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Allergic rhinitis: Systemic inflammation and implications for management

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Allergic rhinitis triggers a systemic increase of inflammation. Within minutes of allergen exposure, immune cells release histamine, proteases, cysteinyl leukotrienes, prostaglandins, and cytokines. Some produce the early symptoms, while others augment the production, systemic circulation, and subsequent infiltration of the nasal mucosa with inflammatory cells that sustain the symptoms. Systemic circulation of inflammatory cells permits their infiltration into other tissues where chemoattractant and adhesion molecules already exist. Consequently, allergic rhinitis is linked to comorbid conditions: asthma, chronic hyperplastic eosinophilic sinusitis, nasal polyposis, and serous otitis media. Effective therapy should be directed at underlying inflammation and its systemic manifestations. It should improve the rhinitis and the comorbid conditions. Antihistamines relieve early symptoms by blocking basophil- and mast cell-generated histamine, but they do not significantly influence the pro-inflammatory loop. They are often little better than placebo. Oral corticosteroids provide the systemic anti-inflammatory efficacy, but their toxicity precludes such an approach. Intranasal corticosteroids effectively target the local inflammatory processes of rhinitis, reducing local inflammatory cells within the nares, but they do not directly access tissues involved in the comorbid conditions. Leukotriene modifiers have both systemic anti-inflammatory effects and an acceptable safety profile. (*J Allergy Clin Immunol* 2003;112:1021-31).

Key words: Allergic rhinitis, asthma, chronic hyperplastic eosinophilic sinusitis, eosinophils, leukotrienes, cytokines, inflammation

Allergic rhinitis (AR) is the most common atopic disorder in the United States, affecting between 9% and 24% of adults¹⁻³ and up to 42% of children.³⁻⁵ Each year, nearly 80 million people in the United States experience 7 or more days of nasal-ocular symptoms as a result of AR.¹ Although it generally is not considered a severe dis-

Abbreviations used

AR:	Allergic rhinitis
CHES:	Chronic hyperplastic eosinophilic sinusitis
CysLT:	Cysteinyl leukotriene
ECP:	Eosinophil cationic protein
INS:	Intranasal corticosteroid
LT:	Leukotriene
LTRA:	Leukotriene receptor antagonist
NP:	Nasal polyposis
PAR:	Perennial allergic rhinitis
PG:	Prostaglandin
QOL:	Quality of life
SAR:	Seasonal allergic rhinitis

order, the socioeconomic costs of AR are substantial.⁶ It is one of the chief reasons for visiting a primary care physician, it adversely affects work productivity and school performance, and it limits socialization.⁶ Its effect goes deeper: AR is associated with a variety of comorbid conditions, including asthma, sinusitis, otitis media, nasal polyposis (NP), lower respiratory tract infections, and dental malocclusion.⁶ Adequately addressing AR requires a thorough understanding of its pathophysiology, its relationship to these comorbid conditions, and the effects of various therapeutic options on the pathophysiology of both AR and its associated comorbidities.

INFLAMMATORY MECHANISMS IN AR

Within minutes of allergen exposure, sensitized mast cells degranulate, releasing preformed and newly synthesized mediators, including histamine, proteases, cysteinyl leukotrienes (CysLTs), prostaglandins, and cytokines.⁷⁻⁹ Some of these mediators produce the characteristic early phase symptoms of AR, namely sneezing, pruritus, rhinorrhea, and, to some extent, congestion,^{10,11} whereas others will stimulate infiltration of the nasal mucosa with inflammatory cells, including basophils, eosinophils, neutrophils, newly synthesized mast cells, and mononuclear cells.^{6,9,12} This infiltration of inflammatory cells and their subsequent release of additional mediators, including histamine and CysLTs, sustains the inflammatory reaction with the continued recruitment of inflammatory cells and produces the late-phase response of AR, which is primarily characterized by nasal congestion.⁹

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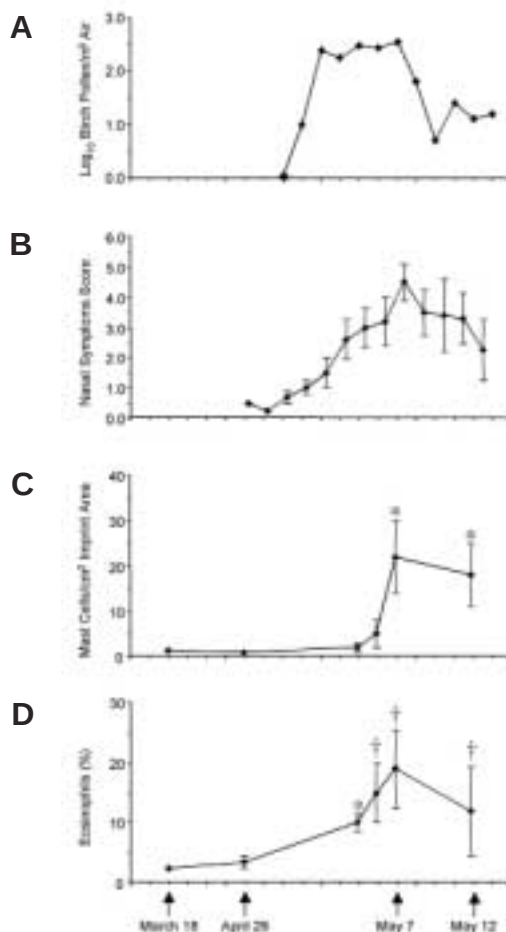


FIG 1. During an allergy season when birch pollen levels were increased (**A**), associated nasal symptom scores gradually increased (**B**) and correlated significantly with the logarithm of the pollen count ($r = 0.68$, $P < .01$). A significant increase in the number of mast cells in the imprint area (**C**) and the percentage of eosinophils in nasal lavage fluid (**D**) also occurred during the allergy season compared with preseason values. * $P < .05$; † $P < .01$. Adapted with permission from Pipkorn et al.²⁶

The inflammation that develops over the course of an allergy season is associated with an approximately 10-fold increase in the numbers of mast cells present in nasal epithelial and submucosal tissue (Table I and Fig 1, C).¹³ This represents a migration of preexisting mast cells into the epithelium and the differentiation and influx of newly synthesized mast cells into the nasal mucosa under the influence of growth factors. In the course of chronic allergen stimulation, these mast cells become associated with increased histamine releasability that reflects increases in the numbers of IgE receptors and surface-bound IgE, as well as enhancement of signal transduction pathways.^{14,15} Together, all of these mast cell processes produce the phenomenon of priming, whereby as an allergen season progresses, less and less allergen is required to trigger mast cell degranulation.¹⁶ With priming, perennial allergens that might not be sufficient by themselves to trigger an allergic reaction might exacerbate symptoms produced during an allergy season.

Although mast cells play an important role during the initial AR response, they might not play as substantive a role in sustaining this response. Although histamine increases during both the early and late phases after an allergen challenge, prostaglandin (PG) D₂ increases only during the early phase.¹⁷ Because mast cells synthesize and release PGD₂, the absence of this mediator during the late phase indicates that mast cells cannot be responsible for the increase in histamine that occurs during the late phase.¹⁷ Basophils release histamine, but in contrast to mast cells, they do not produce PGD₂ and presumably are the source of histamine during the late phase.

In addition to their interaction with mast cells, allergens will also behave like any other foreign antigen and be processed and presented by antigen-presenting cells to T_H lymphocytes. Activation of these antigen-presenting cells, including mononuclear phagocytic cells, B lymphocytes, and especially dendritic cells, might be an important source of cytokines, especially those associated with innate immunity, including IL-1, IL-6, and TNF. The newly activated T lymphocytes will be T_H2 like and characterized by their production of IL-4, IL-5, IL-9, IL-13, and GM-CSF. These cytokines are also major components of the inflammatory response in AR.¹⁸⁻²¹ The generation of these cytokines leads to the increased production, recruitment, and activation of eosinophils, mast cells, and basophils.

