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REVIEW ARTICLE

The Impact of Comorbid Atopic Disease on Asthma: Clinical Expression and Treatment

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Clinically, asthma and allergic rhinitis involve separate regions of the respiratory tract while representing a common underlying inflammatory syndrome. Much evidence supports an epidemiologic association between the diseases, paranasal sinus involvement in both conditions, and parallel relationship in severity and treatment outcomes. Pathophysiologic mechanisms, including immunoglobulin E (IgE)-mediated inflammation, are also shared. Blocking IgE with the recombinant humanized monoclonal antibody omalizumab demonstrated clinical efficacy in patients with upper and lower airway diseases. IgE blockade, leukotriene modulation, and B-cell depletion therapy have all exhibited success in chronic inflammation, reinforcing and expanding the beneficial role of immunomodulation of global mediators.

Keywords allergic rhinitis, asthma, atopy, IgE-mediated inflammation, omalizumab

INTRODUCTION

Asthma and allergic rhinitis are clinical manifestations of the same underlying syndrome of chronic inflammation that affects the upper and lower airways. Asthma and allergic rhinitis are linked epidemiologically, with the clinical severity and treatment of each condition affecting the other. In fact, asthma treatment costs and outcomes are unfavorably influenced by the presence of concurrent allergic rhinitis (1). The common underlying pathophysiologic mechanisms in lower and upper airway inflammation are now well recognized; as a result, the concept of “1 airway, disease” has emerged (Table 1). Differences in the manifestations of this disease in the upper versus lower airway stem largely from anatomical and structural differences of the airways (e.g., the presence of smooth muscle in the lower but not the upper airways). Along with increased recognition of the role of immunoglobulin E (IgE)-mediated inflammation in asthma, common IgE-mediated mechanisms in asthma and allergic rhinitis have been demonstrated.

It is becoming apparent that inflammatory processes in the upper airways can transfer to the lower airways through systemic circulation and vice versa. Guidelines from Allergic Rhinitis and its Impact on Asthma (ARIA), an initiative sponsored by the World Health Organization, recommend that treatment of upper and lower airway disease should be combined for safety and efficacy (2). As a result, therapies that safely target systemic manifestations of inflammation may simultaneously improve allergic rhinitis and asthma. Individual treatment of asthma and allergic rhinitis may include inhaled corticosteroids (ICS), administered either intrabronchially or intranasally, respectively.

EPIDEMIOLOGY

Association Between Asthma and Allergic Rhinitis

The lifetime prevalence of asthma is approximately the same as that of allergic rhinitis in the United States: 20.7 million and 18.4 million adults reported, in 2003, a diagnosis at some point in their life of asthma or hay fever, respectively (3). Epidemiologic studies have shown that allergic rhinitis and asthma frequently co-exist (Table 2), although the prevalence of concomitant allergic rhinitis in patients with asthma and concomitant asthma in patients with allergic rhinitis varies (4–8). A recent population-based study found the risk of asthma to be 19% in subjects with allergic rhinitis but only 2% in those without allergic rhinitis (7). In addition, depending on sensitization to specific allergen, approximately 74% to 81% of subjects with asthma reported allergic rhinitis, while in follow-up to another population-based study 100% of patients with asthma also experienced allergic rhinitis (8). Several clinical trials have shown that more than half of the patients with asthma also have allergic rhinitis (9–11) (Table 2); one large trial in particular reported a 95.6% coincidence of the 2 ailments (11).

The first European Community Respiratory Health Survey found the presence of perennial rhinitis to be a major risk factor for asthma, independent of the atopic status of the patient (12). The adjusted odds ratios (OR) in the atopic and nonatopic populations were 8.1 (95% confidence interval [CI], 5.4–12.1) and 11.6 (95% CI, 6.2–21.9), respectively (12). Several studies have prospectively identified allergic rhinitis as a risk factor for asthma. In a follow-up of 690 middle-aged men 23 years after an original evaluation, a greater proportion of subjects originally diagnosed with allergic rhinitis developed asthma compared with those who did not originally have allergic rhinitis (10.5% vs. 3.6%) (13). In comparing 173 adults (50.81 ± 19.3 years) who had newly developed asthma with 2,177 control subjects (52.96 ± 21.2 years) over 10 years, the Tucson Epidemiologic Study of

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TABLE 1.—Evidence supporting the “1 Airway, 1 Disease” concept.

	Evidence	References
Epidemiology	Allergic rhinitis and asthma frequently co-exist	4–11
	Allergic rhinitis is a risk factor for the development or presence of asthma	12–17
	Sinusitis frequently co-exists with asthma	18, 21, 22
	Sinusitis frequently co-exists with allergic rhinitis	23–25
Pathophysiology	The atopic march: atopic dermatitis, asthma, allergic rhinitis	27–29
	Similar inflammatory cell populations and cytokines present in upper and lower airway inflammation	30,31
	Initially localized inflammation manifests in other regions of the airway	32–40
Pathways of communication	Migration of immune cells directly to adjacent tissues and via the circulation to other regions of the airway; multiple effects of immune/inflammatory cell activation propagated via cytokines and in the bone marrow and lymph nodes	50–53, 161
	Locally applied suppression of inflammation manifests at remote locations (systemic circulation, bone marrow, lymphatic tissue)	54–56
	Nervous system	57, 58, 60, 63, 161
	Physical transfer of allergens/irritants	64, 65, 67
	Lower airway effects of upper airway infection	68
Clinical	Correlation of severity of symptoms in upper and lower airways and clinical improvement in one region following treatment administered in the other	15, 16, 64, 69–80

Obstructive Lung Diseases found OR = 2.59 (95% CI, 1.54–4.34) for developing asthma in rhinitis patients (14). In patients with concomitant rhinitis and sinusitis, OR = 6.28 (95% CI, 4.01–9.82). The Copenhagen Allergy Study, which randomly examined a population of 734 individuals (initially

between 15 to 69 years of age) on two occasions 8 years apart found that all 52 subjects with allergic asthma (IgE-mediated asthma) triggered by pollen also had allergic rhinitis triggered by pollen (8). A total of 28 new cases of allergic asthma triggered by pollen developed in patients who either had allergic

TABLE 2.—Studies of asthma comorbidities.

