

Oral immunotherapy for peanut allergy in clinical practice is ready

Lyndon E. Mansfield, M.D.

ABSTRACT

Oral immunotherapy (OIT) for peanut allergy is ready for clinical allergy practice. Some physicians, particularly at academic centers, believe that OIT is not ready for clinical practice. The shortcomings of the present general recommendations of food avoidance and provision of epinephrine autoinjectors for a select number of patients demand a different approach. In peanut-allergic patients, the rate of accidental reactions is ~10% annually. Between 1 and 2% of these reactions require epinephrine or emergency department visits. Food allergy and peanut allergy, specifically, have a large negative impact on the quality of life (QOL) for patients and their families, which can be psychosocially debilitating. These decreases in health-related QOL continue into adulthood. There is only an ~20% chance of spontaneous remission in peanut allergy. Given this climate, three private allergy practices have begun providing OIT to 150 patients with peanut anaphylaxis. One hundred eleven (74%) patients were able to tolerate eight peanuts (8 g, ~2 g of protein). During outpatient dosing, epinephrine was used at a rate of 8 per 10,000 doses. To date, there have been no long-term (>24–36 months) unexpected reactions. OIT decreases risk and in one study, conducted in a practice setting, it was shown to improve QOL. OIT is a meaningful clinical procedure that can help our patients.

(Allergy Asthma Proc 34:205–209, 2013; doi: 10.2500/aap.2013.34.3666)

There are differing opinions about whether or not oral immunotherapy (OIT) for peanut allergy is a clinical procedure. The question at hand is not about whether or not OIT can be successfully performed by a trained community-based allergist, but rather if the present risks of OIT support its benefit. It is a legitimate medical procedure for the benefit of patients. The question addressed here is whether it should be performed as a procedure for general clinical use of evidence and experience.

It has been suggested that the situation surrounding OIT is in equipoise. This means that we are not certain if the benefits outweigh the risks. Arguments for equipoise are that there is no optimal dosing schedule, a poorly understood mechanism of action, a risk of systemic reactions during OIT, a risk that OIT may induce eosinophilic esophagitis,^{1,2} and that there may be long-term potential side effects we do not know about.^{3,4}

The limitations of the present studies of OIT have been detailed elsewhere.

On the other hand, a number of well-trained clinical allergists find that for many patients, the situation is not in equipoise. The disturbance to quality of life (QOL) for the patient, the parents, and siblings is often very great.⁵ The children do not have a normal QOL. Peanut-allergic children annually have a postdiagnosis rate of accidental reaction of ~10%, and these reactions often require epinephrine or an emergency department visit.⁶ For 80% of peanut-allergic patients, there is little chance of remission and diminishment in risk or improvement in their QOL. The model of avoidance as best strategy thus has significant hidden costs.

Therefore OIT, even with the present shortcomings, to our knowledge, is a justified therapy for these patients to both diminish the long-term risks associated with peanut allergy and to improve QOL. The public will have to answer the question for themselves. Are patients who undergo OIT (and their families) better off, with less risk and life disturbances, than they previously experienced? More importantly, is there room for more than just the academic model in offering this therapy?

THE SITUATION WITH THE PRESENT RECOMMENDATIONS

The number of estimated visits to the emergency room for food-induced anaphylaxis increased from

From the Department of Pediatrics, Paul Foster School of Medicine, El Paso, Texas, and Western Sky Medical Research, El Paso, Texas

Presented at the Eastern Allergy Conference, May 31, 2012, Palm Beach, Florida.

The authors have no conflicts of interest to declare pertaining to this article

Address correspondence and reprint requests to Lyndon E. Mansfield, M.D., 2121 Wyoming Ave, El Paso, Texas 79903

E-mail address: Immunman@westernskymed.com

Copyright © 2013, OceanSide Publications, Inc., U.S.A.

