



Letters

Significantly increased threshold dose after long-term peanut epicutaneous immunotherapy and daily oral peanut intake

In the last decade, large strides have been made regarding immunotherapy for peanut allergy. Although randomized control trials have documented the efficacy and safety of oral immunotherapy (OIT), sublingual immunotherapy, and epicutaneous immunotherapy (EPIT), questions remain regarding long-term outcomes, including optimal maintenance dosing and impact on desensitization and sustained unresponsiveness.^{1–3} Herein, we describe a unique case of long-term peanut tolerance after peanut EPIT within the Viaskin Peanut Efficacy and Safety (VIPES) study, a double-blind, placebo-controlled trial, and subsequent open-label follow-up study to the Viaskin Peanut Efficacy and Safety (OLFUS-VIPES) trial.⁴ The patient then proceeded with peanut oral maintenance dosing, but discontinued maintenance for 6 months and subsequently underwent an oral food challenge—evidence of a real world situation.

Recurrence of food allergy after demonstrated desensitization remains an active concern within previous literature. In 2004, Fleischer et al⁵ described 4 children who tolerated peanut oral food challenge (OFC) with assumed development of natural tolerance, but, after stopping ingestion, developed anaphylaxis upon reexposure.⁵ Directly related to immunotherapy practice, the ability of these therapies to induce long-term sustained unresponsiveness (SU), defined as a lack of clinical reaction upon reexposure to a substance after a prescribed period of immunotherapy discontinuation, remains important to address this concern. Although studies have explored the ability of OIT and sublingual immunotherapy to induce SU, EPIT-induced SU remains largely unstudied.^{6–8} The most comprehensive evidence of EPIT-induced SU thus far was presented at the 2018 EAACI Congress, showing that 80% of patients unresponsive to cumulative dose of at least 1440 mg from the OLFUS-VIPES trial showed no reaction at or above a cumulative dose of 1440 mg 2 months after discontinuing therapy.⁹

The aforementioned patient is a 17-year-old boy with a history of mild intermittent asthma, allergic rhinoconjunctivitis, atopic dermatitis, and immunoglobulin E (IgE)-mediated food allergies to peanut, tree nuts, and egg. He received a peanut allergy diagnosis after positive skin prick testing as an infant (completed before ingestion because of severe atopic dermatitis). At 5 years old, he underwent OFC to better define clinical risk of food allergy reaction before entering school and reacted at 125 mg peanut protein with anaphylaxis, treated with epinephrine, antihistamines, and oral steroids. At age 11 years, he enrolled in the phase IIb VIPES study

after reacting during the double-blind, placebo-controlled food challenge (DBPCFC) at 144 mg cumulative dose with significant coughing, pruritus, and urticaria, and he was treated with epinephrine and antihistamines. He completed the trial requirements for the first year of the study, including the 12-month DBPCFC, and enrolled in the OLFUS-VIPES study. Per protocol, he underwent DBPCFC every 12 months and demonstrated tolerance of increasing cumulative peanut protein doses (Fig 1). After 36 months of EPIT, he tolerated a threshold dose of 5040 mg peanut protein, at which point EPIT was discontinued per study protocol. He had no peanut exposure for the subsequent 2 months and exhibited short-term sustained tolerance when he, again, tolerated 5040 mg peanut protein, developing mild abdominal pain and a few hives, with no treatment required.

He was then recommended by his allergist to consume 2000 mg peanut protein daily to continue regular peanut exposure, an oral maintenance dose in line with ongoing studies at the time. Fourteen months after discontinuing EPIT and after 12 months of consuming 2000 mg peanut nearly every day, the patient requested an OFC to gauge his tolerance and tolerated a cumulative dose of 13,000 mg peanut protein without reaction. After that challenge, he continued to consume 2000 mg peanut protein daily for 18 months, until he had an episode of mild hives after ingestion and exercise. Subsequently, he struggled to coordinate consuming peanut safely without showering or sports within hours of ingestion and discontinued peanut consumption altogether without consultation with his allergist. He returned to care 6 months later, at which point skin prick test was positive (wheal 10 mm, increased from prior), and an OFC was pursued (eTable 1). Despite a period of 6 months without peanut consumption, he ingested a total of 4000 mg peanut protein before developing scattered hives, treated with antihistamine monotherapy. Although the cumulative dose was notably decreased from the highest cumulative tolerated dose 18 months earlier, tolerance markedly improved from the 144-mg dose that precipitated anaphylaxis at age 11 years. After this final OFC, he was instructed to restart daily oral maintenance at 300 mg/day (then standardized OIT long-term maintenance dose), with an emphasis on calling if concerns develop. He has been without reaction with daily ingestion.