Thus rhinitis progression becomes more dependent on mediators associated with the infiltration of cells, such as eosinophils, basophils, neutrophils, mononuclear cells, and T_H lymphocytes, as well as the increasingly primed mast cells. The symptoms of acute rhinitis, such as sneezing, itching, and rhinorrhea, largely reflect vasoactive mediator release, especially histamine. As seasonal AR (SAR) or perennial AR (PAR) persists, however, these infiltrating cells and their continued production of cytokines and other inflammatory mediators lead to the mucus hypersecretion, tissue edema, goblet cell hyperplasia, and tissue damage that become the primary sources of symptoms in allergic patients. The role of histamine diminishes as AR progresses, consequently making antihistamines less effective. This progression and not the development of tolerance might be responsible for the diminished efficacy of antihistamines over the course of an allergy season and for the surprising discordance between the actual and perceived benefits of antihistamines in placebo-controlled clinical trials. Thus antihistamines significantly reduce symptoms; however, in comparison with placebo, this reduction is relatively unimpressive at only approximately 15% to 20%.^{22,23} These trials typically require a run-in phase in which a predefined level of symptoms must be continuously present. As a result, the subject's rhinitis has already entered this relatively histamine-independent phase before these trials institute their therapeutic intervention, leading to the impression that antihistamines are little more effective than placebo. For most patients with mild intermittent disease, antihistamines do remain effective therapy, and this efficacy reflects the intermittent nature of most

TABLE I. Seasonal increase in nasal mast cells: Effect of grass pollen seasonal exposure on nasal mast cell numbers

Month	Nasal mast cells/mm ³		
	Epithelium	Lamina propria	Total
July	13,130	15,145	28,455
October	4649	12,012	16,661
January	1375	7443	8818

subjects' allergen exposures, which are of insufficient duration to drive their disease progression into the more severe and antihistamine-resistant phase.

Eosinophils represent an important component of the inflammation that develops with PAR and the progression of SAR. The natural history of SAR is for symptoms to inexorably worsen over several weeks in the presence of ongoing allergen exposure. As shown in Fig 1, B, symptoms might not peak until well after the pollen counts do (Fig 1, A), and then they might persist after pollen counts have decreased dramatically. These observations reflect the time frame of the onset of nasal inflammation and tissue damage. The influx of eosinophils into the nasal mucosa (Fig 1, D) correlates closely with the development and progression of symptoms.²⁴⁻²⁶ It also reflects the newly synthesized eosinophils derived from the bone marrow, although recent studies have suggested that eosinophils might differentiate directly from precursor stem cells present within allergic inflammatory tissue.²⁷ In summary, the natural history of AR represents an evolution from an acute, primarily mast cell-mediated process that is responsive to antihistamines to a chronic inflammatory process that is primarily eosinophil mediated and is much less responsive to antihistamines.

Eosinophils release a wide variety of pro-inflammatory mediators, including CysLTs, eosinophil cationic protein (ECP), eosinophil peroxidase, major basic protein, IL-3, IL-5, GM-CSF, and platelet-activating factor.²⁸

The CysLTs are major mediators of the allergic inflammatory response. In ragweed-sensitive subjects, CysLT levels were increased in nasal fluid after nasal allergen challenge.²⁹ A similar increase occurred after natural allergen exposure and correlated with ECP levels.^{30,31} CysLTs are major components of both the early and late phases of the allergic response, and they produce several of the symptoms found in AR, including both sneezing and rhinorrhea.¹⁰ They are one of the primary mediators of nasal congestion.³²⁻³⁴ Both nasal airway resistance and nasal obstruction are increased after CysLT challenge.³⁵ More importantly, CysLTs play a key role in eosinophilic airway inflammation. They are chemoattractants for eosinophils *in vitro*^{36,37} and in both animal models³⁸ and human bronchial tissues after CysLT inhalation.³⁹ In addition, they promote eosinophil adhesion by inducing the expression of adhesion molecules, such as complement receptor 3 (Mac-1; Fig 2).^{37,40}

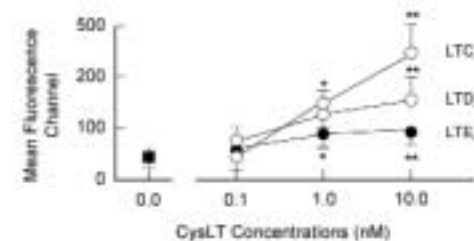


FIG 2. Mean complement receptor 3 (Mac-1) expression by blood eosinophils isolated from atopic subjects. The x-axis depicts varying concentrations of various CysLTs, and the y-axis depicts complement receptor 3 expressed as mean fluorescence channel. **P* < .05; ***P* < .01. Used with permission from Fregonese et al.³⁷

Finally, they maintain eosinophil levels by decreasing eosinophil apoptosis⁴¹ and acting synergistically with GM-CSF and IL-5 to facilitate the growth of eosinophil precursors in the peripheral blood and bone marrow.⁴²

In individuals with AR, significant correlations exist between eosinophil protein X and leukotriene (LT) C₄-LTD₄ levels in nasal lavage fluid⁴³ and between ECP and LTC₄ levels in nasal secretions.³⁰ AR is associated with upregulation of the metabolic enzymes necessary for CysLT synthesis, including 5-lipoxygenase, 5-lipoxygenase activation factor, and LTC₄ synthase, as well as an upregulation of CysLT receptors.⁴⁴ Consequently, patients with AR might not only produce increased levels of CysLTs but also might be predisposed toward an enhanced responsiveness to these mediators.

SYSTEMIC MANIFESTATIONS OF AR

AR is associated with the systemic circulation of activated T lymphocytes and mononuclear phagocytic cells. The activation of these cells is demonstrated by their production of cytokines associated with innate immunity, such as IL-1, TNF- α , and IL-6.⁴⁵⁻⁴⁷ These cytokines are responsible for the acute-phase response of inflammatory and immune diseases, and this has important consequences for patients with AR. These acute-phase responses are associated with central nervous system symptoms of lethargy, fatigue, and diminished cognition and systemic symptoms of arthralgia and myalgia. AR also is associated with cognitive impairment of schoolchildren and adults.^{46,48,49} These systemic symptoms are often the chief complaints of patients with allergy and might contribute largely to the complaints of diminished quality of life (QOL) by patients and to the reported frequent association of AR with chronic fatigue syndrome, depression, and other affective disorders.⁵⁰⁻⁵² Although not regarded as a feature of AR, it is intriguing that the lay terminology for this condition is hay fever, reflecting the pronounced flu-like nature of this disease. These systemic manifestations are exacerbated by the use of first-generation sedating antihistamines. The ability of AR therapies to attenuate systemic symptoms and thus improve QOL should be an important consideration in determining their efficacy (see below).

