

Developing and novel therapies in the treatment of allergic diseases

Berrylin J. Ferguson, MD

The treatment of allergic rhinitis includes avoidance of triggers, immunotherapy, and pharmacotherapy. Today, the drugs available for patients offer greater control of symptoms and fewer side effects than ever before. Current medications include sedating and nonsedating antihistamines, decongestants, nasal steroid sprays, anticholinergic nasal sprays, and cromolyn sprays. Despite the advances made, control of allergic rhinitis for many patients is still incomplete. This article will discuss emerging therapies directed at prevention, redirection of currently available medications, alterations in allergen immunotherapy, and novel medications, which have been developed based on our understanding of the molecular basis of allergy and which hold promise for future therapies. *Curr Opin Otolaryngol Head Neck Surg* 2002, 10:217–221

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Associate Professor of Otolaryngology–Head and Neck Surgery, Chief of the Division of Sino-nasal Disorders and Allergy, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA.

Correspondence to Berrylin J. Ferguson, MD, University of Pittsburgh Medical Center, Suite 500; 200 Lothrop Street, Pittsburgh, PA 15213, USA; e-mail: bjferg@pitt.edu

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Abbreviations

IgE immunoglobulin E
IL interleukin
Th T helper

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Allergic rhinitis and asthma are increasing in the industrialized world. Epidemiological studies indicate that early infection or high allergen exposures in early childhood may actually help prevent the development of allergy [1]. Prevention of the development of this disorder by increasing exposure to harmless bacteria or to animal allergens early in life is reviewed [2•,3].

Medications initially designed for conditions of the lower airway, such as bronchial hyperreactivity, are also effective in the hyperreactive upper airway (such as allergic rhinitis). The most promising unapproved medications for disorders of the upper airway are the leukotriene modulators [4•]. Other potentially effective applications of existent drugs or interventions include heparin [5], alternative medications [6], hot inspired air, and foot warming [7].

Immunotherapy is the only therapeutic modality that has the ability to make a long-term change in the allergic diathesis in an antigen specific manner. Current immunotherapy can cause fatal anaphylaxis, local reactions, and may take many months to achieve a symptom-relieving dose. Future methodologies for improved immunotherapy may involve modified allergens, including peptides of allergens, sublingual swallow delivery, pro Th1 (T helper 1) cytokine combinations with antigens, and adjuvants such as immunostimulatory DNA sequences [8•].

The development of new therapeutic agents for allergic rhinitis increasingly rests on advances in our understanding of the molecular mechanisms of atopy. Those agents most studied but not yet available include mediator antagonists, cytokine modulators, and a humanized monoclonal antibody to immunoglobulin E (IgE) (Table 1) [9•,10].

Prevention

Preliminary studies indicate that exposure to harmless bacteria *in utero* and infancy may be protective. A probiotic refers to the prophylactic exposure to beneficial bacteria. In the most promising study to date regarding the prevention of an atopic diathesis, pregnant women with a strong family history of atopy, were administered the probiotic *Lactobacillus rhamnosus* 2 to 4 weeks before delivery, followed by continued administration to the infants for 6 months. This resulted in only 23% of treated infants developing atopic eczema compared with 46% in

Table 1.

Prevention in utero and early infancy	Disease state
Probiotics	Atopic dermatitis
? High mammal antigen exposure	Allergic rhinitis, asthma
Application of currently nonapproved but available therapies	Seasonal allergic rhinitis
Leukotriene receptor antagonists, alone or in combination with an antihistamine	Unstudied
TNF- α antibodies (infliximab); TNF- α receptor (entercept)	Allergic rhinitis
Heparin (inhaled)	Atopic dermatitis
Traditional Chinese medicine	Allergic rhinitis
Hot humidify air (inhaled)	Allergic rhinitis
Foot warming	
Immunotherapy	Bee venom desensitization
Antihistamine concurrently	Unproven, late phase side effects and some immediate hypersensitivity
Long peptide antigen	Difficulty in commercial production of uniform lots
Modification of allergen (urea, glutaraldehyde, formaldehyde, polyethylene glycol)	
Sublingual swallow	High dosages required
Fusion of allergen to cytokines (<i>ie</i> , IL-12)	Animal studies only
Immunostimulatory sequences (<i>ie</i> , CpG)	Human trials underway
Novel medications	
Anti-IgE monoclonal antibody (omalizumab)	Asthma, seasonal allergic rhinitis
IL-4 receptor (altrakinecept)	Asthma
Anti-IL-5 antibody	Ineffective in one asthma study, although promising
Bradykinin B2-receptor antagonist (icatibant)	Late phase of seasonal allergic rhinitis
Interferon- α 2a [Roferon-A (Roche Laboratories, Nutley, NJ)]	Prevention of recurrent nasal polyposis

