CLINICAL REVIEW

Asthma as an Inflammatory Disease: Implications for Management

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Background: **Eosinophilic inflammation plays a central role in the pathogenesis of asthma. Striking inflammatory changes are present in the airways of patients with all levels of disease severity. The degree of airway inflammation correlates with airway hyperresponsiveness, the primary physiologic abnormality of asthma. Inflammation is typically initiated by immunologic events (including allergy) and is driven by mediators released by various cells of the immune system, particularly eosinophils, monocytes and macrophages, lymphocytes, and mast cells.**

Methods: **Literature on asthma and the inflammatory response was drawn from recent articles presented and reviewed in journal clubs and from selected articles from the National Library of Medicine.**

Results and Conclusions: **The inflammatory process can be divided into six steps: triggering, signaling, migration, inflammatory cell activation, tissue damage, and resolution. Recognition of the importance of inflammation in the pathogenesis of asthma and the progression of the disease has shifted research efforts and the development of new therapeutic agents toward reduction of airway inflammation. Anti-inflammatory therapy, which can be directed against specific steps in the inflammatory process, actually reduces bronchial hyperresponsiveness. Although anti-inflammatory management has assumed a primary role in asthma therapy, short acting ß$_2$-adrenergic receptor agonists are needed for treatment of acute symptoms, and some patients require regular ß$_2$-agonist therapy despite apparently adequate anti-inflammatory therapy. (J Am Board Fam Pract 1996;9:182-90.)**

The central role that inflammation plays in the pathogenesis of asthma has become increasingly clear in the last decade. At one time asthma was viewed as an acute obstructive respiratory disease; research and development of therapeutic agents focused on the mechanisms and mediators that regulated airway smooth muscle contraction. In addition to bronchial smooth muscle contraction, other factors, including airway edema, mucus secretion, and inflammation, contribute to the airway obstruction characteristic of asthma. All collaborate in the development of bronchial hyperresponsiveness or airway hyperreactivity, which is a hallmark of the disease.

Inflammation is now recognized as an important contributor to airway histopathology and to bronchial hyperresponsiveness in patients with asthma. Although the presence of inflammatory changes in the airways of patients with severe asthma has been recognized for some time, recent studies utilizing bronchial biopsy findings have found obvious airway inflammation in patients with all levels of the disease.[1-3] The intensity of inflammation appears to be closely correlated with the severity of clinical disease.

Recognition of the importance of inflammation in the pathogenesis of asthma has shifted research and therapeutic agent development toward anti-inflammatory management. Pharmacotherapy of asthma must now be approached from two directions. ß$_2$-Agonists provide prompt symptom relief. Anti-inflammatory management treats the chronic underlying disease process. Relative use of these two strategies depends upon the severity of disease and is individualized to the specific needs of the patient. I will review current concepts of inflammation in asthma and discuss how understanding this process affects treatment of the disease.

Methods

In this article I will address current concepts of inflammation in asthma, highlighting recent arti-

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cles presented and reviewed in journal clubs and selected in part by search of the MEDLINE databases of the National Library of Medicine, using the key words "inflammation," "asthma—pathophysiology," "drug therapy," anti-inflammatory agents," "bronchodilator agents," "corticosteroids," and "beta$_2$-agonists."

Evidence for Airway Inflammation in Asthma

Inflammation plays a key role in the pathogenesis of asthma, whether the disease is clinically mild or severe. Because earlier investigators of the abnormalities of asthma studied bronchial tissue of patients who died in status asthmaticus, it was once believed that clinically relevant inflammation was found only in patients with severe or fatal asthma. Recent bronchial biopsy studies have shown that inflammation is present in the lower airways of patients with mild as well as asymptomatic asthma.[2,3] Many of the structural changes observed in fatal asthma cases are clearly present in patients with mild, well-controlled disease. These changes include denudation of airway epithelium, deposition of collagen beneath the basement membrane, epithelial cell desquamation, mast cell degranulation, edema, and inflammatory cell infiltration with eosinophils and lymphocytes.[4,5] These findings have contributed to the general agreement that eosinophilic airway inflammation is a consistent component of asthma.

