Review Articles

Advances in Immunology

IAN R. MACKAY, M.D., AND FRED S. ROSEN, M.D.,
Editors

ALLERGY AND ALLERGIC DISEASES

Second of Two Parts

A.B. KAY, M.D., PH.D.

ALLERGIC DISEASES AND THEIR TREATMENT

Allergic Rhinitis

Allergic rhinitis is characterized by episodes of sneezing, itching, rhinorrhea, and nasal obstruction. Perennial allergic rhinitis should be distinguished from nonallergic, noninfectious forms of rhinitis, such as idiopathic ("vasomotor") rhinitis, nonallergic rhinitis with eosinophilia syndrome, hormonal rhinitis, drug-induced rhinitis, and food-induced rhinitis.

The treatment of allergic rhinitis (and other allergic diseases) consists of allergen avoidance (whenever possible and practical), antiallergic medication, and immunotherapy for specific allergens, which is also called hyposensitization or desensitization. Currently, the drugs usually used to treat allergic rhinitis are antihistamines and anticholinergic agents (for the relief of symptoms) and topical corticosteroids (to suppress allergic inflammation). Histamine H_1-receptor antagonists such as loratadine, cetirizine, and fexofenadine are less sedating and more pharmacologically selective than earlier antihistamines. Some H_1-receptor antagonists such as cetirizine reportedly also inhibit allergen-induced infiltration of tissue by eosinophils, an effect that may be independent of their effects on H_1 receptors.[63]

Specific immunotherapy, which has been used for the treatment of allergic disease for nearly 100 years, consists of administering increasing concentrations of extracts of allergen over a long period. In patients with seasonal allergic rhinitis and, to a lesser extent, in those with perennial rhinitis, specific immunotherapy is extremely effective and long lasting, especially when treatment is continued for several years.[64] Unfortunately, all patients who receive conventional specific immunotherapy are at risk for general, and potentially fatal, anaphylaxis, particularly during the induction, or "up-dosing," phase. Attempts to minimize the risk of systemic reactions have included pretreatment of allergen extracts with agents such as formaldehyde (resulting in the formation of so-called allergoids). However, although this approach decreases binding of the allergen by IgE, it also reduces immunogenicity.

The mode of action of specific immunotherapy is complex. IgG "blocking" antibodies compete with IgE for allergen. They may also prevent the aggregation of complexes of IgE and the α chain of the high-affinity IgE receptor (FcϵRI-α) on mast cells by altering the steric conformation. In addition, they may interfere with antigen trapping by IgE bound to antigen-presenting cells.[65] Several studies have shown that specific immunotherapy inhibits the release of pharmacologic mediators from mast cells and basophils, prevents infiltration of allergic lesions by inflammatory cells,[66] and decreases the number of mast cells in tissue.[67]

Central to these effects is the influence of specific immunotherapy on T cells. Specific immunotherapy induces a shift from the production of Th2-type cytokines (interleukin-4 and interleukin-5) to the production of Th1-type cytokines (interferon-γ and interleukin-12).[65,68] These changes may explain the marked inhibition of the late-phase reaction induced by immunotherapy. After several months or years of treatment, the intensity of the early, immediate, wheal-and-flare reaction is also reduced and total serum IgE levels are decreased.[65]

For immunotherapy with bee venom to be successful, the activation of cells that secrete interleukin-10 appears to be critical,[69] but the role of this cytokine in immunotherapy for aeroallergens has yet to be established. Interleukin-10 has a wide range of inhibitory effects on allergic reactions. It induces long-term hyporesponsiveness of allergen-specific CD4+ T cells, decreases the number of mast cells, and inhibits the production of eosinophils.[69,70] Proposed mechanisms responsible for the beneficial effects of specific immunotherapy are summarized in Figure 4.

Asthma

Asthma (which will be the subject of an upcoming article in this series) comprises episodes of wheezy breathlessness due to airway narrowing, which is partially or totally reversible. Airway hyperresponsiveness is almost invariably an accompanying feature. Causes of asthma depend on the interplay between genetic factors, the environment, and several specific and nonspecific triggers (Fig. 2). Nevertheless, most patients

From the Imperial College School of Medicine, National Heart and Lung Institute, London.

