

treatment of asthma by comparing LTRAs with both inhaled glucocorticoids for first-line therapy and long-acting  $\beta_2$  agonists (LABAs) for add-on therapy.

**STUDY POPULATION.** Patients aged 12 to 80 years were considered eligible if they had a Mini Asthma Quality of Life Questionnaire (MiniAQLQ) score of  $\leq 6$  or an Asthma Control Questionnaire (ACQ) score of  $\geq 1$ . Trials were conducted at 53 primary care sites in the United Kingdom.

**METHODS.** Patients were randomly assigned to an LTRA ( $n = 148$ ) or inhaled glucocorticoid ( $n = 158$ ) in the first-line therapy trial and an LTRA ( $n = 170$ ) or an LABA ( $n = 182$ ) in the step-up therapy trial. Patients were managed by their primary care provider during the 2-year trial period, and treatments were given in an open-label fashion. After the initial visit, patients were followed either by telephone or in the clinic at months 2, 6, 12, 18, and 24. Patients' MiniAQLQ score was the primary outcome measure. Secondary outcome measures included the ACQ score, the Royal College of Physicians 3-item asthma questionnaire score, the Mini Rhinoconjunctivitis Quality of Life Questionnaire score, and the frequency of asthma exacerbations that required oral glucocorticoids or hospitalization.

**RESULTS.** Over the 2-year treatment period, the mean MiniAQLQ score increased by 0.8 to 1.0 in both trials. Assessment of data at 2 months revealed noninferiority between LTRAs and inhaled glucocorticoids for first-line therapy on the basis of the primary outcome of MiniAQLQ score. At 2 years, results approached equivalence between the treatment groups in both trials; however, the data could not prove noninferiority. There were no significant differences between treatment groups regarding all other secondary outcome measures at both 2 months and 2 years. There was no significant difference in adherence rates in either trial.

**CONCLUSIONS.** Results at 2 months suggest comparable efficacy between LTRAs and inhaled glucocorticoids as first-line controller therapy and equivalence to LABAs as add-on therapy. Equivalence at 2 years was not proved for either trial.

**REVIEWER COMMENTS.** Although LTRAs are a comparable option for both first-line and step-up therapy in asthma, true long-term equivalence has not been demonstrated. Results of previous randomized trials that examined LTRA use tend to support inhaled glucocorticoids as the preferred choice for first-line therapy and LABAs as the preferred choice for step-up therapy. The authors of a Cochrane review of 27 randomized controlled trials, mainly in adults with mild-to-moderate asthma, concluded that inhaled corticosteroid was more effective than LTRAs. A meta-analysis of 18 randomized controlled trials in children younger than 18 years with

similar asthma found that inhaled corticosteroid was more effective than montelukast for preventing severe asthma exacerbations. The absence of a placebo group makes it difficult to judge whether the changes observed in MiniAQLQ score in either group from baseline are truly clinically meaningful. However, this study does provide a better, although not perfect, real-world perspective, with data approaching equivalence for LTRA use as both first-line and step-up therapy for asthma. Results from previous randomized controlled trials combined with data from this pragmatic study might not change how we currently practice but can guide us in our decision-making process more effectively in the real-world clinic setting.

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### **Effect of Addition of Single Dose of Oral Montelukast to Standard Treatment in Acute Moderate to Severe Asthma in Children Between 5 and 15 Years of Age: A Randomised, Double-Blind, Placebo Controlled Trial**

Todi VK, Lodha R, Kabra SK. *Arch Dis Child.* 2010;95(7):540-543

**PURPOSE OF THE STUDY.** Montelukast has both anti-inflammatory and bronchodilator properties. Does giving a single dose at the time of an emergency department (ED) visit for an asthma exacerbation improve outcomes compared with standard therapy alone?

**METHODS.** One hundred seventeen children who presented to an ED with moderate-to-severe asthma exacerbations defined as a Modified Pulmonary Index Score of  $\geq 9$  were randomly assigned to receive either montelukast ( $n = 60$ ) or placebo ( $n = 57$ ) in addition to standard therapy, which included nebulized albuterol and ipratropium and oral corticosteroids.

**RESULTS.** The percentage of children whose Modified Pulmonary Index Score decreased to  $< 9$  within 4 hours was no different in the montelukast (55%) and placebo (63%) groups ( $P = .37$ ). There were no differences in the improvement in lung function or hospitalization rates.

**CONCLUSIONS.** Single-dose oral montelukast added to standard therapy of inhaled bronchodilators and systemic glucocorticoids did not provide additional clinical benefit for children with acute moderate-to-severe asthma.

**REVIEWER COMMENTS.** Because montelukast can act quickly and works in a different way than other bronchodilators,

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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### **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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### **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.

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