A second factor in establishing the primary role of inflammation in asthma was the determination that the fundamental feature of asthma, airway hyperresponsiveness, correlates with the degree of inflammation. The magnitude of airway hyperresponsiveness correlates with the number of bronchial eosinophils, macrophages, desquamated epithelial cells, and the magnitude of airway wall edema.[6–9] Eosinophils appear to affect airway hyperresponsiveness by altering airway epithelial integrity or causing airway wall edema. Not surprisingly, levels of highly toxic eosinophil mediators (major basic protein, eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin) in the airways correlates with the severity of airway hyperresponsiveness.[7,10,11] Also, serum levels of eosinophil cationic protein correlate with clinical severity of asthma.[12] Platelet-activating factor and leukotriene C4 are other eosinophil mediators that can increase mucosal permeability and are associated with airway reactivity.[13] Because macrophages release products that can regulate the release of histamine from mast cells, and because they might attract and activate eosinophils in the airways, they can have both direct and indirect effects on airway hyperresponsiveness.[13,14] Macrophages also release other compounds, including thromboxanes, tumor necrosis factor, and reactive oxygen species, which might contribute to bronchovascular permeability and edema and, in turn, affect hyperresponsiveness.[15] Airway epithelial damage correlates with airway hyperreactivity. Epithelial desquamation is mediated by inflammation, particularly by the toxic eosinophil granule proteins,[11] producing or increasing airway hyperresponsiveness.[1,16,17]

Although airway inflammation is an integral part of asthma, it is not the sole cause of the disease. Upon allergen exposure, allergic patients who do not have asthma might develop a lower airway inflammatory response that does not necessarily result in bronchoconstriction.[18] It seems likely that as yet undefined inherited factors predispose an individual to develop bronchial hyperreactivity following exposure to viruses, allergens, or other inflammatory triggers. Perhaps only chronic inflammation triggers the onset of clinically overt asthma.

Pathophysiology of Airway Inflammation in Asthma

Inflammation is a complex process involving interactions between numerous cells, cytokines, and mediators. Inflammation is typically initiated by immunologic events and driven by mediators released by the participating cells. There are six general steps in the inflammatory process: triggering, signaling, migration, inflammatory cell activation, tissue stimulation and damage, and resolution. In a study of the pathogenesis of asthma, these steps can be examined individually, both to understand the role of inflammation in the disease and to elucidate potential sites for pharmacologic intervention designed to alter the course of the disease.

To relate the steps in the inflammatory cascade to the pathogenesis of asthma, the biphasic asthmatic response must be briefly reviewed. Bronchial provocation testing with allergen induces three types of asthmatic responses: an isolated early asthmatic response, an isolated late asthmatic response, and a dual asthmatic reaction characterized by both an early and a late response.[19,20] The

early asthmatic response, believed to be the clinical manifestation of bronchial smooth muscle contraction, usually develops within 15 to 60 minutes following allergen exposure. The late asthmatic response usually begins 3 to 4 hours after exposure and resolves within 12 to 24 hours; it is a manifestation of inflammatory changes within the airways and has been associated with increases in nonspecific airway hyperresponsiveness.[21]

Triggering

The inflammatory process is initiated by triggers, of which respiratory infections and allergic or antigenic stimuli are probably the most important. Allergens trigger activation of various cells of the immune system via immunoglobulin E (IgE) receptors, which are located on mast cells, basophils, macrophages, platelets, B lymphocytes, and eosinophils. The early asthmatic response appears to be primarily due to pulmonary mast cell activation, which results in release of mast cell mediators, including histamine, prostaglandin D_2, and leukotrienes C_4, D_4, and E_4.[22–24] The leukotrienes and histamine are capable of contracting airway smooth muscle, thereby contributing to the bronchoconstriction of the early asthmatic response.[25]

