REVIEW ARTICLE

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# Benefits and Risks of Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease

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## Contents



## Abstract

Inhaled corticosteroids have a proven benefit in the management of asthma, but until recently, their efficacy in non-asthmatic, smoking-related chronic obstructive pulmonary disease (COPD) was not evidence-based. Airway inflammation in COPD differs from inflammation in asthma. Some studies have shown an effect of inhaled corticosteroids on airway inflammation in COPD but the clinical relevance of these results are unknown. Short-term studies evaluating the effect of inhaled corticosteroids in patients with COPD were associated with no or modest improvements in lung function. Data from five, long-term, large studies have provided evidence that prolonged treatment with inhaled corticosteroids does not modify the rate of decline of forced expiratory volume in one second

($FEV_1$) in patients with COPD and no reversibility to short-acting $\beta_2$-adrenoceptor agonists. $FEV_1$ was slightly improved over the first 6 months of treatment in two studies and lower airway reactivity in response to methacholine challenge has been observed. Improvement of respiratory symptoms and health status was also reported in three studies. A reduction in the rate of exacerbations was observed in two studies. No survival benefit was demonstrated in any study. The advantage of using inhaled, rather than oral, corticosteroids is a reduction in adverse effects for the same therapeutic effect, because inhaled corticosteroids rely more on topical action than systemic activity. The long-term safety of inhaled corticosteroids is not known in patients with COPD. However, topical adverse effects, and systemic effects such as a decrease of bone density of lumbar spine and femur and cutaneous adverse effects, have been reported in patients with COPD after 3 years of treatment with inhaled corticosteroids.

Worldwide, chronic obstructive pulmonary disease (COPD) is the twelfth most prevalent disease and the sixth most common cause of death, and represents a major public health problem.[1] The World Health Organization predicts that COPD will be the fifth most prevalent disease and the third most common cause of death worldwide in 2020.[2] A marked increase in cigarette smoking and environmental pollution in developing countries are the most important reasons for this probable dramatic increase in COPD. Patients with COPD have persistent airflow limitation that occurs at an accelerated rate. The rate of decline in the forced expiratory volume in 1 second ($FEV_1$) is 20 to 30ml per year in healthy individuals, but is 60 to 80ml per year in patients with COPD.[3] Smoking cessation is the only intervention that has been shown to effectively slow the decline in lung function of patients with COPD.[4] However, largely because of their efficacy in reducing inflammation in patients with asthma, inhaled corticosteroids have been assumed to play an important role in the treatment of COPD. Recent studies, in different countries, have shown that 41 to 50% of patients with stable COPD received inhaled corticosteroids,[5-7] although this treatment was not evidence-based. The aim of this review was to evaluate the benefits and risks of inhaled corticosteroids in patients with COPD from the analysis of both short-term and long-term controlled trials.

## 1. Rationale for the Use of Inhaled Corticosteroids

Tobacco smoking-induced chronic inflammation of the small airways is the main pathogenic mechanism in COPD.[8] The inflammatory response is characterised by bronchial and alveolar infiltration of neutrophils, and the presence of an increased number of macrophages and T lymphocytes. In contrast to asthma, where T lymphocytes are mainly CD4+, T lymphocytes are CD8+ in COPD.[9] The inflammatory mediators involved in COPD are less well defined than those in asthma. Levels of neutrophil-chemotactic mediators [such as leukotriene $B_4$ ($LTB_4$),[10] and the cytokines tumour necrosis factor-$\alpha$ (TNF$\alpha$) and interleukin (IL)-8[11]] are increased in the induced sputum of patients with COPD. Enhanced expression of intercellular adhesion molecule-1 (ICAM-1) and pro-inflammatory cytokines (IL-8, TNF$\alpha$) is also observed in airway epithelium of patients with COPD.[12,13] In contrast to the situation with asthma, the number of eosinophils is not increased in airways of patients with COPD, except during exacerbations.[14] Corticosteroids effectively modify eosinophilic airway inflammation in asthma,[15,16] but there is less evidence that they affect the neutrophilic inflammation and IL-8 production that predominates in COPD.[16] Recent studies have shown that alveolar destruction in people who smoke was negatively correlated with the number of neutrophils but was positively correlated with high num-

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ber of macrophages.[17] Macrophages may be activated by cigarette smoke and other irritants to release neutrophil chemotactic factors such IL-8.[18]

Modulation of bronchial hyper-responsiveness might be a target for corticosteroids. The role of nonspecific airway hyper-responsiveness in development of airway obstruction in patients with COPD has been discussed extensively over the past 30 years. Nonspecific airway hyper-responsiveness is present in 20 to 100% of patients with COPD,[19-25] and has been observed to accelerate the rate of decline in $FEV_1$ in some studies,[19-24] independently of age and cigarette smoking status. Inhaled corticosteroids have been shown to reduce morbidity, nonspecific airway hyper-responsiveness and airway obstruction in nonselected patients with airways bronchial hyper-responsiveness.[25] However, patients who did not smoke [equal number of patients who had never smoked (never smokers; n = 28) and patients who had a history of smoking (ex-smokers; n = 33)], who had allergies, or less than 40 years old benefited more from their treatment than patients who currently smoked (current smokers), did not have allergies or were over 40 years old.[25]

