Original Article

Oral Immunotherapy for Peanut Allergy: Multipractice Experience With Epinephrine-treated Reactions

Richard L. Wasserman, MD, PhD[a], Jeffrey M. Factor, MD[b], James W. Baker, MD[c], Lyndon E. Mansfield, MD[d], Yitzhak Katz, MD[e], Angela R. Hague, PA-C[f], Marianne M. Paul, BS[c], Robert W. Sugerman, MD[a], Jason O. Lee, MD[b], Mitchell R. Lester, MD[b], Louis M. Mendelson, MD[b], Liat Nacshon, MD[g], Michael B. Levy, MD[g], Michael R. Goldberg, MD, PhD[g], and Arnon Elizur, MD[e] *Dallas and El Paso, Tex; West Hartford, Conn; Portland, Ore; and Tel Aviv and Zerifin, Israel*

What is already known about this topic? Oral immunotherapy for IgE-mediated food allergy has been reported for decades but is seldom performed in allergy practices.

What does this article add to our knowledge? This report demonstrates, in 352 patients who received more than 240,000 doses of peanut, that oral immunotherapy for peanut allergy can be performed in a practice setting with a manageable rate of epinephrine-treated reactions.

How does this study impact current management guidelines? This study suggests that some allergists may be able to offer oral immunotherapy for peanut allergy to patients with peanut allergy, in recognizing that mild and serious reactions occur and that long-term efficacy is unproven.

BACKGROUND: Peanut allergy creates the risk of life-threatening anaphylaxis that can disrupt psychosocial development and family life. The avoidance management strategy often fails to prevent anaphylaxis and may contribute to social dysfunction. Peanut oral immunotherapy may address these problems, but there are safety concerns regarding implementation in clinical practice.

OBJECTIVE: The purpose of this report is to communicate observations about the frequency of epinephrine-treated reactions during peanut oral immunotherapy in 5 different allergy/immunology practices.

METHODS: Retrospective chart review of peanut oral immunotherapy performed in 5 clinical allergy practices.

RESULTS: A total of 352 treated patients received 240,351 doses of peanut, peanut butter, or peanut flour, and experienced 95 reactions that were treated with epinephrine. Only 3 patients received 2 doses of epinephrine, and no patient required more intensive treatment. A total of 298 patients achieved the target maintenance dose for a success rate of 85%.

CONCLUSION: Peanut oral immunotherapy carries a risk of systemic reactions. In the context of oral immunotherapy, those reactions were recognized and treated promptly. Peanut oral immunotherapy may be a suitable therapy for patients managed by qualified allergists/immunologists. © **2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:91-6)**

Key words: *Peanut; Oral immunotherapy; Food allergy; Food allergy treatment*

The prevalence of food allergy has increased in recent years. Estimates indicate that 5% of children younger than age 5 years old and 4% of older individuals are affected.[1] Food allergies, especially peanut allergy, are major health problems because of anaphylaxis risk[2] and the adverse effects on quality of life.[3-7] The guideline-recommended treatment for food allergy is strict dietary avoidance and the treatment of systemic reactions with epinephrine autoinjectors (AMS).[8] Both severe and mild reactions create problems: severe reactions because of the possibility of death, mild reactions because the unpredictability of future reactions[9,10] requires the same AMS response as for those with severe reactions. The difficulty of implementing the peanut AMS in school and social environments[11-13] creates major burdens for many affected children and their families. In our experience,

[a]Department of Pediatrics, Medical City Children's Hospital, Dallas, Tex
[b]New England Food Allergy Treatment Center, Connecticut Children's Medical Center, West Hartford, Conn
[c]Department of Allergy and Immunology, Emanuel Hospital, Portland, Ore
[d]Paul Foster School of Medicine, El Paso, Tex
[e]Zerifin Israel and Department of Pediatrics, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[f]DallasAllergyImmunology, Dallas, Tex
[g]Allergy & Immunology Institute, Asaf Harofe Medical Center, Zerifin, Israel
Patient data collection and analysis were supported by each participating allergy practice, without external funding.
Conflicts of interest: J. M. Factor has received lecture fees from TEVA. L. E. Mansfield has received lecture fees from WAO, ECAC, and Compedia. A. R. Hague is employed by Dallas Allergy Immunology. M. R. Lester is part owner of the New England Food Allergy Treatment Center. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication September 1, 2012; revised September 27, 2013; accepted for publication October 1, 2013.
Corresponding author: Richard L. Wasserman, MD, PhD, Medical City Children's Hospital, 7777 Forest Lane, Suite B-332 Dallas, TX 75230. E-mail: drrichwasserman@gmail.com.
2213-2198/$36.00

http://dx.doi.org/10.1016/j.jaip.2013.10.001

Abbreviations used
AMS- Avoidance management strategy
ETR- Epinephrine-treated reaction
IRB- Institutional review board
OIT- Oral immunotherapy
POIT- Peanut oral immunotherapy
PP- Peanut protein
SCIT- Subcutaneous immunotherapy
SPT- Skin prick test

many families subjected to these burdens may seek an alternative approach to AMS for peanut allergy.