Signaling

Following triggering, signaling involves complex communication between cells, resulting in widespread activation of the immune system. T lymphocytes release proinflammatory cytokines, produce allergen-specific T-cell clones, and interact with eosinophils. In allergic asthma, the eosinophilic inflammatory response is driven by Th2 lymphocytes, cells that regulate IgE production through the cytokines interleukin (IL)-4 and IL-13. In nonallergic asthma, Th1 lymphocytes direct the inflammatory process. In either case, lymphocyte activation results in production of the cytokines IL-3 and IL-5, and granulocyte-macrophage colony-stimulating factor, which promote eosinophil differentiation and activation. Activation of T lymphocytes in symptomatic asthma can be detected by measuring surface activation markers in the blood that correlate with disease activity.[26]

Migration

Migration of cells into the airways is the next step in the inflammatory process. The triggering and signaling processes cause release of chemoattractant mediators that stimulate the migration of neutrophils, eosinophils, lymphocytes, and monocytes or macrophages. Chemoattractant mediators include leukotriene B_4 (LTB_4), platelet activating factor, IL-5, and IL-8. Migration of cells is further modulated by mediators (such as IL-1, LTB_4, and tumor necrosis factor), an action that increases cell adhesion to airway epithelium and causes an increase in the adhesion molecules, which anchor the migratory cells to an inflammatory focus and regulate the influx of inflammatory cells into the lungs.[27,28] Eosinophil migration and adhesion to the airway epithelium are believed to be particularly important in the development of the late asthmatic response.

Activation

Inflammatory cells in the airway are not sufficient to produce the physiologic changes associated with asthma. Once in the airways, the cells must be activated by such substances as granulocyte-macrophage colony-stimulating factor and IL-5.[4] Eosinophils in the respiratory mucosa are activated; levels of eosinophils in the sputum, eosinophil cationic protein in epithelial biopsy specimens, and major basic protein (present in eosinophils) in bronchoalveolar lavage fluid correlate with the severity of active disease.[29–31] Activated eosinophils also appear to generate other physiologically important compounds, such as leukotriene C_4 (LTC_4), a potent bronchoconstrictor capable of inducing permeability changes. Levels of LTC_4 in bronchoalveolar lavage fluid are increased during the late asthmatic response, and levels of a metabolite in the urine have been correlated with the presence of active disease.[32] The leukotrienes can be particularly important in patients with aspirin-induced asthma. There is less evidence for macrophage and neutrophil activation during airway inflammation.

Stimulation and Damage

Following activation of the inflammatory cells, tissue stimulation and damage result in clinical manifestations of bronchoconstriction and airway hyperresponsiveness. Pathophysiologic changes in airway epithelium appear to play a key role. Inflammatory enzymes, eicosanoids, growth factors, and cationic proteins released by inflammatory cells affect the epithelium, causing various defects,

including desquamation, an abnormal ratio of glandular cells to normal epithelium, and functional abnormalities. Increased airway hyperresponsiveness could be caused by increased glandular secretions or by increased permeability, allowing greater concentrations of bronchoconstricting substances such as histamine and LTC_4 to enter the nerves and smooth muscle of the airways. The altered epithelium might also facilitate access of allergens to submucosal cells. Additionally, the basement membrane is altered. Connective tissue (collagen) deposition in the membrane is increased, which could contribute to increased airway responsiveness. The nerves and smooth muscle of the airways might also be affected by and perhaps involved in the inflammatory process.[33–35]

Resolution

Normally, inflammation subsides and resolves when the need for inflammation is passed. Yet in asthma, the inflammatory process continues, perhaps as a result of continuous exposure to allergens or other triggers or an abnormality in the resolution of the inflammatory response. Patients with clinically stable asthma have evidence of inflammatory changes within the bronchi.[2,3,36] Also, in occupational asthma (Western red cedar or toluene diisocyanate), removal of the triggering agent does not lead to resolution of inflammation or elimination of asthma symptoms.[37,38] Thus, it is likely that ongoing inflammation resulting from lack of resolution contributes to the chronic nature of asthma.

