

LONG-TERM TREATMENT WITH INHALED BUDESONIDE IN PERSONS WITH MILD CHRONIC OBSTRUCTIVE PULMONARY DISEASE WHO CONTINUE SMOKING

ROMAIN A. PAUWELS, M.D., CLAES-GÖRAN LÖFDAHL, M.D., LAURI A. LAITINEN, M.D., JAN P. SCHOUTEN, PH.D.,
DIRKJE S. POSTMA, M.D., NEIL B. PRIDE, M.D., AND STEFAN V. OHLSSON, PH.D.,
FOR THE EUROPEAN RESPIRATORY SOCIETY STUDY ON CHRONIC OBSTRUCTIVE PULMONARY DISEASE*

ABSTRACT

Background and Methods Although patients with chronic obstructive pulmonary disease (COPD) should stop smoking, some do not. In a double-blind, placebo-controlled study, we evaluated the effect of the inhaled glucocorticoid budesonide in subjects with mild COPD who continued smoking. After a six-month run-in period, we randomly assigned 1277 subjects (mean age, 52 years; mean forced expiratory volume in one second [FEV₁], 77 percent of the predicted value; 73 percent men) to twice-daily treatment with 400 µg of budesonide or placebo, inhaled from a dry-powder inhaler, for three years.

Results Of the 1277 subjects, 912 (71 percent) completed the study. Among these subjects, the median decline in the FEV₁ after the use of a bronchodilator over the three-year period was 140 ml in the budesonide group and 180 ml in the placebo group (P=0.05), or 4.3 percent and 5.3 percent of the predicted value, respectively. During the first six months of the study, the FEV₁ improved at the rate of 17 ml per year in the budesonide group, as compared with a decline of 81 ml per year in the placebo group (P<0.001). From nine months to the end of treatment, the FEV₁ declined at similar rates in the two groups (P=0.39). Ten percent of the subjects in the budesonide group and 4 percent of those in the placebo group had skin bruising (P<0.001). Newly diagnosed hypertension, bone fractures, postcapsular cataracts, myopathy, and diabetes occurred in less than 5 percent of the subjects, and the diagnoses were equally distributed between the groups.

Conclusions In persons with mild COPD who continue smoking, the use of inhaled budesonide is associated with a small one-time improvement in lung function but does not appreciably affect the long-term progressive decline. (N Engl J Med 1999;340:1948-53.)

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CHRONIC obstructive pulmonary disease (COPD) is characterized by a progressive and largely irreversible limitation of airflow. Cigarette smoking is the principal risk factor, and smoking cessation has been shown to decrease the rate of decline in lung function,¹ but the success of smoking-cessation programs is limited.²

The decline in lung function in patients with COPD is related to the presence of inflammatory

changes in the airways and lung parenchyma.³ Airway inflammation in COPD differs from such inflammation in asthma.⁴ Inhaled glucocorticoids are successfully used in asthma.⁵ Some studies have shown an effect of inhaled glucocorticoids on airway inflammation in COPD.⁶⁻⁹ In this study, we tested the hypothesis that regular treatment with the inhaled glucocorticoid budesonide would reduce the decline in lung function in patients with mild COPD who continued smoking.¹⁰

METHODS

Study Design

The study was a parallel-group, double-blind, placebo-controlled, randomized, multicenter study. Thirty-nine study centers in nine European countries (Belgium, Denmark, Finland, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom) participated. Approval from regulatory and ethics committees was obtained at all centers. All subjects gave written informed consent.

The study started with a run-in phase consisting of a three-month smoking-cessation program. All subjects received extensive information about the health hazards of smoking and a starting package of nicotine gum. More extensive smoking-cessation programs were encouraged. In subjects who did not stop smoking, this phase was followed by a three-month period during which compliance with inhaled medication was assessed with the use of a placebo-containing dry-powder inhaler with a hidden mechanical counter. Subjects who continued smoking and were at least 75 percent compliant with the recommended treatment regimen were randomly assigned to twice-daily treatment with either 400 µg of budesonide (Pulmicort, Astra, Stockholm, Sweden) or placebo from a dry-powder inhaler (Turbuhaler, Astra) for three years. The primary outcome variable was the change over time in forced expiratory volume in one second (FEV₁) after use of a bronchodilator.