This case represents a realistic example of the challenges faced by clinicians and patients when pursuing immunotherapy for peanut allergy. Despite an excellent relationship with his allergist and research team, the patient's family discontinued oral maintenance because of lifestyle factors and without informing his care team. Adherence to any chronic medication regimen can be poor in adolescent patients, a phenomenon not necessarily limited to oral immunotherapy. Although clinician, patient, and family alike were quite pleased with the results of his latest OFC, there was no other way to predict the likelihood of a significant reaction on

Disclosures: Terri F. Brown-Whitehorn, MD, is a DBV Technologies grant recipient, clinical advisory board member, and consultant. Megan O. Lewis, CRNP, is a DBV Technologies consultant. Courtney B. Rooney, RN, is a DBV Technologies consultant. The other authors have nothing to disclose.

Funding Sources: None.

<https://doi.org/10.1016/j.anai.2020.01.021>

1081-1206/© 2020 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

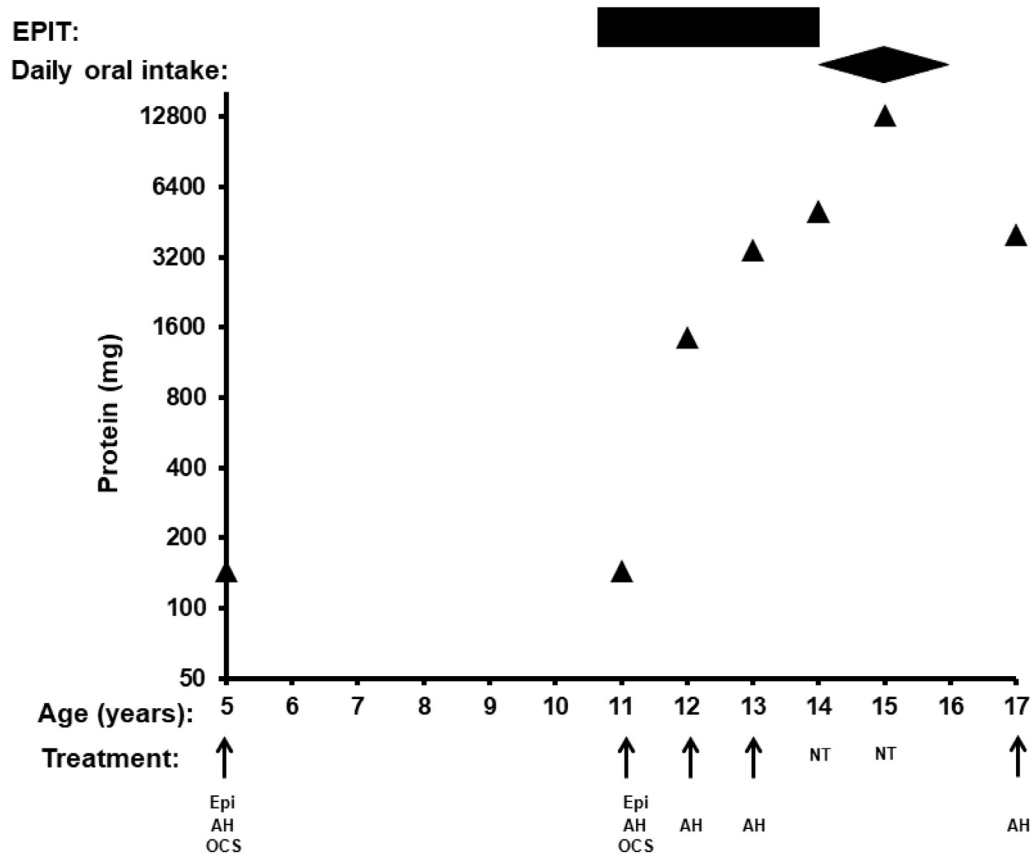


Figure 1. Peanut oral food challenges, immunotherapy, and oral maintenance from age 5–17 years. Abbreviations: AH, antihistamine; Epi, epinephrine; EPIT, epicutaneous immunotherapy; NT, no treatment; OCS, oral corticosteroid.

