Asthma is a chronic inflammatory disease that affects >300 million people worldwide. However, inhaled corticosteroids (ICS), the gold standard therapy for persistent asthma, cannot suppress every component of airway inflammation and often fail to adequately penetrate the small airways in order completely suppress eosinophilia. Cysteinyl leukotrienes are important inflammatory factors that are involved in asthma and allergic diseases, and montelukast, a cysteinyl leukotriene receptor antagonist (LTRA), is a competitive antagonist of these substances for the cysteinyl leukotriene type-1 receptor 1 (LTR1). Montelukast mono-
therapy has been shown to relieve the clinical symptoms of mild persistent asthma. As either a monotherapy or in combination with ICS, montelukast provides clinically relevant improvements to various asthma-related parameters, including symptoms, lung function, quality of life, and asthma exacerbations, and has been found to reduce eosinophilic airway inflammation by downregulating Mac-1 expression and eosinophil chemotaxis in patients with chronic asthma.1,2 Furthermore, montelukast has been reported to produce bronchoprotective effects against both specific and nonspecific bronchoactive stimuli. When treating childhood asthma, montelukast demonstrates faster clinical responses than ketotifen, including improved exhaled nitric oxide, peak expiratory flow, and asthma scores within 1 week.3 Similarly, in patients with allergic rhinitis, montelukast produces substantial improvements in symptoms and quality of life.2 The anti-inflammatory effects of LTRA have been reported widely in both in vivo and in vitro studies.4 Several studies have reported that LTRA may have anti-inflammatory effects, not only as an antagonist to LTR1, but also as an inhibitor of inflammatory cells. For example, montelukast and zafirlukast, two LTRAs, significantly downregulate monocyte chemoattractant protein-1 (MCP-1)-induced chemotaxis of human primary monocytes via the downregulation of MCP-1-induced [Ca²⁺], and p38 MAPK expression.5

Airway inflammation, hyperresponsiveness, and remodeling are the fundamental components of the subsequent pathogenesis that leads to the symptoms and changes in lung function that are the hallmarks of asthma. Airway remodeling consists of the structural changes that occur in the airways of the lungs as a result of asthma, and the remodeling process involves diverse pathological changes that include epithelial metaplasia, subepithelial fibrosis, angiogenesis, and smooth muscle thickening. Airway remodeling will result in the irreversible loss of lung function and airway hyperresponsiveness. Airway remodeling is usually associated with severe and persistent disease with poor control. Current asthma therapies (e.g., ICS) can successfully treat allergic inflammation, an important factor that contributes to remodeling, but these therapies do not specifically target the remodeling processes that can progress despite the optimal control of inflammation. Moreover, airway remodeling might not be prevented despite the widespread use of anti-inflammatory treatments. There is limited evidence demonstrating the effectiveness of leukotriene inhibitors for the treatment or prevention of remodeling changes. The search for novel therapies that can reverse or prevent airway remodeling is a very active area in asthma research. Long-term studies on the effects of LTRA on airway remodeling in human asthma patients are still lacking and need to be performed.

A better understanding of airway remodeling in asthma patients will facilitate the development of new treatments for asthma that go beyond the control of symptoms and inflammation. Treatments that may be useful for preventing airway remodeling include those that target single or multiple components of the airway remodeling process. Matrix metalloproteinase 9 (MMP-9) acts as a proinflammatory molecule that perpetuates immune responses, but it is also involved in the repair processes that are activated following tissue injury and may regulate remodeling during inflammatory reactions. MMP-9 is critically involved in the recruitment of eosinophils and T-helper 2 (Th2) cells to the lungs following allergen challenges and the subsequent development of Th2 responses to allergens. Regarding this issue, Hsu et al presents the effects of a selective LTRA (MK-679) on airway inflammation and MMP expression in a mouse model.6
Asthma, patients on montelukast therapy for 8 weeks demonstrated significantly decreased levels of exhaled nitric oxide and plasma MMP-9 that were associated with improved symptoms and enhanced peak expiratory flow but not significantly associated with increased levels of tissue inhibitor metalloproteinase-1 (TIMP-1). Montelukast also demonstrates anti-inflammatory properties, including reducing or preventing eosinophilia, which may be partially due to reductions in MMP-9 because MMP-9 plays an important role in both airway inflammation and remodeling. LTRA has been shown to regulate MMP-9 expression in both mouse and human studies. Therefore, some LTRAs may demonstrate effects on the airway remodeling of asthma in vitro. Large population and long-term human in vivo studies are still needed to determine the effects of LTRA on airway remodeling.

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References