

Clinical Implications of the Allergic Rhinitis-Asthma Link

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ABSTRACT: A possible link between allergic rhinitis (AR) and allergic asthma has long been a subject of debate. Surveys report that up to 78% of asthma patients have AR and 38% of patients with AR have asthma. Evidence points to a causal or coincidental relation between these upper and lower airway diseases. Various agents used to manage one entity have shown benefit in treating the other. The 2001 Allergic Rhinitis and Its Impact on Asthma guidelines call for patients with either condition to be assessed for the other. Medical therapy for AR or asthma should be chosen with awareness of

the probable coexistence of these diseases. We present the case for and against the united airway theory proposed to explain the association between these diseases. The roles of various therapies for dually afflicted patients are evaluated, including topical corticosteroids, antihistamines, leukotriene modifiers, anti-immunoglobulin E monoclonal antibody, theophylline, and immunotherapy. **KEY INDEXING TERMS:** Allergic rhinitis; Asthma; Allergies; Allergic rhinitis-asthma link. [*Am J Med Sci* 2004;327(3):127-138.]

Allergic rhinitis (AR) and asthma are among the most common chronic respiratory diseases in the industrialized world, and their incidence is on the rise. By conservative estimate, AR affects from 10% to 25% of the world's population.¹ This disease is estimated to affect about 15 million Americans.² AR and asthma frequently coexist in the same patient, and this association is important both clinically and economically. A report by the American Academy of Allergy, Asthma, and Immunology estimates that 38% of AR patients have asthma and that up to 78% of asthma patients have rhinitis symptoms, based on various assessment instruments.² Using a standardized questionnaire in a study of 478 patients, Busse et al³ found that 99% of the adults and 93% of the adolescents with asthma reported concomitant rhinitis.

Together, these disorders represent an enormous burden on the patient, the health care system, and the overall economy, in terms of both direct medical costs and lost productivity caused by absenteeism and impaired function at work and in school. In 1998, medical costs for asthma accounted for an

estimated \$12.7 billion in the United States, and AR costs contributed another \$1.2 billion.⁴ These figures primarily represent direct medical costs; in the case of AR, they do not reflect the substantial additional expenditures for over-the-counter medications and supplements as well as increased absenteeism. In patients with both asthma and AR, the costs increase substantially; Yawn et al⁵ demonstrated that in a population-based asthma cohort, annual medical expenses were on average 46% higher in those who also had AR compared with persons who had asthma alone.

Several lines of epidemiologic, genetic, and pathophysiologic evidence point to either a causal or coincidental relation between AR and asthma. Moreover, various pharmacotherapeutic approaches used to manage one entity have benefited the other. For these reasons, the 2001 Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines,¹ developed in collaboration with the World Health Organization (WHO), call for asthma assessment in all patients with persistent AR and, conversely, for AR assessment in all persons with asthma (Table 1). Similarly, the choice of optimal medical therapy for patients with AR should consider the potential effect on coexistent asthma, and asthma therapy should be selected with an awareness of the probability of concomitant AR.

Epidemiology and Risk Factors

Observations regarding the similarity of disease responses in the nose and lungs were made centuries ago, around the time of Galen. Numerous epi-

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Table 1. ARIA Recommendations Regarding the Interrelation of Allergic Rhinitis and Asthma

- Allergic rhinitis is considered to be a major chronic respiratory disease because of its
 - prevalence
 - impact on quality of life
 - impact on work/school performance and productivity
 - economic burden
 - links with asthma
- Allergic rhinitis should be considered a risk factor for asthma along with other known risk factors
- Patients with persistent allergic rhinitis should be evaluated for asthma by history, chest examination and, if possible and when necessary, the assessment of airflow obstruction before and after bronchodilator
- Patients with asthma should be appropriately evaluated for rhinitis (history and physical examination)
- A combined strategy should ideally be used to treat the upper and lower airway diseases in terms of efficacy and safety

Adapted from reference 1.

demologic studies have now provided scientific support for an asthma-AR link in different populations and age groups. In the Tucson Children's Respiratory Study,⁶ children diagnosed with AR at age 1 year had a higher incidence of asthma by 6 years, along with greater respiratory symptoms and use of medications. A diagnosis of AR was associated with twice the likelihood of developing asthma by age 11. These findings were interpreted to indicate that early atopic sensitization, evidenced by AR or food allergies, is a powerful risk factor for the development of childhood asthma. An Australian study similarly found that atopy acquired before the age of 6 years was associated with development of childhood or adolescent asthma, whereas the later acquisition of atopy was associated with AR but not asthma.⁷