reexposure. The patient demonstrated remarkable improvement from his baseline anaphylaxis at 144 mg peanut protein to only mild hives at 4000 mg peanut protein after treatment with EPIT followed by daily oral maintenance; however, this dramatic increase in threshold dose should not be generalized to all peanut-allergic patients without further randomized research or robust case-based evidence. This case highlights the need for further research to better understand the potential for prolonged treatment with EPIT followed by oral maintenance dosing to induce clinically significant improvement in patient quality of life and safety, but it provides hopeful evidence for use of EPIT in clinical practice.

Whitney Reid Fink, MD
 Peter Capucilli, MD
 Megan O. Lewis, CRNP
 Courtney B. Rooney, RN
 Terri F. Brown-Whitehorn, MD
 Children's Hospital of Philadelphia, Pennsylvania
Finkw@email.chop.edu

Supplementary Data

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.anai.2020.01.021>

References

1. Varshney P, Jones SM, Scurlock AM, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol*. 2011;127(3):654–660.
2. Kim EH, Bird JA, Kulis M, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. *J Allergy Clin Immunol*. 2011;127(3):640–646.
3. Sampson HA, Shreffler WG, Yang WH, et al. Effect of varying doses of epicutaneous immunotherapy vs placebo on reaction to peanut protein exposure among patients with peanut sensitivity: a randomized clinical trial. *JAMA*. 2017;318(18):1798–1809.
4. Shreffler WG, Nadeau KC, Leonard SA, Sussman GL, Sampson HA. Efficacy and safety of long-term epicutaneous immunotherapy (epit) treatment of peanut allergy with viaskin® peanut: results of the two-year extension of the Vipes phase IIb clinical trial. *J Allergy Clin Immunol*. 2017;139(2):AB377.
5. Fleischer DM, Conover Walker MK, Christie L, Burks WA, Wood RA. Peanut allergy: recurrence and its management. *J Allergy Clin Immunol*. 2004;114:1195–1201.
6. Vickery BP, Scurlock AM, Kulis M, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol*. 2014;133(2):468–475.
7. Hsiao KC, Ponsonby AL, Axelrad C, Pitkin S, Tang MLK. Long-term clinical and immunological effects of probiotic and peanut oral immunotherapy after treatment cessation: 4-year follow-up of a randomised, double-blind, placebo-controlled trial. *Lancet Child Adolesc Health*. 2017;1:97–105.
8. Yang L, Steele PH, Hamilton DK, et al. Sustained unresponsiveness after sublingual immunotherapy for peanut-allergic children. *J Allergy Clin Immunol*. 2017;139(2 Supp):AB175.
9. Brown-Whitehorn T, de Blay F, Sampson HA. Sustained unresponsiveness following long-term epicutaneous immunotherapy (EPIT) with VIASKIN peanut: results of the OLFUS-VIPES phase IIb study. Munich, Germany: Poster presented at the EAACI Congress 2018; May 26–30, 2018.

Appendix

eTable 1

Skin Prick Test Results by Age and Major Clinical Event

Age (years)	Clinical event	SPT wheal (mm)
5	Peanut allergy diagnosis	8
8		8
10		10
11	Started EPIT	14
12		10
13		7
14	Finished EPIT	9
14	EPIT discontinued for 2 months	13
	Started oral 2000 mg peanut protein daily	
15	OFC 13,000 mg threshold dose	7
17	Stopped daily oral peanut 6 months prior	10
	OFC 4000-mg threshold dose	
	Restarted oral 300 mg peanut protein daily	

Abbreviations: EPIT, epicutaneous immunotherapy; OFC, oral food challenge; SPT, skin prick test.