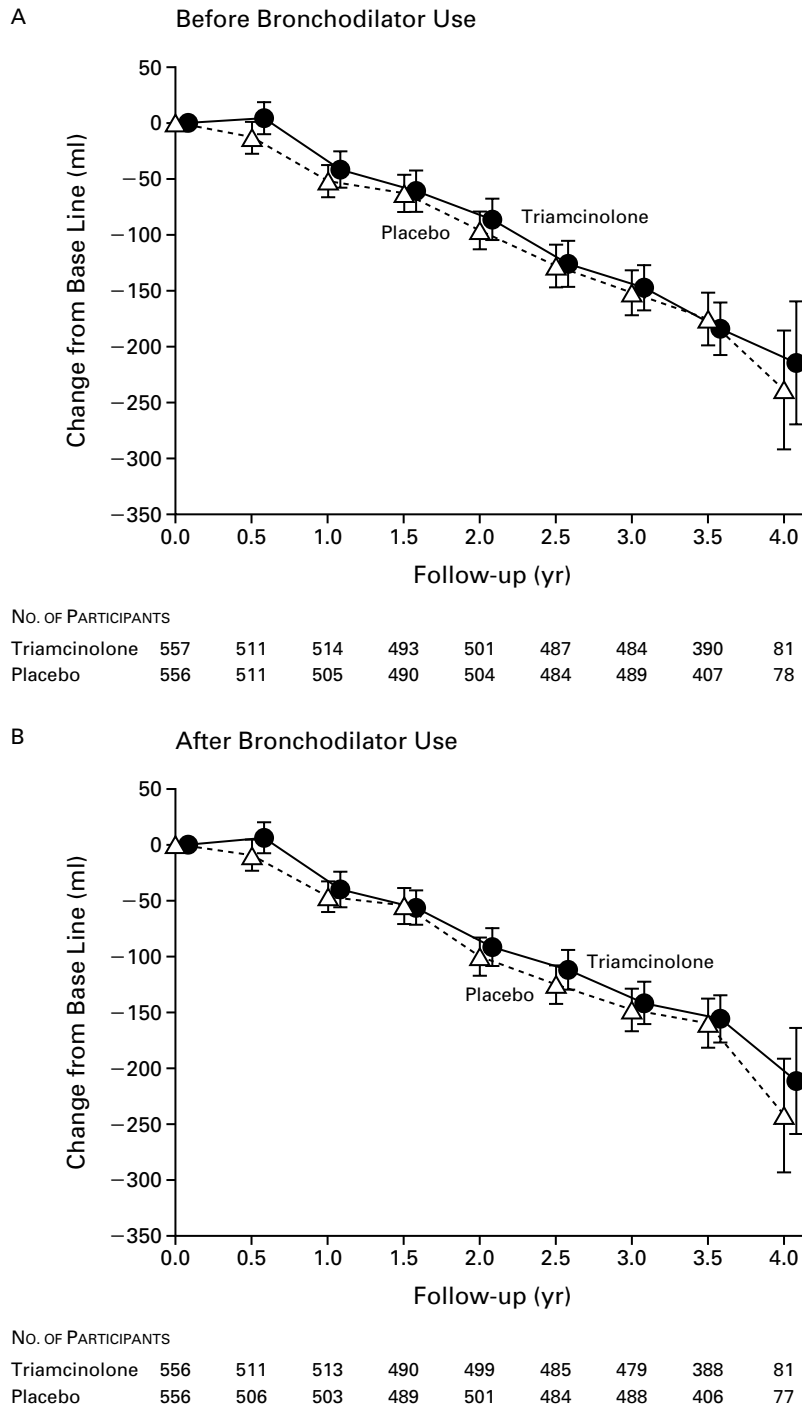


Figure 1. Decline in the Forced Expiratory Volume in One Second (FEV_1) before (Panel A) and after (Panel B) the Use of a Bronchodilator.