30,000 in 1999 to 90,000 in 2012.⁷ Peanut allergy appears to be responsible for 20–28% of these reactions.⁸ This would seem in accordance with the recent prevalence studies suggesting that 1.4% of American children are peanut sensitive, a threefold increase over the last 10 years.⁴ Based on Yocum's data, it has been estimated that there are 150–200 annual deaths from food-induced anaphylaxis.⁹ The prevalence of peanut allergy has increased threefold in the last 20 years.¹⁰ This has been accompanied by an increase in hospitalizations for food-induced anaphylactic reactions. The same phenomena of the increased prevalence of peanut allergy has occurred in the United Kingdom and Australia.⁴ Because the spontaneous remission rate in peanut allergy is 20%, the impact of these recent increases will likely have a dramatic long-term impact on health care resources.¹¹

In a large series of 782 peanut-allergic patients followed for ≥ 5 years, their postdiagnosis rate of reactions was $\sim 10\%$ per year. Between 1 and 2% of the reactions required epinephrine or emergency department visits.⁶ This suggests that avoidance is difficult to achieve for peanut-allergic patients. With only 20% remission, it appears that this could be an ongoing cycle past the 5 years reported.

Provision of epinephrine autoinjectors is a major facet of the avoidance model. However, a number of reports suggest nonadherence by patients and parents from using the autoinjectors when indicated.^{12–14} There is no evidence that providing epinephrine autoinjectors has decreased the number of anaphylactic-related deaths.¹⁵ In fact, in Bock's two-part series on food allergy fatality, the majority of individuals who died actually had epinephrine units prescribed to them, but failed to use them.¹⁴ The calculated lifetime risk of death from food-induced anaphylaxis in nut allergy appears to be 1 in 1000 for women and 5 in 10,000 for men.¹⁵ OIT is a potentially life-saving therapy that could lower the risk of adverse events that occur from the risk taking that has been so well documented.¹⁶

THE EFFECT OF THE PRESENT RECOMMENDATIONS ON THE QOL IN PATIENTS AND PARENTS AND FAMILY

Food allergy, especially if there are multiple sensitizations, anaphylactic reactions, or recent emergency visits, can cause severe psychosocial problems in family members. This is greater typically in mothers than fathers. There was a finding of overprotectiveness of the children who have food allergy. Parents had concerns relating to socialization of their food-allergic children.¹⁷ In the year 2000, it was reported that children with food allergy had more disruption of daily living and activity compared with children who had active rheumatoid disease.¹⁸

A study suggested improved QOL after provision of epinephrine autoinjectors.¹⁹ Other studies suggested an opposite effect in that the references to the risk of dying and anaphylactic reactions actually impaired QOL.¹⁵

Health-related QOL is equally impaired, whether the diagnosis is from the physician or by self-diagnosis.²⁰ In peanut-allergic patients health-related QOL is most impaired if there has been a recent emergency department visit or if the parents are better educated and more informed.²¹ OIT is an intervention that could significantly decrease the likelihood that an emergency department visit or reaction would occur. Using a variety of validated food allergy questionnaires, Lieberman and Sicherer discovered that health-related QOL is decreased to the greatest extent by food-induced anaphylactic reactions and multiple food sensitizations.²¹

THE EFFECTS OF OIT FOR PEANUT ALLERGY IN PRIVATE PRACTICES

The general principles of OIT for food allergies have been known for over 100 years, with case series and case reports in the first half of the 20th century.^{22,23} OIT was described in Tuft's, "Clinical Allergy," and Vaughan and Black's, "Practice of Allergy," the classic textbooks of that era.^{24–26} Beginning in the 1980s a large body of work from Patriarca and colleagues rekindled interest in the outpatient application of OIT.²⁷ The actual procedure follows a near identical protocol of gradually increasing dosing to those being used in the National Institutes of Health (NIH)-sponsored trials.

In unpublished data from three private allergy practices, OIT has been successfully provided to 150 patients, including those with a history of peanut anaphylaxis (personal communication). Approximately 50% of these patients were positive on open office peanut challenges, and the other 50% of the patients enrolled were based on IgE levels or skin test positivity and a strong history. One hundred eleven of these patients were able to complete OIT for peanut allergy and could tolerate 4 g of defatted peanut flour or eight peanuts or more. This provided considerable protection from the usual average accidental exposure of 1 g or less (one peanut).²⁸ Our selection criteria do not differ significantly from those of the NIH-sponsored trials, and in some respects, include a more realistic sample of the typical peanut-allergic patient because severely reactive patients are not excluded, and everyone does not have to fail challenge to be enrolled. Although this is uncontrolled data, only a small segment of the published U.S. data pertaining to peanut OIT are from controlled studies.²⁹

