

Epicutaneous allergen administration: A novel approach for allergen-specific immunotherapy?

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Specific allergen immunotherapy was first used nearly 100 years ago and is now administered worldwide to treat patients with allergic rhinitis, asthma, or venom hypersensitivity. It is considered to be the only effective, specific treatment for IgE-mediated allergic diseases; recent systemic reviews of controlled clinical studies of specific allergen immunotherapy led to it being recommended for the treatment of respiratory allergy because of its efficacy in reducing asthma and rhinitis symptoms.^{1,2} In addition to its proven clinical efficacy, it can alter the natural history of allergic disease and produce sustained clinical remission after discontinuation. Challenges to specific allergen immunotherapy include the need for effective and convenient methods of delivery; in this issue, Senti et al⁶ describe the epicutaneous administration of specific allergen immunotherapy, testing grass pollen allergens in patients with seasonal rhinitis.

Many novel approaches to allergen immunotherapy have been developed to increase the safety and efficacy of allergenic vaccines. New allergen adjuvants have been studied, and modified allergens have been introduced into clinical practice (eg, allergoids, depigmented allergen extracts peptides or small amino acid sequences, recombinant allergens, hypoallergenic vaccines with modified IgE binding sites, or allergen–CpG fusion molecules).³

Although specific immunotherapy has proven to be beneficial in multiple studies, only a small percentage of patients with allergy agree to receive this treatment in clinical practice: it has been estimated that only 5% of patients in the United States with allergic rhinitis, asthma, or both (about 2.5 million) are given specific allergen immunotherapy. Inconvenience (ie, time-consuming procedures and the requirement for injections—the most common route of delivery) has been described as one of the primary reasons for discontinuation of specific allergen immunotherapy and is likely to be a major reason that patients do not even begin therapy.⁴

Whereas subcutaneous specific allergen immunotherapy is effective and subcutaneous injection is the most common method of administration, noninvasive routes (eg, oral, intranasal) have been studied. Sublingual administration is an effective alternative to regular and subcutaneous injections. Although this method of delivery appears to be safe (not associated with life-threatening systemic reactions), local symptoms including angioedema in the mouth have been reported.² Moreover, sublingual immunotherapy is expensive, requiring the daily intake of large amounts of allergens. Furthermore, sublingual immunotherapy might be less effective than subcutaneous immunotherapy and might administer fewer antigens at a time. Therefore, alternative routes for delivery of allergen-specific immunotherapy are needed. The clinical efficacy of epicutaneous allergen administration was reported more than 50 years ago, when a French allergy specialist performed allergen-specific immunotherapy using needle scarification of the volar forearm and described improved or complete relief from hay fever (for as long as 3 weeks) in most of the treated patients.⁵

Senti et al⁶ report the results from a phase I/II study to evaluate the safety and efficacy of epicutaneous administration of specific allergen immunotherapy by using grass pollen allergens in patients with seasonal rhinitis. The authors applied pouches filled with petroleum jelly that contained *Phleum pratense* extract to the patients' upper arm for 48 hours, once weekly for 12 weeks, after tape-stripping of the skin. They report that, during the pollen season, patients given epicutaneous administration of grass pollen allergens had significantly reduced symptoms compared with patients given placebo.

These findings are novel and interesting. However, the effects were not very strong: when they performed nasal provocation tests, Senti et al⁶ did not observe a significant difference between patients given placebo and those given verum, although there was a trend toward attenuation of allergic responses in the verum arm of the study. Moreover, the use of rescue medication was not reduced in the group given grass pollen allergens. The study has some limitations, which are discussed by the authors in detail.⁶ For example, because most patches were applied at home, it was difficult to control for correct application of the therapy. Also, local eczematous reactions, which were observed in patients given verum but not placebo, may have had an unblinding effect. On the other hand, patients with local eczema who were given verum showed the same improvement in symptoms as those without eczema.

The approach of Senti et al⁶ could stimulate further studies to modify allergen dose or the number and duration of epicutaneous applications of allergens and optimize the local conditions. Senti et al⁶ used tape-stripping of the skin before epicutaneous application of allergens, which is known to induce a bystander effect mediated by keratinocyte-derived proinflammatory cytokines such as IL-1, IL-6, IL-8, or TNF- α .⁷ Moreover, tape stripping

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produces an environment that promotes induction of allergy-protective immune responses mediated by Langerhans cells and by skin-infiltrating T lymphocytes, which subsequently upregulate production of IFN- γ in the skin.⁸ In that respect, epicutaneous allergen administration is different from and may be superior to sublingual administration of immunotherapy, in which local bystander effects are a challenge to induce with therapeutic interventions for practical reasons.

This study may stimulate further investigation of epicutaneous immunotherapy for the treatment of other IgE-mediated allergies. For example, subcutaneous, allergen-specific immunotherapy for food allergies has not been established in clinical practice because of the severe side effects described in subcutaneous immunotherapy studies.⁹ In this respect, epicutaneous immunotherapy may increase safety because Langerhans cells can be pulsed with the allergen in a nonvascularized environment (ie, the epidermis). Therefore, the risk of systemic distribution of the allergen may be reduced.

Atopic dermatitis, which was an exclusion criterion for the study of Senti et al,⁶ could be another indication for epicutaneous immunotherapy. Most proof-of-principle studies have suggested that subcutaneous, specific allergen immunotherapy is beneficial to patients with atopic dermatitis^{10,11}; however, many patients with this disorder are too young to accept regular injection therapies. Sublingual immunotherapy was shown to be effective in a controlled study of children with mild atopic dermatitis.¹² Moreover, studies on the atopy patch test, which includes epicutaneous applications of inhalant or food allergens over a period of 48 hours, indicate a low risk for systemic reactions among patients with atopic dermatitis.¹³

In conclusion, this first controlled clinical trial of epicutaneous allergen immunotherapy in patients with rhinoconjunctivitis suggests that this approach is safe and well tolerated. Epicutaneous allergen immunotherapy was moderately effective, ameliorating symptoms to a greater degree than placebo. Because

epicutaneous allergen administration is needle-free and can be performed at home, it may represent a promising alternative to the well established subcutaneous and sublingual methods of immunotherapy administration.

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