

Advances in upper airway diseases and allergen immunotherapy

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The purpose of this review is to highlight important articles on upper airway diseases and immunotherapy that appeared during 2006. Studies from Europe continue to examine the usefulness of the Allergic Rhinitis and its Impact on Asthma classification of allergic rhinitis as intermittent or persistent and its levels of severity as mild or moderate/severe. A number of physical agents were shown to effect nasal inflammation: sudden temperature changes in patients with allergic rhinitis increased eosinophilic inflammation; in children with allergic asthma, the personal exposure to particles <2.5 μm air pollution correlated with percent of nasal eosinophils and levels of markers of nasal exudation; and in patients who developed rhinorrhea on exposure to cold and windy weather, nasal challenge with cold dry air caused sloughing of nasal epithelial cells. A 3-month double-blind, placebo-controlled study of nasal washes with amphotericin B showed no benefit in patients with chronic rhinosinusitis. Studies of immunotherapy with grass and dog dander extracts confirmed the need for doses containing 15 to 20 μg of the major allergen for optimal effectiveness. The protective effect of immunotherapy on the development of asthma in children with allergic rhinitis was shown to still be present 2 years after completion of a 3-year course of treatment. Injection immunotherapy with a moderate dose of house dust mite extract in house dust-sensitive adults with atopic dermatitis reduced symptoms and use of corticosteroids and antihistamines compared with treatment with about 1/1000 of that dose of the same extract. Pretreatment for 9 weeks with the monoclonal anti-IgE antibody omalizumab reduced systemic reactions during rush immunotherapy 5-fold and allowed further build-up at weekly intervals without systemic reactions. A review of sublingual immunotherapy confirmed both efficacy and safety, but evidence for appropriate dosing and for the effectiveness of sublingual immunotherapy employing multiple allergen mixes was still lacking. Two studies with a sublingual grass pollen extract tablet showed a clear dose response and the ability to

initiate sublingual immunotherapy without an up-dosing phase. A pilot study with cytosine phosphorothionate quanosine DNA conjugated to the major allergen of ragweed reported impressive improvement in symptoms the first pollen season that persisted during the second pollen season without any further administration of the conjugate. In conclusion, studies on rhinitis and sinusitis explored the pathophysiology of the disease more than offering new therapeutic approaches. Studies on immunotherapy addressed optimal dosing, but also a variety of safer and more convenient approaches such as reduction of IgE with omalizumab, conjugating allergen to immunostimulatory DNA sequences, or administration by the sublingual route. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Upper airway diseases, allergen immunotherapy

This article continues a series of annual reviews of articles published in the Journal and elsewhere that deal with upper airway diseases and allergen immunotherapy.¹⁻³

THE UPPER AIRWAY

Key advances in upper airway diseases are listed in Table I.

Rhinitis

The Allergic Rhinitis and its Impact on Asthma (ARIA) recommendations included a proposed new classification for allergic rhinitis. Rather than seasonal or perennial, it was suggested that, similar to asthma, rhinitis be classified as intermittent or persistent, and the severity classified as mild or moderate/severe. A study was conducted with 302 patients consulting general practitioners in France for allergic rhinitis to assess the impairment incurred by patients in the different ARIA categories of allergic rhinitis.⁴ Nearly equal numbers of subjects had intermittent and persistent rhinitis. However, when severity was judged by rhinitis-specific quality of life, quality of sleep, and work performance, it was found that approximately 90% of these patients with allergic rhinitis consulting general practitioners had moderate/severe symptoms that were impairing daily activities, sleep, and work. The ARIA classification was also tested in 804 patients enrolled by Belgian general practitioners during the pollen season.⁵ They confirmed that the classification into intermittent and persistent did not correspond to seasonal and perennial. They also found that 98% of their subjects met the criteria for moderate/severe. They therefore

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Abbreviations used

AAAAI:	American Academy of Allergy, Asthma & Immunology
ACAAI:	American College of Allergy, Asthma and Immunology
AIC:	Amb a 1 conjugated to a oligodeoxyribonucleotide
ARIA:	Allergic Rhinitis and its Impact on Asthma
EP:	E-prostanoid
ISS:	Immunostimulatory sequence of DNA
NGF:	Nerve growth factor
PM _{2.5} :	Particles ≤ 2.5 μm in diameter
SCIT:	Subcutaneous immunotherapy
SLIT:	Sublingual immunotherapy
SQ:	Standardized quality

suggested new criteria for severity classification. Patients would be asked whether their symptoms of allergic rhinitis caused sleep disturbance and whether they caused impairment of daily personal and/or profession life. Patients would be categorized as mild if they answered no to both, moderate if they had 1 affirmative response, and severe if they responded affirmatively to both questions. Using these criteria, the patients were now divided into 20.5% mild, 45.9% moderate, and 33.6% severe. Using these new criteria for severity, the researchers found for all symptoms except rhinorrhea that there was a linear increasing trend from mild to moderate to severe as well as a significant association with increasing prescription rate of nasal and oral glucocorticosteroids.