Our group offers OIT because we feel this is a QOL-sparing measure. Most parents and patients reported

marked improvement in their lives after successful OIT for peanuts. There was relief of fear and anxiety and compulsive behaviors. Patients were very grateful for the improved life status of their child and for their family life.³⁰

In a more formal study, Factor and colleagues reported that OIT for peanut was able to improve the food health-related QOL in children and adolescents measured with validated food QOL questionnaires.³¹ Ninety of 100 patients completed OIT and were ingesting three M&M peanuts (450 µg peanut protein). The reactions during buildup were mild and typically gastrointestinal. Seven patients dropped out. There were no serious adverse reactions. This rate of reaction is comparable with the NIH-sponsored studies, but in this series, unlike the NIH-sponsored studies, there were no severe reactions requiring epinephrine.

THE CONCERNS ABOUT OIT FOR PEANUT ALLERGY IN CLINICAL PRACTICE

Regardless of the setting, the primary concern surrounding OIT is the potential for an acute adverse events during any phase of the protocol. A second concern is the potential for longer-term adverse reactions, such as the development of eosinophilic esophagitis.

The NIH-sponsored trials have been very consistent in their message that OIT is both safe and effective. They cite a low number of reactions per dose of therapy provided and specify that most of the immediate reactions have been mild oropharyngeal or gastrointestinal events, notwithstanding a handful of anaphylaxis episodes.³² Again, this is no different than our experience as well, where we denote mostly mild gastrointestinal symptoms and a handful of cases of anaphylaxis. There may be a small risk of developing eosinophilic esophagitis during therapy. Wasserman has reported this related to peanut OIT.³³ We believe this is an infrequent event, but one that is not inconsistent with the natural history of food allergy in that some children go on to develop eosinophilic esophagitis at a later date. In the cases of eosinophilic esophagitis that developed, OIT was stopped with remission of symptoms.^{1,2,33}

There is legitimate concern regarding the potential to provoke an anaphylactic reaction during OIT. We, as well as the NIH-sponsored studies, have both reported this occurrence with home dosing. In our experience of 150 patients with peanut anaphylaxis, the epinephrine use was 8 per 10,000 doses, a rate far below the rate in subcutaneous immunotherapy. As part of our protocol, the parents and patients are instructed and reinstructed to use the epinephrine aggressively, and epinephrine must be available at the location where the peanut dosing was given. There has been no reported

Instructions for outpatient dosing during food desensitization

Take the recommended amount and frequency as per the instructions.

This amount will vary as the desensitization proceeds.

Reactions in most patients have been infrequent and mild, but there is a risk of a stronger reaction. The following advice will decrease this risk.

- 1. Please take the food with other foods if at all possible.**
- 2. Do not have the patient exercise vigorously for at least an hour after taking.**
- 3. If the patient has a high fever 101 or greater, skip a dose.**
- 4. If the patient's asthma is acting up, skip the dose and contact us.**
- 5. Always have your epipen ready to use if necessary. Call us if you use it. If the reactions are ongoing go to the nearest emergency room.**

I received a copy of these instructions and understand them.

Signature

Date

Figure 1. Home dosing instructions.

mortality from OIT of any food. Parents and patients in the private practice are continually reminded to be cautious at dosing time. These instructions and precautions are no different than that of the participants in the NIH-sponsored studies. Figure 1 is the instruction sheet given to patients and parents for outpatient dosing.