The standard AMS[8] of counseling avoidance and dispensing epinephrine autoinjectors is not optimal.[14,15] Most food allergy reactions occur after ingestion of foods thought to be safe.[14] One study found that accidental exposure to peanuts by children with peanut allergy occurs in as many as 11.9% of patients each year.[16] In 1411 children followed up over 5 years, 71% of these exposures resulted in moderate-to-severe reactions. Only 20% of these children who experienced a reaction received epinephrine. In another study, peanut ingestion definitely or probably accounted for 20 of 32 episodes of fatal-food-associated anaphylaxis.[17] Results of studies have shown that an available epinephrine autoinjector is often not used in situations in which its use is indicated.[16,18] Indeed, the rate of use of epinephrine autoinjectors is disappointingly low.[19] As a result, there is increased interest in alternative approaches to treating food allergies, including oral immunotherapy (OIT).[20]

Although OIT for food allergy is not an established treatment, the use of OIT is supported by an extensive body of literature. References to oral desensitization date to 1905.[21] Case series[22-25] and clinical trials of peanut OIT (POIT)[26,27] have shown encouraging results. Similar to the experience with subcutaneous immunotherapy (SCIT), careful observations of clinical practice may provide supplementary information that informs the design of clinical trials.[28,29] Although lacking the power of prospective, controlled trials, this article reports the experience with significant adverse events during POIT in 352 patients who received more than 240,000 doses. Although each site used somewhat different procedures, we believe that it is appropriate to report our observations together because of the total number of patients and doses administered, and because variations within an accepted range of practice are common to the most widely used allergy treatment, SCIT. Several allergists have expressed their views that POIT should not be undertaken outside of controlled clinical trials[30] because of their belief that POIT is as yet unproven and unsafe. We believe that reporting our experience with OIT for food allergy will contribute to consideration of those issues. We report the experiences of 5 allergy practices with POIT, which represents more than 350 treated patients, who received more than 240,000 doses.

METHODS

This article reports a retrospective medical record review of patients who received POIT treatment through July 1, 2012, in 5 allergy practices. Two practices received institutional review board (IRB) approval for the POIT treatment, and 3 practices received IRB approval for retrospective chart review (details are in this article's Online Repository at www.jaci-inpractice.org). Each parent and patient was told that the standard of care for peanut allergy was the AMS. It was further explained that POIT is not a standard treatment and is not recommended in the Food Allergy Guidelines.[8] It was emphasized that POIT administered in these practices is not being done as research but as a form of treatment. Discussions included reference to the unproven nature of the treatment, the limited clinical experience, the rationale for POIT, and the uncertainty of the long-term outcome (desensitization vs tolerance) as well as the risk of anaphylaxis and eosinophilic esophagitis. After the informed consent discussion, each parent or patient signed an informed consent document developed by the individual site.

At site 1, the patients had a history of reaction and a significant peanut anti-IgE (*in vitro* or *in vivo*) or a positive challenge before treatment. At site 2, the patients had a history of an anaphylactic reaction, a nonanaphylactic reaction with symptoms suggestive of IgE-mediated disease within 1 year of beginning POIT, or a positive challenge, except for patients with a high IgE (skin prick test >7-mm wheal or ImmunoCap (Phadia, Portage, Mich) $\geq$ 15 kU/L) who were treated based on sensitization alone. At sites 3, 4, and 5, the initial treatment dose was determined by a positive open challenge. Therefore, 341 of 352 patients' peanut allergy was confirmed at the start of POIT. The remaining 11 patients had peanut IgE >14 kU/L. No patient was excluded because of a history of a severe reaction or a high antipeanut IgE.

Treatment protocols used at each of the 5 sites were developed locally based on previously used approaches.[22,26,31] At each site, treatment began with a dose of peanut flour that contained a quantity of peanut protein (PP) (based on the package label) projected to be below the threshold dose for a reaction. As the dose of PP increased, alternate forms of peanut were used (peanut butter, whole peanuts, Peanut M&M's [Mars Inc, McLean, Va]) (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). All dose increases were administered under direct observation at the treatment sites. The patients who tolerated an increased dose received that dose once or twice a day for a defined period of time and then returned to the site for dose increase(s). Once a patient reached his or her maintenance target dose, that dose was administered at home once or twice a day for a prolonged period. Decisions regarding dose adjustments and discontinuation of therapy were based on the clinical judgment of the physician. The patients who reached maintenance were followed-up periodically. At each site, patients and/or parents were instructed to inform the site of any significant reactions. Detailed descriptions of the methods, including dosing schedules, are available in the Methods section and in Table E2 of this article's Online Repository at www.jaci-inpractice.org. The patients were instructed to avoid exercise for 2 hours after ingesting their peanut dose and to contact the treatment site in the event of illness to discuss dose adjustment. Criteria for epinephrine administration in response to a reaction varied significantly among the sites. At site 1, the patients and/or parents were instructed to use epinephrine for any reaction other than isolated urticaria or mild oral itch. The description of a mild reaction and the minimum criteria for epinephrine administration used by each site are shown in Table I.

