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INHALED STEROIDS FOR COPD?

A E Tattersfield, T W Harrison

Introductory articles

Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial

P S Burge, P M A Calverley, P W Jones, S Spencer, J A Anderson, T K Maslen on behalf of the ISOLDE study investigators

*Objectives: To determine the effect of long term inhaled corticosteroids on lung function, exacerbations, and health status in patients with moderate to severe chronic obstructive pulmonary disease. Design: Double blind, placebo controlled study. Setting: Eighteen UK hospitals. Participants: 751 men and women aged between 40 and 75 years with mean forced expiratory volume in one second (FEV_1) 50% of predicted normal. Interventions: Inhaled fluticasone propionate 500 µg twice daily from a metered dose inhaler or identical placebo. Main outcome measures: Efficacy measures: rate of decline in FEV_1 after the bronchodilator and in health status, frequency of exacerbations, respiratory withdrawals. Safety measures: morning serum cortisol concentration, incidence of adverse events. Results: There was no significant difference in the annual rate of decline in FEV_1 (p=0.16). Mean FEV_1 after bronchodilator remained significantly higher throughout the study with fluticasone propionate compared with placebo (p=0.001). Median exacerbation rate was reduced by 25% from 1.32 a year on placebo to 0.99 a year with fluticasone propionate (p=0.026). Health status deteriorated by 3.2 units a year on placebo and 2.0 units a year on fluticasone propionate (p=0.0043). Withdrawals because of respiratory disease not related to malignancy were higher in the placebo group (25% v 19%, p=0.034). Conclusions: Fluticasone propionate 500 µg twice daily did not affect the rate of decline in FEV_1 but did produce a small increase in FEV_1. Patients on fluticasone propionate had fewer exacerbations and a slower decline in health status. These improvements in clinical outcomes support the use of this treatment in patients with moderate to severe chronic obstructive pulmonary disease. (**BMJ** 2000;320:1297–303)*

Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial

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Background: Some patients with chronic obstructive pulmonary disease (COPD) respond to corticosteroid therapy. Whether these patients have different airway pathology from other COPD patients is unclear. We tested the hypothesis that response to prednisolone is related to the presence of eosinophilic airway inflammation. Methods: We did a randomised, double-blind, crossover trial. Patients who had COPD treated with bronchodilators only were assigned placebo and 30 mg prednisolone daily for 2 weeks each, in a random order, separated by a 4-week washout period. Before and after each treatment period, we assessed patients with spirometry, symptom scores, the chronic respiratory disease questionnaire (CRQ), incremental shuttle walk test, and induced sputum. Analysis was done by intention to treat. Findings: 83 patients were recruited, of whom 67 were randomised. The geometric mean sputum eosinophil count fell significantly after prednisolone (from 2.4% to 0.4%; mean difference sixfold [95% CI 3.1–11.4]) but not after placebo. Other sputum cell counts did not change. After stratification into tertiles by baseline eosinophil count, postbronchodilator forced expiratory volume in 1 s (FEV_1) and total scores on the CRQ improved progressively after prednisolone from the lowest to the highest eosinophilic tertile, compared with placebo. The mean change in postbronchodilator FEV_1, total CRQ score, and shuttle walk distance with prednisolone compared with placebo in the highest tertile was 0.19 L (0.06–0.32), 0.62 (0.31–0.93), and 20 m (5–35), respectively. Interpretation: Our findings suggest that eosinophilic airway inflammation contributes to airflow obstruction and symptoms in some patients with COPD and that the short-term

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*effects of prednisolone are due to modification of this feature of the inflammatory response. The possibility that sputum eosinophilia identifies a subgroup of patients who particularly respond to long-term treatment with inhaled corticosteroids should be investigated. (**Lancet** 2000;356:1480–85)*

Background

Chronic obstructive pulmonary disease (COPD) affects at least 600 000 people in the UK and is the fifth most common cause of death.[1] It results from the inflammatory response in the lung that follows exposure to noxious gases and particles, particularly cigarette smoke, and is characterised by progressive airflow obstruction that varies little from day to day or in response to bronchodilators or corticosteroids. The main pathological features are chronic inflammation and structural changes in the airways, and emphysema due to the body's inability to counter the increased release of protease enzymes from neutrophils and macrophages.

