

RESULTS. There was no significant difference between the treatment groups in the percentage of symptom-free days. Each treatment group had an increase in symptom-free days by ~25% while on treatment compared to baseline ($P < .001$). Furthermore, no significant difference was seen in the percentage of days in which rescue salbutamol was used; both groups had a gradual decline in use of the salbutamol. A combined ranked assessment of all exacerbations among the treatment groups revealed no statistically significant difference between the 2 groups. Lung-function parameters did not differ between groups other than a slightly greater effect on maximal expiratory flow seen in the salmeterol/fluticasone group during the first week of treatment. The 2 groups did not differ in statural growth or number of adverse events.

CONCLUSIONS. The results of this study indicate that the combination of a long-acting bronchodilator with inhaled corticosteroid has equal efficacy in controlling symptoms and preserving lung function when compared with doubling the dose of inhaled corticosteroids in children who were symptomatic on a moderate dose of inhaled corticosteroids. Therefore, combination of a long-acting bronchodilator is likely an appropriate alternative in step-up therapy.

REVIEWER COMMENTS. This study provides us with an adequate alternative step 3 treatment option. The results of this study are in line with those of previous work. Further study is now needed to evaluate whether there might be specific asthma phenotypes that respond more favorably to 1 treatment option versus another. The fear of increased severe asthma exacerbations and asthma-related deaths associated with use of long-acting β_2 agonists in children is still present. Further data from large numbers of children are needed to make a more definite conclusion about this possible risk.

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Once- vs Twice-Daily Budesonide/Formoterol in 6- to 15-Year-Old Patients With Stable Asthma

Eid SE, Noonan MJ, Chipps B, Parasuraman B, Miller CJ, O'Brien CD. *Pediatrics*. 2010;126(3). Available at: www.pediatrics.org/cgi/content/full/126/3/e565

PURPOSE OF THE STUDY. To compare the clinical effectiveness and tolerability of once-daily budesonide/formoterol pressurized metered-dose inhaler (pMDI) versus budesonide pMDI in asthmatic children aged 6 to 15 years old.

STUDY POPULATION. Children aged 6 to 15 years with stable mild-to-moderate asthma were enrolled if they had had

symptoms for ≥ 6 months, bronchodilator response, and forced expiratory volume in 1 second (FEV₁) of 60% to 90% of that predicted at baseline.

METHODS. The study was a multicenter, 12-week double-blind, parallel-group, active-controlled, randomized study. Enrolled patients had a 4- to 5-week run-in with budesonide/formoterol 80/9 μg twice per day and albuterol as needed for rescue. Patients whose asthma was stable after the run-in period were age-stratified and randomly assigned to receive budesonide pMDI 80 μg (2 inhalations daily), budesonide/formoterol 80/4.5 μg (2 inhalations once daily), or budesonide/formoterol 40/4.5 μg (2 inhalations twice daily). Primary outcome data were evening peak expiratory flow rate (PEF). PEF and predose FEV₁ were recorded in an electronic diary by patients or caregivers in the morning and evening. Patients were immediately withdrawn from study if they met predefined worsening asthma symptom criteria. At the end of the study, physicians and caregivers were asked about health status and ability to manage asthma symptoms using a 5 point scale. Health-related quality of life (HRQoL) was assessed by questionnaire.

RESULTS. Of 719 enrolled patients, 522 were randomly assigned. The most common cause of withdrawal before randomization was worsened asthma symptoms or function. Once- and twice-daily budesonide/formoterol pMDI were superior to budesonide pMDI daily as assessed by morning PEF, morning predose FEV₁, or evening PEF. Although the twice-daily budesonide/formoterol group had improved evening PEF during the study versus being unchanged in the once-daily budesonide/formoterol group, there were no statistical differences between these groups. Evening predose FEV₁ increased in the twice-daily budesonide/formoterol group versus decreasing in the once-daily budesonide/formoterol group or budesonide group. Twice-daily budesonide/formoterol resulted in significantly less daytime rescue-medication use versus the once-daily medication study groups and resulted in significantly less nighttime rescue-medication use versus budesonide alone. Patients with at least 1 predefined event of worsened asthma episodes were significantly fewer in the twice-daily budesonide/formoterol group versus once-daily medication groups; however, this was seen entirely in the 6- to 11-year age group. Physician perception of ease of asthma management significantly favored the twice-daily budesonide/formoterol group, but the results of other subjective assessments of asthma control, health status, HRQoL, adverse events, and objective safety data were similar across all groups.

CONCLUSIONS. Once-daily dosing of budesonide-formoterol pMDI resulted in significantly higher evening PEF and most of the assessed pulmonary variables compared with once-daily budesonide pMDI. However, there were no significant differences between once-daily budesonide/

formoterol and once-daily budesonide in measures for asthma control, asthma symptoms, or HRQoL measures. Twice-daily versus once-daily budesonide/formoterol resulted in improved evening predose FEV₁, daytime rescue-medication use, rescue-medication-free days, and worsening asthma events. There were no differences in safety variables between the 3 treatment groups.

