Effects of Long-term Treatment With Corticosteroids in COPD*

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**Study objective:** To determine the effectiveness of treatment with corticosteroids in patients with COPD.

**Methods:** In this study, we investigated the effect of a 2-year treatment with corticosteroids on clinical symptoms and the decline of lung function in 58 nonallergic patients with COPD. Subjects were treated in a double-blind, randomized, placebo-controlled, parallel way with inhaled budesonide (bud), 1,600 μg/d; inhaled budesonide, 1,600 μg/d, plus oral prednisolone, 5 mg/d (bud+pred); or placebo (plac). Clinical assessment (history, physical examination, and spirometry) was carried out every 2 months. The rate of decline in FEV₁ was assessed by calculating individual regression coefficients from linear regression of FEV₁ on time for each subject.

**Results:** Eleven patients dropped out. The number of withdrawals due to pulmonary problems was significantly higher in the plac group (n=5 out of 18) than in the actively treated groups (n=2 out of 40). Treatment with corticosteroids significantly reduced pulmonary symptoms. Median decline of FEV₁ was 60 mL/yr in the plac group, 40 mL/yr in the bud+pred group, and 30 mL/yr in the bud group. Variation was large and differences were not statistically significant. No treatment effect was found on frequency or duration of exacerbations, possibly because of the high number of withdrawals due to pulmonary deterioration in the plac group. Treatment with a combination of inhaled plus oral corticosteroids was not more effective than inhaled corticosteroids alone. Morning plasma cortisol levels remained within the normal range in all three groups.

**Conclusions:** Our study shows beneficial effects of long-term daily treatment with inhaled corticosteroids in patients with COPD with regard to symptoms and drop out due to pulmonary problems. Lung function decline tends to decrease during treatment with inhaled corticosteroids. The observed effects are limited but warrant further studies on the effectiveness of corticosteroids in larger numbers of patients with COPD.

**Key words:** corticosteroids; budesonide; prednisolone; chronic obstructive pulmonary disease; FEV₁; exacerbations; symptoms

**Abbreviations:** bud=budesonide; bud+pred=budesonide+prednisolone; Cₛᵣ=specific compliance; F₁ᵢ=specific inspiratory volume in 1 s; MDI=metered-dose inhaler; PC₉₀=provocative concentration (causing a 20% fall of FEV₁ from baseline); plac=placebo; RV=residual volume; TLC=total lung capacity; VC=vital capacity

The beneficial influence of oral and inhaled corticosteroids is well established in patients with asthma. In contrast, their effectiveness in patients with COPD is controversial, especially during a stable phase of the disease. Short-term studies in patients with COPD, both with oral and inhaled corticosteroids, show little or no effect on the level of airflow limitation and the degree of airway hyperresponsiveness. Reports on the long-term effects of corticosteroids are scarce. Two retrospective studies, performed in patients with moderate to severe COPD, suggest that daily treatment with oral prednisolone may slow down the decline of FEV₁ in these patients. The corticosteroid effect appeared after 6 to 24 months of treatment, and only if a dose of at least 10 mg/d was given. Two recently reported studies with inhaled corticosteroids show a beneficial effect of long-term treatment on symptoms and FEV₁ in patients with COPD. Drawing firm conclusions from these studies, however, is not possible, as results may have been influenced by study design and/or patient selection. Both studies included atopic subjects and one study investigated only patients with COPD with a rapid fall in FEV₁ over time.

Results obtained thus far indicate the need for long-term trials in carefully selected patients with COPD with exclusion of patients with asthma. The need for such studies is emphasized by the fact that COPD is an important cause of morbidity and mor-
tality, and no therapeutic interventions except for smoking cessation and oxygen therapy have been shown objectively to improve the outcome of the disease.9-11

The aim of this study was to investigate whether a 2-year treatment with inhaled budesonide (bud) alone or in combination with a low dose of oral prednisolone (bud+pred) may influence clinical symptoms and the decline of lung function in patients with COPD.

