Asthma is a chronic inflammatory disease of the airways. Anti-inflammatory drug therapy, primarily using corticosteroids, is now considered the first-line treatment in the management of all grades of asthma severity. Although corticosteroids are believed to be the most potent anti-inflammatory agents available, they do not suppress all inflammatory mediators involved in the asthmatic response. Leukotrienes, which are lipid mediators generated from the metabolism of arachidonic acid, play an important role in the pathogenesis of asthma. They produce bronchospasm, increase bronchial hyperresponsiveness, mucus production, and mucosal edema, and enhance airway smooth muscle cell proliferation and eosinophil recruitment into the airways, and their synthesis or release is unaffected by corticosteroid administration. The use of leukotriene synthesis inhibitors or leukotriene receptor antagonists as anti-inflammatory therapies in asthma has therefore been investigated. Beneficial effects of leukotriene-modifying drugs have been demonstrated in the management of all grades of asthma severity, and there is evidence that certain patient groups (such as those with exercise-induced asthma or aspirin-induced asthma) may be particularly suitable for such therapy.

Key words: anti-inflammatory; antileukotrienes; aspirin-induced asthma; asthma; corticosteroids; eosinophil; inflammation

Abbreviations: CysLT = cysteinyl leukotriene; FLAP = 5-lipoxygenase–activating protein; GM-CSF = granulocyte-macrophage colony-stimulating factor; IL = interleukin; 5-LO = 5-lipoxygenase; LTA4 = leukotriene A4; LTB4 = leukotriene B4; LTC4 = leukotriene C4; LTD4 = leukotriene D4; LTE4 = leukotriene E4; TNF-α = tumor necrosis factor-α.

Asthma is one of the most common respiratory diseases encountered in clinical practice, affecting approximately 10% of children and 5% of adults worldwide. It is one of the few chronic diseases in the developed world that is increasing in prevalence, despite better understanding of its pathogenesis and improved treatments. This paradox necessitates continuing efforts to review current knowledge and to search for new insights into the pathogenesis and treatment of this complex disorder. For many years, asthma was regarded as a bronchospastic disease of airway smooth muscles, leading to treatment with oral and inhaled bronchodilators. However, with the institution and use of fiberoptic bronchoscopy with lavage and biopsy along with rapid advances in the fields of cellular and molecular biology, airway inflammation has been found to be an integral component in the pathogenesis of asthma. Even in patients with mild-to-moderate disease, a strong inflammatory component has been noted and is believed to be the driving force responsible for airway hyperresponsiveness and the propensity to airflow obstruction.1

*From the Respiratory Cell and Molecular Biology Division, Department of University Medicine, Southampton General Hospital, Southampton, UK.
Manuscript received March 28, 2000; revision accepted October 12, 2000.
Correspondence to: Sundeep S. Salvi, MD, PhD, Department of University Medicine, Level D Centre Block, Southampton General Hospital, Southampton SO16 6YD, UK; e-mail: sss@soton.ac.uk
A report by the Global Initiative for Asthma\textsuperscript{2} has defined asthma as

a chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells, eosinophils, and T lymphocytes. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and/or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partially reversible either spontaneously or with treatment. The inflammation also causes an associated increase in airway responsiveness to a variety of stimuli.

**Inflammation in Asthma**

The histopathologic characteristics of asthma include shedding of airway epithelium, sub-basement membrane fibrosis, hypertrophy of airway smooth muscle, excessive secretion of mucus, and a multicellular inflammation involving activated mast cells, eosinophils, neutrophils, macrophages, basophils, and lymphocytes. Each of these cells has an important contribution and a specific relation to the development of airway inflammation and airway narrowing.