Because of the variable length of follow-up, not all participants were tested at the final two follow-up points. The error bars show ± 2 SE, which is approximately the same as the 95 percent confidence interval. There were no significant differences in the decline between the triamcinolone group and the placebo group. The decline in the FEV_1 before bronchodilator use was 49 ± 3 ml per year in the triamcinolone group and 50 ± 3 ml per year in the placebo group ($P=0.78$). The annual decline in the FEV_1 after bronchodilator use was 44 ± 3 ml in the triamcinolone group and 47 ± 3 ml in the placebo group ($P=0.50$).

TABLE 3. BONE MINERAL DENSITY OF PARTICIPANTS FOR WHOM ALL THREE MEASUREMENTS WERE AVAILABLE.*

MEASUREMENT	TRIAMCINOLONE	PLACEBO	P VALUE
Lumbar spine			
No. of participants	158	170	
Base line (g/cm ²)	0.988±0.013	0.979±0.013	0.60
12 mo (g/cm ²)	0.988±0.013	0.973±0.013	0.43
36 mo (g/cm ²)	0.985±0.013	0.988±0.014	0.89
% Change from base line to 36 mo	-0.35±0.33	0.98±0.36	0.007
Femoral neck			
No. of participants	176	183	
Base line (g/cm ²)	0.762±0.010	0.754±0.010	0.54
12 mo (g/cm ²)	0.760±0.010	0.751±0.010	0.53
36 mo (g/cm ²)	0.747±0.010	0.752±0.010	0.73
% Change from base line to 36 mo	-2.00±0.35	-0.22±0.32	<0.001

*P values were calculated by the t-test, with only the patients with technically satisfactory measurements at all three visits included. Results are expressed as means ±SE.

efit associated with triamcinolone among the participants with better adherence.

Although we found no significant association between triamcinolone use and chronic cough, production of phlegm, or wheezing, there was less dyspnea and fewer new or worsening respiratory symptoms in those who used triamcinolone (Table 2). Furthermore, there were fewer visits to physicians and hospitalizations for respiratory illnesses in the triamcinolone group.

It is unclear whether our findings can be extrapolated to other doses or formulations of inhaled corticosteroids. Although inhaled corticosteroids differ in absorption, metabolism, and potency, all have similar effects on airway inflammation and reactivity in patients with asthma. Triamcinolone treatment did reduce airway reactivity, suggesting that airway inflammation decreased. Reduced airway reactivity may have been responsible for the reduced incidence of respiratory symptoms and the lower rate of health care visits for respiratory conditions in this group. The reason that inhaled corticosteroids provide less benefit to patients with COPD than to patients with asthma is not clear; inflammation in COPD may not respond as well to corticosteroids or may not be as tightly linked to the clinical course of the disease.³⁰

Both men and women taking triamcinolone had more bone demineralization than those taking placebo. Whereas systemic corticosteroids have the greatest effect on bone in the first year of treatment, we found no effect until year 3, which suggests that prolonged monitoring for osteoporosis is necessary. We also found a trend toward more skin bruising in the triamcinolone group, which suggests a systemic effect on the fragility of capillaries. Although the decrease in the score on the mental-health subscale of the quality-

of-life questionnaire could be a result of the use of corticosteroids, this association is probably spurious, because the effect was small and inconsistent with the results for other subscales.

Several clinical trials have examined the long-term use of inhaled corticosteroids for COPD, with conflicting outcomes.^{14-16,31-37} Some have found short-term increases in lung function or improvement in symptoms, whereas others have not. A meta-analysis³⁸ of studies published from 1983 to 1996 found three acceptable studies enrolling a total of 183 patients with COPD and without asthma who were followed for two years or more. The meta-analysis concluded that inhaled corticosteroids slowed the decline in the FEV₁ but did not prevent exacerbations.