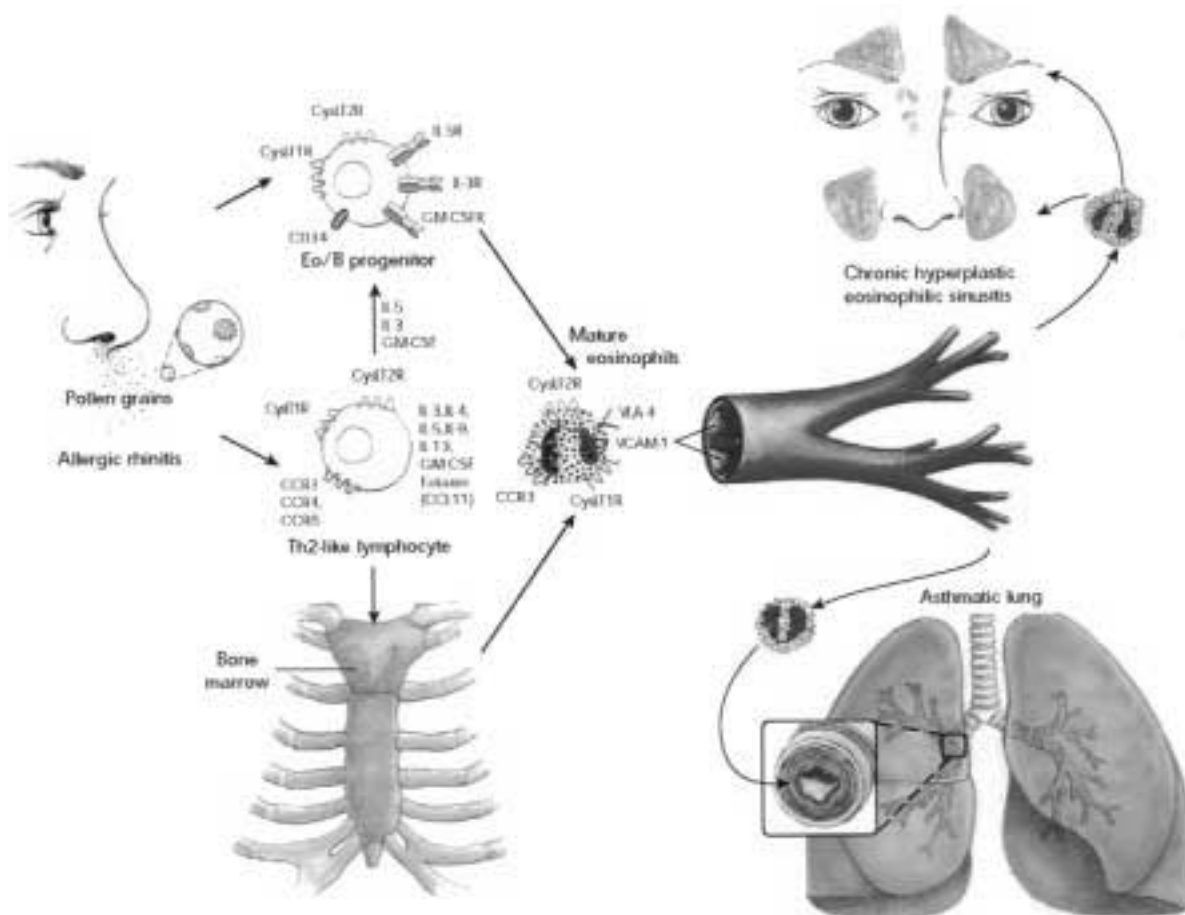


FIG 3. In sensitized subjects allergen exposure activates immune cells, including T_H lymphocytes, dendritic cells, mononuclear phagocytic cells, mast cells, and others, both within the nares and in nasal-associated lymphatic tissues. These cells might also include locally produced $CD34^+$ $IL-5R\alpha^+$ eosinophil-basophil (Eo/B) progenitors. These newly activated T_H lymphocytes will have the phenotype of T_H2 -like cells characterized by their production of IL-3, IL-4, IL-5, IL-9, IL-13, eotaxin (CCL11), and GM-CSF. Some of these T_H cells migrate to the bone marrow, where they stimulate the bone marrow to produce inflammatory cells, including basophils, mast cells, and, most importantly, eosinophils. Ultimately, these newly generated inflammatory cells enter the circulatory system from which they are selectively recruited back to the nose but also to the lungs and sinuses, exacerbating inflammation. This selective recruitment of inflammatory cells into the lungs and sinuses will only occur in individuals with preexisting asthma and CHES in whom specific adhesion molecules, such as vascular cell adhesion molecule 1 (VCAM-1), and chemoattractants, such as eotaxin, already exist. Persons without asthma and CHES do not have these addressins in their airways and thus do not have the machinery in place to recruit these newly synthesized eosinophils and other inflammatory cells into their respiratory tissue during exacerbations of rhinitis.

AR AND COMORBID UPPER AND LOWER AIRWAY DISORDERS

AR is not just an inflammation of the nasal mucosa but is associated with systemic inflammation; consequently, it is often seen with other inflammatory conditions, such as asthma and sinusitis. In individuals with SAR who did not have asthma, nasal allergen provocation, performed such that the allergen did not gain access to the lungs, produced inflammatory changes in both the upper and lower airways, including increased adhesion molecule expression, eosinophil infiltration, and increased bronchial hyperreactivity.^{53,54} These results demonstrate that an allergic nasal reaction produces systemic inflammatory changes.

As shown in Fig 3, in sensitized subjects allergen exposure activates immune cells, including T_H lymphocytes, dendritic cells, mononuclear cells, mast cells, and others, both within the nares and in nasal-associated lymphatic tissues. These cells might also include locally produced eosinophil precursors.²⁷ Some of these T_H cells migrate to the bone marrow, where they stimulate the bone marrow to produce inflammatory cells, including basophils, eosinophils, and mast cell precursors.^{27,55,56} Allergen challenge increased the bone marrow concentrations of both cytokines and progenitor cells both in animal models^{57,58} and in individuals with atopic asthma.⁵⁹⁻⁶¹ In addition, in atopic individuals who had late

asthmatic responses and airway eosinophilia, allergen inhalation caused trafficking of T lymphocytes to the bone marrow, enhancing the ability of these lymphocytes to generate IL-5.⁶¹ Ultimately, these newly generated inflammatory cells enter the circulatory system, from which they are selectively recruited to the lungs and sinuses, exacerbating airway inflammation, as shown in Fig 3. In addition to stimulating inflammatory cell production, cytokines upregulate the expression of adhesion molecules, further facilitating the recruitment of inflammatory cells into nasal and bronchial tissues.⁵³

This selective recruitment of inflammatory cells into the airways would occur only in individuals with preexisting asthma in whom specific adhesion molecules, such as vascular cell adhesion molecule 1, and chemoattractants, such as eotaxin, already exist. Persons without asthma do not have these addressins in their airways and thus do not have the machinery in place to recruit inflammatory cells into their airways during exacerbations of rhinitis.⁶² This increase in bronchial inflammation in response to allergen-induced rhinitis might contribute to the exacerbations of asthma frequently seen in individuals with underlying AR.

Eosinophils are important mediators of inflammation and can be considered a key cellular link between the various airway compartments because eosinophil levels are found to be increased not only in AR but also in asthma,⁶³ chronic hyperplastic eosinophilic sinusitis (CHES),^{24,64-67} and otitis media.^{68,69} Their levels correlate with symptoms in both asthma and sinusitis.^{63,65-67}

Finally, it should be noted that other mechanisms have been hypothesized to play a role in the link between the different levels of the airways. For example, nasal obstruction leads to mouth breathing, which results in colder, less well-conditioned air entering the lower airway. This can elicit asthma symptoms in subjects with underlying bronchial hyperresponsiveness.⁷⁰ Although a rhino-bronchial reflex has been proposed,⁷¹ a neurogenic pathway is not likely to explain development or exacerbation of what is primarily a disorder of eosinophils and T_H2 -like lymphocytes. Similarly, although aspiration of upper airway mediators into the bronchial tree has been proposed as a mechanism,⁷² conflicting studies with instillation of radioisotopes into the upper respiratory tract failed to find evidence to support such a mechanism.⁷³

CHES with or without NP is an inflammatory disease characterized by the accumulation of eosinophils, fibroblasts, mast cells, goblet cells, and T_H2 -like lymphocytes.^{74,75} It is the prominent accumulation of eosinophils, however, which is the diagnostic feature of this condition (Fig 4).^{24,64,75,76} The sinus tissue is infiltrated with a marked increase in cells, including lymphocytes, fibroblasts, and eosinophils, which are expressing cytokines responsible for eosinophilopoiesis (IL-5), survival (IL-3, IL-5, and GM-CSF), recruitment (CCL11 [eotaxin]), and activation (CCL11, CCL5 [RANTES], IL-3, IL-5, GM-CSF, and TNF- α).^{18,77-81} That eosinophils are a prominent source of these cytokines suggests that CHES/NP is a disease of unregulated

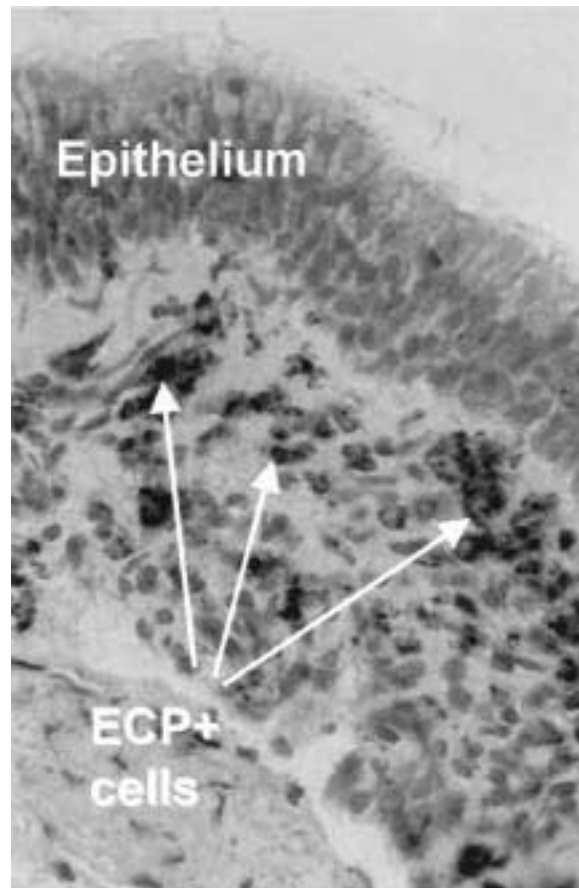


FIG 4. Immunohistochemical analysis of a sinus biopsy specimen from a patient with sinusitis and chronic AR. Eosinophils were labeled with an antibody to ECP and were localized as aggregates within and beneath the epithelium (original magnification $\times 400$). Used with permission from Demoly et al.⁶⁴

inflammation in which eosinophils, once recruited, provide the growth factors necessary for their further recruitment, proliferation, and activation.