Subjects

Persons 30 to 65 years of age were eligible if they were currently smoking at least five cigarettes per day and had smoked cigarettes for at least 10 years or had a smoking history of at least 5 pack-

From the Department of Respiratory Diseases, University Hospital, Ghent, Belgium (R.A.P.); the Department of Respiratory Medicine, University Hospital, Lund, Sweden (C.-G.L.); the Department of Medicine, University Central Hospital, Helsinki, Finland (L.A.L.); the Department of Epidemiology and Statistics, University of Groningen, Groningen, the Netherlands (J.P.S.); the Division of Respiratory Disease, University Hospital, Groningen, the Netherlands (D.S.P.); the Respiratory Division, Imperial College School of Medicine, Hammersmith Hospital, London (N.B.P.); and Clinical Research and Development, Astra Draco, Lund, Sweden (S.V.O.). Address reprint requests to Dr. Pauwels at the Department of Respiratory Diseases, University Hospital, De Pintelaan 185, B9000 Ghent, Belgium, or at romain.pauwels@rug.ac.be.

*The other participants in the study are listed in the Appendix.

years. The FEV₁ after the use of a bronchodilator had to be between 50 percent and 100 percent of the predicted normal value,¹¹ and the ratio of prebronchodilator FEV₁ to slow vital capacity had to be less than 70 percent. The increase in FEV₁ after the inhalation of 1 mg of terbutaline from a dry-powder inhaler had to be less than 10 percent of the predicted normal value. The change in FEV₁ between the end of the first three-month period of the run-in phase and the end of the second had to be less than 15 percent. Subjects with a history of asthma, allergic rhinitis, or allergic eczema and those who had used oral glucocorticoids for more than four weeks during the preceding six months were excluded. The use of inhaled glucocorticoids other than the study medication, beta-blockers, cromones, or long-acting inhaled β_2 -adrenergic agonists was not allowed.

Outcome Measures

Clinic Visits

The subjects were seen at the clinics every three months for spirometry and evaluation of smoking habits, compliance with medication, and safety-related variables. At selected centers, bone density was measured before treatment and after 6, 12, 24, and 36 months. Spine radiographs were obtained before and at the end of treatment.

Spirometry

Each center was supplied with a dry rolling-seal spirometer (model SMI III, Spirometrics, Auburn, Me.). The criteria of the American Thoracic Society¹² were used to determine FEV₁. All technicians attended an initial training session about the spirometer and the techniques to be used. Thereafter, regular visits were made by a monitor to check the calibration of the spirometer and to monitor the technique.

Spirometry was performed with the subject seated and wearing a nose clip. At recruitment and at the end of the study, slow vital capacity and FEV₁ were measured after at least 6 hours without inhaled bronchodilators and after 24 hours without oral bronchodilators. Three technically adequate and two reproducible maneuvers were required for the measurement of slow vital capacity and FEV₁. The largest values measured for slow vital capacity and FEV₁ were accepted, provided the second largest measurement was within 0.1 liter or 5 percent of the largest measurement. At all clinic visits, FEV₁ was obtained 15 minutes after the inhalation of 1 mg of terbutaline. Values were corrected for body temperature, ambient pressure, and water saturation and compared with the reference values of the European Community for Coal and Steel.¹¹

Safety Studies and Serum Analysis

At each visit, subjects were specifically asked whether they had received a diagnosis of glucocorticoid-related diseases or conditions such as hypertension, bone fractures, posterior subcapsular cataracts, myopathy, or diabetes in the preceding period. The number of skin bruises larger than 50 mm in diameter on the volar side of the forearms was noted. All other adverse events were recorded. Serious adverse events were those that were judged by the investigators to constitute a hazard or handicap to the subject.

