ONE AIRWAY: THE LINK BETWEEN ALLERGIC RHINITIS AND ASTHMA*

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ABSTRACT

The concept of “one airway, one disease” was highlighted in the Allergic Rhinitis and Its Impact on Asthma guidelines and has arisen as a result of the now well-established link between the upper and lower airways. Whether the relationship represents a causal association or whether it is more simply the result of a common mucosal susceptibility remains to be determined. Similarly, from a clinical viewpoint, the important question of whether treating the upper airway will have consequences on treating the lower airway or on responses in the lower airway is currently under investigation. This paper describes the similarities and differences between rhinitis and asthma and focuses on the influence of treatment, namely of nasal corticosteroids, allergen immunotherapy, and antihistamine treatment, on both the upper and lower airways.


The link between the lower and upper airways is now well established. Anatomically, these 2 airways have a common respiratory epithelium and a common mucosal susceptibility to disease. Epidemiologic studies have consistently shown that asthma and rhinitis often coexist in the same patient. For example, 50% to 80% of patients with bronchial asthma have allergic rhinitis and 20% to 30% of patients with rhinitis have associated bronchial asthma. An important question is whether the relationship between the upper and lower airways is a causal association or whether it simply represents a common mucosal susceptibility.

ALLERGIC RHINITIS AND ITS IMPACT ON ASTHMA

The important link between the upper and lower airways has been highlighted in the Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines. Developed in 1999, the ARIA guidelines replaced the International Consensus on Rhinitis (IRC) guidelines of 1994 and offer the advantage of being evidence based (2500 references). In addition, the new guidelines include new drugs that have become available since the IRC guidelines and are relevant to patients in underdeveloped and developing countries. This document offers a novel way of looking at the classification of allergic rhinitis and comprises several important aspects.

CLASSIFICATION OF ALLERGIC RHINITIS

The guidelines propose a new classification for allergic rhinitis using symptoms and quality-of-life parameters. Based on duration, allergic rhinitis is subdivided into intermittent or persistent; this differs from the previous classification of seasonal or perennial.

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Similarly, based on severity, allergic rhinitis is subdivided simply into mild or moderate-to-severe based on whether the patient has an associated impairment of usual activities, including sleep, daily activities, work, and exercise. As a result of the ARIA guidelines, future patient populations used in allergic rhinitis treatment studies may be selected according to these guidelines.

**TREATMENT OF ALLERGIC RHINITIS**

The ARIA guidelines also provide an evidence-based recommended treatment profile for patients with allergic rhinitis (Figure 1). Accordingly, patients are divided into mild intermittent, moderate severe intermittent, mild persistent, and moderate severe persistent. As shown in Figure 1, the use of oral or topical antihistamines represents first-line treatment in patients with mild intermittent and moderate severe disease, whereas topical corticosteroids are introduced in patients with more moderate disease and in those with persistent disease, regardless of severity. In addition, according to the guidelines, treatment with immunotherapy is restricted to those patients with persistent disease of either mild or moderate severity.

**PERENNIAL RHINITIS: AN INDEPENDENT RISK FACTOR FOR ASTHMA**

As part of the “one airway, one disease” concept, the ARIA guidelines also highlight the importance of perennial allergic rhinitis as a risk factor for bronchial asthma. This important link between the upper and lower airways is exemplified in a study carried out by Leynaert et al, which examined the association between perennial rhinitis and asthma by assessing both patients with nonatopic rhinitis and patients with atopic rhinitis. The results of this study showed a marked increase in bronchial asthma in patients with atopic rhinitis compared with atopic controls. Moreover, the association remained strong, even when the analysis was restricted to nonatopic individuals.

**RHINITIS AND ASTHMA: SIMILARITIES**

In terms of anatomy, the upper and lower airways share a common respiratory mucosa, and pathophysiologic studies have suggested a strong relationship between allergic rhinitis and asthma. Increasing understanding of the mechanisms underlying allergic inflammation of the airways indicates that the upper and lower airways are affected by a common, and probably evolving, inflammatory process. For example, patients with concomitant allergic rhinitis and asthma have a higher number of eosinophils in both their nasal mucosa and in the lower bronchial mucosa. In addition, a recent study showed an increased number of bronchial mucosal eosinophils following endobronchial allergen challenge in patients with allergic rhinitis, which correlated with increased concentrations of cell adhesion molecules and the asthmatic symptom score. Other studies have shown that the transepithelial migration of eosinophils is identifiable in both the upper and lower airways and seems remarkably consistent; for example, in both regions, these cells migrate into the epithelium during the pollen season. Similarly, examination of Langerhans cells and the mediators that they produce shows a clear increase in production during the pollen season in both the upper and lower airways.

