
Is oral immunotherapy too good to be true?

The pure and simple truth is rarely pure and never simple.—Oscar Wilde

Immunotherapy, which modifies the allergic immune response, is at the core of clinical allergy. A variety of techniques and methods have come and gone, leaving high-dose, subcutaneous immunotherapy (SCIT) as the standard. This standard is supported by clinical experience; double-blind, placebo-controlled clinical trials; and the science of immunologic changes induced by the therapy.

Providing immunotherapy by routes other than subcutaneous injection has been considered and has shown some benefits.¹ These alternatives include oral immunotherapy (OIT), sublingual swallow immunotherapy (SLIT-swallow) in which the vaccine is held in the mouth for 2 to 3 minutes before swallowing, sublingual-spit immunotherapy in which the allergen is held in the mouth for 2 to 3 minutes and then expectorated, and local immunotherapy in the nose or bronchial airway. The simplicity of the oral route encouraged use in the early part of the 20th century, but subsequent trials showed limited efficacy,² which may have resulted from insufficient dosing. This concern is particularly germane due to the expected allergen modification or breakdown by digestive enzymes before absorption.

Reports and documentation of adverse effects with SCIT and the increased understanding of the mucosal-associated lymphoid tissue rekindled interest in immunotherapy delivered via mucosal routes.^{1,3,4} Theoretically, the immune mechanisms modified in mucosal tissues may target the immune deviation away from allergy in other mucosal tissues, such as the ocular, nasal, and bronchial mucosa.^{5–9} Mucosal immunity seems more relevant to clinical disease. Studies of SLIT-swallow in allergic rhinitis and/or asthma and in children or adults have shown efficacy, although efficacy is less convincing with dust mite allergen.^{1,10–12} In general, SLIT-swallow compared with SCIT does not result in the same degree of systemic changes in measurable immune parameters, for example, decrease in specific IgE or increase in specific IgG.¹³ SLIT-swallow enhances safety compared with SCIT, with significantly fewer systemic adverse effects.^{14–18} Currently, SLIT-swallow is viewed by many experts as equivalent, or approximately equivalent, in efficacy compared with SCIT with pollen allergens.^{19–21} In contrast, only 3 of 9 double-blind, placebo-controlled trials of OIT show beneficial effects.^{1,22–30} Four of the 9 trials used enteric-coated tablets in an attempt to avoid digestion of the allergen, but this adjustment did not ensure success. An explanation for the apparent success of SLIT-swallow compared with OIT is not available. No absorption of allergen apparently occurs through the oral

mucosa.¹ However, radiolabeled antigen is detectable in the mouth for 20 hours after SLIT-swallow, suggesting a local effect before swallowing or transport selectively to the oral mucosa after absorption.^{31,32} This information supports the importance of allergen contact with the oral mucosa, despite the lack of mouth absorption.

The trial performed by TePas et al, which is described in this issue of the *Annals*, is a stimulating addition to the literature of OIT.³³ Although small, this study demonstrates clinical benefits of OIT with microencapsulated timothy grass vaccine using a rapid, dose-escalation protocol. The notable advantage of the microencapsulated allergen is the requirement of lower dosages than usually used in SLIT-swallow or OIT. Efficacy was statistically demonstrated in a small number of patients within a 10-week treatment period, arguing for the likely strength of benefit. Finally, as is true of most OIT or SLIT-swallow studies, the treatment was safe, with even fewer gastrointestinal symptoms than many other OIT or SLIT-swallow studies.

The mechanism of action was addressed with limited immunologic studies. Similar to other data, there were no changes in specific immunoglobulins or cytokine message after lymphocyte stimulation in vitro. However, in vitro T-cell proliferation with allergen was decreased. This seems remarkable in a 10-week study. The authors argue that OIT, and perhaps SLIT-swallow, works via mechanism(s) distinct from SCIT. Their idea is that OIT induces a cellular tolerance to the allergen, whereas SCIT enhances T_H1 rather than T_H2 response. Thus, immunologic changes documented in SCIT may not occur in OIT, despite clinical efficacy since the latter may work via cellular tolerance.

