

New methods of allergen immunotherapy

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Allergen-specific immunotherapy has been used empirically for many years to effectively treat allergic disease. As knowledge of immunology has grown, greater effort has been made to determine effective immunotherapeutic techniques and discover the mechanisms of action of immunotherapy. Recent studies have demonstrated the efficacy of various forms of immunotherapy. Traditional subcutaneous or injective immunotherapy has been fairly well investigated, although too little emphasis has been placed on the outcome of therapy and the effect of therapy on health status. In efforts to improve safety, efficacy, and economy, modified or new forms of immunotherapy have recently been developed and tested. Modified extracts and alternative delivery techniques, such as those used in sublingual and intranasal immunotherapy, present promising alternatives to current standard subcutaneous techniques.

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Abbreviations

IT immunotherapy
SLIT sublingual immunotherapy

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Many placebo-controlled clinical trials have demonstrated the efficacy of specific injective immunotherapy in alleviating the symptoms of allergic rhinitis and favorably modulating the immune response [1]. This form of immunotherapy can be expensive, time-consuming, and dangerous; systemic reactions occur with regularity and can even be fatal. As a result, researchers and clinicians have sought alternatives to classic subcutaneous immunotherapy. The search has evolved in two directions: toward improvement of existing allergenic extracts and toward changes in delivery technique or site of administration.

Extract improvement or modification

In the past, it was not uncommon for an allergist to compound his or her own extracts for testing and treatment. Great insight is not required to realize that this created considerable variation in extract potency. Many allergen extracts are currently standardized, and this has improved lot-to-lot consistency; however, much work still remains to be done, particularly with antigen groups, such as molds and foods.

Another improvement has been the modification of current extracts in order to decrease the frequency of injections, decrease the frequency of reactions to immunotherapy, or reduce the severity of reactions to immunotherapy while permitting larger doses of allergens to be administered. Three major methods have been used to modify extracts [2]. The first and oldest method is that of preparing the extract in a depot form to slow the absorption of antigen (*eg*, alum-precipitated extract). In a study of Allpyral extracts, Clarke found that only one of 200 patients had a mild systemic reaction while being treated with a high-dose protocol for grass allergy [3]. No deaths have ever been reported with Allpyral extracts. A second method is that of using extracts conjugated to polyethylene glycol. This has been shown to be effective in suppressing IgE in animal studies, but its effectiveness has not yet been shown in humans. Perhaps the most promising method has been that of modifying allergens to maintain their immunogenicity while reducing their allergenicity. Formalin-treated allergoids and allergens that are polymerized with glutaraldehyde are currently being investigated. In theory, on a weight-to-weight basis, fewer molecules of polymer are available to react with mediator-containing cells. One double-blind, histamine-placebo-controlled study of polymerized ragweed immunotherapy in 81 patients (cited by Patterson *et al.* [2]) consisted of only 15 injections per patient over 3 months. However, no systemic reactions occurred, levels of blocking antibody increased in the treat-

ment group, and antigen E antibody levels increased nine-fold in the treatment group compared with the placebo group ($P = 0.00001$). If standard methods had been used, this group would have received approximately 1215 injections; if a reaction rate of 1% had been maintained, 12 patients would have had a systemic reaction.

Recombinant allergens produced from genes cloned into an expression system, such as *Escherichia coli* or a yeast, have been used to diagnose and treat allergic diseases. Studies with these specific, well-defined proteins provide more precise immunologic information about immunotherapy. Once a protein is cloned and synthesized, a designer peptide molecule that does not interact with IgE but still engages the specific T-cell receptor could be produced. Peptide binding of the T-cell receptor will theoretically inhibit activation of the TH2 cell, which is critical for IgE production. It is hoped that these molecules will not cause systemic reactions, which are a significant danger with current allergen immunotherapy [4].

Alterations of method, site, or technique

Although sublingual and oral immunotherapy have been used for many years by some allergists, the practice has been considered controversial, or at least experimental, by some allergy groups in the United States. Several factors have generated renewed interest in these alternative delivery methods. A superb discussion of the subject was recently published in the European allergy literature. This monograph, which resulted from an investigation by de Weck [5••], deserves careful study by all allergists. The number of clinical trials supporting the efficacy of sublingual and oral immunotherapy is rapidly increasing. Data from the extant literature (taking into consideration only double-blind, placebo-controlled studies) confirm the clinical effectiveness of sublingual and oral immunotherapy for common antigens (Table 1). Having garnered the opinions of several experts and thoroughly reviewing the literature, de Weck provided an opinion about the growing clinical trend of sublingual or oral immunotherapy.

