

Sublingual immunotherapy

Few things excite more argument among allergists than specific allergen immunotherapy. For some, specific immunotherapy (SIT) is the treatment that defines our specialty. For others, it is a relic of 19th century clinical practice that we should discard in favor of modern pharmacotherapy. The evidence for SIT was mostly gathered long before the modern era of double-blind, placebo-controlled randomized trials.^{1,2} Revisiting the effectiveness of SIT has been difficult, partly because of the entrenched views held by some proponents and some antagonists. Those who consider SIT to be an effective therapy point to the many thousands of satisfied customers and to the ability of SIT to achieve lasting benefit, in contrast to drug therapy, which works only while it is being taken regularly.³⁻⁷ Those who oppose SIT point to its dangers and the weak evidence base for this form of antiallergy therapy.^{1,2,8}

Fortunately for those of us who believe in the benefits of SIT, the last 10 years have seen the publication of several carefully conducted controlled trials that have shown unequivocal evidence of the efficacy of SIT in selected patient groups.⁹⁻¹⁶ However, it has also become clear that SIT is potentially dangerous, especially if it is administered by nonspecialists or by practitioners inexperienced in treating anaphylaxis.^{2,8,17-19} This limits both the attractiveness of SIT to patients and its availability. With the steadily increasing number of patients with allergic disease, we need to develop treatment strategies that will allow all patients to benefit, not just those who can find an experienced allergist. Of course, at a population level we also need to find ways of preventing the onset of allergies, but for the individual who has allergic disease, cheap, safe, and effective therapy is a priority.

Although we now have evidence of the short- and long-term clinical efficacy of conventional injection immunotherapy and some data indicating that SIT can prevent the onset of sensitization to new allergens,²⁰ there remains a clear need to find safer forms of immunotherapy.²¹ One approach has been to try to develop more targeted vaccines, such as T-cell peptides. We now know that SIT works by altering the T-cell response to allergen rather than by inducing blocking IgG anti-

Abbreviation used

SIT: Specific immunotherapy

bodies.²²⁻²⁵ Recognizing that T cells and B cells differ in their antigen recognition requirements, it should be possible to develop peptide vaccines that are recognized by T cells but not by IgE molecules. T-cell peptides have shown some initial promise^{26,27} but thus far have not proved as effective as conventional SIT, while questions of the likely cost and safety remain unanswered. The fundamental problem with T-cell peptide vaccines is that different MHC class II antigens have different recognition requirements for small peptides. This in turn means that small peptide vaccines must either be personalized according to the individual MHC phenotype or else contain many different peptides to ensure that the relevant sequences are included for all patients. If a larger peptide that can be given to all and then be digested internally to generate the relevant peptide fragment is made, there will be a greater potential for side effects resulting from retention of epitopes recognized by IgE molecules. There is also interest in the possibility of DNA-based vaccines^{28,29} or modified protein vaccines that retain T-cell reactivity but have reduced binding to IgE.^{30,31}

Others have looked for alternative and safer routes of administering conventional allergen extracts. Several alternative routes have been tried, including administration of conventional doses of conventional extracts by the nasal, oral, and sublingual routes,³²⁻⁴³ as well as more unconventional approaches using homeopathic extracts or admixtures of allergen with enzymes.^{44,45}

Several recent studies have reported beneficial effects of sublingual immunotherapy on symptoms of allergic rhinitis.³⁹⁻⁴³ Although some of the early studies had methodologic flaws, these more recent studies appear sound and so consensus opinion is now moving toward accepting the validity of the sublingual route.⁴⁶ In this month's issue of the Journal, La Rosa et al⁴⁷ report on a 2-year study of sublingual immunotherapy in children aged 6 to 14 years with allergic rhinoconjunctivitis caused by *Parietaria*. This study provides encouragement for those interested in this novel route of administration and provides some useful evidence of efficacy in younger patients, but it also illustrates several of the methodologic problems associated with the existing body of evidence for sublingual immunotherapy.

Like previous trials, this study was relatively small (41 patients, of whom 20 were randomized to active treatment) and almost one fourth of the patients dropped out of the study or were lost to follow-up. Some withdrawals are

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inevitable and if unexplained can mean that side effects are underreported or masked. Withdrawals can also threaten the power of studies and can compromise the generalizability of findings. Analysis on an intention-to-treat basis rather than on a per-protocol basis indicates the extent to which the effects of treatment may be realized when the therapy is used in a clinical rather than a trial setting.

When there is no baseline assessment over a run-in pollen season, the randomization process is hostage to the possibility that the 2 groups will prove to be unbalanced in respect of symptom severity or other key outcome measures. For example, in the study of La Rosa et al⁴⁷ the active group had a shorter duration of symptoms before therapy and also higher symptom and drug scores at the start of the 1996 pollen season. Although these differences are not critical to the analysis, they do mean that there was more scope for improvement in the actively treated group, which can artificially enhance the likelihood of the active treatment showing benefit.