In a Clinical Pearls article, Dr Richard Lockey⁶ addressed the problem of rhinitis medicamentosa and the stuffy nose. He pointed out that patients often begin using topical decongestants because of pre-existing chronic nasal obstruction. Therefore, the patients should have a detailed work-up to identify the underlying condition. The exception would be those who begin the intranasal decongestant after a respiratory infection and continue it indefinitely because of the self-induced rebound phenomena. Nasal corticosteroids are the most effective treatment for underlying conditions leading to nasal obstruction. In those patients in whom topical steroids are not sufficient to control obstruction, he recommended that judicious use of topical decongestants together with topical corticosteroids may provide the patient with symptomatic relief.

Two reviews of pharmacotherapy for rhinitis were published.^{7,8} The first reviewed the epidemiology and classification of both allergic and nonallergic rhinitis and evidence for the effectiveness of the available treatment, including topical corticosteroids, antihistamines, decongestants, cromolyn, antileukotrienes, ipratropium, omalizumab, and nasal saline irrigation.⁷ The second looked at complementary and alternative medicine.⁸ Although randomized, preferably double-blind trials were sought in reviewing the literature, in reality the methodology of the trials with complementary-alternative medicine was frequently inadequate. Meta-analysis provided no clear evidence for efficacy of acupuncture in rhinitis and

TABLE I. Key advances in upper airway diseases in 2006

1. The published literature on the therapeutic efficacy of complementary-alternative treatments for allergic rhinitis and asthma was reviewed, and this treatment was found not to be supported by concurrently available evidence.⁸
2. Sudden temperature changes in patients with allergic rhinitis can increase eosinophilic inflammation in the nose.¹⁰
3. In children with allergic asthma, the personal exposure to PM_{2.5} air pollution correlated with nasal eosinophils and markers of nasal exudation.¹²
4. In patients who develop rhinorrhea on exposure to cold and windy weather, nasal challenge with cold dry air caused sloughing of nasal epithelial cells.¹¹
5. Studies in mice and human beings suggest an important role for nerve growth factor, dendritic cells, and IL-13 in allergic rhinitis, whereas IL-15 may have a suppressive effect.¹⁴⁻⁷
6. A 3-month double-blind, placebo-controlled study of nasal washes with amphotericin B showed no benefit in patients with chronic rhinosinusitis.²²
7. Improvement of nasal polyps with prednisone treatment was documented in a double-blind, placebo-controlled study.²⁵
8. Nasal polyps responded to a monoclonal anti-IL-5 antibody only in subjects with elevated levels of IL-5 in their nasal secretions.²⁶
9. Decreased EP₂ receptors were found on nasal inflammatory cells in biopsies of aspirin-sensitive compared with nonaspirin-sensitive patients with rhinitis.²⁷

asthma. Although some trials of homeopathy reported positive results in rhinitis, other studies were negative. Therefore, no evidence-based recommendation for homeopathy in the treatment of allergic rhinitis could be provided. There was a limited number of studies of herbal preparations in rhinitis, some of which reported efficacy. Their number was too few to make any recommendations for treatment. Furthermore, there were concerns regarding the standardization and purity of the herbal preparations. The conclusion was that the therapeutic efficacy of complementary-alternative treatments for rhinitis and asthma is not supported by currently available evidence. More conventional treatment for seasonal allergic rhinitis was discussed in an article on the new nasal corticosteroid ciclesonide.⁹ Ciclesonide nasal spray demonstrated a significant improvement in the total nasal symptoms versus placebo by the second day of treatment. Over the first 2 weeks, symptoms declined by 17% in the placebo groups and 27% in the ciclesonide groups.

Nasal response to stimuli

The response of the nasal mucosa to stimulation with sudden temperature changes; cold, dry air; and fine particulate air pollution was reported this year in the Journal.¹⁰⁻¹² The effects of experimental air conditioning-like temperature changes on the nasal mucosa of individuals with persistent allergic rhinitis were examined.¹⁰ Sudden temperature changes in the patients with rhinitis led to a significant increase in symptoms, total cells, percent of eosinophils, and epithelial shedding as well as albumin in nasal secretions compared with baseline. Ten subjects who reported rhinorrhea with cold and windy