The AR-Asthma Association in the United States and Other Countries

In 1961, researchers evaluated and skin-tested approximately 700 first-year students at Brown University who had no previous history of bronchial asthma. Results of a 23-year follow-up indicated that those students who had shown evidence of AR in 1961 were 3 times more likely to have developed asthma in that period, compared with those who did not have AR.⁸ A survey of 6563 residents of Tecumseh, Michigan, in 1974 showed that new diagnoses of AR or allergic asthma were 2- to 4-fold greater in persons who already had 1 of the 2 diseases.⁹ French investigators polled 20,000 households regarding symptoms of perennial rhinitis; almost 17,000 responded.¹⁰ Perennial rhinitis, defined as at least 6 months of continuous symptoms, was reported in 4.1% of responses. Analysis of a cross-sectional group of 1367 responders with perennial rhinitis found that 13.4% also reported symptoms of asthma

compared with 3.8% who did not, for a highly statistically significant odds ratio (OR) of 3.26. In 1999, Leynaert et al¹¹ analyzed data from the European Community Respiratory Health Survey (ECRHS) to assess the association between asthma and perennial allergic rhinitis in patients aged 18 to 44 years. After adjustment for sex, age, smoking, family history, and geography, asthma was shown to be significantly associated with rhinitis in both atopic subjects (OR, 8.1) and nonatopic subjects (OR, 11.6).

Family History as a Predictor

Family history has also been shown to play an important predictive role. Results of a study in northern Sweden indicated that adults with a family history of asthma or rhinitis had a 3- to 4-fold increased risk for developing asthma and a 2- to 6-fold increased risk for developing AR compared with adults with no such family history.¹² A recent report by Illi et al¹³ and the German Multicenter Allergy Study (MAS) group found that a history of maternal asthma or maternal smoking were powerful predictors of childhood asthma, even more powerful than early atopic sensitization and AR. The investigators followed 1314 children from birth to 7 years by the frequent administration of parental questionnaires regarding asthma symptoms, yearly specific in vitro testing for food and inhalant allergens, and, at age 7, administration of bronchial histamine challenge. They found that children with atopic asthma at the age of 7 years were significantly more likely to have exhibited early sensitization to food or inhalant allergens before 1 year of age compared with nonasthmatic children. Only those sensitized to any allergen by 1 year of age, and sensitized by 7 years to inhalant allergens, were at a significantly increased risk of developing asthma by age 7. Considering these persistently sensitized children, only those with a family history—especially a maternal history—of asthma or of maternal smoking showed a significantly increased risk for asthma.

These findings support the concept that a specific genetic and/or environmental "lung factor" may determine whether a patient will develop asthma independent of allergic sensitization or will develop asthma in parallel.¹⁴ The MAS authors suggest that this predisposition to asthma precedes—and may actually determine—the pattern of allergic sensitization, contrary to the view that asthma results from a sequential progression of atopic sensitization beginning in childhood with early food allergy and AR.¹³

Pathophysiology of Allergic Diseases

There are important similarities and differences in the pathophysiology of AR and asthma, beginning with the idea that both involve a common mechanism. The Th2 paradigm of inflammation is systemic,

Table 2. Pathophysiologic Similarities and Differences between Allergic Rhinitis and Asthma

Characteristic	Similarities	Differences
Mechanism	Both seem to be manifestations of a systemic immunologic disorder that produces inflammation in differing organs	
Airway structure	Mucosa, epithelium, cilia	Airway size, geometry, blood supply, effect on smooth muscle, protection against airborne allergens or irritants
Key triggering events	IgE-mediated sensitization to inhaled allergen Interaction of neurogenic and inflammatory pathways	Role of neurotransmitters; <i>In asthma</i> , muscarinic receptor subtypes <i>In late-phase AR response</i> : basophils
Key immune/inflammatory components	T lymphocytes, Th2 cytokines, mast cells, eosinophils	
Acute effect on airway	Obstruction, inflammation, mucosal edema (especially in AR)	<i>In asthma</i> , smooth muscle contraction; <i>in AR</i> , vasodilation, edema, exudation
Late-phase response	4–8 hours after acute episode; airway hyper-responsiveness; eosinophil influx	<i>In AR</i> , influx of basophils
Chronic effect on airway	Inflammation with eosinophilia	<i>In asthma</i> , airway remodeling, smooth muscle hyperplasia and hypertrophy, epithelial shedding, thickening of subbasement membrane

IgE, immunoglobulin E. Adapted from reference 15.

not organ-specific. The association between AR and allergic asthma probably results from a common alteration of the immune system that tips the balance of T-helper cell responses in favor of the Th2 pattern of proinflammatory cytokine activity^{14,15} (Table 2).

Similarities

The similarities in the pathophysiology of AR and allergic asthma outweigh the differences. Identical stimuli such as inhaled allergens and irritants affect both upper and lower respiratory tracts in a similar fashion. These allergic diseases involve many elements of a systemic disease in that effector cells are recruited from the circulation, white cell progenitors are stimulated in the bone marrow, and systemic effector cells are primed.^{16,17} Exposing the lower airways of animals to the allergen causes the white cell progenitors in the bone marrow to proliferate and differentiate, which in turn leads to persistent increases in the number of eosinophils in the lung, suggesting that—after allergen exposure—signaling takes place between the lung and bone marrow. The pathways involved include interleukin (IL)-5, further reinforcing the idea of a common mechanism in allergic disease.¹⁷ IL-5 is one of several cytokines important in Th2-driven allergic responses in the respiratory tract.