**Materials and Methods**

**Patients**

Fifty-eight male patients were recruited from the pulmonary medicine outpatient clinic. All patients met the following selection criteria: (1) clinical diagnosis of COPD based on history (persistent dyspnea, mainly on exertion, without sudden attacks of dyspnea); (2) FEV₁ less than 80% of the predicted value; (3) residual volume (RV) greater than 100% of the predicted value; (4) specific compliance expressed as a percentage of the predicted value (CSP % pred) greater than 100% after bronchodilatation; when, however, air trapping (calculated as thoracic gas volume measured by body plethysmography minus functional residual capacity measured with an indicator gas)13 was greater than 1.5 L, CSP was allowed to be less than 100% of predicted; (5) no signs of allergy (negative skin test results, total serum IgE <200 U/mL, eosinophils in peripheral blood <250×10⁶/L); and (6) stable phase of the disease.

Excluded were patients older than 70 years at entry, patients receiving continuous corticosteroid therapy, and patients with severe concomitant disease, likely to interfere with the purpose of the study. All patients had α₁-antitrypsin serum levels within the normal range. All patients were smokers or ex-smokers. Smoking history was expressed as cigarette years (estimated average number of cigarettes smoked per day/number of years of smoking).

All ex-smokers had stopped smoking at least 1 year before entering the study, except for 1 patient who stopped 4 months before entry. For all patients except 1 (who stopped smoking during the study, after 14 months of treatment), smoking habits remained remarkably constant during the study. In the data analysis, the one patient that who stopped smoking during the study was considered as a continuous smoker.

**Study Design**

The study was performed according to a randomized, double-blind, placebo-controlled, parallel design. After a 3-month run-in period without any corticosteroid medication, baseline measurements were carried out and the patients were allocated blindly (by computerized randomization stratified for smoking) to 1 of the 3 following 2-year treatment regimens: (1) inhaled bud, 800 µg bid, plus placebo (plac) tablet once daily; (2) inhaled bud, 800 µg bid, plus oral prednisolone, 5 mg, once daily (bud+pred); and (3) plac inhalations bid plus plac tablet once daily. Bud (or plac inhalation) was inhaled from a metered-dose inhaler (MDI) through a 750-mL spacer (Nebuhaler; Astra, Rysswele, The Netherlands).

Initially, patients were characterized by measurement of slow inspiratory vital capacity (VC), FEV₁, and forced inspiratory volume in 1 s (FIV₁), before as well as after terbutaline (2 puffs of 250 µg per MDI), lung volumes, lung compliance, and provocative concentration (PC₂₀) of histamine. Prior to the study, all patients received a short course of oral prednisolone (40 mg/d, during 5 days) to assess corticosteroid responsiveness.

During the study, the patients were seen 12 times at 2-monthly intervals by the first or last author at the outpatient clinic. Clinical assessment at each visit consisted of history taking, physical examination, and spirometry. Using a standardized questionnaire, patients were asked about complaints of cough, sputum, wheeze, dyspnea, and frequency and duration of exacerbations. Patients were asked to rate the severity of dyspnea (scale, 0 to 5), dyspnea on exertion (scale, 0 to 3), early morning dyspnea (scale, 0 to 3), cough (scale, 0 to 3), and wheeze (scale, 0 to 3). A score of 0 was given if the complaint was absent; a higher value corresponded with increasing severity. A total complaint score (scale, 0 to 17) was calculated by adding up the scores from each question. The aerosol inhalation technique was checked. Drug intake was expressed as percentage of the prescribed intake by weighing of canisters and counting of tablets. Lung function measurements were always carried out on the same time of day, after the patients had refrained from bronchodilator therapy for at least 8 h. Adrenal activity was assessed before and at the end of the 2-year treatment by measurement of fasting morning plasma cortisol levels.

Throughout the study, patients were maintained on regimens of their usual bronchodilator medication, consisting of anticholinergics, β-agonists, theophylline, or a combination of these drugs. Theophylline was given in individually fixed doses, with regular measurement of theophylline serum levels (therapeutic range, 8 to 15 mg/L). Exacerbations (defined as conditions with increased complaints of dyspnea and/or cough and/or sputum production, with or without fever) were treated in a standardized way with a short course of oral prednisolone (35 mg/d decreasing by 5 mg/d to 0 mg in 7 days), which was combined with an antibiotic (amoxicillin or doxycycline) in case of a microbial infection; meanwhile, treatment with all other medication was continued. Patients were free to withdraw from the study at any time. Patients were withdrawn by the investigators in case of (1) three or more exacerbations within 3 consecutive months or (2) severe, progressive deterioration of lung function without infectious origin and failing to react to a short course of oral prednisolone therapy.

