

The Role of Leukotriene Receptor Antagonists in Asthma Care

EBEM Commentator Contact

Neil M. Skjodt, MD, MSc,

FRCPC, FCCP

Brian H. Rowe, MD, MSc, FCCP

From the Divisions of Pulmonary and Critical Care Medicine and Department of Emergency Medicine, University of Alberta, Edmonton, Alberta, Canada.

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SYSTEMATIC REVIEW ABSTRACT SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Ducharme F, Schwartz Z, Kakuma R. Addition of anti-leukotriene agents to inhaled corticosteroids for chronic asthma. *Cochrane Database Syst Rev*. 2004;Issue 1. Chichester, UK: John Wiley and Sons. DOI: 10.1002/14651858.CD003133.pub2.

The *Annals* EBEM editor assisted in the preparation of the abstract of this Cochrane systematic review, as well as selection of the Evidence-Based Medicine Teaching Points.

OBJECTIVE

To examine the safety and efficacy of daily antileukotrienes plus inhaled corticosteroids compared to corticosteroid alone and determine the corticosteroid-sparing effect of antileukotrienes when added to corticosteroid in chronic asthma.

DATA SOURCES

The authors searched MEDLINE, EMBASE, CINAHL (until August 2003), and reference lists of review articles and trials; contacted international headquarters of antileukotriene manufacturers; and examined American Thoracic Society and European Respiratory Society meeting abstracts (1998 to 2003).

STUDY SELECTION

Randomized placebo-controlled trials of asthmatic patients aged 2 years and older, with at least 1 month of intervention.

DATA EXTRACTION AND ANALYSIS

Two reviewers assessed quality and extracted data independently. Trials were grouped by asthma control at baseline (symptomatic or well controlled) and dose of corticosteroid in the control group (same or double). Where possible, data were pooled and relative risks (RRs) and weighted mean differences, each with 95% confidence intervals (CIs), were calculated using fixed- or random-effects models, as appropriate.

MAIN RESULTS

Of 587 citations, 27 (25 adult and 2 pediatric) trials met inclusion criteria. Sixteen trials were published in full text, and 16 trials reported data in a way that allowed meta-analysis. In symptomatic patients, addition of licensed doses of antileukotrienes to corticosteroid resulted in a nonsignificant reduction in the risk of exacerbations requiring systemic steroids (RR 0.64; 95% CI 0.38 to 1.07). A modest improvement group difference in peak expiratory flow was observed (weighted mean difference 7.7 L/minute; 95% CI 3.6 to 11.8 L/minute), together with decreased use of rescue short-acting β_2 -agonist use (weighted mean difference 1 puff/week; 95% CI 0.5 to 2 puffs/week). Only 3 trials compared the use of licensed doses of antileukotrienes with increasing the dose of corticosteroid; no firm conclusion can be drawn about the equivalence of both treatment options. In corticosteroid-sparing studies of patients who were well controlled at baseline, addition of antileukotrienes produced no overall difference in dose of corticosteroid (weighted mean difference $-21 \mu\text{g/d}$; 95% CI -65 to $23 \mu\text{g/d}$); however, it was associated with fewer withdrawals caused by poor asthma control (RR 0.63; 95% CI 0.42 to 0.95).

CONCLUSIONS

The addition of licensed doses of antileukotrienes to add-on therapy of corticosteroid results in modest improvement in lung function. Although this strategy appears comparable to increasing the dose of inhaled steroids, the power of the review is insufficient to confirm the equivalence of both treatment options. Addition of antileukotrienes is associated with superior asthma control after corticosteroid tapering; although the corticosteroid-sparing effect cannot be quantified at present, it appears modest.

Systematic Review Abstract Contact

Francine Ducharme, MD, MSc, FCRCP

Department of Pediatrics

McGill University

Montreal, Quebec, Canada

E-mail: francine.ducharme@muhc.mcgill.ca

COMMENTARY: CLINICAL IMPLICATION

Acute asthma is a common emergency department (ED) presentation in North America and elsewhere. Many patients

with acute asthma presenting to the ED represent preventable failures in disease control. Emergency physicians can treat acute asthma and initiate management strategies that help regain asthma control. According to consensus guidelines, asthma control now means no unplanned medical care, absenteeism, activity limitation, symptoms, or spirometry abnormalities.¹ Such control has been elusive for many asthmatic patients; however, control is possible through education, trigger reduction, and, for most patients with asthma, long-term asthma controller medications. Antileukotrienes are agents that are administered orally or intravenously and block the cysteinyl leukotriene inflammatory cascade. Unlike systemic corticosteroids, which act on a variety of components of the inflammatory cascade, leukotriene antagonists act much more selectively and upstream by either blocking leukotriene receptors or inhibiting 5-lipoxygenase (zileuton). Clinically, along with long-acting β -agonists, antileukotrienes represent options in managing asthma refractory to inhaled corticosteroids.

