Rostrum

Time for a paradigm shift in asthma treatment: From relieving bronchospasm to controlling systemic inflammation

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Inflammation is a key pathology in asthma. In the central airways local inflammation leads to irreversible remodeling and airway dysfunction. Complex inflammatory changes also occur in the nose, sinuses, and small airways. In particular, rhinitis and asthma are linked by a common pathogenic process with common inflammatory cells, mediators, and cytokines. Cross-communication between the airways and bone marrow through inflammatory mediators in the circulation leads to systemic propagation of airway inflammation. Treatment of asthma has traditionally focused on relieving bronchospasm with β_2-agonists, which do not affect inflammation. Treatment of eosinophilic inflammation in the central airways with inhaled corticosteroids reduces local inflammation and improves pulmonary function but does not improve the systemic manifestations of asthma. If asthma is a systemic disease, the underlying systemic pathology should be targeted by identifying common disease mediators, mechanisms, or both that are triggered only during active disease. Of currently available therapies, leukotriene receptor antagonists block the action of cysteinyl leukotrienes and thus improve both asthma and rhinitis and other conditions systemically linked with asthma. Other potential treatments include receptor-blocking molecules and synthesis inhibitors related to eicosanoid inflammation. Treatment of asthma as a systemic disease requires clinical trials that evaluate the effects of new treatments on both lung function and the wider systemic pathology. (J Allergy Clin Immunol 2007;120:1269-75.)

Key words: *Anti-inflammatory effects, anti-IgE, asthma, atopic dermatitis, β_2-agonist, eosinophilic inflammation, inflammatory mediators, inhaled corticosteroids, leukotriene receptor antagonist, paradigm shift, small airways, systemic inflammation, rhinitis*

Abbreviations used
Cys-LT1: Cysteinyl leukotriene receptor
ICS: Inhaled corticosteroid
LTRA: Leukotriene receptor antagonist

In the industrialized world asthma has increased in prevalence and severity for the past 2 decades. Approximately 300 million persons are estimated to be affected, a figure that is projected to increase to 400 million by 2025.[1] In Europe the prevalence varies from 5% to 10%, with relatively lower rates in the Mediterranean region and higher rates in the United Kingdom and Scandinavia.[2] In the United States asthma is the leading chronic illness among children: 6 million children were reported to be affected in 2004.[3] The increase in the prevalence of asthma has been associated with an increase in atopic sensitization and increases in other allergic disorders, such as rhinitis.[1]

Asthma is associated with a wide range of signs and symptoms, including wheezing, cough, chest tightness, and shortness of breath. It has been suggested that these symptoms manifest as a result of airway inflammation, which can occur when susceptible individuals are exposed to triggers that have a role in disrupting airway epithelia. This, in turn, can lead to eosinophilic infiltration, bronchial smooth muscle spasm, hyperreactivity, and airway obstruction.[4] Ultimately, chronic inflammation leads to airway remodeling, which involves smooth muscle hypertrophy, angiogenesis and increased vascularity, chronic inflammatory cellular infiltration, goblet cell hyperplasia, collagen deposition, thickening of the basement membrane, and reduced elasticity of the airway wall. These changes are irreversible and appear to play a role in airway dysfunction in asthma.

The inflammation seen in asthma is not restricted to the central airways. Complex inflammatory changes are also seen in the upper and small airways and in the sinuses. This is illustrated by the similarity in bronchial mucosal inflammation seen in patients with asthma and in those with rhinitis.[5] In addition, there is profound cross-communication between the airways and bone marrow through inflammatory mediators in the body's circulation. As a result, systemic reactions might magnify the local asthmatic response and lead to distant reactions. In atopic individuals, for example, the skin can be involved, whereas other evidence suggests effects on sleep and cognition and inflammatory intestinal disease. This evidence has led researchers to conclude that asthma is a systemic disease.[6]

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Although there is increasing appreciation that asthma is a systemic disease, current treatment remains focused on relieving symptoms and treating inflammation in the central airways. This article will review evidence that reveals the systemic nature of asthma and will discuss the importance of developing new systemic approaches to treatment.

