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What will allergen immunotherapy look like in the future?

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Allergen immunotherapy just celebrated its 100th anniversary. During the past century, at least in the United States, there were relatively few changes in how it was practiced. Granted, the indication was extended from rhinitis to include asthma and Hymenoptera sensitivity, and the allergens treated were extended beyond the pollens to house dust mites, animal danders, and fungi, but the administration by subcutaneous injection, the gradual buildup in dose, and the prolonged course of treatment persisted. Double-blind, placebo-controlled trials established the efficacy of immunotherapy for rhinitis, asthma, and Hymenoptera sensitivity. Studies led to an appreciation of the profound response to immunotherapy that results in a redirection of the allergen-specific immune response toward that seen in nonallergic individuals. These immunologic changes are paralleled by modification of the disease process, such as preventing new sensitization in monosensitized individuals, preventing the progression from rhinitis to asthma, and providing persisting benefit for years after discontinuation of treatment. The wealth of positive findings has raised immunotherapy to a level well above symptomatic treatment, which relieves symptoms but is not disease modifying and has no persisting benefit after discontinuation.

Despite the unique position of immunotherapy in the treatment of allergic diseases, only a relatively small percentage of suitable individuals receive this treatment. The principal reasons for this low number are inconvenience, concern about safety, dislike of repeated injections, and cost. For immunotherapy to gain wider acceptance, these concerns must be addressed.

What are the prospects for improved immunotherapy? There are certainly many being considered. They may be thought of in 2 strategies: those approaches that use the currently available extracts, sometimes by a different route of administration, and those that involve changes in the extracts to reduce their potential for reactivity with IgE, making them safer and allowing administration by more accelerated schedules. Finally, there are approaches that use our increasing knowledge of the innate immune system to

direct the immune response to the allergen away from the allergic, or T_H2 , phenotype.

Increased Safety and Efficacy With Currently Available Extracts

Table 1 details the safety and efficacy of currently available extracts. Adsorption of the proteins in the allergen extract to an insoluble material, such as aluminum hydroxide, creates a depot effect. Because systemic reactions occur only after allergens are absorbed from the injection site into the general circulation, the slow elution from the aluminum greatly decreases the likelihood of a systemic reaction. There is one commercially available line of pollen extracts in the United States that is aluminum absorbed. It is unlikely that any additional depot extracts will be introduced in the United States because of the extensive studies that would be required to obtain US Food and Drug Administration approval.

Reducing the levels of circulating allergen specific IgE by administration of an anti-IgE monoclonal antibody is another approach to reduce systemic reactions with currently available extracts. This approach has been shown to reduce systemic reactions during rush treatment of allergic rhinitis¹ and cluster treatment of allergic asthma.² Although effective, use of this approach is limited by the cost of the monoclonal antibody.

Administering the allergen extracts sublingually is an approach already dominant in a number of European countries and under investigation in the United States. Currently, use of sublingual immunotherapy (SLIT) in the United States is limited by lack of extracts approved for this route of administration. However, studies are currently under way with both liquid preparations and tablets, and approval of one or more preparations appears likely within the next couple of years. There are several considerations that may hinder the widespread acceptance of SLIT in the United States: (1) only standardized extracts will be studied; therefore, the approved extracts will be limited to grass, ragweed, cat, and house dust mite allergens; (2) the tablets will only offer monotherapy, although a strategy for taking several tablets together may be developed; (3) the only study that addressed administering a mixture of multiple allergen extracts by SLIT suggested that there may be impaired response compared with that achieved with monotherapy³; and (4) it is not clear whether the therapeutic response achieved with SLIT is equal to that observed with subcutaneous immunotherapy

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Table 1
Increased safety and/or efficacy with currently available extracts

Delayed absorption
Aluminum
Tyrosine
Encapsulation (liposomes)
Reduced levels of IgE
Omalizumab
Alternative routes of administration
Sublingual
Epicutaneous
Intralymphatic

Table 2
Increased safety and/or efficacy with modified allergens

Chemical treatment
Allergoids
Recombinant technology
Unmodified major allergens
Site-directed mutagenesis and deletion
Peptides
Fusion proteins
Stimulation of innate immunity
CpG-DNA
Monophosphoryl lipid A

(SCIT).⁴ Another emerging problem with SLIT is the documentation of very low adherence during a 3-year course of treatment.⁵

Two novel approaches to immunotherapy that have attracted attention are epicutaneous and intralymphatic. Studies with epicutaneous administration have demonstrated that a good clinical response can be obtained that persists through the next pollen season without further treatment.^{6,7} An attractive feature is the home application of the patches. There are, however, many details that will require study: (1) the optimal dose, (2) the optimal number of patch applications and the duration they should be left on, and (3) the best adjuvant for enhancing penetration of the allergen through the skin. Both local and mild systemic reactions have been reported, so determination of optimal methods for this approach is critical.⁷

Injection of the allergen extract directly into an inguinal lymph node is perhaps the most interesting of the new routes. Three injections at monthly intervals produced a clinical response that still persisted after 3 years and equaled that achieved with 3 years of high-dose SCIT.⁸ The advantages are (1) the need for only 3 injections, (2) very little discomfort, (3) a need for only a very small amount of allergen extract, (4) consistency with treating with multiple allergen extracts, and (5) no requirement for an expensive development program because the current allergen extracts are approved for injection.