1. Oral IT [immunotherapy], in the sense of allergen ingestion, appears to be effective only at high doses and not for every allergen. This precludes for the time being its general use, at least if the major clinically important allergens are presented in the forms used to date. It does not preclude the possibility that improved knowledge about the mechanisms of oral tolerance induction in man may provide some modified form of oral IT in the future.

2. SLIT [sublingual immunotherapy] may be based on a different mechanism, and several recent studies, although partially flawed and still leaving open some questions, tend to show a reasonable efficacy. Before extending this form of IT to a large variety of allergens, we need to know more about the absorption and degradation of these allergens through the oral mucosa, as well as to determine their effect objective

criteria (immunological and/or provocation tests). A multi-center controlled trial would be most useful.

3. Research in SLIT should be encouraged, particularly to investigate whether some of the tolerance-inducing mechanisms observed in rodents also occur in higher species and in man.

4. Determination of the indications and control of SLIT should remain in the hands of trained allergologists. Although SLIT is more agreeable for the patient, compliance and side effects require the intervention of trained specialists. If SLIT becomes widely available and used without proper allergological control, the results will be disastrous for patients, for the reputation of immunotherapy (in general), and particularly for the finances of the agencies that bear the cost of healthcare. The only effective way to prevent indiscriminate use of SLIT in the future is to make its prescription and reimbursement contingent upon indication by an allergologically-trained physician.

Thus, it seems that the science of sublingual and oral immunotherapy is catching up with clinical practice. It would be perverse indeed if scientific inquiry did not support a practice that has been useful to practitioners and patients in the United States and many other countries for many years. Table 2 describes the ideal candidate for sublingual or oral immunotherapy.

Clinical trials of local nasal immunotherapy done using aqueous allergen preparations have revealed frequent local reactions to be a problem [6,7]. In addition, aqueous allergen preparations have disadvantages, namely, poor stability and the difficulty of administering allergens in a precise manner [8,9]. The introduction of an extract in powder form has achieved better stability and standardization of allergens [10].

Seven studies [11–17•] cataloguing the success of local nasal immunotherapy have recently been published in the world literature. These studies, which were all conducted by various Italian investigators and were all double-blind, placebo-controlled trials, have shown the clinical efficacy and safety of intranasal powder immunotherapy. The use of micronized powdered extracts of dust mite, grass pollen, *Parietaria officinalis*, and birch pollen resulted in significantly decreased symptom-medication scores and increased specific nasal threshold to these allergens. The authors concluded that local nasal immunotherapy was a suitable alternative to traditional subcutaneous immunotherapy in terms of clinical efficacy and safety. Here, as has been shown with oral and sublingual immunotherapy, the mucous membrane is an alternate site for antigen administration, and this seems to be safer than traditional subcutaneous immunotherapy.

Because local nasal immunotherapy may conceptually be the most unfamiliar of the newer techniques, a more thorough review of one of the aforementioned studies would be