Activation of mast cells by specific antigens through cell-bound IgE releases histamine and causes synthesis of cysteinyl leukotrienes (CysLTs); these acute-phase mediators cause airflow obstruction by directly increasing airway smooth muscle tone. Mast cells also release proteases (eg, tryptase,stromelysin, and chymase) and many pro-inflammatory cytokines (eg, tumor necrosis factor-\alpha [TNF-\alpha], granulocyte-macrophage colony-stimulating factor [GM-CSF], interleukin [IL]-3, IL-4, IL-5, IL-13), and chemokines, which contribute to airway inflammation and airway hyperresponsiveness.\textsuperscript{3}

Eosinophils are considered to be one of the major cells that mediate much of the pathology and disordered airway function that characterizes atopic and nonatopic asthma. Upon activation, these cells release several toxic mediators (major basic protein, eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin), reactive oxygen, and leukotrienes, as well as several proinflammatory cytokines including GM-CSF, IL-3, IL-4, and IL-5, all of which contribute to increased airway hyperresponsiveness and damage to the airway epithelium. Eosinophil numbers are found to be increased in the peripheral blood, sputum, BAL fluid, and bronchial tissues of patients with active asthma,\textsuperscript{4} and their numbers correlate positively with asthma severity.\textsuperscript{5}

T lymphocytes, through their capacity to recognize foreign proteins processed by antigen-presenting cells, generate a wide range of cytokines relevant to asthma pathogenesis and play a central role in the initiation and persistence of the inflammatory response. On activation, CD4+ T-helper cells differentiate along two broad pathways, termed Th1 and Th2, based on their pattern of cytokine secretion. Th1-like cells secrete IL-2, interferon-\gamma, and TNF-\alpha, which mediate delayed-type hypersensitivity reactions, while the Th2-like cells secrete IL-4, IL-5, and IL-13 and mediate allergic inflammatory responses.\textsuperscript{6} A clear differentiation between Th1 and Th2 does not occur in humans (rather there occurs a biased cytokine repertoire toward Th1 or Th2), and it is also important to realize that there are other cell sources of these cytokines in addition to CD4+ T cells. Asthma is characterized by selective recruitment of Th2-like cells, with a resultant increase in cytokines encoded in a cluster on chromosome 5q31–33. IL-4 and IL-13 induce and enhance IgE synthesis, while IL-13 also causes mucus hypersecretion, subepithelial fibrosis, and increases the levels of the eosinophil chemoattractant, eotaxin.\textsuperscript{7} IL-5 and GM-CSF induce eosinophil chemotaxis, differentiation, and activation, and enhance eosinophil survival.\textsuperscript{8–10}

Macrophages contribute to asthma pathogenesis by secreting a range of inflammatory mediators, including cytokines (TNF-\alpha, IL-1\beta, IL-6, IL-8, IL-12), chemokines, and leukotrienes; neutrophils, which are found in large numbers in the airways of patients with severe asthma, are believed to produce a wide range of inflammatory mediators, including IL-8 and other chemokines, leukotrienes, and reactive oxygen,\textsuperscript{11} which further perpetuate the inflammatory response.

Epithelial cells, which until recently were considered to act mainly as a physical barrier participating in mucociliary clearance and the removal of noxious agents, have been shown to participate actively in the asthmatic airway inflammatory response by releasing eicosanoids, peptidases, matrix proteins, proinflammatory cytokines, chemokines, and nitric oxide, as well as performing an antigen presenting function by their capacity to express major histocompatibility complex class II (human leukocyte antigen-DR) antigens.\textsuperscript{12} More recently, airway smooth muscle cells\textsuperscript{13,14} and fibroblasts\textsuperscript{15} have also been shown to contribute to asthma pathogenesis by acting as a cellular source for proinflammatory cytokines involved in asthma pathogenesis.

Thus, on activation, epithelial cells, mast cells, eosinophils, neutrophils, macrophages, and fibroblasts release a wide range of inflammatory mediators, including histamine, proteases, growth factors, platelet-activating factor, cytokines, and leukotrienes, which lead to bronchospasm, airway hyperresponsiveness, airway smooth muscle hypertrophy, denudation of airway epithelium, subepithelial fibrosis,
thickening of basement membrane, mucus hypersecretion, and activation of sensory nerves, all of which contribute to the pathophysiology of asthma (Fig 1).

