

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

O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med*. 2001 Oct 15;164:1392-7.

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

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 $\geq 80\%$ of predicted normal after inhaling terbutaline, 1 mg. 1272 corticosteroid-treated patients (group B) (mean age 37 y, 57% women) were receiving ≤ 400 $\mu\text{g}/\text{d}$ of inhaled budesonide or the equivalent for ≥ 3 months, with an FEV₁ $\geq 70\%$ 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 $\geq 20\%$ 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 for-

moterol 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, 100 μg twice daily, to budesonide was better than doubling the dose of budesonide.

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For correspondence: Dr. P.M. O'Byrne, St. Joseph's Healthcare, Hamilton, Ontario, Canada. E-mail obyrne@mcmaster.ca.

*See Glossary.

†Information provided by author.

COMMENTARY

Patients diagnosed with mild asthma and their physicians may underestimate the morbidity associated with this condition. Such morbidity can be appreciable and can include severe exacerbations (1), despite normal lung function results on "good" days. In the trial by O'Byrne and colleagues, patients classified as having mild asthma had a mean baseline FEV₁ $> 85\%$ of predicted normal. However, one third of patients in the placebo group (who did not receive inhaled corticosteroids) had severe exacerbations (with $> 70\%$ needing oral corticosteroids), and 47% had nocturnal awakenings. Interventions to reduce the effects of these exacerbations are therefore important.

Patients not previously receiving inhaled corticosteroids had a substantial benefit with 100 μg of budesonide twice each day. Lung function improved, but adding formoterol conferred no further symptomatic benefit.

In patients who were already treated with inhaled corticosteroids, adding formoterol was more effective at preventing exacerbations than was doubling the dose of budesonide; this finding may be related to a flattening of the dose-response relation for inhaled corticosteroids in

patients with mild asthma.

The effects 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.

Dion Grosser, MBBS

Brian Smith, MBBS

Queen Elizabeth Hospital

Woodville, South Australia, Australia

References

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