Both sensitivity to multiple allergens and sensitivity to perennial allergens, such as dust mites, increase the risk of CHES.⁸² More than 50% of individuals with PAR have abnormal sinus radiographs.^{83,84} Allergens are unlikely to gain access to the sinus cavities, even in healthy subjects, and are even less likely to do so in the presence of the sinus ostia occlusions characteristic of this disorder. Studies performed with insufflation of radiolabeled ragweed particles confirm the inability of these pollens to enter the sinuses.⁸⁵ The link between AR and sinusitis could involve a systemic inflammatory process similar to that described between AR and asthma (Fig 3). Nasal allergen challenges in sensitive individuals produce radiographic changes of the maxillary sinuses, including edema and opacification.⁸⁶ Nasal allergen challenges in allergic individuals produce significant increases in eosinophils, ECP, histamine, and albumin not only in the nose but also in the maxillary sinus.⁸⁷ Sinus lavage fluid from both maxillary sinuses was col-

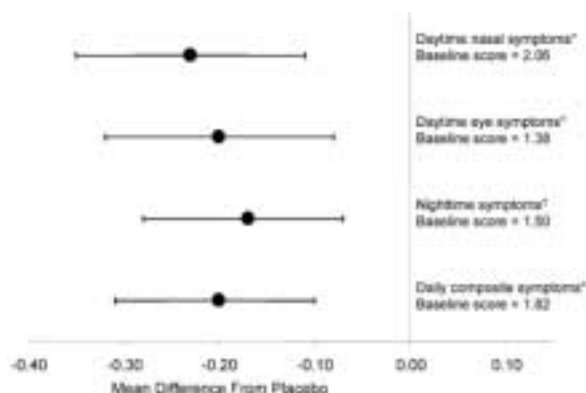


FIG 5. Symptom score improvements with montelukast.¹⁰⁵ The improvements of symptoms are expressed as the least-squares mean difference from placebo. The negative difference means an improvement in symptom with montelukast compared with placebo. The bars represent the 95% CI. Symptom scores were rated on a scale of 0 to 3 points (0 = best and 3 = worst) for subjects with fall rhinitis treated with montelukast. The baseline score for each symptom is given for the montelukast group. * $P \leq .001$; † $P = .002$.

lected and analyzed after a nasal allergen challenge was performed in only one side of the nose. Both albumin levels and eosinophil counts were significantly increased in these specimens, with no significant differences detected in specimens obtained from the ipsilateral and contralateral maxillary sinuses.⁸⁸ Because both sinuses were equally affected, these results are consistent with a systemic response. Inflammatory cells newly generated both in the nasal lymphatic tissue and in the bone marrow as a result of the intranasal allergen challenge entered the circulatory system and infiltrated susceptible tissues, such as sinuses or lungs,²⁷ thereby exacerbating sinusitis and asthma.⁵⁶ In addition, there presumably would also be direct recirculation of these allergic inflammatory cells among the nares, local lymphatic tissue, and the sinuses.

MANAGEMENT OF AR

The increasing recognition of AR as a systemic inflammatory disorder has many implications for its management. Treatment should be directed not only at relieving nasal symptoms but also at the underlying inflammatory processes; options consist of allergen avoidance, pharmacotherapy, and immunotherapy.

Allergen avoidance

Allergen exposure leads to symptoms. Thus allergen avoidance is a logical approach that is recommended by all asthma and rhinitis guidelines.⁶ Avoidance studies are limited, however, especially with respect to rhinitis, and the amount of allergen reduction needed to reduce symptoms effectively is unknown.⁶ Allergen-impermeable covers might reduce allergen levels, but as a single intervention, they fail to cause clinically significant improvements.^{89,90} Furthermore, individuals frequently are sensi-

tized to multiple allergens, making it difficult, if not impossible, to limit allergen exposure adequately. As a result, pharmacotherapy is required frequently.

Pharmacotherapy

Antihistamines are the oldest drugs used in the treatment of allergic disorders. First-generation antihistamines have significant sedative and anticholinergic effects resulting from their ability to cross the blood-brain barrier, and they should be avoided for the treatment of AR.⁶ Second-generation antihistamines have a longer duration of action and minimal, if any, sedative effects.⁶ These drugs reduce pruritus, sneezing, and watery rhinorrhea associated with AR but have minimal effects on nasal obstruction.⁶ Moreover, antihistamines are not generally considered anti-inflammatory drugs, although studies suggest that second-generation antihistamines might possess some anti-inflammatory properties.^{91,92} In a recent double-blind crossover trial in subjects with SAR, however, 7 days of fexofenadine was no more effective than placebo at reducing either the nasal symptom score or the production of inflammatory cytokines after a nasal allergen challenge.⁴⁵

Antihistamines are uniquely effective for acute allergic reactions, which are mediated predominantly by mast cell-derived histamine, and might be beneficial in patients with intermittent allergen exposures, such as occasional outdoor exposure during the pollen season. In patients with continuous allergen exposures, however, such as PAR caused by indoor allergens or after several days of continuous exposure to seasonal allergens, they might be little better than placebo.^{22,93,94}

Intranasal corticosteroids (INSs) are the most effective pharmacotherapy approved for the treatment of AR. They are considered first-line therapy in the management of adults with moderate-to-severe SAR or PAR.⁶ Several studies have demonstrated that the efficacy of INSs is superior to that of antihistamines.^{95,96} Regular prophylactic use of INSs effectively reduces sneezing, pruritus, watery rhinorrhea, and nasal blockage in both children and adults.⁶ Although efficacy is greatest with continuous administration,⁶ as-needed INSs have proved efficacious.⁹⁷

INSs are not, however, universally effective and might not provide complete relief in all patients, making additional or alternate therapies necessary. Combining an INS with an antihistamine is no more effective than monotherapy with the INS.⁹⁵ The failure of INSs to provide more complete relief might reflect in part that these agents have only limited effects on CysLTs.⁹⁸⁻¹⁰² Finally, despite the excellent safety profile on INSs, many patients remain reluctant to use them.

LT modifiers have confirmed efficacy in AR^{23,103-107} and have a level of efficacy comparable with that of antihistamines.²³ In patients with asthma, synergistic benefits were seen when an LT receptor antagonist (LTRA) was combined with a corticosteroid¹⁰⁸; a similar synergy should exist in AR. Zileuton, an LT synthesis inhibitor, significantly reduced nasal congestion in subjects with AR undergoing a nasal allergen challenge.¹⁰⁴ Similarly,

pranlukast, an LTRA approved for use in Japan, significantly improved nasal edema in subjects with PAR. In contrast, an antihistamine did not affect nasal mucosa swelling significantly.¹⁰⁶

The LTRAs are effective against other components of AR. Compared with placebo, zafirlukast significantly reduced sneezing, rhinorrhea, and nasal congestion in patients with SAR who spent 8 hours per day for 2 consecutive days in a park during the peak of ragweed season.¹⁰³ Similarly, in patients with fall AR, montelukast (an LTRA recently approved for AR) significantly improved the daytime nasal symptom score, nighttime symptom score, daytime eye symptom score, and rhinoconjunctivitis QOL (daily composite symptoms score) score compared with placebo (Fig 5).¹⁰⁵ Comparable results were seen with montelukast in subjects with spring AR.¹⁰⁷ This ability to reduce symptoms of sneezing and pruritus, which are not symptoms prominently associated with CysLT challenges, suggests that LT modifiers might be acting secondarily to reduce inflammation in the airway, including production, recruitment, and activation of histamine-producing cells, such as mast cells and basophils. Furthermore, peripheral blood eosinophil counts were reduced in subjects with AR given montelukast, which is consistent with the synergistic influences between CysLTs and IL-5 on eosinophilopoiesis.^{42,105,107}

Immunotherapy should be considered in patients with a constant need for pharmacotherapy,⁶ patients with adverse effects from pharmacotherapy, and patients with refractory symptoms. Immunotherapy decreases the severity of AR, reduces the need for pharmacotherapy, and significantly improves QOL.⁶ In patients with severe rhinoconjunctivitis that is poorly controlled by antihistamines and INSs, specific immunotherapy reduced allergen sensitivity by more than 10-fold, significantly decreasing total symptoms and reducing total antiallergic drug use.¹⁰⁹ Furthermore, immunotherapy is the only treatment that produces long-term immunomodulation. Both avoidance and pharmacotherapies are effective only as long as the therapy is sustained. The effects of immunotherapy, on the other hand, might persist for years after treatment has been discontinued.^{6,110}

Many patients have multiple antigen sensitivities, however, and specific immunotherapy at effective doses might not be practical. Furthermore, immunotherapy has poor efficacy for many antigens, such as molds. This has led to a search for new immune-based therapies capable of attenuating allergic inflammation. One such agent is a humanized anti-IgE antibody, rhuMAB-E25 (omalizumab), which has been evaluated in the treatment of SAR. In individuals with pollen-induced AR, rhuMAB-E25 safely reduced serum-free IgE levels.^{111,112} Furthermore, rhuMAB-E25 significantly improved daily nasal symptom scores, use of rescue antihistamines, and QOL in individuals with pollen-induced AR.¹¹² RhuMAB-E25 can also reduce anaphylaxis risk in subjects who are receiving it, a fact that could lead to an additional use of this treatment.¹¹³ RhuMAB-E25, however, is approved only for adults with moderate-to-severe asthma.