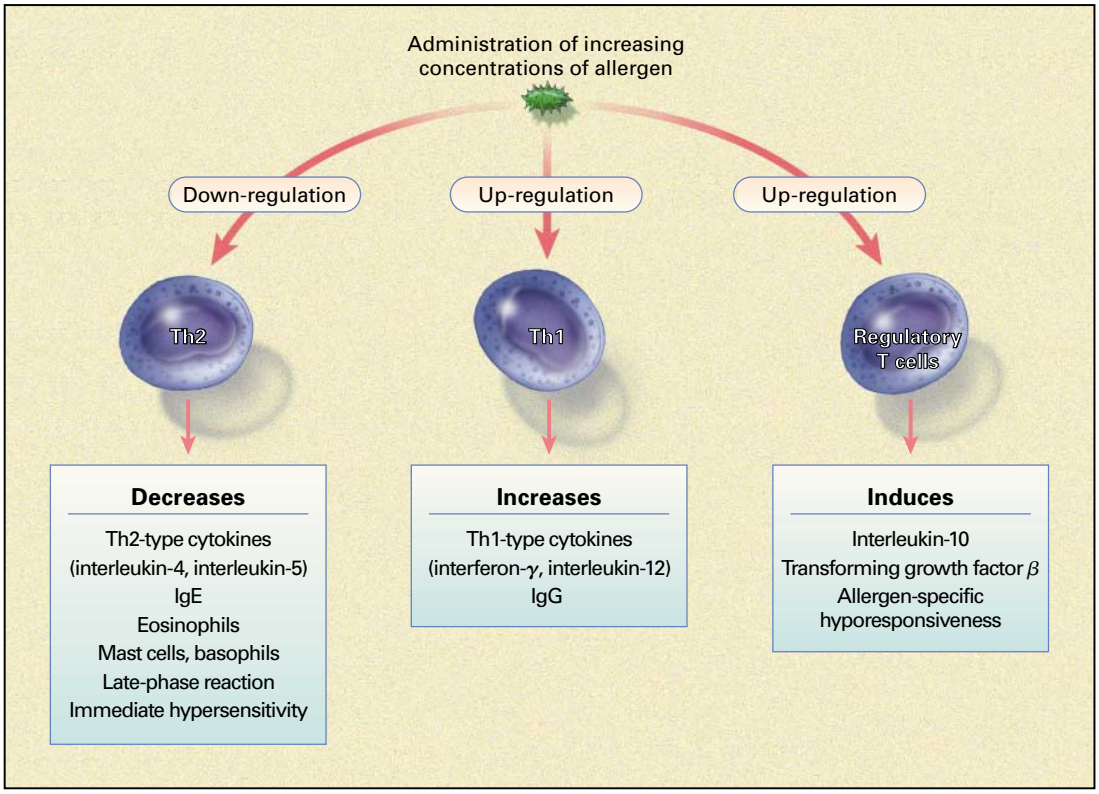

Figure 4. Proposed Mechanisms of Specific Immunotherapy (Hyposensitization or Desensitization).
Specific immunotherapy is associated with down-regulation of the cytokines produced by Th2 cells, up-regulation of cytokines produced by Th1 cells, and the induction of regulatory T cells. These changes in turn lead to the inhibition of allergic inflammation, increases in cytokines that control the production of IgE (interferon-γ and interleukin-12), the production of "blocking" antibodies (IgG), and the release of cytokines involved in allergen-specific hyporesponsiveness (interleukin-10 and transforming growth factor β).

with asthma are atopic, although a minority have intrinsic, nonatopic asthma that often has a later onset and a more protracted course than atopic asthma. Recent studies indicate that there are more similarities than differences in the airway abnormalities of atopic and nonatopic asthma.[71] Both variants are characterized by tissue infiltration by eosinophils and activated T cells and increased production of interleukin-4, interleukin-5, interleukin-13, and CC chemokines. In both types, there are also similar numbers of bronchial mucosal cells that contain messenger RNA for the ε germ-line transcript (Iε) and ε heavy chain of IgE (Cε).[71] This suggests that intrinsic asthma may be associated with local production of IgE antibodies against unknown antigens and that immunologic triggers have a role in both nonatopic and atopic asthma.

Anaphylaxis

Anaphylaxis is a severe, systemic allergic reaction caused by the systemic release of histamine and other pharmacologic mediators. It comprises a constellation of symptoms, of which the most serious are laryngeal edema, lower-airway obstruction, and hypotension. The common causes of anaphylaxis are IgE-mediated sensitivity to foods (e.g., peanuts, nuts, fish, shellfish, and dairy products), bee and wasp stings, drugs, and latex. Treatment of anaphylaxis involves prompt administration of epinephrine, repeated if necessary, since epinephrine reverses the actions of histamine within minutes. This treatment can be followed by an H_1-receptor–antagonist and corticosteroids. Preloaded epinephrine syringes are available for self-administration.