## 2. Evidence for a Biological Effect of Inhaled Corticosteroids in Stable Chronic Obstructive Pulmonary Disease (COPD)

Confalonieri et al.[26] found that the proportion of neutrophils present in induced sputum samples decreased and the proportion of macrophages increased over 2 months in patients with stable COPD treated with inhaled high dose inhaled beclomethasone dipropionate 1500 μg/day. These findings supported the results of Llewellyn-Jones et al.[27] who also treated patients with COPD with high-dose inhaled fluticasone propionate 1500 μg/day for 8 weeks. They showed a significant reduction in chemotactic activity and an increase in neutrophil elastase inhibitory capacity of the sputum sol phase of the patients with COPD in the fluticasone propionate recipients, compared with those who received placebo. These results would be consistent with a decrease in neutrophil recruitment and suggest that fluticasone propionate might reduce the speed of disease evolution by affecting the proteinase/antiproteinase balance. Similar results have been obtained in patients with diffuse bronchiectasis where intense neutrophil infiltration of the tracheobronchial tree occurs.[28] In a parallel-group, randomised, double-blind, placebo-controlled study evaluating the effects of 4 weeks of administration of inhaled fluticasone propionate (1000 μg/day) in 24 patients with bronchiectasis, a significant decrease in sputum leucocyte density, and in sputum levels of IL-1β, IL-8 and $LTB_4$ was found after fluticasone propionate treatment, whereas no change was observed with placebo.[29] In a preliminary short-term open-label study, Balbi et al.[30] observed a decrease in the total number of cells, the percentage of neutrophils and the level of IL-8 and myeloperoxydase in bronchoalveolar lavage fluid of 8 patients who were current smokers with COPD following 6 weeks of treatment with beclomethasone 1500 μg/day.

In some studies, however, inhaled corticosteroids were not shown to modify the local inflammatory indices. For example, Culpitt et al.[31] evaluated the effect of inhaled fluticasone propionate (1000 μg/day) on markers of activity of airway inflammation and protease/antiprotease imbalance in induced sputum. 13 current or ex-smokers (2/13) with COPD were treated for 4 weeks in a double-blind, crossover study. Induced sputum inflammatory cells, percentage of neutrophils and IL-8 levels were unchanged. Sputum supernatant elastase activity, matrix metalloproteinase (MMP)-1, MMP-9 and the antiproteases secretory leukoprotease inhibitor (SLPI) and tissue inhibitor of metalloproteinase (TIMP)-1 were similarly unaffected by treatment. The differences in selection of patients, dose and duration of treatment could explain the different results observed in these studies.[26-31]

Thus, it appears that although corticosteroids effectively modify eosinophilic airway inflammation in asthma,[15,16] evidence that they affect the neutrophilic inflammation that predominates in COPD is more limited. One possibility is that cor-

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ticosteroids are effective in patients with COPD who have eosinophilic airway inflammation.[32-34] Recently, the results of one study[35] suggested that eosinophilic airway inflammation (evaluated by sputum eosinophil count) may contribute to airflow obstruction and symptoms in some patients with COPD, and that the effects of corticosteroids could be explained by inhibition of this kind of inflammatory response in COPD. The possibility that sputum eosinophilia identifies a subgroup of patients who respond to long-term corticosteroids would be of great interest. A simple induced sputum test might allow inhaled corticosteroids therapy to be targeted to a population who would especially benefit. Further studies to evaluate the role of induced sputum as a predictor of long-term response to inhaled corticosteroids are needed.

## 3. Short-Term Studies Evaluating the Effect of Inhaled Corticosteroids in COPD

Clinical trials with small numbers of patients, 2 to 12 weeks duration, and different doses of inhaled corticosteroids, were associated with no or modest improvements in lung function.[16,36-43] Data are summarised in table I. In some of these studies, inhaled corticosteroids improved $FEV_1$ [37-39,41] and/or symptoms scores[36,39,42] but had no effect on bronchial responsiveness.[36,39,40,42,43] Differences in inclusion criteria existed in these trials and possibly some patients with asthma were not excluded. For example, a recent 4-week crossover, randomised study was designed to investigate the maximal obtainable benefits of high-dose inhaled corticosteroids in 30 patients with stable COPD. Patients had a mean $FEV_1$ of 0.97L (37% of predicted) and no history of asthma, and were randomised to beclomethasone (3000 μg/day) or placebo.[41] The mean increase in prebronchodilator $FEV_1$ was 0.11L during the beclomethasone period compared with the placebo period ($p < 0.001$). Five patients were identified as responders to inhaled corticosteroids (mean absolute improvement in $FEV_1$ of 0.34L, compared with 0.06L in the 25 nonresponders). However, the five responders also had a 12.5 ± 4% predicted increase $FEV_1$ in response to inhaled salbutamol (albuterol) 400μg, a result that clearly suggests an overlap with asthma.

Recently a small prospective, randomised, placebo-controlled, crossover trial evaluated the effect of inhaled corticosteroids withdrawal on lung function, exercise capacity, respiratory symptoms and quality-of-life in 24 patients with at least a 20 pack-year

