Little Benefit from Inhaled Corticosteroids in COPD

Burge PS, Calverley PM, Jones PW, et al. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320:1297–303.

Study Overview

Objective. To determine the long-term effects of inhaled fluticasone on lung function, health status, and number of exacerbations in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Design. Randomized, double-blind, placebo-controlled trial.

Setting and participants. Men and women with nonasthmatic COPD between 40 and 75 years of age recruited from 18 hospitals in the United Kingdom. Participants' baseline forced expiratory volume in 1 second (FEV_1) after bronchodilator use was at least 0.8 L but less than 85% of the predicted normal, and the ratio of FEV_1 to forced vital capacity was less than 70%. Patients were excluded whose response to inhaled salbutamol during FEV_1 testing exceeded 10% of predicted normal, whose life expectancy was less than 5 years, and who used β blockers. Previous use of oral steroids was permitted, as were nasal and ophthalmologic corticosteroids and theophylline. Participants were enrolled between 1992 and 1995 and followed for 3 years.

Intervention. 990 eligible patients entered an 8-week run-in period after withdrawal from any inhaled or oral corticosteroids. 239 were withdrawn and 751 were randomized. Patients received either 500 μg of fluticasone (n = 372) or placebo (n = 370) twice daily. Preparations were dispensed through an inhaler and a spacer. Before this double-blind phase of the trial, subjects with no contraindications received oral prednisolone 0.6 mg/kg/day for 14 days to test whether the acute response could predict those patients who would respond best to long-term inhaled steroids. During the 3-year double-blind phase, patients were seen in a clinic every 3 months for spirometry, monitoring of exacerbations, and safety assessments.

Main outcome measures. The primary outcome was the rate of decline of FEV_1 values after bronchodilator use. Secondary outcomes included change in health status, as measured by the St. George's respiratory questionnaire [1]; frequency of exacerbations, defined as a worsening of respiratory status requiring oral corticosteroids, antibiotics, or both; patient withdrawals because of respiratory disease; adverse events (cardiac, malignant, and others); and morning serum cortisol concentrations. Patients were also questioned about their smoking status during each clinic visit. Participants were withdrawn from the study if they experienced more than 2 exacerbations requiring corticosteroids in any 3-month period.

Main results. Both intervention groups were matched in terms of age, smoking status, previous use of steroids, and FEV_1 values. Among patients who initially received 2 weeks of oral prednisolone, 4 in the fluticasone group and 5 in the placebo group withdrew from the study. A total of 212 fluticasone-group patients (57%) and 175 placebo-group patients (47%) completed the study.

A drop in the mean FEV_1 after bronchodilator use was observed during the run-in period. This decline was greater in patients who had been on inhaled corticosteroids (89 mL) compared with those who were steroid naive (47 mL). All patients who received oral steroids showed a significant improvement in their FEV_1 (60 mL ± 170 mL) after receiving bronchodilators. Subsequently, mean FEV_1 declined gradually in the fluticasone group, while values for the placebo group returned within 3 months to pre–oral steroid levels. The yearly rate of FEV_1 decline was slightly slower in the treatment group (50 mL) compared with placebo (59 mL) but was not statistically significant (P = 0.16). Interestingly, this trend was not affected by smoking status, age, sex, or initial response to oral corticosteroids. An analysis of covariance showed that FEV_1 in the fluticasone group was higher than in the placebo group by at least 70 mL at each time point ($P \leq 0.001$). Basically, the gain noted in the fluticasone group during the first 3 months was maintained during the duration of the study.

The rate of exacerbations was lower in the fluticasone group (0.99) compared with that seen in the placebo group (1.32) (relative reduction, 25%; P = 0.026). Respiratory questionnaire scores declined at a faster rate in the placebo group (2.0 units per year versus 3.2 units per year, P = 0.004), and more patients in the placebo group with-

drew for reasons not associated with malignancy (25% versus 19%, $P = 0.034$).

Conclusion

Fluticasone use did not affect the rate of decline of the FEV_1 in study patients, although those who received fluticasone had fewer exacerbations and a slower decline in their health status.

Commentary

Many studies have demonstrated that steroids are useful in asthma treatment, yet few studies have shown significant long-term benefits from either inhaled or oral steroids. Although 1 study by Niewoehner et al [2] suggested that oral steroids provide benefits in acute COPD exacerbation, the efficacy of chronic oral steroid use has not been definitively established. Studies examining inhaled steroids have been limited in scope. A recent trial by Vestbo and colleagues [3] failed to show any benefits associated with long-term inhaled steroid use; however, these investigators did not measure health status, and exacerbations were infrequent. Research by Pauwels et al [4] indicated that benefit of inhaled budesonide was very limited in patients who smoked and had COPD.

This study by Burge et al was well conducted and had no major flaws. The original make-up of the intervention groups was comparable, and the interventions themselves (with the exception of the treatment formulation) were the same. Drop-out rates in the treatment group were high but similar to those seen in the placebo group. One curious finding was that the rate of decline in FEV_1 after the first 3 months was similar in both groups. According to research results, responsiveness to oral steroids did not predict future response to inhaled fluticasone; thus, the reason why members of the fluticasone group showed a slower initial decline and then later exhibited the same rate of decline as those who took placebo remains unclear. The absolute risk reduction of events (eg, exacerbations) was not provided, which would have allowed the number needed to treat to be easily calculated. Further studies are needed to determine whether some subgroups of COPD patients would respond better to corticosteroids than others. For example, a slower rate of decline in FEV_1 may be achieved in nonsmokers or in patients with a higher initial FEV_1. Some inhaled corticosteroids may provide more benefits or have different effects on acute COPD exacerbations than others.

Applications for Clinical Practice

Inhaled steroids seem to have very little benefit in patients with COPD. These agents can improve quality of life and reduce rates of exacerbations but only to a small degree and along with minor side effects such as local irritation and oral candidiasis. Because of these findings, inhaled corticosteroid therapy for COPD cannot be fully endorsed at this time.

References

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