weather, 6 of whom had allergic rhinitis, received nasal challenges with cold, dry air and with warm, moist air.¹¹ A 6-fold increase in sloughed nasal epithelial cells followed cold, dry air but not warm, moist air challenge. No similar increase in sloughing of nasal epithelial cells was observed after cold, dry air challenge in subjects not reporting symptoms on exposure to cold or windy weather. It was concluded that the nasal mucosa of individuals sensitive to cold dry air cannot compensate for the water loss that occurs under extreme conditions, leading to epithelial damage. Forty-one children in Paris with asthma and 44 healthy children were monitored for 48 hours for their personal exposure to particles 2.5 μm or less in diameter ($\text{PM}_{2.5}$).¹² At the end of the measurement period, subjects underwent nasal lavage. In the children with asthma but not in the healthy children, personal $\text{PM}_{2.5}$ levels were correlated with nasal percentage eosinophils and with markers of nasal exudation. The study demonstrated the association between exposure to fine particulate air pollution and nasal inflammation in children with allergic asthma in an urban area.

Mechanisms of rhinitis

The role of the nervous system in rhinitis was reviewed.¹³ Sensory nerves transmit signals from the mucosa, generating sensations such as pruritus, motor reflexes such as sneezing, and parasympathetic and sympathetic reflexes that affect the glandular and vascular nasal apparatuses. Reflexes affecting nasal symptoms also arise from other body regions, and reflexes arising in the nose can affect the lower airway. Nasal hyperresponsiveness can arise as a result of inflammatory products such as neurotrophins, among which is the nerve growth factor. Nasal tissue samples from patients undergoing partial turbinectomy for nasal obstruction were examined for nerve growth factor (NGF) and nerve growth factor receptors.¹⁴ NGF was localized to activated eosinophils and submucosal glands and less to epithelial lining. NGF receptors were localized not only on nerves but also on nasal epithelium, submucosal glands, and some interstitial cells. It was concluded that the distribution of NGF and its receptors and its established release during allergic reactions suggest that this factor participates in the pathophysiology of allergic rhinitis.

The role of dendritic cells in allergic rhinitis was examined in both human beings and mice.¹⁵ In nasal mucosal biopsies from symptomatic patients with perennial rhinitis, the number of dendritic cells in the epithelium and lamina propria was increased compared with healthy controls. Furthermore, they were found in proximity to T lymphocytes. Similarly, in a mouse model of allergic rhinitis, dendritic cells were found clustered with CD4^+ lymphocytes. When the dendritic cells were depleted, nasal challenge in the sensitized mice did not induce nasal eosinophilia, boost specific IgE levels, or increase $\text{T}_\text{H}2$ -type cytokine production. However, when allergen-pulsed dendritic cells were administered intranasally to sensitized mice, nasal eosinophilia and $\text{T}_\text{H}2$ cytokine production were enhanced. The authors concluded

that dendritic cells in the nose play an essential role in the activation of $\text{T}_\text{H}2$ lymphocytes, leading to allergic rhinitis.

A similar model of murine allergic rhinitis was used to explore the possible role of IL-15 in the allergic response.¹⁶ IL-15 knockout mice responded to nasal allergen challenge with increased sneezing, infiltration of eosinophils, and $\text{T}_\text{H}2$ cytokine production compared with controls. Adoptive transfer of CD8^+ T cells from sensitized mice to control mice suppressed the $\text{T}_\text{H}2$ responses but was ineffective in IL-15 knockout mice. However, the administration of IL-15 at the time of nasal allergen challenge prevented the development of allergic rhinitis in sensitized mice. It was concluded that IL-15 plays an important role in suppression of allergic rhinitis, probably through activation of memory CD8^+ T cells that downregulate the $\text{T}_\text{H}2$ response to allergen.

The contribution of IL-13 to the early and late nasal response to allergen challenge in sensitized mice was explored by using IL-13 knockout mice and a fusion protein of the IL-13 receptor and the Fc portion of human IgG, which binds to and neutralizes IL-13.¹⁷ The early response to nasal allergen challenge was little affected. On the other hand, the late response, measured by nasal obstruction at 24 hours postchallenge, was markedly reduced. The reduction in the late nasal response did not appear to be dependent on reduction in the infiltration with eosinophils. The results suggested to the authors that blockage of IL-13 may have therapeutic application to reduce nasal obstruction in allergic rhinitis.

Consequences of allergic rhinitis

Because of epidemiologic data showing a frequent association between allergic rhinitis and asthma, the relationship between allergic rhinitis and pathologic changes in the lower airway was reviewed.¹⁸ Two groups of patients with only rhinitis symptoms, one seasonal and the other perennial, underwent spirometry and methacholine challenge. Asymptomatic lower airway abnormalities were found in both groups. In the 100 patients with perennial rhinitis, 5 had an abnormal FEV_1 , 25 an abnormal FEF_{25-75} , and 72 a positive methacholine challenge. Two studies were performed in patients with both allergic rhinitis and asthma. A highly significant correlation was observed between nasal eosinophils ($r = .91$) and nasal airflow ($r = .89$) on the one hand and the FEV_1 as a percent predicted. On the basis of their review, the authors recommend that patients with allergic rhinitis should be evaluated to detect possible bronchial involvement.