Lateral thoracic and lumbar spinal radiographs were obtained with standard values for target-to-film distance and centering. The films were sent to a central evaluator who was unaware of the treatment received and were analyzed according to a standardized computerized protocol. The presence or absence of vertebral fractures at base line was determined by comparing each subject's base-line vertebral height ratio with reference values. A new fracture was defined as a reduction of at least 20 percent, with an absolute decrease of at least 4 mm, in the height of any vertebral body.¹³

We measured the bone mineral density of the lumbar spine (L2 to L4), the femoral neck, Ward's triangle, and the trochanter by dual-energy x-ray absorptiometry with a densitometer (model QDR-1000, Hologic, Waltham, Mass., or model DPX-L, Lunar, Madison, Wis.). The quality of the instruments was assessed before

and then monthly during the study by an external organization (Bona Fide, Madison, Wis.).

At randomization a blood sample was taken to test for IgE antibodies (Phadiatop, Pharmacia & Upjohn, Uppsala, Sweden).

Statistical Analysis

The sample size was based on an estimated standard deviation of the mean slope of the FEV₁ of 100 ml per year according to a previous study,¹⁴ a withdrawal rate of 40 percent, and a power of 80 percent to detect a difference in treatment response of 20 ml per year. Data on the randomized subjects were analyzed on an intention-to-treat basis. Student's *t*-test was used to compare treatment groups with respect to normally distributed variables, and the Wilcoxon rank-sum test was used for other variables. The χ^2 test was used to compare categorical variables. Differences were assessed with two-sided tests, with an alpha level of 0.05.

Several models were used to assess the serial changes in the variables of interest in the longitudinal data. First, the change in the variables over time was examined graphically. Unweighted and weighted individual regression lines of the variable of interest against time were used to estimate the slopes for each subject. The weighted regression lines were estimated by linear-mixed-effects modeling,¹⁵⁻¹⁷ with intercept and time in the model as both fixed and random effects. The slopes were calculated for various periods with stratification according to confounders, effect modifiers, or both, and were compared between treatment groups.

Piecewise linear regression analysis of FEV₁ against time within the budesonide group with a linear-mixed-effects model showed a best fit with one breakpoint after three or six months of treatment and fitted significantly better than a model that assumed linearity over the whole study period. The study period was therefore partitioned into two periods. The best fit was determined with the likelihood-ratio test for nested models or with Akaike's information criterion statistic.¹⁸

The data are presented either as absolute changes for all subjects who were in the study at a certain time or as unweighted slopes on the intention-to-treat population. These data are presented as median values, since their distribution was not normal.

RESULTS

From January 1992 to July 1993, 2157 potential subjects were recruited at the participating centers. Of these, 462 were found to be ineligible, and the remaining 1695 were enrolled in the smoking-cessation program, during which 169 (10 percent) stopped smoking. Of the remaining 1526 subjects, 1277 (84 percent) were compliant with the inhaled medication, continued smoking, and were randomly assigned to treatment (643 to placebo and 634 to budesonide). Nine hundred twelve subjects (71 percent) remained in the study for three years. During the study, 198 subjects were withdrawn because of non-compliance with the study procedures, 132 were withdrawn because of adverse events, and 35 were lost to follow-up, resulting in 176 withdrawals from the budesonide group and 189 from the placebo group. The reasons for withdrawal were similar in the two groups.

The base-line characteristics of the subjects in the two groups were similar (Table 1). The mean age was 52 years; 354 (27 percent) were women. The majority had been heavy cigarette smokers for many years and had mild, poorly reversible airflow limitation. The subjects had decreased their cigarette consumption during the six months before randomization (to a mean of 18.8 and 17.3 cigarettes per day, respec-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 1277 SUBJECTS AT ENROLLMENT.*