Asthma and allergic rhinitis		
Study	Description	Findings
Greisner et al.* (4)	N = 738; 84 with asthma; 338 with AR	85.7% of patients with asthma had a history of AR; 32.1% had a history of nonseasonal AR; 21.3% of patients with AR had a history of asthma
Mullarkey et al.* (5)	N = 142; 48 with AR	58% of patients with AR had histories or findings consistent with asthma
Leynaert et al.* (7)	N = 10, 210	50%–70% of subjects with asthma reported rhinitis, depending on sensitization to specific allergens
Linneberg et al.* (8)	N = 734	Asthma prevalence was >6 × higher in subjects with rhinitis than in those without
Leynaert et al.* (12)	N = 6610	89%–100% of subjects with allergic asthma to a specific allergen had AR to that allergen
Settipane et al.* (13)	N = 690; 84 with asthma	The frequency of asthma was 16.2% among individuals with rhinitis vs. 1.0% among those without
		Asthma was strongly associated with rhinitis among atopic subjects (OR = 8.1; 95% CI, 5.4–12.1) and nonatopic subjects (OR = 11.6; 95% CI, 6.2–21.9)
		Individuals with positive allergy skin test have 2.3× risk of developing new HF than do those with a negative skin test
Guerra et al.* (14)	N = 2,350; 173 with asthma	Individuals with AR have >3× risk of developing new asthma (10.5% vs. 3.6%; <i>p</i> < 0.002)
Wright et al.* (15)	N = 747; 311 with rhinitis	Rhinitis was a significant risk factor for asthma (OR = 2.59; 95% CI, 1.54–4.34)
		This relationship was stronger when both rhinitis and sinusitis were present (OR = 6.28; 95% CI, 4.01–9.82)
Arrighi et al.* (16)	N = 1,602; 188 with asthma; 152 with HF diagnosis; 386 with HF symptoms and no diagnosis	Asthma was a risk factor for physician-diagnosed AR (OR = 4.06; 95% CI, 2.06–7.99)
		Children with AR in the first year were almost 2× as likely to have an asthma diagnosis by age 6 as children without (23% vs. 13%, <i>p</i> < 0.005)
Holgate et al. [†] (9)	N = 246 with severe allergic asthma	22% of patients with an HF diagnosis were diagnosed with asthma
Soler et al. [†] (10)	N = 546 with asthma	21% of patients with HF symptoms but no diagnosis were diagnosed with asthma
		43% of asthma patients had HF symptoms
		49.6% of patients had SAR;
Reicin et al. [†] (11)	N = 136 with asthma	63.4% of patients had PAR
Masuda et al. [†] (17)	N = 107 children with bronchial asthma	65.9% of patients had SAR;
		77.3% of patients had PAR
		95.6% of individuals had AR
		82.2% had persistent nasal symptoms consistent with AR
		Asthma and sinusitis
Study	Description	Findings
ten Brinke et al.* (21)	N = 89 with severe bronchial asthma	Extensive paranasal sinus disease was found in 23.6% (95% CI, 15%–33%) of patients
Bresciani et al.* (22)	N = 69 with asthma	70%–74% of patients had symptoms of rhinosinusitis
Rachelefsky et al.* (23)	N = 70 children with AR	88%–100% of patients had abnormal sinuses (CT scan)
		Sinonasal involvement, as evaluated by clinical symptoms and CT scan, is significantly greater in patients with severe steroid-dependent asthma than in those with mild to moderate asthma
		53% of patients showed abnormal sinus radiographs
Savolainen et al.* (24)	N = 224 with acute maxillary sinusitis	15.2% of patients had a history of rhinitis
Harlin et al.* (25)	N = 26 with chronic sinusitis	25% of patients had allergy (including past/present asthma/AR symptoms)
		19.2% of patients had bronchial asthma
		Up to 58% of patients had AR

AR = allergic rhinitis; OR = odds ratio; CI = confidence interval; HF = hay fever; SAR = seasonal allergic rhinitis; PAR = perennial allergic rhinitis; CT = computed tomography.

*Epidemiological survey.

†Asthma treatment trial.

rhinitis to pollen at baseline or had allergic rhinitis to pollen at follow-up (8).

Although a high incidence of viral infections in children makes a diagnosis of noninfectious rhinitis challenging, allergic rhinitis in children has been shown to be a risk factor for developing asthma. The Tucson Children's Respiratory Study found that children with allergic rhinitis in the first year of life were almost twice as likely to have an asthma diagnosis by age 6 as those children without allergic rhinitis (23% vs. 13%, $p < 0.005$) (15). Of the children with a physician's diagnosis of asthma 43% had diagnosed hay fever or hay fever symptoms (16), and 82.2% overall of children with asthma reported persistent nasal symptoms (17).

Association Between Sinusitis and Asthma

Paranasal sinus involvement in asthma as well as allergic rhinitis is further evidence that supports the 1 airway, 1 disease concept (Table 2) (18,19). In fact, over 50% of patients with sinusitis have asthma (20,21), and approximately 90% of patients with mild-to-moderate asthma show evidence of abnormal sinuses (22). In patients with severe steroid-dependent asthma, approximately 100% have been reported to have abnormal sinus computed tomography (CT) scans (22).

Association Between Sinusitis and Allergic Rhinitis

Radiographs have shown abnormal sinuses in 53% of patients with allergic rhinitis (23), and 15% to 58% patients with allergic rhinitis also report having sinusitis (24, 25).

Association Between Atopic Dermatitis, Allergic Rhinitis, and Asthma

The atopic march is a characteristic sequence of IgE-mediated manifestations and remissions of atopic symptoms throughout a patient's life. It often begins with atopic dermatitis, which has the highest incidence and prevalence during the first 3 months of life (26). This is followed by a predictable progression into more serious IgE-mediated diseases, such as allergic rhinitis and then asthma. In fact, children with atopic dermatitis are at an increased risk of developing asthma or allergic rhinitis before age 7 (27–29).