Informed consent was obtained from all participants. The study protocol was approved by the Medical Ethics Committee of the hospital.

**Methods**

Slow inspiratory VC, FEV₁, and FIV₁ were measured with a water-sealed spirometer (Lode B.V.; Groningen, The Netherlands). RV and total lung capacity (TLC) were determined by the closed-circuit helium dilution method. All volumes are expressed at BTPS. Static compliance was calculated from the volume-pressure diagram, obtained by means of an intraesophageal balloon. Predicted values for lung volumes and lung mechanics were those of the European Community for Coal and Steel.12 Airway hyperresponsiveness was measured with serial inhalations of histamine diphosphate solutions in doubling concentrations ranging from 0.5 to 32 mg/mL.14 The solutions were nebulized (Wiesbadener Doppelspray; Wiesbadener Inhalatoren-Vertrieb; Wiesbaden, Germany) with an airflow of 8 L/min. Nebulizer output was 0.12 mL/min, and particle size was less than 5 µm.15 The aerosols were inhaled for 30 s during tidal breathing in a semiclosed system, until a fall in FEV₁ of 20% or greater as compared with baseline, or until the highest concentration was reached. The provocation concentration of histamine required to produce a fall in FEV₁ of 20% (PC₂₀ value) was calculated from the log dose-response curve.

**Statistical Analysis**

Statistical analysis was performed (SPSS/PC+programs).16 Values are expressed as mean ± 1 SE or median (range), unless stated otherwise. The distribution of data was examined with the Kolmogorov-Smirnov test for normal distributions. Differences between patient groups with regard to initial characteristics, exacerbation frequency and duration, and symptom scores were subjected to parametric and non-parametric analysis of variance as appropri-
ate, with the above-mentioned parameters as dependent variables, and treatment group as the independent variable. Differences within patient groups were analyzed with paired t tests and Wilcoxon signed rank tests as appropriate. The rate of decline in FEV₁, expressed as FEV₁ slope, was assessed by calculating individual regression coefficients from linear regression of FEV₁ on time for each subject. Linear regression is considered to be sufficiently accurate over a study period of several years, and individual data plots of our patients had shown that the change of FEV₁ in time was best expressed by a linear function. Patients were excluded from the analysis if less than three FEV₁ measurements were available.

**RESULTS**

Fifty-eight nonallergic patients with clinical signs of COPD, all male, were included in this study. Their baseline characteristics are shown in Table 1. The three treatment groups did not differ significantly with regard to age, height, percentage of smokers, smoking history, initial FEV₁, degree of airflow limitation, reversibility on a regimen of terbutaline, degree of bronchial hyperresponsiveness, IgE serum levels, and number of peripheral blood eosinophils. Corticosteroid responsiveness, as assessed from the effect of a short course of oral prednisolone therapy, was low in each treatment group: mean FEV₁ percent predicted decreased with prednisolone. If response was expressed as an increase in FEV₁ of more than 20% from baseline, there were only three responders (Table 1). Sputum production was low (median production ≤5 mL/24 h) in all three groups. There was no significant difference in bronchodilator maintenance treatment among the three treatment groups (Table 1).

**Compliance**

Weighing of the canisters and counting of the tablets showed that patient compliance was very high. Mean use of tablets was not significantly different in the three treatment groups (100±1%, 98±1%, and 102±2% of the prescribed intake in the bud group, bud+pred group, and plac group, respectively), nor was mean inhalation of puffs (101±2, 99±2, and 106±2% of the prescribed intake in same groups, respectively). Compliance was not significantly different between patients who completed the whole study and withdrawals (mean use of tablets, 100±1% and 100±4% and mean intake of puffs 101±1% and 109±6% in completers and withdrawals, respectively).

**Withdrawals**

Eleven patients dropped out of the study. Two patients dropped out of the bud group (after 2 and 10 months of treatment, respectively), 4 out of the bud+pred group (after 2, 4, 12, and 14 months,
respectively), and 5 out of the plac group (after 4, 12, 16, 20, and 22 months, respectively). Withdrawals were divided into two categories: patients who dropped out because of pulmonary problems (frequent exacerbations and/or severe deterioration of lung function; seven patients) and those who dropped out irrespective of pulmonary condition (four patients). Three patients of the latter category dropped out because they were unable to combine the intensive, two-year study protocol with their usual daily activities; one patient withdrew because he was unwilling to take any medication.