Furthermore, similarities between rhinitis and asthma are seen in relation to the drugs used for treatment of these conditions. For example, corticosteroids are highly effective and important first-line agents in patients with persistent disease. Similarly, anticholinergics are also effective in the upper and the lower airways, although they have different effects on either mucus secretion in the upper airway or bronchoconstriction in the lower airway.
Rhinitis and Asthma: Differences

When considering the concept of "one airway, one disease," the distinct differences between the upper and the lower airways must be considered. A striking difference seen when comparing patients who have bronchial asthma with patients who have allergic rhinitis is that the epithelium is fragile and more easily disrupted in patients with bronchial asthma. In addition, when analyzing the subbasement membrane zone, observable abnormalities are found in patients with bronchial asthma, highlighting the importance of the remodeling process in this disease. By contrast, such changes are less apparent in the upper airway, where, at least at the light microscopy level, the basement membrane zone appears largely normal. Structural differences between the upper and the lower airways are also discernible. The nose has no airway smooth muscle compared with the lower airway, which contains a large amount of peribronchial smooth muscle. Furthermore, the upper airway contains prominent venous sinusoids and submucosal glands, whereas none of the former and far fewer of the latter are found in the lower airway.

With respect to drug treatment, the importance of inhaled beta-agonists in the lower airway, and their lack of effect on the upper airway, is well known. By contrast, although the role of antihistamine therapy in the treatment of allergic rhinitis in the upper airway is well established, a current source of debate and one of the focuses of this review is the potential role of antihistamines for the treatment of bronchial asthma. Conversely, the effects of antileukotrienes in bronchial asthma have been shown in a number of controlled clinical trials, and recent research suggests that antileukotrienes may also be effective in patients with allergic rhinitis. However, these studies have only been performed in a small number of patients, and an additional problem with the antileukotrienes is trying to select those groups of patients who are likely to respond to treatment.

Treatment Options

Overall, an important question from a clinical viewpoint is to ask whether treating the upper airway will have consequences on treating the lower airway or on responses in the lower airway. Accordingly, clinical studies have been performed to assess the effects of nasal corticosteroids, allergen immunotherapy, and antihistamine treatment on both the upper and lower airways.

Nasal Corticosteroids

Nasal Corticosteroids Decrease Asthma Symptoms

A number of studies have examined the effects of topical nasal corticosteroids in patients with allergic rhinitis and coexistent asthma. Such studies have shown improvement in both nasal and asthma symptoms as well as in the level of bronchial hyperresponsiveness. For example, in a study carried out by Welsh and colleagues, the effects of 2 standard topical nasal corticosteroids, beclomethasone and flunisolide, and of cromolyn were assessed in the treatment of patients with seasonal, ragweed-induced hay fever. Analysis of the mean weekly hay fever scores showed that all 3 drugs were superior to placebo and that the topical nasal corticosteroids were more effective than cromolyn. Interestingly, analysis of weekly asthma symptoms showed that these intranasal treatments also considerably reduced the symptoms of seasonal asthma. A number of other studies have also shown similar beneficial effects of topical nasal corticosteroids in improving chest symptoms during the pollen season.

Nasal Corticosteroids Decrease Bronchial Responsiveness

Similarly, several studies, mainly in patients with seasonal allergic rhinitis but also in patients with perennial allergic rhinitis, suggest that treatment with topical nasal corticosteroids can affect bronchial hyperresponsiveness. In one of these studies, a 4-week crossover, double-blind, placebo-controlled study, the effects of intranasal beclomethasone were assessed in 21 children with perennial allergic rhinitis and associated allergic asthma with house dust mite sensitivity. As expected, intranasal beclomethasone significantly reduced the global rhinitis symptom scores ($P = .05$). In addition, a significant improvement in the level of airway methacholine responsiveness, measured by methacholine $PC_{20}$, was observed following treatment with intranasal beclomethasone compared with placebo.

Currently, the mechanism for the effects of nasal corticosteroids on the lower airways remains unclear, although several possible explanations have been proposed. For example, one suggestion is that nasal corticosteroids could produce or suppress inflammatory mediators from the upper airway, or suppress antigen presentation by reducing the number of antigen-presenting cells. However, whether nasal corticosteroids suppress a nasobronchial reflex or

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simply open and improve the function of the upper airway remains unknown.