**The Role of Leukotrienes in Asthma Pathogenesis**

Leukotrienes are lipid mediators synthesized from the ubiquitous precursor arachidonic acid, a normal constituent of the phospholipid bilayer that is present in many biological membranes, particularly the nuclear membrane. These molecules have received renewed interest as one of the major inflammatory mediators involved in asthma pathogenesis. They fall into two classes: the dihydroxy acids such as leukotriene B4 (LTB4), which are neutrophil chemoattractants, and the cysteinyl conjugates leukotriene C4 (LTC4), leukotriene D4 (LTD4), and leukotriene E4 (LTE4), which are potent smooth muscle contractants (constituting the slow reacting substance of anaphylaxis) and eosinophil chemoattractants.

**Leukotriene Synthesis**

A variety of biological signals activates cytosolic phospholipase A2 to liberate arachidonic acid from membrane phospholipid, including receptor activation, antigen-antibody interaction, physical stimuli such as cold or altered ionic environment, or stimuli that directly increase intracellular Ca$^{2+}$. Once released, metabolism of arachidonic acid gives rise to a group of pharmacologically active compounds collectively known as eicosanoids, made up of the prostaglandins, thromboxanes, leukotrienes, and hydroxyeicosatetraenoic acids. Arachidonic acid cleaved from the membrane interacts with 5-lipoxygenase–activating protein (FLAP), which helps to transfer it to the enzyme 5-lipoxygenase (5-LO). The result of this enzyme-substrate interaction is the production of 5-hydroperoxyeicosatetraenoic acid, which is transformed into the unstable intermediate leukotriene A4 (LTA4) by the same oxygenase. In neutrophils and monocytes, LTA4 is converted predominantly to the chemoattractant LTB4 by LTA4 hydrolase; in human eosinophils, mast cells, and basophils, LTA4 is conjugated with reduced glutathione by LTC4 synthase to form the first of the CysLTs, LTC4. After carrier-mediated cellular export, sequential cleavage of the glutathionyl side chain of LTC4 generates the extracellular metabolites LTD4 and LTE4 (Fig 2).

**Cellular Origin of Leukotrienes**

Expression of 5-LO is essentially restricted to various myeloid cells (neutrophils, eosinophils, monocytes/macrophages, mast cells/basophils, and B lymphocytes). Eosinophils and pulmonary mast cells, as well as fragments of human lung parenchyma in vitro, generate essentially CysLTs and little LTB4. Monocytes and macrophages produce both LTB4 and LTC4, while neutrophils secrete LTB4 as their principal 5-LO product. Endothelial cells and platelets do not express 5-LO, but have LTC4 synthase or LTA4 hydrolase and can therefore participate in leukotriene production via a transcellular mecha-

![Figure 1. Factors involved in the pathophysiology of asthma.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21962/ on 06/26/2017)
Human airway epithelial cells are thought to express 5-LO, LTA4 hydrolase, FLAP, and 15-lipoxygenase and may be an important source of LTB4 and 15-hydroxyeicosatetraenoic acid in the lung. However, it should be noted that evidence for the expression of 5-LO by epithelial cells is still limited.

**Leukotriene Receptors**

Leukotrienes exert their biological effects by acting on leukotriene receptors present on cell membranes. In man, three types of membrane leukotriene receptors have been identified, and it is likely that several more will be identified in the future. The non-CysLT LTB4 activates the BLT receptor, while the CysLTS (LTC4, LTD4, LTE4) activate CysLT receptors 1 and 2 (CysLT1 and CysLT2) subtypes. The BLT receptor has been recently cloned and belongs to the family of seven transmembrane G protein-coupled receptors. The CysLT1 receptor has also been recently cloned by two independent groups.