Many questions remain to be answered. Is OIT with microencapsulated allergen cost-effective? Although the dose of allergen is less than other OIT studies, the dose during the 10th week was approximately 45,000 bioequivalent allergy units per week. The cost of the microencapsulation would be another factor in a cost-benefit analysis. Would the microencapsulation work for nonstandardized allergens? Would the benefits occur with non-pollen allergens, particularly dust mite? Are the beneficial effects of OIT with microencapsulated allergen sustained over time? If multiple allergens are used, would the benefits persist and the adverse effects remain low? What about disease modification with OIT, such as reduction of asthma development in the treatment of allergic rhinitis or the limitation of the development of additional sensitization?

Immunotherapy is alive and well. We should continue to demand good science so that as clinicians we provide the most beneficial, cost-effective care to our patients. The cynic in us will say if it is too good to be true then it isn't. The idealist in us

will want to jump on the exciting bandwagon. The scientist in us will await further studies in search of the truth.

DENNIS K. LEDFORD, MD
University of South Florida College of Medicine
James A. Haley VA Hospital
Joy A. McCann Airways Disease Research Center
Tampa, Florida

REFERENCES

1. Valovitra E, Passalacqua G, Cononica GW. Non-injection routes for immunotherapy of allergic diseases. In: Lockey RF, Bukantz SC, Bousquet J, editors. *Allergen and Allergen Immunotherapy for Allergic Disease*. 3rd ed. New York, NY: Marcel Dekker; in press.
2. Black JH. The oral administration of pollen. *J Lab Clin Med*. 1927;12:1156.
3. Committee on the Safety of Medicines. CSM update: desensitizing vaccines. *BMJ*. 1986;203:948.
4. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy and skin testing. *J Allergy Clin Immunol*. 1987;79:660–677.
5. Reid MJ, Lockey RF, Turkeltaub PC, Platt-Mills TA. Survey of fatalities from skin testing and immunotherapy. *J Allergy Clin Immunol*. 1993;92:6–15.
6. Frew AJ, Smith HE. Sublingual immunotherapy. *J Allergy Clin Immunol*. 2001;107:441–444.
7. Lockey RF. “ARIA”: global guidelines and new forms of allergen immunotherapy. *J Allergy Clin Immunol*. 2001;108:497–499.
8. Mowat AM. The regulation of immune responses to dietary proteins. *Immunol Today*. 1987;8:93–96.
9. van-Wilsem EJ, van Hoogstraaten IM, Breve J, Scheper RJ, Kraal G. Dendritic cells of the oral mucosa and the induction of oral tolerance. *Immunology*. 1994;83:128–132.
10. Wilson DR, Torres Lima M, Durham SR. Sublingual immunotherapy for allergic rhinitis (Cochrane Review). In: *The Cochrane Library*. Oxford, UK: Update Software; 2003:2.
11. Hirsch T, Sahn M, Leupold W. Double blind controlled study of sublingual immunotherapy with house dust mite extracts in children. *Pediatr Allergy Immunol*. 1997;8:21–27.
12. Cuez S, Vatrinet C, Fadel R, Andre C. House dust mite sublingual swallow immunotherapy in perennial rhinitis: a double blind placebo controlled study. *Allergy*. 2000;55:369–375.
13. Mungan D, Misirligil Z, Burbuz L. Comparison of the efficacy of subcutaneous and sublingual immunotherapy in mite sensitive patients with rhinitis and asthma: a placebo controlled study. *Ann Allergy Asthma Immunol*. 1999;82:485–490.
14. Di Rienzo V, Pagani A, Parmiani S, Passalacqua G, Canonica GW. Post-marketing surveillance study on the safety of sublingual immunotherapy in children. *Allergy*. 1999;54:1110–1113.
