Low-dose budesonide improved asthma control in mild asthma; adding formoterol improved control in corticosteroid-treated patients


QUESTION
In patients with mild asthma, do regular low doses of inhaled budesonide, or without low doses of inhaled formoterol, reduce severe exacerbations and improve asthma control?

DESIGN
Randomized [allocation concealed†††, blinded patients, clinicians, data collectors, outcome assessors, data analysts, and monitoring committee††, †] placebo-controlled trial with 1-year follow-up.

SETTING
198 centers in 17 countries.

PATIENTS
1970 patients who were ≥ 12 years of age and had mild asthma. 698 corticosteroid-free patients (group A) (mean age 31 y, 60% women) had not used an inhaled corticosteroid for ≥ 3 months and had an FEV₁ ≥ 80% of predicted normal after inhaling terbutaline, 1 mg. 1272 corticosteroid-treated patients (group B) (mean age 37 y, 57% women) were receiving ≤ 400 µg/d of inhaled budesonide or the equivalent for ≥ 3 months, with an FEV₁ ≥ 70% of predicted normal after terbutaline. Data from 1947 patients (99%) were included in the analysis.

INTERVENTION
During a 4-week run-in period, group-A patients received placebo and group-B patients received budesonide, 100 µg twice daily. Patients were then allocated to twice-daily treatment for 1 year. Group-A patients were allocated to budesonide, 100 µg (n = 228); budesonide, 100 µg, plus formoterol, 4.5 µg (n = 231); or placebo (n = 239). Group-B patients were allocated to budesonide, 100 µg (n = 322); budesonide 100 µg, plus formoterol, 4.5 µg (n = 323); budesonide, 200 µg (n = 312); or budesonide, 200 µg, plus formoterol, 4.5 µg (n = 315). All doses were delivered by Bricanyl Turbuhaler (AstraZeneca, Lund, Sweden), and stated doses were metered doses for budesonide and delivered doses for formoterol.

MAIN OUTCOME MEASURES
Main outcomes were time to first severe asthma exacerbation (need for treatment with oral corticosteroids, hospital admission or emergency treatment for worsening asthma, or a decrease in morning peak expiratory flow rate [PEFR] > 25% from baseline on 2 consecutive d) and poorly controlled asthma days (d with morning PEFR ≥ 20% below baseline, use of rescue medication ≥ 2 d above baseline, or nocturnal awakening by asthma).

MAIN RESULTS
Analysis was by intention to treat. Among group-A patients, budesonide, 100 µg twice daily, reduced the risk for a first severe asthma exacerbation (relative risk [RR] 0.40, 95% CI 0.27 to 0.59) and the rate of poorly controlled asthma days (RR 0.57, CI 0.46 to 0.72) and the rate of poorly controlled asthma days. Adding formoterol twice daily was more effective than budesonide, 200 µg twice daily, for reducing the risk for a severe exacerbation day (RR 0.71, CI 0.52 to 0.96) or a poorly controlled asthma day (RR 0.81, CI 0.66 to 0.99).

CONCLUSIONS
In corticosteroid-free patients with mild asthma, adding formoterol improved control in corticosteroid-treated patients; this finding may be related to a flattening of the dose-response relation for inhaled corticosteroids in patients with mild asthma.

The benefits of these medications on underlying disease processes are still unknown, which means that the long-term effects on airway remodeling and airway inflammation cannot be predicted (2). However, on the basis of the current evidence, an appropriate management strategy for patients with mild asthma would be initial treatment with inhaled corticosteroids and the addition of long-acting β-agonists if control subsequently worsens rather than increasing the dose of inhaled corticosteroids. Combination therapy also reduces the potential for long-term side effects of higher-dose monotherapy, which is contributing to expanding interest in compliance-friendly combination inhaler devices.

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References