Oral Immunotherapy
An Overview

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KEYWORDS

• Oral immunotherapy • OIT • Food allergy • Tolerance
• Sustained unresponsiveness • Peanut • Milk • Egg

KEY POINTS

- Avoidance has historically been the sole treatment option for Immunoglobulin E (IgE)-mediated food allergy, although oral immunotherapy (OIT) is now an alternative approach.
- OIT effects may be dependent on dose, duration, and frequency of dosing as well as patient-specific factors, such as age and food-specific IgE levels.
- There is only one U.S. Food and Drug Administration (FDA)-approved OIT product (Palforzia, for peanut); otherwise, OIT occurs through the use of commercially available food products.
- Multifood OIT protocols seem to be as safe as single-food protocols, and biological therapies may assist with tolerability of OIT protocols and further improve success rates.
- Studies to date looking at sustained unresponsiveness and remission suggest that OIT needs to be continued in some manner for most individuals to have persistent effects.

INTRODUCTION

The prevalence of IgE-mediated food allergy (FA) continues to increase across the globe, with rates as high as 9% in children and 4% in adults[1–5] and a noted 50% increase in the United States from 1999 to 2011.[1,2,6] Despite decades of research, there is no known cure for FA,[6] and strict dietary elimination and food avoidance have been the basis of treatment.[7] Given the ubiquitous presence of the most common allergenic foods, avoidance is challenging, and accidental ingestions are seen frequently[1]; nearly 40% of the estimated 5.9 million FA children in the United States have experienced a severe life-threatening reaction.[8] Both financial and social costs in FA are also high. The economic impact of pediatric FA in the United States

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amounts to US$4.3 billion annually in direct medical costs,[3,9] and studies show negative quality of life indicators for both patients and caregivers,[10] with 50% of FA children experiencing bullying.[6]

More recently, oral immunotherapy (OIT) has emerged as a promising alternative treatment strategy in FA. OIT is a program of supervised swallowed food introduction, typically involving 1 day of desensitization, multiple-dose escalation visits, and maintenance dosing thereafter (**Fig. 1**). The primary goal of OIT in clinical practice is protection against accidental exposure to an allergen triggering anaphylaxis. Some patients will reach an amount of food ingestion that, secondarily, allows them to incorporate the food unrestrictedly into their diet. Although OIT should be pursued only under the direction of an allergist, it is important for primary care physicians who diagnose, guide appropriate referral to specialty care, and are likely to also participate in the care of increasing numbers of individuals choosing OIT as an FA treatment strategy to be aware of this novel approach to FA.

OIT is not without the risk of adverse reactions (ARs). Most ARs occur during dose escalation (but may occur at any time during OIT) and most commonly include self-limited or antihistamine-treated oropharyngeal pruritus or transient abdominal pain.[11] At times, these early symptoms may require extensive protocol adjustment. Not insignificantly, up to 10% of OIT patients can exhibit respiratory symptoms,[7] and an estimated 10% to 15% of patients withdrew from studies due to severe, intolerable abdominal pain.[7,11] Frequency of anaphylaxis and epinephrine use among OIT patients is generally increased compared to the those practicing food avoidance.[12] Eosinophilic esophagitis has also been postulated as a complication of OIT treatment, although it is unclear if this is present before or resulting from OIT.[11,13] Factors increasing the risk of ARs include concurrent illness, physical exertion following dose administration, menstruation, poorly controlled asthma, and timing with food ingestion.[11] OIT-dosing guidances are advised to diminish the risk of ARs but can affect lifestyle and be challenging in individuals of varying age and taste preference. As such, size, formulation, and frequency of OIT doses as well as coadministration of biological therapies to improve tolerability remain current hot topics in OIT research.

Oral tolerance is the state of unresponsiveness to an antigen. Desensitization is an increase in reaction threshold to a food allergen while receiving active therapy such as OIT. Sustained unresponsiveness (SU) is the safe reintroduction of a food after a period of avoidance, often used as a surrogate marker for more permanent clinical unresponsiveness after OIT. Remission has been used more recently to describe those with longer term SU. Use of biomarker profiles and commercially available tests, such

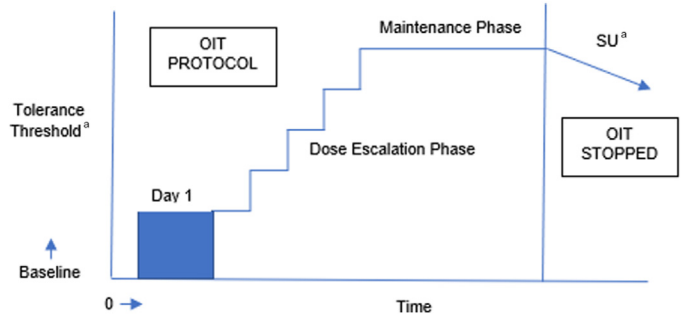

Fig. 1. Overview of OIT protocol and results. [a]May be dependent on age, dose, duration, frequency of dosing, among others.

as basophil activation testing[14] and bead-based epitope assay,[15] to more reliably predict clinical tolerance threshold and those who will maintain SU or enter remission show promise but require further investigation and validation for consistent application in clinical practice and OIT.