A well-recognized consequence of the allergic reaction in the nose, induced by both allergen challenge and natural exposure, is the phenomenon of nasal priming. After allergen exposure, there is a lowering of the nasal threshold to subsequent allergen exposure that is not allergen-specific. This phenomenon was carefully investigated and described by Dr John Connell.^{19,20} His work and subsequent studies of nasal priming are discussed in the Allergy Archives in the November 2006 issue of the Journal.

A most unusual consequence of allergic rhinitis was described in a 33-year-old man hospitalized for sudden hearing loss; the only associated problem was seasonal allergic rhinitis. The hearing problem cleared rapidly on systemic steroids but recurred during the same spring pollen season the next 10 years. At the time he was symptomatic, magnetic resonance imaging revealed an inflammatory edema of the acoustic nerves bilaterally. The symptoms did not occur the following season when rhinitis symptoms were controlled with nasal steroids and an antihistamine.

Sinusitis

The debate over the role of antifungal therapy for chronic rhinosinusitis that was reported in last year's *Advances*³ continues. A study from The Netherlands reported the results of 3 months of treatment of chronic rhinosinusitis with twice-daily amphotericin B or placebo nasal washes in 116 randomly assigned patients.²² Ninety-nine subjects completed the study. There were no differences either before or after 13 weeks of treatment between the 2 groups for nasal symptoms, quality of life, peak nasal inspiratory flow values, nasal endoscopy scores, or polyp scores. Radiologic assessment of the sinuses was not performed. The authors concluded that amphotericin B nasal lavages, as administered in this study, are ineffective and therefore not advised in the treatment of patients with chronic rhinosinusitis.

In 2004 a distinguished panel consisting predominantly of allergist/immunologists and otorhinolaryngologists developed a report entitled, "Rhinosinusitis: Establishing definitions for clinical research and patient care," that appeared in the *Journal*.²³ In the *Journal* this year, a follow-up panel report appeared entitled, "Rhinosinusitis: Developing guidance for clinical trials."²⁴ The new report provides templates for clinical trials with antimicrobial, anti-inflammatory, and symptom-relieving medication for the following conditions: (1) acute presumed bacterial rhinosinusitis, (2) chronic rhinosinusitis without nasal polyps, (3) chronic rhinosinusitis with nasal polyps, and (4) classic allergic fungal rhinosinusitis. There are also appendices on (1) health outcomes, (2) nasal endoscopy and staging of chronic rhinosinusitis, (3) radiologic imaging, (4) microbiology, (5) laboratory measures, and (6) biostatistical methods. The stated purpose of the report is to promote better clinical research and improved patient care for individuals with rhinosinusitis.

Nasal polyps

Systemic corticosteroids are often used to treat nasal polyposis, but placebo-controlled studies of this treatment have been lacking. Forty patients with symptomatic nasal polyposis were randomized to either prednisone 50 mg per day or placebo for 14 days.²⁵ The rhinosinusitis outcome measure improved by 21% with placebo and 53% with prednisone. Mean magnetic resonance imaging scores did not change with placebo but were reduced 45% with prednisone, whereas visualized polyp size did not improve with placebo and decreased 48% with prednisone. Sixty-

three percent of the prednisone-treated patients had at least a 40% reduction in polyp size. Side effects were those anticipated with prednisone, but the only significant difference was insomnia in 8 subjects on prednisone versus 2 on placebo.

A trial of a mAb to IL-5 (reslizumab) was conducted in 24 patients with massive nasal polyposis.²⁶ Twenty-four patients received a single dose of placebo or 1 or 3 mg/kg of reslizumab and were followed for safety and pharmacokinetics for 36 weeks. The study was not powered to detect significant differences in clinical outcomes, however; only 1 patient on placebo had improvement in nasal polyp score, compared with 5 on the low dose and 4 on the high dose of reslizumab. Post hoc analysis comparing 8 responders and 8 nonresponders revealed the former had significantly higher levels of IL-5 in their nasal secretions at baseline. By logistic regression analysis, increased nasal IL-5 levels in nasal secretions predicted the response to anti-IL-5 treatment with an odds ratio of 21 and a *P* value of .009.