| CHARACTERISTIC | PLACEBO GROUP (N=643) | BUDESONIDE GROUP (N=634) |
|---|-----------------------|--------------------------|
| Age (yr) | 52.4±7.7 | 52.5±7.5 |
| Male sex (%) | 72.2 | 73.5 |
| Height (cm) | 173±9 | 173±8 |
| Weight (kg) | 73.9±13.6 | 74.7±13.2 |
| Prebronchodilator FEV ₁ (liters) | 2.54±0.64 | 2.53±0.64 |
| Prebronchodilator FEV ₁ (% of predicted) | 76.9±13.2 | 76.8±12.4 |
| FEV ₁ :SVC | 61.7±7.0 | 62.2±6.8 |
| Reversibility of FEV ₁ (% of predicted)† | 2.8±3.6 | 2.9±3.8 |
| Pack-years of smoking | 39.2±20.1 | 39.4±20.1 |
| Age when started smoking (yr) | 16.4±3.8 | 16.8±3.9 |
| Duration of smoking (yr) | 35.9±8.2 | 35.8±7.8 |
| Smoking at entry (no. of cigarettes/day) | 22.4±11.1 | 22.0±9.8 |
| Smoking at randomization (no. of cigarettes/day) | 17.3±10.5 | 18.8±11.1 |
| Positive Phadiatop test (%)‡ | 18.9 | 17.7 |

*Plus-minus values are means ±SD. FEV₁ denotes forced expiratory volume in one second, and SVC slow vital capacity.

†This variable was measured after the inhalation of 1 mg of terbutaline.

‡The Phadiatop test detects the presence in serum of IgE antibodies to a panel of common inhalant allergens.

tively, in the budesonide and placebo groups at randomization). An increasing number of subjects in both treatment groups reported quitting smoking during the treatment period. At the end of the study, approximately 10 percent of the subjects (9.1 percent of the budesonide group and 11.2 percent of the placebo group) reported not smoking during the previous six months.

Changes in FEV₁ Values after Bronchodilator Use over Time

The changes in postbronchodilator FEV₁ over time differed between the two treatment groups (Fig. 1). The placebo group showed a linear decline in FEV₁ over time, with a slope of -65 ml per year. In the budesonide group, the FEV₁ improved over the first six months at a rate of 17 ml per year, as compared with a decline of 81 ml per year in the placebo group (P<0.001). However, the slopes from nine months to the end of treatment were similar in the two groups: -57 ml per year in the budesonide group and -69 ml per year in the placebo group (P=0.39) (Table 2). During that period, 55 percent of the subjects in the placebo group had a rapid decline in FEV₁ (more than 60 ml per year), as compared with 49 percent of the subjects in the budesonide group (P=0.06). In the 912 subjects who completed the study, the median decline in FEV₁ over the three-year period was 140 ml in the budesonide group and