15. La Rosa M, Reanno C, Andre C, et al. Double blind placebo controlled evaluation of sublingual swallow immunotherapy with standardized *Parietaria judaica* extract in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 1999;104:425–432.
16. Andre C, Vatrinet C, Galvain S, Carat F, Sicard H. Safety of sublingual swallow immunotherapy in children and adults. *Int Arch Allergy Immunol*. 2000;121:229–234.
17. Lombardi C, Gargioni S, Melchiorre A, et al. Safety of sublingual immunotherapy in adults: a post marketing surveillance study. *Allergy*. 2001;56:889–892.
18. Marcucci F, Sensi L, Frati F, et al. Sublingual tryptase and ECP in children treated with grass pollen sublingual immunotherapy (SLIT): safety and immunologic implications. *Allergy*. 2001;56:1091–1095.
19. Ongari S, Domeneghetti P, Parmiani S. Comparison among drugs, injective IT and sublingual IT in grass allergic patients. *Allergy*. 1995;50:358.
20. Benardis P, Agnoletto M, Puccinelli P, Parmiani S, Pozzan M. Injective vs sublingual immunotherapy in *Alternaria tenuis* allergic patients. *J Invest Allergol Clin Immunol*. 1996;6:55–62.
21. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*. 2001;108:S147–S334.
22. Cooper PJ, Darbyshire J, Nunn AF, Warner JO. A controlled trial of oral hyposensitization in pollen asthma and rhinitis in children. *Clin Allergy*. 1984;14:541–550.
23. Taudorf E, Laursen LC, Djurup R, et al. Oral administration of grass pollen to hay fever patients: an efficacy study of oral hyposensitization. *Allergy*. 1985;40:321–335.
24. Moller C, Dreborg S, Lanner A, Bjorkston B. Oral immunotherapy of children with rhinoconjunctivitis due to birch pollen allergy. *Allergy*. 1986;41:271–279.
25. Mosbech H, Dreborg S, Madsen F, et al. High dose grass pollen tablets used for hyposensitization in hay fever patients: a one year double blind placebo controlled study. *Allergy*. 1987;42:415–455.
26. Taudorf E, Laursen CL, Lanner AT, et al. Oral immunotherapy to birch pollen hay fever. *J Allergy Clin Immunol*. 1987;80:153–156.
27. Giovane A, Bardere M, Passalacqua G, et al. A three year double blind placebo-controlled study with specific oral immunotherapy to *Dermatophagoides*: evidence of safety and efficacy in pediatric patients. *Clin Exp Allergy*. 1994;24:53–59.
28. Oppenheimer J, Areson JG, Nelson HS. Safety and efficacy of oral immunotherapy with standardized cat extract. *J Allergy Clin Immunol*. 1994;93:61–67.
29. Liwin A, Flanagan M, Entis G, et al. Oral immunotherapy with short ragweed in a novel encapsulated preparation: a double blind study. *J Allergy Clin Immunol*. 1997;100:30–38.
30. Van Deusen MA, Angelini BL, Gordoro KM, et al. Efficacy and safety of oral immunotherapy with short ragweed extract. *Ann Allergy Asthma Immunol*. 1997;78:573–580.
31. Bagnasco M, Mariani G, Passalacqua G, et al. Absorption and distribution kinetics of the major *Parietaria* allergen administered by non injectable routes to healthy human beings. *J Allergy Clin Immunol*. 1997;100:121–129.
32. Bagnasco M, Passalacqua G, Villa G. Pharmacokinetics of an allergen and a monomeric allergoid for oromucosal immunotherapy in allergic volunteers. *Clin Exp Allergy*. 2001;31:54–60.
33. TePas E, Hoyte EG, McIntire JJ, Umetsu DT. Clinical efficacy of microencapsulated timothy grass pollen extract in grass-allergic individuals. *Ann Allergy Asthma Immunol*. 2004;92:25–31.