

The evolving role of intravenous leukotriene modifiers in acute asthma

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Despite significant advances in long-term preventative treatments that reduce the frequency of asthma exacerbations, acute asthma remains a common and important medical problem. In particular, some patients have an inadequate response to available first-line therapies for acute asthma, including inhaled short-acting β -agonists and anticholinergic agents and systemic corticosteroids. In this issue of the *Journal of Allergy and Clinical Immunology*, Camargo et al¹ present a randomized controlled trial of intravenous montelukast, a cysteinyl leukotriene 1 (CysLT₁) receptor antagonist, added to current standard care for the treatment of acute asthma. Based on the prespecified, primary end point of the time-weighted average change in FEV₁ over 60 minutes after drug administration, the investigators found that intravenous montelukast resulted in greater improvement in FEV₁ than standard care by a magnitude of 0.10 L. Despite this early improvement in lung function, there was no significant difference in treatment failures defined as hospitalization or as inability to discharge from the emergency department by 3 hours after study drug infusion; however, subgroups, including subjects with less severe exacerbations and enrolled at sites in the United States, did have fewer treatment failures after receiving intravenous montelukast.

In a previous, dose-ranging pilot study comparing 7- and 14-mg doses of intravenous montelukast with placebo, the investigators found that the improvement in FEV₁ at 20 minutes after administration was 14.8% from baseline in the combined treatment groups compared with 3.6% in the placebo group, with no difference between the 2 active treatment arms.² This prior study was criticized for not including an inhaled anticholinergic agent in the standard treatment regimen, and corticosteroid

administration was left to the treating physician's judgment.^{3,4} In the present study all patients received nebulized short-acting β_2 -agonist and anticholinergic therapy and a systemic corticosteroid according to a standardized treatment algorithm. Other differences were that the pilot study was conducted in subjects with relatively mild exacerbations (ie, FEV₁ $\leq$ 70% at presentation) who were not treated with any concomitant therapy with systemic corticosteroids or leukotriene modifiers, whereas the present study was restricted to patients with more severe disease (ie, FEV₁ $\leq$ 50% at presentation), some of whom were treated with parenteral corticosteroids and leukotriene modifiers before the 12-hour period before enrollment.^{1,2}

The difference in lung function between montelukast treatment and standard care amounted to a modest difference of 0.10 L, a difference that was lower than the expected difference of 0.33 L used to power the study. In comparing the 2 studies, it is apparent that the better response to standard therapy that included ipratropium bromide in the present study was responsible for the reduced magnitude of difference between the active treatments versus placebo. This result is not surprising given that addition of ipratropium bromide to albuterol resulted in a 0.35-L improvement in FEV₁ at 60 minutes after randomization in a similar patient population with FEV₁ of 50% or less of predicted value caused by acute asthma.⁵ How these early improvements in lung function compare with other adjunctive therapies, such as intravenous magnesium and heliox-driven nebulizers, was not addressed. The improvement in lung function was greater in those patients with milder exacerbations, which is similar to the findings in the pilot study in which patients with less severe exacerbations were enrolled. It remains unclear why the patients with more severe disease did not benefit to the same degree.

Although there was no overall difference in treatment failure between the groups, at US sites there were fewer treatment failures in subjects treated with montelukast, but this difference was not observed at non-US sites. In addition, subjects who reported prior therapy with systemic corticosteroids or leukotriene antagonists had fewer treatment failures when treated with montelukast, as did the less severe group with FEV₁ of greater than 30% of predicted value during the initial evaluation in the emergency department. In the prior pilot study in which systemic corticosteroids were administered at the discretion of the treating physician, montelukast was associated with less corticosteroid and short-acting β_2 -agonist use and a trend toward a reduction in treatment failures that was statistically significant if baseline lung function was accounted for in the model.² These results indicate that montelukast might reduce treatment failures in some patients with acute asthma, although the difference related to this treatment might be attenuated when patients are treated with systemic corticosteroids. These results are consistent with a study of the oral CysLT₁ receptor antagonist zafirlukast that reduced the rate of relapse in subjects with acute asthma who

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received oral prednisone in the emergency department and over the week after discharge.⁶ From a biological standpoint, treatment with antileukotriene therapies and corticosteroids are likely complementary because corticosteroids fail to directly decrease endogenous leukotriene synthesis *in vivo*.⁷

One question raised by these results is whether oral leukotriene modifiers should be used during an acute asthma exacerbation. The 7-mg dose of intravenous montelukast has a similar area under the curve treatment response during the 24 hours following administration as the 10-mg oral formulation of montelukast; however, the onset of action is earlier with intravenous montelukast.⁸ In the oral zafirlukast study mentioned above, there was no significant difference in lung function over 3 or more hours of observation in the emergency department after administration of drug relative to placebo.⁶ Another recent pilot study of children with acute asthma treated with 5 mg of oral montelukast versus placebo in addition to usual care was terminated early because of lack of efficacy at the interim data analysis because of an insufficient difference in FEV₁ at 3 hours after oral administration.⁹ An additional limitation of oral administration is that genetic variation in transporter proteins mediating intestinal absorption of montelukast affects the absorption of the drug into plasma.¹⁰

Based on the biology of leukotrienes, it is expected that a CysLT₁ receptor antagonist should reverse ongoing bronchoconstriction; however, the effects on the progression of cellular inflammation during an acute episode of asthma are less certain. Leukotrienes are synthesized from arachidonic acid through the action of 5-lipoxygenase/5-lipoxygenase-activating protein in response to stimuli such as allergen challenge, viral infection, and exercise in susceptible subjects.¹¹ The CysLTs (ie, leukotriene [LT] C₄, LTD₄, and LTE₄) are most strongly implicated in asthma. Some patients with persistent asthma can have dramatic improvements in lung function after treatment with a leukotriene modifier.¹² During acute asthma, CysLT levels are increased, as measured by urinary levels of LTE₄, which is the predominant CysLT in biological fluids because of its greater stability. The CysLT₁ receptor has the highest affinity for LTD₄, whereas the CysLT₂ receptor has equal affinity for LTC₄ and LTD₄, and neither of these receptors appreciably binds LTE₄. Although LTD₄ initiates bronchoconstriction through the CysLT₁ receptor, the major mechanism controlling CysLT-mediated cellular influx might be through LTE₄ because inhalation of LTE₄, but not LTD₄, initiates a cellular influx into the airways in asthmatic subjects.¹³ Recent work with mice lacking CysLT₁ or CysLT₂ receptors indicates that LTE₄ mediates edema formation through a receptor designated the CysLT_E receptor¹⁴ and cellular trafficking to the airways through the adenosine diphosphate-reactive purinergic P2Y₁₂ receptor.¹⁵ A specific CysLT_E receptor antagonist is not currently available.

In summary, intravenous montelukast has an additive benefit in terms of early improvement in lung function as an adjunct to standard therapy for acute asthma that is modest in magnitude and most beneficial to those with less severe exacerbations. The effect of intravenous montelukast on the progression of an asthma exacerbation is less certain, but the data suggest that some patients might benefit. Additional studies that assess alterations in leukocyte trafficking to the airways and the production of inflammatory mediators over the course of an asthma exacerbation would lead to a better understanding of the place of leukotriene modifiers in acute asthma.

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