

## Clinical Update

### Inhaled corticosteroids and COPD

Burge PS, Calverley PMA, Jones PW, Spencer S, Anderson JA, Maslen TK, on behalf of the ISOLDE study investigators. 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.

#### Background

Although inhaled corticosteroid therapy has been well validated as the mainstay for the pharmacological management of asthma,<sup>1</sup> its role in the treatment of chronic obstructive pulmonary disease (COPD) remains less certain.

#### Question

What is the effect of long-term inhaled corticosteroid therapy on lung function, frequency of exacerbations and health status in patients with moderate to severe COPD?

#### Design

In this double-blind clinical trial, conducted in 18 hospitals in the United Kingdom, 751 patients with nonasthmatic COPD were randomly assigned to receive either fluticasone, 500 µg twice daily, or placebo. All subjects were given a 14-day course of prednisolone, 0.6 mg/kg daily, before randomization. Bronchodilator therapy with salbutamol or ipratropium bromide, or both, was continued during the trial, and the use of theophyllines and nasal and ophthalmic corticosteroids was also allowed. Subjects were seen quarterly for 3 years to measure their forced expiratory volume in 1 second (FEV<sub>1</sub>) and to record self-reported exacerbations, and every 6 months to measure their health status and serum cortisol levels. Exacerbations were defined as worsening respiratory symptoms requiring orally administered corticosteroids or antibiotics, or both, and health status was measured using the St. George's Respiratory Questionnaire, a disease-specific

instrument. Subjects were withdrawn if they reported more than 2 exacerbations in 3 months that required treatment with corticosteroids.

#### Results

The subjects were predominantly male (74%), and the mean age was 64 years. The mean number of cigarette pack-years was 44 at the time of randomization; about 40% of the subjects smoked throughout the trial. The mean FEV<sub>1</sub> was 1.4 L (50% predicted), in keeping with moderate to severe COPD. Each group demonstrated a slight improvement in FEV<sub>1</sub> (by about 60 mL) after taking prednisolone. In the placebo group, however, the mean FEV<sub>1</sub> fell within 3 months to pre-prednisolone levels and remained at least 70 mL lower than in the fluticasone group at each 3-month interval throughout the study period ( $p < 0.001$ ). In the fluticasone group, there was no correlation between prednisolone response and subsequent response to inhaled corticosteroid therapy. Over the study period, the rate of FEV<sub>1</sub> decline did not differ between the fluticasone and placebo groups (50 v. 59 mL/yr respectively,  $p = 0.16$ ). However, patients receiving fluticasone experienced 25% fewer exacerbations (0.99 v. 1.32 per year,  $p = 0.026$ ) and a significantly slower decline in health status ( $p = 0.004$ ). Withdrawal rates were high in both groups (fluticasone 43%, placebo 53%), but withdrawals related to respiratory disease (chiefly exacerbations of COPD) were significantly more frequent in the placebo group (25% v. 19%,  $p = 0.034$ ). Rates of adverse events were comparable, with a slightly higher incidence of hoarseness, throat irritation

and oropharyngeal candidiasis in the fluticasone group. Although serum cortisol levels were slightly decreased in that group as compared with the placebo group ( $p < 0.032$ ), the levels were no more than 5% below the lower limit of normal at any time.

#### Commentary

Results from this trial were similar to those from 2 previously published studies of long-term use of inhaled corticosteroid therapy for COPD: it showed a modest improvement in FEV<sub>1</sub> but no effect on the rate of FEV<sub>1</sub> decline.<sup>2,3</sup> However, this study differed from the others because, in addition to assessing physiologic end points, it measured exacerbation rates and quality of life. Although the study's chief limitation was the high withdrawal rates in both groups, it is conceivable that the higher rate of withdrawal in the placebo arm may have led to an underestimate of treatment effect.

#### Practice implications

Although this study confirms that long-term inhaled corticosteroid therapy does not alter the rate of decline of FEV<sub>1</sub> in COPD, it does provide evidence of modest clinical benefit in terms of health status and frequency of exacerbations. These findings add a measure of justification for what is fast becoming widespread practice in the management of patients with this common condition. — *Donald Farquhar*

The Clinical Update section is edited by Dr. Donald Farquhar, head of the Division of Internal Medicine, Queen's University, Kingston, Ont. The updates are written by members of the division.