Aspirin-exacerbated airway disease is thought to be associated with impaired braking of cysteinyl leukotriene production by prostaglandin E₂. Because prostaglandin E₂ acts via a series of E-prostanoid (EP) receptors, the expression of these receptors was compared in nasal biopsies from aspirin-sensitive, nonaspirin-sensitive, and healthy subjects.²⁷ Although mucosal expression of EP₁ and EP₂ was increased in both groups of patients with asthma, the percentages of neutrophils, mast cells, eosinophils, and T cells expressing EP₂ were significantly reduced in the aspirin-sensitive compared with nonaspirin-sensitive patients. The authors concluded that the reduced expression of EP₂ on inflammatory leukocytes in aspirin-sensitive patients with rhinosinusitis may be partly responsible for the increased inflammatory infiltrate and increased production of cysteinyl leukotrienes that characterize these patients.

Ocular diseases

Patients with a variety of ocular diseases and some normal individuals complain of symptoms of itching, tearing, burning, and photophobia after exposure to stimuli such as wind, smoke, light, and cold or warm air or water. This nonspecific hyperactivity of the conjunctiva was evaluated in a group of normal subjects and subjects with allergic conjunctivitis who were in remission using a graded challenge with glucose solutions of increasing concentrations.²⁸ Six of 50 healthy subjects and 12 of 19 subjects with allergy gave a history of ocular discomfort triggered by nonspecific stimuli. The response to the hyperosmolar provocation was compared in those with a positive and negative history for ocular hypersensitivity. A positive erythematous response to a 40% glucose solution showed the highest sensitivity (89%) and specificity (86%) for identifying those subjects with conjunctival hyperactivity. The authors suggest this test may be clinically useful to identify conjunctival hyperactivity in subjects with a history of ocular discomfort.

SKIN TESTING AND ALLERGEN IMMUNOTHERAPY

Key advances in skin testing and allergen immunotherapy are listed in Table II.

Skin testing

The skin testing practice patterns of allergists in the United States were assessed by a questionnaire posted on the Web site of the American College of Allergy, Asthma and Immunology (ACAAI).²⁹ Of the 539 who responded, 92% were board-certified in allergy/immunology. At least some intradermal skin tests were used by 85.2% to diagnose the presence of allergy in their patients. The average number of skin prick tests used was 43.5, and the average number of intradermals was 18.1. For reporting the results of skin tests, 53.8% used a grading system of 0 through 4+, whereas 28.3% measured the orthogonal diameters of the reaction. The devices used for skin prick testing were as follows: Multitest (Lincoln Diagnostics, Decatur, Ill), 25.5%; DermaPik (Biomedix, Spokane, Wash) (by prick method), 20.5%; Duotip (Lincoln Diagnostics) (by prick method), 12.2%; Quintest (Hollister-Steir, Spokane, Wash), 11.8%; DermaPik (by twist method), 7.2%; smallpox needle (Hollister-Steir), 4.1%; and Duotip (by twisting), 2.7%. Thus, there are major differences in the manner of skin testing and its reporting even among certified allergists.

Immunotherapy

Subcutaneous immunotherapy. Two studies examined the dose response with subcutaneous immunotherapy (SCIT), one with grass pollen extract and the other with dog dander extract. In the United Kingdom, 410 subjects with seasonal allergic rhinitis caused by grass pollen, whose symptoms in previous years had been inadequately controlled by symptomatic therapy, were recruited for a study of preseasonal immunotherapy with an alum precipitated grass pollen extract.³⁰ Up-dosing was achieved with 15 injections during 8 visits by a cluster schedule. Half the subjects received a maintenance dose containing 20 µg of the major allergen of timothy, Phl p 5; one quarter received a maintenance dose containing 2 µg Phl p 5; and one quarter received placebo. Compared with placebo, the reduction in symptom and medication scores for the whole pollen season were 29% ($P=.0001$) and 32% ($P=.0007$) for the high-dose group and 22% ($P=.013$) and 16% (NS) for the low-dose group. Clinically relevant changes of 0.5 or greater compared with placebo in the rhinitis quality of life score were observed in 5 of 7 domains with the high-dose group compared with 1 of 7 domains in the low-dose group. Systemic reactions were more common with the high-dose group. Four were considered severe, but none were considered life-threatening. The conclusion from this first year of treatment was that both doses produced clinical improvement, greater with the high dose, but at the expense of increased reactions to treatment.