PATHOPHYSIOLOGIC RELATIONSHIPS OF ATOPIC DISEASES

Mechanisms of Inflammation

Allergic rhinitis begins when patients become sensitized to allergens that come into contact with the nasal mucosa. This ultimately leads to the systemic production of allergen-specific IgE, which binds to high-affinity IgE receptors (FcεRI) on mast cells, basophils, and dendritic cells and binds to low-affinity IgE receptors (FcεRII) on B lymphocytes, eosinophils, and macrophages. Subsequent exposure to the allergen causes cross-linking of surface receptor-bound IgE molecules, inflammatory cell activation with release of inflammatory mediators and cytokines, and the early- and late-phase inflammatory reactions, resulting in perpetuation of airway inflammation and clinical symptoms (30, 31).

The same inflammatory cells and proinflammatory mediators are typically present in the nasal and bronchial mucosa of patients with upper and lower airway disease. These cells include eosinophils, mast cells, T lymphocytes, and mediators including histamine, prostaglandins, cysteinyl leukotrienes,

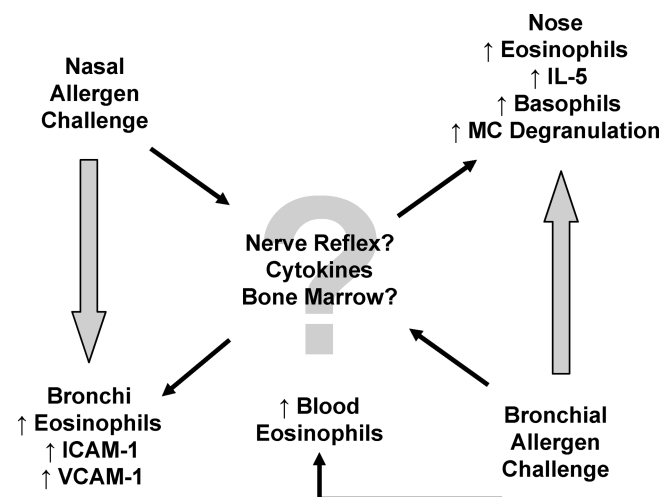


FIGURE 1.—The bidirectional allergic link between the nose and bronchi (18). Reproduced from Passalacqua et al., with kind permission from Lippincott Williams & Wilkins.

T helper-2 (Th2) cytokines (interleukin- [IL] 4, IL-5, IL-9, IL-13, and granulocyte-macrophage colony-stimulating factor), chemokines, and adhesion molecules (30, 31).

Systemic Manifestations of Local Inflammation

Several investigations have demonstrated that allergic nasal or intrabronchial challenge results in generalized airway inflammation, suggesting that local inflammation is communicated to other regions of the respiratory tract directly or through systemic channels.

Nose and bronchi. In three early studies, nasal allergen challenge of patients with allergic rhinitis and asthma resulted in a significant increase in bronchial responsiveness to methacholine (32, 33) and a significant reduction in forced expiratory volume at 1 second (FEV₁) and forced vital capacity (FVC) (33, 34). More recent experimental data have confirmed a bidirectional link between the nose and bronchi (Figure 1) (18). Braunstahl et al. performed a nasal allergen challenge so that the allergen did not enter the lungs in patients who had allergic rhinitis without asthma. Nonetheless, it produced inflammatory changes in both the upper and lower airways, including increased expression of adhesion molecules, eosinophil infiltration, and increased bronchial hyperreactivity (35). In another experiment, intrabronchial allergen challenge induced bronchial and nasal symptoms, reduced pulmonary and nasal function, and increased the number of eosinophils in the blood, bronchial mucosa, and nasal mucosa (36).

Nose and sinuses. Evidence suggests that a systemic inflammatory process links the nose and sinuses. Pelikan and Pelikan-Filipek found that nasal allergen challenge produced radiographic changes, including edema and opacification, in the maxillary sinuses of allergen-sensitive individuals (37). In allergic individuals, Baroody et al. demonstrated that a nasal allergen challenge produced significant increases in eosinophils, histamine, and albumin in the nose and the maxillary sinus (38). As radiolabeled pollen placed in the nose has been shown not to enter the paranasal sinuses (39), the

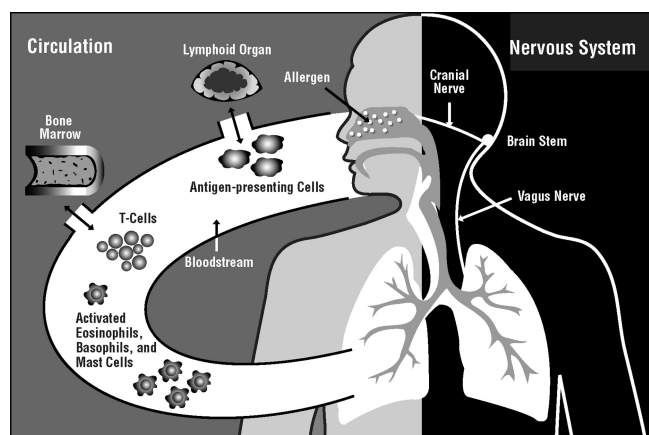


FIGURE 2.—Mechanisms linking upper and lower airway inflammation (allergic rhinitis and asthma) (161).

allergic response in the sinuses (38) is evidence of an indirect link. Furthermore, allergen challenge of a single nostril increased the number of eosinophils and albumin levels in the ipsilateral and contralateral maxillary sinuses (38, 40). Although the allergen sprayed in 1 nostril could possibly reach the ipsilateral maxillary sinus, the inflammatory response in the contralateral sinus suggests transmission through a systemic mechanism.