Inflammation with marked infiltration of eosinophils into the affected tissues is a common finding of AR and allergic asthma. Allergic inflammation can be thought of as a systemic immunologic response that is manifested in specific organ systems such as

the upper respiratory tract (AR), the lungs (asthma), the gastrointestinal tract (gastroenteritis), and the skin (atopic dermatitis).¹⁷

Responses in the Airways. In both AR and allergic asthma, the disease process begins with atopic sensitization and generation of allergen-specific IgE in response to airborne allergens settling on the airway surface. Antigenic fragments of the allergens are presented to T-helper cells, which release cytokines that induce allergen-specific IgE antibody production by B lymphocytes and plasma cells. These allergen-specific IgE antibodies then bind to the surface of mast cells and basophils present in the mucosa of both the upper and lower airways. Upon re-exposure to the airborne allergen, antigenic binding to the cell-surface specific IgE activates the mast cells and basophils, resulting in degranulation and release of inflammatory mediators, including histamine, cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄), and various proteases and cytokines. These mediators, in turn, trigger vasomotor and glandular responses in the upper airway and smooth muscle contraction and mucosal edema in the lower airway, leading to airway obstruction.^{14,18}

A more prolonged late-phase response occurs approximately 4 to 8 hours after the initial IgE-mediated reaction to allergen exposure. In the upper and lower airways, this late response is characterized by obstruction (eg, nasal congestion or bronchoconstriction), and by increased hyper-responsiveness to the same or different allergens or irritants. An influx of eosinophils and other inflammatory cells marks the

late-phase response in the airways. Evidence suggests that basophils may also play an important role in the late phase of AR.

Differences

The nose reduces exposure of the airways to environmental allergens and pollutants. Thus, the nasal mucosa constitutes a critical barrier. The nose is supplied by a rich and complex microcirculation that serves multiple functions, including the heating and humidifying of inspired air and the regulation of airflow, via vasodilation and vasoconstriction. Sub-epithelial and glandular capillaries are fenestrated, allowing the exudation of plasma into the submucosa and providing the necessary fluid for copious secretions. Inflammation and excessive mucosal secretions then lead to nasal congestion and rhinorrhea, the hallmarks of AR.¹⁹

The surface area of the lower airway is much larger than that of the upper airway. Lower airway patency is mainly controlled by smooth muscle. The airway smooth muscle cells are themselves secretory and are therefore part of the autocrine process. In allergic asthma, the characteristic response is bronchial smooth muscle contraction or bronchospasm. The latter is mediated by various inflammatory and neurogenic factors, including muscarinic pathways specific to the lower airway, resulting in reduced airflow. Other hallmarks of chronic asthma are structural changes or remodeling of the lower airway, which takes the form of epithelial shedding, sub-basement membrane thickening, and smooth muscle hypertrophy and hyperplasia. However, in AR, the epithelium of the nasal mucosa tends to remain intact, and the degree and clinical importance of upper airway remodeling are less pronounced than in allergic asthma.²⁰

Asthma-AR Interaction

Although the nature of the interaction between allergic asthma and AR remains controversial, the acute symptoms of AR (sneezing, rhinorrhea, nasal congestion) frequently precede the onset of asthmatic coughing and wheezing. Even in patients without clinically defined allergic asthma, active AR is associated with increased airway hyper-reactivity.²¹ Several hypotheses have been proposed to explain how AR may aggravate concomitant lower airway disease (summarized in Table 3).

Adverse Effects of AR on Respiration. One explanation emphasizes the logistic and mechanical aspects of respiration. The nose is the primary access for airborne allergens, and so it is not surprising that the upper airway tends to be affected first. AR is marked by nasal congestion and obstruction, which may in turn promote mouth breathing. Mouth breathing bypasses the air-conditioning effect of the upper airway and leads to a more direct exposure of the lower airway to cold, dry air and other asthma

Table 3. Proposed Causes of Asthma Exacerbations Related to Allergic Rhinitis

- Mouth breathing resulting from nasal obstruction alters the normal air conditioning and thus adversely affects lower airway patency
—*This theory conforms with clinical observations; supported by evidence of increased lower airway response to cold air inhaled orally versus nasally*
- Drainage or silent aspiration of inflammatory material from the nasal pharynx into the lungs
—*No clinical evidence; unlikely to occur in conscious humans*
- Absorption of upper airway inflammatory mediators into the systemic circulation, with dissemination to the lungs
—*No scientific evidence in humans*
- Neurogenic reflex linking upper and lower airways
—*No definitive clinical evidence; based on distal airway response to local provocation and on an increased understanding of the interaction between neurogenic and inflammatory pathways in the airway wall*

triggers. Mouth breathing also bypasses the nasal mucociliary blanket, which entraps particles and irritants, reducing access to the lower airway. This hypothesis is both practical and intuitive, and is supported by studies showing that the inhalation of cold air via mouth breathing has a greater impact on pulmonary function compared with nose breathing.²²

Aspiration/Absorption of Upper Airway Secretions/Inflammatory Substances. It has also been suggested that inflammatory mediators released in the nasal pharynx may drain postnasally to be aspirated into the lower airway. However, this idea is not supported by the scientific evidence and seems unlikely to occur in conscious humans.²³ In an animal model, another variation is the absorption of inflammatory substances from the upper airway into the systemic circulation, with subsequent dissemination to the lungs. Although there is no direct evidence to support this hypothesis,²⁴ Braunstahl et al²⁵ observed that nasal allergen provocation increases the number of eosinophils and adhesion molecules in the bronchial mucosa.