TNF, tumor necrosis factor; IL, interleukin; IgE, immunoglobulin E.

the control group at age 24 months. There were no adverse side effects from ingestion of these harmless bacteria [2••].

Although it appears clear that early exposure to dust mite antigen is sensitizing, early exposure to farm animals or high levels of cat allergen may actually prevent the development of allergy [3,11,12]. These observations are from epidemiological studies. There are no interventional studies regarding the effect of high animal allergen exposure in the first year of life on the development of allergies.

Application of currently available modalities to allergic rhinitis

Although double-blind studies have indicated the usefulness of leukotriene receptor antagonists in seasonal allergic rhinitis (SAR), approval by the FDA for this indication is still probably one or two years away. Nevertheless these agents may be useful in some patients in ameliorating the symptoms of rhinorrhea and nasal congestion [13].

The combination of montelukast with the nonsedating antihistamine loratadine was significantly more effective than placebo in relieving SAR symptoms. There was a trend toward using the combination rather than using either drug alone. This combination is appealing because nonsedating antihistamines, while effective for sneezing and itching, have minimal efficacy for congestion or rhinorrhea, which are symptoms effectively targeted by the leukotriene receptor antagonists [14]. Nasal steroid sprays currently offer the most comprehensive relief of nasal allergy symptoms. In one small, placebo-controlled

study in patients with SAR, a nasal steroid spray, mometasone furoate, was no more effective than the combination of a leukotriene receptor antagonist, montelukast, with an antihistamine, cetirizine. Both treatments were significantly more effective than placebo, by both objective and subjective measures. Although results tended to favor the nasal steroid spray, there was no statistically significant difference between the two treatment groups [4•].

Tumor necrosis factor α (TNF- α) is increased in asthmatic airways. TNF- α monoclonal antibodies (infliximab) and TNF receptors (etanercept) are already available for the management of rheumatoid arthritis. Their efficacy in allergic rhinitis and asthma has not been studied [9•]. Both agents have been associated with increased susceptibility to infections, including tuberculosis and invasive fungal disease [15].

Heparin has been known almost exclusively for its anticoagulant activity, but it also possesses antiinflammatory properties. Among otolaryngic allergists it is also used in the treatment of anaphylaxis in patients on β -blockers. Heparin can modulate T-lymphocyte activities, inhibit neutrophil chemotaxis, and regulate complement activation. Inhaled heparin prevents exercise-induced asthma. Proposed mechanisms include inhibition of mast cell functions, binding of platelet activating factor, and neutralizing damaging cationic proteins, such as eosinophil cationic protein and major basic protein, because heparin is highly anionic. In a small double-blind, placebo-controlled, randomized, crossover trial of patients with allergic rhinitis, intranasal heparin significantly reduced eosinophil recruitment and nasal symptoms in allergen-challenged patients [5].

Alternative medical therapies are increasingly popular and do not require FDA approval if they are marketed as dietary supplements without claims for efficacy of a disease state. Standardized herbs used in traditional Chinese medicine (TCM) have shown efficacy in controlled and blinded trials in atopic dermatitis. The underlying mechanism is unknown, although TCM does downregulate the expression of the low affinity IgE receptor, CD23, on the surface of antigen-presenting cells *in vivo* in atopic dermatitis. Efficacy of TCM in allergic rhinitis can be postulated as an extension of efficacy in atopic dermatitis [6].