Another recurring theme in trials of sublingual immunotherapy is the unexpected direction of a change in a particular outcome measure. Thus in the study of La Rosa et al skin reactivity was unchanged in the active group but deteriorated in the placebo-treated group. It is not clear whether we should attribute this to chance, to a genuine deterioration in the placebo group, or to technical factors (eg, a difference in dilution or activity of the skin test materials used at the 2 time points). Statistical tests can tell us how likely the observed change is to have occurred by chance but cannot help us interpret the biological significance of such changes.

In common with many previous studies of allergic disease, La Rosa et al used an arbitrary scoring system to assess concomitant medication use. Although it is tempting to allocate differential points for different drugs to derive a numeric score, this tends to give an unwarranted numeric validity to an unvalidated construct. Should we blindly accept that 1 dose of antihistamine equates to 4 puffs of nasal steroid or that 12 drops of topical cromoglycate are equivalent to 1 prednisone tablet?

Conjunctival provocation tests are often used to provide a more objective end point, but these scoring systems are dependent on subjective observations. Although nonparametric tests are used for analysis, it is important to consider whether it is reasonable to create a single outcome measure by adding the scores in several domains as if they were continuous variables.

Despite these reservations, the proportion of patients improving on active therapy was very high (85%), although more than half of the placebo-treated group also showed improvement in their symptom scores by at least 30%. This improvement was not accompanied by any reduction in the use of concomitant medication in either group. This contrasts with studies of conventional (injection) SIT, where there is usually a parallel reduction in symptoms and in medication usage.⁸⁻¹⁵ Separately, the physician needs to ask whether active treatment is really indicated in a condition that shows a spontaneous rate of improvement exceeding 50%.

Giving allergen by mouth rather than by injection should decrease the costs of SIT by reducing the need for medical and nursing time, as well as consumables such as syringes and needles. However, the cumulative dose of allergen used in the study of La Rosa et al was 375 times greater than that given to patients for conventional SIT. Other studies of sublingual immunotherapy have used between 20 and 200 times the usual cumulative dose of allergen.^{36,43,46} The increased cost of the allergen extracts is partly offset by the reduced costs of administering the allergen, but clearly a formal economic analysis is required before we can comment on cost effectiveness.

La Rosa et al considered adverse events to be relatively unimportant, although we note that more than half of those receiving active therapy reported some problems. Local gastrointestinal symptoms were the most common in this and other studies.⁴⁷ Most studies of oral and sublingual immunotherapy have reported either no side effects or no difference between active and placebo treatment,⁴⁶ but others have reported local side effects to be common.^{37,39} This has implications for the blinding of studies of sublingual SIT: maintaining adequate blinding is extremely important in immunotherapy studies where the principal end points are symptom scores, which are assessed subjectively by the patient. Although this is not specifically discussed in the study of La Rosa et al, even minor local side effects may alert patients to the fact that they have received active therapy, which may influence their reporting of symptoms. In trials of conventional SIT, this problem can be minimized by spiking the placebo extracts with histamine so that some local reactions will occur even in the placebo group, although it is obviously impossible to mimic delayed local reactions.

Finally, it is important to keep in mind the purpose of sublingual immunotherapy: to deliver safe and effective specific immunotherapy in nonspecialist settings. Ideally, it should be simple and safe enough for delivery outside the hospital. Currently sublingual immunotherapy continues to look promising, but further studies are needed. More small-scale studies are not the answer—future studies should be large, properly randomized, and controlled. Baseline symptom levels should be prospectively assessed to ensure precise balancing of the groups for all relevant major end points. A prolonged period of baseline data collection may also help to reduce the size of the spontaneous improvement during observation (the so-called Hawthorne effect) seen in most previous studies. Side effects and adverse reactions need to be sought out, described, and quantified so that if the therapy proves effective we can gain an accurate appraisal of the safety issues involved before we go on and recommend this form of immunotherapy for use in nonspecialist settings or at home.