Mechanisms Linking Sinusitis, Rhinitis, and Asthma

Systemic manifestation of local inflammation. Several potential mechanisms may connect sinusitis, rhinitis, and asthma (Figure 2). Allergens that make contact with the nasal mucosa can be absorbed by dendritic cells, which process allergenic particles, mature into active antigen-presenting cells, and migrate to adjacent lymphatic tissues (41). Dendritic cells present antigen peptides to T lymphocytes, which become activated and differentiate into Th2 lymphocytes (41). Th2-derived IL-4, IL-5, and IL-13 stimulate B lymphocytes to produce IgE (42, 43). IL-5 can also promote production, migration, activity, and survival of eosinophils (44), while IL-4 can activate mast cells (45–48). A local allergic reaction also can produce distant effects through inflammatory mediators or cells that circulate in the blood; for example, Saini et al. showed that intranasal allergen challenge increased FcεRIβ on circulating basophils (49). Alternatively, activated Th2 cells may enter the circulation and migrate back to the nose, sinuses, or lungs and contribute to local inflammation. Eosinophils and mast cells may also enter the circulation and be drawn to the respiratory tract by adhesion molecules and chemoattractants, where they can further exacerbate inflammation.

Communication may also occur between local inflammatory modulators and bone marrow progenitors. After allergen inhalation, asthma patients produce increased numbers of eosinophil colony forming units (50) and CD34+/IL-5 receptor alpha (IL-5Rα)+ hematopoietic progenitors (51) in the bone marrow, as well as increased circulating progenitors (52). Allergen inhalation may result in downregulation of SDF-1α expression in the bone marrow and CXCR4 expression on CD34+ cells in subjects with asthma. CD34+ cells

from asthma patients were also more migratory in response to eotaxin, a molecule known to promote eosinophil recruitment to sites of inflammation (53). Local allergen exposure can therefore modulate the distant bone marrow microenvironment, and this process may direct progenitor cells to the periphery.

Suppression of inflammation through application of local anti-inflammatory medications also produces systemic results. Wood et al. showed that the ICS budesonide selectively reduced baseline numbers of IL-5-responsive eosinophil/basophil progenitors and absolute numbers of CD34+ and CD34+/IL-3Rα+ progenitors in the bone marrow of allergic patients with asthma (54). The authors speculated that local application of budesonide had a systemic effect, resulting in inhibition of certain progenitor cell subpopulations in the bone marrow (54). Furthermore, intranasal application of budesonide to mice inhibited allergen-induced increases in the number of bone marrow eosinophil progenitors (55). Additionally, in patients with allergic rhinitis, locally applied fluticasone propionate inhibited pollen-induced increases in the number of CD34+/CXCR4+ hematopoietic progenitors (56). Thus, the upper and lower respiratory tracks maintain a systemic connection and may affect each other distantly after local stimulation or suppression of inflammation.

The nervous system. The nervous system also responds to inhaled allergens. Stimulation of the nasal mucosa of one nostril by histamine (57) or hyperosmolar saline (58) affects sensory nerve endings that produce an ipsilateral secretory response and a neurally mediated contralateral response; however, clinical relevance only appears in patients with perennial allergic rhinitis or symptomatic seasonal disease (58, 59). Mechanical force in one area may also affect the other; one study showed that nasal provocation and activation mechanoreceptors altered pulmonary resistance (60). Neural cells (as well as airway epithelia) also secrete neuropeptides, which may have immunomodulatory effects. The neuropeptide substance P is increased in bronchoalveolar and nasal lavage in the airways of asthma patients after allergen provocation (61) and may contribute to various aspects of airway inflammation, such as mast cell degranulation (62). There is the potential for many interactions and influences between the upper and lower airways, either directly or indirectly, via combinatorial communication between inflamed tissue, the circulation, and the nervous system.

Other mechanisms. The nose acts as a filter and conditioner, warming and humidifying inhaled air and possibly enriching it with nitric oxide (NO); all these functions serve to protect the lower airways (63–65). NO has strong antiviral and bacteriostatic activity, improves oxygenation, exerts bronchodilatory effects, and modulates lower airway responsiveness (64). Consequently, nasal obstruction may lead to mouth breathing and allergens entering the lower airways, producing asthma symptoms in susceptible patients (66). Aspiration of nasal secretions containing inflammatory cells and mediators into the bronchial tree could also be responsible for inflammatory effects on the lower airways (66, 67). Finally, viral infections of the upper airways—particularly those caused by rhinoviruses—can be an important cause of asthma exacerbations (68), especially in children.

CLINICAL RELATIONSHIPS OF ATOPIC DISEASES

Allergic Rhinitis and Asthma

In addition to the fact that allergic rhinitis and allergic asthma often co-exist, allergic rhinitis affects the severity of asthma. Patients whose allergic rhinitis is severe or poorly controlled experience worse asthma symptom control and tend to have more persistent asthma than those with mild or well-controlled rhinitis (64). In addition, treatment of inflammation in the upper airways indirectly improves asthma symptoms and decreases bronchial hyperreactivity (69, 70). Likewise, in patients with severe asthma, nasal symptoms are worse than in patients with moderate asthma (16). Although the majority of allergic rhinitis patients do not have asthma, they may have pathologic evidence of lower airway disease similar to mild asthma, but without the clinical signs. Patients with more severe allergic rhinitis might show evidence of lower airway hyperresponsiveness along with their rhinitis. In general, more severe allergic rhinitis and more severe asthma tend to parallel each other (64).

Treatment of allergic rhinitis can improve the symptoms of asthma. Although intranasal corticosteroids (INS) do not directly access the lower airways, they have improved asthma symptoms (70–74). In a study of patients with seasonal ragweed hay fever, a subgroup that had seasonal asthma experienced almost complete elimination of chest symptoms following treatment with INS (71). Two retrospective analyses have shown that treatment of nasal symptoms reduces the risk of asthma-related emergency department visits and hospitalizations (72, 73). Other investigations have found that nasal steroids may reduce bronchial hyperresponsiveness in patients with allergic rhinitis (70, 74). In addition, it has been shown that antihistamine treatment for allergic rhinitis can improve symptoms of concomitant asthma (75).