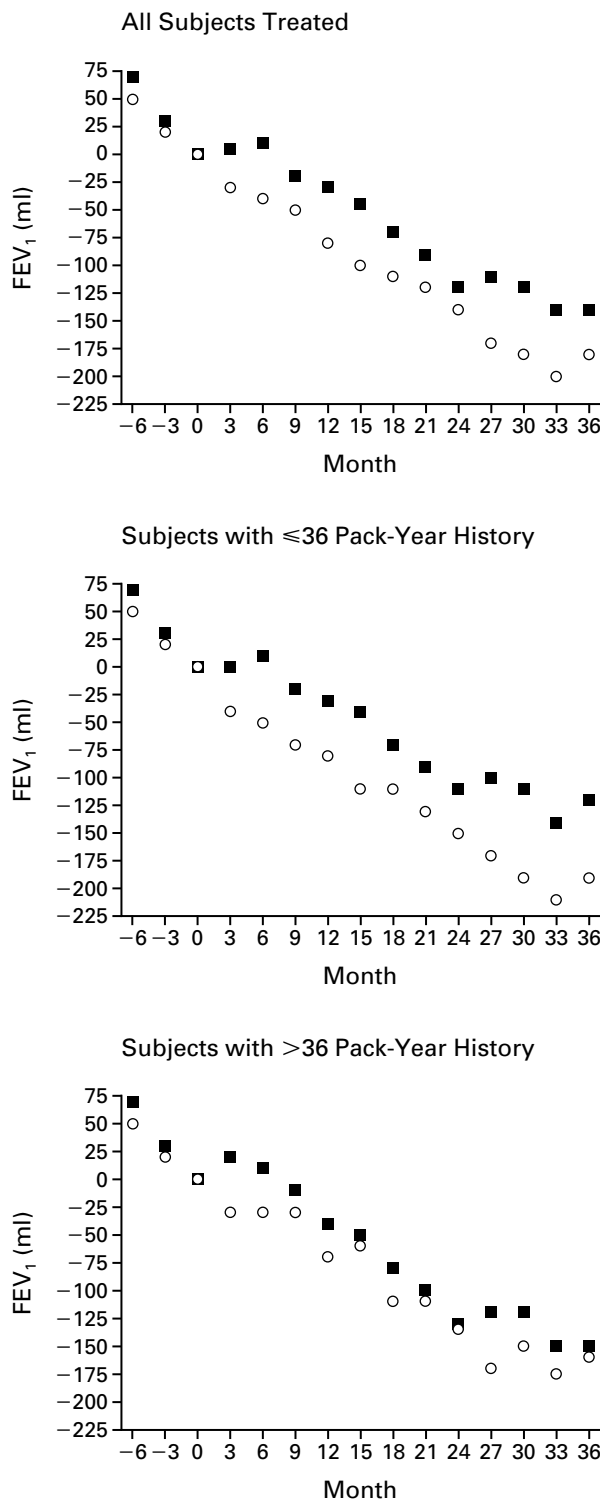


Figure 1. Median Change in Forced Expiratory Volume in One Second (FEV₁) as Compared with the Value at Randomization (Month 0) in the Placebo (○) and Budesonide (■) Groups.

The change is shown for all subjects treated, for subjects with a smoking history of 36 pack-years or less, and for subjects with a smoking history of more than 36 pack-years.

TABLE 2. CHANGE IN FEV₁ OVER TIME IN THE TWO TREATMENT GROUPS ACCORDING TO SMOKING HISTORY.*

| SMOKING HISTORY | TREATMENT PERIOD | CHANGE IN FEV ₁ † | | P VALUE |
|-----------------------------------|------------------|------------------------------|------------|---------|
| | | PLACEBO | BUDESONIDE | |
| | mo | ml/yr | | |
| All subjects | 0-6 | -81 | 17 | <0.001 |
| | 9-36 | -69 | -57 | 0.39 |
| Subjects with ≤36 pack-yr history | 0-6 | -90 | 30 | <0.001 |
| | 9-36 | -71 | -47 | 0.08 |
| Subjects with >36 pack-yr history | 0-6 | -70 | 0 | 0.57 |
| | 9-36 | -65 | -67 | 0.65 |

*Subjects were divided into two equal groups according to their smoking history at enrollment. The median was 36 pack-years. FEV₁ denotes forced expiratory volume in one second.

†The change is shown as the median of the FEV₁ slopes (in milliliters per year) during different parts of the study.

TABLE 3. SERIOUS ADVERSE EVENTS, DISCONTINUATIONS DUE TO ADVERSE EVENTS, DEATHS, AND GLUCOCORTICOID-RELATED SIDE EFFECTS.

| EVENT* | SUBJECTS WITH AT LEAST ONE ADVERSE EVENT | | P VALUE |
|---|--|------------------|---------|
| | PLACEBO GROUP | BUDESONIDE GROUP | |
| Serious adverse event — no. | 161 | 177 | 0.37 |
| Neoplasm | 25 | 21 | |
| Cardiovascular disorder | 32 | 28 | |
| Gastrointestinal disorder | 15 | 17 | |
| Respiratory disorder | 14 | 17 | |
| Musculoskeletal disorder | 16 | 14 | |
| Discontinuation due to adverse events — no. | 62 | 70 | 0.51 |
| Bronchial carcinoma | 10 | 7 | |
| Myocardial infarction | 5 | 5 | |
| Oropharyngeal candidiasis | 0 | 8 | |
| Coughing | 4 | 3 | |
| Urinary-bladder carcinoma | 4 | 3 | |
| Deaths — no.† | 10 | 8 | 0.64 |
| Glucocorticoid-related side effects | | | |
| Oropharyngeal candidiasis — no. | 10 | 31 | <0.001 |
| Pharyngeal irritation or hoarseness — no. | 28 | 46 | 0.04 |
| New lumbar fractures | | | 0.50 |
| No. of subjects | 3 | 5 | |
| No. of fractures | 3 | 8 | |
| Skin bruises — no. of subjects (%) | 27 (4) | 63 (10) | <0.001 |
| Cumulative no. of bruises | 42 | 364 | <0.001 |

*The five most frequent categories of serious adverse events and the five most frequent adverse events leading to discontinuation are listed. A serious adverse event was defined as an adverse event that was judged by the investigators to constitute a hazard or a handicap to the subject.