**Table I.** Recent, randomised, placebo-controlled, short-term trials of inhaled corticosteroids in patients with chronic obstructive pulmonary disease

| Study | No. of patients | Drug/dosage (μg/day) | Length of follow-up (wks) | Study design | Results | | |
|---|---|---|---|---|---|---|---|
| | | | | | $FEV_1$ | Bronchial responsiveness[a] | Symptoms |
| Weir et al.[38] | 127 | BDP 1500 | 2 | Crossover | ↑ | ND | ND |
| Keatings et al.[16] | 13 | BUD 1600 | 2 | Crossover | 0 | ND | ND |
| Weir & Burge[39] | 105 | BDP 1500 or 3000 | 3 | Parallel | ↑ | 0 | ↑ |
| Wempe et al.[42] | 10 | BUD 1600 | 3 | Crossover | 0 | 0 | ND |
| Nishimura et al.[41] | 30 | BDP 3000 | 4 | Crossover | ↑[b] | ND | ↑ |
| Rutgers et al.[40] | 44 | BUD 1600 | 6 | Parallel | 0 | 0 | ND |
| Thompson et al.[37] | 30 | BDP 2000 | 6 | Parallel | ↑ | ND | ND |
| Auffarth et al.[36] | 24 | BUD 1600 | 8 | Parallel | 0 | 0 | ↑[c] |
| Watson et al.[43] | 14 | BUD 1200 | 12 | Crossover | 0 | 0 | 0 |

a To histamine or methacholine.

b With 5 objective responders.

c Reduction in dyspnoea.

**BDP** = beclomethasone; **BUD** = budesonide; **$FEV_1$** = forced expiratory volume in 1 second; **ND** = not done; **0** = no effect; ↑ = improved.

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tabacco history.[44] Mean $FEV_1$ was 1.61 ± 0.1L (47% of predicted). All the patients were receiving beclomethasone at the time of study entry and were randomised to either 6 weeks of placebo metered-dose inhaler (MDI) followed by 6 weeks of beclomethasone 84mg four times daily versus 6 weeks of beclomethasone followed by 6 weeks of placebo.

The study found a deterioration of lung function with a decrease in $FEV_1$ at 6 weeks while using the placebo inhaler (–0.1L, $p < 0.05$), an increase of dyspnoea scores with exercise after discontinuation of beclomethasone but no change in the distance walked during the 6-minute walk test, no change in the chronic respiratory disease questionnaire scores and a nonstatistically significant increased frequency in exacerbations of COPD.[44]

## 4. Long-Term Studies Evaluating the Effect of Inhaled Corticosteroids in COPD

Prior to 1998, few studies had evaluated the long-term effects of inhaled corticosteroids on clinical parameters and pulmonary function in patients with COPD. Some studies had no control group[45,46] and others included patients that possibly had asthma.[25,47] A study by Renkema et al.[48] and also a recent meta-analysis based on these studies,[49] suggested that inhaled corticosteroids reduced the decline of lung function.

Five major (more than 250 patients) recent randomised placebo-controlled trials have evaluated effects of long-term (6 months or more) inhaled corticosteroids in patients with COPD.[50-54] Patients with reversibility of airflow limitation after inhalation of short-acting $\beta_2$-adrenoceptor agonist ($\beta_2$-agonist) were carefully excluded from these studies. Data are summarised in table II.

### 4.1 International COPD Study Group

In a 6-month, double-blind, placebo-controlled study, Paggiaro et al.[50] showed significant improvements associated with fluticasone propionate compared with placebo in $FEV_1$, peak expiratory flow rate (PEFR), symptoms, exacerbation rates and 6-minute walking distance. 281 current (n = 138) or ex-smokers (142) with irreversible airway obstruction and a mean $FEV_1$ of 1.56L (57% of predicted) were randomly assigned to receive inhaled fluticasone propionate (1000 μg/day, via MDI, with a spacer device if desired) or placebo. Over the 6-month study period, 37% of the subjects in the placebo group and 32% of the active treatment group experienced at least one COPD exacerbation. This difference was not statistically significant ($p = 0.449$). Importantly, more patients had moderate or severe exacerbations in the placebo group than in the fluticasone propionate group (86 compared with 60%, $p < 0.001$). Morning PEFR (mean difference at 6 months of 15 L/min between the 2 groups in favour of fluticasone propionate, $p = 0.048$), $FEV_1$ (adjusted mean change of 0.15L in favour of fluticasone propionate at the end of treatment, $p < 0.001$), and respiratory symptoms (daily cough score and daily sputum volume in favour of fluticasone propionate, $p = 0.004$ and $p = 0.016$ respectively) were also improved in the fluticasone propionate group, compared with placebo. Patients on fluticasone propionate increased their 6-minute walking distance more than those receiving placebo (adjusted mean change of 27m and 8m, respectively; $p = 0.032$).

### 4.2 European Respiratory Society on Chronic Obstructive Pulmonary Disease Study

The European Respiratory Society on COPD (EUROSCOP) study[51] was a multicentre, double-blind, placebo-controlled trial that enrolled patients who were current smokers at the end of a 6-month run-in period with an initial phase of 3 months smoking-cessation programme.[51] Patients with an $FEV_1$ to slow vital capacity (SVC) ratio of less than 70%, $FEV_1$ between 50 and 100% of predicted normal value and less than 10% improvement in $FEV_1$ in response to 1mg inhaled terbutaline, were recruited.[51] Post-bronchodilator lung function tests were measured every 3 months for 3 years and adverse events were evaluated. The 1277 study participants had a mean baseline $FEV_1$ of 77% of predicted and were randomly assigned