DISCUSSION

Peanut Oral Immunotherapy

Peanut has been one of the most studied foods used in OIT and is the only food for which there is a current FDA-approved OIT product (Palforzia). Several randomized trials[16–29] and several uncontrolled studies[30–38] have demonstrated that peanut OIT (POIT) is highly effective at inducing desensitization and increasing tolerance threshold, up to 2 to 18 times the maintenance dose,[18–20,25,27,28,30,32,35,37–40] although this may be dependent on duration[41] and frequency of dosing.[42] A systematic review of 12 trials with 1041 patients showed that POIT increased the likelihood of passing an in-clinic supervised food challenge (relative risk [RR] 12.42) but also increased anaphylaxis risk (RR 3.12), anaphylaxis frequency (incidence rate ratio 2.72), and epinephrine use (RR 2.21) compared with those strictly avoiding peanut.[42] SU is much less common and may be dependent on dose and duration as well as dependent on the age of the individual when POIT is initiated and certain biomarker parameters (such as food-specific IgE).[16,22,31,38,42,43,44] Only 2 studies have evaluated longer term SU, or remission, and both noted a decreasing tolerance threshold effect with increased time from POIT end,[22,44] although this remained higher than baseline and different from those who never started POIT.[44] Lower baseline peanut-specific IgE and younger age at screening predicted remission.[22]

Milk Oral Immunotherapy

To date, milk OIT (MOIT) has only been studied in children to a typical target maintenance dose of 100 to 250 mL milk, and desensitization was achieved in 36% to 97%.[45–60] Low-dose (0.5–10 mL) milk with escalation to 150 to 200 mL has demonstrated high rates of desensitization (98%) when started in infants aged younger than 1 year,[54,61,62] and longer term lower dose MOIT can also increase tolerance threshold[63] and rates of desensitization[64,65] as well as induce SU.[66,67] Meta-analysis of 5 MOIT trials with 218 children showed that MOIT increased the likelihood of developing full tolerance to milk by 10-fold but also increased the risk of AR by 34-fold, with an RR of 5.8 for needing epinephrine.[68] Fewer studies have evaluated SU in MOIT, with rates varying from 25.6%[49] to 40%[57] and increasing with longer duration of MOIT.[49]

Roughly 70% of patient with cow's milk allergy may tolerate baked milk (BM), and tolerating BM may accelerate the resolution of cow's milk allergy.[69–72] Formalized introduction of baked milk OIT (BMOIT) can significantly increase tolerance threshold[73] and time to desensitization to unbaked milk compared with controls.[72–74] In addition, one study noted no difference in rates of desensitization or daily dose of cow's milk being consumed at end of study between those treated with BMOIT or MOIT, although there was a significant trend to increased adverse events in the BMOIT group.[59]

Egg Oral Immunotherapy

Egg OIT (EOIT) has been evaluated in children in several controlled[75–84] and uncontrolled studies[85–90] with rates of desensitization ranging from 36% to 94%[79,82,91–93] and increase in tolerance threshold by 2 to 10-fold,[81,94] likely dependent on age,[81]

protocol design,[83] maintenance dosing regimens,[84] and duration of therapy.[83,95] A Cochrane review performed in 2018 that included 10 RCTs with 439 children aged from 1 to 18 years showed EOIT increased tolerance threshold to egg and complete recovery from allergy compared with controls.[96] Those studies looking at SU show higher rates in those treated with EOIT compared with avoidance[75,78,88,96,97] and in those on longer duration of therapy.[78]

Tolerance of baked egg (BE) may occur before tolerance to unbaked egg,[98] and early BE introduction, even at low dose, can decrease the rate of unbaked egg allergy.[99] Baked egg OIT (BEOIT) can desensitize and increase tolerance threshold to unbaked egg in BE-intolerant children, although these effects may be dependent on dose and duration and have not been rigorously evaluated against a control population.[89,90,100,101] One study looking at low-dose BEOIT has demonstrated increased rates of desensitization and SU to unbaked egg compared with controls.[88] Only one study has compared outcomes in 55 children aged 3 to 16 years tolerant to BE who continue BE ingestion or completed a course of EOIT.[102] In this study, the EOIT group had better outcomes at the year 1 and 2 food challenges compared with the BE group ($P = .002$ and $P < .0001$, respectively) and significantly more of the EOIT group achieved 8 to 10 week SU compared with the BE group (43.5% vs 11.1%, $P = .009$).[102]

Wheat Oral Immunotherapy

Six small pilot studies[103–108] and one controlled trial[109] of wheat OIT (WOIT) in children reported 85% to 100% desensitization with a wide range of maintenance doses (400–70,000 mg) during 3 to 24 months, although these effects may be dependent on dose and duration.[109–111] Fewer studies have evaluated SU in WOIT,[109,111] with increasing rates of 2 week SU with increased duration of WOIT[111,112] even when low-dose (53 mg) WOIT is used.[111]