Sinusitis and Asthma

A positive correlation exists between surrogate markers of asthma severity, including bronchial eosinophilia, exhaled NO, and pulmonary function and the severity of sinusitis measured by CT (21). Patients with severe corticosteroid-dependent asthma have been shown to have clinical and CT scores of sinus abnormalities greater than those of patients with mild-to-moderate asthma (22).

As with allergic rhinitis, treatment of sinusitis can improve the symptoms of asthma. Surgical intervention for chronic sinusitis may have a favorable long-term effect on asthma symptoms (76–78). In a trial of 18 children with poorly controlled moderate asthma and concurrent chronic rhinosinusitis, treatment with a combination of amoxicillin/clavulanate, fluticasone propionate, and a short course of oral corticosteroids improved sinus and asthma symptoms, respiratory function, and signs of inflammation compared with baseline (79). A larger pediatric study showed that aggressive treatment of sinusitis with amoxicillin/clavulanate decreased bronchial hyperresponsiveness to methacholine (80). The subsequent reduction in asthma symptoms, however, may be the result of the restored ability of the nose to protect the lower airways rather than an effect on systemic manifestations of local inflammation.

Clinical Management

Increased severity of asthma is associated with the presence of allergic rhinitis and is affected by treatment of allergic rhinitis. As a result, a clinical assessment of the patient with asthma should include an evaluation of atopic comorbidities. Awareness of the 1 airway, 1 disease concept and the systemic nature of IgE-mediated inflammation would encourage a more accurate evaluation of the patient's airway inflammation and a comprehensive approach to treatment that should increase the likelihood of a better clinical outcome.

Treatment of upper and lower airway inflammation with ICS requires the use of two separate inhalers. As this is less convenient than using a single medication, patients may have difficulty adhering to the dual prescribed regimen. The ARIA guidelines recommend that treatment of upper and lower airway disease be combined, although this clearly cannot be done with orally ICS (2).

Rationale for IgE Blockade

IgE plays a key role in the early development of inflammation in allergic rhinitis and asthma, and both disorders are associated with production of allergen-specific IgE (81–85). Furthermore, the number of cells that express FcεRI (86) and the expression level of FcεRI on the surface of mast cells and basophils (82, 87, 88) can be increased in these diseases. As a result, IgE is an appropriate therapeutic target to reduce airway inflammation.

Omalizumab is a recombinant humanized monoclonal antibody (mAb) that binds specifically to the cell-surface receptor (FcεRI and FcεRII) binding site on free circulating IgE. By preventing IgE-FcεRI interactions on mast and other cells, omalizumab blocks the airway inflammatory cascade at initiation, inhibiting both the early and late response to allergen exposure (89). Omalizumab reduces free circulating IgE and cell-surface receptor-bound IgE as well as the number of FcεRI receptors expressed on mast cells, basophils, and dendritic cells (90–92). Omalizumab also has been shown to significantly reduce the numbers of inflammatory cells such as eosinophils, T helper and T cytotoxic lymphocytes, and B lymphocytes in patients with asthma (93, 94) and allergic rhinitis (95).

CLINICAL EFFICACY OF OMALIZUMAB

Efficacy in Asthma

Omalizumab is indicated for use in the treatment of adolescent and adult patients (≥ 12 years of age) with moderate-to-severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICS.

In several randomized, double-blind, placebo-controlled phase 3 trials, omalizumab reduced asthma exacerbations in patients with moderate-to-severe allergic asthma when added to ICS, and lowered corticosteroids requirements (Table 3) (9, 10, 96–100). Long-term safety was demonstrated in the 24-week double-blind extensions to both 28-week core trials (98, 99). Long-term treatment was well tolerated, and the incidence of adverse events was comparable with patients receiving placebo.

Omalizumab also reduced the rate of asthma-related emergency department visits and hospitalizations. Bousquet et al.

TABLE 3.—Efficacy of omalizumab in asthma.

Study	Design	Patients	Duration	Outcomes
Busse et al. (97)	R, DB, PC	525 patients with severe asthma [‡] (OMA, <i>n</i> = 268) (Placebo, <i>n</i> = 257)	28 weeks	Significant decrease in exacerbations during stable-steroid phase (0.28 vs. 0.54 [<i>p</i> = 0.006]) and steroid-reduction phase (0.39 vs. 0.66 [<i>p</i> = 0.003]) for omalizumab group compared with placebo Significant reduction in ICS requirement for omalizumab group compared with placebo (median 75% vs. 50% [<i>p</i> = 0.003])
Lanier et al.* (98)	R, DB, PC	460 of the initial 525 patients from the Busse study (OMA, <i>n</i> = 245) (Placebo, <i>n</i> = 215)	24 weeks	Significantly reduced exacerbations vs. placebo (0.60 and 0.83 exacerbations per patient, <i>p</i> = 0.023)
Soler et al. (10)	R, DB, PC	546 patients with moderate-to-severe asthma [‡] (OMA, <i>n</i> = 274) (Placebo, <i>n</i> = 272)	28 weeks	58% fewer exacerbations per patient during the stable-steroid phase (<i>p</i> < 0.001) 52% fewer exacerbations during steroid-reduction phase (<i>p</i> < 0.001)
Buhl et al. [†] (99)	R, DB, PC	483 of the initial 546 patients from the Soler study (OMA, <i>n</i> = 254) (Placebo, <i>n</i> = 229)	24 weeks	More omalizumab-treated patients (33.5%) than placebo-treated patients (13.5%) able to complete extension period without requiring ICS Disease control sustained in 76% of omalizumab patients compared with 59.4% of placebo patients
Ayres et al. (96)	R, OL	312 patients with poorly controlled moderate-to-severe asthma [‡] (OMA, <i>n</i> = 206) (Placebo, <i>n</i> = 106)	52 weeks	Mean clinically significant asthma exacerbations rates reduced from 2.86 with best standard care alone to 1.12 per patient year (<i>p</i> < 0.001) 41.4% of omalizumab-treated patients required rescue medication <1 day/week compared with 20.7 for patients on best standard care alone (<i>p</i> < 0.001)
Holgate et al. (9)	R, DB, PC	246 patients with severe asthma [‡] (OMA, <i>n</i> = 126) (Placebo, <i>n</i> = 120)	32 weeks	Median reductions in ICS dose significantly greater with omalizumab than placebo: 60% vs. 50% (<i>p</i> = 0.003) Fluticasone reduction to <500 µg/day occurred in 60.3% of omalizumab-treated patients vs. 45.8% of placebo-treated patients (<i>p</i> = 0.026)
Vignola et al. (100)	R, DB, PC	405 patients with concomitant asthma [‡] and persistent allergic rhinitis (OMA, <i>n</i> = 209) (Placebo, <i>n</i> = 196)	28 weeks	Fewer asthma exacerbations in omalizumab-treated patients than placebo-treated patients (20.6% vs. 30.1% respectively, <i>p</i> = 0.02) Significantly reduced Wasserfallen symptom scores for asthma (<i>p</i> = 0.023)