IMPLICATIONS OF AR MANAGEMENT ON COMORBID DISEASES

Poorly controlled AR might contribute to the development or worsening of other diseases, such as asthma, serous otitis media, and CHES, but adequate treatment of AR can improve the symptoms of these comorbid disorders. The inflammation of AR starts locally in the nares. It is in the nares and regional lymphatic tissue that allergens primarily interact with the immune system. T_H2 lymphocytes and eosinophils activated in the upper airway can migrate through the circulatory system and back to the nares, where they sustain the inflammatory reaction leading to chronic rhinitis, and to other susceptible target organs, such as the sinuses and lung, where they increase existing inflammatory processes.

INSs provide significant protection against comorbid conditions. Recent data support the use of INSs in subjects with AR and asthma. In these patients INSs significantly reduced the risk of an asthma-related emergency department visit. Prescription antihistamines, on the other hand, had no detectable effect on emergency department visits.¹¹⁴ Consistent with this finding, daily intranasal beclomethasone significantly reduced bronchial hyperresponsiveness, an indicator of lower airway inflammation, in patients with PAR¹¹⁵ and eliminated the increase in bronchial hyperresponsiveness that occurs in sensitized patients with SAR.¹¹⁶ Intranasal fluticasone significantly reduced blood eosinophil levels and attenuated the increase in bronchial hyperresponsiveness during pollen season in patients with SAR.¹¹⁷ These findings are consistent with a systemic link between AR and asthma. Blocking the inflammatory reaction in the nares ultimately reduces bone marrow stimulation, the resultant increase in circulating inflammatory cells, and the recruitment of these cells into the airway (or, by extension, the sinuses, eyes, or other target organs), thereby reducing bronchial hyperresponsiveness.¹¹⁸

In contrast to these findings, however, neither intranasal fluticasone nor beclomethasone significantly influenced bronchial hyperresponsiveness during the pollen season in subjects with mild asthma.¹¹⁸ These conflicting results suggest that environmental conditions, such as pollen load during the season being evaluated, or patient characteristics, such as allergen or airway sensitivity, might influence this response significantly.¹¹⁸ Although INSs have not been shown to ameliorate CHES,¹¹⁹ this lack of perceived benefit might reflect deficiencies in study design. Clinical scores are notoriously unreliable in assessing the presence and severity of CHES¹²⁰⁻¹²² and should not be used as outcome variables in assessing therapeutic responses. The most objective indication of CHES is a computed tomographic scan appropriately scored to reflect volume of inflammatory tissue within the sinuses.⁶⁷ Thus it remains plausible that through their influences on systemic and local recirculation of inflammatory cells, INSs might reduce tissue inflammation in the sinuses.

LT modifiers have systemic bioavailability and, consequently, direct access to the inflamed tissue of CHES and asthma. In addition, LT modifiers might improve these conditions indirectly through their ability to ameliorate AR. Systemic anti-inflammatory effects of LTRAs have been shown in patients with chronic asthma, in whom montelukast significantly reduced both peripheral blood and sputum eosinophil counts.^{123,124} This suggests an effect of LTRAs on bone marrow (or on locally derived eosinophil precursors), possibly by decreasing IL-5 production by T_H2-like lymphocytes, and the subsequent stimulation of eosinophil production. Alternatively, LT modifiers might also act to block the synergistic influence of CysLTs with IL-5 on eosinophil precursors.⁴² It should be noted, however, that simply reducing eosinophil production by bone marrow does not reduce tissue eosinophilia sufficiently to produce a clinical benefit, as shown by the failure of studies involving humanized anti-IL-5 antibodies^{125,126} and rIL-12.¹²⁷ The ideal clinical agent (or combination) might need to block both the bone marrow eosinophilopoietic response and the migration of eosinophils into the tissue. Corticosteroids, through their inhibitory effects, including reduction of cell migration and adhesion molecule expression, and LTRAs, through their ability to block the chemotactic and adhesion-promoting effects of CysLTs, can block both facets of this inflammatory process. Thus the use of LT modifiers in asthma was associated with a reduction in eosinophilia in the lung.¹²³ This ability of LTRAs to reduce eosinophil migration into the lungs should also apply to the sinuses, and it might ameliorate other disorders characterized by eosinophilic inflammation, such as CHES and NP. Several studies have suggested a beneficial influence of LT modifiers in CHES; however, studies using an objective outcome, such as computed tomography scanning measures, need to be performed. In asthmatic patients with CHES and NP, adding zileuton to conventional inhaled or oral corticosteroid therapy resulted not only in a significant improvement of asthma but also in significant improvements in both rhinorrhea and olfaction and in a trend toward less nasal stuffiness and higher nasal inspiratory flow.¹²⁸ Similarly, in patients with NP and sinusitis, treatment with either zileuton or zafirlukast significantly improved headache, facial pain and pressure, ear discomfort, dentalgia, purulent nasal discharge, postnasal drip, nasal congestion, nasal polyp size, and olfaction.¹²⁹

Consequently, a therapy that addresses the systemic aspects of AR is more beneficial than a therapy with only local effects because it improves both AR and concomitant inflammatory disorders that might be present. Several studies have demonstrated that treating AR decreases asthma symptoms.^{130,131} In asthmatic children with AR, topical nasal treatment with either cromolyn or beclomethasone produced an 84% improvement in bronchial asthma despite the absence of asthma maintenance therapy; furthermore, this effect appeared to be independent of the specific drug chosen for the treatment of rhinitis.¹³⁰ In adults with SAR, asthma symptoms during the peak of the

ragweed season were decreased 3-fold and 10-fold by intranasal cromolyn and beclomethasone, respectively.¹³¹ Antihistamines block a single local mediator but are unlikely to have beneficial effects on any of the steps involved in this systemic loop. Topical intranasal steroids have beneficial effects on many of these steps but cannot cross into the sinuses. LT modifiers provide systemic anti-inflammatory effects with an acceptable safety profile.

CONCLUSIONS

AR triggers a systemic increase of the elements of inflammation. In addition to sustaining the rhinitis, inflammatory cells and mediators travel through the circulatory system and are able to target other susceptible tissues, leading to the exacerbation of comorbid conditions, including asthma and sinusitis. To be effective, long-term therapy for AR should be directed at its underlying inflammation and the systemic manifestations of this inflammation. Such anti-inflammatory therapies have been shown to have beneficial effects not only on AR but also on these comorbid conditions.

REFERENCES

1. Nathan RA, Meltzer EO, Selner JC, Storms W. Prevalence of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997;99(suppl):S808-14.
2. Adams PF, Hendershot GE, Marano MA. Current estimates from the national health interview survey, 1996. Atlanta: Centers for Disease Control and Prevention/National Center for Health Statistics; 1999; 10(200):1-141.
3. Ma X, Fick RB, Kaplowitz HJ. Prevalence of allergic rhinoconjunctivitis in the United States: data from the third National Health and Nutrition Examination Survey, 1988-94 (NHANES III) [abstract]. *Am J Crit Care Med* 2000;161:A325.
4. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics* 1994;94:895-901.
5. Arrighi HM, Maier WC, Redding GJ, Morray BH, Llewellyn RN. The impact of allergic rhinitis in Seattle school children [abstract]. *J Allergy Clin Immunol* 1995;95:192.
6. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108(suppl):S147-334.
7. Young MC. Rhinitis, sinusitis, and polyposis. *Allergy Asthma Proc* 1998;19:211-8.
8. Baroody FM, Ford S, Proud D, Kagey-Sobotka A, Lichtenstein L, Naclerio RM. Relationship between histamine and physiological changes during the early response to nasal antigen provocation. *J Appl Physiol* 1999;86:659-68.
9. Ledford DK, Lockey RF. Allergic rhinitis: Understanding the process (a major contributor to health problems—and on the rise). *J Respir Dis* 1998;19:576-84.
10. White MV, Kaliner MA. Mediators of allergic rhinitis. *J Allergy Clin Immunol* 1992;90:699-704.
11. Togias A. Unique mechanistic features of allergic rhinitis. *J Allergy Clin Immunol* 2000;105(suppl):S599-604.
12. Bascom R, Pipkorn U, Lichtenstein LM, Naclerio RM. The influx of inflammatory cells into nasal washings during the late response to antigen challenge. Effect of systemic steroid pretreatment. *Am Rev Respir Dis* 1988;138:406-12.
13. Viegas M, Gomez E, Brooks J, Gatland D, Davies RJ. Effect of the pollen season on nasal mast cells. *BMJ* 1987;294:414.
14. Smurthwaite L, Walker SN, Wilson DR, Birch DS, Merrett TG, Durham SR, et al. Persistent IgE synthesis in the nasal mucosa of hay fever patients. *Eur J Immunol* 2001;31:3422-31.
15. Boyce JA. Mast cells: beyond IgE. *J Allergy Clin Immunol* 2003;111:24-32, quiz 3.