Enhanced Safety and Efficacy With Modified Allergens

Table 2 details the safety and efficacy of modified allergens. Exposure of allergenic proteins to glutaraldehyde results in mild denaturation and cross-linking that alters the conformational IgE epitopes and reduces the allergenicity of the extract. However, there is evidence that the treatment may also reduce the ability of the extract to induce T-cell activation.⁹ Despite this reservation, allergoids are widely used in Europe and are a component of one of the new immunotherapy products being studied in the United States.¹⁰

Recombinant technology offers great promise for developing new and improved products for immunotherapy. The simplest approach is to identify the major allergens of the extracts and then insert the encoding DNA for these proteins into an expression vector. Immunotherapy with the single major allergen of birch (Bet v 1) and with a mixture of major allergens of grass has been clinically successful. Although this approach ensures a reproducible extract, it offers no advantage over the native extract in terms of safety or efficacy.¹¹

With the same technology, mutations or deletions can be introduced into the encoding DNA, creating molecules that no longer express the IgE epitopes but retain the T-cell epitopes. Studies that use this approach have to date been limited in number and somewhat disappointing in results.¹²

Because the IgE epitopes are, for the most part, conformational, that is, exposed on the surface of the 3-dimensional molecule, whereas the T-cell epitopes are composed of relatively short amino acid sequences, a logical application of recombinant technology is

to create short peptides containing only the T-cell epitopes. When first attempted, this approach showed some promise.¹³ A second-generation of peptides have overcome many of the shortcomings of the earlier attempt, particularly addressing HLA-DR binding and shortening the peptides to prevent stimulation of specific IgE.¹⁴ Peptides for cat, grass, house dust mite, and ragweed are under development, and initial results appear favorable.¹⁵

Another approach using recombinant technology is to create fusion proteins that consist of an allergen covalently bound to an immunoglobulin-derived molecule that can activate inhibitory receptors.¹⁶ Although this concept is intriguing, clinical studies have not yet been reported.

Stimulation of the Innate Immune System

The Toll-like receptors (TLRs) of the innate immune system recognize molecular patterns common to bacteria and viruses and when stimulated release a number of interferons and interleukins that favor a T_H1 response. One approach has been to synthesize a DNA segment with an unmethylated CpG configuration common to bacteria and virus. This configuration binds to TLR-9. Studies were conducted with short CpG segments (called immunostimulatory sequences) covalently bound to the major allergen of short ragweed (Amb a 1). The initial studies in a small group of patients at Johns Hopkins were promising, with an appreciable reduction in symptoms in the first pollen season that persisted through a second pollen season without further treatment.¹⁷ Subsequent studies in larger numbers of patients produced smaller but significant improvement. However, the product is not being actively pursued at this time.

This CpG is known as type B and is stable to destruction by DNases. Type A CpG, on the other hand, is susceptible. To protect it after introduction into the body, it was incorporated into a nonreplicating, viruslike particle derived from a bacteriophage.¹⁸ When 6 weekly injections were given to patients who were also receiving injections of house dust mite extract, those patients receiving the higher dose of CpG had significantly improved symptom medication scores, Mini Rhinoconjunctivitis Quality of Life Questionnaire scores, and tolerance of conjunctival challenge with house dust mite extract.¹⁸ Flulike adverse effects were observed in 5% of patients.

Monophosphoryl lipid A, a derivative of the cell wall of *Salmonella minnesota*, binds to TLR-4. It has been administered sublingually as an adjuvant to grass pollen extract, where it appeared to enhance the clinical and immune response.¹⁹ Monophosphoryl lipid A has also been combined with a grass allergoid, with both being adsorbed to tyrosine and monophosphoryl lipid A acting as a depot agent. The results of a large study with this product have been recently reported.⁹ Overall, the clinical improvement was modest (13.4%). However, subgroup analyses suggested that part of the reason for this limited improvement was suboptimal subject and site selection.

Predicting What the Future Holds for Immunotherapy

SLIT

- If SLIT tablets or liquid extracts for grass, ragweed, house dust mite, and cat are approved, they will be widely used.
- Approval of the tablets will encourage some physicians to use conventional allergen extracts for SLIT, even if they are not approved.
- One motivation for using unapproved extracts for SLIT will be to treat patients with significant sensitivity to nonstandardized allergens for which there will be no approved extracts (liquid or tablets).
- Undoubtedly, multiple allergen mixes will be administered sublingually because many patients have multiple clinically relevant allergies. Sublingual administration will occur despite the fact that there are no controlled studies showing that multiple allergen mixes are effective by sublingual administration.

