



Perspective

An update on the controversy around offering oral immunotherapy to peanut-allergic children outside of research



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Introduction

Oral immunotherapy (OIT) has emerged as an exciting treatment with the potential to help food-allergic children tolerate a food they have previously been told to avoid, sometimes for years, and often with substantial emotional and financial costs. However, an abundance of controversy surrounds OIT. This article reviews safety and efficacy, explores arguments in favor of and against use of OIT outside of research, and addresses the role of licensed products for OIT.

Is Peanut OIT Safe?

There is a risk of anaphylaxis with OIT, as shown in research and clinical practice (Table 1). A recent Phase 3 clinical trial evaluating the investigational product AR101 (defatted roasted peanut flour) for peanut OIT in patients 4 through 17 years of age reported adverse events (AEs) in 95% of participants; in the treatment group, 4.3% had severe AEs, and 14% were given epinephrine (vs 0.8% and 6.5% in the placebo group).² Blumchen et al³ found that although all 31 patients 3 to 17 years of age on peanut OIT experienced AEs, none required epinephrine. Vickery et al⁴ reported a 2.5% rate of epinephrine use for OIT (1/40 patients) in 1- to 3-year-olds; no severe AEs were seen.⁴ Conversely, the PP-OIT (Probiotic and Peanut Oral Immunotherapy) randomized double-blind, placebo-controlled, single-center trial, which recruited children 1 to 10 years of age, had a much higher rate of severe AEs (45.2%). Interestingly, 32.3% of placebo patients also experienced severe AEs,

which the authors attribute to anxiety. The high rate of severe AEs in the PP-OIT and placebo groups could be attributable to the fact that it was defined as “any symptom that prevents daily activities and might require therapeutic intervention,” which could be overreported by participants.

Of special concern is that although allergic reactions during buildup and maintenance can occur because of co-factors such as viral infections and exercise, others occur without any predisposing factors and at a dose that had previously been tolerated. For example, in a retrospective analysis of peanut OIT in clinical practice, 38 of 95 reactions requiring epinephrine occurred when patients had reached maintenance; reasons for these reactions were not clearly described.⁶

Although patients do experience anaphylaxis while undergoing OIT, most reactions are mild, including oral itching and gastrointestinal complaints.⁵ In comparison, 1% to 2% of patients who are avoiding peanut require epinephrine or an emergency department visit for accidental ingestion every year.¹ Also, new onset of eosinophilic esophagitis (EoE), which may or may not be causal, occurs in up to 2.7% (range, 0.99%–5.33%) of patients on OIT.⁹ Lucendo et al⁹ concluded that the actual occurrence might be lower than 2.7% because of a funnel plot analysis showing significant publication bias in favor of reporting EoE development after OIT; conversely, patients with gastrointestinal symptoms may not undergo endoscopy, so the true prevalence of EoE may be underrepresented.

How Effective Is Peanut OIT?

A 2017 meta-analysis reported a substantial benefit of peanut OIT in desensitizing children.⁵ Since its publication, others have corroborated these findings. In 2017, a study of 40 children 9 to 36 months of age with suspected peanut allergy, randomized to receive low-dose (300 mg protein) or high-dose (3000 mg) peanut OIT over a median of 29 months, found that 85% of children on low-dose and 76% on high-dose OIT were desensitized, although there was no

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Table 1
Comparison of Peanut Avoidance, Peanut OIT in Research, and Peanut OIT in Clinical Practice

