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)**

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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
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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.
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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