Nasal inhalation of hot, humid air reduces the early allergic response. Warming of the feet by immersing them in warm water (42°C) results in increased nasal mucosal temperature and a statistically significant reduction in the early response to nasal challenge with antigen. The mechanism is unknown but postulated to be secondary to a temperature-dependent reduction in nasal secretion osmolality [7]. Although probably harmless, the requirement to warm one's feet to prevent an allergic attack is a cumbersome therapy for most sufferers on a warm summer day, but potentially more appealing in the cold weather for the mold or dust mite allergen sufferer.

Immunotherapy

Local and systemic side effects from allergy shots are reduced in patients premedicated with antihistamines. This has been demonstrated in venoms, grass, and tree pollen immunotherapy. T cells have histamine receptors. Expression of these receptors may be altered during immunotherapy. A retrospective analysis of the long-term protective effect of immunotherapy with bee venom showed that pretreatment with an antihistamine (terfenadine), was not detrimental to the efficacy of immunotherapy and actually enhanced the efficacy [16•].

Studies with mice have shown that administration of long peptides of an allergen (bee venom) results in tolerance to the antigen with a reduction of specific IgE, if given prophylactically (before the development of sensitization), as well as a switch toward a Th1 profile in mice, if given therapeutically to presensitized mice [17]. Peptides stimulate only T cells via binding of the specific T-cell receptor. The immunoglobulins of B cells are able to recognize complex protein binding but do not usually recognize a straight sequence of protein, such as a peptide. Peptide immunotherapy holds promise in potentially inducing tolerance without the risk of inducing anaphylaxis or other serious reactions. To date, this theoretic advantage has not been proven in a large clinical trial. In addition, anti-peptide IgE develops in some subjects and is occasionally associated with increased immediate reactions. There have also been unexpected late phase side effects [8•,18,19].

Other approaches to reduce IgE reactivity and yet retain immunogenicity with capability of inducing interferon- γ (IFN- γ) production in T-cells are to modify the allergen with urea, formaldehyde, glutaraldehyde, or polyethylene glycol. Significant difficulty in producing uniform lots of these modified proteins despite some studies indicating efficacy has reduced commercial interest in this idea [8•].

Sublingual swallow immunotherapy is effective in reducing symptoms of allergic rhinitis and asthma and may have less risk of anaphylaxis and bronchospasm. The underlying mechanism is poorly understood. High doses of allergen are required to overcome digestion in the gastrointestinal tract [20,21].

The fusion of a cytokine that enhances a Th1 biased immune response with an allergen shows promise in animal studies involving linkage of antigen with interleukin-12 (IL-12). IL-12 induces potent IFN- γ production and enhances Th1-biased immune responses [22]. This fusion strategy may overcome the significant morbidity and mortality of administration of IL-12 alone [8•,23].

Unmethylated CpG dinucleotides in a particular pattern are characteristic of bacterial DNA. Several types of human immune cells possess pattern recognition receptors for these CpG motifs. These CpG motifs, also referred to as immunostimulatory DNA sequences (ISS), can activate both innate and acquired immune responses (which have evolved to protect against intracellular infections). This immune response is toward a Th1 immune response, rather than the proallergy, Th2 response. In an animal model, ISS given once were as effective as daily corticosteroids for 7 days in reducing eosinophilia. Evidence toward a Th1 response was demonstrated by induction of IFN- γ and inhibition of IL-5 generation. In addition, activation of B cells, dendritic cells, macrophages, and natural killer (intake) cells occurs [24]. Conjugates of ISS covalently linked to allergen are 100-fold more efficient in reducing airway eosinophilia and hyperreactivity than unconjugated mixtures [25]. This form of immunization may some day offer the promise of switching patients from a Th2 allergic bias, to a Th1 nonallergic bias. Human clinical trials using CpG are underway [26].

Novel medications

Omalizumab, a recombinant humanized anti-IgE monoclonal antibody, binds with IgE at the same site as the high-affinity IgE receptor (Fc ϵ RI-binding site), forming IgE-anti-IgE complexes. Its safety and efficacy has been studied in asthma and seasonal allergic rhinitis [10,27•, 28]. It is able to bind to the constant portion of the IgE molecule designed to fit into the Fc receptor of IgE on various cells, such as mast cells, eosinophils, and basophils. This binding is independent of specific antigen

recognition of the IgE molecule by the Fab portion. Therefore, cross-linking of IgE molecules on IgE-sensitized cells is averted. Omalizumab does not bind to other immunoglobulin classes or to already cell-bound IgE. The effective dose of omalizumab must be equal to or higher than 0.5mg/kg for most patients, and most trials to date have excluded patients with IgEs higher than 700 IU/mL. The efficacy of omalizumab is proportional to the IgE of the patient. A clear dose-response relation has been demonstrated for omalizumab and seasonal allergic rhinitis symptom scores [28]. No problems have been encountered with the re-administration of omalizumab [29].