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REFERENCES

- Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma: a meta-analysis of randomized controlled trials. *Am J Respir Crit Care Med* 1995;151:969-74.
- British Society for Allergy and Clinical Immunology. Injection immunotherapy. *Clin Exp Allergy* 1993;23(3 Suppl):1-44.
- Des Roches A, Paradis L, Knani J, Hejjaoui A, Dhivert H, Chanez P, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract, V: duration of the efficacy of immunotherapy after its cessation. *Allergy* 1996;51:430-3.
- Jacobsen L, Nüchel Petersen B, Wihl JA, Lowenstein H, Ipsen H. Immunotherapy with partially purified and standardized tree pollen extracts, IV: results of long term follow-up. *Allergy* 1997;52:914-20.
- Bousquet J, Hejjaoui A, Michel FB. Specific immunotherapy in asthma. *J Allergy Clin Immunol* 1990;86:292-305.
- Creticos PS, Reed CE, Norman PS, Khoury J, Adkinson NF, Buncher CR, et al. Ragweed immunotherapy in adult asthma. *N Engl J Med* 1996;334:501-6.
- Ohman JL. Allergen immunotherapy in asthma: evidence for efficacy. *J Allergy Clin Immunol* 1989;84:133-9.
- Committee on the Safety of Medicines. CSM update: immunotherapy. *BMJ* 1986;293:948.
- Lilja G, Sundin B, Graff-Lonnevig V, Hedin G, Heilborn H, Norrind K, et al. Immunotherapy with partially purified and standardized animal dander extracts, IV: effects of 2 years of treatment. *J Allergy Clin Immunol* 1989;83:37-44.
- Varney VA, Gaga M, Frew AJ, Aber VR, Kay AB, Durham SR. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by anti-allergic drugs. *BMJ* 1991;302:265-9.
- Löfkvist T, Agrell B, Dreborg S, Svensson G. Effects of immunotherapy with a purified standardized allergen preparation of *Dermatophagoides farinae* in adults with perennial allergic rhinoconjunctivitis. *Allergy* 1994;49:100-7.
- Peroni DG, Piacentini GL, Martinati LC, Warner JO, Boner AL. Double-blind trial of house dust mite immunotherapy in asthmatic children resident at high altitude. *Allergy* 1995;50:925-30.
- Olaguibel JM, Tabar AI, Garcia Fuguera BE, Cortes C. Immunotherapy with standardized extract of *Dermatophagoides pteronyssinus* in bronchial asthma: a dose titration study. *Allergy* 1997;52:168-78.
- Pichler CE, Marquardson A, Sparholt S, Lowenstein H, Bircher A, Bischof M, et al. Specific immunotherapy with *Dermatophagoides pteronyssinus* and *D farinae* results in reduced bronchial hyperreactivity. *Allergy* 1997;52:274-83.
- Olsen OT, Larsen KR, Jacobsen L, Svendsen UG. A one year placebo-controlled double-blind house dust mite immunotherapy study in asthmatic adults. *Allergy* 1997;52:853-9.
- Varney VA, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ. Clinical efficacy of specific immunotherapy to cat dander: a double blind placebo controlled trial. *Clin Exp Allergy* 1997;27:860-7.
- Lockey RF, Benedict L, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy and skin testing. *J Allergy Clin Immunol* 1987;79:660-7.
- Reid MJ, Lockey RF, Turkeltaub PC, PLatts-Mills TAE. Fatalities from immunotherapy and skin testing [abstract]. *J Allergy Clin Immunol* 1990;85:180.
- Reid MJ, Lockey RF, Turkeltaub PC, PLatts-Mills TAE, Lehrer SB. Fatalities from immunotherapy 1990-91 [abstract 823]. *J Allergy Clin Immunol* 1992;89.
- Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract, VI: specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 1997;99:450-3.
- Wheeler AW, Drachenberg KJ. New routes and formulations for allergen-specific immunotherapy. *Allergy* 1997;52:602-12.
- McHugh SM, Deighton J, Stewart AG, Lachman PJ, Ewan PW. Bee venom immunotherapy induces a shift in cytokine responses from a Th2 to a Th1 dominant pattern: comparison of rush and conventional immunotherapy. *Clin Exp Allergy* 1995;25:828-38.
- Durham SR, Ying S, Varney VA, Jacobson MR, Sudderick RM, Mackay IS, et al. Grass pollen immunotherapy inhibits allergen-induced infiltration of CD4⁺ T-lymphocytes and eosinophils in the nasal mucosa and increases the number of cells expressing mRNA for interferon-gamma. *J Allergy Clin Immunol* 1996;97:1356-65.
- Ebner C, Siemann U, Bohle B, Willheim M, Wiedermann U, Schenk S, et al. Immunological changes during specific immunotherapy of grass pollen allergy: reduced lymphoproliferative responses to allergen and shift from Th2 to Th1 in T-cell clones specific for Phl p1, a major grass pollen allergen. *Clin Exp Allergy* 1997;27:1007-15.
