

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

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

Abbreviations used

Cys-LT1: Cysteinyl leukotriene receptor

ICS: Inhaled corticosteroid

LTRA: Leukotriene receptor antagonist

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 Study⁷ 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

disease.²³ Both asthma and ulcerative colitis share common inflammatory mechanisms, with recruitment of eosinophils²⁴ and leukotriene involvement.²⁵ Patients with asthma, atopy, or both who do not have intestinal symptoms have evidence of increased inflammatory activity with activated eosinophils and lymphocytes in the intestinal mucosa.²⁶ Moreover, disturbed intestinal membrane function, which is followed by intestinal inflammation, might facilitate sensitization to environmental allergens, thus further increasing the risk burden.²⁷

Cardiovascular disease. It is well known that inflammatory activity in the airways is reflected in the blood circulation. Eosinophil/basophil progenitors are recruited from the bone marrow during seasonal allergy, leading to increased circulating progenitors.²⁸ This systemic inflammation might also involve mechanisms related to remodeling in the vascular system. Increased angiogenesis is known to occur in the lower airways during chronic asthmatic inflammation with upregulation of vascular epithelial growth factor. Vascular epithelial growth factor in turn appears to be involved both in increased airway mucosal vascularity and in the subepithelial fibrosis seen in asthmatic patients.²⁹ These epithelial changes can occur in early childhood and might manifest in atopic children, even in the absence of overt asthma symptoms.³⁰

It is possible that these vascular effects could have an effect on the systemic circulation as a whole, possibly also representing a risk factor for cardiovascular disease. Animal studies have shown an increased myocardial vulnerability in rabbits with systemic allergy and asthma.³¹ Systemic increases in platelet activation are seen in patients with allergic asthma when challenged with allergen³² and when experiencing an acute asthma exacerbation.³³ In women asthma has been shown to be associated with an increased prevalence of carotid atherosclerosis,³⁴ and recent data from the United Kingdom show that patients with asthma, as well as those with chronic obstructive pulmonary disease, have increased cardiovascular comorbidity.³¹ Although cardiovascular complications in asthmatic patients have mostly been attributed to asthma treatment,^{35,36} it cannot be excluded that systemic inflammatory mechanisms might make some contribution to the observed increase in risk.

If inflammation affects the systemic circulation, anti-inflammatory treatment might have the potential to reduce the risk of cardiovascular complications. This has been suggested by Suissa et al,³⁷ who showed a significant reduction in the risk of myocardial infarction episodes in patients who were treated with inhaled corticosteroids (ICSs) for at least 1 year.

APPROACHES TO TREATMENT

The perception of a disease directly influences the way it is treated. Historically, bronchospasm has been perceived as the hallmark of asthma, and treatment has therefore focused on relieving bronchospasm (Fig 1). Almost 5000 years ago, asthma and allergy were treated

with the Chinese herb ma-huang (*Ephedra sinica*), which was later found to contain the muscle relaxant ephedrine. Isoprenaline, which is closely related to adrenaline and activates β -adrenergic receptors, was developed in the 1940s. More recently, both short- and long-acting β_2 -agonists have been used to treat bronchospasm. These therapies are very useful for short-term relief and allow patients to breathe more freely and easily. However, they do not affect inflammation or any of the other underlying systemic disease processes. More recently, treatment paradigms have evolved to include treatment of underlying inflammation.

Treating inflammation in the airways

Eosinophilic inflammation in the central airways. Airway inflammation is a key pathology in asthma. Allergen binding to IgE leads to the release of histamine and leukotrienes in the early phase. In the late phase cytokines and chemokines are released into the circulation, stimulating the release of inflammatory leukocytes, particularly eosinophils, from the bone marrow.⁴ Although eosinophils were first observed in the sputum of asthmatic patients in the 1800s, eosinophilic inflammation did not become a target for therapy until the advent of oral corticosteroid therapy. However, despite their effectiveness as systemic anti-inflammatory agents, the use of oral corticosteroids is now limited to short courses in severe asthma because of side effects. Instead, ICSs are used, which significantly reduce the pathologic signs of airway inflammation³⁸ and hyperresponsiveness³⁹ and thus improve lung function.

Small airways and airway remodeling. The central and intermediate airways account for 90% of airway resistance in the lungs. Routine peak flow or spirometric testing thus measures airflow in those regions. Because the small airways (bronchial passages <2 mm in diameter) account for only 10% of airway resistance, routine lung function tests do not provide information on small airway obstruction.⁴⁰ In fact, these measures might indicate improved lung function, despite the presence of pathologic changes in the small airways. This has important consequences for patient outcomes because the small airways account for 80% of the total surface area of the lungs. Clinically, inflammatory changes in the small airways might significantly worsen asthma exacerbations, nocturnal asthma, and exercise-induced asthma.

