
High-dose sublingual immunotherapy: too much of the good?

When first applied in the early 1980s, oral mucosal immunotherapy proved to be ineffective because most of the allergen was immediately destroyed in the stomach.^{1,2} The use of much higher doses than those in subcutaneous immunotherapy² and of enteric-coated capsules³ did not alter this disappointing situation substantially. Only the introduction of sublingual immunotherapy (SLIT), where the allergen is kept under the tongue for several minutes, yielded acceptable results, although no direct systemic absorption of radiolabeled allergen through the oral mucosa could be observed.⁴ On the other hand, a significant part of the allergen remains in the oral mucosa for several hours,⁴ suggesting a facilitated capture by sentinel dendritic cells that, in turn, might induce an initial T-lymphocyte stimulation, leading to T-cell-mediated immune memory and long-term tolerance.⁵ Against this background, the concept of high-dose (at least 50–300 times that of subcutaneous immunotherapy) SLIT has been established, and several clinical studies^{6,7} have shown a clear-cut dose-efficacy ratio. In this issue of the *Annals*, Bordignon and Burastero⁸ present an opposite perception of this problem. By applying low amounts (only 5% of the estimated cumulative subcutaneous dose) of allergen multiple times daily, they found a remarkable correlation between the number of daily doses and clinical efficacy. However, the design of this trial does not allow direct comparison with established forms of SLIT. Further studies are needed in which the normal “high” dose is divided into multiple fractions and compared with the usual once-daily administration. Consequently, and when the authors’ hypotheses are correct, the outcome should be even higher efficacy compared with “normal” SLIT. Furthermore, a satisfying explanation for the results of this study is lacking. High allergen doses have been shown to stimulate T_H1 CD4⁺ cells, whereas low doses induce T_H2 responses.⁹ On the other hand, at least in the gut, minimal doses seem to be efficient at eliciting interleukin 10⁺ transforming growth factor β ⁺ T_H3 cells.¹⁰ It might be speculated that the oral mucosa and the immunocompetent cells within are saturated already at low allergen concentrations; thus, a quasipermanent confrontation with an antigen by multiple daily administrations could be more effective in the promotion of a long-lasting T-cell response. In this way, strategies to enhance the allergen

presentation to local dendritic cells, eg, by regulatory T-cell adjuvants, should be intensified.

NORBERT REIDER, MD
Department of Dermatology
Medical University of Innsbruck
Innsbruck, Austria

REFERENCES

1. Igea JM, Cuevas M, Lazaro M, Quirce S, Cuesta J. Susceptibility of grass-pollen oral immunotherapy extract to the saliva and gastric fluid digestive process. *Allergol Immunopathol (Madrid)*. 1994;22:55–59.
2. 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;42:451–455.
3. Moller C, Dreborg S, Lanner A, Bjorksten B. Oral immunotherapy of children with rhinoconjunctivitis due to birch pollen allergy. *Allergy*. 1986;41:271–279.
4. Bagnasco M, Altrinetti V, Pesce G, et al. Pharmacokinetics of Der p 2 allergen and derived monomeric allergoid in allergic volunteers. *Int Arch Allergy Immunol*. 2005;138:197–202.
5. Martin-Fontecha A, Sebastiani S, Höpken UE, et al. Regulation of dendritic cell migration to the draining lymph node: impact on T lymphocyte traffic and priming. *J Exp Med*. 2003;198:615–621.
6. Marcucci F, Sensi L, Di Cara G, Incorvaia C, Frati F. Dose dependence of immunological response to sublingual immunotherapy. *Allergy*. 2005;60:952–956.
7. Andre C, Perrin-Fayolle M, Grosclaude M, et al. A double-blind placebo-controlled evaluation of sublingual immunotherapy with a standardized ragweed extract in patients with seasonal rhinitis: evidence for a dose-response relationship. *Int Arch Allergy Immunol*. 2003;131:111–118.
8. Bordignon V, Burastero SE. Multiple daily administrations of low-dose sublingual immunotherapy in allergic rhinoconjunctivitis. *Ann Allergy Asthma Immunol*. 2006;97:158–163.
9. Taams LS, van Eden W, Wauben MH. Dose dependent induction of distinct phenotypes: multiple level of T-cell anergy. *J Immunol*. 1999;162:1974–1981.
10. Weiner HL. Induction and mechanism of action of transforming growth factor- β -secreting Th3 regulatory cells. *Immunol Rev*. 2001;182:207–214.