We have not seen any unusual side effects or adverse events in the patient group, which includes a few patients taking peanuts for as long as 6 years. This would be in accord with the long-term outcomes of subcutaneous and sublingual immunotherapy. Our experience may not be sufficient to answer the concern of long-term potential adverse events, but again, we reemphasize that this experience is nearly identical to that of the NIH-sponsored trials in terms of the number of years of experience with this therapy and the outcomes to date. We take safety as seriously as the academic groups do and strictly adhere to the recommendations as specified by Thyagarajan *et al.* to further reduce any incidents of reaction.³⁴ There is no published NIH-sponsored study that we are aware of that has evaluated QOL

as an outcome of OIT as did Gallucci and colleagues and as Factor *et al.* have reported.^{30,31}

LIFE IS NOT ENTIRELY NORMAL AFTER PEANUT OIT

Although OIT, as presently practiced, offers a tremendous potential relief of anxiety and poor QOL, it does not completely normalize life. At the present time, no study has established a lasting tolerance that can be achieved that does not require the patient to ingest peanut protein at some fixed interval. However, the patients and family have an element of control and, hopefully, life slowly normalizes as the therapy increases one's ability to withstand a reaction. To attain the goal of a totally normalized life would require proof that we can induce immune tolerance or a significantly persistent desensitization that continues a protective threshold for the dose response to peanut ingestion.

Peanut allergy for many reasons may not be representative of all food allergies. The facts are that few "outgrow" peanut allergy, and that there is a serious impact on QOL in certain families. Total peanut avoidance is difficult. This means that these patients and families will have problems for a long time, unless there is an intervention. For such patients and families, OIT for peanut allergy, even without being perfect, offers a worthwhile informed choice. Although not normal, after OIT, there is improved QOL and loss of fear and risk from accidental ingestions. These are important outcomes that we have been able to accomplish through our OIT program in a private practice. This indicates the therapy can be successfully conducted in the community. What we offer is not fundamentally different than the NIH-sponsored studies. Their studies suggest the procedure is safe and effective; however, their lead investigator has called for OIT to remain in a state of equipoise, which is a puzzling paradox.³⁵

There is no doubt that we will learn more about OIT for peanuts and other foods and how to better apply these therapies for our patients' benefit. In the meantime, this therapy can be performed in the community setting by a qualified committed well-trained allergists and staff. Our data and experience have shown it is an important clinical procedure that can provide substantial benefits for many of our patients.

REFERENCES

- Ridolo E, De Angelis G, and Dall'aglio P. Eosinophilic esophagitis after specific oral tolerance induction for egg protein. *Ann Allergy Asthma Immunol* 106:73–74, 2011.
- Sanchez Garcia S, Rodriguez Del Rio P, Escudero C, and Martinez Gomez MJ. Possible eosinophilic esophagitis induced by milk oral immunotherapy. *J Allergy Clin Immunol* 29:1156–1157, 2011.
- Thyagarajan A, Pooja V, Jones SM, et al. Peanut oral immunotherapy is not ready for clinical use. *J Allergy Clin Immunol* 126:31–22, July 2009.
- Sicherer SH, Munoz-Furlong A, Godbold JH, and Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol* 125:1322–1326, 2010.
- Akeson N, Worth A, and Sheikh A. The psychological impact of anaphylaxis on young people and their parents. *Clin Exp Allergy* 37:1213–1220, 2007.
- Neuman-Sunshine DL, Eckman JA, Keet CA, et al. The natural history of persistent peanut allergy. *Ann Allergy Asthma Immunol* 108:326–333, 2012.
- Jarvinen KM. Food-induced anaphylaxis. *Curr Opin Allergy Clin Immunol* 11:255–261.
- Koplin JJ, Martin PE, and Allen KJ. An update on epidemiology of anaphylaxis in children and adults. *Curr Opin Allergy Clin Immunol* 11:492–496.
- Yocum MW, Butterfield JH, Klein JS, et al. Epidemiology of anaphylaxis in Olmsted County: A population-based study. *J Allergy Clin Immunol* 104:452–456, 1999.
- Rinaldi M, Harnack L, Oberg C, et al. Peanut allergy diagnoses among children residing in Olmsted County, Minnesota. *J Allergy Clin Immunol* 130:945–950, 2012.
- Patel DA, Holdford DA, Edwards E, and Carroll NV. Estimating the economic burden of food-induced allergic reactions and anaphylaxis in the United States. *J Allergy Clin Immunol* 128:110–115, 2011.
- Pumphrey R. When should self-injectable epinephrine be prescribed for food allergy and when should it be used? *Curr Opin Allergy Clin Immunol* 8:254–260, 2008.
- Sicherer SH, and Simons FE. Quandaries in prescribing an emergency action plan and self-injectable epinephrine for first-aid management of anaphylaxis in the community. *J Allergy Clin Immunol* 115:575–583, 2005.
- Bock SA, Munoz-Furlong A, and Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001–2006. *J Allergy Clin Immunol* 119:1016–1018, 2007.
- Pumphrey R. Anaphylaxis: Can we tell who is at risk of a fatal reaction? *Curr Opin Allergy Clin Immunol* 4:285–290, 2004.
- Sampson MA, Munoz-Furlong A, and Sicherer SH. Risk-taking and coping strategies of adolescents and young adults with food allergy. *J Allergy Clin Immunol* 117:1440–1445, 2006.
- Springston EE, Smith B, Shulruff J, et al. Variations in quality of life among caregivers of food allergic children. *Ann Allergy Asthma Immunol* 105:287–294, 2010.
- Primeau MN, Kagan R, Joseph L, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. *Clin Exp Allergy* 30:1135–1143, 2000.
- Cummings AJ, Knibb RC, Erlweyn-Lajeunesse M, et al. Management of nut allergy influences quality of life and anxiety in children and their mothers. *Pediatr Allergy Immunol* 21:586–594, 2010.
- Sicherer SH, Noone SA, and Munoz-Furlong A. The impact of childhood food allergy on quality of life. *Ann Allergy Asthma Immunol* 87:461–464, 2001.
- Lieberman JA, and Sicherer SH. Quality of life in food allergy. *Curr Opin Allergy Clin Immunol* 11:236–242.
- Keston BM, Waters I, Hopkins JG. Oral desensitizations the common foods. *J Allergy* 6:428–431, 1935.