Implications for Management

Recognition of asthma as an inflammatory disease has resulted in the use of anti-inflammatory drugs as primary elements in the treatment and prevention of disease manifestations, along with short-acting inhaled $ß_2$-agonists for symptom relief. Early intervention with anti-inflammatory agents might improve the long-term prognosis of the disease, resulting in fewer exacerbations or reductions in the severity of exacerbations when they do occur.

The two major types of drugs currently used in asthma management are anti-inflammatory agents and bronchodilators. The major anti-inflammatory agents used in the treatment of asthma are corticosteroids (inhaled or oral), cromolyn sodium (sodium cromoglycate), and nedocromil sodium. These agents have broad, nonspecific anti-inflammatory effects that are only beginning to be understood in relation to airway inflammation in asthma. Anti-inflammatory agents, however, do not reverse the bronchospasm characteristic of acute asthma and are not indicated for treatment of acute asthma exacerbations. Bronchodilators with a rapid onset of action, primarily $ß_2$-agonists and in some cases the anticholinergic agents, promptly and effec-tively reverse acute bronchoconstriction.[39] Short-acting inhaled $ß_2$-agonists remain the time-honored agents of choice for the treatment of acute asthma and for the prevention of exercise-induced asthma.[40,41] The asthma diagnosis and management guidelines of the National Institutes of Health recommend that therapy be aimed at alleviating acute symptoms and at preventing exacerbations and controlling chronic symptoms by reducing inflammation.[40,41] For most patients a stepped-care approach to therapy is used, and medications are increased when necessary to control symptoms.

In patients with allergic asthma, allergen avoidance is a first step in anti-inflammatory management and reduction of bronchial hyperreactivity.[42] In patients allergic to dust mites, a dust-free bedroom reduces symptoms, decreases medication use, elevates home peak flow measurements,[43] and reduces eosinophil activation.[44] Allergen immunotherapy can decrease nonspecific bronchial hyperreactivity in patients allergic to dust mites,[45] cats,[46] pollen,[47] and fungi.[48] Thus, allergy evaluation is indicated for patients with mild, moderate, or severe asthma.

The NIH guidelines recommend that every asthma patient have a short-acting inhaled $ß_2$-agonist such as albuterol available for acute treatment of asthma exacerbations. $ß_2$-Agonists exert their effects on the pathophysiology of asthma through several mechanisms: relaxation of airway smooth muscle, enhancement of mucociliary clearance, and reduction of vascular permeability.[41] Short-acting inhaled $ß_2$-agonists provide prompt bronchodilation with minimal side effects and are the agents of choice for acute exacerbations. Long-acting inhaled $ß_2$-agonists such as salmeterol are not indicated for rescue therapy of acute asthma exacerbations.[41,49] Salmeterol has a slower onset of action than shorter-acting inhaled $ß_2$-agonists, making it inappropriate for rescue therapy.[50]

For mild asthma short-acting inhaled $ß_2$-ago-

nists are first-line therapy for relief of symptoms in patients with mild, intermittent asthma (up to two episodes a week, asymptomatic between episodes, nocturnal episodes fewer than two times a month, or a peak flow rate [PEFR] or a forced expiratory volume [FEV_1] of more than 80 percent predicted).[39,41] Most patients with mild asthma can be maintained with monotherapy using a short-acting inhaled $ß_2$-agonist taken on an as-needed basis. If treatment results in disappearance of symptoms and normalized pulmonary function, short-acting inhaled $ß_2$-agonists can be used on an as-needed basis indefinitely.[40,41] Use of $ß_2$-agonists exceeding 3 to 4 times a day suggests worsening of the patient's condition and warrants a reevaluation of therapy. The long-acting inhaled $ß_2$-agonists are currently not recommended for treatment of mild, intermittent asthma.[41,49]

