

Leukotriene modifiers: What is their position in asthma therapy?

Leukotrienes have been recognized as potent mediators of inflammation released by a number of cells involved in the inflammatory response to an allergic stimulus, namely mast cells, basophils, eosinophils, neutrophils, and macrophages, all present in the airways of patients with asthma. They are produced by the 5-lipoxygenase pathway of arachidonic acid metabolism and mediate bronchoconstriction and inflammatory changes important in the pathophysiology of asthma, such as the permeability of the microvasculature, mucus secretion, neutrophil recruitment, and airway edema.¹

In 1996, 2 medications in the leukotriene modifier class were approved for use in the treatment of asthma in the United States: zileuton, a 5-lipoxygenase enzyme inhibitor, and zafirlukast, a specific LTD₄ receptor antagonist. Another LTD₄ antagonist, montelukast, has recently been approved by the Food and Drug Administration. One of the advantages of montelukast over the previous 2 medications in this class is that studies were conducted in children as young as 6 years of age and are presently being conducted in children with asthma as young as 2 years of age. This has implications for the treatment of asthma in young children. In general, the medications in this class have the following properties in subjects with mild-to-moderate persistent asthma²⁻⁵: (1) immediate bronchodilator effect as demonstrated by improvement in FEV₁ by 10% to 15% over baseline, (2) reduction of as needed bronchodilator use by approximately 33% per day, (3) improvement in FEV₁ over time with chronic administration by approximately 10%, (4) reduction in nocturnal symptoms, (5) reduction in acute exacerbations requiring rescue medication, (6) ability to reduce inhaled glucocorticoid dose, (7) additive effect to inhaled glucocorticoid therapy, (8) additive effect to inhaled β -agonist effect, (9) reduced cellular inflammatory response to an inhaled allergen challenge in allergen-sensitized patients, (10) reduction in blood eosinophil count demonstrated for zileuton and montelukast suggesting a reduced chronic inflammatory response, (11) improved exercise tolerance demonstrated with single-dose (zafirlukast) and chronic therapy (montelukast), (12) efficacy in blocking aspirin-induced pulmonary response in aspirin-sensitive patients, and (13) no indication of tolerance or tachyphylaxis to the medication with chronic administration.

The report by Hamilton et al⁶ in this issue of The Journal indicates that pranlukast, another in a series of leukotriene receptor antagonists, can attenuate allergen-induced early- and late-phase pulmonary responses. Of particular interest, the increase in airways hyperresponsiveness measured after 24 hours that occurs after an allergen challenge was also attenuated. The investigators conclude that this observation adds further support for an important role for the cysteinyl leukotrienes in mediating allergen-induced asthmatic responses. Several studies have shown that pranlukast can alter airways hyperresponsiveness over time when administered on a regular basis.^{7,8} Another interesting study with pranlukast conducted by Tamaoki et al⁹ demonstrated that pranlukast prevented a breakdown in symptom control and pulmonary function, as well as an increase in serum eosinophilic cationic protein and exhaled nitric oxide when the dose of inhaled beclomethasone dipropionate was reduced by one half in patients with moderate persistent asthma. Although attenuation of the early- and late-phase response to an allergen challenge in allergen-sensitive patients has been demonstrated with several other leukotriene modifiers, there is only one study, the study conducted with zafirlukast, that shows an effect on the attenuation of increased airways hyperresponsiveness after allergen challenge in allergen-sensitive subjects.¹⁰ This was measured only 6 hours after the allergen challenge. The available studies with pranlukast support a potential antiinflammatory effect of this medication and perhaps some unique properties of pranlukast as compared with the other leukotriene modifiers. Therefore it is important to obtain similar information on the other available leukotriene modifiers. Until then, the results obtained with pranlukast can not be extended to these other leukotriene modifiers.

PRESENT STATUS OF ASTHMA THERAPY

Recent guidelines for the diagnosis and treatment of asthma highlight inhaled glucocorticoids as the cornerstone of asthma therapy and the *preferred* long-term controller medication for asthma management.¹¹ It is apparent that inhaled glucocorticoids are effective in controlling asthma symptoms and reducing the intensity of the inflammatory response. This effect lasts only as long as the treatment continues. There is no known treatment that can induce a lasting remission in the disease. Understanding the onset and progression of the inflammation, as well as its persistence, could provide insight into defining appropriate strategies for treatment depending on the

stage of the disease. For example, it has been suggested that early recognition of the onset of asthma and early intervention with inhaled glucocorticoids could prevent irreversible changes in pulmonary function.¹² Alternatives to inhaled glucocorticoids identified in recent guidelines include cromolyn, nedocromil, theophylline, and the leukotriene modifiers (specifically zileuton or zafirlukast).¹¹ No studies show that these medications have an effect on reducing airway inflammation that is comparable with that of inhaled glucocorticoids.