Although chronic airway inflammation is found in both asthma and COPD, the nature of the inflammation differs. Eosinophils, mast cells and lymphocytes, particularly CD4 T cells, predominate in asthmatic airways whereas the inflammatory response in COPD is dominated by neutrophils, particularly in more severe disease, with some increase in macrophages and lymphocytes, predominantly CD8 cells.[2]

Cigarette smoking is the most important cause of COPD, but only a relatively small proportion of smokers develop clinically important airflow obstruction. The rate of decline in forced expiratory volume in 1 second (FEV_1) is used to predict such patients, with values ranging from 30 ml/year or less in healthy subjects to over 100 ml/year in some heavy smokers.[3] There is marked heterogeneity in the FEV_1 response between smokers, however, showing that factors other than cigarette smoke help to determine the rate of decline in FEV_1, including other exogenous factors such as air pollution and occupational exposures. Endogenous factors are also important and include, at a mechanistic level, alpha-1 antitrypsin deficiency[4] and the MZ phenotype,[5] sputum neutrophilia,[6] plasma cortisol concentrations,[7] and a poor response to bronchodilators.[8]

Dutch workers in the 1960s suggested that patients with asthma and smokers with irreversible COPD shared a common allergic predisposition and bronchial hyperresponsiveness (known as the "Dutch hypothesis").[9] Several studies have looked at the association between smoking, rate of decline in FEV_1, and features of allergy and, although the findings are somewhat variable, in general smoking has been associated with higher eosinophil counts[10–13] and increased IgE levels.[12–14] A low FEV_1 and increased rate of decline in FEV_1 have also been associated with higher blood eosinophil counts and IgE levels and positive skin tests in some but not all studies.[12 13 15 16]

Bronchial responsiveness to non-specific stimuli such as histamine shows a close correlation with FEV_1 in subjects with COPD, reflecting the dependence of bronchial responsiveness measurements on airway calibre. After controlling for baseline lung function, however, bronchial responsiveness has been shown to predict the subsequent rate of decline in FEV_1 in several large studies.[17–19] There is still debate as to whether the increase in bronchial responsiveness is responsible for the accelerated fall in FEV_1, as anticipated by the Dutch hypothesis, or whether it mirrors the fall in FEV_1 because of its dependence on airway geometry. The latter suggestion was supported by a four year follow up of 27 patients with COPD in which both percentage predicted FEV_1 and bronchial responsiveness remained stable in patients who stopped smoking but both fell in parallel in those who continued to smoke.[20]

Any treatment that is able to reduce the rate of decline in FEV_1 will postpone the time when patients develop exercise limitation and symptoms. So far only smoking cessation has been shown to be effective.[21] Since the inflammatory response within the lung appears to be responsible for the damage to airways and alveoli, a treatment that reduced the inflammatory response would be expected to reduce the rate of decline in FEV_1. Since inhaled corticosteroids reduce inflammation in asthma, the question of whether they might reduce inflammation and hence the decline in FEV_1 in patients with COPD has been pursued.

The ISOLDE study

The study by Burge and colleagues (ISOLDE study, introductory article 1) is one of four placebo controlled studies[22–25] that have addressed the question of whether regular use of an inhaled corticosteroid can reduce the rate of decline in FEV_1 in patients with COPD. A meta-analysis of 95 patients in three small studies had given equivocal results.[26]

In the ISOLDE study the effect of a relatively large dose of fluticasone propionate (1000 µg/day) and placebo were compared in 751 subjects with moderately severe COPD (mean age 64 years, mean post-salbutamol FEV_1 1.4 l); the main end point was the rate of decline of post-bronchodilator FEV_1. Before starting treatment with fluticasone or placebo, subjects received oral prednisolone 0.6 mg/kg/day for 2 weeks and this was associated with a mean increase in post-bronchodilator FEV_1 of 60 ml. Three months into the study the mean post-bronchodilator FEV_1 had fallen below the pre-prednisolone baseline level in the placebo group but remained above the baseline level in the subjects taking fluticasone. However, there was no difference between the two groups in the decline in post-bronchodilator FEV_1 over the 3 years of the study. With respect to secondary end points, fluticasone was associated with a smaller decline in health status (assessed with the St George's respiratory questionnaire), fewer exacerbations (defined as a requirement for oral corticosteroids and/or antibiotics; 0.99 *v* 1.32/year), and fewer withdrawals due to non-malignant respiratory disease (19% *v* 25%).