DB = double-blind; OL = open-label; OMA = omalizumab; PC = placebo-controlled; R = randomized; ICS = inhaled corticosteroid.

*Extension phase to the core study conducted by Busse et al.

[†]Extension phase to the core study conducted by Soler et al.

[‡]With a positive skin test or in vitro reactivity to a perennial aeroallergen.

pooled data from seven clinical trials to determine the effect of omalizumab on emergency department visits in patients with severe persistent asthma (101). Omalizumab significantly reduced the rate of asthma exacerbations by 38% (*p* < 0.0001), emergency department visits by 47% (*p* < 0.0001), and hospital admissions by 52% (*p* = 0.041).

Efficacy in Allergic Rhinitis

The results of several clinical trials evaluating the effects of omalizumab on seasonal and perennial allergic rhinitis are summarized in Table 4. Treatment with omalizumab resulted in significantly lower symptom severity scores and reduced use of rescue antihistamine medication (102–105). Even when administered during sequential seasons, omalizumab was well tolerated with no difference in the rate of adverse events (104). Omalizumab also showed significant benefit in adult patients who received rush immunotherapy for ragweed-induced seasonal allergic rhinitis. Omalizumab pretreatment decreased the risk of anaphylaxis caused by rush immunotherapy by five-fold (odds ratio, 0.17; *p* = 0.026) and improved severity scores by 20% compared to patients receiving immunotherapy alone (*p* = 0.044) (106).

Efficacy in Patients with Asthma and Allergic Rhinitis

The Study of Omalizumab in comorbid Asthma and Rhinitis (SOLAR) assessed the effectiveness of omalizumab in patients with both disorders (Tables 3 and 4) (100). Omalizumab treatment resulted in parallel improvements in perennial allergic rhinitis and comorbid moderate-to-severe asthma and

resulted in more clinically significant (≥ 1.0 point) improvements in both asthma quality of life and rhinitis quality of life than placebo (57.7% vs. 40.6%; *p* < 0.001). The mean rate of asthma exacerbations during treatment was lower with omalizumab than with placebo (0.25 and 0.40 respectively; *p* = 0.02). Asthma and rhinitis symptoms also were reduced as evidenced by the significant reductions in Wasserfallen symptom scores for asthma (−1.8; *p* = 0.023), rhinitis (−3.53; *p* < 0.001) and the composite asthma/rhinitis scores (*p* < 0.001). As with previous studies, omalizumab was well tolerated, and the incidence of serious adverse events was low and comparable in both treatment groups.

OTHER SYSTEMIC TREATMENTS FOR INFLAMMATION

The successful use of omalizumab in treating concomitant asthma and allergic rhinitis suggests that the future treatment of airway disease lies in systemically available biologics that may be able to target central immunomodulatory molecules common to upper and lower airway inflammation. A therapeutic approach targeting general immune modulators has been clinically beneficial in a number of inflammatory diseases.

Leukotriene Modifiers

Systemically available orally administered leukotriene modifiers have been used successfully to treat both asthma and allergic rhinitis. The use of leukotriene modifiers has been incorporated into the National Asthma Education and Prevention Program (NAEPP) and Global Initiative for Asthma

TABLE 4.—Efficacy of omalizumab in seasonal and perennial allergic rhinitis.

Study	Design	Patients	Duration	Outcomes
Adelroth et al. (102)	R, DB, PC	251 patients with seasonal allergic rhinitis (OMA, <i>n</i> = 164) (Placebo, <i>n</i> = 86)	8 weeks	Significant difference from baseline in favor of omalizumab observed in average daily nasal symptom severity score at the end of treatment (<i>p</i> < 0.001) Average number of rescue antihistamines taken per day significantly lower (<i>p</i> < 0.001) in the omalizumab group (0.59 tablets per day) than in the placebo group (1.37 tablets per day)
Casale et al. (103)	R, DB, PC	536 patients with seasonal allergic rhinitis (OMA, <i>n</i> = 400) (Placebo, <i>n</i> = 136)	12 weeks	Nasal symptom severity scores significantly lower in patients who received 300 mg of omalizumab than in those who received placebo (least squares means, 0.75 vs. 0.98, respectively; <i>p</i> = 0.002)
Nayak et al.* (104)	R, OL	287 of the initial 536 patients from the core study (OMA, <i>n</i> = 287)	12 weeks	Retreatment during second pollen season well tolerated and not associated with any significant immunologic reactions Overall incidence and pattern of adverse events similar to those reported in primary study
Chervinsky et al. (105)	R, DB, PC	289 patients with perennial allergic rhinitis (OMA, <i>n</i> = 144) (Placebo, <i>n</i> = 145)	16 weeks	Mean daily nasal severity scores significantly lower in omalizumab-treated patients than with placebo (<i>p</i> < 0.001) Reduction in use of rescue antihistamine (<i>p</i> < 0.005 overall) and improved rhinitis-specific quality of life
Vignola et al. (100)	R, DB, PC	405 patients with concomitant asthma† and persistent allergic rhinitis (OMA, <i>n</i> = 209) (Placebo, <i>n</i> = 196)	28 weeks	Omalizumab more effective than placebo for all Rhinitis Quality of Life Questionnaire domains Wasserfallen symptom scores for rhinitis significantly reduced in omalizumab-treated patients (<i>p</i> < 0.001)
Casale et al. (106)	R, DB, PC	159 patients with a minimum 2-year history of ragweed allergic rhinitis (OMA plus IT, <i>n</i> = 39) (OMA, <i>n</i> = 40) (IT, <i>n</i> = 40) (Placebo, <i>n</i> = 40)	21 weeks	Anaphylaxis risk (odds ratio, 0.17; <i>p</i> = 0.026) and adverse events were less in patients who received omalizumab plus IT Omalizumab plus IT-treated patients had improved severity scores during the ragweed season (0.69 vs. 0.86 for patients who received IT alone; <i>p</i> = 0.044)