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**Table II.** Recent, randomised, placebo-controlled long-term trials of inhaled corticosteroids in patients with COPD

| Study name | No. of patients | Study centres | Patient inclusion criteria | Drug/dosage (μg/day) | Length of follow-up (y) | Patient characteristics (mean) | | Results |
|---|---|---|---|---|---|---|---|---|
| | | | | | | $FEV_1$ (L; % pred.) | age (years) | |
| International COPD Study Group[50] | 281 | 13 European countries, New Zealand and South Africa | Current or ex-smokers (>10 pack-years) $FEV_1$ 35-90% pred. $FEV_1$ : FVC <70% Reversibility to 400 or 800μg salbutamol (albuterol) <15% | FP 1000 | 6 mo | 1.56; 57% | 63 | Small improvement in $FEV_1$, PEFR and 6 min walking distance. Equal numbers of overall exacerbation, but severe exacerbations reduced in FP group. Improvements in daily cough and sputum volume |
| EUROSCOP[a][51] | 1277 | 39 study centres, international study | Current smokers (5 cigarettes/day >10 years or >5 pack-years) $FEV_1$ 50-100% pred. $FEV_1$ : SVC <70% Response to terbutaline <10% | BUD 800 | 3 | 2.5; 77% | 52 | No change in rate of $FEV_1$ decline. Small initial improvement in $FEV_1$ during the first 6 mo of treatment. More beneficial effect in patients with history of smoking <36 pack-years than >36 pack-years |
| Copenhagen City Lung Study[52] | 290 | Single-centre study | $FEV_1$ : FVC <70% Reversibility to 1mg terbutaline or 10 days prednisolone <15% 4% of patients had never smoked | BUD 1200 for 6 mo then BUD 800 for 30 mo | 3 | 2.4; 86% | 59 | No change in rate of decline in $FEV_1$. No difference in rates of exacerbations and respiratory symptoms |
| ISOLDE[53] | 751 | 18 study centres in UK | $FEV_1$ >0.8L and <85% $FEV_1$ : FVC <70% Response to 400μg salbutamol <10% Current (38%) or ex-smokers | FP 1000[b] | 3 | 1.4; 50% | 64 | No change in rate of decline in $FEV_1$. No significant relationship between $FEV_1$ response to oral corticosteroid or inhaled FP. Lower decline of the respiratory health status and fewer of exacerbations (-25%) in patients who received FP |
| Lung Heath Study II[54] | 1116 | 10 study centres in US and Canada | $FEV_1$ 30-90% pred. $FEV_1$ : FVC <70% Current (90%) or ex-smokers | TRI 1200 | 40 mo | 2.3; 68% | 56 | No change in rate of decline in $FEV_1$. Lower airway reactivity in patients who received active therapy. Less respiratory symptoms and fewer visits to a physician because of respiratory illness in patients who received active therapy |

a Patients underwent a 6 months run-in period with 3 months smoking cessation programme.

b Patients received 2 weeks oral prednisolone.

**BUD** = budesonide; **EUROSCOP** = European Respiratory Society on COPD; **$FEV_1$** = forced expiratory volume in 1 second; **FP** = fluticasone propionate; **FVC** = forced vital capacity; **ISOLDE** = Inhaled Steroids in Obstructive Lung Disease Study; **PEFR** = peak expiratory flow rate; **pred.** = predicted; **SVC** = slow vital capacity; **TRI** = triamcinolone.

to treatment [643 to placebo and 634 to inhaled budesonide 800 μg/day via a dry-powder inhaler (DPI)]. Change in $FEV_1$ over the first 6 months of treatment was +17 ml/year in the budesonide group and –81 ml/year in the placebo group. However, the rate of decline of $FEV_1$ from 9 months to the end of treatment were similar in the 2 groups: –57 ml/year in the budesonide group and –69 ml/year in the placebo group ($p = 0.39$). Budesonide appeared to be more beneficial in patients who had smoked less. The loss of $FEV_1$ in 3 years among patients with a history of less than 36 pack-years of smoking was 120ml during budesonide treatment compared with 190ml during placebo treatment ($p < 0.001$). In patients with a history of more than 36 pack-years of smoking, the loss of $FEV_1$ was 150ml during budesonide treatment compared with 160ml during placebo treatment ($p = 0.57$).

### 4.3 Copenhagen City Lung Study

Vestbo et al.[52] used a randomised, double-blind, placebo-controlled design in a single-centre study, nested in a continuing epidemiological survey (the Copenhagen City Heart Study). Patients with an $FEV_1$ to forced vital capacity (FVC) ratio of less than 70%, $FEV_1$ reversibility in response to 1mg inhaled terbutaline of less than 15% of prebronchodilator $FEV_1$ and $FEV_1$ reversibility after 10 days of treatment with oral prednisolone of less than 15% of prebronchodilator $FEV_1$, were recruited. It must be noted that a history of cigarette smoking was not part of inclusion criteria. 290 individuals were included and randomly assigned to receive inhaled budesonide 1200 μg/day via a DPI for 6 months followed by budesonide 800 μg/day for 30 months or placebo. The main outcome measure was the rate of $FEV_1$ decline over 3 years. Mean baseline $FEV_1$ was 86% of predicted and 3.4% of patients had never smoked in the budesonide group (compared with 4.8% in placebo group). 40% of the study population stated that they had no breathing problems. Vestbo et al.[52] did not find a significant difference in the estimated rate of $FEV_1$ decline from a regression model between the inhaled corticosteroid group (–46 ml/year) and placebo (–49.1 ml/year, a difference of 3.1 ml/year, $p = 0.7$). There was no effect of active treatment on respiratory symptoms. Exacerbations of COPD were not significantly reduced in the budesonide group.