RESULTS

Patients (59% male), ages 3 through 24 years of age, were treated in 4 community-based private allergy/immunology practices in the United States and 1 hospital-based practice in Israel by using locally developed treatment protocols. Each protocol

TABLE I. Epinephrine-treated reactions during peanut oral immunotherapy

	Site no.					
	1	2	3	4	5	Total
Patients who began treatment	98	112	86	34	22	352
Escalation doses	30,378	34,650	7,224	6,451	1,023	79,726
Maintenance target dose of PP (mg)	2,000	415	2,000-3,200	4,000-8,000	3,600	—
No. (%) of patients who achieved maintenance dose	81 (83)	104 (93)	65 (76)	28 (82)	20 (91)	298 (85)
Definition of mild reaction	Urticaria, oral itch, mild abdominal pain without nausea or vomiting	Urticaria, oral itch, mild abdominal pain without nausea or vomiting	Any reaction that does not involve throat closing or chest tightness or loss of consciousness	Urticaria, oral itch, mild abdominal pain without nausea or vomiting	Rash, mild itch, respiratory symptoms responsive to β agonist	
Criteria for administering epinephrine	Any angioedema or respiratory tract symptoms or vomiting within 1 h of dosing	Cough or wheeze or throat tightness or hoarseness, or generalized urticaria and/or angioedema or severe abdominal pain or vomiting	Throat or chest tightness or loss of consciousness	Chest tightness or wheezing or cough plus urticaria	Respiratory symptoms not responsive to inhaled β agonist	
ERT during escalation	48	0	1	2	6	57
No. (%) of patients with ERT during escalation	30 (31)	0 (0)	1 (1)	2 (6)	3 (14)	36 (12)
Maintenance doses	52,656	55,250	35,776	12,820	4,123	160,265
ERT during maintenance	14	13	3	7	1	38
No. (%) of patients with ERT during maintenance	4 (5)	9 (9)	2 (3)	2 (7)	1 (5)	19 (6)
ETR location, medically supervised or not medically supervised	23/39	0/13	1/3	1/8	3/4	28/67

involved a dose escalation and a maintenance phase analogous to the approaches used previously for OIT for food allergy[21-24,26,27] and similar to rush or cluster approaches used for SCIT.[32] Of the 352 patients treated, 89% had exhibited at least 1 IgE-mediated symptom, and more than 57% of patients had a history consistent with a multisystem IgE-mediated reaction to peanut (Table II). Sixteen of 352 patients (4.5%) exhibited only gastrointestinal reactions (vomiting) to peanut exposure without other signs or symptoms. Four patients had eczema, which improved with peanut elimination and worsened with peanut exposure, without a history of other IgE-mediated reactions; 5% had strongly positive *in vivo* or *in vitro* tests for peanut-specific IgE but had never been exposed to peanut. All the patients were tested *in vivo* or *in vitro* or both for peanut-specific IgE (Table III). More than 50% of patients exhibited peanut-specific IgE predictive of a >95% risk of a reaction on exposure (Table III).[33]

Fifty-seven reactions that required epinephrine occurred during the administration of 79,726 escalation doses for a reaction rate of 0.7 per 1000 doses (Table I). The lowest dose that triggered an epinephrine-treated reaction (ETR) was 1.0 mg of PP. Thirty-eight reactions that required epinephrine occurred during maintenance administration of 160,625 doses, for a rate of 0.2 per 1000 doses. As has been previously reported, risk factors for ETRs included exercise close to the time of dosing, viral illness, and uncontrolled asthma.[34] For some patients, ETRs were associated with significant delays in dosing or failure to take the dose with other food.

The majority (293 of 352) of patients (85%) who started treatment reached the target maintenance dose. Twelve of the patients who reached maintenance dropped out before this data compilation, for an overall success rate of 80%. Reasons for withdrawal included gastrointestinal symptoms (abdominal pain or vomiting hours after dosing), taste aversion, mild (urticarial) reactions, ETRs, anxiety, uncontrolled asthma (symptoms not temporally related to peanut dosing), poor adherence and/or inconvenience, and lost to follow up. There was considerable patient-to-patient variability in the time to reach maintenance. The available data do not permit a meaningful comparison of the contributing sites. The minimum time to maintenance was 104 days, but some patients took more than 1 year. The follow-up on maintenance ranged from a few weeks to more than 7 years.

DISCUSSION

The AMS of peanut allergy is very difficult and often unsuccessful.[3-12,14-17] Emergency department visits for allergic reactions are common,[35-38] and death due to anaphylaxis is well documented.[2,14,17] The fear of these allergic reactions can be anxiety provoking and disruptive for patients and parents. In addition, patients may be stigmatized, isolated, and

TABLE II. Patient characteristics and pretreatment peanut reaction history

	Site no.					
	1	2	3	4	5	Total
Median age (y)	8.0	9.0	8.1	5.0	5.8	—
Male patients (%)	57	58	64	55	60	59
Total no. treated	98	112	86	34	22	352
Indications for treatment‡						
Multisystem reaction	62	60	40	20	20	202
Cutaneous or mild oral symptoms only	24	38	39	9	2	112
Respiratory symptoms	36	45	25	37	20	163
Abdominal pain/vomiting without other symptoms	10	5	24	1	0	16
Eczema	0	0	0	4	0	4
Sensitized but no known exposure	2*	9*	7†	0	0	18

*Peanut IgE >14 kU/L.
†Positive challenge at the start of OIT.
‡Number of patients.