These findings need to be compared with those in the other three studies that have looked at the effect of regular inhaled corticosteroid use on decline in FEV_1 in patients with COPD.[23–25] All four studies were large and of at least 3 years' duration, but there were some differences in methodology, patient entry criteria, and dose of inhaled corticosteroid as shown in table 1. Despite these differences, all four studies showed no benefit from the inhaled corticosteroid for the main end point—that is, rate of decline in FEV_1 (table 2). Both the ISOLDE and EUROSCOP studies showed a small initial increase in FEV_1 in the inhaled corticosteroid group but this was not seen in the other two studies. The inhaled corticosteroid had no significant effect on any secondary end point in the study by Vestbo *et al*,[24] but triamcinolone was associated with a small reduction in symptoms, unscheduled physician visits for respiratory problems, and bronchial responsiveness in the Lung Health Study.[25] Some systemic adverse effects were evident in three of the four studies—an increase in bruising,[22 23 25] a reduction in morning serum

Table 1 Details of four long term placebo controlled studies looking at effect of inhaled corticosteroids on decline in FEV_1

Study	No of patients, withdrawals (%), mean age, study duration (years)	Dose inhaled steroid (µg/day) and device	Mean FEV_1 (% predicted) post-bronchodilator	Bronchodilator reversibility in ml (% of baseline)*	Rate of decline in FEV_1 (ml/year)		Difference (95% CI)	p value
					Active	Placebo		
Burge *et al* (2000)[22]	751; 48%; 64; 3	Fluticasone 1000 µg; MDI + spacer	50	130† (10%)	50	59	–9 (–20 to 3)	0.16
Pauwels *et al* (1999)[23]	1277; 29%; 52; 3	Budesonide 800 µg; Turbuhaler	80	92‡ (3.6%)	57	69	–12 (no 95% CI)	0.39
Vestbo *et al* (1999)[24]	290; 30%; 59; 3	Budesonide 1200 µg for 0.5 years, 800 µg for 2.5 years; Turbuhaler	86	182‡ (7.7%)	46	49	–3 (–19 to 13)	0.7
Lung Health Study Research Group (2000)[25]	1116; 6%; 56; 3.3 (mean)	Triamcinolone 1200 µg; MDI	68	120† (6.65%)	44	47	–3 (–11 to 5)	0.5

FEV_1 = forced expiratory volume in one second; MDI = metered dose inhaler; CI = confidence interval.
*Calculated from FEV_1 values in papers (after salbutamol 400 µg† or terbutaline 1 mg‡).

cortisol levels in the ISOLDE study, and a reduction in bone mineral density in the Lung Health Study[25] but not in the EUROSCOP study.[23]

These four studies have therefore answered the primary question they addressed by showing clearly that inhaled corticosteroids do not have any worthwhile effect on the rate of decline in FEV_1 in patients with COPD. That leaves us with the secondary end points such as symptoms, measures of health status, and exacerbations. Of the two studies reporting symptoms, Vestbo *et al*[24] found no difference between groups whereas the Lung Health Study[25] found a small reduction in some symptoms, although this did not translate into any improvement in health status. In contrast, the ISOLDE study showed a smaller decline in health status in the inhaled corticosteroid group.[22] Exacerbations were reported in two of the studies, with no difference between groups in the Copenhagen study[24] compared with a reduction of 0.33 exacerbations/year with fluticasone in the ISOLDE study.[22] No reduction in exacerbations had been seen in an earlier 6 month study although their severity appeared to be reduced with fluticasone.[27]