16. Connell JT. Quantitative intranasal pollen challenge. II. Effect of daily pollen challenge, environmental pollen exposure, and placebo challenge on the nasal membrane. *J Allergy* 1968;41:123-39.
17. Naclerio RM, Proud D, Togias AG, Adkinson NF Jr, Meyers DA, Kagey-Sobotka A, et al. Inflammatory mediators in late antigen-induced rhinitis. *N Engl J Med* 1985;313:65-70.
18. Hamilos DL, Leung DY, Wood R, Cunningham L, Bean DK, Yasruel Z, et al. Evidence for distinct cytokine expression in allergic versus non-allergic chronic sinusitis. *J Allergy Clin Immunol* 1995;96:537-44.
19. Braunstahl GJ, Kleinjan A, Overbeek SE, Prins JB, Hoogsteden HC, Fokkens WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. *Am J Respir Crit Care Med* 2000;161:2051-7.
20. Cameron L, Hamid Q, Wright E, Nakamura Y, Christodoulou P, Muro S, et al. Local synthesis of epsilon germline gene transcripts, IL-4, and IL-13 in allergic nasal mucosa after ex vivo allergen exposure. *J Allergy Clin Immunol* 2000;106:46-52.
21. Nouri-Aria KT, O'Brien F, Noble W, Jacobson MR, Rajakulasingam K, Durham SR. Cytokine expression during allergen-induced late nasal responses: IL-4 and IL-5 mRNA is expressed early (at 6 h) predominantly by eosinophils. *Clin Exp Allergy* 2000;30:1709-16.
22. Bernstein DI, Schoenwetter WF, Nathan RA, Storms W, Ahlbrandt R, Mason J. Efficacy and safety of fexofenadine hydrochloride for treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 1997;79:443-8.
23. Meltzer EO, Malmstrom K, Lu S, Prenner BM, Wei LX, Weinstein SF, et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. *J Allergy Clin Immunol* 2000;105:917-22.
24. Harlin SL, Ansel DG, Lane SR, Myers J, Kephart GM, Gleich GJ. A clinical and pathologic study of chronic sinusitis: the role of the eosinophil. *J Allergy Clin Immunol* 1988;81:867-75.
25. Juliusson S, Pipkorn U, Karlsson G, Enerback L. Mast cells and eosinophils in the allergic mucosa response to allergen challenge: changes in distribution and signs of activation in relation to symptoms. *J Allergy Clin Immunol* 1992;90:898-909.
26. Pipkorn U, Karlsson G, Enerback L. The cellular response of the human allergic mucosa to natural allergen exposure. *J Allergy Clin Immunol* 1988;82:1046-54.
27. Denburg JA, Sehmi R, Saito H, Pil-Seob J, Inman MD, O'Byrne PM. Systemic aspects of allergic disease: bone marrow responses. *J Allergy Clin Immunol* 2000;106(suppl):S242-6.
28. Bjornsdottir US, Cypcar DM. Asthma: an inflammatory mediator soup. *Allergy* 1999;54:55-61.
29. Creticos PS, Peters SP, Adkinson NF Jr, Naclerio RM, Hayes EC, Norman PS, et al. Peptide leukotriene release after antigen challenge in patients sensitive to ragweed. *N Engl J Med* 1984;310:1626-30.
30. Wang D, Clement P, Smitz J, Derde MP. Concentrations of chemical mediators in nasal secretions of patients with hay fever during natural allergen exposure. *Acta Otolaryngol* 1994;114:552-5.
31. Wang D, Clement P, Smitz J, De Waele M, Derde MP. Correlations between complaints, inflammatory cells and mediator concentrations in nasal secretions after nasal allergen challenge and during natural allergen exposure. *Int Arch Allergy Immunol* 1995;106:278-85.
32. Bisgaard H, Olsson P, Bende M. Effect of leukotriene D₄ on nasal mucosa blood flow, nasal airway resistance and nasal secretion in humans. *Clin Allergy* 1986;16:289-97.
33. Howarth PH. Mediators of nasal blockage in allergic rhinitis. *Allergy* 1997;52:12-8.
34. Okuda M, Watake T, Mezawa A, Liu CM. The role of leukotriene D₄ in allergic rhinitis. *Ann Allergy* 1988;60:537-40.
35. Miadonna A, Tedeschi A, Leggieri E, Lorini M, Folco G, Sala A, et al. Behavior and clinical relevance of histamine and leukotrienes C₄ and B₄ in grass pollen-induced rhinitis. *Am Rev Respir Dis* 1987;136:357-62.
36. Spada CS, Krauss AH, Nieves AL, Woodward DF. Effects of leukotrienes B₄ (LTB₄) and D₄ (LTD₄) on motility of isolated normodense human eosinophils and neutrophils. *Adv Exp Med Biol* 1997;699:706.
37. Fregonese L, Silvestri M, Sabatini F, Rossi GA. Cysteinyl leukotrienes induce human eosinophil locomotion and adhesion molecule expression via a CysLT₁ receptor-mediated mechanism. *Clin Exp Allergy* 2002;32:745-50.
38. Spada CS, Woodward DF, Hawley SB, Nieves AL. Leukotrienes cause eosinophil emigration into conjunctival tissue. *Prostaglandins* 1986;31:795-809.
39. Laitinen LA, Laitinen A, Haahtela T, Vilkkla V, Spur BW, Lee TH. Leukotriene E₄ and granulocytic infiltration into asthmatic airways. *Lancet* 1993;341:989-90.
40. Pedersen KE, Bochner BS, Undem BJ. Cysteinyl leukotrienes induce P-selectin expression in human endothelial cells via a non-CysLT₁ receptor-mediated mechanism. *J Pharmacol Exp Ther* 1997;281:655-62.
41. Lee E, Robertson T, Smith J, Kilfeather S. Leukotriene receptor antagonists and synthesis inhibitors reverse survival in eosinophils of asthmatic individuals. *Am J Respir Crit Care Med* 2000;161:1881-6.
42. Braccioni F, Dorman SC, O'Byrne PM, Inman MD, Denburg JA, Parameswaran K, et al. The effect of cysteinyl leukotrienes on growth of eosinophil progenitors from peripheral blood and bone marrow of atopic subjects. *J Allergy Clin Immunol* 2002;110:96-101.
43. Knani J, Campbell A, Enander I, Peterson CG, Michel FB, Bousquet J. Indirect evidence of nasal inflammation assessed by titration of inflammatory mediators and enumeration of cells in nasal secretions of patients with chronic rhinitis. *J Allergy Clin Immunol* 1992;90:880-9.
44. Figueroa DJ, Borish L, Baramki D, Philip G, Austin CP, Evans JF. Expression of cysteinyl leukotriene synthetic and signaling proteins in inflammatory cells in active seasonal allergic rhinitis. *Clin Exp Allergy* 2003;33:1380-8.
45. Bensch GW, Nelson HS, Borish LC. Evaluation of cytokines in nasal secretions after nasal antigen challenge: lack of influence of antihistamines. *Ann Allergy Asthma Immunol* 2002;88:457-62.
46. Borish L, Schmaling K, DiClementi JD, Streib J, Negri J, Jones JF. Chronic fatigue syndrome: identification of distinct subgroups on the basis of allergy and psychologic variables. *J Allergy Clin Immunol* 1998;102:222-30.
47. Togias A, Bieneman A, Bloom D, Schleimer R, Iezzoni D, Harris A, et al. Changes in blood leukocyte cytokine expression following repeated nasal allergen provocation: evidence for systemic manifestations [abstract]. *J Allergy Clin Immunol* 2002;109(suppl):S2362.
48. Vuurman EF, van Veggel LM, Uiterwijk MM, Leutner D, O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy* 1993;71:121-6.
49. Marshall PS, O'Hara C, Steinberg P. Effects of seasonal allergic rhinitis on selected cognitive abilities. *Ann Allergy Asthma Immunol* 2000;84:403-10.
50. Cuffel B, Wamboldt M, Borish LC, Kennedy S, Crystal-Peters J. Economic consequences of comorbid depression, anxiety, and allergic rhinitis. *Psychosomatics* 1999;40:491-6.
51. Baraniuk JN, Clauw D, Yuta A, Ali M, Gaumond E, Upadhyayula N, et al. Nasal secretion analysis in allergic rhinitis, cystic fibrosis, and non-allergic fibromyalgia/chronic fatigue syndrome subjects. *Am J Rhinol* 1998;12:435-40.
52. Baraniuk JN, Clauw DJ, Gaumond E. Rhinitis symptoms in chronic fatigue syndrome. *Ann Allergy Asthma Immunol* 1998;81:359-65.
53. Braunstahl GJ, Overbeek SE, Kleinjan A, Prins JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. *J Allergy Clin Immunol* 2001;107:469-76.
54. Corren J, Adinoff AD, Irvin CG. Changes in bronchial responsiveness following nasal provocation with allergen. *J Allergy Clin Immunol* 1992;89:611-8.
55. Gaspar Elsas MI, Joseph D, Elsas PX, Vargaftig BB. Rapid increase in bone-marrow eosinophil production and responses to eosinopoietic interleukins triggered by intranasal allergen challenge. *Am J Respir Cell Mol Biol* 1997;17:404-13.
56. Inman MD, Ellis R, Wattie J, Denburg JA, O'Byrne PM. Allergen-induced increase in airway responsiveness, airway eosinophilia, and bone-marrow eosinophil progenitors in mice. *Am J Respir Cell Mol Biol* 1999;21:473-9.
57. Saito H, Howie K, Wattie J, Denburg A, Ellis R, Inman MD, et al. Allergen-induced murine upper airway inflammation: local and systemic changes in murine experimental allergic rhinitis. *Immunology* 2001;104:226-34.
58. Wood LJ, Inman MD, Denburg JA, O'Byrne PM. Allergen challenge increases cell traffic between bone marrow and lung. *Am J Respir Cell Mol Biol* 1998;18:759-67.
59. Sehmi R, Wood LJ, Watson R, Foley R, Hamid Q, O'Byrne PM, et al. Allergen-induced increases in IL-5 receptor α -subunit expression on bone marrow-derived CD34⁺ cells from asthmatic subjects. A novel