Neurogenic Reflex/Pathway. The concept of asthma resulting from a nasal reflex was proposed by Sluder in 1919.²⁶ Since that time, considerable evidence has been accumulated to support the concept of rhinitis-associated asthma resulting from a common neurogenic pathway, with upper airway activation leading directly to reflex-mediated bronchoconstriction.¹⁴ Cold-air nasal provocation has been shown to produce a reflexive reduction in pulmonary function, as measured by forced expiratory volume in 1 second (FEV₁).¹⁸ Nasal challenge with histamine has also been shown to produce a significant decline in FEV₁.²⁷ Conversely, bronchial challenge with histamine increases nasal airflow resistance, suggesting a centrally mediated reflex affecting both the upper and lower airways.¹⁴ Respiratory viral infections often trigger nasal and bronchial responses, typically following a pattern of rhi-

Table 4. Drug Classes Demonstrating Benefit in Both Allergic Rhinitis and Asthma

-
- Topical corticosteroids
 - Antihistamines^a
 - Leukotriene modifiers
 - Theophylline
 - Immunotherapy
 - Anti-IgE monoclonal antibody
-

IgE, immunoglobulin E.

^a This includes antihistamine monotherapy as well as antihistamine combinations: antihistamines + decongestants, antihistamines + topical corticosteroids, and antihistamines + leukotriene modifiers.

nititis preceding asthma exacerbation. Increased production of IL-11 during rhinovirus infection may facilitate the effects of neurotransmitters and other mediators on airway inflammation.²⁸

The airway hyper-responsiveness characteristic of both asthma and AR is the result of complex interactions of the neurogenic and inflammatory pathways. In fact, it can be argued that virtually all aspects of airway inflammation are influenced by neurogenic pathways and released neurotransmitters.¹⁵ The mucosa, vasculature, and epithelium of the airways are densely innervated. Action potentials traveling not only centrally but also antidromically via neural axon reflexes may provoke the release of neuropeptides.^{29–31} These neuropeptides interact with nearby airway cells that regulate glandular secretion, vasodilation, smooth muscle tone, and possibly cellular recruitment.¹⁴ They also seem to interact with proinflammatory cytokines and other mediators in a cyclic fashion that promotes the further release of both neuronal and inflammatory mediators.³²

Crossover Benefits of Certain Medical Therapies

The strongest argument for the association between AR and asthma is that many of the drugs used primarily to treat one disease have also been shown to relieve or, in some cases, to prevent symptoms of the other (Table 4). The nature and extent of this crossover benefit have not been precisely determined, and clinical guidelines have not been established for the management of the concomitant disease. The recommended clinical approach is to manage the 2 disorders discretely but simultaneously. Nevertheless, previous studies, including some involving immunotherapy and experimental anti-IgE monoclonal antibody, suggest a systemic approach to atopic disease, as discussed above.^{33–39}

Two recently published reports point out the positive health impact of standard, appropriate therapy for AR in patients with concomitant AR and asthma. Crystal-Peters et al⁴⁰ analyzed data from health insurance claims submitted in 1994 to 1995 by al-

most 5000 patients, aged 12 to 60 years, with allergic asthma and rhinitis, of whom approximately 73% were treated for AR. The risk of an asthma-related event, defined as an emergency room (ER) visit or hospital admission, was about twice as great in the untreated subjects compared with those who were being treated for AR; this difference was highly statistically significant ($P = 0.001$). Most of the treated AR patients in this study received oral antihistamines and/or intranasal corticosteroids; the majority of the treated population—61%—received both types of agents. An even larger study⁴¹ also analyzed data from health insurance claims in almost 14,000 patients with both asthma and upper airway disease (rhinitis, sinusitis, or otitis media). This study found that the greatest reduction in ER visits for asthma occurred in patients receiving the greatest number of prescriptions for nasal corticosteroids. These findings clearly suggest that treatments aimed at symptomatic improvement in the upper airway may provide important preventive effects in asthma as well.

The next section summarizes the major classes of agents with demonstrated benefit in both asthma and AR, among them topical corticosteroids, antihistamines, leukotriene modifiers, combination therapies, theophylline, immunotherapy, anti-IgE, and other treatments.

Topical Corticosteroids

For more than a decade, topical corticosteroids have been the cornerstone of respiratory tract anti-inflammatory therapy. These agents are the most effective anti-inflammatory therapy in both allergic asthma, for which it has been administered by oral inhalation, and AR, for which it has been administered intranasally. The mechanism of action of these agents has been well described in the literature.⁴² Topical corticosteroids have been shown to reduce the infiltration of inflammatory cells in asthma and AR and to modulate the release and activity of inflammatory mediators and other critical components in both diseases.