This Cochrane review has addressed the role of antileukotrienes in asthma management. Using a comprehensive search strategy to avoid publication bias and an independent assessment process that avoids selection bias, the authors identified 27 trials in chronic asthma. The review suggests minimal benefit in acute asthma but that adding an antileukotriene to an inhaled corticosteroid may improve asthma control without increasing the dose (adverse effects and cost) of corticosteroid therapy. Two important points must be added to the systematic review. First, antileukotrienes are the only long-term asthma therapy available in tablet form if inhaler use is impossible; however, they have been found to be less efficacious than inhaled corticosteroid.² Second, adding a long-acting β -agonist to an inhaled corticosteroid may be more effective than adding an antileukotriene.³⁻⁵

The role of antileukotrienes in acute asthma is unclear at this point. There is emerging evidence that these agents (eg, montelukast, zafirlukast), initiated in the ED during asthma exacerbations, may rapidly improve lung function and reduce the risk of relapse after ED discharge.^{6,7} Outside of the ED, other trials show slight to modest reductions in exacerbations, corticosteroid dose, prescription of systemic steroids, and rescue medication use when antileukotrienes are used for weeks to months. Further research is therefore needed to clarify the incremental benefit (and risks) of combining corticosteroids with other agents (eg, inhaled/oral corticosteroid with long-acting bronchodilators, inhaled/oral corticosteroid with leukotriene modifiers) during asthma exacerbations, focusing on strong clinical outcomes. Large, simple, multicenter trials are ideally suited to address these questions.

Why is this information important to emergency physicians? Emergency physicians will assess patients who present to the ED with acute asthma and are currently receiving antileukotrienes. Knowledge that these agents are only one of several options may be important if patients are currently using them as a monotherapy. In addition, emergency physicians need to be

aware that systemic corticosteroids are more potent and proven anti-inflammatory agents in the acute setting. Finally, in consultation with the patient's primary care provider, emergency physicians may need to initiate changes in asthma management to achieve asthma control. In patients who have failed with standard treatments such as corticosteroid, antileukotrienes should be a consideration in those who are unable to use inhalers or when long-acting β -agonists use is not possible (eg, prior adverse reaction). When antileukotrienes are prescribed, disclosure and follow-up for rare hepatotoxicity are required, and their use in pregnancy or lactation is less well studied than other asthma therapies.

TAKE-HOME MESSAGE

Understanding the role of antileukotrienes in asthma is important for emergency physicians. These agents have been used in acute asthma; however, the evidence is limited. Consequently, systemic and inhaled corticosteroids remain the mainstay of management after ED discharge. Prescribing antileukotrienes as part of a discharge asthma management plan may be useful in certain circumstances.

EBEM Commentator Contact

Neil M. Skjodt, MD, MSc, FRCPC, FCCP
Divisions of Pulmonary and Critical Care Medicine
University of Alberta
Edmonton, Alberta, Canada
E-mail: neil.skjodt@ualberta.ca

EBEM TEACHING POINT

Direct versus indirect comparisons. In many situations in which clinicians are required to make clinical management decisions, there is often a variety of comparisons from which to choose. *Direct comparisons* involve 2 interventions head to head; for example, antileukotriene versus corticosteroid. When head-to-head trials are pooled in a meta-analysis, this direct comparison can determine the relative benefits of the 2 interventions. *Indirect comparisons*, on the other hand, require inference and some statistical assumptions before conclusions can be made. For example, pooling results from several antileukotriene versus placebo trials would inform the reader that antileukotrienes improve outcomes in asthma compared with placebo. Similarly, pooling results from several long-acting β -agonists versus placebo trials would inform the reader that long-acting β -agonists improve outcomes in asthma compared with placebo. An indirect comparison would involve the results of both of these reviews to identify the relative benefits of antileukotrienes versus long-acting β -agonists in asthma. Although empirical research has shown that most direct and indirect comparisons are concordant, there are some problems associated with the inferences associated with unadjusted indirect comparisons.⁸ To better understand the effectiveness of one therapy when many are available, the evidence for the one therapy both against and with each of its alternative therapies

should be sequentially assessed. This is often not possible, requires a number of systematic reviews to arrive at the desired clinical decision, or requires a direct comparison trial or systematic review. In this example, the Cochrane database does contain another systemic review that provides direct comparison evidence.⁹

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