Table 1

Double-blind trials of oral and sublingual immunotherapy

Author, y	Journal (volume:page number)	Allergen	Patients, n	Duration	Extract	Clinical efficacy
Oral immunotherapy						
Urbanek, 1982	<i>MonatKind</i> (130:150)	Dust mite	32	10 mo	Oral drops	No
Taudorf, 1983	<i>Allergy</i> (38:561)	Grass pollen	12	6 mo	Oral drops	No
Cooper, 1984	<i>Clin Allergy</i> (14:541)	Grass pollen	54	3 mo	Oral drops	No
Taudorf, 1985	<i>Allergy</i> (40:321)	Grass pollen	58	6 mo	Tablets	No
Moller, 1986	<i>Clin Allergy</i> (41:271)	Birch pollen	30	10 mo	Tablets	Yes
Mosbech, 1987	<i>Allergy</i> (42:45)	Grass pollen	42	10 mo	Tablets	No
Taudorf, 1987	<i>J Allergy Clin Immunol</i> (80:153)	Birch pollen	39	18 mo	Tablets	Yes
Creticos, 1990	<i>J Allergy Clin Immunol</i> (85:165)	Ragweed pollen	34	3 mo	Oral drops	Yes
Xiao-Leng, 1990	<i>Ann Allergy</i> (64:27)	Artemisia pollen	18	3 mo	Tablets	Yes
Urbanek, 1990	<i>Eur J Pediatr</i> (149:545)	Grass pollen	22	9 mo	Tablets	No
Creticos, 1992	Not published	Ragweed pollen	20	6 mo	Oral drops	Yes
Giovane, 1993	<i>Clin Exp Allergy</i> (24:53)	Dust mite	18	3 y	Oral drops	Yes
Oppenheimer, 1994	<i>J Allergy Clin Immunol</i> (93:61)	Cat dander	53	2 mo	Oral drops	No
Bordignon, 1994	<i>G Ital All Immunol Clin</i> (4:153)	Grass pollen	60	1 y + 2 open	Oral drops	Yes
Sublingual immunotherapy						
Scadding, 1986	<i>Clin Allergy</i> (16:483)	Dust mite	18	5 mo		Yes
Van Niekerk, 1987	<i>Clin Allergy</i> (17:507)	Grass	29	24 mo		Yes
Tari, 1990	<i>Allergol Immunopathol</i> (18:277)	Dust mite	58	18 mo		Yes
Novembre, 1991	<i>Ital J Pediatr</i> (17:75)	Dust	13	12 mo		Yes
Nelson, 1993	<i>J Allergy Clin Immunol</i> (92:229)	Cat dander	41	35 mo		No
Sabbath, 1994	<i>Allergy</i> (49:309)	Grass	58	4 mo		Yes
Casanovas, 1994	<i>J Inv Allergy</i> (4:305)	Olea	15	2 mo		Yes
Troise, 1994	<i>J Inv Allergy</i> (5:1)	Parietaria	31	10 mo		Yes
Feliziani, 1995	<i>Allergol Immunopathol</i> (24:148)	Grass	34	3 mo		Yes
Horak, 1995	<i>Allergy</i> (50:279)	Birch	41	3 mo		Yes
Clavel, 1995	<i>Allergy</i> (50:279)	Grass	136	7 mo		Yes

helpful. In a study of preseasonal intranasal immunotherapy in birch-alder allergic rhinitis, conducted by Cirila *et al.* [17•] in Lombardy, Italy, 22 patients who had allergies strictly in the early spring were treated preseasonally with micronized powder birch-alder pollen extract. They received escalating intranasal doses according to the study protocol. The nasal mucosa were pretreated with cromolyn sodium spray 20 minutes before insufflation to help prevent local side effects; this is standard practice in local nasal immunotherapy. Analysis of the data showed that the patients who received active treatment had less sneezing and rhinorrhea than the patients in the placebo group. Less rescue drug was required, and the active treatment group had much less nasal reactivity, as determined by specific nasal provocation testing. Higher threshold doses of birch-alder allergen were required to provoke nasal reactions in the active treatment group. Although these doses were high, they were about one third as large as the doses typically required to achieve the same effect on nasal reactivity. It must be noted,

however, that local nasal immunotherapy did not significantly affect nasal obstructive or ocular symptoms. This finding underscores the reduced or lacking systemic effectiveness of local nasal immunotherapy, which may be considered a real local hyposensitization. More investigation is needed to determine the mechanisms of action of local nasal immunotherapy.

Safety and convenience for patients are clear advantages with local nasal immunotherapy because treatment is self-administered at home. Obviously, appropriate patient selection and education are required for optimal results. In the study by Cirila *et al.* [17•], the simple preseasonal schedule produced a satisfactory clinical response while improving the quality of life of patients with allergy. The authors therefore concluded that local nasal immunotherapy was a valid alternative to conventional subcutaneous immunotherapy in birch-alder tree allergic rhinitis.

Efficacy, safety, and economy are key drivers in the health care system today, and only treatments that are efficacious, safe, and economical will be maintained. The new types of immunotherapy hold considerable promise with respect to these characteristics. Table 3 compares the costs of sublingual immunotherapy with those of conventional subcutaneous immunotherapy. Sublingual immunotherapy may be delivered more safely and less expensively. Acceptance of oral or sublingual immunotherapy by patients is greater than acceptance of traditional injective immunotherapy.

Table 2

The ideal candidate for oral or sublingual immunotherapy

Pediatric patient
Asthma, rhinitis, or both
Previous reactions to subcutaneous immunotherapy
Refusal of subcutaneous immunotherapy
Low compliance due to lifestyle or working habits

Adapted from De Week [6]; with permission.

Table 3

Annual costs of immunotherapy

Variable	Oral or sublingual immunotherapy, \$	Subcutaneous immunotherapy, \$
Patient's costs		
Antigen	400	400
12 injections per year	—	200
50 injections per year	—	750
Physician visits	300	300
Social costs		
Loss of work time for		
12 injections	—	480
Loss of work time for		
50 injections	—	2000
Totals		
12 injections per year	700	1080
50 injections per year	—	3150

particularly in children. This point has been driven home forcefully in my own practice. Compliance can be enhanced by the increased convenience of home-based sublingual immunotherapy, oral immunotherapy, or local nasal immunotherapy.

