

# ORAL IMMUNOTHERAPY FOR FOOD ALLERGY

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## ABSTRACT

The IgE-mediated food allergy associated with risk for fatal anaphylaxis has been the subject of multiple immunotherapy studies in the past decade. The growing body of evidence suggests that for IgE-mediated food allergy immunomodulation through food immunotherapy is possible; however, the extent of protection provided by such treatment is highly variable. The capacity for food immunotherapy to restore permanent oral tolerance to food has not been demonstrated conclusively. In this review we discuss the most relevant studies of food oral immunotherapy.

Key words: food immunotherapy; food oral immunotherapy; food sublingual immunotherapy; oral tolerance, desensitisation

*This article has been peer reviewed.*

## INTRODUCTION

Food allergies affect an estimated 5% of adults and 8% of young children in countries with Western lifestyles and appear to be on the increase in developing countries.<sup>1–3</sup> Peanuts, tree nuts, cow's milk, eggs, soya beans, wheat and seafood are responsible for more than 90% of food allergies in children. In adults, peanuts, tree nuts and seafood are the primary food allergens causing anaphylaxis.<sup>4</sup> Whereas childhood food allergy to cow's milk, eggs, soya beans and wheat typically resolve with time, peanut, tree nut and seafood allergies tend to be life-long.<sup>5</sup> Peanuts in particular have garnered significant attention, as they are the leading trigger of food allergy fatalities;<sup>6,7</sup> and data indicate that peanut allergy has at least doubled in the past two decades.<sup>8,9</sup>

The current standard management of food allergy involves the avoidance of the food, prompt recognition and treatment of allergic reactions, and nutritional support.<sup>4,10,11,12</sup> No therapies have been proven to accelerate the development of oral tolerance or provide effective protection from accidental exposures.<sup>13</sup> However, novel allergen-specific and allergen non-specific approaches to food allergy therapy are being developed and studied.<sup>14</sup>

While various routes of immunotherapy are being explored, oral immunotherapy (OIT) has emerged as the most actively investigated novel therapy for food allergy.<sup>15</sup> A first case of successful egg OIT was reported in 1908.<sup>16</sup> The renewed interest in the OIT emerged in the 1990s, starting with small, uncontrolled studies in Europe that provided

a proof of concept for larger controlled clinical trials.<sup>17–34</sup> Whereas multiple studies have been published to date, the interpretation of the results is affected by significant heterogeneity in the design that hampers the ability to compare the results directly.<sup>35–38</sup>

## BAKED MILK AND EGG DIET AS AN ALTERNATIVE OIT

The introduction of extensively heated (baked) milk and egg into the diet of milk- and egg-allergic children induces immunologic changes comparable to OIT.<sup>39</sup> Children with transient egg and milk allergy produce IgE antibodies directed primarily against conformational epitopes that are destroyed with high temperature, enzymatic digestion or food processing.<sup>40,41</sup> Heated egg-white proteins undergo enhanced gastric digestion, and ovomucoid bound to grain matrices in baked products forms insoluble complexes, which decreases allergenicity.<sup>42,43</sup> Two large clinical trials have investigated tolerance to extensively heated (baked into wheat muffins and waffles) milk and egg in children.<sup>44,45</sup> In both studies, tolerance to baked milk and egg was determined in the majority (approximately 75%) of children during a physician-supervised oral food challenge. Additional studies have confirmed that baked milk and egg diets are tolerated by the majority of milk- and egg-allergic children.<sup>46–49</sup>

Compared to the children who continued strict dietary avoidance according to the current standard of care, children ingesting baked milk or egg developed tolerance to unheated milk and egg at an accelerated rate.<sup>50,51,52</sup>

These findings suggest that for the majority of milk- and egg-allergic children who can tolerate milk or egg in baked products, strict avoidance of baked products is unnecessary and may account for the delayed acquisition of tolerance to unheated milk or egg.<sup>53</sup> The results of these baked milk and egg trials have changed the paradigm of the current management of milk and egg allergy, allowing for a more personalised approach based on the reactivity to baked milk and egg.<sup>4,12,54–56</sup>