TABLE III. Antigen-specific IgE before beginning treatment

	Site no.				
	1	2	3	4	5
IgE					
<3 kU/L*	9	5	2	3	ND
3-8.9 kU/L	11	9	0	5	ND
9-14.9 kU/L	12	6	4	11	ND
15-49.9 kU/L	29	11	3	2	ND
50-99.9 kU/L	11	12	7	4	ND
>100 kU/L	26	45	5	9	ND
SPT wheal					
<7 mm†	ND	6‡	3‡	0§	3‖
8-12 mm	ND	37‡	16‡	0§	7‖
>13 mm	ND	53‡	62‡	4§	¶

ND, Not done; *SPT,* skin prick test.
*Antigen-specific IgE was measured by ImmunoCap or by activated cellulose solid-phase immunoassay (Hycor Biomedical Inc, Garden Grove, Calif).
†Skin test reagents were purchased from different vendors by each site at different times.
‡Orthogonal diameter of the wheal.
§Orthogonal diameter of the wheal that is 7 mm> negative control.
‖Orthogonal diameter of the wheal ≥3 mm is considered positive.
¶This site does not differentiate SPT results ≥8 mm.

bullied.[11,39-42] Food-allergy-specific quality-of-life surveys have shown impairment in children with peanut and other food allergies.[4,5,43] Clearly, the AMS does not normalize life for many individuals with peanut allergy and their families.

The literature contains numerous case series and controlled studies of OIT for food allergy using a wide variety of treatment protocols.[23-27,31,44] Thoughtful clinicians can contribute significantly to the field of food allergy treatment by applying their knowledge, experience, and skill in patient care to clinical problems as occurred during the development of SCIT.[32] A key question is whether OIT can be performed safely in a clinical practice setting. This article provides data to help answer this question.

Each site, in an effort to minimize the burdens of peanut allergy for patients and their families, offered oral desensitization modeled after the 100-year-old allergen desensitization strategy. Each site took a somewhat different approach (see Methods in this article's Online Repository at www.jaci-inpractice.org) but each reached a similar result (approximately 85% of patients reached maintenance). Because site 1 used a very low threshold for epinephrine administration (any reaction that involved any system other than skin), the ETR at that site was markedly higher than the other 4 sites; 0.7 per 1000 doses versus an average of 0.2 per 1000 doses at the other 4 sites. Despite differences in methodology and the duration of the follow-up, we believe that reporting the treatment of similar patients treated using similar algorithms is not only reasonable but emphasizes that, just as with SCIT, a variety of approaches can be successful.

Ninety-five ETRs occurred in 352 patients after administration of more than 240,000 doses. Only 3 patients received 2 doses of epinephrine for a single ETR, and no patient required intravenous fluids for hypotension or other manifestations of shock. Most of the reactions during maintenance occurred close to the time of dosing when parents were closely observing patients. The ETR use in 36 of 352 patients (10%) is comparable with a controlled study in which the subjects underwent double-blind, placebo controlled food challenge at entry, during which there were 2 ETRs during OIT in 19 patients.[45] Analysis of these data suggests that the patients reported in this article are likely peanut allergic and the risk of ETR in a practice setting is similar to that in a trial experience. The overall rate of systemic ETRs per dose during OIT is higher but comparable with the 0.1% systemic reaction rate observed with high-dose SCIT.[46,47]

Although SCIT for treatment of rhinitis, a disruptive morbidity, has been an integral part of clinical allergy practice for more than a century with refinements in safety and efficacy achieved by prospective controlled trials, often based on clinical experience, unanswered clinical and procedural questions remain. There is similar uncertainty regarding the use of OIT to reduce the risk of fatal food reactions, and the prudent clinician will proceed with caution. This report provides data that support the feasibility of oral immunotherapy to desensitize patients with peanut allergy with a manageable rate of significant allergic reactions. Similar to SCIT reactions that rarely require more intensive treatment than epinephrine, none of the 95 OIT reactions reported here required treatment with intravenous fluids. Other, less severe reactions are not addressed in this report.

When patients elect POIT or parents elect to have their children treated with POIT, they trade the known risk of POIT dosing for the uncertainty of accidental exposure, a valid concern. The incidence of accidental exposure to peanut is reported to be between 4.7% and 11.9%.[15,16,48,49] The severity of a food allergy reaction is a poor predictor of the severity of subsequent reactions. In several reports of patients who died from food allergy, their histories did not include any life-threatening event.[9,14,50]

Based on reported data,[16] 41 multisystem reactions to inadvertent peanut ingestion would have been expected during the approximately 490 patient years described in this article. Ninety-five ETRs occurred, but all followed an ingestion during which heightened attention to symptoms had been specifically emphasized. Thus, the risk of ETR is increased 2-fold, with the benefit of no inadvertent ETR during this time period.