Several studies conducted in AR patients have demonstrated that corticosteroids administered by the intranasal route, despite their minimal deposition in the lungs, produce beneficial effects in the lower airway, ranging from reductions in nonspecific bronchial hyper-responsiveness to improvements in pulmonary function scores and in asthma symptoms.^{43–46} For example, Welsh et al⁴⁵ evaluated the prophylactic effects in ragweed-sensitive AR of 2 different intranasal corticosteroids, flunisolide and beclomethasone dipropionate, versus cromolyn sodium as well as placebo. A subgroup of AR patients also had seasonal asthma. The intranasal corticosteroids proved more effective than either cromolyn sodium or placebo in improving rhinitis scores in the

overall population and in reducing asthma symptoms in the subgroup.

Interestingly, the intranasal administration of a corticosteroid has demonstrated a greater effect on bronchial responsiveness than a comparable dose of the corticosteroid given by oral inhalation. Aubier et al⁴⁷ compared 400 µg/day beclomethasone dipropionate delivered intranasally and bronchially in patients with AR but without asthma. After 2 weeks, those treated intranasally showed marked improvement in bronchial reactivity compared with the oral inhalant group. Nonetheless, orally inhaled corticosteroids improve the symptoms of AR in patients who are being treated for asthma.⁴⁸ The results suggest a systemic anti-inflammatory effect of topical corticosteroids, regardless of their local administration and deposition.⁴⁸

Antihistamines

Oral antihistamines, administered alone or in combination with decongestants, are a mainstay of treatment for AR. Their primary effect is to bind competitively to H₁ receptors on the sensory nerves and vascular tissue of the nose, resulting in a reduction in rhinorrhea, sneezing, and nasal congestion.^{15,18} H₁ receptors are also distributed throughout the lower airway, and histamine has been identified as a potentially important mediator in allergic asthma.⁴⁹ Numerous other mediators are involved in asthma, however, which may explain why antihistamines alone do not exhibit a predominant antiasthmatic effect. Nevertheless, antihistamines may be beneficial in asthma by reducing H₁-mediated effects on smooth muscle contraction, vascular permeability, and nerve activation. In addition, antihistamines exhibit a range of non-H₁-mediated anti-inflammatory effects, including inhibition of mediator release by mast cells and basophils, inhibition of the migration of eosinophils and other inflammatory cells into the airway, and reduction in inflammatory cell adhesion to the airway wall.⁵⁰ Indeed, antihistamines (administered orally or topically) generally have been found to have both antihistaminic and anti-inflammatory effects.

From a clinical perspective, antihistamines are effective in relieving AR symptoms, which in turn tends to lead to better asthma control. As described above, this clinical impression is supported by substantial scientific evidence. Several clinical studies have demonstrated a positive therapeutic effect in AR and asthma, particularly with the newer low-sedating antihistamines such as cetirizine, and with nonsedating antihistamines such as fexofenadine and loratadine.

Two of the larger multicenter trials evaluated the response to approved dosages of oral antihistamines in patients with concomitant AR and asthma.^{51,52} Grant et al⁵¹ reported that cetirizine 10 mg admin-

istered once daily reduced symptoms of seasonal AR (SAR) and asthma compared with placebo. Corren et al⁵² studied a twice-daily combination of 5 mg of loratadine and 120 mg of pseudoephedrine in patients with SAR and asthma, and demonstrated that asthma symptoms, pulmonary function, and asthma-specific quality of life were significantly improved in the treated group compared with control subjects. Available data suggest that nonsedating antihistamines (eg, fexofenadine, loratadine, and desloratadine) can be used safely, without causing drowsiness, impairing motor coordination, or interfering with cognition in most patients, and can provide effective adjunctive therapy in patients with concomitant AR and asthma. Note, however, that increasing effects of sedation and impairment are observed with higher-than-recommended dosages of loratadine and desloratadine—and that relatively high dosages of antihistamines may be required for the treatment of asthma. Antihistamines administered in combination with decongestants, topical corticosteroids, or leukotriene modifiers have demonstrated benefits in both diseases.

Leukotriene Modifiers

Leukotrienes are released spontaneously or in response to specific challenges in AR and allergic asthma. These mediators have been associated with the influx of inflammatory cells and early- and late-phase airway symptoms in both diseases. Cysteinyl leukotrienes have demonstrated 3,000 to 10,000 times greater potency than histamine or methacholine in inducing bronchoconstriction; they also contribute to mucosal edema, mucus production, and the recruitment of eosinophils.⁵³ Accordingly, recent studies have examined the possible role of leukotriene-modifying agents in treating patients with concomitant AR and asthma.^{54–56} Several studies have suggested use of leukotriene modifiers for the therapy of both diseases. Indeed, montelukast has recently been approved for the treatment of AR.