23. Edwards HE. Oral desensitization in food allergy. *Can Med Assoc J* 31:234–236, 1942.
24. Tuft L. V. Methods and principles of treatment. In *Clinical Allergy*. Philadelphia, PA, and London: W.B. Saunders, Vaughn W and Black HJ (Eds)., 178–179, 1937.
25. Tuft L. VII. Food allergy. In *Clinical Allergy*. Philadelphia, PA, and London: W.B. Saunders, Vaughn W and Black HJ (Eds)., 615–619, 1937.
26. Vaughn W, and Black HJ. XXXIV. The treatment of food allergy. In *Practice of Allergy*. St. Louis, MO: C.V. Mosby Co., Vaughn W and Black HJ (Eds), 328–330, 1948.
27. Patriarca G, Nucera E, Roncallo C, et al. Oral desensitizing treatment in food allergy: clinical and immunological results. *Aliment Pharmacol Ther* 17:459–465, 2003.
28. Sicherer SH, and Sampson HA. Peanut allergy: Emerging concepts and approaches for an apparent epidemic. *J. Allergy Clin Immunol* 120:491–503, 2007 .
29. Sheikh A, Venderbosch I, and Nurmatov U. Oral immunotherapy for peanut allergy. *Br Med J* 340:c2938, 2010.
30. Gallucci AR, Wasserman RL, Sugerman RW, et al. Oral immunotherapy (OIT) of food allergy (FA) successfully desensitizes most patients. *J Allergy Clin Immunol* 127:83 (Abs), 2010.
31. Factor JM, Mendelson L, Lee J, et al. Effect of oral immunotherapy to peanut on food specific quality of life. *Ann Allergy Asthma Immunol*. 109:348–352, 2012.
32. Hofmann AM, Scurlock AM, Jones SM, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. *J Allergy Clin Immunol* 124:286–291, 2009.
33. Wasserman RL, Sugerman RW, Mireku-Akomeah N, et al. Peanut oral immunotherapy (OIT) of food allergy (FA) carries a significant risk of eosinophilic esophagitis (EoE). *J Allergy Clin Immunol* 127:AB15, 2011 (Abs).
34. Thyagarajan A, Varshney P, Jones SM, et al. Peanut oral immunotherapy (OIT) is not ready for clinical use. *J Allergy Clin Immunol* 126:31–32, 2010.
35. Sampson HA. Peanut oral immunotherapy: Is it ready for clinical practice? *J Allergy Clin Immunol: In Practice* 1:15–21, 2013. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.