### 4.4 Inhaled Steroids in Obstructive Lung Disease Study

The Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study[53] was a multicentre, randomised, double-blind, placebo-controlled, parallel-group trial. Patients were current (38% throughout the trial) or ex-smokers who had a baseline $FEV_1$ after bronchodilator use of more than 0.8L (but less than 85% of predicted normal), an $FEV_1$ to FVC ratio of less than 70%, and airway reversibility, assessed as an improvement in $FEV_1$ as a response to salbutamol 400μg, of less than 10% of the predicted normal value. After an 8-week run-in period and a 2-week open-trial of oral prednisolone, if not contraindicated, patients were randomised to receive either inhaled fluticasone propionate 1000 μg/day via an MDI with an attached spacer device or placebo. Post-bronchodilator lung function tests were measured every 3 months for 3 years. The primary end-point was the decline (in ml/year) in post-bronchodilator $FEV_1$; other end-points were frequency of exacerbation, changes in health status, withdrawals because of respiratory disease, morning serum cortisol levels and adverse events. The 751 subjects randomly assigned to treatment had a mean post-bronchodilator $FEV_1$ of 50% predicted. Thus, this study included patients with more severe disease than other long-term studies.

The annual rate of decline in $FEV_1$ was similar in the placebo (–59 ml/year) and fluticasone propionate groups (–50 ml/year, $p = 0.16$). There was no significant correlation between patients' $FEV_1$ response to oral corticosteroids or inhaled fluticasone propionate. However, the rate of exacerbations (0.99 per year compared with 1.32 per year, $p = 0.026$) and withdrawals because of respiratory disease (19 compared with 25%, $p = 0.034$) were lower in the fluticasone propionate group. The rate of decline of respiratory health status was signifi-

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cantly reduced in the fluticasone propionate group compared with placebo (total respiratory questionnaire score of 3.2 units/year and 2.0 units/year, respectively; p = 0.004). The clinical relevance of this measure is difficult to interpret, although the authors suggest that fluticasone propionate delayed the average time for clinically important reduction in health status from 15 to 24 months.[54]

### 4.5 Lung Health Study II

The Lung Health Study II[54] was a multicentre, randomised placebo-controlled trial with current (90%) or ex-smokers (who had quit within the previous 2 years). Patients who had previously participated in or had been screened for the Lung Health Study I[4] and who had a baseline $FEV_1$ of 30 to 90% of the predicted value and an $FEV_1$ to FVC ratio of less than 70% were recruited. Lung function tests were measured every 6 months and methacholine bronchial provocation (to evaluate airway reactivity) was done initially and repeated at the 9-month and 33-month visits. The participants were followed from randomisation until a common ending date 4.5 years after the initiation of the trial. Patients were randomised to receive either triamcinolone (1200 μg/day via an MDI) or placebo. The primary end-point was the decline (in ml/year) in post-bronchodilator $FEV_1$; other endpoints that were assessed included respiratory symptoms, use of healthcare services and airway reactivity. The substudy of 412 patients who underwent bone density measurement at baseline and 1 and 3 years after the beginning of treatment is detailed in section 5.3.

The mean baseline post-bronchodilator $FEV_1$ of the 1116 study participants was 68% of predicted. The mean duration of follow-up was 40 months. The rate of decline of post-bronchodilator $FEV_1$ was similar in the 559 patients of the triamcinolone group (–44.2 ml/year ) and the 557 patients of the placebo group (–47ml/year). Fewer respiratory symptoms (21.1 per 100 person-years compared with 28.2 per 100 person-years, p = 0.005) and fewer visits to a physician because of respiratory illness (1.2 per 100 person-years compared with 2.1 per 100 person-years, p = 0.03) were observed in the triamcinolone group, compared with placebo. The number of hospitalisations for respiratory conditions tended to be lower in patients receiving triamcinolone compared with placebo (0.99 compared with 2.1, p = 0.07). Lower airway reactivity in response to methacholine challenge at 9 months and 33 months was also seen in the active treatment group (p = 0.02).

### 4.6 Summary of Long-Term Study Data

*In summary*, long-term inhaled corticosteroids do not slow the rate of $FEV_1$ decline in patients with COPD.[51-54] $FEV_1$ was slightly improved over the first 6 months of treatment[50,51] and lower reactivity in response to methacholine challenge was observed in one study.[54] Improvement of respiratory symptoms and health status were also reported.[50,53,54] A reduction of the rate of exacerbations was observed in the two studies with patients with more severe COPD.[50,53] These studies may have more relevance to clinical practice than those with patients with very mild or no disease. No survival benefit was demonstrated.

## 5. Adverse Effects of Inhaled Corticosteroids in COPD

Many studies have been conducted on the long-term efficacy and tolerability of inhaled corticosteroids in asthma but very few studies have been conducted in patients with COPD. Patients with COPD have very important characteristics that differentiate them from patients with asthma and from healthy individuals:

- patients tend to be elderly;
- patients have a significant smoking history, and some are current smokers;
- patients are relatively inactive because of dyspnoea and because of comorbidity (arteriopathy, coronary arthropathy);
- patients with severe COPD have a limited life expectancy;
- most patients with COPD have coexisting disease because of age and because of their common risk factor, tobacco.

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Local inflammation of the tracheobronchial tree and changes in the alveolar space could significantly influence the bioavailability of the drugs and their systemic adverse effects, as previously shown in people with asthma.[55] In these conditions, the best method to determine the true incidence of the different adverse effects of inhaled corticosteroids in this particular population is a large, prospective randomised study on long-term safety.