There are practical clinical and patient problems that affect the success of asthma management in individual patients. Limited application of pulmonary function testing, poor adherence to prolonged treatment programs, cost of medical care, access to medical care, poor asthma knowledge of caretakers in day care and school programs, inability to monitor inflammation and gauge treatment based on measures of inflammation, and the complexity of the many forms of treatment administration and dosing schedules are a few of these problems. We have no practical measure of airways inflammation for clinical application and therefore we must rely on symptoms and pulmonary function to guide therapy. Some medications, described as *controllers*, relieve and even prevent symptoms and also improve pulmonary function, but do not prevent or resolve airways inflammation (eg, long-acting β -agonists).

The leukotriene modifiers offer a potential advantage of ease of administration as compared with the need for careful administration of inhaled medications. Unlike theophylline, the leukotriene modifiers do not have a narrow margin of safety. The newest leukotriene modifier, montelukast, can be administered once daily, has no reported drug interactions, and to date has a good safety profile even in children as young as 6 years of age.⁵

POTENTIAL APPLICATIONS OF LEUKOTRIENE MODIFIERS IN ASTHMA THERAPY

This is an interesting new class of medications that have the benefits of oral administration. Potential applications of these medications include the following:

1. They are an alternative to inhaled glucocorticoid therapy in patients with mild persistent asthma who are unable to take inhaled medication, and they offer the convenience of oral administration. It is not clear whether they could prevent potential irreversible changes caused by inflammation associated with asthma, but it is not clear whether any medication, other than inhaled glucocorticoids,¹² could be helpful in alleviating this component of asthma pathogenesis.
2. As a supplement to inhaled controller medications they can reduce the need for high-dose inhaled glucocorticoid therapy.
3. They are medications with a different mechanism of action that could have an additive effect with other medications in improving the overall response to treatment.
4. They could be a potential benefit in the management of asthma patients with aspirin sensitivity.

5. They could allow an opportunity to individualize the approach to therapy as we begin to understand the differences in asthma pathophysiology among patients. Perhaps some patients have a primary leukotriene-mediated disease process.

AREAS OF NEED

Although the studies by Hamilton et al⁶ and others⁷⁻⁹ suggest pranlukast may have unique antiasthma properties as compared with other leukotriene modifiers, additional comparisons are needed between the leukotriene modifiers, as well as other long-term controller asthma medications. Of note, there are no available bronchoscopic studies showing a reduction in airway inflammation of persistent asthma with chronic use of the leukotriene modifiers. Inhaled corticosteroids clearly reduce inflammation in the airways of asthmatic patients.¹³ In addition, there are no studies that show a reduction in collagen deposition with chronic therapy with a leukotriene modifier similar to that reported with inhaled glucocorticoid therapy.¹⁴ Collagen deposition has been implicated as a component of airway remodeling. It would also be very useful to demonstrate that this class of medications has an effect on other allergic disorders, such as rhinitis, atopic dermatitis, conjunctivitis, and potentially sinusitis and otitis. The latter property would enhance the selection of a leukotriene modifier as a first-line, long-term controller medication as compared with an inhaled antiasthma medication. To date, there have been no reports of their beneficial effects in patients with severe persistent asthma (ie, oral steroid-sparing effect) or improvement in clinical parameters. This does not mean that they may not be useful in patients with severe persistent asthma, just that studies are needed to verify their effect in this group of patients.

Another interesting observation, first reported by DuBuske et al,¹⁵ suggests that a proportion of patients may not respond to leukotriene modifier therapy. Zileuton was the medication evaluated in this study, and approximately 25% of the patients evaluated in an open-label trial failed to show significant improvement in pulmonary function. This has raised questions of whether there may be genetic differences that could influence response to treatment. In et al.¹⁶ recently reported mutations in the human 5-lipoxygenase gene promoter that can modify reporter gene transcription. Further studies are needed to determine whether genetic differences in expression of 5-lipoxygenase influence the asthmatic response, as well as the capacity of 5-lipoxygenase inhibitors to alter the asthmatic response.