IL-4 is critical in development of allergic inflammation. It is associated with isotype switching to IgE production, upregulation of the high-affinity IgE receptor on mast cells, and induction of expression of vascular cell adhesion molecule 1 (VCAM-1, which promotes eosinophil transmigration). It stimulates mucus production and drives differentiation of naive Th0 lymphocytes into a Th2 phenotype, which in turn can secrete IL-4, as well as IL-5, IL-9 and IL-13. Although humanized IL-4 antibodies are currently in development, the approach most developed to date is the use of soluble interleukin-4 receptor (altrakinecept) to inhibit active IL-4. Borish *et al.* showed that nebulized soluble IL-4 receptors (IL-4R) when given as a once weekly nebulization to patients with moderate asthma were effective clinically and objectively in preventing the deterioration in asthma after reduction in inhaled corticosteroids [30]. The most common adverse events in the IL-4R group was headache (13%) and nausea (13%) compared with a placebo rate of 6% and 0% [9,30].

IL-5 is one of the most important cytokines in the production, maturation, activation, and survival of eosinophils and in eosinophil chemoattraction. Most cases of nasal polyposis and refractory chronic rhinosinusitis are characterized histologically with eosinophilia. Eosinophilia is common to asthma and allergic rhinitis. Results of the humanized anti-IL-5 antibody in patients with asthma have been disappointing. Although circulating eosinophils and airway eosinophils were markedly reduced, a study by Leckie *et al.* demonstrated no effect on early or late responses to allergen or significant reduction in airway hyperreactivity [31]. However, O'Brien *et al.* point out that the methodological limitations of the Leckie *et al.* study invalidate their conclusions regarding the inefficacy of an anti-IL-5 antibody in allergen-induced asthma [32]. Better designed studies will be required to answer the question of whether an anti-IL-5 is effective in asthma and allergic rhinitis.

Kinin mediated release of IL-8 results in eosinophilia. Icatibant, a bradykinin B2 receptor antagonist, may block this. While it has no impact on the acute allergic response, it does reduce the late-phase reaction and anti-

gen-based hyperresponsiveness and associated eosinophilia in adults with seasonal allergic rhinitis [33].

The cause of nasal polyps is multifactorial; although approximately 50% of cases of nasal polyps are associated with perennial allergens, particularly dust mites and molds, and 81% with positive intradermal food tests [34,35,36]. Control of recurring nasal polyposis can be difficult. Systemic low-dose INF- α 2a has been shown in a small series to prevent recurrence. Some patients experienced flu like symptoms during the first few days of INF- α 2a [Roferon-A (Roche Laboratories, Nutley, NJ)], but no other side effects were noted [37]. INF- α down-regulates IL-5 synthesis *in vitro* in human CD4-positive cells. IL-5 is important in the recruitment of eosinophils in nasal polyposis. This is an exciting preliminary report in treating patients with refractory nasal polyposis, a condition for which we have no effective and safe interventions. Further study is required, but INF- α 2a may well have a more benign long-term side effect profile than oral corticosteroids.

Conclusions

In summary, inhaled IL-4 R antagonists have some clinical benefit in asthma. Additional studies are required to determine if anti IL-5 antibody will be clinically useful. INF- γ inhibits eosinophilia, but in studies to date it has not been effective in asthma. IL-12 may have efficacy when combined with antigens; however, it also has significant morbidity if used alone. While inhibition of Th2 and upregulation of Th1 cytokines may relieve symptoms of allergy and asthma, such therapies may increase the risk of nematode infection or predispose to Th1-dominated inflammatory disorders, such as type-1 diabetes, multiple sclerosis, Crohn disease, rheumatoid arthritis, and sarcoidosis [38].

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