The number of withdrawals due to pulmonary problems was highest in the plac group (five patients), intermediate in the bud+pred group (two patients), and lowest in the bud group (none). Treatment group and rate of withdrawal were not statistically independent ($\chi^2$, 6.68; df; 2; p=0.036).

Effect of Corticosteroid Treatment on Rate of Decline of FEV$_1$

For the whole group (n=58), the number of FEV$_1$ measurements obtained per patient during follow-up was distributed as follows: there were 29 patients with 12 FEV$_1$ measurements, the maximum obtainable number; 14 patients with 11 measurements; 5 with 10; 2 with 8; 1 with 7, 5, and 4, respectively; 3 with 2 measurements; and 2 patients with 1 measurement. A FEV$_1$ slope was calculated for each patient from whom three or more FEV$_1$ measurements had been obtained (n=53, Fig 1). Although the distribution of the FEV$_1$ slopes was not significantly different from a normal distribution (Kolmogorov-Smirnov test, p=0.12), skewness and large spread of the distribution resulted in considerable differences between median and mean values. In this case, median values are considered to represent more reliably the central tendency of the FEV$_1$ slopes within the subgroups.$^{17}$ In the plac group, median FEV$_1$ slope was $-60$ mL/yr (range, $-570$ to $+140$ mL/yr; n=17). In both actively treated groups, median slopes were less negative: $-30$ mL/yr (range, $-150$ to $+870$ mL/yr; n=20) in the bud group, and $-40$ mL/yr (range, $-340$ to $+60$ mL/yr; n=16) in the combination group. The extreme positive slope of $+870$ mL/yr was found in a patient who withdrew from the study after 10 months of treatment for personal reasons. He could not be classified as a prednisolone responder (reversibility while receiving a short course of prednisolone (Spearman rank correlation, $r=0.39$, p<0.01). This, however, was due to two (positive) outliers: leaving these outliers out, a weaker, nonsignificant correlation was found (Spearman rank correlation, $r=0.31$, p>0.05). No significant correlations were found between FEV$_1$ slope and age, baseline FEV$_1$, baseline PC$_{20}$ histamine, and reversibility on terbutaline, respectively.

In the group as a whole, median FEV$_1$ slope was significantly more negative in smokers than in ex-smokers (Mann-Whitney U test; p=0.049). In the whole group, FEV$_1$ slope was significantly correlated with the degree of reversibility while receiving an oral course of prednisolone (Spearman rank correlation, $r=0.39$, p<0.01). This, however, was due to two (positive) outliers: leaving these outliers out, a weaker, nonsignificant correlation was found (Spearman rank correlation, $r=0.31$, p>0.05). No significant correlations were found between FEV$_1$ slope and age, baseline FEV$_1$, baseline PC$_{20}$ histamine, and reversibility on terbutaline, respectively.

Figure 1. Individual FEV$_1$ slopes (calculated from linear regression of FEV$_1$ on time for each subject) per treatment group. Horizontal bars indicate the median value in the treatment group. Closed circles=smokers; open circles=ex-smokers.

Figure 2. Mean (±SE) symptom scores per treatment group prior to treatment, after 1 year of treatment, and after 2 years of treatment. For calculation of the symptom scores, see "Materials and Methods" section. Asterisk=p<0.05 as compared with symptom score prior to treatment.
Table 2—Frequency of Exacerbations*  

<table>
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<th>Prestudy Year</th>
<th>Study Year 1</th>
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<tr>
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<td>1</td>
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<tr>
<td></td>
<td>(0.6)</td>
<td>(0.7)</td>
<td>(0.4)</td>
</tr>
<tr>
<td>bud+pred</td>
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<td>1.5</td>
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<tr>
<td></td>
<td>(0.3)</td>
<td>(0.4)</td>
<td>(0.4)</td>
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<tr>
<td>placebo</td>
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<td>2</td>
<td>2.5</td>
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<tr>
<td></td>
<td>(0.3)</td>
<td>(0.5)</td>
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</table>

*Median (range) frequency of exacerbations (expressed as number of exacerbations per year) per treatment group during the year prior to the study, the first year of the study, and the second year of the study.