Leukotriene production is increased in asthma. Blood eosinophils from patients with asthma synthesize fivefold to 10-fold greater amounts of CysLTS than those from normal subjects, and this can be mimicked in vitro by treatment of normal eosinophils with the Th-2 cell-derived eosinophilpoietic cytokines IL-3, IL-5, and GM-CSF. This enhanced production probably relates to the upregulation of 5-LO and FLAP messenger RNA observed in asthmatic subjects.

**Leukotriene Production in Asthma**

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The biological properties of leukotrienes are summarized in Table 1. CysLTs are the most potent bronchoconstrictor agents, being approximately 1,000 times more potent than histamine. After aerosol challenge, they have been shown to increase bronchial hyperresponsiveness to methacholine or histamine, especially in patients with asthma. More recently, CysLTs have been shown to partly mediate eotaxin-induced bronchial hyperresponsiveness and eosinophilia in IL-5 transgenic mice.

LTD₄, acting via CysLT₁ receptors, has been shown to induce airway smooth muscle proliferation when combined with an appropriate growth factor such as epidermal growth factor or insulin-like growth factor, an effect that can be blocked by CysLT₁ receptor antagonists.

CysLTs are potent inducers of mucus hypersecretion. They also increase microvascular permeability and impair ciliary activity. In addition, CysLTs have been shown to induce influx of eosinophils into the airways of guinea pigs, which can persist for up to 4 weeks. Similar effects have been observed in vivo as well as in vitro in patients with asthma and probably are the result of eotaxin induction and secretion. Evidence from studies in guinea pigs suggests that these mediators can also potentiate the release of acetylcholine from vagal nerve endings and of tachykinins from capsaicin-sensitive afferent C fibers.

In summary, CysLTs induce bronchoconstriction, enhance airway hyperresponsiveness and smooth muscle hypertrophy, cause mucus hypersecretion and mucosal edema, and induce influx of eosinophils into the airway tissue (Fig 3). Thus, the biological properties of leukotrienes strongly suggest that they play a key mediator role in the pathogenesis of asthma.

LTB₄ does not exhibit any contractile effect on airway smooth muscle cells, but is one of the most potent chemotactic agents and activators for neutrophils. LTB₄ also induces the expression of adhesion proteins on the surface of endothelial cells and polymorphonuclear leukocytes, which are essential for margination and diapedesis.

The Role of Anti-inflammatory Drugs in Asthma Management

Based on an understanding of the role of inflammation in the pathogenesis of asthma, reversal of existing airway inflammation is considered to be a primary aim of asthma treatment, and therapeutic strategies have focused on either reducing inflammatory cell influx, reducing the production of inflammatory mediators, or blocking their effects. Antihistamines and platelet-activating factor antagonists have undergone trials in asthma management; however, their efficacy is minimal. The role of cytokines in the pathogenesis of asthma has been recently reviewed by Chung and Barnes, and trials are now underway to study the effects of blocking some of the major cytokines involved in asthma pathogenesis. Clinical trials using monoclonal antibody directed against IL-5 have shown reduction in eosinophils in peripheral blood and sputum, but have demonstrated no effect on the late asthmatic response or bronchial hyperresponsiveness after allergen challenge. Similar results have been obtained with recombinant IL-12 (S.A. Bryan, MBChB; unpublished data; October 2000).

The Effects of Corticosteroid Treatment on Asthma

Corticosteroids are the most effective anti-inflammatory agents currently available for the treatment of asthma. They produce a marked reduction in the numbers of mast cells, macrophages, T lymphocytes, and eosinophils in the bronchial epithelium and submucosa. Furthermore, they reverse the shedding of epithelial cells and the goblet cell hyperplasia characteristically seen in biopsy specimens of bronchial epithelium from patients with asthma; reduce microvascular permeability; block the activation of inflammatory cells; suppress mediator generation from lymphocytes; and reduce the expression of vascular adhesion molecules. By reducing airway inflammation, inhaled corticosteroids modify airway hyperresponsiveness, downregulate production of proinflammatory cytokines, and upregulate anti-inflammation.