ASTHMA AS A SYSTEMIC DISEASE

Relationship between asthma and rhinitis

The systemic nature of asthma is illustrated by the strong epidemiologic pathogenic and immunologic association between asthma and rhinitis. Data from the European Community Respiratory Health Study[7] demonstrated that rhinitis is an independent risk factor for asthma in both atopic and nonatopic individuals, even after controlling for factors such as age, sex, and season at the time of examination. In addition, allergic rhinitis usually precedes the onset of asthma, suggesting that it might be an early manifestation of allergic airway disease.[5]

The relationship between the upper and lower respiratory tracts has been described as the *integrated airways disease hypothesis*.[8] Accordingly, asthma and rhinitis are considered to be manifestations of an inflammatory process within a continuous airway rather than separate pathologies. In patients with rhinitis, nasal allergen provocation has been shown to produce eosinophilic inflammation in both the upper and lower airways, and provocation of the lower airway by bronchial segmental allergen challenge results in eosinophilic inflammation in both the upper and lower airways.[5] Similarly, bronchial inflammation and hyperresponsiveness were seen after stimulation of the nasal mucosa in patients with allergic rhinitis and without asthma.[9] Patients with rhinitis alone might thus already have subclinical involvement of the lower airways.

Many of the cells, mediators, and cytokines involved in the inflammatory pathology of asthma and rhinitis are the same, suggesting a systemic immunologic connection through soluble mediators and bone marrow response.[10] This implies a crosstalk between the upper and lower airways, resulting in inflammatory responses in both airways after either one is challenged. In patients with rhinitis alone, a single nasal challenge with allergen induced an increase in markers of allergic inflammation in the lower respiratory tract, including IL-5, which correlated with an increase in sputum eosinophils.[11] In asthmatic patients several studies report the presence of eosinophil infiltration in the nasal mucosa, even in the absence of rhinitis.[12] Further highlighting the importance of the bone marrow response is the observation that after bone marrow transplantation, marrow-derived immune cells from allergic donors can transfer the predisposition to allergy and asthma to nonatopic recipients.[13]

These data illustrate the intimate connection between the upper and lower respiratory tracts and suggest that treatment strategies should target both asthma and rhinitis when present.

Systemic consequences outside the respiratory system

The effects of asthma are not restricted to the airways. Several existing conditions, including atopic dermatitis and inflammatory bowel disease, either are exacerbated by asthma or are associated with an increased risk of asthma. Moreover, asthma morbidity is increased in children sensitized to food allergens,[14] and sensitization to food allergens is an independent risk factor for life-threatening asthma.[15]

Atopic dermatitis. In patients with atopic dermatitis, several studies have described a link between skin symptoms and bronchial hyperresponsiveness after bronchial challenge. Among patients being treated for eczema, allergen inhalation challenge caused a flare-up of skin lesions in patients, which was worse in those with allergic asthma.[16] The same authors examined early and late asthmatic responses after allergen inhalation challenge in groups of patients with varying degrees of atopic dermatitis and asthma.[17] After bronchial challenge, patients with atopic dermatitis and without asthma demonstrated increased bronchial responsiveness and early asthmatic responses, suggesting a latent predisposition to bronchial asthma. Patients with severe atopic dermatitis and mild asthma had significantly higher levels of total serum IgE and allergen-specific serum IgE and tended to have pronounced late asthmatic responses after allergen exposure. Thus eosinophils, which are activated in atopic dermatitis, might contribute to airway inflammation in these individuals. In support of this finding, both eosinophilic airway inflammation and bronchial hyperresponsiveness were recently found to be significantly more common in patients with moderate-to-severe atopic dermatitis compared with control subjects.[18]

Sleep and cognitive disorders. There is a link between sleep-related breathing disorders and airway inflammation; approximately two thirds of patients with asthma are awakened once a week by breathing difficulties, and about 40% experience symptoms every night.[19] In addition to sleep disturbance caused by mechanical factors, such as a blocked nose, sleep quality can also be reduced by the allergic condition itself.[20] Snoring and sleep apnea are more prevalent in adults with asthma-related symptoms than those without, and the apnea observed in individuals with asthma-related symptoms impairs quality of life.[21] Sleep disturbances in children are associated with neurocognitive problems, such as reduced attention, hyperactivity, irritability, and emotional and peer problems, as well as somatic complaints.[22] In addition, allergy alone is associated with increased fatigue, poor performance, and reduced quality of life.[22]

Inflammatory bowel disease. Bronchial hyperresponsiveness and asthma are more common in patients with inflammatory bowel disease, particularly ulcerative colitis, compared with patients without gastrointestinal