	Peanut avoidance	Peanut OIT in research	Peanut OIT in clinical practice
Risk of anaphylaxis	10% annual rate of accidental reactions, with 1%-2% requiring epinephrine or emergency department visits ¹	4.3% had severe adverse events, and 14% were given epinephrine (vs 0.8% and 6.5% in the placebo group) ² 12 AEs of severity grade 2, (0.1% of total OIT doses) 50 AEs of severity grade 3 (0.4% of total OIT doses) 11 AEs of severity grade 4 (0.1% of total OIT doses); but no reactions received epinephrine ³ 2.5% of patients received epinephrine ⁴ % receiving epinephrine for allergic reactions while on OIT: 1%-10% ⁵ 6 SAEs in 3 patients (9.68%) in active group (all anaphylaxis, 3 treated with epinephrine), 4 SAEs (12.9%) in placebo group (2 anaphylaxis treated with epinephrine) ⁵	57 reactions requiring epinephrine during administration of 79,726 doses; reaction rate 0.7 per 1000 doses during buildup ⁶ 12.4% of patients in clinic, 14.5% at home ⁷ 100 reactions occurred in 270 (23%) patients (65 reactions required 1 dose, 5 required 2 doses, 2 required 3 doses) ⁸
Risk of EoE	~43 to 56 of 100,000 inhabitants (children and adults) in Europe and the United States ⁹	Biopsy proven: 2.7% (range, 0.99–5.33%) ⁹ 1/496 = 0.2% ²	Not biopsy proven: 6.21% gastrointestinal symptoms unrelated to the dose and resolved with dose reduction ⁷ 13.7% experienced episodic vomiting >2 hours after dose ⁸
Quality of life effects	Strong adverse impact on QoL for children with peanut allergy and their parents which is worse with increasing age, and worse QoL compared with other pediatric diseases such as type 1 diabetes ¹⁰	Improved QoL for 'social and dietary limitations' post OIT for mothers in peanut OIT group, no change in placebo. For children, improvements noted for 'risk of accidental exposure' and 'emotional impact' and overall score ³ Improved parental QoL in patients who completed OIT to peanut (with probiotic), especially for those acquiring sustained unresponsiveness ¹⁰ Patients with lower QoL at baseline experience improvements in QoL with OIT, whereas those with higher QoL at baseline experience deterioration of QoL with OIT ¹¹	Not available
Desensitization	Not applicable	67.2% of active patients were able to tolerate 600 mg or more of peanut protein at exit OFC (vs 4.0%) of placebo patients ² 59% in active group and placebo group reached planned maintenance dose; maximum tolerated dose during OFC increased from 30–1000 mg for active group, but only changed from 20–30 mg for the placebo group. ³ 85% of children on low-dose and 76% on high-dose were desensitized, but there was no placebo group ⁴ Meta-analysis showed Risk Ratio = 0.11 ⁵ 60%–90% desensitization rate ⁵ 89.7% desensitized in active group vs 7.1% in placebo group ¹²	77.9% full desensitization to 3000 mg ⁷ 79% desensitized ⁸ 85% desensitization ⁶
Tolerance development	20% spontaneous remission ¹	91% 4-week SU ⁴ 82.1% 2- to 5-week SU ⁵ 58% 8-week SU ¹²	Only 1 study reported sustained unresponsiveness in 6.5% ⁸

Abbreviations: AE, adverse event; EoE, eosinophilic esophagitis; OFC, oral food challenge; OIT, oral immunotherapy; QoL, quality of life; SAE, serious adverse event; SU, sustained unresponsiveness.

placebo group in this study. The primary outcome was sustained unresponsiveness (SU) at 4 weeks and was attained in 78% of patients.⁴ Sustained unresponsiveness is defined as the ability to consume all of the oral food challenge (OFC) material without symptoms after stopping OIT for a defined period. A phase 2 randomized controlled crossover single-center trial enrolled children 7 to 16 years of age and found a 62% desensitization rate using a maintenance dose of 800 mg.⁵ The PP-OIT trial had a maintenance dose of 2000 mg protein, and unlike Vickery and the phase 2 trial, this study included a daily probiotic.⁵ It had a similar desensitization rate to Vickery's study (89.7% vs 7.1% placebo). The PP-OIT attained its primary outcome (2- to 5-week SU) in 82.1% of patients, and 4-year follow-up data found an 8-week SU of 58%.¹² Patients who passed the 2-week SU OFC in the initial study were told to consume peanut "ad lib" without requiring daily dosing; therefore, some patients may have become resensitized. Of note, the absence of

probiotic-only and OIT-only groups limits the ability to delineate the individual contributions of the 2 components of PP-OIT.

The Phase 3 AR101 results from 496 participants aged 4 to 17 years demonstrated that 250 of 372 (67.2%) on active peanut therapy were able to ingest a target dose of 600 mg or more peanut protein on exit OFC, compared with 5 of 124 (4.0%) on placebo.² Similarly, Blumchen et al³ report that 74.2% of patients 3 to 17 years of age on active treatment in a placebo-controlled trial of peanut OIT were able to tolerate 300 mg or more at the final OFC, compared with only 16.1% in the placebo group.

Should Peanut OIT Be Offered outside of Research?

Most international food allergy guidelines do not currently recommend OIT in clinical practice. The 2010 United States National Institute of Allergy and Infectious Diseases (NIAID) guideline noted

that additional safety and efficacy data are required before OIT can be recommended in clinical practice.¹³ However, since the guideline was published, there is increasing evidence in favor of OIT as a safe and effective treatment for children with peanut allergy.^{2–5} Recently, 2 guidelines allow OIT outside of research, with the European Academy of Allergy and Clinical Immunology stating that OIT should only be undertaken in highly specialized clinical centers with expertise and facilities to safely deliver this therapy, and the Spanish Society of Pediatric Allergology, Asthma and Clinical Immunology and Spanish Society of Allergology and Clinical Immunology providing clinical guidelines for OIT to milk and egg outside of research.^{14,15}

Arguments against use of OIT outside of research include insufficient knowledge about dosing schedules, risks, long-term clinical efficacy, parent/patient treatment preference and cost-effectiveness,¹⁶ the potential need for years-long daily treatment, as well as a poorly understood mechanism of action.¹ Also, until recently, randomized trials of OIT have recruited small numbers of subjects with strict protocols that may not reflect safety in the real world.

However, many costs of peanut allergy must be taken into account, including the risk of accidental ingestion, fear of fatality, the low rate of outgrowing peanut allergy, the economic impact of food allergy, and the significant impact on quality of life (QoL).¹³ This argument is echoed by multiple studies noting improvements in QoL with use of peanut OIT (Table 1), although food allergy QoL instruments are not designed for use in this context, and not all studies support this finding. Indeed, more research is needed to better understand the true costs of peanut avoidance vs peanut OIT.