In the AMS approach, re-education regarding recognition of reactions and the availability and use of epinephrine autoinjectors may occur once or a few times a year. During OIT, these

principles are reenforced at each visit. In our experience, individuals with peanut allergy are vigilant after an OIT dose and, therefore, identify and treat systemic reactions promptly (R. L. Wasserman, oral observation, January 2009-June 2012). Early treatment correlates with favorable outcomes in severe food allergic reactions.[50] The environment of intentional ingestion contrasts dramatically with the potential for exposures that may occur with inadvertent ingestion. Although experiencing a reaction caused some patients to discontinue treatment, most families judged the risk of reaction due to POIT to be more acceptable than the risks of accidental ingestion. Notably, there were no accidental peanut ingestions that led to reactions that required epinephrine during treatment.

There is a paucity of data concerning the impact of food OIT on patients and families. However, 2 reports used validated food-allergy quality-of-life tools to assess the impact of OIT. A small, retrospective evaluation of family quality of life showed that, 6 months after reaching OIT maintenance, the quality-of-life score was 0.21,[51] compared with 2.8 (on a 7-point Likert scale) among historic control families by using the AMS approach.[43] A report of a larger group of patients demonstrated similar findings in a different patient population.[52] This report supports previous observations that exercise, viral illness, and unstable asthma are risk factors for systemic ETRs during food OIT.[34] The overwhelming majority of ETRs occurred during concomitant illness or exercise within 2 hours of dosing; however, some ETRs occurred without an identified risk factor. Clinicians who offer food OIT must be appropriately trained and experienced in the diagnosis of food allergy, food allergy reactions, and anaphylaxis. They must carefully and thoroughly educate their patients and parents about reaction risk factors as well as the recognition and treatment of systemic reactions. They must also be prepared to assess reactions, for example, a single perioral hive or mild oral itch, in the context of the individual patient's experiences during POIT and concurrent risk factors (eg, viral infection or exercise) to make appropriate dose adjustments. This requires diligent patient and/or parent reeducation at every opportunity as well as a willingness to be continuously available to make decisions regarding OIT dosing.

Knowledge of POIT is in the public domain. An imperfect but reasonable measure of public interest, a Google search (Google Inc, Mountain View, Calif) on "peanut oral immunotherapy" performed December 23, 2012, yielded 119,000 hits. This information is available to nonallergist physicians, nonphysician practitioners, and the lay public, including parents. Restricting POIT to research studies creates the concern that nonallergist physicians or patients and/or parents will undertake POIT on their own because it is not otherwise available. However, additional well-controlled, long-term, prospective studies are needed to prove the efficacy and long-term safety of POIT. Indeed, a recent long-term follow-up of a milk OIT study[53] reported that some, apparently desensitized, subjects continued or developed symptoms of milk sensitivity years after reaching maintenance. Our article demonstrates that peanut OIT can be administered as a treatment with an acceptable ETR rate. Practicing allergists may consider offering this treatment to patients with peanut allergy.

Acknowledgments

We thank the investigators and clinicians who are caring for patients with peanut allergy on whose work our treatments have been based. In addition, we recognize the crucial role that our colleagues and staffs have played in the care of these patients and the assembly of the data presented. Most of all, we acknowledge the trust in their physician evidenced by patients and their families when they embarked on this novel therapy to improve their lives.