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**Table 1—Effects of Leukotrienes in Asthma Pathophysiology**

<table>
<thead>
<tr>
<th>Leukotrienes</th>
<th>Cell types</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CysLTs (LTC₄, LTD₄, LTE₄)</td>
<td>Airway smooth muscle</td>
<td>Constriction, proliferation</td>
</tr>
<tr>
<td></td>
<td>Airway blood vessel</td>
<td>Plasma leakage</td>
</tr>
<tr>
<td></td>
<td>Mucus glands</td>
<td>Mucus hypersecretion</td>
</tr>
<tr>
<td></td>
<td>Inflammatory cells</td>
<td>Eosinophil chemotaxis</td>
</tr>
<tr>
<td></td>
<td>Nerve fibers</td>
<td>Acetylcholine release</td>
</tr>
<tr>
<td></td>
<td>Neutrophils</td>
<td>Chemotaxis and activation</td>
</tr>
</tbody>
</table>

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Inflammatory cytokines such as IL-10. Several clinical studies have clearly demonstrated that inhaled corticosteroid therapy greatly reduces asthma symptoms, improves lung function, reduces nonspecific airway hyperreactivity, and reduces the consumption of bronchodilating drugs. Validated by international consensus meetings, glucocorticoids have become the first-line treatment for asthma management.

Glucocorticoids Do Not Suppress All Inflammatory Responses in Asthma

Despite the well-recognized efficacy of inhaled corticosteroid treatment in improving the symptoms of asthma, it appears that inflammation still persists at a low level in the airways of patients with asthma who have poor airway function, despite regular and prolonged treatment with inhaled steroids, even at dosages up to 2,000 μg/d. Corticosteroids only affect certain inflammatory mediators involved in asthma. In general, glucocorticoids substantially reduce the eosinophil/lymphocyte driven processes, while leaving behind or even augmenting a neutrophil-mediated process. Patients with severe asthma treated with oral glucocorticoids for 1 year have demonstrated dramatically increased numbers of neutrophils in biopsy and lavage specimens, while effectively eliminating eosinophils. Previous reports have also suggested that glucocorticoids enhance neutrophil function through increased leukotriene and superoxide production, as well as inhibition of apoptosis. A recent study by Pizzichini et al has demonstrated that, although glucocorticoids reduce eosinophil numbers and eosinophil cationic

![Diagram of the inflammatory cascade in asthma pathophysiology.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21962/)
protein levels in the airways of patients with severe asthma, they have no effect on neutrophil numbers, fibrinogen, or IL-5. In addition, some reports suggest that glucocorticoids can induce growth factors and/or collagen synthesis in certain conditions.

At one time, it was thought that glucocorticoids effectively inhibit phospholipases by inhibiting gene transcription of phospholipase A₂ through upregulation of gene transcription of lipocortin-1, a protein exerting an inhibitory activity of phospholipase A₂, hence, decreasing prostanoid and leukotriene production. However, this inhibition is limited only to certain conditions and/or cells. Numerous in vitro and in vivo studies have demonstrated minimal suppression of leukotriene production by glucocorticoids, and in some cases an enhanced production. The FLAP gene promoter contains a glucocorticoid response element, and glucocorticoids enhance gene transcription and protein production of FLAP in human neutrophils, monocytes, and eosinophils in vitro. Dexamethasone is ineffective in inhibiting the LTB₄/LTC₄ release from human lung fragments, purified lung mast cells, and purified blood neutrophils. In addition to these in vitro results, oral or IV administration of corticosteroids have similarly been reported to have no inhibitory effect on the unstimulated or stimulated release of leukotrienes by whole-blood leukocytes, purified neutrophils, or monocytes, or even to increase ex vivo leukotriene biosynthesis by blood neutrophils. Similarly, treatment of healthy volunteers with dexamethasone (8 mg/d for 3.5 days) did not show any significant inhibition of the triggered release of LTB₄ as well as other arachidonic acid metabolites from alveolar macrophages obtained by BAL. These data suggest that glucocorticoids have minimal or no effect on LT synthesis and that their anti-inflammatory effects are mainly because of inhibition of the synthesis and release of other mediators, particularly cytokines.