Some investigators have reported a statistical association between regular $ß_2$-agonist use and worsening control of asthma, as well as increased risk of death or near death from asthma.[51,52] Although regular $ß_2$-agonist use might simply reflect disease severity, adjustment of data in a case control study[52] for asthma severity did not affect the investigators' conclusions.[53] Conceivably, overdependence on $ß_2$-agonists could mask symptoms of worsening asthma and prompt certain patients to wait too long before seeking medical attention. Likewise, the long-acting $ß_2$-agonists have also been implicated as masking symptoms or increasing severity of the underlying disease.[51,54,55] Currently, the possibility of a cause-and-effect relation between $ß_2$-agonist use and asthma severity is controversial, but it cannot be dismissed, remaining a concern for clinicians caring for patients with asthma. The need for regular $ß_2$-agonist use strongly suggests a need for concomitant anti-inflammatory management. Furthermore, the shorter-acting agents should not be used more than four times daily, and the long-acting agents should not be used more than twice daily.

Moderate Asthma

Patients with increasing or more persistent symptoms should be maintained on allergy management as appropriate and prescribed inhaled anti-inflammatory drugs to reduce the underlying airway inflammation.[39,41] Short-acting inhaled $ß_2$-agonists should be available on an as-needed basis. The NIH recommendations for patients with moderate asthma (exacerbations more than one to two times a week, nocturnal asthma more often than twice a month, almost daily use of a short-acting $ß_2$-agonist, PEFR or FEV_1 60 to 80 percent predicted, and 20 to 30 percent variability) are daily use of an inhaled corticosteroid (200 to 500 µg), cromolyn sodium, or nedocromil sodium. For many patients with moderate asthma, the combination of regular use of an inhaled anti-inflammatory agent plus a short-acting inhaled $ß_2$-agonist taken on an as-needed basis provides good asthma control. If further therapy is required for adequate control, inhaled corticosteroids can be increased up to 1000 µg/d. Alternatively, additional long-acting bronchodilators given regularly may be added, particularly if nocturnal symptoms predominate. Long-acting bronchodilators include sustained-release theophylline, oral $ß_2$ agonists, and long-acting inhaled $ß_2$-agonists.[41]

Severe Asthma

For severe asthma characterized by continuous symptoms and PEFR or FEV_1 less than 60 percent of predicted, with greater than 30 percent variability, oral corticosteroids might be necessary for adequate control; many experts recommend a trial of very high dose inhaled corticosteroids in an attempt to reduce or discontinue oral steroids. A once-a-day, regularly scheduled, short-acting inhaled $ß_2$-agonist may also be added, usually upon awakening.[41]

Inhaled Corticosteroids in Asthma

Corticosteroids are the most effective anti-inflammatory drugs for the treatment of reversible airflow obstruction. Postulated mechanisms of action include interference with arachidonic acid metabolism and the synthesis of prostaglandins and leukotrienes, decreased microvascular leakage, inhibition of cytokine production, prevention of migration and activation of inflammatory cells, and enhanced responsiveness of $ß_2$-receptors in the airway smooth muscle.[41] Inhaled corticosteroids are effective in nearly all asthma patients, but are recommended only for patients with moderate to severe asthma. Agents used in asthma management include beclomethasone, triamcinolone, and flunisolide. They reduce the need for concurrent medications, reduce the re-

quirement for oral corticosteroids, decrease airway reactivity, and decrease the frequency of acute exacerbations.[56–60] Additionally, inhaled corticosteroids decrease airway hyperresponsiveness as a function of duration of therapy; hyperresponsiveness increases again when corticosteroid administration is stopped.[61] The precise mechanisms for these effects have not been elucidated, although they could be related to alterations in inflammatory cell infiltrates.[62,63]

Inhaled corticosteroids are safe and effective for chronic asthma treatment when administered in low doses or when high doses are administered for a limited time.[64,65] Well-recognized side effects of larger doses of inhaled corticosteroids are oropharyngeal candidiasis and dysphonia in a small proportion of patients. Reported systemic effects include suppressed adrenal function, cataract formation, abnormal bone metabolism, and thinning of the skin.[66] These potential disadvantages must be balanced with the substantial advantages of long-term use of the inhaled corticosteroids, particularly when use of inhaled corticosteroids reduces the need for chronic use of oral corticosteroids, which have considerably greater toxicity.[41] Chronic use of the oral corticosteroids, such as prednisone, is a last resort in patients with severe asthma when other agents, including high doses of inhaled corticosteroids, have proved unsuccessful at improving the patient's condition.