TABLE II. Key advances in immunotherapy in 2006

1. In patients with grass pollen-allergic rhinitis, a maintenance dose containing 20 µg of the major allergen of timothy, Phl p 5, was effective, whereas a maintenance dose containing only 2 µg Phl p 5 was less effective, although it also caused fewer systemic reactions.³⁰
2. The immunologic responses to 3 doses of dog dander extract were examined. The most consistent responses were produced with a maintenance dose containing 15 µg Can f 1, the major allergen of dog. The dose containing 3 µg was less effective, and that containing 0.6 µg produced results generally similar to placebo.³¹
3. In a previously reported study, 3 years of immunotherapy had decreased the number of children with allergic rhinitis who developed asthma. Now, 2 years after discontinuing immunotherapy, the protective effect of immunotherapy was shown to still be present.³³
4. Injection immunotherapy with a moderate dose of house dust mite extract in adults with atopic dermatitis and sensitivity to mites reduced symptoms and use of corticosteroids and antihistamines compared with treatment with about 1/1000 that dose of the same extract.³⁵
5. Pretreatment for 9 weeks with the monoclonal anti-IgE antibody, omalizumab, reduced systemic reactions during rush immunotherapy 5-fold.³⁷
6. An ACAAI/AAAAI joint task force reviewed 103 articles on SLIT. There was evidence for both efficacy and safety, but evidence for appropriate dosing and for effectiveness with multiple allergen mixes was lacking. Additional problems were the absence of a US product approved for sublingual administration and lack of a billing code.³⁸
7. Studies with a sublingual grass pollen extract tablet show a clear dose response and the ability to initiate sublingual immunotherapy without an up-dosing phase.⁴⁰
8. A pilot study with cytosine phosphorothionate quanosine DNA conjugated to the major allergen of ragweed reported impressive improvement in symptoms the first pollen season that persisted through the second pollen season without any further administration of the conjugate.⁴⁹

The second SCIT study examined the dose response to dog dander extract by using an acetone-precipitated extract that contained 161 µg/mL of the major allergen of dog, Can f 1.³¹ Twenty-eight subjects with dog allergy were recruited. Maintenance doses were achieved in 8 visits over 4 weeks by using a cluster schedule. The maintenance doses of dog extract contained 0.6 µg, 3.0 µg, or 15 µg Can f 1 or a matching placebo. Outcomes were measured before institution of SCIT and after the first weekly maintenance injection at 5 weeks. There was dose-dependent suppression of the titrated immediate skin prick test reaction as well as the late cutaneous response measured at 6 hours and an increase in dog-specific IgG₄, all greatest and consistently significant only in the high-dose group. Assay of cytokines secreted by stimulated PBMCs revealed dose-dependent suppression of TNF-α and increase in TGF-β, with suppression of IL-4 in the high-dose group. The conclusion was that the greatest and most consistent immunologic response to immunotherapy with dog dander extract was achieved with a dose containing 15 µg Can f 1.

Another study from the United Kingdom reported the results of immunotherapy with grass pollen extract in children with asthma requiring treatment with inhaled corticosteroids during the grass pollen season only.³² Maintenance doses containing 20 µg Phl p 5 were achieved with an 8-visit cluster regimen and continued through 2 grass pollen seasons in 35 children. There was a significant reduction of 50% in the mean symptom score and a similar but not significant reduction in use of inhaled corticosteroids during the second pollen season.

A five-year follow-up on the Preventative Allergy Treatment study was reported.³³ This study enrolled children allergic to either timothy or birch pollen and treated them with immunotherapy for 3 years. Outcomes were compared with an observational control group. Children without asthma symptoms the first season were followed for the development of asthma. At the end of treatment, significantly less asthma had developed in those receiving active treatment.³⁴ This article reports the status of 183 of the children seen in follow-up 2 years after the discontinuation of immunotherapy. The significant improvement in hay fever and conjunctival provocation test results observed after 3 years persisted at the 5-year follow-up. Those children who received immunotherapy had an odds risk of 2.68 to be less likely to have manifest asthma symptoms within the last year, a result virtually identical to that observed at the time immunotherapy was discontinued.

The use of immunotherapy in the treatment of atopic dermatitis was explored in a study from Germany.³⁵ Eighty-nine adults with chronic atopic dermatitis and high levels of IgE for house dust mite were treated with an alum-precipitated house dust mite extract. One group received a homeopathic dose of 20 standardized quality (SQ) units, one a medium dose of 2000 SQ units, and one a relatively high dose of 20,000 SQ units (although this is still only 1/5 the customary maintenance dose for treatment of inhalant allergy). The results were evaluated by a dermatologist blind to treatment allocation. Symptom scores were reduced by 10% in the low-dose, 16.9% in the medium-dose, and 19% in the high-dose group. The reduction in the high-dose group was significantly greater than in the low-dose group. There was also significantly less use of topical steroids and antihistamines in the 2 higher-dose groups compared with the lowest. This study supports previous observational reports of benefit of immunotherapy in selected patients with atopic dermatitis.