The Role of Leukotriene-Modifying Drugs as Anti-inflammatory Agents in Asthma Treatment

Leukotrienes are potent inflammatory mediators that play an important role in asthma pathogenesis. It would therefore seem logical that drugs that modify their effects would be anti-inflammatory. Although glucocorticosteroids are one of the most potent anti-inflammatory agents available, they do not suppress either leukotriene production or release into airways. It is therefore logical to consider that leukotriene synthesis inhibitors or CysLT₁ antagonists may have complementary anti-inflammatory effects in asthma management, and as a result offer additional clinical benefit. In line with this hypothesis, clinical studies have shown that addition of leukotriene synthesis inhibitors or CysLT₁ antagonists to inhaled glucocorticoids improves asthma control. The 5-LO inhibitors are classified into those that inhibit 5-LO directly and those that bind to FLAP. Zileuton is the only 5-LO inhibitor currently available for clinical use, while three CysLT₁ antagonists are available: montelukast, zafirlukast, and pranlukast. Zileuton inhibits leukotriene synthesis by approximately 70 to 90%, while montelukast, zafirlukast, and pranlukast (available in Japan and Korea) are selective antagonists of the CysLT₁ receptor.

Effects on Airway Responsiveness to Allergen Challenge

Hyperresponsiveness to histamine is a key feature of a variety of pathologic conditions, including bronchial asthma. It has been demonstrated that Cys-LTs prime histamine responses by recruiting additional histamine-1 receptors in human peripheral blood mononuclear cells and umbilical smooth muscle cells in vitro. A single dose of the 5-LO inhibitor zileuton, 400 mg, or the CysLT₁ receptor antagonist zafirlukast have been shown to attenuate bronchial hyperresponsiveness to histamine and distilled water in patients with asthma who were receiving regular treatment of inhaled beclomethasone dipropionate or budesonide. Treatment with 1.6 to 2.4 g/d of zileuton for 7 days has been shown to produce beneficial effects on airway responsiveness to cold, dry air. In patients with mild asthma, zafirlukast and montelukast have been shown to attenuate both the early-phase and late-phase responses to inhaled allergen, reduce lymphocyte and basophil recruitment to the airways, and attenuate bronchial hyperresponsiveness to histamine that normally accompanies antigen inhalation. More recently, pranlukast has been shown to suppress the production of IL-4 (a cytokine that affects IgE antibody production), IL-5, and GM-CSF (cytokines that affect eosinophil activation) by peripheral blood mononuclear cells under stimulation with specific antigens in patients with bronchial asthma.
Leukotrienes and Aspirin-Induced Asthma