When data such as those reviewed here are more widely known, third-party payers and managed care plans should find the decreased costs and increased safety of these new methods appealing, and these techniques should be fully endorsed shortly thereafter.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest

1. Cook PR: **Allergic rhinitis: outcomes of immunotherapy on symptom control.** *Otolaryngol Clin North Am* 1998, In press.
2. Patterson R, Grammar LC, Shaughnessy MA: **New Directions in Allergen Immunotherapy.** Teaching Slide Series, vol 2. Milwaukee, WI: American Academy of Allergy, Asthma, and Immunology; AAAAI.
3. Clarke PS: **Titration of immunotherapy by periodical nasal challenges in the treatment of allergic rhinitis.** *Med J Aust* 1992, 157:11–13.

4. Lockey RF: **Immunotherapy: now and in the future.** In: *Current Views in Allergy and Immunology*, v XXIV. Augusta, GA: The Medical College of Georgia; 1996.

5. de Week AL: **Oral or sublingual immunotherapy? A topic deserving new evaluation.** *Allergy Clin Immunol Int* 1996, 8:19–29.

This monograph provides expert opinion as well as data from numerous clinical studies on the efficacy of oral and sublingual immunotherapy. A must read.

6. Cook N: **Preseasonal local nasal desensitization in hay fever.** *J Laryngol* 1974, 88:1169–1170.
7. Metha SB, Morrison Smith J: **Nasal hyposensitization and hay fever.** *Clin Allergy* 1975, 5:279–284.
8. Anderson MC, Baer H: **RAST-Inhibition Procedure.** Bethesda, MD: Allergic Products Branch, Food and Drug Administration; 1983.
9. Ariano R, Panzani RC, Chiapella M, Augeri G, Falagiani P: **Local immunotherapy of seasonal allergic rhinitis in children due to *Parietaria officinalis*: a preliminary report.** *Pediatr Asthma Allergy Immunol* 1993, 7:227–237.
10. Schiano S, Cocco G, Balzano DG, D'Agostino F, Melillo G: **Nasal provocation with allergen in powder form.** In Melillo G, Cocco G, Centanni G, eds. *The Use of Allergen in Powder Form for Provocation Test and for Local Immunotherapy in Allergic Asthma.* Naples: Forum Editoriale; 1986:77–81.
11. Andri L, Senna G, Betteli C, Giovanni S, Andri G, Falagiani P: **Local nasal immunotherapy for Dermatophagoides-induced rhinitis: efficacy of a powder extract.** *J Allergy Clin Immunol* 1993, 91:987–996.
12. Andri L, Senna G, Betteli C, Giovanni S, Andri G, Dimitri G, Falagiani P, Mezzelani P: **Local nasal immunotherapy with extract in powder form is effective and safe in grass pollen rhinitis: a double-blind study.** *J Allergy Clin Immunol* 1996, 91(Part 1): 34–41.
13. Andri L, Senna G, Andri G, Dama A, Giovanni S, Betteli C, Dimitri G, Falagiani P, Mezzelani P: **Local nasal immunotherapy for birch allergic rhinitis with extract in powder form.** *Clin Exp Allergy* 1995, 25:1092–1099.
14. Ariano R, Panzani RC, Chiapella M, Augeri G, Falagiani P: **Local nasal immunotherapy with allergen in powder in atopic patients sensitive to *Parietaria officinalis* pollen.** *J Investig Allergol Clin Immunol* 1995, 5:126–132.
15. D'Amato G, Lobefalo G, Liccardi G, Cazzola M: **A double-blind, placebo-controlled trial of local nasal immunotherapy in allergic rhinitis to *Parietaria* pollen.** *Clin Exp Allergy* 1995, 25:141–148.
16. Fanales-Belasio E, Ciofalo A, Zambetti G, Ansotegui IJ, Scala E, Paganelli R, Filiaci F: **Intranasal immunotherapy with Dermatophagoides extract: in vivo and in vitro results of a double-blind, placebo-controlled trial.** *Rhinology* 1995, 33:126–131.
17. Cirila AM, Sforza N, Roffi GP, Alessandrini A, Stanizzi R, Dorigo N, Sala E, Della Torre F: **Preseasonal intranasal immunotherapy in birch-alder allergic rhinitis: a double-blind study.** *Allergy* 1996, 51:299–305.

This paper describes the technique of local nasal immunotherapy. The study itself was beautifully designed and executed.