## References

1. Boulet LP, Becker A, Bérube D, Beveridge R, Ernst P, on behalf of the Canadian Asthma Consensus Group. Canadian asthma consensus report, 1999. *CMAJ* 1999;161(11 Suppl):S24-7. Available: [www.cma.ca/cmaj/vol-161/issue-11/asthma/index.htm](http://www.cma.ca/cmaj/vol-161/issue-11/asthma/index.htm)
2. Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 1999;353:1819-23.
3. Pauwels RA, Lofdahl CG, Latinen LA, Schouten JP, Postma DS, Pride NB, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Pulmonary Disease. *N Engl J Med* 1999;340:1948-53.

## ACE inhibitors and high-risk patients

**Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:145-53.**

### Background

Angiotensin-converting-enzyme (ACE) inhibitors lower morbidity and mortality among patients with congestive heart failure. In addition to a reduction in afterload, ACE inhibitors have a protective effect on the vasculature, which may lead to a reduction in cardiovascular events in high-risk patients without a history of left ventricular dysfunction.<sup>1</sup>

### Question

Do ACE inhibitors lower the incidence of cardiovascular events and death among high-risk patients who do not have a history of congestive heart failure?

### Design

A double-blind, multicentre, randomized controlled trial was conducted to compare the effects of ramipril to placebo in 9297 patients over the age of 55 who were at high risk for cardiovascular events. Eligible patients included those with coronary artery disease, stroke, peripheral vascular disease or a history of diabetes mellitus plus another cardiovascular risk factor. Exclusion criteria included congestive heart failure, overt nephropathy or a history of myocardial infarction or stroke within 4 weeks of the study. The primary study outcome was the combination of myocardial infarction, stroke or death from any cardiovascular event.

### Results

Almost half of the subjects were older

than 65, and just over one-quarter were women. Most patients (80%) had a history of coronary artery disease, about half were hypertensive (46.8%), and many (38.5%) had diabetes mellitus.

A chart audit found that more than half of the patients had had their ventricular function assessed before the study. Of this group, 8.1% had a low ejection fraction without a clinical history of congestive heart failure.

The study was designed to continue for 5 years, but it was stopped early because of the beneficial effects of ramipril on the primary outcome. The primary end point occurred in 14.0% of the patients in the treatment group, as compared with 17.8% in the placebo group.

This result was consistent in both men and women and in all predefined subgroups, including patients with diabetes, hypertension and left ventricular dysfunction. Treatment with ramipril was associated with significant reductions in secondary end points such as cardiac arrest, congestive heart failure, revascularization procedures and death from any cause. The incidence of new diagnoses of diabetes was significantly lower in the ramipril group than in the placebo group (102 v. 155 patients).

### Commentary

This large, randomized study documents the beneficial effects of ACE inhibitors in patients at high risk for cardiovascular events. The results were consistent across subgroups, and benefit extended to a number of secondary outcomes. Ramipril was well tolerated,

with cough resulting in discontinuation of the medication in 7.3 % of patients.

The intriguing reduction in the incidence of diabetes corresponds to observations in the Captopril Prevention Project study of antihypertensive therapy.<sup>2</sup>

### Practice implications

When given ramipril therapy, high-risk patients over age 55 with normal left ventricular function have a reduced rate of myocardial infarction, stroke and death from cardiovascular causes. Ramipril, started at a dose of 2.5 mg/d and titrated over 1 month to a dose of 10 mg/d, is well tolerated. Whether the findings of this study can be extended to angiotensin II receptor inhibitors is unknown.

The reduction in the incidence of diabetes among patients taking the ACE inhibitor is an important observation that merits further investigation. — *Kathryn A. Myers*

The Clinical Update section is edited by Dr. Donald Farquhar, head of the Division of Internal Medicine, Queen's University, Kingston, Ont. The updates are written by members of the division.

### References

1. Lonn EM, Yusuf S, Jha P, Montague TJ, Teo KK, Benedict CR, Pitt B. Emerging role of angiotensin-converting enzyme inhibitors in cardiac and vascular protection. *Circulation* 1994;90:2056-69.
2. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project randomised trial. *Lancet* 1999;353:611-6.