REFERENCES

1. Branum AM, Lukacs SL. Food allergy among children in the United States. Pediatrics 2009;124:1549-55.
2. Yunginger JW, Squillace DL, Jones RT, Helm RM. Fatal anaphylactic reactions induced by peanuts. Allergy Proc 1989;10:249-53.
3. Herbert LJ, Dahlquist LM. Perceived history of anaphylaxis and parental overprotection, autonomy, anxiety, and depression in food allergic young adults. J Clin Psychol Med Settings 2008;15:261-9.
4. King RM, Knibb RC, Hourihane JO. Impact of peanut allergy on quality of life, stress and anxiety in the family. Allergy 2009;64:461-8.
5. Ostblom E, Egmar AC, Gardulf A, Lilja G, Wickman M. The impact of food hypersensitivity reported in 9-year-old children by their parents on health-related quality of life. Allergy 2008;63:211-8.
6. Akeson N, Worth A, Sheikh A. The psychosocial impact of anaphylaxis on young people and their parents. Clin Exp Allergy 2007;37:1213-20.
7. Bollinger ME, Dahlquist LM, Mudd K, Sonntag C, Dillinger L, McKenna K. The impact of food allergy on the daily activities of children and their families. Ann Allergy Asthma Immunol 2006;96:415-21.
8. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol 2010;126:S1-58.
9. Vander Leek TK, Liu AH, Stefanski K, Blacker B, Bock SA. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. J Pediatr 2000;137:749-55.
10. Levy MB, Goldberg MR, Nachshon L, Tabachnik E, Katz Y. Lessons from cases of mortality due to food allergy in Israel: cow's milk protein should be considered a potentially fatal allergen. Isr Med Assoc J 2012;14:29-33.
11. Young MC, Munoz-Furlong A, Sicherer SH. Management of food allergies in schools: a perspective for allergists. J Allergy Clin Immunol 2009;124:175-82, 182.
12. Lieberman JA, Weiss C, Furlong TJ, Sicherer M, Sicherer SH. Bullying among pediatric patients with food allergy. Ann Allergy Asthma Immunol 2010;105:282-6.
13. Muñoz-Furlong A. Daily coping strategies for patients and their families. Pediatrics 2003;111:1654-61.
14. Bock SA, Muñoz-Furlong A, Sampson H. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol 2007;119:1016-8.
15. Clark S, Espinola J, Rudders SA, Banerji A, Camargo CA. Frequency of US emergency department visits for food-related acute allergic reactions. J Allergy Clin Immunol 2011;127:682-3.
16. Nguyen-Luu NU, Ben-Shoshan M, Alizadehfar R, Joseph L, Harada L, Allen M, et al. Inadvertent exposures in children with peanut allergy. Pediatr Allergy Immunol 2012;23:133-9.
17. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol 2001;107:191-3.
18. Gold M, Sainsbury R. First aid anaphylaxis management in children who were prescribed an epinephrine autoinjector device (Epipen). J Allergy Clin Immunol 2000;106:171-6.
19. Simmons FER, Clark S, Camargo CA Jr. Anaphylaxis in the community: learning from the survivors. J Allergy Clin Immunol 2009;124:301-6.
20. Nowak-Węgrzyn A, Sampson HA. Future therapies for food allergies. J Allergy Clin Immunol 2011;127:558-73.
21. Edwards HE. Oral desensitization in food allergy. Can Med Assoc J 1940;40:234-6.
22. Mansfield L. Successful oral desensitization for systemic peanut allergy. Ann Allergy Asthma Immunol 2006;97:266-7.
23. Anagnostou K, Clark A, King Y, Islam S, Deighton J, Ewan P. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. Clin Exp Allergy 2011;41:1273-81.
24. Yu GP, Weldon B, Neale-May S, Nadeau KC. The safety of peanut oral immunotherapy in peanut-allergic subjects in a single-center trial. Int Arch Allergy Immunol 2012;159:179-82.
25. Sheikh A, Nurmatov U, Venderbosch I, Bischoff E. Oral immunotherapy for the treatment of peanut allergy: systematic review of six case series studies. Prim Care Respir J 2012;21:41-9.

26. Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, Steele PH, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. J Allergy Clin Immunol 2009;124:286-91, 291.e1-6.
27. Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, et al; Consortium of Food Allergy Research (CoFAR). Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol 2013;131:119-27.e1-7.
28. Harvey SM, Laurie S, Hilton K, Khan DA. Safety of rush immunotherapy to multiple aeroallergens in an adult population. Ann Allergy Asthma Immunol 2004;92:414-9.
29. Parmiani S, Fernandez Tavora L, Moreno C, Guardia P, Rico P. Clustered schedules in allergen specific immunotherapy. Allergol Immunopathol (Madr) 2002;30:283-91.
30. Thyagarajan A, Varshney P, Jones SM, Sicherer S, Wood R, Vickery BP, et al. Peanut oral immunotherapy is not ready for clinical use. J Allergy Clin Immunol 2010;126:31-2.
31. Meglio P, Bartone E, Plantamura M, Arabito E, Giampietro PG. A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. Allergy 2004;59:980-7.
32. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011;127(Suppl):S1-55. Erratum in: J Allergy Clin Immunol 2011; 127:840.
33. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. J Allergy Clin Immunol 1997;100:444-51.
34. Varshney P, Steele PH, Vickery BP, Bird AJ, Thyagarajan A, Scurlock AM, et al. Adverse reactions during peanut oral immunotherapy home dosing. J Allerg Clin Immunol 2009;124(6):1351-2.
35. Mulla ZD, Simon MR. Hospitalizations for anaphylaxis in Florida: epidemiologic analysis of a population-based dataset. Int Arch Allergy Immunol 2007; 144:128-36.
36. Ross MP, Ferguson M, Street D, Klontz K, Schroeder T, Luccioli S. Analysis of food-allergic and anaphylactic events in the National Electronic Injury Surveillance System. J Allergy Clin Immunol 2008;121:166-71.
37. Decker WW, Campbell RL, Manivannan V, Luke A, St Sauver JL, Weaver A, et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. J Allergy Clin Immunol 2008; 122:1161-5.
38. Lin RY, Anderson AS, Shah SN, Nurruzzaman F. Increasing anaphylaxis hospitalizations in the first 2 decades of life: New York State, 1990-2006. Ann Allergy Asthma Immunol 2008;101:387-93.
39. Roy KM, Roberts MC. Peanut allergy in children relationships to health-related quality of life, anxiety, and parental stress. Clin Pediatr 2011;50:1045-51.
40. Hullmann SE, Molzon ES, Eddington AR, Mullins LL. Dating anxiety in adolescents and young adults with food allergies: a comparison to healthy peers. J Asthma Allergy Ed 2012;3:172-7.
41. Lyons AC, Forde EME. Food allergy in young adults: perceptions and psychological effects. J Health Psychol 2004;9:497-504.
42. Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. Allergy 2010;65:933-45.
43. Cohen BL, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in families with a child with food allergy. J Allergy Clin Immunol 2004;114:1159-63.
44. Allen KJ, O'Hehir RE. The evolution of oral immunotherapy for the treatment of peanut allergy. Clin Exp Allergy 2011;41:1172-4.
45. Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol 2011; 127:654-60.
46. Phillips JF, Lockey RF, Fox RW, Ledford DK, Glaum MC. Systemic reactions to subcutaneous allergen immunotherapy and the response to epinephrine. Allergy Asthma Proc 2011;32:288-94.
47. Bernstein DI, Blaiss MS, Cox LS, Feingold I, Lanier RQ, Nelson HS, et al. Current standards and future directions in immunotherapy: perspectives on challenges. Ann Allergy Asthma Immunol 2010;104:530-5.
48. Neuman-Sunshine DL, Eckman JA, Keet CA, Matsui EC, Peng RD, Lenehan PJ, et al. The natural history of persistent peanut allergy. Ann Allergy Asthma Immunol 2012;108:326-31.
49. Fleischer DM, Perry TT, Atkins D, Wood RA, Burks AW, Jones S, et al. Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. Pediatrics 2012;130:e25-32.
50. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med 1992;327:380-4.
51. Hague AR, Wasserman RL, Sugerman RW. Food Allergy Quality of Life (FAQOL) Is Improved For Food Oral Immunotherapy (OIT) Treated Patients and Their Families. J Allergy Clin Immunol 2012;129(Supplement):AB29.
52. Factor JM, Mendelson LM, Lee JO, Nouman G, Lester MR. Effect of oral immunotherapy to peanut on food-specific quality of life. Ann Allergy Asthma Immunol 2012;109:348-52.
53. Keet CA, Seopaul S, Knorr S, Narisety S, Skripak J, Wood RA. Long-term follow-up of oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol 2013;132:737-9.e6.