There are some important differences between the ISOLDE study and the other three long term studies which might account for some of the differences in secondary outcomes. The dose of inhaled corticosteroid was high in the ISOLDE study and the patients were older and had more severe COPD; the placebo group therefore had more exacerbations and the study had more power to detect a difference in exacerbations. Bronchodilator reversibility was also fairly high, raising the question of whether the ISOLDE study included more subjects with an element of asthma, in addition to smoking related COPD, than the other studies. This also raises the question of whether there is a small subgroup of patients who might benefit in terms of reduced exacerbations and symptoms within the COPD population and whether such patients can be identified. The study by Vestbo and colleagues,[24] the most convincingly negative of the four studies, was the only one to exclude patients if they had a 15% increase in FEV_1 in response to a 10 day course of prednisolone.

Sputum eosinophils and response to prednisolone

Brightling *et al*[28] addressed the question of how the clinical response to prednisolone 30 mg daily for 2 weeks relates to sputum eosinophil count in patients with COPD, studying 67 patients (mean age 66 years, mean FEV_1 1.1 l) in a placebo controlled crossover study. Prednisolone was associated with a sixfold reduction in sputum eosinophil count (no change after placebo) and a significant increase in various end points, although the magnitude of these effects was small compared with placebo (150 ml for post-bronchodilator FEV_1; 12 m for shuttle walk distance). When patients were divided into tertiles according to their initial sputum eosinophil count the response to prednisolone was greatest in those with the highest eosinophil count, but the difference between the highest and lowest tertiles was still fairly modest (190 ml for FEV_1; 20 m for the shuttle test). The findings are similar to those seen in a previous smaller study.[29]

Although sputum eosinophilia has been associated with a greater bronchodilator response and increased exhaled nitric oxide (NO),[30] Brightling and colleagues discount misclassification by asthma to account for their findings since they went to some lengths to exclude patients with asthma,

Table 2 Effect of an inhaled corticosteroid in patients with COPD in four long term placebo controlled studies

	Burge et al[22] (ISOLDE)	Pauwels et al[23] (EUROSCOP)	Vestbo et al[24]	Lung Health Study[25]
Efficacy variables:				
Primary				
Decline in FEV_1	No effect	No effect	No effect	No effect
Secondary				
Symptoms	NR	NR	No effect	Fewer new symptoms, dyspnoea slightly less
Exacerbations	Reduced (25%)*	NR	No effect	NR
Quality of life	Smaller decline with ICS	NR	NR	No difference overall (1 of 8 worse with ICS)
Visits to A&E, physicians	NR	NR	NR	No effect on A&E or total visits, unscheduled doctor visits reduced by ICS
Bronchial responsiveness	NR	NR	NR	Reduced
Adverse effects:				
Morning cortisol	Reduced	NR	NR	NR
Bone mineral density	NR	No effect (n=194)	NR	Reduced (n=359)
Bruising	Increased (significance not given)	Increased	NR	Increased

NR = not reported; ICS = inhaled corticosteroid.
*Also reduced withdrawals for non-malignant respiratory conditions (19% *v* 25%).

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Learning points

- Inhaled corticosteroids do not alter the decline in FEV_1 in patients with COPD who continue to smoke.
- Inhaled corticosteroids may have a small effect on other clinical end points although the findings in different studies have not been consistent. Whether this is due to differences in drug, dose, or patients studied is not clear. Nor is it clear whether any such effect occurs in a small subgroup with some features of asthma.
- Patients with COPD who have eosinophils in their sputum but without other features of asthma are more likely to show a clinical response, albeit modest, to 30 mg prednisolone for 2 weeks. Whether such patients benefit from regular inhaled corticosteroids has not been shown.
- COPD is a large public health problem so any small benefits from inhaled corticosteroids in COPD need to be weighed carefully against potential adverse effects in this group of patients. Before their widespread use can be recommended, more information is needed on whether a high dose is needed to obtain benefit, the balance of beneficial and adverse effects in relation to dose, and whether a subgroup who benefit can be identified.
- These studies are a reminder that smoking cessation is the only intervention that has been shown to affect the underlying disease process in COPD and reduce the decline in lung function over time.

including anyone with respiratory problems during childhood. Furthermore, the range of eosinophil counts appears to have a reasonably normal distribution, suggesting that the patients were a fairly homogeneous group. A more likely explanation according to the authors is that smoking, whilst recruiting neutrophils to the airways, also recruits eosinophils but to a varying extent between patients. They also question whether COPD might start as an eosinophilic bronchitis, and that this is associated with a more rapid decline in FEV_1 and the development of COPD.