†The causes of death in the placebo group were bronchial carcinoma (3 subjects), sudden cardiac arrest (2), trauma (2), myocardial infarction (1), pulmonary embolism (1), and exacerbation of COPD (1). The causes of death in the budesonide group were bronchial carcinoma (3), myocardial infarction (2), sudden cardiac arrest (1), ruptured aortic aneurysm (1), and gastric carcinoma (1).

180 ml in the placebo group (P=0.05), or 4.3 percent and 5.3 percent of their respective predicted values (P=0.04).¹¹

Budesonide had a more beneficial effect in subjects who had smoked less (Fig. 1). Subjects with a history of smoking that was at or below the median of 36 pack-years at enrollment had a decrease in FEV₁ of 190 ml during placebo treatment and of 120 ml during budesonide treatment (P<0.001). The loss of FEV₁ in three years among subjects with more than 36 pack-years of smoking was 160 ml during placebo treatment and 150 ml during budesonide treatment (P=0.57). Analysis of FEV₁ slopes indicated that age, sex, base-line FEV₁, the presence or absence of serum IgE antibodies, and reversibility of airflow limitation had no significant effects on the outcome of treatment.

Similar percentages of subjects stopped smoking in both treatment groups; thus, stopping smoking did not explain the difference in the change in FEV₁ between the groups. When we compared the change in FEV₁ between the subjects who continued smoking at the same rate and those who either decreased their consumption by more than five cigarettes per day or stopped completely, we found a nonsignificant trend toward a beneficial effect in addition to the effect of budesonide.

Side Effects and Safety

More subjects in the budesonide group had skin bruising (Table 3). In total, 10 percent of subjects in the budesonide group and 4 percent of those in the placebo group had bruises during the study (P<0.001). The highest prevalence of bruises at any visit was 4.9 percent in the budesonide group and 1.4 percent in the placebo group.

Bone density was measured in 194 subjects (102 in the budesonide group and 92 in the placebo group). There was no significant change over time and no significant effect of treatment on bone density, except for a small but significant difference at the femoral trochanter in favor of budesonide. The yearly decline in the bone density of the trochanter was 0.38 percent in the placebo group and 0.04 percent in the budesonide group (P=0.02).

Two sets of radiographs of the spine were assessed in 653 subjects, 185 women and 468 men. At randomization, 43 in the budesonide group (13.4 percent) and 38 in the placebo group (11.5 percent) had at least one vertebral fracture. During the study, new fractures were unusual (three in the placebo group and eight in the budesonide group) and were similarly distributed (P=0.50).

Newly diagnosed hypertension, bone fractures, postcapsular cataracts, myopathy, and diabetes occurred in less than 5 percent of the subjects and were equally distributed between the groups (data not shown).

Serious Adverse Events

Serious adverse events were equally distributed between the groups (Table 3). Seventy patients in the budesonide group were withdrawn from the study, as compared with 62 in the placebo group ($P=0.51$). More subjects in the budesonide group withdrew from the study because of nonserious adverse events (35, vs. 23 in the placebo group), mainly oropharyngeal candidiasis (8 in the budesonide group and none in the placebo group) and local irritation of the throat or dysphonia (8 in the budesonide group and 2 in the placebo group).

DISCUSSION

Patients with COPD must always be advised and encouraged to stop smoking, and they should be offered treatment programs to facilitate smoking cessation. Nonetheless, some patients continue to smoke. In such patients with mild COPD, we found that the use of inhaled budesonide was associated with a small, one-time improvement in the FEV₁ after bronchodilator use, but that it did not appreciably affect the long-term progressive decline in lung function.