- marker of progenitor cell commitment towards eosinophilic differentiation. *J Clin Invest* 1997;100:2466-75.
60. Wood LJ, Inman MD, Watson RM, Foley R, Denburg JA, O'Byrne PM. Changes in bone marrow inflammatory cell progenitors after inhaled allergen in asthmatic subjects. *Am J Respir Crit Care Med* 1998;157:99-105.
 61. Wood LJ, Sehmi R, Dorman S, Hamid Q, Tulic MK, Watson RM, et al. Allergen-induced increases in bone marrow T lymphocytes and interleukin-5 expression in subjects with asthma. *Am J Respir Crit Care Med* 2002;166:883-9.
 62. Chakir J, Laviolette M, Turcotte H, Boutet M, Boulet LP. Cytokine expression in the lower airways of nonasthmatic subjects with allergic rhinitis: influence of natural allergen exposure. *J Allergy Clin Immunol* 2000;106:904-10.
 63. Louis R, Lau LC, Bron AO, Roldaan AC, Radermecker M, Djukanović R. The relationship between airways inflammation and asthma severity. *Am J Respir Crit Care Med* 2000;161:9-16.
 64. Demoly P, Crampette L, Mondain M, Campbell AM, Lequeux N, Enander I, et al. Assessment of inflammation in noninfectious chronic maxillary sinusitis. *J Allergy Clin Immunol* 1994;94:95-108.
 65. Rasp G, Thomas PA, Bujía J. Eosinophil inflammation of the nasal mucosa in allergic and non-allergic rhinitis measured by eosinophil cationic protein levels in native nasal fluid and serum. *Clin Exp Allergy* 1994;24:1151-6.
 66. ten Brinke A, Grootendorst DC, Schmidt JT, De Bruine FT, van Buchem MA, Sterk PJ, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol* 2002;109:621-6.
 67. Newman LJ, Platts-Mills TA, Phillips CD, Hazen KC, Gross CW. Chronic sinusitis. Relationship of computed tomographic findings to allergy, asthma, and eosinophilia. *JAMA* 1994;271:363-7.
 68. Amin K, Hurst DS, Roomans GM, Venge P, Sevéus L. Eosinophils and neutrophils in biopsies from the middle ear of atopic children with otitis media with effusion. *Inflamm Res* 1999;48:626-31.
 69. Caffarelli C, Cavagni G, Giordano S, Savini E, Piacentini G. Increased nasal eosinophils in children with otitis media with effusion. *Otolaryngol Head Neck Surg* 1996;115:454-7.
 70. Griffin MP, McFadden ER Jr, Ingram RH Jr. Airway cooling in asthmatic and nonasthmatic subjects during nasal and oral breathing. *J Allergy Clin Immunol* 1982;69:354-9.
 71. Fontanari P, Burnet H, Zattara-Hartmann MC, Jammes Y. Changes in airway resistance induced by nasal inhalation of cold dry, dry, or moist air in normal individuals. *J Appl Physiol* 1996;81:1739-43.
 72. Gleeson K, Eggli DF, Maxwell SL. Quantitative aspiration during sleep in normal subjects. *Chest* 1997;111:1266-72.
 73. Bardin PG, Van Heerden BB, Joubert JR. Absence of pulmonary aspiration of sinus contents in patients with asthma and sinusitis. *J Allergy Clin Immunol* 1990;86:82-8.
 74. Kaliner MA, Osguthorpe JD, Fireman P, Anon J, Georgitis J, Davis ML, et al. Sinusitis: bench to bedside. Current findings, future directions. *J Allergy Clin Immunol* 1997;99(suppl):S829-48.
 75. Hamilos DL, Leung DY, Wood R, Bean DK, Song YL, Schotman E, et al. Eosinophil infiltration in nonallergic chronic hyperplastic sinusitis with nasal polyposis (CHS/NP) is associated with endothelial VCAM-1 upregulation and expression of TNF- α . *Am J Respir Cell Mol Biol* 1996;15:443-50.
 76. Ferguson BJ. Eosinophilic mucin rhinosinusitis: a distinct clinicopathological entity. *Laryngoscope* 2000;110:799-813.
 77. Hamilos DL, Leung DY, Wood R, Meyers A, Stephens JK, Barkans J, et al. Chronic hyperplastic sinusitis: association of tissue eosinophilia with mRNA expression of granulocyte-macrophage colony-stimulating factor and interleukin-3. *J Allergy Clin Immunol* 1993;92:39-48.
 78. Finotto S, Ohno I, Marshall JS, Gauldie J, Denburg JA, Dolovich J, et al. TNF- α production by eosinophils in upper airways inflammation (nasal polyposis). *J Immunol* 1994;153:2278-89.
 79. Bachert C, Wagenmann M, Hauser U, Rudack C. IL-5 synthesis is upregulated in human nasal polyp tissue. *J Allergy Clin Immunol* 1997;99:837-42.
 80. Minshall EM, Cameron L, Lavigne F, Leung DY, Hamilos D, Garcia-Zepeda EA, et al. Eotaxin mRNA and protein expression in chronic sinusitis and allergen-induced nasal responses in seasonal allergic rhinitis. *Am J Respir Cell Mol Biol* 1997;17:683-90.
 81. Hamilos DL, Leung DY, Huston DP, Kamil A, Wood R, Hamid Q. GM-CSF, IL-5 and RANTES immunoreactivity and mRNA expression in chronic hyperplastic sinusitis with nasal polyposis (NP). *Clin Exp Allergy* 1998;28:1145-52.
 82. Emanuel IA, Shah SB. Chronic rhinosinusitis: allergy and sinus computed tomography relationships. *Otolaryngol Head Neck Surg* 2000;123:687-91.
 83. Rachelefsky GS, Goldberg M, Katz RM, Boris G, Gyepes MT, Shapiro MJ, et al. Sinus disease in children with respiratory allergy. *J Allergy Clin Immunol* 1978;61:310-4.
 84. Shapiro GG. Role of allergy in sinusitis. *Pediatr Infect Dis* 1985;4(suppl):S55-9.
 85. Borts MR, Slavin RG, Samuels LD, Druce HM, Gentilecore R. Further studies in allergic sinusitis utilizing single photon emission computerized tomography (SPECT) [abstract]. *J Allergy Clin Immunol* 1989;83:302.
 86. Pelikan Z, Pelikan-Filipek M. Role of nasal allergy in chronic maxillary sinusitis—diagnostic value of nasal challenge with allergen. *J Allergy Clin Immunol* 1990;86:484-91.
 87. Baroody FM, de Tineo M, Haney L, Clark K, Blair C, Naclerio RM. Influx of eosinophils into the maxillary sinus after nasal challenge with allergen [abstract]. *J Allergy Clin Immunol* 2000;105(suppl):S70-1.
 88. Baroody FM, Saengpanich S, de Tineo M, Haney L, Votypka V, Naclerio RM. Nasal allergen challenge leads to bilateral maxillary sinus eosinophil influx [abstract]. *J Allergy Clin Immunol* 2002;109(suppl):S84.
 89. Woodcock A, Forster L, Matthews E, Martin J, Letley L, Vickers M, et al. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N Engl J Med* 2003;349:225-36.
 90. Terreehorst I, Hak E, Oosting AJ, Tempels-Pavlica Z, de Monchy JG, Bruijnzeel-Koomen CA, et al. Evaluation of impermeable covers for bedding in patients with allergic rhinitis. *N Engl J Med* 2003;349:237-46.
 91. Abdelaziz MM, Devalia JL, Khair OA, Bayram H, Prior AJ, Davies RJ. Effect of fexofenadine on eosinophil-induced changes in epithelial permeability and cytokine release from nasal epithelial cells of patients with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1998;101:410-20.
 92. Murris-Espin M, Melac M, Charpentier JC, Didier A. Comparison of efficacy and safety of cetirizine and ebastine in patients with perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 1998;80:399-403.
 93. Kemp JP, Buckley CE, Gershwin ME, Buchman E, Cascio FL, Chretien JH, et al. Multicenter, double-blind, placebo-controlled trial of terfenadine in seasonal allergic rhinitis and conjunctivitis. *Ann Allergy* 1985;54:502-9.
 94. Golden S, Teets SJ, Lehman EB, Mauger EA, Chinchilli V, Berlin JM, et al. Effect of topical nasal azelastine on the symptoms of rhinitis, sleep, and daytime somnolence in perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2000;85:53-7.
 95. Nielsen LP, Mygind N, Dahl R. Intranasal corticosteroids for allergic rhinitis: superior relief? *Drugs* 2001;61:1563-79.
 96. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H₁ receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *BMJ* 1998;317:1624-9.
 97. Jen A, Baroody F, de Tineo M, Haney L, Blair C, Naclerio R. As-needed use of fluticasone propionate nasal spray reduces symptoms of seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000;105:732-8.
 98. Togias AG, Proud D, Kagey-Sobotka A, Freidhoff L, Lichtenstein LM, Naclerio RM. In vivo and in vitro effects of antihistamines on mast cell mediator release: a potentially important property in the treatment of allergic disease. *Ann Allergy* 1989;63:465-9.
 99. Sebaldt RJ, Sheller JR, Oates JA, Roberts LJ 2nd, FitzGerald GA. Inhibition of eicosanoid biosynthesis by glucocorticoids in humans. *Proc Natl Acad Sci U S A* 1990;87:6974-8.
 100. O'Shaughnessy KM, Wellings R, Fuller RW. Differential effects of fluticasone propionate on allergen-evoked bronchoconstriction and increased urinary leukotriene E₄ excretion. *Am Rev Respir Dis* 1993;147:1472-6.
 101. Dworski R, Fitzgerald GA, Oates JA, Sheller JR. Effect of oral prednisone on airway inflammatory mediators in atopic asthma. *Am J Respir Crit Care Med* 1994;149:953-9.
 102. Karaman O, Gunbay A, Uzuner N, Gunbay U, Gulay Z, Sarioglu S, et al. The comparison of the efficacy of fluticasone propionate with cetirizine in perennial allergic rhinitis. *Allergol Immunopathol (Madr)* 2001;29:55-9.
 103. Donnelly AL, Glass M, Minkwitz MC, Casale TB. The leukotriene D₄-