Initial assessment of the reactivity to baked milk and egg is usually done during a physician-supervised oral food challenge because a subset of children with a more severe allergy may react with anaphylaxis to the first introduction of baked milk or egg. However, if the child has already been ingesting baked products in the diet, it is appropriate to continue home introduction. Serologic and skin-prick test-based cut-off levels have been proposed for baked milk and egg, but these values require further validation before introduction into clinical practice.<sup>47,57–61</sup>

The baked egg and milk diets add complexity compared to strict allergen avoidance, but can improve patient lifestyle. Nutritional counselling is important to facilitate adherence to the guidelines for baked-food preparation at home and buying commercial baked-food products. The incorrect preparation of baked foods or purchase of foods that contain unbaked milk and egg may put patients at risk for acute allergic reactions.<sup>62,63</sup>

## OIT MECHANISM

OIT uses the pathways operative in oral tolerance, the default immune response in the gut to the ingested food protein antigens.<sup>21,64,65</sup> The aim of OIT is to first achieve desensitisation and then to re-establish permanent oral tolerance. Desensitisation is a state of temporary antigen hypo-responsiveness (increased threshold) that depends on the regular ingestion of the food. Dosing interruption may lead to the loss of the protective effect of desensitisation. So-called augmentation factors such as viral infection, exercise, use of NSAIDs or menstruation can trigger reactions to the previously tolerated maintenance dose.<sup>66,67</sup> The exact mechanism of desensitisation is not known; the associated immunologic changes include the decreased reactivity of mast cells (measured with skin-prick test reactivity) and basophils, increased food-specific serum and salivary IgG<sub>4</sub> and IgA antibodies and, initially, increased but eventually decreased serum food-specific IgE antibodies.<sup>68–70</sup> Similarly, the mechanism of permanent tolerance is not known, but may involve the development of regulatory T-cells followed by anergy and/or the deletion of food allergen-specific effector T-cells.<sup>21,70–73</sup>

Oral tolerance is defined as the ability to ingest the food without symptoms despite prolonged periods of avoidance or irregular intake. The permanence of protection is usually tested with the intentional interruption of OIT

dosing for at least 4–12 weeks followed by a ‘tolerance’ food challenge.<sup>28,74</sup> To date, no adequately controlled rigorous trials of OIT have demonstrated the development of permanent tolerance (or even long-term desensitisation) due to therapy as opposed to natural acquisition. Individualised up-dosing and maintenance dosing as well as the prolonged administration of egg OIT may be necessary to enhance sustained unresponsiveness for some subjects with egg allergy.<sup>29,75</sup> In a long-term study of peanut OIT, 24 subjects were treated up to five years with maintenance daily doses of 4 000 mg peanut protein.<sup>76</sup> Twelve (50%) of the 24 passed a peanut challenge to 5 000 mg of peanut protein one month after stopping OIT and were considered to have achieved sustained unresponsiveness and added unrestricted peanut to their diet. With a shorter duration of peanut OIT, after 24 months of daily dosing with 4 000 mg of peanut protein, 20 out of 23 (87%) treated subjects became desensitised, as determined by a peanut challenge.<sup>72</sup> However, after three months of strict peanut elimination, seven (30%) only passed the peanut challenge with 4 000 mg of peanut protein. Following an additional three months of peanut avoidance (a total of six months after discontinuation of peanut OIT), three of the seven subjects (3/23; 13%) remained tolerant to peanut during the final peanut challenge.

Therefore, it may be possible to improve rate of tolerance with a longer duration of OIT, comparable to the standard duration of subcutaneous immunotherapy (SCIT) for aeroallergens or venom (usually three to five years) and with higher maintenance dosing.<sup>77</sup>