**Symptom Scores**  
Symptom scores were calculated at baseline and after 1 and 2 years of treatment for those patients who completed the whole study (n=47; Fig 2). In both actively treated groups, symptom scores after 1 and after 2 years of treatment were significantly lower as compared with baseline (paired t test, p<0.05), whereas in the placebo group, the observed scores after 1 and 2 years were not significantly different from baseline values (paired t test, p>0.05). In the actively treated patients, the decrease of symptoms after 2 years was significantly greater than in the placebo group (analysis of variance, p<0.05).

**Frequency and Duration of Exacerbations**  
The frequency and duration of exacerbations (expressed as number of exacerbations per year and number of exacerbation days per year, respectively) were calculated for those patients who completed the whole study (n=47). The frequency and the duration of exacerbations in the year prior to the study, the first year of the study, and the second year of the study were not significantly different in the three treatment groups (Tables 2 and 3). No significant changes in exacerbation frequency or duration during the study were observed within or among the three groups. Comparing all actively treated patients with the placebo group did not change the results.

Table 3—Duration of Exacerbations*  

<table>
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<th>Prestudy Year</th>
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<th>Study Year 2</th>
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<tbody>
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<td>bud</td>
<td>14</td>
<td>14</td>
<td>10</td>
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<tr>
<td></td>
<td>(0.84)</td>
<td>(0.46)</td>
<td>(0.45)</td>
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<tr>
<td>bud+pred</td>
<td>10</td>
<td>15</td>
<td>17.5</td>
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<tr>
<td></td>
<td>(0.168)</td>
<td>(0.35)</td>
<td>(0.41)</td>
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<tr>
<td>placebo</td>
<td>14</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>(0.42)</td>
<td>(0.54)</td>
<td>(0.57)</td>
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</table>

*Median (range) duration of exacerbations (expressed as number of exacerbation days per year) per treatment group during the year prior to the study, the first year of the study, and the second year of the study.

**Adrenal Activity**  
Mean fasting morning plasma cortisol levels at the beginning of the study were not significantly different in the three treatment groups (487±31, 551±37, and 503±38 nmol/L in the bud, bud+pred, and placebo group, respectively). After 2 years of treatment, mean plasma cortisol level had decreased significantly in the bud+pred group, whereas no significant change was observed in the bud or the placebo groups (levels at the end of the study being 331±35 nmol/L in the bud+pred group, and 467±26 and 513±32 nmol/L in the bud and placebo groups, respectively). Despite the decrease of plasma cortisol level in the combination group, mean level at the end of the study in this group was still within the normal range (reference value of our laboratory being 300 to 900 nmol/L).

**DISCUSSION**  
To our knowledge, our study is the first placebo-controlled prospective study on the effects of long-term treatment with inhaled and combined oral and inhaled corticosteroids in patients with COPD. It shows that treatment with corticosteroids causes a significant reduction of pulmonary symptoms. The decline of FEV₁ in patients actively treated with corticosteroids is smaller than in placebo-treated patients. Variation is large, however, and differences were not statistically significant. Withdrawal rate due to pulmonary problems is significantly higher in the placebo group than in the actively treated groups. No treatment effect is found on frequency or duration of exacerbations. Treatment with a combination of inhaled bud and oral prednisolone is not more effective than treatment with bud alone.

Studies performed thus far have shown that patients with COPD who benefit most from therapy with corticosteroids are often those with a substantial reversibility of airflow limitation,20-23 blood or sputum eosinophilia,24,25 atopy,23,26 and those with wheezing as a predominant symptom,22,26 that is, patients with signs and symptoms of asthma. The efficacy of treatment with corticosteroids is well established in patients with asthma. To assess the effectiveness of these drugs in patients with COPD, it is therefore essential to exclude patients with asthma. This is not a problem in the most extreme forms. Yet in clinical practice it is difficult, if not impossible, to exactly distinguish patients with asthma from those with COPD. In our study, potential candidates were not included in case of blood eosinophilia, positive skin test results, or increased serum levels of total IgE. The predominant complaint of our patients was dyspnea on exertion, and their airway obstruction was mostly irreversible. Moreover, treatment with a short course of oral prednisolone prior to the study showed the absence of significant steroid...
responsiveness in all but three patients. Thus, our results are obtained in a well-defined population of nonallergic patients with COPD.