Safety data are available for 3 of the 5 long-term randomised, double-blind, placebo-controlled studies of inhaled corticosteroids in patients with COPD.[52-54]

Corticosteroid therapy may be associated with adrenal insufficiency, osteoporosis, peptic ulcer disease, cataract formation, dermal thinning, diabetes mellitus, hypertension, hyperadrenocorticism, psychosis, infections and myopathy.[56,57] Not all of these have been conclusively linked to corticosteroid therapy, but there is a reasonably strong association between corticosteroid use and these events. Nevertheless, the actual incidence and severity are not known. This is especially true for inhaled corticosteroids, which rely more on topical action, and might have different tolerability profiles according to the drugs available and to characteristics of the patients treated. The risk-benefit equation would probably be different in each population of patients with COPD according to the severity of their disease.

### 5.1 Topical Adverse Effects

The most common adverse effects associated with inhaled corticosteroids include dysphonia, hoarseness, sore throat and oropharyngeal candidiasis. They are caused by the deposition of corticosteroids in the oropharynx. The importance of these adverse effects depends on the dose, the duration and the delivering system used.

In the ISOLDE study,[53] 78 patients (21%) in the fluticasone propionate group had dysphonia or throat irritation compared with 43 patients (11.6%) in the placebo group. Candidiasis was found in 41 patients (11%) of fluticasone propionate group compared with 24 patients (6.5%) in the placebo group.

In the Lung Health study research group, patients who were receiving placebo were more likely to report moderate or severe mouth irritation than those who were taking triamcinolone (2.3% and 1.1%, respectively; $p = 0.02$).[54]

In EUROSCOP study, 31 (5%) patients in the budesonide group had oropharyngeal candidiasis compared with 10 (1.6%) patients in placebo group ($p < 0.001$); and 46 (7.3%) and 28 (4.5%) of patients, respectively, reported pharyngeal irritation or hoarseness ($p = 0.04$).[51]

### 5.2 Adrenal Suppression

Long-term administration of oral corticosteroids is known to have effects on hypothalamic pituitary-adrenal function. In adult patients with asthma, inhaled corticosteroids have been shown to modify biological indices of pituitary adrenal function with a clear dose-response relationship.[58] However, the clinical significance of these biological variations has not been demonstrated, although sporadic cases of adrenal insufficiency in patients with asthma have been reported in adults after withdrawal of inhaled corticosteroids.[59]

The adrenal function of patients with COPD was explored in the ISOLDE study.[53] Morning serum cortisol levels were measured at baseline and every 6 months during treatment for 370 patients in the placebo group and 372 patients in the fluticasone propionate group. A small decrease in mean cortisol levels ($p = 0.032$) was found in the fluticasone propionate group. Only 5% of the patients in the fluticasone propionate group had cortisol levels that were below the normal range, and none had clinical signs of hypoadrenalism.

Paggiaro et al.[50] reported that the mean serum cortisol level was significantly lower in the fluticasone propionate group than the placebo group at 6 months (345 nmol/L compared with 385 nmol/L, $p = 0.024$), but no clinical effect was observed. 19 patients (14% of 134 patients) in the fluticasone propionate group and 13 patients (11% of 116 patients) in the placebo group, had values

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below the normal range for cortisol at any time during treatment (p value not mentioned in the original paper).

### 5.3 Bone Effects

Osteoporosis is a major complication of chronic oral corticosteroid therapy. Inhaled corticosteroids are supposed to be better tolerated than oral corticosteroids and several studies have failed to identify increased incidence in bone fractures or lower bone density in patients with long-term inhaled therapy.[56,57] However, a recent 3 year prospective study showed that inhaled triamcinolone led to a dose related loss of bone at the hip in premenopausal women with asthma.[60] The importance of the risk for patients with COPD is difficult to determine because smoking and COPD themselves are risk factors for osteoporosis.[61,62] McEvoy et al.[63] conducted a cross-sectional study to evaluate the association between corticosteroid use and vertebral fractures. All the 312 study participants were men aged more than 50 years, with a diagnosis of COPD (with a $FEV_1$ to FVC ratio less than 70%) and a smoking history of at least 20 pack-years. They were evaluated according to their corticosteroid use: (i) never steroid users (NSU, n = 117) were defined as those men with no exposure to inhaled or systemic corticosteroids; (ii) inhaled steroid users (ISU, n = 70) were defined as those men using inhaled corticosteroid preparation for at least 6 months of the previous year; and (iii) systemic steroid users (SSU, n = 125) were defined as those men who have used prednisone for more than 2 weeks continuously in their lifetime. The percentage of participants with at least one vertebral fracture on radiographs of the thoracic and lumbar spine was 48.7% in the NSU group, 57.1% in the ISU group and 63.3% in the SSU group. Compared with NSU, the aged-adjusted odds ratio for vertebral fracture of SSU patients was 1.80, with a confidence interval (CI) of 1.08 to 3.07. It was weaker for ISU compared with NSU with an aged-adjusted odds ratio of 1.35 (CI of 0.77, 2.56). In addition SSU patients had more multiple and severe fractures than either NSU or ISU patients ($p < 0.05$). In this study the prevalence of vertebral fractures was higher than previously reported, regardless of whether or not they had been exposed to corticosteroids. Indeed, in the Framingham cohort the prevalence of vertebral fractures in older men (more than 84 years old) was 36%.[64] This result suggests that COPD by itself, independently of the use of corticosteroids, could raise the incidence of osteoporosis. It would be useful to include a control group of individuals without COPD to test this hypothesis.