## SELECTION OF PATIENTS FOR FOOD ORAL IMMUNOTHERAPY

OIT clinical trials have been conducted in healthy children and young adults. For safety reasons, most studies excluded subjects with a history of severe anaphylaxis and more than mild persistent asthma. For efficacy concerns, some studies required reactions to a relatively low threshold at the baseline food challenge to show the treatment effect, preselecting the subjects less likely to outgrow food allergy spontaneously but also less likely to respond to OIT. While it is always the case that food OIT may induce tolerance in those who would develop spontaneous tolerance, evidence shows that immunotherapy could still be beneficial and potentially might accelerate the process in this context.<sup>28,74</sup> More accurate diagnostic tests, including molecular allergy diagnostic tests, may facilitate the preselection of subjects with a favourable profile regarding response to OIT, as well as to help identify subjects who are not likely to outgrow the allergy spontaneously.<sup>13,75,78</sup>

## OIT DOSING SCHEDULE

During OIT, food is mixed with a vehicle and eaten in gradually increasing doses. Dose escalations occur in a controlled setting, usually every two weeks.<sup>13,38</sup> Most studies include an initial rapid dose escalation day that is

followed by further dose escalation in the clinic on a bi-weekly schedule until the maintenance dose is achieved. Daily ingestion of tolerated doses during the build-up and maintenance phases occurs at home. The need for daily dosing may affect long-term adherence as well as incidental dosing interruptions due to illness or travel. Therefore, less frequent intervals for maintenance dosing in OIT are attractive. A small clinical trial of milk OIT suggested that twice-weekly maintenance dosing is as safe and efficacious as daily maintenance dosing.<sup>79</sup> If these findings are confirmed by large clinical trials and with different foods, twice-weekly maintenance dosing will represent a practical approach to long-term food OIT.

### FOOD ORAL IMMUNOTHERAPY SUCCESS RATES

Figure 1 presents the different phases of OIT as well as the general trends of immunologic change seen in OIT. It is unclear which factors determine a response to OIT. It is possible that desensitisation failure is associated with the most severe food allergy phenotype, as opposed to desensitisation success that may be associated with a milder, transient phenotype and higher chances of spontaneous resolution of food allergy.<sup>13,76</sup> This is particularly important in milk and egg allergy that have a high likelihood of spontaneous resolution.<sup>28,74</sup> In general, lower pre-treatment serum levels of specific egg and peanut IgE antibodies are associated with better response rates and enhanced sustained unresponsiveness.<sup>76,80</sup>

### OIT SAFETY

OIT is associated with acute adverse allergic reactions in virtually all patients, which are more common during dose escalation than during maintenance (see Table I).<sup>66,67,81,82</sup> Most of the adverse reactions are mild and limited to the oropharynx. However, systemic reactions are seen and may occur at previously tolerated doses in the presence of augmentation factors, even during the maintenance phase.<sup>66</sup> Outside of acute allergic reactions, many patients complain of chronic gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhoea) that may lead to discontinuation of OIT.<sup>23,25,26</sup> Gastrointestinal side-effects affect a majority of patients, and those undergoing OIT may be at higher risk (estimated at up to 2%) for developing eosinophilic esophagitis than the general allergic population.<sup>25,83–86</sup> Compared to sublingual and epicutaneous immunotherapy, OIT is associated with higher rates of systemic adverse events but also with higher efficacy.<sup>87–89</sup>

### DISCONTINUATION OF OIT

The discontinuation (drop-out) rates from OIT trials range between 10% and 20%.<sup>20,71</sup> About 5–10% discontinue due to failure to progress to the minimum tolerated dose during the initial rapid dose escalation day, and subsequent discontinuations can be related to adverse reactions, such as gastrointestinal symptoms.

