

## THERAPEUTICS

## Review: Inhaled corticosteroids slow the progression of airflow limitation in COPD

Sutherland ER, Allmers H, Ayas NT, Venn AJ, Martin RJ. Inhaled corticosteroids reduce the progression of airflow limitation in chronic obstructive pulmonary disease: a meta-analysis. *Thorax*. 2003;58:937-41.

### QUESTION

In patients with chronic obstructive pulmonary disease (COPD), do inhaled corticosteroids (ICSs) reduce the progression of airflow limitation?

### DATA SOURCES

Studies were identified by searching MEDLINE (1966 to February 2003), CINAHL (1982 to February 2003), International Pharmaceutical Abstracts (1970 to February 2003), and the Cochrane Controlled Trials Register; scanning the references of retrieved articles; and contacting experts in the field.

### STUDY SELECTION AND ASSESSMENT

Studies were selected if they were full reports of randomized controlled trials of ICSs in patients with COPD, had  $\geq 1$  year of follow-up, examined change in FEV<sub>1</sub> over time, patients with asthma were

excluded, and patients were studied when COPD was stable.

### OUTCOMES

Progression of airflow limitation measured by annual rate of change in FEV<sub>1</sub>.

### MAIN RESULTS

8 trials ( $n = 3715$ ) were included. All trials were  $\geq 2$  years in duration (range 24 to 40 mo). The ICSs studied were fluticasone, triamcinolone, budesonide, and beclomethasone. ICSs reduced the rate of decline in FEV<sub>1</sub> more than did placebo (Table). Meta-

analysis with trials of high-dose ICS regimens (4 trials, 2416 patients) also favored ICSs (Table).

### CONCLUSION

In patients with chronic obstructive pulmonary disease, inhaled corticosteroids reduce the progression of airflow limitation.

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### Inhaled corticosteroids vs placebo for chronic obstructive pulmonary disease at 24 to 40 months\*

Trials	Annual reduction in FEV <sub>1</sub> decline (95% CI)
All trials (8 trials, $n = 3715$ )	7.7 mL/y (1.3 to 14.2)
Trials with high-dose regimens (4 trials, $n = 2416$ )	9.9 mL/y (2.3 to 17.5)

\*Values are means. CI defined in Glossary. A random-effects model was used.

### COMMENTARY

COPD is largely a disease of vulnerable smokers in whom the normal age-related decline in lung function is accelerated from a mean of 30 mL/y to 60 mL/y. Unlike asthma, the airflow obstruction and airway inflammation of COPD respond poorly to corticosteroids. The review of randomized controlled trials by Sutherland and colleagues shows a statistically significant reduction in the annual rate of decline in FEV<sub>1</sub> of 7.7 mL/y with higher dose regimens, and patients with more severe disease obtained greater benefit. Although the absolute reduction was small, it represents a reduction in the rate of decline of about 15% in smokers compared with a reduction of about 50% as a result of smoking cessation (1).

COPD is now our fourth most common cause of death, and no drugs apart from oxygen alter the natural history of the disease. But should any intervention that slows the inexorable decline in lung function be welcomed? Arguably, the small advantage in terms of reduced decline in FEV<sub>1</sub> is of little clinical relevance. Furthermore, widespread introduction of high-dose ICSs for all patients with COPD would be expensive given the prevalence of the disease and its long-term course. In my opinion, we should put the resources into vigorous smoking prevention and cessation programs that are more effective in terms of preserving lung function (as well as preventing cancer and heart disease). Pressure to prescribe these drugs for many patients with essentially irreversible airflow obstruction can be resisted, but the need to resist emphasizes the importance of distinguishing asthma from COPD.

The discrepancy between the results of the systematic reviews of Highland (2) and Sutherland and colleagues will also fuel current anxieties about the validity of meta-analysis, especially as nearly identical trial data were incorporated in these 2 reviews. In fact, the rate of decline in FEV<sub>1</sub> in both analyses was very similar (5 mL/y and 7.7 mL/y, respectively), but the former failed to reach statistical significance. The differences emphasize how apparently uncontroversial assumptions made during data extraction can have substantial effects on the primary outcome and might lead to very different recommendations in "evidence-based" clinical guidelines. Readers of meta-analyses need to be vigilant regarding the absolute size of the effects of any intervention and aware that pooling trial data can be a hazardous activity.

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### References

1. Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. *Am J Respir Crit Care Med*. 2002;166:675-9.
2. Highland KB, Strange C, Heffner JE. Long-term effects of inhaled corticosteroids on FEV<sub>1</sub> in patients with chronic obstructive pulmonary disease. A meta-analysis. *Ann Intern Med*. 2003;138:969-73.