Only one case report of osteoporotic fractures due to inhaled corticosteroids has been published; that of a 65-year-old man who had been taking inhaled beclomethasone for 7 years for the treatment of COPD.[65] Lumbar x-rays disclosed fractures of all the vertebral bodies from T8 through L5 and crush fractures of T8 and L2. The histomorphometric study evidenced an increased bone resorption. The investigations for the classical causes of osteoporosis in men were negative, and the serum levels of cortisol and corticotropin (adrenocorticotrophic hormone) were low and consistent with a diagnostic of treatment-induced hypercorticism.

Prospective double-blind, placebo-controlled studies are necessary to better analyse the actual risk of osteoporosis during long-term inhaled corticosteroid therapy in patients with COPD.

In the EUROSCOP study,[51] 912 patients were followed up for 3 years. Bone density was measured in 102 patients from the budesonide group and in 92 patients from the placebo group. No significant effect of budesonide on bone density was observed, aside from a small but significant difference in density at the femoral trochanter, in favour of budesonide. Systematic x-rays of the spine were performed in 653 patients. At randomisation 43 (13.4%) patients from the budesonide group and 38 (11.5%) patients from the placebo group had at least one vertebral fracture. During the study, 8 new fractures occurred in patients in the budesonide group and 3 in the placebo group. The difference was not significant ($p = 0.5$).

In the Lung Health Study,[54] 1116 patients with COPD were followed up, of which 559 received

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inhaled triamcinolone 1200 μg/day, for 3 years. Bone density in the lumbar spine and femur was measured in 412 patients (at baseline, and after 1 and 3 years). Only 328 technically satisfactory bone scans of the lumbar spine and 359 of the femoral neck were obtained. For femoral neck, the percentage of change from baseline to 3 years later was –2.00 ± 0.35% in the triamcinolone group and –0.22 ± 0.32% in the placebo group ($p < 0.001$). For lumbar spine, the percentage of change was –0.35 ± 0.33% in the triamcinolone group and +0.98 ± 0.36% in the placebo group ($p = 0.007$). After 3 years of treatment, both men and women taking inhaled corticosteroids had more bone demineralisation than placebo recipients; no difference was noted after 1 year of treatment. There were no data on the incidence of vertebral fractures.

In the ISOLDE study,[53] 751 patients were followed up for 3 years. The incidence of fracture was low (2% for corticosteroid recipients and 4.5% for placebo recipients) and similar to that reported in the EUROSCOP study.[51] Bone density was not measured.

After analysis of these three randomised, double-blind, placebo-controlled studies, new vertebral fractures were rare and occurred in less than 5% of the population studied. It is still difficult to determine if longer duration of high doses of inhaled corticosteroids may increase the risk of 'clinical' osteoporosis in the specific population of COPD, and if the use of triamcinolone bears more risk than other corticosteroids.

### 5.4 Ocular Effects

Long-term use of systemic corticosteroids is classically associated with an increased risk of developing posterior subcapsular cataracts but the association between inhaled corticosteroids and cataract remains uncertain.

In a retrospective case-control study, Garbe and Lelorier[66] reported an increased risk of cataracts and intra-ocular hypertension after 2 years of treatment with inhaled corticosteroids. 25 545 patients aged at least 70 years were studied; patients who were administered at least 1000 μg/day of inhaled corticosteroids (beclomethasone or budesonide), for at least 2 years, had an increased risk of cataracts and ocular hypertension [odds ratio (OR) = 3.40; 95% CI 1.49, 7.76].

Cumming et al.[67] conducted a cross-sectional study of 3654 people aged 49 to 97 years investigating common eye diseases. A higher prevalence of posterior subcapsular cataracts was found among the patients currently using inhaled corticosteroids (OR = 3.20; 95% CI 1.7, 6.0). The principal limitations of the study included some missing data on the actual exposure to inhaled corticosteroids and a difficulty assessing a temporal relation between the use of inhaled corticosteroids and the presence of cataract.

The incidence rate of cataracts among inhaled corticosteroid users of all ages has been measured in a retrospective cohort study.[68] 103 289 patients were identified in the inhaled corticosteroid cohort, and 98 527 people in the non-exposed cohort. The risk ratio (RR) of cataract was slightly increased among inhaled corticosteroids users (RR = 1.3, 95% CI 1.1, 1.5). The effects of both dose and duration of inhaled corticosteroids were evaluated and the risk ratio increase with both parameters. When the results were stratified by age, the effect of high doses of inhaled corticosteroids was more pronounced in the group older than 69 years and was not found for the group under 40 years.

In the EUROSCOP study, the incidence of cataract was less than 5% and equally distributed between the 2 groups of patients (budesonide compared with placebo) who had a mean age of 52 ± 8 years.[51] In the ISOLDE study, the incidence of cataracts was 1.3% in fluticasone propionate recipients compared with 1.9% in placebo recipients, who had a mean age of 64 ± 7 years.[53] In the Lung Health study, the incidence of cataracts was surprisingly high but equally distributed (22 compared with 20%) although the population was young (56 ± 7 years).[54]

*In summary*, there was no significant difference in the incidence of cataracts observed between the active treatment or placebo group in these prospective, long-term studies. However, the patients en-