Institutional Review Boards

Two practices received IRB approval for the POIT treatment (site 2 [Quorum Review IRB Inc, 1601 Fifth Avenue, Suite 1000, Seattle, Washington 98101; telephone 877-472-9882; FAX 206-448-4193], and site 5 [Assaf-Harofeh Medical Center IRB, Zerifin, Sackler School of Medicine, Tel Aviv University, Israel; Eitan Scapa, MD, chairman]); and sites 1, 3, and 4 received IRB approval for retrospective chart review (North Texas IRB at Medical City Hospital, Dallas, Tex).

METHODS

Site 1

Treatment comprises 3 phases. Phase I is a single day beginning with 1.025 mcg of PP (the amount of PP in peanut flour is based on the package label) dissolved in Kool-Aid (Kraft Foods Group, Northfield, Ill), followed by increasing doses administered every 15 minutes until there is any symptom or until the 6.15-mg dose is reached. PP dissolved in Kool-Aid is made fresh on the day of use. PP in Kool-Aid at the appropriate concentration is provided to patients and stored refrigerated for no more than 7 days. Patients begin phase II by taking the last tolerated dose at home twice a day and returning weekly to be challenged with the next dose until they reach 12 peanuts twice a day or the equivalent amount of PP in peanut butter or peanut flour. Peanut flour is provided in capsules (commercial peanut flour is compounded into capsules by a compounding pharmacist), which contain different amounts that the patient or the parent opens into food or liquid immediately before dosing. Patients receive peanut flour until they have tolerated 205 mg of PP. Although there is significant variation in the weight of individual peanuts by brand (based on weighing 100 peanuts from several packages of different brands), for the purposes of this treatment, a peanut was defined as weighing 450 mg (40% of which is protein or 180 mg of protein). In an effort to enhance the safety of the transition from flour to whole peanuts, dose escalation with peanut flour continued until the patient was ingesting approximately 10% more PP as flour than would be contained in a whole peanut. The patients then are given the option of using peanut flour, peanut butter, Peanut M&M's (Mars Chocolate North America, Hackettstown, NJ), or 1 of 3 brands of whole peanuts. When patients are able to tolerate 12 peanuts per dose (or equivalent), most patients are challenged with 24 peanuts. If they pass the challenge, then they continue to phase III, maintenance of 8 peanuts twice a day for 3 months, then once a day for at least 3 years.

Site 2

Peanut flour in water is mixed with apple sauce or pudding, and is administered starting with 0.1 mg of PP. Doses are doubled every 30 minutes to a maximum of 6 mg on day 1. On day 2, the 6-mg dose is repeated. Patients then take 6 mg once daily for 2 weeks and return every 2 weeks for dose increases until they reach a dose of 383 mg of PP as peanut flour. Patients were dispensed preweighed peanut unit dose covered cups. Parents mix the peanut flour with a carrier food at the time of dosing. At 383 mg of PP, dosing is changed to 3 Peanut M&Ms (approximately 450 mg) daily; the maintenance dose that is continued for an indefinite period to maintain the desensitized state.