Zafirlukast. Phipatanakul et al⁵⁴ evaluated the LTD₄ antagonist, zafirlukast, versus placebo in a crossover study of 18 patients with asthma and AR induced by exposure to cat dander. Zafirlukast treatment was associated with a significant lessening in pulmonary function decline, as assessed by FEV₁, and with a significant reduction in nasal congestion, as assessed by nasal patency. Zafirlukast also was associated with significantly reduced upper and lower airway symptom scores in this study. However, the clinical relevance of these findings is unclear.

Montelukast. Wilson et al⁵⁶ compared the antiasthmatic efficacy of inflammatory mediator blockade with montelukast plus cetirizine versus an intranasal corticosteroid. The latter was given by oral as well as intranasal inhalation. Using a crossover design, the authors evaluated in single-blind fashion

the responses of 14 patients with SAR and asthma who evidenced bronchial hyper-reactivity. Giving both regimens for 2 weeks showed antiasthmatic efficacy in terms of the response to challenge with adenosine monophosphate, exhaled nitric oxide, as well as spirometric improvement. The patients' symptoms were significantly improved by both the montelukast-cetirizine and the topical corticosteroid regimens, with similar improvement seen with both.

A study with montelukast in asthma by Currie et al⁵⁷ indicated a comparable bronchodilator action of montelukast and fluticasone in patients with moderate asthma, but fluticasone showed an additional attenuation of airway inflammation.

A series of studies on the efficacy of montelukast, loratadine, and placebo in treating patients with SAR, showed the superiority of each active agent versus placebo.^{58–60} The generally favorable efficacy and safety of montelukast has led to its recent FDA approval.

A recent review of head-to-head comparator studies and data from placebo-controlled trials evaluated the place of leukotriene receptor antagonists in the treatment of AR.⁵⁹ Nathan concluded from the study findings that these agents are sometimes more effective than placebo, no more effective than non-sedating antihistamines, and less effective than intranasal corticosteroids in AR treatment. Of particular significance to the current discussion, he also concluded that the data do not clearly support a unique role for leukotriene receptor antagonists in the treatment of AR, even when asthma is also present.⁵⁹ However, a single oral agent that has the potential to treat both diseases has considerable appeal. With the approval of montelukast for AR, substantial information should be forthcoming on how and where to place this agent for the treatment of AR with or without asthma.

Combination Therapies

The administration of a leukotriene modifier in conjunction with an antihistamine may be useful in managing patients who have both AR and asthma. Zafirlukast combined with loratadine was found to be more effective than either agent given alone for reducing early- and late-phase lower airway obstruction in asthmatic patients.⁶¹ A combination of montelukast with loratadine proved superior to either agent alone in reducing rhinitis symptoms in patients with SAR.⁶² Nevertheless, the crossover study by Wilson et al⁶³ comparing a montelukast-loratadine combination with fexofenadine alone in treating SAR showed that fexofenadine monotherapy was as effective as the montelukast-loratadine combination in relieving nasal blockage, discharge, itching, sneezing, and in improving nasal peak flow. In a recently published study,⁶⁴ monotherapy with the intranasal corticosteroid fluticasone was more effective than either montelukast or

combined montelukast-antihistamine (loratadine) therapy for control of nasal symptoms and reduction of pollen-induced nasal eosinophilic inflammation.

Whether montelukast would confer additive effects in 22 patients with mild-to-moderate asthma who were receiving a combination of fluticasone/salmeterol or fluticasone alone was evaluated in a placebo-controlled trial. After a 2-week run-in period using only fluticasone/salmeterol, montelukast or placebo was added for the next 3 weeks. Compared with the fluticasone/salmeterol run-in, adding montelukast to fluticasone/salmeterol was significantly better than placebo for inflammatory markers but not for lung function.⁵⁷

Theophylline

Theophylline is a prime example of a traditional asthma drug that was discovered to provide some benefit in the treatment of AR. Theophylline, a phosphodiesterase inhibitor, is typically classified as a bronchodilator, but it has also been shown to have relevant anti-inflammatory effects, such as regulating the mediator release by mast cells and the production of eosinophil cationic protein.^{65,66} From a clinical perspective, theophylline has demonstrated a protective effect on bronchial hyper-responsiveness in patients with AR.⁶⁶ Aubier and colleagues⁶⁵ found that after treating AR patients with slow-release theophylline or placebo for 3 weeks, the theophylline-treated group had a reduction in nasal symptoms, including obstruction, compared with the placebo-treated subjects. Nevertheless, theophylline is infrequently used in clinical practice, mainly because of its unpleasant side effects, its potential for interaction with other drugs, and its narrow therapeutic window.

Immunotherapy

Immunotherapy with a specific allergen is an established approach to systemic treatment that has demonstrated benefits in AR and asthma. A detailed discussion of the scientific literature, rationale, and issues related to clinical use of immunotherapy appear in a WHO Position Paper.³⁴ Recent studies raise the intriguing possibility that specific immunotherapy not only is effective in treating selected patients with AR but that it can also reduce the risk for asthma development in children with AR. For example, the Preventive Asthma Treatment (PAT) study results indicated that a 3-year course of specific immunotherapy significantly reduces the number of schoolchildren aged 6 to 14 years who progress from hay fever to asthma over that time.³⁵ Data thus support the idea that specific immunotherapy can prevent the development of asthma in children with SAR.