DB = double-blind; OL = open-label; OMA = omalizumab; PC = placebo-controlled; R = randomized; IT = immunotherapy.

*Retreatment phase to core study conducted by Casale et al.

†With a positive skin test or in vitro reactivity to a perennial aeroallergen.

(GINA) guidelines as add-on or alternative therapy to ICS in patients with varying asthma severities (107, 108) and the ARIA guidelines for adults with seasonal allergic rhinitis (2). Cysteinyl leukotrienes (cys-LTs) are major contributors to the pathophysiology of upper and lower airway inflammation; these lipid derivatives of arachidonic acid bind to cys-LT₁ receptors on airway smooth muscle cells to promote bronchoconstriction, or on leukocytes to cause activation, migration into the airways, and edema (109). Leukotriene modifiers block cys-LT function either through antagonism of the cys-LT₁ receptor (montelukast and zafirlukast, the leukotriene receptor antagonists [LTRAs]) or via interference with the leukotriene synthesis pathway (zileuton). It is well established that many asthma patients on LTRA therapy experienced improved lung function and quality of life, decreased asthma symptoms, airway hyperresponsiveness, and the need for short-acting β -agonists (110), although meta-analyses of clinical trials have shown that efficacy was not as high as ICS (111, 112). In patients with allergic rhinitis, clinical improvements due to LTRA therapy included reduced daytime nasal and eye symptoms, reduced nighttime symptoms, and improved quality of life (110). However, a recent systematic review and meta-analysis showed that LTRAs did not provide greater clinical benefit than nasal corticosteroids (113). Studies of patients with concomitant asthma and allergic rhinitis have shown symptom improvement with LTRA over placebo of both upper and lower airway symptoms (114) with similar efficacy to nasal corticosteroids (115, 116). While these data suggest that patients with asthma and allergic rhinitis may benefit from treatment with leukotriene modifiers, more evidence is required to determine the exact contribution(s) of anti-leukotriene therapy to each disease manifestation.

Cytokine Modulation

The Th2 cytokines. Asthma pathogenesis is strongly associated with a T-helper cell imbalance favoring the production and activation of Th2 cells; therefore, inhibition of the pro-inflammatory Th2 cytokines has been the subject of much research. The orally administered investigational drug suplatast tosilate inhibits the production of numerous Th2 cytokines (i.e., IL-4, IL-5, and IL-13); clinical efficacy has been observed in asthma patients with disease ranging from mild to severe, including decreased airway responsiveness, decreased eosinophils in blood and sputum, improved lung function, and improved asthma symptom scores (117–119). A recent study in 25 patients with asthma showed that suplatast tosilate administered for 3 months may prevent goblet cell metaplasia and mucous production (as measured by histological staining of bronchial biopsies) (120). Suplatast tosilate has also shown clinical efficacy in upper airway disease; in 1 small study of 12 patients with perennial nasal allergies, suplatast tosilate significantly decreased nasal symptom scores, nasal inflammatory cell infiltration, and Th2 cytokine levels (121). While the mechanism of action is largely unknown, suplatast tosilate was shown to inhibit eosinophilic chemotaxis toward IL-5 and eotaxin in vitro (122). A combinatorial inhibition of eosinophil migration and cytokine release may therefore contribute to the observed clinical efficacy of the drug. Currently available only in Japan, suplatast tosilate shows potential for the future treatment of airway inflammation.

Recent preliminary studies in mouse models of chronic asthma targeting the cytokine IL-13 have also shown promise. An anti-IL-13 mAb lowered airway hyperresponsiveness, eosinophil infiltration, cytokine production, serum IgE levels, and mucus production in mice provoked with ovalbumin

(123, 124). Decreased subepithelial fibrosis and matrix metalloproteinase-9 levels suggest a potential role for anti-IL-13 therapy in airway remodeling (123, 124). In a murine model of allergic rhinitis, intranasal ovalbumin challenge resulted in concomitant upper and lower airway inflammation, which was attenuated with polyclonal anti-IL-13 antibody treatment (125).

The role of IL-9 in allergic inflammation is well established (126). IL-9 expression is increased in the airways of patients with allergic rhinitis and/or asthma after allergen challenge, making it a potential therapeutic target (127, 128). However, studies targeting IL-9 in airway disease have been limited. In a mouse model of asthma, an anti-IL-9 antibody inhibited airway inflammation and methacholine-induced hyperreactivity (129) and reduced bone marrow eosinophilia, mature eosinophils, and blood neutrophils after airway ovalbumin challenge (130). Studies in humans are needed to evaluate the potential efficacy of anti-IL-13 and anti-IL-9 treatment in upper and lower airway disease.