Regardless of the controversy, OIT has been offered in clinical settings for many years. A website created by parents listing certified allergists in the United States and other countries who are offering OIT outside of research has been in existence for some time (www.oit101.org). Recently, Food Allergy Support Team (a nonprofit organization that supports food OIT in community practice) published the results of a multidisciplinary meeting, noting that although OIT does place a “burden” on an allergy clinic in terms of increased volume and emergencies, many physicians noted OIT to be “the most impactful thing that they have done in medicine.”¹⁷ A survey distributed in January 2013 found that only 61 of 442 (13.8%) allergists in the United States were offering OIT.¹⁸ Reasons for not offering OIT included awaiting Food and Drug Administration (FDA) approval before offering the therapy, better established safety data, insurance coverage, and long-term data supporting efficacy of the treatment. Among providers not providing OIT, a few factors were significantly predictive of them being able to offer it if they had sufficient staff: lack of importance of FDA approval, lack of importance of a standardized food product, and lack of importance for better safety data. Very recently, Chipps et al¹⁹ reported that 48 of 101 (47.5%) American allergists who participated in a 2018 survey had used OIT in the past year, which is much higher than the 13.8% from 2013. Similar to the 2013 survey, reasons for not offering OIT were lack of FDA approval and safety concerns, but 94.1% indicated patient/caregiver motivation as extremely/very important. Both of these studies are subject to similar biases, because response rates were quite low; nevertheless, these data suggest a trend toward more practitioners offering OIT over time, and this is likely to increase even further once there are FDA-approved products.

Three publications report on OIT in clinical practice (Table 1). A retrospective review of 4 community-based practices in the United States and 1 hospital-based practice in Israel in 352 children (5–9 years of age) found peanut OIT to be safe (reactions requiring epinephrine: 0.7 per 1,000 doses, and only 3 patients received 2 doses of epinephrine) and effective (achieved target maintenance dosing in 85%).⁶ In 2018, the same group published a retrospective

review of 270 patients who received peanut OIT, of which 96.7% had a history of an immunoglobulin E (IgE)-mediated reaction. They confirmed efficacy of OIT, with 93% of patients completing buildup to 3000 mg within 12 months and all but 1 patient passing a 6000 mg OFC (4 on a second attempt). One hundred reactions required epinephrine in 63 of 270 (23%) patients during buildup.⁸ Finally, a single-center peanut OIT program of 145 Israeli children found that 77.9% of patients were fully desensitized to 3000 mg, and 14.5% required epinephrine for home-dose reactions during buildup.⁷ Variation in inclusion/exclusion criteria, age group, criteria for epinephrine use, and target maintenance dose make comparison of these publications difficult.

A voice that is rarely heard is the parent/patient perspective and how it compares with allergist perspectives. A recent qualitative study of 22 caregivers whose children were receiving food immunotherapy (either oral or epicutaneous) in clinical trials demonstrated that their primary goal was to develop a buffer against an unintentional peanut exposure (desensitization); none of the parents viewed immunotherapy as a “cure” (tolerance).²⁰ This is in stark contrast to the 2013 survey of allergists in which 92.5% answered that data indicating OIT can produce long-term tolerance would motivate them to offer OIT in the future.¹⁸

Will FDA-Approved Treatments Address the Controversy of Peanut OIT outside of Research?

A very recent development has been the arrival of Phase 3 clinical trial data for peanut OIT, which support its safety and efficacy in children and adolescents²; the company developing this product submitted a Biologics License Application in December 2018 to the FDA. Arrival of this treatment would control for different maintenance doses and peanut formulations between products currently being used for OIT (eg, peanut flour, peanuts). In addition, an FDA-approved product would come with a protocol that allergists in the community, or other health care providers in underserved areas, may be more comfortable using.

Conclusion

The safety and efficacy of peanut OIT within research has been, and is being, studied, and although the data appear promising, variability across studies makes it difficult to interpret the data and form definitive conclusions. Whether OIT results in SU or desensitization remains unclear, leaving the child still at risk of reactions unless very regular ingestion is maintained. However, the consequence of continued controversy over whether to use OIT outside of research, together with an increasing number of practitioners offering OIT outside of research, has created a situation of confusion for families and the medical community. Importantly, the treatment goals of parents/patients (desensitization) may not be aligned with the goals of many allergists (tolerance) and also must be taken into account.^{18,20} Although there will likely soon be FDA-approved treatments, what the cost of such treatments will be is unclear. The few guidelines currently allowing OIT outside of research lack the specific details needed to conduct OIT in a standardized fashion. In conclusion, as evidence develops, the controversy around use of OIT outside of research will be further resolved, and hopefully more well-designed studies (that can answer remaining questions about dosing, sustained unresponsiveness, and risk) as well as creation of more detailed guidelines will serve to provide guidance for both families and practitioners.

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