Specific immunotherapy with venom is highly effective in patients with hypersensitivity to bee and wasp venom. At present, specific immunotherapy has no place in the treatment of food-induced anaphylaxis, since severe reactions have been reported during treatment and there is no evidence of efficacy. However, food allergens can be modified to reduce their allergenicity, indicating that such strategies may have therapeutic potential. For example, 10 IgE-binding

epitopes have been identified in the main peanut allergen Ara h 2. Analyses of the epitopes indicated that changes in a single residue resulted in the reduction of IgE binding by the allergen and reduced reactivity on skin-prick tests in patients who were allergic to peanuts.[72]

A different approach to immunotherapy, so far tested only in mice, is oral immunization with a plasmid vector containing DNA that encodes Ara h 2. To protect it from digestion, the DNA was bound to the polysaccharide chitosan.[73] This experimental immunization reduced the incidence of allergen-induced anaphylaxis, decreased the production of allergen-specific IgE, and induced the production of protective, secretory IgA and IgG2a.

Atopic Eczema

Atopic eczema affects 10 to 20 percent of children in Western populations. It is characterized by an itchy red rash, consisting of tiny papules, sometimes with an urticarial component, which may form confluent red sheets. Acute exacerbations of eczema may be weepy and crusted, usually signifying superinfection with staphylococci. Chronic excoriated lesions are often thickened and lichenified. Total serum IgE levels may be markedly elevated, and high levels of IgE antibodies against aeroallergens and food allergens are common. After cutaneous challenge with allergen, there is an initial local production of interleukin-4 and interleukin-5 (Th2-mediated response), followed by a mixed pattern of response, involving interferon-γ, interleukin-4, and interleukin-5.[74]

Avoidance of allergens, with the possible exception of certain foods in children[75] (particularly eggs, peanuts, and milk) and the house-dust mite in adults,[76] is usually not effective in treating this condition. The mainstay of therapy is topical corticosteroids and, when necessary, antibiotics for bacterial superinfection. Superantigens derived from *Staphylococcus aureus* may cause polyclonal T-cell proliferation. Treatment with low doses of cyclosporine can be highly beneficial. This suggests a role for T cells in atopic eczema. Recently, topical tacrolimus, whose mode of action is similar to that of cyclosporine, has also been shown to be useful in the treatment of severe eczema and reduces the need for systemic immunosuppressants.[77]

Urticaria and Angioedema

Urticaria (widespread, itchy wheals or hives) and angioedema (deep mucocutaneous swelling) often occur together. Acute urticaria is associated with sensitivity to foods, certain drugs, and latex. It is often IgE-mediated, and the treatment is allergen avoidance. Chronic urticaria includes the physical urticarias and urticarial vasculitis; allergic causes of chronic urticaria are rarely identified. Some cases of chronic urticaria have been associated with circulating IgG autoantibodies against FcϵRI-α[78] and autoantibodies against IgE.[79] Uncharacterized, low-molecular-weight histamine-releasing factors that are not immunoglobulins have also been identified in patients with urticaria. A cause-and-effect relation between levels of autoantibodies, histamine-releasing factors, and the clinical manifestations of chronic urticaria has yet to be established. However, severe cases often respond dramatically to plasmapheresis, suggesting that autoantibodies or circulating histamine-releasing factors do have a role.[80] Hereditary angioedema is a rare autosomal dominant disorder caused by the absence of the inhibitor of the first component of complement.

NEW APPROACHES TO THE TREATMENT OF ALLERGIC DISEASES

Unlike antiallergic drugs, allergen-specific immunotherapy attenuates symptoms for several years after it is discontinued.[64] However, the potential adverse effects of this treatment, particularly anaphylaxis, and the relatively crude allergen extracts involved limit its usefulness. To overcome these problems, newer approaches have been assessed in animals or are undergoing clinical evaluation. Naturally occurring isoforms of allergens from plants and trees have been shown to have a reduced capacity to be bound by IgE as a result of the substitution or deletion of amino acids.[81] The use of these hypoallergenic isoforms in immunotherapy may minimize the risk of anaphylaxis. The use of recombinant allergens should circumvent the problem of standardization of crude extracts by allowing production and purification of many of the major allergens in ways that eliminate variation between batches.[82]

Immunotherapy involving T-cell–peptide epitopes entails the administration of short, synthetic, allergen-derived peptides that induce T-cell anergy or tolerance but, because of their short length, are unable to cross-link IgE and induce anaphylaxis. Early clinical trials in patients with allergy to cat dander showed that treatment with T-cell peptides afforded limited protection against allergic symptoms induced by exposure to cats.[83] The use of mixtures of allergen-derived peptides selected on the basis of their ability to bind to common major-histocompatibility-complex class II molecules may have greater efficacy, since they will be recognized by T cells of most persons within a population.[48,84]