Aspirin-induced asthma is present in 3 to 8% of patients with asthma and causes profound and sometimes life-threatening bronchoconstriction as well as naso-ocular, dermal, and GI responses. By inhibiting the cyclo-oxygenase pathway, nonsteroidal anti-inflammatory drugs either shunt arachidonic acid through the 5-LO pathway to produce more LTB₄, LTD₄, LTE₄, and LTD₅,²¹ or remove the inhibitory effect of prostaglandin E₂ on the CysLT pathway.³⁶ After aspirin challenge, CysLTs are released into nasal and bronchial secretions and can be collected in the urine. LTC₄ synthase, the terminal enzyme for CysLT production, is markedly overexpressed in eosinophils and mast cells from bronchial biopsy specimens of most patients with aspirin-induced asthma,³¹ and many of these patients have elevated levels of CysLTs even in the absence of exposure to aspirin.³⁴ Pretreatment with the CysLT₁ receptor antagonists or 5-LO inhibitors prevents physiologic responses after oral administration of aspirin.¹⁰⁹,¹¹⁴,¹¹⁹,¹₂⁰ It has been recently demonstrated¹²¹ that pranlukast protected against analgesic-induced bronchoconstriction through mechanisms that were not related to the bronchodilator property, but to improvements in bronchial hyperresponsiveness and hypersensitivity to analgesics. These results support the view that CysLTs are one of the most important components in the pathogenesis of aspirin-intolerant asthma, and that leukotriene-modifying drugs greatly relieve asthma symptoms induced by aspirin and other nonsteroidal anti-inflammatory drugs.

Leukotrienes and Exercise-Induced Asthma

Exercise stimulates bronchoconstriction in 70 to 80% of patients with asthma.¹²² CysLTs have been recovered from urine during exercise-induced bronchospasm,¹²³,¹²⁴ while the CysLT₁ receptor antagonists MK-571,¹²⁵ zafirlukast,¹²⁶ montelukast,¹²⁷ and cilomilast¹²⁸ all inhibit the maximal bronchoconstrictor response after exercise by 50 to 80%, an effect that supports an important role of the CysLTs in exercise-induced airway obstruction. Treatment with zileuton has demonstrated similar effects in patients in whom bronchoconstriction was induced by either cold air, hyperventilation, or exercise.¹²⁹ In a recent randomized, double-blind, placebo-controlled study,¹³⁰,¹³¹ montelukast was found to be more effective than salmeterol in the long-term treatment of exercise-induced bronchospasm in patients with mild asthma, as demonstrated by effect size, maintenance of effect, and fewer respiratory clinical adverse events. Montelukast has also demonstrated significant protection against exercise-induced asthma in children aged 6 to 12 years who have mild asthma.¹³² In addition, a recent study¹³³...
has demonstrated that regular treatment with zafirlukast protects against exercise-induced bronchoconstriction for at least 8 h after dosing.

**The Place for Antileukotrienes in the Asthma Management Guidelines**

Antileukotrienes are the first new class of anti-asthma drugs developed in the last 20 years. Unlike most antiasthma controller medications, the leukotriene modifiers offer a potential advantage of ease of administration (usually as a once-daily or twice-daily oral medication), compared with the need for careful administration of inhaled medications. They are therefore more likely to improve patient compliance, especially in children and adolescents. In addition, antileukotrienes may be effective in concomitant allergic diseases, common in patients with asthma, such as rhinitis and eczema.

Currently, available studies indicate that antileukotrienes are highly effective in patients with aspirin-induced asthma, and in those with exercise-induced asthma exacerbations. Leukotriene-modifying drugs therefore merit recommendation as first-line therapy in these subgroups of patients.

Although > 35 clinical trials with this drug class reveal efficacy in asthma management, the issue of the positioning of the antileukotrienes in asthma management guidelines continues to attract much attention: in particular, whether they should be used in step 2 of the asthma management guidelines (either as an alternative or in addition to low-dose inhaled corticosteroids), or whether they sit more comfortably at step 3 as an alternative to increasing the dose of inhaled steroid or the introduction of a leukotriene modifier to a multifaceted asthma treatment program will not have a complementary effect. In patients with moderate-to-severe chronic persistent asthma, leukotriene-modifier therapy can be combined with inhaled glucocorticoids to maintain control of asthma with lower doses of the latter, or it can be added to an existing regimen to achieve better control of asthma. In European Union countries, montelukast and zafirlukast have been launched with therapeutic indications that are for the time being mostly limited to add-on therapy in patients with mild-to-moderate persistent asthma who are inadequately controlled on inhaled corticosteroids, and in whom as-needed short-acting β-agonists provide inadequate clinical control of asthma. A subgroup of patients in step 3 of the asthma management guidelines who do not perceive that their symptoms, despite poor lung function measurements (poor perceivers), are more likely to benefit from antileukotrienes, because they are not only more likely to comply with oral antileukotriene medications, may continue with these medications, which have a better safety profile than long-acting theophyllines. In addition, the rapid onset of action of the leukotrienes (often seen after the first dose) may help to reinforce patient compliance and encourage their continued use.