Chronic inflammation of the airways eventually leads to irreversible structural changes, including goblet cell hyperplasia, vascularization, increased collagen and fibronectin deposition in the airway wall, thickening of airway smooth muscle, wall thickening, and abnormalities in elastin.⁴¹ However, because these changes take place not only in the central airways but also in the small airways, it is important to treat patients with an agent that treats inflammation and can reach the small airways. Although central airways account for the vast majority of the increased airway resistance, increased peripheral resistance seems to be associated with a degree of bronchial

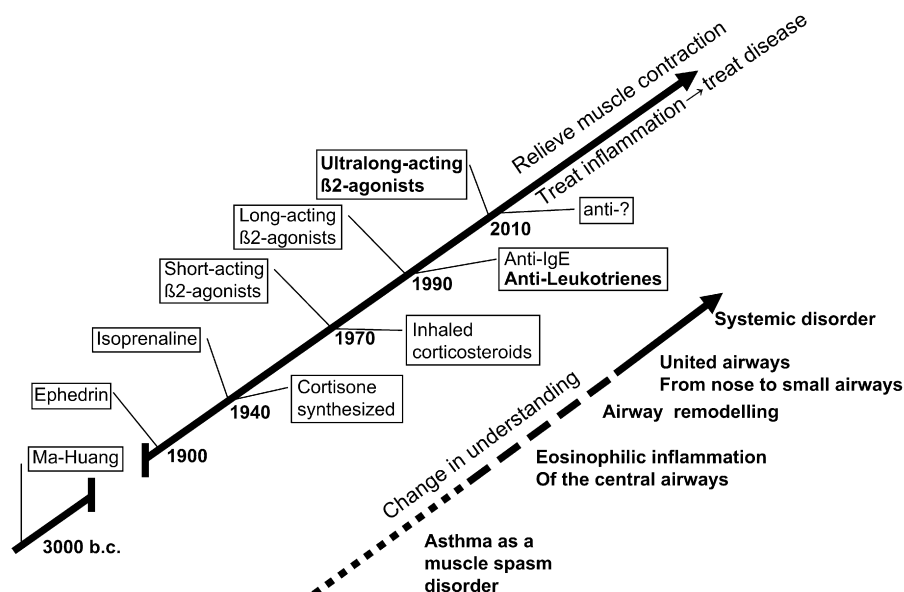


FIG 1. The evolution of asthma treatment from relieving dyspnea attacks to treating systemic inflammation.

hyperresponsiveness,⁴⁰ and small airway remodeling is the most likely explanation for the development of irreversible airflow obstruction.⁴²

ICSs reduce inflammation and improve pulmonary function, leading to reductions in symptoms and exacerbations with an acceptable side-effect profile at standard doses.¹ However, there is evidence that ICSs do not effectively treat all inflammation in the lungs, particularly in the small airways.⁴⁰ Patients might therefore have persistent inflammation and disease symptoms despite treatment, which can lead to the remodeling changes described above, small airway fibrosis, and a decrease in overall lung function. These small airway inflammatory and fibrotic changes appear to be important physiologically because they are reported to be particularly evident in patients who progress to chronic asthma and to fatal attacks.⁴³

Given the difficulty in reaching the small airways with ICSs, oral systemic treatment might be useful. Because oral corticosteroids produce severe side effects during long-term use, leukotriene receptor antagonists (LTRAs) might be a useful alternative. LTRAs block cysteinyl leukotriene receptor (Cys-LT1) on airway smooth muscle cells, thus inhibiting bronchoconstriction. LTRAs have also been shown to have beneficial effects on clinical correlates of small airway function,⁴⁴ and there is evidence that they prevent airway remodeling in animal models of asthma.⁴⁵

Treating concomitant rhinitis

It has become clear that the upper and lower airways are pathogenically and immunologically linked. Concomitant allergic rhinitis leads to worsening asthma and doubles the risk of emergency department visits in patients with

asthma.⁴⁶ If the rhinitis is treated, there is some evidence that both hospitalizations and emergency department visits might decrease.⁴⁷ Treatment of asthma has thus evolved to include treatment of rhinitis when present. Leukotriene receptors are found in the nasal mucosa,⁴⁸ and LTRA treatment significantly improves symptoms in patients with asthma and concomitant rhinitis.⁴⁹ Concomitant treatment with LTRAs and antihistamines improves rhinitis symptoms more than either treatment alone.⁵⁰

It should be noted that local steroid treatment in the nose can also affect reactivity in the lower airways,⁵¹ and local steroid treatment can suppress the increase in allergen-specific IgE levels during the pollen season.⁵² Moreover, in one study inhaled budesonide failed to suppress the increase in bone marrow inflammatory progenitor cells after allergen challenge.⁵³ Thus although some evidence suggests that local treatment in one organ appears to affect the inflammatory and reactive response in another, further work is needed to assess the full clinical relevance.