Des Roches et al³⁶ conducted a prospective, case-control study of 44 asthmatic children younger than 6 years of age whose only allergic sensitivity was to

house dust mites. After 3 years, 10 of the 22 children who received specific immunotherapy did not develop any new sensitivities, compared with 0 of the 22 control subjects, a significant difference ($P = 0.001$). The authors concluded that immunotherapy altered the natural course of allergy in this patient population.

Researchers in Italy and the United Kingdom compared the response to immunotherapy with that of placebo administration in 44 adults with AR (mean age, 19 years). These persons initially showed sensitivity to house dust mites and bronchial hyper-responsiveness to methacholine challenge.³⁷ After 2 years of immunotherapy, bronchial hyper-responsiveness, assessed by the dosage of methacholine required to produce a 20% decrease in FEV₁, was significantly reduced in the patients receiving immunotherapy compared with placebo. The FEV₁ was within the normal range in 50% of the subjects so treated. Over the course of the study, 9% of the placebo group developed asthma, whereas none of the subjects receiving immunotherapy did. The investigators noted that specific immunotherapy may provide effective prophylaxis for AR patients with hyper-reactive airways. Such findings may encourage investigators to explore the possible role of immunotherapy in asthma prevention in patients with AR, especially young children.

Anti-IgE and Other Experimental Therapies

Another systemic therapeutic approach currently under development for AR and asthma involves the use of anti-IgE monoclonal antibody (omalizumab).³⁸ Given the critical role played by IgE in atopic sensitization and responses in the upper and lower airways, specific antibodies that would inhibit IgE present a logical target for drug development. By binding to and decreasing serum levels of free IgE, these antibodies would reduce the amount of antigen-specific IgE available to sensitize mast cells and basophils. The result, ideally, would be decreased mediator release and reduced symptoms.

The effect of omalizumab on moderate-to-severe SAR was studied in a randomized, double blind, placebo-controlled trial ($n = 536$; ages 12–75 years). After 12 weeks, nasal symptom scores were significantly lower in the omalizumab-treated (300 mg/day) subjects than in the control subjects. Quality of life also improved significantly. Adverse events were similar in treatment and placebo groups.³³

A placebo-controlled, double-blind study of severe allergic asthma patients ($n = 525$) demonstrated that when added to standard asthma therapy, omalizumab significantly reduces asthma exacerbations and decreases inhaled corticosteroid and rescue medication use.⁶⁷ A follow-up study with this severe asthma cohort showed that the improvement in asthma control with add-on omalizumab therapy is paralleled by clinically meaningful improvements in

asthma-related quality of life.⁶⁸ This effect of omalizumab on quality of life has been confirmed in children as well.⁶⁹ A combined analysis of 3 recent studies (1071 adolescents and adults, 334 children) concluded that omalizumab reduces the rate of serious asthma exacerbations, unscheduled outpatient visits, ER visits, and hospitalizations in patients with moderate-to-severe asthma.⁷⁰

Numerous other novel therapies for the treatment and prevention of AR and asthma are under development, with an emphasis on systemic immunomodulating and/or anti-inflammatory effects. These include agents that prevent T-cell activation, those that prevent or reverse Th2-mediated effects, and others that inhibit downstream mediators of inflammation or of eosinophil migration and activation.³⁹

Case Study

The following case illustrates the current approach to management of concurrent mild persistent asthma and AR. A 13-year-old girl presented in the physician's office complaining of tightness in the chest that occurred 3 or 4 times a week and that awakened her at night about 7 to 8 times a month. These symptoms became troublesome a few months before presentation. There was a clear rhinorrhea with nasal congestion and bouts of sneezing. The patient breathed through her mouth, and a trail of tissues marked her progress through the office and examining room.

Physical examination showed a nasal crease as well as dark circles under the eyes, both signs of chronic nasal/sinus disease. Examination of the nose showed a pale, boggy nasal mucosa bilaterally with clear rhinorrhea, but no signs of infection or polyps, and chest examination revealed very faint expiratory wheezes bilaterally. Spirometric (FEV₁) values obtained without a bronchodilator were 80% of those predicted. Fifteen minutes after the administration of an inhaled bronchodilator, the values improved to 100% of the predicted value, an absolute increase of >12% and 200 mL.

Questioning revealed that this patient shared her bed with a devoted spaniel. The patient was diagnosed as having mild persistent allergic asthma and perennial rhinitis⁷¹ and was referred to an allergist for skin testing to determine the allergen or allergens responsible. The goal of therapy was to minimize with rapidity the number and severity of the chronic asthmatic symptoms, as well as to relieve the rhinorrhea and other signs/symptoms of AR.