- Hamid QA, Schotman E, Jacobson M, Walker S, Durham SR. Increases in IL-12 mRNA⁺ cells accompany inhibition of allergen-induced late skin responses after successful grass pollen immunotherapy. *J Allergy Clin Immunol* 1997;99:254-60.
- Norman PS, Ohman JL, Long AA, Creticos PS, Gefter MA, Shaked Z, et al. Treatment of cat allergy with T-cell reactive peptides. *Am J Respir Crit Care Med* 1996;154:1623-8.
- Muller U, Akdis CA, Fricker M, Akdis M, Blesken T, Bettens F, et al. Successful immunotherapy with T-cell epitope peptides of bee venom phospholipase A2 induces specific T-cell anergy in patients allergic to bee venom. *J Allergy Clin Immunol* 1998;101:747-54.
- Hsu CH, Chua KY, Tao MH, Lai YL, Wu HD, Huang SK, et al. Immunoprophylaxis of allergen-induced IgE synthesis and airway hyperresponsiveness in vivo by genetic immunization. *Nature Med* 1996;2:540-4.
- Spiegelberg H, Orozco EM, Roman M, Raz E. DNA immunization: a novel approach to allergen-specific immunotherapy. *Allergy* 1997;52:964-70.
- Ortolani C, Pastorello EA, Incorvaia C, Spano M, Farioli L, Zara C, et al. A double-blind, placebo-controlled study of immunotherapy with an alginate-conjugated extract of *Parietaria judaica* in patients with *Parietaria* hay fever. *Allergy* 1994;49:13-21.
- Tari MG, Mancino M, Ghezzi E, Frank E, Cromwell O. Immunotherapy with an alum-adsorbed *Parietaria*-pollen allergoid: a 2-year double blind placebo controlled study. *Allergy* 1997;52:65-74.
- Andri L, Senna G, Betteli C, Givanni S, Andri G, Dimitri G, et al. 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;97:34-41.
- Andri L, Senna G, Betteli C, Givanni S, Andri G, Falagiani P. Local nasal immunotherapy for *Dermatophagoides*-induced rhinitis: efficacy of a powder extract. *J Allergy Clin Immunol* 1993;91:987-96.
- Giovane AL, Bardare M, Passalacqua G, Ruffoni S, Scordamaglia A, Ghezzi E, et al. A three year double-blind placebo-controlled study with specific oral immunotherapy to *Dermatophagoides*: evidence of safety and efficacy in paediatric patients. *Clin Exp Allergy* 1994;24:53-9.
- Litwin A, Flanagan M, Entis G, Gottschieb G, Esch R, Gartside P, et al. Oral immunotherapy with short ragweed extract in a novel encapsulated preparation: a double-blind study. *J Allergy Clin Immunol* 1997;100:30-8.
- Oppenheimer J, Areson JG, Nelson HS. Safety and efficacy of oral immunotherapy with standardized cat extract. *J Allergy Clin Immunol* 1994;93:61-7.
- Sabbah A, Hassoun S, Le Sellin J, Andre C, Sicard H. A double-blind, placebo-controlled trials by the sublingual route of immunotherapy with a standardized grass pollen extract. *Allergy* 1994;49:309-13.
- Leng X, Fu YX, Ye ST, Duan SQ. A double-blind trial of oral immunotherapy for Artemisia pollen asthma with evaluation of bronchial response to the pollen allergen and serum-specific IgE antibody. *Ann Allergy* 1990;64:27-31.
- Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mites: a double-blind study. *Allergol Immunopathol* 1990;18:277-84.
- Feliziani V, Lattuada G, Partimiani S, Dall'aglio PP. Safety and efficacy of sublingual rush immunotherapy with grass allergen extracts: a double-blind study. *Allergol Immunopathol* 1995;23:224-30.
- Troise C, Voltolini S, Canessa A, Pecora S, Negrini AC. Sublingual immunotherapy in *Parietaria* pollen-induced rhinitis: a double-blind study. *J Invest Allergol Clin Immunol* 1995;5:25-30.
- Clavel R, Bousquet J, Andre C. Clinical efficacy of sublingual-swallow immunotherapy: a double-blind placebo-controlled trial of a standardised five-grass-pollen extract in rhinitis. *Allergy* 1998;53:493-8.
- Bousquet J, Scheinmann P, Guinneepein MT, Perrin-Fayolle M, Sauvaget J, Tonnel AB, et al. Sublingual-swallow immunotherapy in patients with asthma due to house dust mites: a double-blind, placebo-controlled study. *Allergy* 1999;54:249-60.
- Fell P, Brostoff J. A single dose desensitization for summer hay fever. *Eur J Clin Pharmacol* 1990;38:77-9.

45. Reilly DT, Taylor MA, McSharry C, Aitchison T. Is homeopathy a placebo response: controlled trial of homeopathic potency with pollen in hay fever as a model. *Lancet* 1986;2:881-6.
46. Bousquet J, Lockey RF, Malling HJ. WHO position paper, allergen immunotherapy: therapeutic vaccines for allergic disease. *Allergy* 1998;53(44 Suppl):1-42.
47. La Rosa M, Ranno C, Andre C, Carat F, Tosca A, Canonica GW. Double-blind placebo-controlled evaluation of sublingualswallow immunotherapy with standardized *Parietaria judaica* extract in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1999;104:425-32.