There are no published clinical trial data directly comparing the efficacy and safety of two or more leukotriene-modifying drugs in the same or matched patient populations. Clinical trials of leukotriene receptor antagonists were mostly performed in mild-to-moderate asthmatic subjects, while many trials of the leukotriene synthesis inhibitor zileuton were in moderate asthmatic subjects, but clinical experience suggests that leukotriene receptor antagonists and leukotriene synthesis inhibitors provide similar therapeutic benefit across the spectrum of asthma severity. Relatively few trials have been performed in patients with severe asthma, but early clinical experience suggests that therapeutic benefits may be substantial.

**Conclusion**

Anti-inflammatory therapy is now considered first-line treatment for all grades of asthma severity. Although corticosteroids are thought to be the most potent anti-inflammatory agents available, they do not affect all the inflammatory processes occurring in the asthmatic airways. Leukotrienes, which are lipid mediators generated from the metabolism of arachidonic acid, have been shown to play an important role in the pathogenesis of asthmatic inflammation. CysLTs, acting on CysLT1 receptors, produce bronchospasm, airway hyperresponsiveness, airway smooth muscle proliferation, excess mucus production, and mucosal edema and airway eosinophilia, features that are characteristic of the inflammatory responses seen in asthma. Because corticosteroids do...
Clinical presentation

| Symptoms:  <1 time/week asymptomatic and normal PEF between attacks |
| Nighttime symptoms:  1-2 times/month |
| PEF:  180% predicted variability <20% |

| Symptoms:  1-11 time/week but <1 time/day |
| Nighttime symptoms:  >2 times/month |
| PEF:  180% predicted variability 20%—30% |

| Symptoms:  daily use β2-agonists daily attacks affect activity |
| Nighttime symptoms:  >1 time/week |
| PEF:  >60% < 80% predicted variability >30% |

| Symptoms:  continuous limited physical activity |
| Nighttime symptoms:  Frequent |
| PEF:  160% predicted variability >30% |

Treatment

| Inhaled short-acting β2-agonists as required (not more than once a day) |

| Inhaled short-acting β2-agonists as required + Low dose inhaled steroid OR ?? Anti-leukotriene |

| High dose inhaled steroid + Inhaled short-acting β2-agonists as required Anti-leukotriene OR Low dose theophylline |

| High dose inhaled steroid + Long acting β2-agonists Anti-leukotriene Slow release theophylline |

| Same as step 4 + Regular oral Prednisolone |

**STEP 1**

**STEP 2**

**STEP 3**

**STEP 4**

**STEP 5**

Figure 4. The place of leukotriene receptor antagonists in asthma guidelines. PEF = peak expiratory flow.

not inhibit either leukotriene production or release, it therefore seems logical to incorporate leukotriene-modifying drugs in the management of asthma. 5-LO inhibitors and CysLT receptor antagonists improve airway function, decrease the need for rescue medication with β-adrenergic agonists, relieve asthma symptoms, decrease the frequency of exacerbations of asthma requiring oral glucocorticoid therapy, and reduce the dose of inhaled glucocorticoid required to maintain control of asthma. Several clinical studies have demonstrated beneficial effects of leukotriene-modifying drugs in the management of all grades of asthma severity. Patients with aspirin-induced asthma and those with exercise-induced asthma exacerbations seem to benefit the most; therefore, these agents should be considered as a potential first-line therapy in these patients.

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