In the placebo group, the postbronchodilator FEV₁ declined by a median of 180 ml over a period of three years, the median slope being -65 ml per year. In the budesonide group, the median decrease in FEV₁ over the three years was 140 ml. The benefit of budesonide was limited to the initial six months of treatment. The beneficial effect of budesonide was greater in subjects with a history of fewer pack-years of smoking.

We studied subjects with mild COPD (mean FEV₁, 77 percent of the predicted value at base line) and a history of moderate-to-heavy cigarette smoking. These characteristics are similar to those of the patients in the Lung Health Study.¹ We attempted to exclude subjects with asthma by eliminating those with a history of asthma or any other atopic disease or with reversible airflow limitation. The presence or absence of IgE antibodies or the degree of reversibility of the airflow limitation did not influence the effect of budesonide. The decline in FEV₁ in the placebo group corresponds with findings in other long-term follow-up studies of COPD.^{1,19,20}

Most studies of glucocorticoid treatment in patients with COPD have examined short-term effects on airflow limitation.^{8,14,21-29} Results have been variable, but several studies have found an increase in FEV₁ after treatment with oral or inhaled glucocorticoids.^{21,22,25,29} The change in FEV₁ during the first months of our study is in line with these findings. Few studies have investigated the effect of glucocorticoid treatment on the long-term change in FEV₁ in patients with COPD. Two retrospective studies suggested that daily treatment with prednisolone might slow the progressive decline in FEV₁.^{30,31} In a small group of patients with COPD who had previously

been treated with bronchodilators, Dompeling et al.^{23,32} observed that daily treatment with 800 μ g of beclomethasone was associated with an increase in prebronchodilator FEV₁ during the first 6 months of treatment, followed by a decline during the remaining 18 months of the treatment period. In a two-year controlled study in a small group of patients with COPD, Renkema et al.¹⁴ did not find a significant effect of treatment with budesonide (800 μ g twice daily alone or in combination with 5 mg of prednisolone daily) on the decline in FEV₁.

We also examined the side effects of inhaled glucocorticoids in a group of middle-aged smokers. An increased prevalence of skin bruising in patients treated with high doses of inhaled glucocorticoids has been reported in cross-sectional studies.^{33,34} In our study, the budesonide group had an overall incidence of skin bruising of 10 percent, as compared with 4 percent in the placebo group, with a maximal prevalence at any time of 4.9 and 1.4 percent, respectively. There was also a higher incidence in the budesonide group of oropharyngeal candidiasis and local irritation of the throat, both well-known side effects of inhaled glucocorticoids. We found no significant effect of budesonide on bone density or the fracture rate, although all subjects were smokers and many of the women were postmenopausal — both of which are well-known risk factors for fracture.

The overall effect of three years of treatment with budesonide on FEV₁ in subjects with mild COPD who continued smoking was quite limited as compared with the beneficial effects of inhaled glucocorticoids in asthma. Although the base-line FEV₁ is significantly related to the prognosis of patients with COPD,²⁰ we cannot extrapolate our findings to assess the potential effect on disability or mortality. The small, overall, one-time beneficial effect on pulmonary function and the possibly more pronounced effect in the subgroup of those who had smoked less must be balanced against the risk of local and systemic side effects.

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APPENDIX

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Netherlands; and O. Johnell (evaluation of radiographs and dual-energy x-ray absorptiometric measurements), Sweden. The following Astra employees were involved in the study: G. Jönsson (study coordinator), H. Hansson (data entry), M. Broddé (safety evaluation), and H. Holm (bioanalysis). The national medical monitors were C. Wouters, A. Vandenbossche, M. Vilstrup, C. Olsen, T. Svahn, E.-L. Kiiskilä, C.M. Morelli, M. Schiassi, E. Tammeling, M. van den Dobbelsteen, V. van Driel-Schroijen, S. Holthe, R. Estiarte Navarro, E. Pellicer Thoma, A. MacLean, F. Glen, and E. Story.

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