Other routes of administration

- If the questions of dosing, number, and duration of applications and adjuvant are resolved, epicutaneous administration may be used by many allergists. Unless extensive studies are conducted in the United States to obtain US Food and Drug Administration approval, this form of immunotherapy will be off-label. Nevertheless, it preserves allergist control over the treatment because allergists will oversee preparation of the patches. Furthermore, this approach would allow treatment with nonstandardized allergens and possibly multiple allergen therapy.
- It will probably be difficult to get over the aesthetic objections to intralymphatic immunotherapy. This is too bad because there is much to recommend it.

Recombinant allergens

- Recombinant technology offers the brightest prospect for a true breakthrough in immunotherapy. Cocktails of major allergens offer little advantage over natural allergens but at an increased cost. Modified molecules should offer safety advantages and therefore accelerated schedules of immunotherapy but have yet to be proven to be effective.
- Peptides, on the other hand, have shown promise in initial studies, requiring just a few intradermal injections to produce prolonged improvement. If they are approved in the United States, it is likely they will be widely used.

Immune stimulation

- Stimulating the innate immune system to bias the response toward T_H1 and regulatory T-cell responses seems promising, but large-scale studies with both TLR-9 and TLR-4 stimulation have not lived up to expectations. Both approaches, however, offer significant clinical improvement with just a few injections. Therefore, if they gain approval, they will undoubtedly be widely used.

SCIT

- SCIT as it is currently practiced will continue to be used in the near future. Until there is a highly effective treatment that requires only a few applications and accommodates multiple allergen treatment with both standardized and nonstandardized extracts, there will be a place for SCIT.

References

- [1] Casale TB, Busse WW, Kline JN, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2006;117:134–140.
- [2] Massanari M, Nelson H, Casale T, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. *J Allergy Clin Immunol*. 2010;125:383–389.
- [3] Amar SM, Harbeck RJ, Sills M, et al. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. *J Allergy Clin Immunol*. 2009;124:150–156.
- [4] Khinchi MS, Poulsen LK, Carat F, et al. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy*. 2004;59:45–53.
- [5] Senna G, Lombardi C, Canonica GW, Passalacqua G. How adherent to sublingual immunotherapy prescriptions are patients? the manufacturers' viewpoint. *J Allergy Clin Immunol*. 2010;126:668–669.
- [6] Agostinis F, Forti S, Di Berardino F. Grass transcutaneous immunotherapy in children with seasonal rhinoconjunctivitis. *Allergy*. 2010;65:410–411.
- [7] Senti G, von Moos S, Tay F, et al. Epicutaneous allergen-specific immunotherapy ameliorates grass pollen-induced rhinoconjunctivitis: a double-blind, placebo-controlled dose escalation study. *J Allergy Clin Immunol*. 2012;129:128–135.
- [8] Senti G, Prinz Vavricka BM, Erdmann I, et al. Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial. *Proc Natl Acad Sci U S A*. 2008;105:17908–17912.
- [9] Henmar H, Lund G, Lund L, et al. Allergenicity, immunogenicity and dose-relationship of three intact allergen vaccines and four allergoid vaccines for subcutaneous grass pollen immunotherapy. *Clin Exp Immunol*. 2008;153:16–23.
- [10] DuBuske LM, Frew AJ, Horak F, et al. Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy Asthma Proc*. 2011;32:239–247.
- [11] Pauli G, Larsen TH, Rak S, et al. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2008;122:951–960.
- [12] Purohit A, Niederberger V, Kronqvist M, et al. Clinical effects of immunotherapy with genetically modified recombinant birch pollen Bet v 1 derivatives. *Clin Exp Allergy*. 2008;38:1514–1525.
- [13] 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;154:1623–1628.
- [14] Worm M, Lee HH, Kleine-Tebbe J, et al. Development and preliminary clinical evaluation of a peptide immunotherapy vaccine for cat allergy. *J Allergy Clin Immunol*. 2011;127:89–97.
- [15] Circassia. www.circassia.co.uk. Accessed June 4, 2012.
- [16] Saxon A, Kepley C, Zhang K. "Accentuate the negative, eliminate the positive": engineering allergy therapeutics to block allergic reactivity through negative signaling. *J Allergy Clin Immunol*. 2008;121:320–325.
- [17] Creticos PS, Schroeder JT, Hamilton RG, et al. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. *N Engl J Med*. 2006;355:1445–1455.
- [18] Klimek L, Willers J, Hammann-Haenni A, et al. Assessment of clinical efficacy of CYT003-QbG10 in patients with allergic rhinoconjunctivitis: a phase IIb study. *Clin Exp Allergy*. 2011;41:1305–1312.
- [19] Pfaar O, Barth C, Jaschke C, et al. Sublingual allergen-specific immunotherapy adjuvanted with monophosphoryl lipid A: a phase I/IIa study. *Int Arch Allergy Immunol*. 2011;154:336–344.