Discontinuation of inhaled fluticasone led to increased exacerbations in chronic obstructive pulmonary disease

van der Valk P, Monninkhof E, van der Palen J, Zielhuis G, van Herwaarden C. **Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: the COPE study.** Am J Respir Crit Care Med. 2002;166:1358-63.

QUESTION

In patients with moderate-to-severe chronic obstructive pulmonary disease (COPD), does discontinuation of the inhaled corticosteroid fluticasone propionate (FP) affect exacerbations and health-related quality of life (HRLQ)?

DESIGN

Randomized (unclear allocation concealment*), blinded (clinicians, patients, {data collectors, outcome assessors, data analysts, and data safety and monitoring committee}†),* placebo-controlled trial with 6-month follow-up.

SETTING

An outpatient pulmonary clinic in Enschede, the Netherlands.

PATIENTS

After a 4-month run-in phase during which 263 patients received 500 µg of FP twice daily and 40 µg of ipratropium bromide 4 times daily, 244 patients who were 40 to 75 years of age (mean age 64 y, 84% men) were randomized. Inclusion criteria included stable COPD with no history of asthma, no exacerbations in the previous month, no oral steroids or antibiotics, and no serious medical condition or other lung disease. Follow-up was 99%.

INTERVENTION

Patients were allocated to continue on FP, 500 µg twice daily (n = 123), or placebo (n = 121) through a Diskus inhaler for 6 months.

MAIN OUTCOME MEASURES

≥ 1 exacerbation (respiratory symptoms requiring treatment with corticosteroids or antibiotics), recurrent exacerbations, and HRQL (measured by the Dutch version of the St. George's Respiratory Questionnaire and the Euroqol 5D self-rated health status scale).

MAIN RESULTS

Analysis was by intention to treat. Fewer patients in the FP group developed ≥ 1 exacerbation than did those in the placebo group (Table). Patients in the FP group took longer to first exacerbation (75 vs 43 d, mean difference 35 d, 95% CI 15 to 54). Fewer patients receiving FP had rapid recurrent exacerbations that required unblinded treatment with FP (Table). Patients in the FP group had less deterioration in the total scores, symptoms, and activity domains for HRQL than did patients in the placebo group.

CONCLUSIONS

In patients with moderate-to-severe chronic obstructive pulmonary disease, discontinuation of the inhaled corticosteroid fluticasone propionate led to increased exacerbations and deterioration of health-related quality of life.

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For correspondence: Dr. P. van der Valk, Medisch Spectrum Twente, Enschede, The Netherlands. E-mail valkpapa@knmg.nl.

*See Glossary.

†Data provided by author.

Fluticasone propionate vs placebo for moderate-to-severe obstructive pulmonary disease at 6 months‡

Outcomes	Fluticasone	Placebo	RRR (95% CI)	NNT (CI)
≥ 1 exacerbation§	48%	58%	24% (3 to 42)	8 (5 to 54)
Rapid, recurrent exacerbations	4.9%	22%	77% (49 to 90)	7 (4 to 12)

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

§Calculated for data in article using Cox proportional-hazards ratio.

COMMENTARY

Inhaled corticosteroids (ICSs) are overprescribed in COPD (1), and long-term use poses risks for important adverse effects. The study by van der Valk and colleagues of the consequences of ICS discontinuation is therefore valuable and timely. Particular strengths of the study include the completeness of follow-up and the intention-to-treat analysis, factors that have impaired the validity of previous ICS studies (2, 3).

Deterioration after ICS withdrawal does not necessarily imply that ICSs are an effective therapy for COPD. However, the observations of a small but measurable effect on exacerbations but no clinically meaningful effects on lung function, exercise capacity, or breathlessness are consistent with results of existing trials of ICS efficacy (2–4). A novel finding was that quality-of-life benefits seemed to be attributable almost entirely to the effect on exacerbations.

The increased risk for rapid recurrent exacerbations associated with ICS discontinuation is troubling. Most important, it indicates the need for a rational, rather than an indiscriminate, prescribing approach. Patients with COPD who are unlikely to benefit from ICS should not receive them in the first place. It is reassuring that many patients in the van der Valk study discontinued ICS without any adverse consequences, and deterioration was mainly seen in patients with more severe obstruction (FEV_1 < 50% predicted). Thus, these findings should not preclude physicians from attempting to discontinue ICSs in patients with COPD who do not seem to benefit from them. Such patients should be monitored closely, and if clinical deterioration occurs, resuming ICS therapy is appropriate.

Matthew B. Stanbrook, MD
University of Toronto
Toronto, Ontario, Canada

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