

Evidence for sustained desensitization after sublingual peanut immunotherapy



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Sublingual immunotherapy (SLIT) has become an accepted alternative treatment modality of IgE-mediated allergy, in particular, for allergic rhinoconjunctivitis.¹ Recent meta-analyses have provided robust evidence that 3 years of SLIT with respiratory allergens are required to obtain a long-term clinical benefit and persistent immunologic alterations.² The latter comprise reduced allergen-specific IgE levels, induction of IgE-blocking antibodies, and general downregulation of the allergen-specific T_H2 cell response.³ Thanks to an excellent safety profile, SLIT has also been considered as a treatment option for allergy to food, including peanut. Peanut allergy is a burdensome disease that affects approximately 2% of children and often persists into adulthood.⁴ It is the most common cause for food-induced anaphylaxis. Because of its high anaphylactic potential, this food allergy is difficult to treat. However, administration of peanut allergen under the tongue, where it is kept for a few minutes to allow the mucosal transfer of allergens before swallowing and enzymatic digestion, has mostly induced local adverse effects confined to the oropharynx, with rare gastrointestinal and systemic symptoms.⁵ Several randomized controlled trials have demonstrated an increase in the tolerated dose following long-term peanut SLIT.⁵ For example, children aged 7 to 13 years who received a maintenance dose of 3.7 mg of peanut for 52 weeks tolerated a 22-fold higher dose in post-SLIT food challenges.⁶ SLIT with a maintenance dose of 2 mg of peanut for 48 months in children aged 1 to 11 years achieved partial but clinically significant desensitization that could be maintained by an extended treatment of 3 to 5 years.^{7,8} Along these lines, regular self-administration of peanut at home after the completion of immunotherapy has been considered as a realistic approach to maintaining long-term desensitization.⁹ Together, these findings made SLIT a treatment modality for peanut allergy that promises easy administration, good tolerability, and an acceptable safety profile. However, the duration of sustained unresponsiveness

(ie, the ability to tolerate peanut after withdrawal of peanut SLIT) has not yet been addressed in detail.

In this issue of the *Journal of Allergy and Clinical Immunology*, Kim et al¹⁰ introduce a new approach to addressing this issue (Fig 1). They evaluated clinical and immunologic results of an open-label, prospective, 48-month peanut SLIT with a maintenance dose of 4 mg of peanut in 47 children aged 1 to 11 years.¹⁰ Desensitization was monitored by double-blind, placebo-controlled food challenge and accompanied by skin prick testing. After treatment, 70% of the individuals tolerated a successfully consumed dose (SCD) of 800 mg or more. Kim et al¹⁰ ascribed this strong clinical effect to the higher dosing compared to their previous peanut SLIT in children of the same age.⁷ Despite the doubling of the peanut maintenance dose, the majority of adverse events were oral allergy syndromes. In addition, Kim et al¹⁰ detected alterations of peanut allergen-specific immune responses (ie, significantly enhanced IgG4 antibody levels as well as significantly reduced basophil reactivity, allergen-specific IgE levels, and T_H2 cell-like responses).¹⁰ To assess sustained desensitization after the cessation of SLIT, active treatment was followed by a randomly assigned period of strict peanut avoidance for up to 17 weeks in 37 participants who had tolerated 300 mg or more of peanut in double-blind, placebo-controlled food challenge (Fig 1). A modeled loss of desensitization over time was calculated for an SCD of at least 800 mg; it yielded an estimated median value of 22 weeks until a fall below this threshold. This is promising information for concerned individuals for 2 reasons. First, during the long-lasting treatment required for successful desensitization and its maintenance, patients may occasionally miss their daily dosing or face even longer gaps in the continuity of regular allergen exposure. In this respect, the current study by Kim et al¹⁰ supports previous evidence for a low risk of severe reactions when patients resume treatment after short-term incidents off peanut and thereby contributes to better adaptation to the real-life situation of individuals undergoing peanut treatment. Second, the expectation of a treatment-induced maintained tolerance after several weeks of strict peanut avoidance mitigates the fear of inevitable accidental exposure to a peanut-containing or peanut-contaminated product. Certainly, more studies of this kind are required, particularly, because the durability of desensitization was studied in a selected group of individuals who tolerated at least 300 mg of peanut. Thus, the estimated time period cannot be universalized to every subject undergoing peanut SLIT, as the degree of desensitization varies strongly among different individuals. Nevertheless, the study by Kim et al¹⁰ indicates that short-term breaks in peanut SLIT will not immediately enhance the risk of anaphylactic reactions. Future studies should also monitor the persistence of the immunologic alterations during the off-peanut period, as this approach may identify possible indicators of a loss of tolerance. Finally, prospective evaluations of treatment and immune effects as well as the sustained efficacy of peanut SLIT should be performed with US Food and Drug