Sesame Oral Immunotherapy

One study with sesame OIT showed that 88.3% achieved full desensitization to 4000 mg sesame at end of dose escalation, and 100% of these individuals maintained 4000 mg desensitization even with maintenance dose reduction to 1200 mg for at least 6 months (compared with no controls).[113]

Tree Nut Oral Immunotherapy

One controlled study[114,115] and one retrospective[116] study evaluated tree nut OIT (TNOIT). These have shown that walnut, cashew, and hazelnut OIT can induce desensitization and increase tolerance thresholds,[114–116] with possible increase with longer duration of therapy.[116] Additionally, walnut and cashew OIT can desensitize to coallergic tree nuts.[114,115] After walnut-specific TNOIT, 100% pecan, 93% hazelnut, and 60% hazelnut or cashew coallergic individuals were desensitized to the coallergic nut(s).[115] Following cashew-specific TNOIT, 100% pistachio and 50% walnut coallergic patients were desensitized to their coallergic nut(s).[114]

Multifood Oral Immunotherapy

There has been one randomized trial evaluating the safety and efficacy of multifood OIT as a sole therapeutic intervention compared with single food OIT.[117] In this study, up to 5 food allergens could be used with dose escalation to 4000 mg protein of each allergen.[117] Time to reach 300, 1000, 4000 mg, and a 10-fold increase in threshold dose were significantly longer in the multifood OIT group compared with the single

food OIT group ($P \leq .005$).[117] Rates of reaction per dose did not differ significantly between the 2 groups ($P = .31$).[117]

Other Considerations

Modified food sources, adjuvants, and coadministration of other therapies to improve OIT outcomes have been evaluated. Extensively hydrolyzed MOIT and EOIT did not desensitize to intact protein,[77,118] although *partially* hydrolyzed milk and wheat OIT[119] did improve tolerance threshold. Peanut plus probiotic OIT subjects achieved desensitization, although there was no comparison with POIT alone.[120] A preclinical study in mice showed that nanoparticles containing peanut protected from anaphylaxis.[121]

Coadministration of etokimab (IL33 antagonist) and omalizumab (IgE antagonist) improved tolerance threshold in OIT patients,[122,123] and omalizumab has also decreased food reactions and improved safety in OIT.[123] There are 3 current studies underway to evaluate the effectiveness of omalizumab in multifood OIT, alone[124–126] and in combination with a Chinese herbal.[127] There are 3 planned studies looking at dupilumab (IL4/13 antagonist), the first to evaluate if its concomitant use increases the proportion of individuals on Palforzia OIT who pass a challenge at 4 months[128] and the second to evaluate if peanut-allergic individuals can achieve full tolerance without OIT.[129] A third study will evaluate whether omalizumab plus dupilumab will act synergistically to improve tolerance to 2 or more foods compared with omalizumab alone.[130]

SUMMARY

OIT is an alternative treatment of IgE-mediated FA that has been shown to increase tolerance threshold to many of the top food allergens, although this effect may be dependent on age, dose, frequency, and duration. OIT has been shown to be effective and safe in infants, and early initiation can improve rates of desensitization even for those foods whose natural history favors loss of allergy. Studies looking at protocol modification to improve OIT success are ongoing as is the evaluation of clinical tools to help monitor OIT effects.

CLINICS CARE POINTS

- IgE-mediated FA prevalence is increasing across the globe, with no known cure. Avoidance has been the historically sole treatment option.
- OIT is now an alternative treatment of IgE-mediated FA.
- OIT effects may be dependent on dose, duration, and frequency of dosing as well as patient-specific factors, such as age and food-specific IgE levels.
- There is only one FDA-approved OIT product (Palforzia, for peanut); otherwise, OIT occurs through use of commercially available food products.
- Multifood OIT protocols seem to be as safe as single-food protocols.
- Biological therapies may assist with tolerability of OIT protocols and further improve success rates.
- Studies to date looking at SU and remission suggest that OIT will need to be continued in some manner for most individuals for persistence of effects.
- Individuals who present with shortness of breath, wheezing, coughing, hives, nausea/vomiting, swelling, and loss of consciousness following food ingestion should be

evaluated for the potential of IgE-mediated FA. If diagnosed, they should also be counseled on the availability of OIT as a treatment option and referred to an allergist for comanagement.

- When a patient experiences systemic symptoms while undergoing OIT therapy, these symptoms should be treated as with any other accidental ingestion, including the use of epinephrine if warranted.
- If systemic symptoms are experienced during OIT, a detailed history is required to evaluate for modifiable cofactors that can influence OIT dose reactivity, such as concurrent illness, exercise/activities surrounding timing of dose, food ingestions, menstruation, and oral sores, among others.
- Onset of abdominal pain and nausea/vomiting after initiation of OIT should prompt the evaluation for OIT-adverse effects, such as eosinophilic esophagitis, which may necessitate cessation of OIT therapy.
- If OIT protocol deviations are encountered and doses are missed, patients are at risk of systemic reaction with reinitiation of dosing, and dosing should only be restarted under the guidance of an allergist experienced in OIT.

DISCLOSURE

The authors have nothing to disclose.

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