

it was worth investigating whether it would have additive benefit for acute asthma, but this study found that it does not.

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John M. Kelso, MD  
San Diego, CA

### **The Back to School Asthma Study: The Effect of Montelukast on Asthma Burden When Initiated Prophylactically at the Start of the School Year**

Weiss KB, Gern JE, Johnston NW, et al. *Ann Allergy Asthma Immunol.* 2010;105(2):174-181

**PURPOSE OF THE STUDY.** To determine the efficacy of prophylactic montelukast therapy in reducing asthma morbidity at the start of the school year.

**STUDY POPULATION.** Patients 6 to 14 years of age with a diagnosis of asthma for a minimum of 1 year were recruited for this international study that took place in 39 US states and 3 Canadian provinces from June 2006 through November 2006.

**METHODS.** This was a randomized, multicenter, double-blind, placebo-controlled study for patients who received either 5-mg montelukast or placebo beginning on the night before school started and continued for an 8-week period. Patients were randomly assigned during a screening period from 2 to 12 weeks before the school start date. Patients were interviewed by telephone to review symptoms, use of study medications, and need for additional  $\beta$  agonists 4 weeks after starting school. A final study visit at 8 weeks was conducted to document daytime symptoms, "awake all night," inhaled corticosteroid use, increased  $\beta$ -agonist use, and visits to a health care professional or facility for asthma. Inclusion criteria included treatment of asthma within 6 months of screening and patients having at least 1 exacerbation of asthma symptoms in the previous year that were associated with a cold. Exclusion criteria included forced expiratory flow volume in 1 second below 60% of that predicted, use of systemic steroids within 4 weeks of randomization, and more than 3 hospitalizations for asthma in the previous year. Patients on treatment with a long-acting  $\beta$  agonist or leukotriene receptor antagonist within 10 days of randomization were also excluded.

**RESULTS.** Of 1162 patients (580 randomly assigned to the montelukast group and 582 randomized to the placebo group), no significant difference was seen for the percentage of days with worsening asthma. A trend for montelukast to reduce worsening asthma days in those who began school after August 15 was seen but was not significant. A nonsignificant trend in older children and boys favoring treatment with montelukast was also seen.

**CONCLUSIONS.** The use of montelukast did not significantly reduce the number of days with worsening asthma when begun as prophylactic therapy at the start of the school year.

**REVIEWER COMMENTS.** The start of the school year presents a challenge for asthmatic children, who have greater disease burden with respiratory illnesses. In the group of children treated with montelukast, the percentage of days with worsening asthma was stable, whereas this percentage increased in weeks 3 to 4 in the placebo group and subsequently decreased for the remainder of the study. Because this study did not answer the need to prevent morbidity from asthma during the fall, additional studies are needed to address this concern.

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Vivian Hernandez-Trujillo, MD  
Miami, FL

### **Combination Therapy Salmeterol/Fluticasone Versus Doubling Dose of Fluticasone in Children With Asthma**

Vaessen-Verberne AA, van den Berg NJ, van Nierop JC, et al; COMBO Study Group. *Am J Respir Crit Care Med.* 2010;182(10):1221-1227

**PURPOSE OF THE STUDY.** To determine if the addition of a long-acting bronchodilator is noninferior to doubling the dose of inhaled corticosteroids in children whose asthma is not controlled with use of low-to-moderate doses of inhaled corticosteroids alone.

**STUDY POPULATION.** Children aged 6 to 16 years who were using fluticasone propionate (100  $\mu$ g twice daily) to treat their asthma were enrolled in this study ( $N = 257$ ). A 4-week run-in period was used to monitor these children. Those who were still symptomatic despite regular use of fluticasone propionate were included in the randomization of study groups ( $n = 158$ ). The study was conducted at multiple pediatric medical centers throughout Europe.

**METHODS.** Symptomatic children were randomly assigned to 1 of 2 treatment groups: fluticasone propionate (200  $\mu$ g twice per day) or salmeterol/fluticasone propionate (50/100  $\mu$ g twice per day), used for a 26-week treatment period. Lung-function measurements were recorded at the start of the run-in period, at time of randomization, and at all visits during the treatment period. The provocative dose of methacholine that causes a 20% decrease ( $PD_{20}$ ) in the forced expiratory volume in 1 second ( $FEV_{1}$ ) and exhaled nitric-oxide levels were measured at the start and end of the treatment period. The number of symptom-free days and asthma exacerbations were logged at each clinic visit. Exacerbations were classified as mild, moderate, or severe on the basis of the medical interventions needed.

**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  $\beta_2$  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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Todd A. Mahr, MD  
Jennilee Mumm, PA-C  
La Crosse, WI

### 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](http://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  $\geq 6$  months, bronchodilator response, and forced expiratory volume in 1 second (FEV<sub>1</sub>) 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  $\mu\text{g}$  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  $\mu\text{g}$  (2 inhalations daily), budesonide/formoterol 80/4.5  $\mu\text{g}$  (2 inhalations once daily), or budesonide/formoterol 40/4.5  $\mu\text{g}$  (2 inhalations twice daily). Primary outcome data were evening peak expiratory flow rate (PEF). PEF and predose FEV<sub>1</sub> 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 FEV<sub>1</sub>, 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 FEV<sub>1</sub> 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/

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