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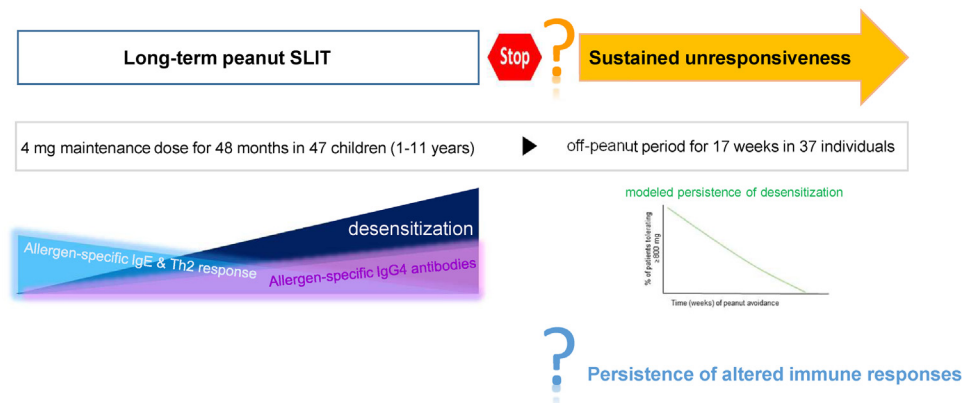


FIG 1. Evaluation of sustained unresponsiveness after peanut SLIT. Children underwent peanut SLIT and double-blind, placebo-controlled food challenge before and after treatment. Individuals who tolerated an SCD of at least 300 mg of peanut were randomly assigned to a peanut avoidance period culminating in double-blind, placebo-controlled food challenge. An SCD of at least 800 mg of peanut before and after the off-peanut period was chosen for calculation of the duration of desensitization. Future studies should include monitoring of the persistence of the altered peanut-specific immune response.

Administration— and/or European Medicines Agency—approved standardized and fully licensed products that do not yet exist as opposed to oral immunotherapy of peanut allergy.

REFERENCES

1. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, et al. EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. *Allergy* 2018;73:765-98.
2. Penagos M, Durham SR. Long-term efficacy of the sublingual and subcutaneous routes in allergen immunotherapy. *Allergy Asthma Proc* 2022;43:292-8.
3. Bohle B, Kinaciyan T, Gerstmayr M, Radakovics A, Jahn-Schmid B, Ebner C. Sublingual immunotherapy induces IL-10-producing T regulatory cells, allergen-specific T-cell tolerance, and immune deviation. *J Allergy Clin Immunol* 2007;120:707-13.
4. Abrams EM, Chan EMS, Sicherer S. Peanut allergy: new advances and ongoing controversies. *Pediatrics* 2020;145:e20192102.
5. Schworer SA, Kim EH. Sublingual immunotherapy for food allergy and its future directions. *Immunotherapy* 2020;12:921-31.
6. Narisety SD, Frischmeyer-Guerrero PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. *J Allergy Clin Immunol* 2015;135:1275-82.e1-6.
7. Kim EH, Yang LN, Ye P, Guo RS, Li QF, Kulis MD, et al. Long-term sublingual immunotherapy for peanut allergy in children: clinical and immunologic evidence of desensitization. *J Allergy Clin Immunol* 2019;144:1320-6.e1.
8. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. *J Allergy Clin Immunol* 2011;127:640-6.e1.
9. Cook Q, Yang LN, Hamad A, Barber H, Herlihy L, Burks AW, et al. Dosing, safety, and quality of life after peanut immunotherapy trials: a long-term follow-up study. *J Allergy Clin Immunol Pract* 2020;8:2805-7.
10. Kim EH, Keet AC, Virkud YV, Chin S, Ye P, Penumarti A, et al. Open-label study of the efficacy, safety and durability of peanut sublingual immunotherapy in peanut-allergic children. *J Allergy Clin Immunol* 2023;151:1558-65.e6.