DNA vaccines also hold promise in the treatment of allergic diseases. Approaches include the administration of CpG motifs such as GACGTC, which induce strong Th1-mediated responses, either alone or in combination with allergen proteins.[85] Plasmid vectors containing genes that encode allergens have been injected into animals, either before or after allergen challenge, and can markedly decrease Th2-mediated responses, enhance Th1-mediated responses, and suppress the allergic response. Virus-like particles, such as

the yeast-derived Ty, can also induce interferon-γ–producing CD8+ T cells, rather than a Th2-mediated response, in a vector expressing a Der p 1 peptide.[86]

Other therapeutic approaches under evaluation include strategies to block IgE or its synthesis and to interrupt the Th2-dependent allergic cascade. For example, treatment with a recombinant humanized monoclonal antibody against IgE (rhuMAB-E25, or omalizumab) virtually eliminated IgE and markedly decreased the expression of FcϵRI on basophils.[87] Although rhuMAB-E25 neutralized IgE in blood and inhibited the production of IgE by B cells, it did not activate mast cells, basophils, or monocytes (i.e., it was not anaphylactogenic). The agent reduced symptoms of allergic rhinitis[88] and corticosteroid requirements in patients with chronic asthma.[89] It also inhibited the allergen-induced early-phase and late-phase asthmatic reactions.[90]

Several ways of inhibiting interleukin-4 are currently under investigation. Treatment with soluble recombinant interleukin-4 receptor moderately improved severe atopic asthma in a placebo-controlled trial.[91] Other approaches for inhibiting the interleukin-4 receptor include the administration of antibodies against the receptor and mutant interleukin-4 proteins.[92] Transcription factors involved in interleukin-4 signaling, such as STAT-6 and c-maf, are also attractive molecular therapeutic targets. Agents that interfere with the function of FcϵRI, such as peptides that block interactions between IgE and FcϵRI-α or inhibitors of Syk (required for intracellular signaling through FcϵRI-α), are also worth investigating.

In theory, chronic allergic inflammation should be controlled by targeting interleukin-5. In monkeys with ascaris-induced asthma, a monoclonal antibody against interleukin-5 almost completely eliminated eosinophilia and airway hyperresponsiveness.[93] A recent study in patients with mild asthma showed that a high-affinity humanized IgG1 monoclonal antibody against interleukin-5 abolished eosinophils in blood and reduced the number of eosinophils in sputum but, surprisingly, had no apparent effect on the allergen-induced late-phase asthmatic reaction or nonspecific airway hyperresponsiveness.[94] Long-term studies, in which eosinophils are eliminated in tissue, will be required to establish conclusively the role of eosinophils and interleukin-5 in chronic atopic allergic disease and asthma. Other strategies for reducing the number of eosinophils include inhibition of $\alpha_4\beta_1$ integrin (also referred to as very late antigen 4, or VLA-4) or CCR3, the receptor on eosinophils that binds eotaxin and other chemotactic CC chemokines that attract eosinophils.[95]

I am indebted to Drs. Mark Larché, Douglas Robinson, Paul Cullinan, William Oldfield, and William Cookson for reviewing the manuscript.