REVIEWER COMMENTS. This study was designed by scientists employed by a pharmaceutical company and conducted by a large group of clinicians. It adds to the data regarding safety of inhaled corticosteroid (ICS)/long-acting β_2 agonist (LABA) combinations in young children. In the twice-daily budesonide/formoterol group, the mean evening PEF and evening predose FEV₁ continued to increase during the study, which raises the question of whether the patients achieved true baseline status at the time of randomization. A longer run-in might have led to different results in the comparisons between twice-daily and once-daily budesonide/formoterol. The authors warned that stepping-down from twice-daily budesonide/formoterol to once-daily dosing might lead to increased asthma symptoms without a change in safety profile but did not discuss potential long-term harm from ongoing unnecessary LABA/ICS use. Current product information and national asthma guidelines should continue to be followed regarding ICS/LABA use in children, but in individual patients for whom twice-daily dosing is not feasible, once-daily dosing (with careful monitoring) might be appropriate.

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Use of Beclomethasone Dipropionate as Rescue Treatment for Children With Mild Persistent Asthma (TREXA): A Randomized, Double-Blind, Placebo-Controlled Trial

Martinez FD, Chinchilli VM, Morgan WJ, et al. *Lancet*. 2011;377(9766):650-657

PURPOSE OF THE STUDY. To determine the effectiveness of inhaled beclomethasone dipropionate when used as a rescue treatment for symptoms in children with mild persistent asthma.

STUDY POPULATION. Children and adolescents aged 5 to 18 years with well-controlled mild persistent asthma were enrolled from 5 clinical centers in a 44-week, randomized, double-blind, placebo-controlled trial.

METHODS. Participants who remained well controlled during the 4-week run-in period were stratified according to clinical center and age group and randomly assigned to 1 of 4 treatments: twice-daily beclomethasone with beclo-

methasone plus albuterol as rescue (combined group); twice-daily beclomethasone with placebo plus albuterol as rescue (daily beclomethasone group); twice-daily placebo with beclomethasone plus albuterol as rescue (rescue beclomethasone group); and twice-daily placebo with placebo plus albuterol as rescue (placebo group). Twice-daily treatment was 1 puff of beclomethasone (40 μ g) or placebo, and rescue treatment for symptoms was 2 puffs of beclomethasone or placebo for every 2 puffs of albuterol (180 μ g). The primary outcome, time to first exacerbation that required oral prednisone, and secondary outcome, linear growth, were analyzed according to intention to treat.

RESULTS. Of the 843 participants enrolled, 288 were assigned to a treatment group (combined, $n = 71$; daily, $n = 72$; rescue, $n = 71$; placebo, $n = 74$). Baseline characteristics were similar between included and excluded participants and among those in the 4 treatment groups. The frequency of exacerbations was lower in the combined (31% [95% confidence interval (CI): 21%-43%]; $P = .07$), daily (28% [95% CI: 18%-40%]; $P = .03$), and rescue (35% [95% CI: 24%-47%]; $P = .07$) groups compared with the placebo group (49% [95% CI: 37%-61%]). The frequency of treatment failure was 5.6% (95% CI: 1.6%-14%; $P = .012$) in the combined, 2.8% (95% CI: 0%-10%; $P = .009$) in the daily, and 8.5% (95% CI: 2%-15%; $P = .024$) in the rescue groups compared with 23% (95% CI: 14%-43%) in the placebo group. Compared with the placebo group, linear growth was 1.1 cm (SD: 0.3 cm) less in the combined and daily groups ($P < .0001$) but no different in the rescue group ($P = .26$).

CONCLUSIONS. Daily inhaled corticosteroids are the most effective treatment for children with mild persistent asthma. For children not taking a daily inhaled corticosteroid, inhaled beclomethasone used as a rescue medication with albuterol can lower the risk of exacerbations and treatment failures more effectively than albuterol alone but to a lesser extent than daily inhaled beclomethasone. Children with mild persistent asthma should not be treated with only rescue albuterol.

REVIEWER COMMENTS. This study differs from previous trials of inhaled corticosteroids during asthma exacerbations in that it evaluated the benefit of adding a low-dose inhaled corticosteroid as rescue medication whenever albuterol was needed for treatment of symptoms. The results confirm the relative effectiveness of low-dose daily inhaled corticosteroids, which remain the first-line maintenance therapy for children with mild persistent asthma. Compared with rescue albuterol alone, the results also suggest a possible benefit without increased risk of growth impairment from inhaled corticosteroids added as rescue medication for children not taking a daily inhaled steroid. Among children with well-controlled

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