Cromolyn sodium is a nonsteroidal, inhaled anti-inflammatory agent that improves lung function and decreases airway hyperresponsiveness. When used prophylactically, cromolyn inhibits the allergen-induced early asthmatic response and late asthmatic response, as well as the response to exercise and cold dry air challenge, presumably by stabilizing and preventing mediator release from mast cells.[41] It is difficult to predict which patients will respond to cromolyn therapy, although it has been particularly recommended for allergic patients with seasonal asthma.[39] Efficacy in individual patients is best established by implementing a 4- to 6-week trial of cromolyn before the beginning of the allergy season or before exercise. One major advantage of cromolyn is that it is free of side effects.[64]

The decision of whether to use inhaled corticosteroids or cromolyn sodium is an individual one. A number of studies have shown corticosteroids to have greater efficacy than cromolyn in asthma, whereas others have shown the two to have similar efficacy.[67–69]

Nedocromil sodium, a pyranoquinaline, is a newer alternative anti-inflammatory agent for maintenance therapy of asthma. Long-term therapy reduces nonspecific airway responsiveness in nonallergic patients with asthma and improves symptoms and lung function consistent with its anti-inflammatory properties.[70,71] Like cromolyn sodium, it is rarely associated with any serious adverse effects.

The methylxanthines, primarily theophylline, are usually considered to have mainly bronchodilator effects. They might, however, have some anti-inflammatory effects as well, such as altering mast cell and basophil mediator release and influencing neutrophil leukotriene production.[72] The cumulative effects of these actions on a wide variety of cells might give theophylline considerable anti-inflammatory effect.[73] The long duration of action of the sustained-release formulation of theophylline makes it useful for controlling nocturnal asthma. Disadvantages of using theophylline include its narrow therapeutic index (which necessitates periodic monitoring of serum theophylline levels) and drug interactions with many prescription and over-the-counter preparations.

Potent anti-inflammatory agents proposed as steroid-sparing agents for patients with severe asthma requiring oral corticosteroids include methotrexate, cyclosporine, and gold. Because efficacy is not well established and because these agents have considerable toxicities, their use should remain investigational.[66] Agents targeting specific steps of the inflammatory cascade are currently being developed. Specific leukotriene receptor antagonists and 5-lipoxygenase inhibitors can increase airflow and reduce symptoms in asthma patients.[74,75] Early success of the leukotriene inhibitors is encouraging, and as more is learned about the role of inflammation in the pathogenesis of asthma, more focused and specific treatments for prevention of the inflammatory process will be developed.

Summary

The understanding that airway inflammation underlies much of the disordered airway function in asthma has had considerable impact on current treatment of the disease. Anti-inflammatory man-

agement improves lung function and has a measurable effect on airway hyperresponsiveness. Anti-inflammatory therapies (allergen avoidance, immunotherapy, inhaled corticosteroids, cromolyn, and nedocromil), however, are not effective at reversing the acute symptoms of asthma. Short-acting inhaled β_2-agonists remain the agents of choice for acute treatment of asthma symptoms and exacerbations. For patients with symptomatic mild asthma, the treatment of choice is monotherapy with a short-acting inhaled β_2-agonist taken on an as-needed basis. For patients with moderate or severe asthma, prophylactic anti-inflammatory therapy should be initiated to prevent the chronic effects of the underlying disease. Regardless of which anti-inflammatory agents are being used, all patients should have short-acting inhaled β_2-agonists available for as-needed treatment of acute asthma exacerbations.

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