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, with or without low doses of inhaled formoterol, reduce severe exacerbations and improve asthma control?

Design
Randomised [allocation concealed†], blinded [patients, clinicians, data collectors, outcome assessors, data analysts, and monitoring committee]†,* placebo controlled trial with 1 year of follow up.

Setting
198 centres in 17 countries.

Patients
1970 patients who were ≥ 12 years of age and had mild asthma. 608 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/day 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=522); 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=313). 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 days) and poorly controlled asthma days (days 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 0.52, CI 0.40 to 0.67) more than did placebo. Adding formoterol to budesonide did not affect these 2 outcomes.

Among group B patients, budesonide, 100 μg and 200 μg twice daily, did not differ for risk for a first severe exacerbation or for rate of poorly controlled asthma days. Adding formoterol to budesonide, 100 μg or 200 μg, reduced the risk for a first asthma exacerbation (RR 0.57, CI 0.46 to 0.72) and the rate of poorly controlled asthma days (RR 0.70, CI 0.60 to 0.82). Budesonide, 100 μg plus 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, budesonide, 100 μg twice daily, reduced severe exacerbations and poorly controlled asthma days; the addition of formoterol conferred no added benefit. In patients already receiving inhaled corticosteroids, adding formoterol to budesonide, 100 μg twice daily, was better than doubling the dose of budesonide.

†See glossary.
‡Information provided by author.