Brightling and colleagues question whether induced sputum might be used to identify patients who would be more likely to benefit from an inhaled corticosteroid. They showed an increase in FEV_1 with prednisolone as was seen at the start of the ISOLDE study, and it may well be that much of the small early increase in FEV_1 seen in the ISOLDE and EUROSCOP studies was due to a subgroup of patients with sputum eosinophilia. However, the patients in the ISOLDE study who responded to prednisolone did not show a reduced rate of decline in FEV_1 nor, as far as is reported, any other long term benefit. The measurement of sputum eosinophils cannot therefore yet be justified as a useful clinical measure. A further consideration would be whether the test's repeatability, which is reasonable when carried out in specialist centres, can be maintained if it were to be used more widely.

Clinical implications

The crucial question, coming back to the longer term studies, is whether inhaled corticosteroids should be prescribed to patients with COPD on the basis of the benefit seen in some of the secondary end points in the ISOLDE and Lung Health studies. The beneficial effects have not been entirely consistent between studies and are at best relatively modest, so they have to be balanced against the cost of treatment and the risk of systemic adverse effects from high dose inhaled corticosteroids in this group of patients. The duration of treatment will, in general, be less in COPD than in asthma, but patients with COPD are older and hence already at risk of problems such as cataracts and osteoporotic fracture. The risk is likely to be less with drugs that have a high first pass metabolism such as fluticasone and budesonide when compared with triamcinolone,[31] and this may explain why a reduction in bone mineral density was detected in the Lung Health study but not in the EUROSCOP study. Little is known about the extent of pulmonary absorption of different inhaled corticosteroids in patients with COPD.

Taken together, the studies suggest that there probably are some small benefits from the long term use of inhaled corticosteroids, but they also suggest that a high dose of inhaled corticosteroid may be required to achieve these effects and it is not clear whether it is only a subgroup of patients within the COPD population who benefit. Although the most convincing evidence of benefit comes from the ISOLDE study, this is still very modest, bearing in mind that publications invariably emphasise positive results and this study had the highest withdrawal rate. For example, exacerbations were only reduced by 0.33/year by fluticasone—that is, one exacerbation every 3 years. This compares with a reduction of 0.79 exacerbations/year with oral mucolytic drugs in a recent meta-analysis.[32] If a high dose of inhaled corticosteroid is required to achieve these small effects, it is difficult to justify their use for patients with mild to moderate COPD or, indeed, for the small reduction in frequency of exacerbations seen in the ISOLDE study. Can they be justified on the basis of the quality of life data from this study?[33] This is also difficult since the Lung Health Study, which was slightly larger, showed no benefit in quality of life measures and a small euphoriant effect from fluticasone cannot be excluded, particularly as the questionnaire was unable to detect a difference in health

status between patients who continued to smoke and those who stopped. It may be that patients with more severe COPD, those having more frequent exacerbations, and those with sputum eosinophilia would benefit more from an inhaled corticosteroid, but these questions need to be answered before drugs that are costly and may have adverse effects are recommended for widespread use.

COPD is a very large public health problem and more information is needed, particularly on the effect of different doses of inhaled corticosteroids on clinical end points, health status, and adverse effects so that any benefits can be placed in perspective.

Perhaps the most important message from these studies is that more effective treatment is needed for patients with COPD. Having said that, no drug can—or is ever likely to—produce anything like the beneficial health effects seen with smoking cessation.

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Conflict of interest: AET was on the safety committee for EUROSCOP and contributed patients to the study. The department has received support for studies from several pharmaceutical companies including GlaxoSmithKline and AstraZeneca.

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