TNF- α . Neutralizing the effects of the pleiotropic pro-inflammatory cytokine TNF- α has been achieved with the use of anti-TNF- α mAbs (infliximab and adalimumab) or TNF- α receptor fusion proteins (etanercept). Infliximab has been particularly effective, showing significant clinical improvement in a variety of inflammatory disorders: Crohn's disease (131), rheumatoid arthritis (RA) (132), ankylosing spondylitis (133), and psoriatic arthritis (134). The use of anti-TNF- α therapies in a variety of chronic inflammatory diseases suggests a potential benefit in patients with inflammatory airway disease. TNF- α is an attractive target for asthma and allergic rhinitis therapy as it is overexpressed in the airways of patients with asthma compared with healthy patients (135) and is released by mast cells in response to allergen challenge and IgE-mediated cross-linking (136, 137). Although there are no published studies in humans, a recent study showed that pre-administration of anti-TNF- α antibodies to dust-challenged mice resulted in significantly fewer bronchiolar lavage fluid inflammatory cells and lung eotaxin (138). Conversely, a recent small study of 26 human (steroid-naïve) patients with mild-to-moderate allergic asthma indicated that although subcutaneously injected etanercept was successfully delivered to the lung, there was no change in airway eosinophil number or response to methacholine challenge; in addition, 1 patient had transient hemiplegia (139). While anti-TNF- α treatment of airway disease may be promising, more research is needed to determine the correct therapy regimen and benefiting patient population.

Other cytokines. IL-16 expression is increased in the inflammatory airways of patients with asthma and allergic rhinitis compared with healthy individuals and is enhanced by allergen challenge (140–143). Compared with healthy individuals, serum IL-16 is increased and significantly correlated with peripheral blood eosinophils in patients with allergic rhinitis (144). In a murine allergic asthma model, intraperitoneal administration of exogenous IL-16 inhibited aerosolized ovalbumin-induced airway hyperresponsiveness and decreased the number of eosinophils in airway tissue and bronchoalveolar lavage fluid (145). Further, T cells isolated from IL-16-treated mice secreted much less IL-5 (<85%)

and IL-4 (<77%) after antigen rechallenge compared with T cells derived from mice not treated with IL-16 (145). Recently, a polymorphism in the promoter region of the IL-16 gene was associated with decreased promoter activity and asthma in family-based association tests of white subjects in England, suggesting that some patients with asthma may have decreased levels of IL-16 (146). Based on these studies, it is reasonable to speculate that allergic patients with IL-16 deficiencies might benefit from exogenous IL-16 administration.

Complement. The complement anaphylatoxins C3 a and C5 a have been implicated in promoting airway disease, modulating airway hyperresponsiveness, inflammation, and Th2 cytokine levels (147–151). Segmental allergen provocation produced increased levels of C3 a and C5 a in patients with asthma compared with healthy individuals (152). Further, expression of the receptors for these are increased in the airway tissue of patients who died from asthma compared with patients who died from non-pulmonary causes or live patients with mild intermittent asthma (153). Specific targeting of anaphylatoxins may show clinical benefit; a recent study showed that inhibiting C3 a and C5 a receptors reduced serum IL-4 levels as well as neutrophil and eosinophil numbers in the bronchoalveolar lavage fluid of allergen-challenged mice (154).

Signal Transduction Pathways

Targeting central signal transduction molecules, such as tyrosine kinases, has shown spectacular efficacy in other models of disease. The Bcr-abl tyrosine kinase inhibitor, imatinib mesylate, has been efficacious in the treatment of chronic myeloid leukemia (155). Imatinib mesylate also inhibits the kinase activity of stem cell factor and platelet-derived growth factor receptor (156), molecules that have been implicated in allergy. One study showed that cockroach allergen-challenged mice treated with imatinib mesylate had decreased airway hyperresponsiveness, bronchial eosinophils, and Th2 cytokines compared with untreated control subjects (157), suggesting that this may be a potential treatment for allergy. Another central tyrosine kinase, Syk, modulates mast cell and basophil activation; in a phase II double-blind randomized study during spring 2004, treatment with an intranasal Syk inhibitor, R112, reduced symptom scores compared with placebo (158).

B-Cell Depletion

In February 2006, the US Food and Drug Administration approved the use of the chimeric mAb rituximab as an alternative treatment in adult patients with moderate-to-severe active rheumatoid arthritis who inadequately responded to anti-TNF therapies. Treatment of rheumatoid arthritis is the second indication for rituximab, following 8 years of approved use in certain patients with non-Hodgkin's lymphoma. Rituximab treatment selectively and transiently depletes peripheral B-cells by targeting the CD20 antigen on the surface of normal and malignant B-cells (159). In a randomized, double-blind controlled study of patients with active rheumatoid arthritis, a single course of rituximab (two infusions, either alone or in combination with methotrexate or cyclophosphamide) significantly improved disease symptoms after 24 and 48 weeks of treatment; rituximab was well tolerated with an expected

safety profile (160). Although the precise role of B-cells in the pathogenesis of rheumatoid arthritis is unknown, the use of rituximab in inflammatory disease demonstrates that targeting of a global immune modulator can have profound clinical efficacy in a variety of inflammatory diseases.

CONCLUSION

The current understanding of IgE-mediated chronic inflammation, expressed clinically in the airways as asthma and allergic rhinitis, goes beyond the 1 airway, 1 disease concept to a truly systemic phenomenon, with pathophysiologic pathways extending through the bloodstream and neuronal circuits. The term 1 airway, 1 disease refers to clinical expressions of one underlying pathologic inflammatory process along the confluent mucosa as well as the reciprocal influences between the upper and lower airways. As a result, triggers in one area may cause symptoms to appear in the other, and the favorable effects of localized treatment in one area may improve symptoms in the other. This reciprocal relationship appears to be mediated through the movement of inflammatory and immune cells throughout the systemic circulation, including the bone marrow and other immune system organs, and via neuronal pathways that traverse the central and peripheral nervous systems. As a result, a therapy such as omalizumab, which clearly affects key pathogenetic mechanisms at the airway mucosa but is distributed systemically, provides beneficial effects in patients whose symptoms are inadequately controlled with ICS, which are delivered only to the mucosal layer of the upper or lower airway.

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