

How effective are leukotriene inhibitors for asthma in children?

■ EVIDENCE-BASED ANSWER

Evidence on the use of leukotriene inhibitors in children is insufficient to permit conclusions regarding efficacy. Given the proven efficacy of inhaled corticosteroids in asthma management, leukotriene inhibitors should not replace inhaled corticosteroids for maintenance of asthma in children (strength of recommendation: **B**).

Current guidelines that list leukotriene inhibitors as a potential addition or alternative to corticosteroid therapy in children with asthma appear to be based on scant studies and extrapolation from adult research.

■ EVIDENCE SUMMARY

Asthma is characterized by inflammation of the bronchial airways. Leukotrienes are potent mediators of inflammation and are believed to contribute significantly to the inflammatory pathophysiology of asthma. Leukotriene inhibitors interfere with leukotriene production or leukotriene receptors and thus inhibit inflammation.¹

Leukotriene inhibitors are administered orally, a significant advantage over inhalation in the pediatric population. For children, the theoretical corticosteroid-sparing effect of leukotriene inhibitors is appealing but has not been demonstrated.

In January 2002, Cochrane reviewers identified 3 studies of leukotriene inhibitor use in children that met their quality criteria for meta-analysis. Unfortunately, recent changes in asthma classification terminology make it difficult to precisely translate past studies into current practice. Based on these studies, the Cochrane reviewers concluded there is insufficient evidence to support the use of leukotriene inhibitors in children as monotherapy or as an addition to corticosteroids.^{1,2}

One randomized, double-blind crossover study of 279 children with corticosteroid-dependent

(persistent) asthma compared montelukast 5 mg (Singulair) once a day plus inhaled budesonide 200 µg (Pulmicort) twice a day with placebo plus budesonide (Rhinocort). Each study period lasted only 4 weeks, starting after a 4-week run-in period. Montelukast modestly improved asthma control over placebo. Compared with the placebo period, montelukast decreased the average use of beta-agonists by 1 puff per day. Asthma exacerbation days decreased by about 1 per month during montelukast treatment. The effects of montelukast and placebo on forced expiratory volume in 1 second (FEV₁), quality of life, and adverse events did not differ significantly.³

One randomized, open-label crossover study of 124 children with "mild" asthma found that montelukast provided equivalent control and superior patient and parent satisfaction when compared with inhaled corticosteroids. Outcomes assessed were FEV₁, school and work loss, medical resource utilization, safety, and patient and parent satisfaction. Children entering this study were self-selected to extend participation from a previous larger study that did not meet Cochrane quality criteria for inclusion in meta-analysis. The authors acknowledge the potential for selection bias.⁴

A randomized, double-blind, placebo-controlled study of 338 patients aged 12 years to adult compared zafirlukast (Accolate) with fluticasone propionate (Flovent) for control of persistent asthma. This study concluded that fluticasone was superior for all clinical outcomes measured including symptom scores, albuterol use, nighttime awakenings pulmonary function, and number of exacerbations requiring oral corticosteroids. Pooling of adult and adolescent cases in this study limits generalized application of these results to pediatric practice.⁵

■ RECOMMENDATIONS FROM OTHERS

The National Asthma Education and Prevention Program⁶ and the Global Initiative for Asthma⁷ guidelines conclude that inhaled corticosteroid, at the lowest effective dose, is the preferred therapy for children of all ages with persistent asthma whether mild, moderate, or severe.

Both guidelines list leukotriene inhibitors as a potential adjunct to corticosteroids for moderate persistent asthma, as an alternative to corticosteroids plus long-acting beta₂-agonist. The guidelines also list leukotriene inhibitors as an alternative treatment to inhaled corticosteroids for mild persistent asthma in patients aged >5 years. Montelukast (Singulair) is approved for use in children aged ≥12 months, zafirlukast (Accolate) is approved for children aged ≥5 years, and zileuton (Zyflo) is approved only for children aged >12 years.

Nancy E. Morden, MD, Department of Family Medicine, University of Washington, Seattle; Leilani St. Anna, MLIS, AHIP, University of Washington Health Sciences Library, Seattle

■ CLINICAL COMMENTARY

An inhaled corticosteroid controller should be the first step

Until evidence supports a different conclusion, I think we should continue to follow current national and global guidelines. The most important concept in both is that once a child is diagnosed with persistent asthma, starting an inhaled corticosteroid controller should be the first step.

Leukotriene inhibitors should be considered as second or third choice as a controller. The main indications for using a leukotriene inhibitor are aspirin-sensitive, exercise-induced, and nocturnal asthma. I would use a leukotriene inhibitor as a controller only if a patient could not comply with inhaled corticosteroids.

Lawrence S. Slotnick, MD, Moses Cone Health System, Greensboro, NC

REFERENCES

1. Ducharme F, Hicks G, Kakuma R. Addition of anti-leukotriene agents to inhaled corticosteroids for chronic asthma. *Cochrane Database Syst Rev* 2002; (1):CD003133.
2. Ducharme FM, Hicks GC. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database Syst Rev* 2002; (3):CD002314
3. Simons FE, Villa JR, Lee BW, G et al. Montelukast added to budesonide in children with persistent asthma: a randomized, double-blind, crossover study. *J Pediatr* 2001; 138:694–698.
4. Maspero JF, Duenas-Meza E, Volovitz B, et al. Oral montelukast versus inhaled beclomethasone in 6- to 11-year-old children with asthma: results of an open-label extension study evaluating long-term safety, satisfaction and adherence with therapy. *Curr Med Res Opin* 2001; 17:96–104.
5. Busse W, Wolfe J, Storms W, et al. Fluticasone propionate compared with zafirlukast in controlling persistent asthma: a randomized double-blind, placebo-controlled trial. *J Fam Pract* 2001; 50:595–602.
6. National Asthma Education and Prevention Program. *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma*. 1997 (rev 2002). Available at: www.nhlbi.nih.gov/guidelines/asthma/. Accessed on March 5, 2004.
7. Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention*. Rockville, Md: National Heart, Lung, and Blood Institute. 1995 (revised 2002). Available at: www.ginasthma.com/wr.html. Accessed on March 5, 2004.

Which blood tests are most helpful in evaluating pelvic inflammatory disease?

■ EVIDENCE-BASED ANSWER

No individual or combination of blood tests can reliably diagnose pelvic inflammatory disease (PID) (strength of recommendation [SOR]: **A**, meta-analysis). The combination of white blood cell count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and vaginal white blood cells can reliably exclude PID if results for all 4 tests are normal (sensitivity=100%) (SOR: **B**, cohort study, reference standard not uniformly applied).

The combination of CRP and ESR is helpful in excluding PID (sensitivity=91%) and may be especially useful in distinguishing mild from complicated cases (SOR: **B**, small cohort study). Individual tests do not appear to significantly improve diagnostic accuracy, although the CRP and ESR are somewhat useful to rule out PID (SOR: **B**, small cohort study).

■ EVIDENCE SUMMARY

Because of the significant inflammatory sequelae of PID, it is the standard of care to treat women with suggestive signs and symptoms. Clinical

CONTINUED