Four trials of corticosteroids in COPD have been published recently. An international study of the use of fluticasone in 281 people found an improvement in the FEV₁ and in symptoms over a period of six months.³⁷ A Danish trial of budesonide in 290 people with mild COPD did not find a reduction in the decline in the FEV₁ or a reduction in exacerbations over a period of three years.¹⁴ A three-year European study of 1277 smokers with mild-to-moderate COPD who were treated with budesonide found an initial improvement in the FEV₁ but no change in the subsequent decline in the FEV₁.¹⁵ A three-year British study of 751 patients with moderate-to-severe COPD who were treated with fluticasone showed initial improvement in the FEV₁, with a trend toward a slower decline in the FEV₁ and a reduction in exacerbations.¹⁶ Although smaller, short-term trials of inhaled corticosteroids have not shown improvement in airway reactivity,^{8,39} we found declines in airway reactivity in response to methacholine challenge at both 9 and 33 months.

In summary, we found that inhaled triamcinolone does not reduce the decline in the FEV₁ in patients with COPD but is associated with less severe airway reactivity and reduced respiratory symptoms. Triamcinolone use is also associated with loss of bone mineral density and increased skin bruising. In patients with COPD, therefore, the symptomatic benefits of inhaled corticosteroids must be weighed against the potential long-term adverse effects. We observed no effect on the long-term progression of the disease.

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APPENDIX

The principal investigators and senior staff of the clinical and coordinating centers and of the National Heart, Lung, and Blood Institute, and the members of the Data and Safety Monitoring Board, were as follows: *Case Western Reserve University, Cleveland* — M.D. Altose (principal investigator), S. Redline (co-principal investigator), C.D. Deitz, and K.J. Quinlan; *Henry Ford Hospital, Detroit* — M.S. Eichenhorn (principal investigator), W.A. Conway (co-principal investigator), R.L. Jentons, K. Braden, and M. Ketchum; *Johns Hopkins University School of Medicine, Baltimore* — R.A.

Wise (principal investigator), S. Permutt (co-principal investigator), C.S. Rand (co-principal investigator), M. Daniel, V. Santopietro, and K.A. Weeks; *Mayo Clinic, Rochester, Minn.* — P.D. Scanlon (principal investigator), A.M. Patel (co-principal investigator), J.P. Utz (co-principal investigator), D.E. Williams (co-principal investigator), G.M. Caron, and K.S. Miras; *Oregon Health Sciences University, Portland* — A.S. Buist (principal investigator), L.R. Johnson (Lung Health Study pulmonary function coordinator), V.J. Bortz, S.L. Persons, and H.A. Schueler; *University of Alabama at Birmingham* — W.C. Bailey (principal investigator), C.M. Brooks (co-principal investigator), L.B. Gerald, and L. Montiel; *University of California, Los Angeles* — D.P. Tashkin (principal investigator), A.H. Coulson (co-principal investigator), E.C. Kleerup (co-principal investigator), V.C. Li (co-principal investigator), M.A. Nides, I.P. Zuniga, and Y.E. Lee; *University of Manitoba, Winnipeg, Canada* — N.R. Anthonisen (principal investigator), J. Manfreda (co-principal investigator), S.C. Rempel-Rossum, and J.M. Stoyko; *Coordinating Center, University of Minnesota, Minneapolis* — J.E. Connett (principal investigator), M.O. Kjelsberg (co-principal investigator), M.T. Bollenbeck, K.J. Kurnow, T.C. Madhok, M.A. Skeans, and H.T. Voelker; *University of Pittsburgh, Pittsburgh* — R.M. Rogers (principal investigator), G.R. Owens (principal investigator) (deceased), E.M. Vitale, and M.E. Pusateri; *University of Utah, Salt Lake City* — R.E. Kanner (principal investigator), G.M. Villegas, C. Esplin, and R.S. Stayner; *Data and Safety Monitoring Board* — R. Bascom, J.R. Landis, J.R. Maurer, Y. Phillips, S.I. Rennard, J.K. Stoller, I. Tager, and A. Thomas, Jr.; *Mortality and Morbidity Review Board* — R.E. Hyatt (Mayo Clinic, Rochester, Minn.), C.T. Lambrew (Maine Medical Center, Portland), and B.A. Mason (Oncology Hematology Associates, Philadelphia); *National Heart, Lung, and Blood Institute, Bethesda, Md.* — S.S. Hurd (director, Division of Lung Diseases), G. Weinmann (project officer), and M.C. Wu (Division of Epidemiology and Clinical Applications).

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