Treatment with corticosteroids led to a significant reduction of respiratory symptoms. The same observation was made by Kerstjens et al. and Dompeling et al. Another beneficial effect of corticosteroids was reflected by the pattern of withdrawal. The number of withdrawals due to pulmonary problems, defined as severe progressive deterioration of lung function and/or the occurrence of frequent exacerbations, was higher in the plaq group than in the actively treated groups. Statistical analysis showed that withdrawal rate and treatment were not independent, suggesting that treatment with corticosteroids has a preventive effect on pulmonary deterioration and a favorable influence on “stability” in patients with COPD. We did not observe a treatment effect on frequency or duration of exacerbations. It has to be noted, however, that this observation may have been biased by the pattern of withdrawal. In the plaq group, with its highest number of withdrawals due to pulmonary problems, a higher frequency and a longer duration of exacerbations could be expected if it had been possible to include withdrawals in this analysis. Because only data from patients who completed the whole study could be analyzed, the real treatment effect may have been underestimated.

Median decline of FEV₁ was 60 mL/yr in the plaq group, corresponding well with values generally presented in the literature (40 to 100 mL/yr). Treatment with inhaled corticosteroids, alone or in combination with oral prednisolone, did not significantly improve the decline of FEV₁ in our study. This contrasts with the results of Kerstjens et al. and Dompeling et al. Both groups of investigators, studying the effects of long-term treatment with inhaled corticosteroids in patients with asthma and COPD, observed an improvement of FEV₁ in patients with COPD, although the effect was smaller in the COPD group than in the asthma group. The difference in results may be due to patient selection. In the study of Dompeling et al., only patients with a very rapid decline of FEV₁ were selected. Moreover, allergic patients were included in their COPD group. The latter was also the case in the study of Kerstjens et al. In both studies, the improvement of FEV₁ with long-term corticosteroid treatment occurred rather rapidly (within 6 months after start of treatment). An identical pattern of improvement is generally observed in patients with asthma. In our nonallergic patients with COPD, the change of FEV₁ over time was best represented by a linear decrease with divergent slopes in treated and control patients. This interesting difference may also have its origin in differences in patient population.

Studies performed thus far show that the beneficial effects of long-term treatment with corticosteroids in patients with COPD are small and less prominent than in patients with asthma. There is general agreement that the inflammatory processes involved in the pathogenesis of the two disease entities are different in nature, and it is not inconceivable that the inflammatory processes in COPD are less sensitive to the anti-inflammatory action of corticosteroids.

It may be that still higher doses of corticosteroids are needed in patients with COPD. Increasing the dose of inhaled corticosteroids or replacement by inhaled corticosteroids with stronger anti-inflammatory action are possible options. Increasing the dose of prednisolone is undesirable because of unacceptable side effects. It is important to start treatment in patients with COPD in a relatively early stage of the disease, as treatment effects may be lacking in far advanced disease when extensive and irreversible loss of functional pulmonary tissue has occurred. As COPD generally was rather mild in our population, we do not think that the moment of institution of therapy was too late to expect improvement in our patients. However, our results and those of other studies do not exclude the possibility that some patients with COPD benefit from corticosteroids, whereas others do not, maybe not even while receiving higher doses. Factors determining treatment response in patients with COPD are unknown, and our group was too small for such an analysis.

Measurement of plasma cortisol levels showed that treatment with bud, inhaled through a spacer, is safe: a 2-year treatment with a daily dosage of 1,600 µg did not cause a significant change in mean fasting cortisol level. Although there was a significant decrease of plasma cortisol level in the bud-pred cortisol level, mean level at the end of the study in this group was still within the normal range. Other tests of adrenal activity may be required to clarify the exact meaning of this observation.

Several studies have been undertaken to detect factors that may predict the decline of FEV₁ and hence the outcome of disease in patients with COPD. Factors detected thus far include age, initial FEV₁, and smoking. The latter is confirmed by our study: whether patients were treated with corticosteroids or not, FEV₁ declined more rapidly in smokers than in ex-smokers. This observation again stresses the importance of smoking cessation in these patients.

In conclusion, our study shows some beneficial influence of long-term daily treatment with inhaled bud in nonallergic patients with COPD. The beneficial effects are limited and the results give no definite answer to the question whether all patients with COPD should be treated with inhaled corticosteroids or not. The observed
effects, however, warrant further studies to clarify this issue in larger numbers of patients with COPD.

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