The report by Hamilton et al⁶ advances our understanding of this specific leukotriene modifier, pranlukast, on influencing an important consequence of allergen-induced inflammation, namely bronchial hyperresponsiveness. However, there are a number of gaps that must be filled in our understanding of the mechanism of action of pranlukast, as well as of the other leukotriene modifiers. If airways inflammation is a key component of asthma and it influences disease progression, then the challenge for the future

will be to show that the leukotriene modifiers have significant effects on reducing airway inflammation and disease progression. This would be important in establishing the role of leukotriene modifiers in asthma control. If this is accomplished, the leukotriene modifiers may become one of the *preferred* long-term controller therapies for asthma.

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REFERENCES

- Holgate ST, Bradding P, Sampson AP. Leukotriene antagonists and synthesis inhibitors: new directions in asthma therapy. *J Allergy Clin Immunol* 1996;98:1-13.
- Israel E, Cohn J, Dube L, Drazen JM. Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma. A randomized controlled trial. Zileuton Clinical Trial Group. *JAMA* 1996;275:931-6.
- Liu MC, Dube LM, Lancaster J, and the Zileuton Study Group. Acute and chronic effects of a 5-lipoxygenase inhibitor in asthma: a 6-month randomized multicenter trial. *J Allergy Clin Immunol* 1996;98:859-71.
- Spector SL, Smith LJ, Glass M. Effects of 6 weeks of therapy with oral doses of ICI 204,219, a leukotriene D₄ receptor antagonist, in subjects with bronchial asthma. ACCOLATE Asthma Trialists Group. *Am J Respir Crit Care Med* 1994;150:618-23.
- Knorr B, Matz J, Bernstein JA, Nguyen H, Seidenberg BC, Reiss TF, et al. Montelukast for chronic asthma in 6- to 14-year-old children: a randomized, double-blind trial. Pediatric Montelukast Study Group. *JAMA* 1998;279:1181-6.
- Hamilton AL, Faiferman I, Stober P, Watson RM, OByrne PM. Pranlukast, a cysteinyl leukotriene receptor antagonist, attenuates allergen-induced early and late phase bronchoconstriction and airway hyperresponsiveness in asthmatic subjects. *J Allergy Clin Immunol* 1998;102:177-183.
- Fujimura M, Sakamoto S, Kamio Y, Matsuda T. Effect of a leukotriene antagonist, ONO-1078, on bronchial hyperresponsiveness in patients with asthma. *Respir Med* 1993;87:133-8.
- Taki F, Suzuki R, Torii K, Matsumoto S, Taniguchi H, Takagi K. Reduction of the severity of bronchial hyperresponsiveness by the novel leukotriene antagonist 4-oxo-8-[4-(4-phenyl-butoxy)benzoylamino]-2-(tetrazol-5-yl)-4H-1-benzopyran hemihydrate. *Drug Res* 1994;44:330-3.
- Tamaoki J, Kondo M, Sakai N, Nakata J, Takemura H, Nagai A, et al. Leukotriene antagonist prevents exacerbation of asthma during reduction of high-dose inhaled corticosteroid. The Tokyo Joshi-Idai Asthma Research Group. *Am J Respir Crit Care Med* 1997;155:1235-40.
- Taylor IK, O'Shaughnessy KM, Fuller RW, Dollery CT. Effect of cysteinyl-leukotriene receptor antagonist ICI 204,219 on allergen-induced bronchoconstriction and airway hyperactivity in atopic subjects. *Lancet* 1991;337:690-4.
- National Asthma Education and Prevention Program Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health, National Heart, Lung and Blood Institute; 1997. Pub. No. 97-4051.
- Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88:373-81.
- Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. *Am J Respir Crit Care Med* 1998;157(Pt 2):S1-53.
- Olivieri D, Chetta A, Del Donno M, Berorelli G, Casalini A, Pesci A, et al. Effect of short-term treatment with low-dose inhaled fluticasone propionate on airway inflammation and remodeling in mild asthma: a placebo-controlled study. *Am J Respir Crit Care Med* 1997;155:1864-71.
- DuBuske LM, Grossman J, Dube LM, Swanson LJ, Lancaster JF, and the Zileuton Study Group. Randomized trial in patients with moderate asthma: effect of reduced dosing frequency and amounts on pulmonary function and asthma symptoms. *Am J Managed Care* 1997;3:633-40.
- In KH, Asano K, Beier D, Grobholz J, Finn PW, Silverman ES, et al. Naturally occurring mutations in the human 5-lipoxygenase gene promoter that modify transcription factor binding and reporter gene transcription. *J Clin Invest* 1997;99:1130-7.