REFERENCES

63. Slater JW, Zechnich AD, Haxby DG. Second-generation antihistamines: a comparative review. Drugs 1999;57:31-47.
64. Durham SR, Walker SM, Varga E-M, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341:468-75.
65. Durham SR, Till SJ. Immunologic changes associated with allergen immunotherapy. J Allergy Clin Immunol 1998;102:157-64.
66. Creticos PS, Adkinson NF Jr, Kagey-Sobotka A, et al. Nasal challenge with ragweed pollen in hay fever patients: effect of immunotherapy. J Clin Invest 1985;76:2247-53. [Erratum, J Clin Invest 1986;78:1421.]
67. Durham SR, Varney VA, Gaga M, et al. Grass pollen immunotherapy decreases the number of mast cells in the skin. Clin Exp Allergy 1999;29:1490-6.
68. Varney VA, Hamid QA, Gaga M, et al. Influence of grass pollen immunotherapy on cellular infiltration and cytokine mRNA expression during allergen-induced late-phase cutaneous responses. J Clin Invest 1993;92:644-51.
69. Akdis CA, Blesken T, Akdis M, Wüthrich B, Blaser K. Role of interleukin 10 in specific immunotherapy. J Clin Invest 1998;102:98-106.
70. Borish L. IL-10: evolving concepts. J Allergy Clin Immunol 1998;101:293-7.
71. Humbert M, Menz G, Ying S, et al. The immunopathology of extrinsic (atopic) and intrinsic (non-atopic) asthma: more similarities than differences. Immunol Today 1999;20:528-33.
72. Stanley JS, King N, Burks AW, et al. Identification and mutational analysis of the immunodominant IgE binding epitopes of the major peanut allergen Ara h 2. Arch Biochem Biophys 1997;342:244-53.
73. Roy K, Mao HQ, Huang SK, Leong KW. Oral gene delivery with chitosan — DNA nanoparticles generate immunologic protection in a murine model of peanut allergy. Nat Med 1999;5:387-91.
74. Grewe M, Bruijnzeel-Koomen CA, Schopf E, et al. A role for Th1 and Th2 cells in the immunopathogenesis of atopic dermatitis. Immunol Today 1998;19:359-61.
75. Sampson HA. The immunopathogenic role of food hypersensitivity in atopic dermatitis. Acta Derm Venereol Suppl (Stockh) 1992;176:34-7.
76. Tan BB, Weald D, Strickland I, Friedmann PS. Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. Lancet 1996;347:15-8.
77. Lipper GM, Arndt KA, Dover JS. Recent therapeutic advances in dermatology. JAMA 2000;283:175-7.
78. Hide M, Francis DM, Grattan CEH, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med 1993;328:1599-604.
79. Sabroe RA, Seed PT, Francis DM, Barr RM, Black AK, Greaves MW. Chronic idiopathic urticaria: comparison of the clinical features of patients with and without anti-FcϵRI or anti-IgE autoantibodies. J Am Acad Dermatol 1999;40:443-50.
80. Grattan CEH, Francis DM, Slater NGP, Barlow RJ, Greaves MW. Plasmapheresis for severe, unremitting, chronic urticaria. Lancet 1992;339:1078-80.
81. Ferreira F, Hirtenlehner K, Jilek A, et al. Dissection of immunoglobulin E and T lymphocyte reactivity of isoforms of the major birch pollen allergen Bet v 1: potential use of hypoallergenic isoforms for immunotherapy. J Exp Med 1996;183:599-609.
82. Breiteneder H, Ferreira F, Hoffmann-Sommergruber K, et al. Four recombinant isoforms of Cor a I, the major allergen of hazel pollen, show different IgE-binding properties. Eur J Biochem 1993;212:355-62.
83. Norman PS, Ohman JL Jr, Long AA, et al. Treatment of cat allergy with T-cell reactive peptides. Am J Respir Crit Care Med 1996;154:1623-8.
84. Texier C, Pouvelle S, Busson M, et al. HLA-DR restricted peptide candidates for bee venom immunotherapy. J Immunol 2000;164:3177-84.
85. Tighe H, Corr M, Roman M, Raz E. Gene vaccination: plasmid DNA is more than just a blueprint. Immunol Today 1998;19:89-97.
86. Allsopp CE, Plebanski M, Gilbert S, et al. Comparison of numerous delivery systems for the induction of cytotoxic T lymphocytes by immunization. Eur J Immunol 1996;26:1951-9.
87. MacGlashan DW Jr, Bochner BS, Adelman DC, et al. Down-regulation of FcϵRI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. J Immunol 1997;158:1438-45.
88. Casale TB, Bernstein IL, Busse WW, et al. Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. J Allergy Clin Immunol 1997;100:110-21.
89. Milgrom H, Fick RB Jr, Su JQ, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. N Engl J Med 1999;341:1966-73.
90. Fahy JV, Fleming HE, Wong HH, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen in-

halation in asthmatic subjects. Am J Respir Crit Care Med 1997;155:1828-34.
91. Borish LC, Nelson HS, Lanz MJ, et al. Interleukin-4 receptor in moderate atopic asthma: a phase I/II randomized, placebo-controlled trial. Am J Respir Crit Care Med 1999;160:1816-23.
92. Ryan JJ. Interleukin-4 and its receptor: essential mediators of the allergic response. J Allergy Clin Immunol 1997;99:1-5.
93. Mauser PJ, Pitman AM, Fernandez X, et al. Effects of an antibody to interleukin-5 in a monkey model of asthma. Am J Respir Crit Care Med 1995;152:467-72.
94. Leckie MJ, ten Brinke A, Khan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. Lancet (in press).
95. Heath H, Qin S, Rao P, et al. Chemokine receptor usage by human eosinophils: the importance of CCR3 demonstrated using an antagonistic monoclonal antibody. J Clin Invest 1997;99:178-84.