A new paradigm: A systemic disease needs a systemic approach

If asthma is viewed as a systemic illness, it requires a systemic approach to treatment. Therapies should address not only the inflammation in the central and small airways but should also target the systemic inflammation that underlies the disease, concomitant rhinitis, and other comorbidities. Systemic treatment should not only improve asthma and related comorbidities but also improve quality of life.

Of the currently available treatments, allergen-specific immunotherapy is an obvious example of a systemic,

disease-specific intervention. In children it has been shown that early allergen-specific immunotherapy can interfere with the natural course of allergic disease, preventing the development of asthma and bronchial hyperresponsiveness.⁵⁴

LTRAs represent another option to treat the systemic manifestations of asthma, including respiratory, dermatologic, and sleep-related symptoms. As described above, LTRAs have positive effects on the key underlying inflammation in the central and small airways and on concomitant rhinitis. In addition, LTRAs protect against asthma exacerbations in adults.⁵⁵ Some studies indicate that these drugs can also be effective in the treatment of atopic dermatitis^{56,57} and chronic idiopathic urticaria,⁵⁸ although these results have yet to be confirmed. In children with mild sleep-disordered breathing, which appears to be a symptom of a chronic, systemic inflammatory process, treatment with the LTRA montelukast induced significant reductions in adenoid size and respiratory-related sleep disturbances.⁵⁹ Montelukast also improved airway patency and sleep patterns after tonsillectomy and adenoidectomy.⁶⁰

Anti-IgE treatment is another example that has been shown to reduce disease activity in both asthma and rhinitis⁶¹ and is the only drug to have shown efficacy in patients with very severe asthma.⁶² This treatment targets both compartments and has been shown not only to decrease symptoms but to improve quality of life and reduce the risk of asthma exacerbations.⁶³ Interestingly, exacerbation prevention is achieved despite a modest effect on lung function, indicating that the treatment is truly systemic (ie, affects important mechanisms in the small airways). The role of omalizumab in the management of asthma has yet to be precisely defined because it is expensive and must be administered by means of injection.

Anticytokine treatment also attempts to target disease-specific mechanisms,⁶⁴ but results have been disappointing thus far, partly because of the lack of a significant clinical effect, as shown from the experience with anti-IL-5.⁶⁵ Other trials using an IL-4 receptor blocking strategy⁶⁶ or administering T_H1-promoting cytokines like IL-12⁶⁷ have shown some clinical effect but were accompanied by unacceptable side effects.

Other potential targets related to eicosanoid inflammation include the prostanoids thromboxane A₂ and prostaglandin D₂, which are potent bronchoconstrictors that act synergistically with cysteinyl leukotrienes to enhance allergen-induced responses in the respiratory tract.⁶⁸ Concomitant blockade of Cys-LT1 and thromboxane A₂ receptors abolished allergen-induced bronchoconstriction in a human lung slice model.⁶⁹ Prostaglandin D₂, the major prostanoid released from activated mast cells, affects the D prostanoid 1 and D prostanoid 2 receptors; the latter appears to be involved in eosinophil chemotaxis and activation.⁷⁰ Other modified receptor-blocking molecules and synthesis inhibitors are under investigation. However, because these agents are expected to have minor effects when used as monotherapy, a

clinically relevant combination strategy that blocks 2 or more receptors will be required.

CONCLUSION

Lung function testing and local treatment have been key asthma management strategies for the last 30 years. However, it is now clear that lung function alone does not reflect inflammatory status or disease progression. It correlates poorly with asthma symptoms and quality of life and does not predict asthma attacks or exacerbations. If asthma is viewed as a systemic disease, it is clear that involvement of one organ will influence the activity and progression of disease in other parts of the body. This new view of asthma thus requires a new management strategy that is directed not to the individual organ but instead to the underlying systemic pathology.

The link between asthma and rhinitis is a perfect example of the systemic nature of asthma. A treatment strategy that targets both will achieve better overall disease control. Inflammatory bowel disease and atopic dermatitis are other examples of disorders that directly or indirectly affect respiratory disease outcomes. The key strategy is to identify common disease-specific targets that can be treated systemically: mediators, mechanisms, or both that are activated or increased only during active disease. Eicosanoid-related inflammation is a particularly useful target for treatment. LTRAs, which block the eicosanoid Cys-LT1 receptor, have shown efficacy in asthma and rhinitis, as well as a range of conditions systemically linked with asthma, while inducing no or minor side effects. In addition, new eicosanoid receptors have been identified where combined blockade shows promising effects. New treatment strategies will require clinical trials that respect traditional primary end points but also evaluate the systemic effect of treatment.

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