Safety is always a concern with SCIT. As part of a survey of fatal reactions to allergen immunotherapy during the period 1990 to 2001, physicians were also queried regarding near-fatal reactions characterized by respiratory compromise, hypotension, or both.³⁶ Initially 273 of 646 respondents reported knowledge of 1 or more near-fatal reactions, suggesting a rate of 5.4 per million injections. Asthma was present in 46% of the near fatal reactions, compared with 88% of those that were fatal. Also, administration of epinephrine was absent or delayed in only 6% of the near-fatal reactions, compared with 30% of those that were fatal. Where details were provided, 25% of near-fatal reactions were associated with dosing errors.

Rush immunotherapy is frequently used with venom treatment, but its use for inhalant allergen sensitivity is limited by the high incidence of systemic reactions. A study was conducted to determine to what extent pretreatment with the mAb to IgE, omalizumab, would reduce the occurrence of these reactions.³⁷ One hundred fifty-nine subjects with seasonal allergic rhinitis caused by ragweed pollen were randomized to received pretreatment for 9 weeks with either omalizumab or placebo, followed by a 1-day placebo-controlled rush administration of ragweed extract to a dose of 1.2 µg of the major allergen Amb a 1. They then continued on omalizumab or placebo while the dose of ragweed was increased at weekly clinic visits to 12 µg Amb a 1. Systemic reactions during the day of rush immunotherapy were reduced 5-fold by the preadministration of omalizumab. During the subsequent weekly build-up, there were no anaphylactic reactions in subjects receiving immunotherapy plus omalizumab compared with 9.7% of subjects receiving immunotherapy plus placebo. This proof-of-concept study confirmed the hypothesis that reduction of free IgE would improve the safety of rush and high-dose immunotherapy.

Sublingual immunotherapy. A joint American Academy of Allergy, Asthma & Immunology (AAAAI)/ACAAI task force reviewed the available literature on sublingual immunotherapy (SLIT) and reported their findings in the May issue of the Journal.³⁸ Among the 103 articles that the task force reviewed, 47 were selected for analysis of efficacy because they were either double-blind or randomized but open trials. The doses used, expressed as the monthly cumulative dose by SLIT compared with that used by the same investigators for SCIT, ranged from 0.5 to greater than 500. Despite this wide range in doses, there was not clear differentiation in outcome when studies using <5 times the SCIT dose were compared with those using 5 to 50 times or >50 times the SCIT dose. This lack of clear indication of a dose response was one of the major findings of the review. Overall, most SLIT studies reported improvement, but about 35% of the randomized studies did not demonstrate any improvement in either symptoms or medication use in the first year of treatment. Additional findings were that most of the immunologic changes that have been reported with SCIT have also been reported with SLIT, although perhaps not as consistently. The overall safety of SLIT was confirmed. Although oral side effects are common, and some serious adverse events have been reported including worsening asthma and gastrointestinal complaints, no reports of life-threatening or fatal reactions were found. The review concluded that many questions remain to be answered regarding dosing and schedules. Additional barriers to the use of SLIT at this time in the United States are the lack of extracts approved for sublingual use and consequently the lack of a current procedural terminology code for SLIT.

The question of dose response in SLIT has been addressed by 2 articles. The first examined the proposition that the absorptive capacity of the sublingual area is limited and that better results might be obtained by

frequent dosing.³⁹ The researchers recruited 64 subjects with seasonal allergic rhinoconjunctivitis to grass or birch pollen and assigned them to treatment with placebo, or with very low doses of pollen extract that were to be administered once, twice, or 3 times daily the first year, then 3 times daily in all 3 groups the second year. The cumulative dose administered even in the 3 times daily schedule was less than the customary monthly dose by SCIT. After the first year of treatment, there was significant reduction in the immediate skin reaction only in the 3 times daily group and reduction in medication use in the 2 times and 3 times daily groups. After the second year, when all 3 groups had been administering SLIT 3 times daily, all 3 groups had similar suppression of immediate skin tests and antihistamine use. The authors felt their study confirmed the greater importance of frequency over dosage, although a higher dose was not actually compared in their study.

The first large dose-response study of SLIT was conducted with grass pollen extract tablets.⁴⁰ Patients with grass pollen-allergic rhinitis were randomized to receive sublingual tablets that were placebo or contained 2500, 25,000, or 75,000 SQ units of timothy grass (the latter equal to 15 μ g of the major timothy allergen Phl p 5). No up-dosing was performed. When those subjects who, per protocol, had received at least 8 weeks of treatment before the season were compared, there was no difference between the placebo and the 2 lower doses, but the highest-dose group had significant reductions in symptoms (21%) and medication use (29%). The effective dose, 75,000 SQ units, was then employed in a projected 5-year study in 634 subjects with grass pollen-induced rhinoconjunctivitis, with treatment the first year to commence at least 16 weeks before the season.⁴¹ The first season results have been reported. Symptoms were reduced 30% and medication use 38%. There were no serious side effects, despite no build-up phase; however, oral pruritus was reported by 46% of actively treated subjects versus 4% of placebo-treated; edema of the mouth was reported by 18% and 1%, respectively; and ear pruritus and throat irritation were also more common in the active treatment groups.