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**Table III.** Glucocorticoid-related adverse effects in recent trials of inhaled corticosteroids in patients with chronic obstructive pulmonary disease

| Study | Patient numbers | COPD severity | Treatment (μg/day; duration) | Topical complication or infection | Effects on bone | Adrenal suppression | Glucose intolerance | Myopathy | Cutaneous effects | Ocular effects (post-capsular cataracts) |
|---|---|---|---|---|---|---|---|---|---|---|
| Pauwels et al.[51] | 1277 | Mild and moderate | BUD 800; 3 y | Oropharyngeal candidiasis: BUD = 31 of 634 patients PLA = 10 of 643 patients ($p < 0.001$) Local irritation or dysphonia: BUD = 46 of 634 patients PLA = 28 of 643 patients ($p = 0.04$) | Bone density: less yearly decline at femoral trochanter in BUD group New fractures: <5% of the patients and similarly distributed between the groups | ND | <5% of the subjects and similarly distributed between groups | <5% of the subjects and similarly distributed between groups | Bruises: BUD = 10% PLA = 4% ($p < 0.001$) | <5% of the subjects and similarly distributed |
| Lung Health Study[54] | 1116 | Moderate and severe | TRI 1200; 3 y | Local irritation: TRI = 1.1% PLA = 2.3% ($p = 0.02$) | Bone density: after 3 years higher % of decrease from baseline | ND | Diabetes mellitus: no difference | No difference | Bruises: TRI = 0.8% per year PLA = 0.4% per year ($p = 0.16$) | No difference TRI = 122 of 559 patients PLA = 114 of 557 patients |
| Burge et al.[53] | 751 | Severe | FP 1000; 3 y | Local irritation or dysphonia: FP = 78 (21%) PLA = 43 (11.6%) Candidiasis: FP = 41 (11%) PLA= 24 (6.5%) | Bone density: ND Fractures: FP = 9 of 372 patients PLA = 17 of 370 patients | Small decrease in mean cortisol concentrations compared with PLA ($p < 0.032$) but no signs of hypoadrenalism | ND | ND | Bruises: FP = 27 of 372 patients PLA = 15 of 370 patients | Cataracts: FP = 5 of 372 patients PLA = 7 of 370 patients |
| Vestbo et al.[52] | 290 | Mild | BUD 1200 for 6 mo then BUD 800 for 30 mo | Pneumonia: BUD = 16 of 145 patients PLA = 24 of 145 patients Viral infections: BUD = 34 of 145 patients PLA = 34 of 145 patients | ND | ND | ND | ND | ND | ND |

**BUD** = budesonide; **FP** = fluticasone propionate; **ND** = not done; **PLA** = placebo; **TRI** = triamcinolone.

rolled were under 75 years old and most of them were under 65 years old,[52-54] which is a low-risk population for cataracts. Moreover, longer periods of treatment may be needed to induce the development of cataracts.

### 5.5 Cutaneous Effects

A tendency to bruise easily is a well-known adverse effect of inhaled corticosteroids. One study in asthma has shown that its prevalence increase with age, dose and duration of use.[69]

Long-term studies in patients with COPD have also reported cutaneous adverse effects. In the EUROSCOP study,[51] bruisings were mentioned in 10% of patients taking budesonide compared with 4% in the placebo group ($p < 0.001$); in the Lung Health Study,[54] which enrolled younger patients, the annual incidence was 0.8% in the triamcinolone group compared with 0.4% in the placebo group ($p = 0.16$). In the ISOLDE study,[53] 7.3% of patients in fluticasone propionate group reported bruising, compared with 4% in placebo group (p value not mentioned in the original paper).

### 5.6 Other Adverse Effects

Cardiovascular and gastrointestinal disorders, myopathy and diabetes occurred with similar incidence in the EUROSCOP study,[51] and were not mentioned in other studies. None of the four recent long-term studies reported increased risks of respiratory or systemic infections in patients using inhaled corticosteroids (table III).

## 6. Conclusions

Long-term inhaled corticosteroids have beneficial effects in patients with COPD with reversibility of airways obstruction in response to short-acting $\beta_2$-agonists.[25] Data from five, long-term, large studies, provide evidence that prolonged treatment with inhaled corticosteroids does not modify the rate of decline of $FEV_1$ in patients with COPD without demonstrated reversibility to short-acting $\beta_2$-agonist.[51-54] $FEV_1$ was slightly improved over the first 6 months of treatment in two studies[50,51] and lower reactivity in response to methacholine challenge was observed in one study.[54] Improvement of respiratory symptoms and health status were also reported in three studies.[50,53,54] A reduction of exacerbations rate was observed in two studies.[50,53] No survival benefit was demonstrated in any of the studies.

A recent international workshop proposed that regular treatment with inhaled corticosteroids is only appropriate for symptomatic patients with COPD with a documented spirometric response to inhaled corticosteroids or in those with $FEV_1$ less than 50% predicted and repeated exacerbations requiring treatment with antibacterials or oral corticosteroids.[70] This is not supported by available literature data. Moreover, long-term effect of inhaled corticosteroids in severe patients with COPD with $FEV_1$ less than 30% has not been studied. Identification of patients with COPD who might benefit from long-term treatment with inhaled corticosteroids remains crucial. Results from the ISOLDE study[53] provide evidence that the use of a short course of oral corticosteroids is a poor predictor of the long-term response to inhaled corticosteroids of patients with COPD. Although eosinophilic airway inflammation could be affected by corticosteroids in some patients with COPD,[35] further studies are needed to assess sputum eosinophilia as a predictor of the long-term response to inhaled corticosteroids in patients with COPD. The long-term safety of inhaled corticosteroids has not been adequately studied in patients with COPD but topical adverse effects,[51,53,54] and systemic effects such as a decrease of bone density of lumbar spine and femur (for triamcinolone[54] but not for budesonide[51]), and cutaneous adverse effects,[51,53,54] have been reported after 3 years of treatment.

Nevertheless, smoking cessation remains the single most effective way to stop the progression of COPD and smoking cessation programmes must always be encouraged in these patients.

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