**Allergen Immunotherapy**

Studies using conventional high-dose allergen immunotherapy have also shown improvement in asthma symptoms and reductions in bronchial hyperresponsiveness. A recent study assessed the effects of high-dose conventional grass-pollen immunotherapy on symptoms of rhinitis and asthma during the pollen season. In this study, 44 patients with severe summer hay fever (36 of whom reported seasonal chest symptoms and 28 of whom had seasonal bronchial hyperresponsiveness) were followed up during a baseline year, treated for 2 years with subcutaneous immunotherapy, then assessed after 2 years of treatment. Patients treated with immunotherapy showed a reduction in hay fever symptoms and rescue medication. Furthermore, immunotherapy treatment also reduced chest symptoms and decreased bronchial responsiveness. This has recently been confirmed in patients with perennial asthma and house dust mite allergy.

**Antihistamines**

Several studies have assessed the antiasthmatic effects of antihistamines, such as loratadine, cetirizine, astemizole, and azelastine, in patients with both allergic asthma and rhinitis. These double-blind, placebo-controlled and either parallel group or crossover studies used a wide range of outcome measures, including pulmonary function (forced expiratory volume in 1 second and peak expiratory flow rate), asthma symptoms, and reduction in the use of beta-agonists. For example, in a 6-week, double-blind, placebo-controlled study, treatment with cetirizine not only improved rhinitis symptoms but also significantly improved asthma symptom scores in 5 of the 6 weeks. However, no significant associated changes in subjective measures of lung function were noted. Importantly, many of the clinical trials have demonstrated relief of asthma symptoms only when using higher doses than those used in the treatment of seasonal allergic rhinitis, which, in turn, may be associated with safety issues, such as sedation and cardiotoxicity. The differences in safety of the antihistamines and their impact on the therapeutic index of these agents are discussed in another article.

In recent years, growing evidence has suggested that most antihistamines have anti-inflammatory properties in addition to their effects at histamine-1 (H1)-receptors, and these antihistamines are hypothesized to be able to confer greater therapeutic potential in a range of allergic conditions compared with those that inhibit histamine alone.

Such anti-inflammatory effects include regulation and/or release of cytokines, chemokines, adhesion molecules, and/or inflammatory mediators. The cells involved in allergic inflammation include antigen-presenting cells (such as macrophages, mast cells, basophils, T cells, and eosinophils. Additionally, recent studies have shown the potential for some antihistamines to modify epithelial and endothelial cell activation. The antihistamines fexofenadine, cetirizine, loratadine, and desloratadine have all been shown to alter adhesion molecule expression on epithelial cells and/or on eosinophils. Similarly, cetirizine has been shown to decrease in vitro cytokine-enhanced eosinophil survival, and fexofenadine has been shown to alter...
eosinophil activation/granule release.29 Other studies have shown that fexofenadine, desloratadine, and cetirizine can alter the production of certain cytokines, including inflammatory cytokines (such as tumor necrosis factor alpha, interleukin [IL]-1β and IL-6) and immunoregulatory TH1/TH2 cytokines (such as IL-4 and IL-13).30-32 In addition, cetirizine has been shown to downregulate inflammatory mediators such as superoxide generation and chemotaxis of neutrophils and eosinophils.33 The following section describes in more detail the anti-inflammatory properties of fexofenadine.

Fexofenadine is a potent and selective H1-receptor antagonist with a wide therapeutic index. It has proven efficacy in allergic rhinitis and chronic idiopathic urticaria, and has been shown to improve quality of life.34-38

A number of in vitro studies with fexofenadine have highlighted the potential of this agent to produce significant anti-inflammatory effects at clinically relevant concentrations.29 For example, fexofenadine has been shown to significantly reduce the release of granulocyte macrophage-colony stimulating factor and IL-8 from epithelial cells39 (Figure 2). These effects were observed when fexofenadine was used at concentrations of 10-9 to 10-6 mol/L. The inhibitory effects of fexofenadine on the release of pro-inflammatory mediators have also been observed in mast cells and basophils.40,41 In vitro studies have also shown the role of histamine in activating IL-6 production from lung macrophages, which can be inhibited with fexofenadine.42,43 By contrast, the H2-receptor antagonist ranitidine had no effect. Fexofenadine has also been shown to have anti-inflammatory effects in vivo, in that it has been shown to suppress human late-phase responses in the skin.44,45

These data show that fexofenadine and other antihistamines have potent anti-inflammatory properties, which may be relevant at therapeutic doses. These anti-inflammatory properties combined with the wide therapeutic window exhibited by some antihistamines suggest that these agents may have significant effects in bronchial asthma.

**Conclusion**

The ARIA guidelines recommend evaluating both the upper and lower airways in the diagnosis of rhinitis or asthma. In view of the link between the upper and lower airways, recognizing and treating diseases of both airways is important. An increasing number of clinical studies have been performed to assess the effects of nasal corticosteroids, allergen immunotherapy, and antihistamine treatment on both the upper and lower airways. The results are important in moving closer to answering the important question of whether treatment of the upper airway will have consequences on either the treatment or responses of the lower airway.

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