An attempt was made to assess patient compliance with SLIT.⁴² Treatment was dispensed in packs of 90 single-unit doses. Patients throughout Italy were contacted by unscheduled telephone calls during the 3rd and 6th months of treatment. They were asked to count the number of remaining unit doses. A total of 443 adults and adolescents were contacted. Compliance greater than 90% was reported by about 75% of patients and compliance greater than 75% by about 88% of patients. There was no difference in the rate of compliance between the third and sixth months. Thus compliance appeared to be satisfactory despite the fact that the treatment is self-administered at home.

Modified extracts

Modification of allergen extracts to reduce allergenicity and perhaps enhance immunogenicity continues. Two

studies from Spain reported successful results with glutaraldehyde polymerized extracts.^{43,44} A single season's treatment with *Salsola kali* (Russian thistle) pollen extract initiated by a cluster schedule resulted in improvement in symptoms and quality of life compared with placebo.⁴³ Administration for 1 year of a mixed *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* extract to patients with allergic asthma also significantly reduced symptoms, improved quality of life, and improved the bronchial response to inhaled mite allergen.⁴⁴

A group of healthy volunteers were immunized with Der p 1 coupled to a bacteriophage-derived protein QB,⁴⁵ a combination that has previously been shown to elicit a strong B-cell response in mice. A single injection produced high and prolonged titers of IgM, IgG₁, and IgG₃ against Der p 1. The IgG₄ response was, however, negligible. Mice were immunized with a plasmid vector expressing a ubiquitinated version of the major allergen of birch, Bet v 1, resulting in decreased expression of the conformationally intact antigen.⁴⁶ Immunization resulted in no antibody, but a strong T_H1 response, resulting in suppression of IgE, reduction of eosinophils in bronchoalveolar lavage fluid, and alleviation of lung pathology in sensitized animals. In another approach, DNA sequences encoding Phl p 5, the major allergen of timothy, were expressed in a replicon vector encoding an alphaviral replicase and a strong promoter to initiate transcription.⁴⁷ The replicon DNA vaccines differ from conventional DNA vaccines by greatly enhanced immunogenicity and short-term expression of the plasmid resulting from apoptotic death of transfected cells. In this study in mice, the replicon DNA vaccine suppressed IgE, reduced bronchoalveolar fluid eosinophilia, and lung pathology at a 100-fold lower dose compared with the conventional DNA vaccine.

Immunostimulatory DNA sequences containing cytosine phosphorothionate quanosine motifs are recognized by Toll-like receptor 9 and stimulate the production of T_H1-type cytokines such as IL-12 and IFNs from a variety of cells. They can drive T_H1 responses to allergens, and this effect is enhanced by direct linkage of immunostimulatory sequence of DNA (ISS) to the protein. A study was conducted to investigate how the number of ISS linked to Amb a 1 protein affects the Amb a 1-specific immunogenicity in mice and in PBMCs from subjects with ragweed allergy.⁴⁸ IgE recognition of Amb a 1 showed an inverse relation to the number of ISS molecules linked to the Amb a 1. ISS number did not affect the T-cell response in mice, but the higher the number of ISS molecules, the lower the antibody response. Thus varying the number of ISS bound to an allergen can reduce IgE recognition without affecting T_H1-inducing properties.

The results of a trial of the ISS-Amb a 1 conjugate, Amb a 1 conjugated to an oligodeoxyribonucleotide (AIC), in 25 subjects with ragweed seasonal allergic rhinitis was published in the *New England Journal of Medicine*.⁴⁹ Patients received 6 escalating doses of the AIC to a maximum of 12 μ g Amb a 1. During the first ragweed season, the mean peak season rhinitis score was 13.2 in the treated

vs 40.8 in the placebo group ($P=.006$). Seventeen of the subjects were followed through a second ragweed season without receiving any further immunotherapy. Again, the group who had received active treatment had markedly reduced symptom scores during the peak ragweed season (13.9 vs 49.4 for the placebo; $P=.02$). Local reactions to injections of AIC were common, but no systemic reactions occurred.

CONCLUSION

Studies of the upper airway focused on pathophysiology with little new in the way of therapeutics. Studies of immunotherapy confirmed the importance of high-dose therapy for optimum results. New advances included evidence of effectiveness of injection immunotherapy in atopic dermatitis in house dust mite-sensitive adults; the use of omalizumab to reduce IgE levels, making rush immunotherapy safer; large-scale dose response studies with SLIT; and favorable results with injections of the major allergen of ragweed linked to ISSs.

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