- receptor antagonist, ICI 204,219, relieves symptoms of acute seasonal allergic rhinitis. *Am J Respir Crit Care Med* 1995;151:1734-9.
104. Knapp HR. Reduced allergen-induced nasal congestion and leukotriene synthesis with an orally active 5-lipoxygenase inhibitor. *N Engl J Med* 1990;323:1745-8.
105. Nayak AS, Philip G, Lu S, Malice MP, Reiss TF. Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial performed in the fall. *Ann Allergy Asthma Immunol* 2002;88:592-600.
106. Numata T, Konno A, Yamakoshi T, Hanazawa T, Terada N, Nagata H. Comparative role of peptide leukotrienes and histamine in the development of nasal mucosa swelling in nasal allergy. *Ann Otol Rhinol Laryngol* 1999;108:467-73.
107. Philip G, Malmstrom K, Hampel FC, Weinstein SF, LaForce CF, Ratner PH, et al. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy* 2002;32:1020-8.
108. Lavolette M, Malmstrom K, Lu S, Chervinsky P, Pujet JC, Peszek I, et al. Montelukast added to inhaled beclomethasone in treatment of asthma. *Am J Respir Crit Care Med* 1999;160:1862-8.
109. Varney VA, Gaga M, Frew AJ, Aber VR, Kay AB, Durham SR. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. *BMJ* 1991;302:265-9.
110. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999;341:468-75.
111. Casale TB, Bernstein IL, Busse WW, LaForce CF, Tinkelman DG, Stoltz RR, et al. Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. *J Allergy Clin Immunol* 1997;100:110-21.
112. Ådelroth E, Rak S, Haahela T, Aasand G, Rosenhall L, Zetterstrom O, et al. Recombinant humanized mAb-E25, an anti-IgE MAb, in birch pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000;106:253-9.
113. Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, Von Berg A, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2002;109:274-80.
114. Adams RJ, Fuhlbrigge AL, Finkelstein JA, Weiss ST. Intranasal steroids and the risk of emergency department visits for asthma. *J Allergy Clin Immunol* 2002;109:636-42.
115. Watson WT, Becker AB, Simons FE. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. *J Allergy Clin Immunol* 1993;91:97-101.
116. Corren J, Adinoff AD, Buchmeier AD, Irvin CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol* 1992;90:250-6.
117. Foresi A, Pelucchi A, Gherson G, Mastropasqua B, Chiapparino A, Testi R. Once daily intranasal fluticasone propionate (200 µg) reduces nasal symptoms and inflammation but also attenuates the increase in bronchial responsiveness during the pollen season in allergic rhinitis. *J Allergy Clin Immunol* 1996;98:274-82.
118. Thio BJ, Slingerland GL, Fredriks AM, Nagelkerke AF, Scheeren RA, Neijens HJ, et al. Influence of intranasal steroids during the grass pollen season on bronchial responsiveness in children and young adults with asthma and hay fever. *Thorax* 2000;55:826-32.
119. Parikh A, Scadding GK, Darby Y, Baker RC. Topical corticosteroids in chronic rhinosinusitis: a randomized, double-blind, placebo-controlled trial using fluticasone propionate aqueous nasal spray. *Rhinology* 2001;39:75-9.
120. Borish L. Sinusitis and asthma: entering the realm of scientific study [editorial]. *J Allergy Clin Immunol* 2002;109:606-8.
121. Bresciani M, Paradis L, Des Roches A, Vernhet H, Vachier I, Godard P, et al. Rhinosinusitis in severe asthma. *J Allergy Clin Immunol* 2001;107:73-80.
122. Peters EJ, Hatley TK, Crater SE, Phillips CD, Platts-Mills TA, Borish L. Sinus computed tomography scan and markers of inflammation in vocal cord dysfunction and asthma. *Ann Allergy Asthma Immunol* 2003;90:316-22.
123. Pizzichini E, Leff JA, Reiss TF, Hendeles L, Boulet LP, Wei LX, et al. Montelukast reduces airway eosinophilic inflammation in asthma: a randomized, controlled trial. *Eur Respir J* 1999;14:12-8.
124. Reiss TF, Chervinsky P, Dockhorn RJ, Shingo S, Seidenberg B, Edwards TB. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. Montelukast Clinical Research Study Group. *Arch Intern Med* 1998;158:1213-20.
125. Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000;356:2144-8.
126. Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. *Am J Respir Crit Care Med* 2003;167:199-204.
127. Bryan SA, O'Connor BJ, Matti S, Leckie MJ, Kanabar V, Khan J, et al. Effects of recombinant human interleukin-12 on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000;356:2149-53.
128. Dahlen B, Nizankowska E, Szczeklik A, Zetterstrom O, Bochenek G, Kumlin M, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* 1998;157:1187-94.
129. Parnes SM, Chuma AV. Acute effects of antileukotrienes on sinonasal polyposis and sinusitis. *Ear Nose Throat J* 2000;79:18-25.
130. Sarti W, Gomes-Monteiro LA, Machado CSM. The treatment of allergic rhinitis improves the recovery from asthma and upper respiratory infections. *Sao Paulo Med J* 1995;113:968-72.
131. Welsh PW, Stricker WE, Chu CP, Naessens JM, Reese ME, Reed CE, et al. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. *Mayo Clin Proc* 1987;62:125-34.