A stepwise approach to therapy is recommended to relieve the asthma symptoms rapidly and to maintain their control.⁷¹ An inhaled corticosteroid was prescribed for the asthma, and a nonsedating antihistamine was given for the rhinitis. On her return visit after 2 weeks, the FEV₁ improved to about 95% of predicted, and the nasal symptoms

were diminished markedly. The patient also seemed markedly brighter and seemed more comfortable, with no “tissue trail” evident. She said she could now sleep through the night without nighttime asthma symptoms, even though she still shared her bed with her pet. The allergist’s report is awaited.

Comment

If allergy to dog dander proves to be responsible for the patient’s symptoms, excluding the pet from the bedroom is a compromise solution, because it is likely that the patient will still have significant exposure to the dog unless it is removed from the home. Frequently bathing and brushing the dog (by someone other than the patient) may help to reduce the amount of dander indoors, but controlled studies have not consistently demonstrated that this will produce significant clinical improvement. If the dog remains, it may be worthwhile to invest in a high-efficiency particulate air (HEPA) cleaner, which has been shown to significantly reduce airborne dog dander allergen. A HEPA filter, along with preventing access by the dog to the bedroom and, if possible, the living room, may reduce total inhaled allergen load.⁷²

Although immunotherapy might be an option if there were a poor response to medications (not seen in this patient), immunotherapy for dog allergen is not as effective as that for other common aeroallergens such as pollen, mold spores, other pet dander, and dust mite residues. However, if the patient has several other clinical sensitivities identified by history and skin testing, this may be a good option after first implementing environmental control measures. The nasal inflammation typical of AR may have contributed to hyper-responsiveness of the lower airways in this case. In addition, mouth breathing caused by nasal obstruction may have contributed to bronchospasm from the intake of cool air. Considering treatment over the long term, the goal is to “step down” the dosage of the orally inhaled corticosteroid to the lowest possible level. Although an inhaled corticosteroid is the preferred treatment for mild persistent asthma in adults and children over the age of 5 years, alternative choices are cromolyn, a leukotriene modifier, nedocromil, or a sustained-release theophylline preparation.⁷¹ The antihistamine may be given in combination with a decongestant for AR if required for symptomatic control. An intranasal corticosteroid is another option for rhinitis treatment and would be recommended for more severe rhinitis or as an alternative to an antihistamine for milder rhinitis.

Conclusions

The many clinical and pathophysiologic links between AR and asthma have led researchers to reassess their classifications. Instead of 2 different syn-

Table 5. Summary: Pros and Cons of the Unified Airway Disease Theory

Pros

- AR and asthma are linked epidemiologically
- AR and asthma have a similar pathophysiology/underlying mechanism
- AR is a powerful risk factor for subsequent development of asthma
- New diagnoses of AR or asthma are 2- to 4-fold greater in persons who already have one of these diseases
- Persons with a family history of asthma or AR have a 3- to 4-fold increased risk for developing asthma and a 2- to 6-fold risk for developing AR
- Drugs used to manage one entity have shown benefit in treating the other

Cons

- Differences exist in surface area and geometry of upper and lower airways
- Bronchial smooth muscle contraction is a hallmark of asthma but not of AR
- Structural remodeling of the lower airway (epithelial shedding, sub-basement membrane thickening, smooth muscle hypertrophy/hyperplasia) is characteristic of asthma
- In AR there is less remodeling and the epithelium tends to remain intact
- The role of neural pathways and neurotransmitters is distinct

Alternative Concept

- AR and asthma are manifestations of a systemic immunologic disease that produces atopic disorders with inflammation involving different organ systems
- Common predisposing genetic factors have been identified
- Systemic therapy is the most effective treatment for both diseases
- Th2 paradigm of inflammation is universal, not organ-specific

Modified from reference 18.

dromes affecting 2 distinct organs—the nose and lungs—some authors have proposed a “united airways disease” theory, whereby AR and asthma are viewed as a single entity that affects different aspects of the same respiratory organ system.^{73–75} This theory is supported by many—but by no means all—epidemiologic, clinical, and laboratory findings (Table 5). A problem is that this theory overlooks important structural and mechanistic differences and also fails to account for evident distinctions in rhinitis and asthma phenotypes.

An alternative viewpoint is that AR, asthma, and atopic dermatitis are all manifestations of a systemic immunologic disorder that produces a variety of allergic diseases that affect different organ systems (summarized in Table 5; see reference 18 thereto).¹⁴ This hypothesis acknowledges both the apparent overlap and the differences between these conditions and points toward the development of new therapies targeting the underlying systemic cause.

For the clinician, the primary issue is that many patients who present with AR either have allergic asthma or are at risk for it. Conversely, the great

majority of patients with allergic asthma also have AR. As recommended in the ARIA guidelines, it is essential that persons who present with persistent AR (defined as symptoms present more than 4 days a week for more than 4 weeks) be carefully evaluated for asthma by history, chest examination, and change in airflow measured before and after administration of a bronchodilator.¹ Patients with allergic asthma also should be evaluated for a history or physical signs of AR. The clinical approach previously recommended had been to control the asthma first and to then treat the AR. However, strategies for simultaneously managing upper and lower airway diseases with agents that affect the mechanisms of allergic airway inflammation should provide the best clinical outcome.

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