Site 3

Peanut flour is mixed in juice to make a 250 mg/mL solution that is then serially diluted to 2.5 mg/mL for use. Peanut flour solution is used until the 100-mg dose. For larger doses, flour is mixed with food. At 1000 mg, solid peanut is begun. Treatment comprises 3 phases. Phase I begins with a dose of 0.1 mg of PP in grape juice followed by increasing doses administered every 15 minutes until there is any symptom or until the 50 g of peanuts (which contains 20 g of PP) is reached. Patients who tolerate 50 g of peanuts are judged to be not allergic to peanut and are not included in this report. Patients begin phase II by taking the last tolerated dose at home twice a day and return weekly to be challenged with the next dose until they reach 4 g of peanuts (1600 mg PP) for patients $<$27.8 kg, 8 g of peanuts (3200 mg PP) for patients $>$27.8 kg administered twice daily for 3 months, then once daily. At this site, each patient purchases a balance and weighs each dose to account for the variability in the size of peanuts. Patients continue the maintenance dose twice a day for 3 months and then change to phase III, taking the dose maintenance once a day for at least 3 years.

Site 4

Patients undergo an open challenge to increasing doses of peanut flour beginning with 0.13 mg of PP and doubling every 15 minutes until a reaction occurs or the patient tolerates 1000 mg of peanut flour (approximately 1 peanut). The initial home treatment dose is the highest tolerated dose before the sign or symptom elicited by the provoking dose. The patient then takes the treatment dose 3 times a day (if the dose is $<$1 mg) or twice a day (if the dose is $>$1 mg) and returns every 7 days for a dose increase of twice the previous week's dose that then becomes the dose for the next week at home. This continues until the patient is able to tolerate 4-8 g of peanuts or the equivalent of peanut flour or peanut butter. The choice of the PP source was made jointly by the parents and the clinician. The 4-8 g maintenance dose is taken twice daily for 1 year, then once daily for a year, and then every other day to 2-3 times a week. Initially, the maintenance target was determined by the clinician based on the weight and age of the child and the child's ability to consume peanut. During the last year of observation, the maintenance dose was 4 g daily.

Site 5

Patients undergo 3 rounds of induction, performed every 4 weeks, each comprising 4 days. Peanut flour suspended in liquid is used until the patient tolerates 300 mg PP when whole peanuts are used. On day 1, the starting dose of 0.1 mg PP is doubled every 15 minutes up to 10 mg, then increased every 30 minutes to 15, 25, 50 mg. If there is no reaction, then there are further increases on day 2 (see Table E2). If there is a reaction, then, on the second day, the dose is decreased 2 steps and increased to a dose between the last tolerated dose and the dose that triggered a reaction. On the third day, the last 2 tolerated doses are repeated, and, on the fourth day, the tolerated dose is repeated twice at 120-minute intervals. This is then the home dosing regimen. Home treatment then continues for 24 days until the next 4-day dose escalation. Patients who require a longer treatment to reach the target dose return for 1 day per month to be challenged with a 50% increase and then continue this dose at home. Maintenance is 1 dose a day indefinitely.

TABLE E1. Peanut products used for desensitization at each site

	Site				
	1	2	3	4	5
Peanut flour, defatted	×	×	×	×	×
Whole roasted peanuts	×	×	×	×	×
Peanut M&M's	×	×	×	×	×
Peanut butter	×		×	×	×

TABLE E2. Dosing schedules

Site				
1	2	3	4	5
0.001*	0.1	0.1	0.13	0.1
0.002	0.2	0.2	0.26	0.2
0.004	0.4	0.4	0.52	0.5
0.01	0.8	1.0	1.04	1.25
0.021	1.6	2.0	2.08	5
0.041	3.2	4.0	4.2	10
0.103	6.0	10	8.4	15
0.205	End day 1	20	16.8	25
0.410	6.0	End day 1	32.5	End day 1
1.025	12	40	65	10†
2.05	25	40	130	15
4.1	50	100	260	25
6.15	75	200	520	50
6.15	125	400	1040	100
10.25	156	800	End day 1	200
20.5	195	1600‡	2000§	300
End day 1	245	3200	4000	300‖
20.5	306		8000	600
41	383			
72	3 M&M's (approximately 450 mg)			
102.5				
205				
250				
500				
750				
1000				
1250				
1500				
1750				
2000				
2500				
3000				

*Dose in mg of PP.
†If there was no reaction on day 1, then dosing proceeded to day 2; if there was a reaction, then, on day 2, dosing dropped back 3 steps and then continued.
‡Maintenance for patients <27.8 kg.
§For the past year of the observation period at site 4, maintenance was reduced to 2000 mg/d.
‖This dose and subsequent doses were administered as whole peanuts.