**Figure: 1 OIT time course and immunologic changes**

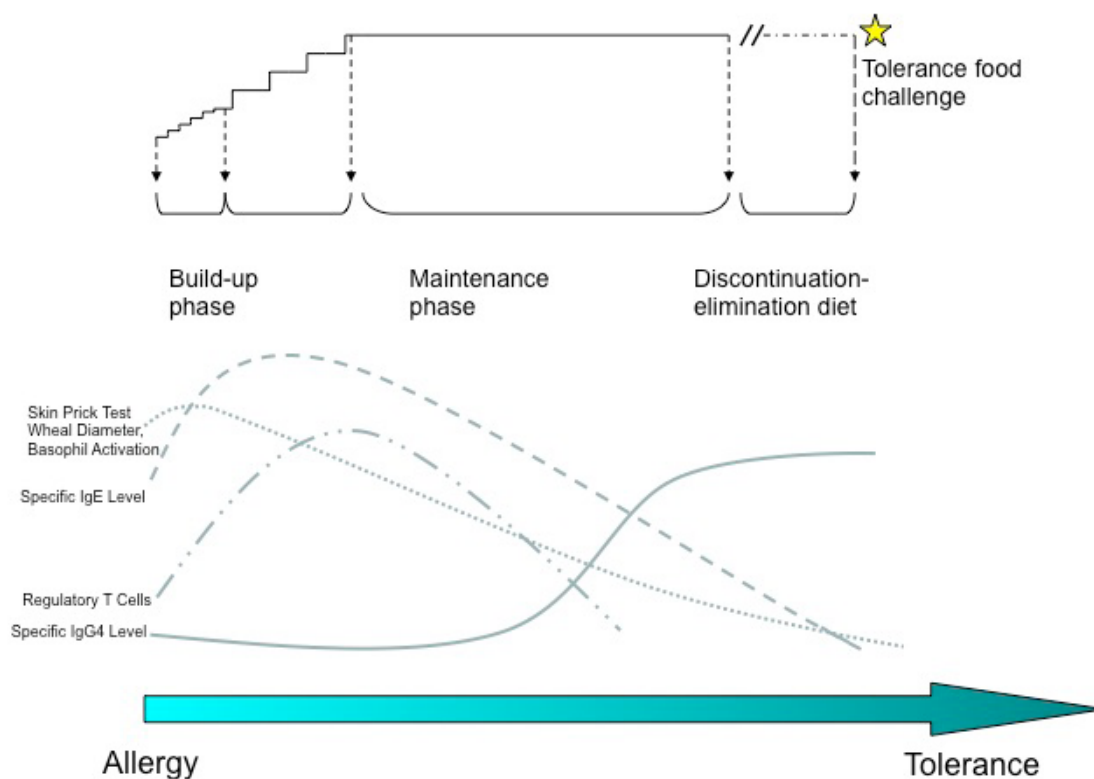


TABLE I: ADVERSE REACTIONS REPORTED FROM SELECTED CLINICAL TRIALS OF FOOD OIT

| Author (year)                     | Patients in the active arm | Age                     | Food   | Duration | % doses associated with AE in the active group                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                  |
|-----------------------------------|----------------------------|-------------------------|--------|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Longo (2008), Italy               | 30                         | 7–15 years              | Milk   | 1 year   | Rush escalation<br>Mouth/lip/tongue pruritus or swelling: 100%;<br>Abdominal pain: 75%;<br>Erythema/urticaria: 48%;<br>Mild asthma: 35%;<br>Epinephrine used in four patients                                                                                                                                                                             | Maintenance (at home):<br>Emergency department admission and epinephrine treatment: two patients; no details on other AEs                                                                                                                        |
| Jones (2009), United States       | 29                         | 57.5 months (12–111 mo) | Peanut | 3 years  | Initial dose escalation<br>Any symptoms: 92%;<br>Mild sneezing/itching/ laryngeal symptoms: 69%;<br>Mild/moderate nausea or abdominal pain: 44%;<br>Mild diarrhoea/emesis: 21%<br>Needing epinephrine: four patients (10%)                                                                                                                                | Build up phase and maintenance phase<br>Any symptoms: 46%;<br>Upper respiratory: 1.2%<br>Skin: 1.1%<br>Treatment with epinephrine after home dosing: two subjects, each had one episode                                                          |
| Blumchen (2010), Germany          | 23                         | 3.2–14.3 years          | Peanut | 9 weeks  | Initial dose escalation<br>Any symptoms: 7.9%;<br>Gastrointestinal: 3.5%;<br>Skin: 3.2%;<br>Respiratory: 2.8%;<br>Upper respiratory: 1.6%<br>No treatment with epinephrine                                                                                                                                                                                | Build-up phase and maintenance phase<br>Any symptoms: 2.6%;<br>Gastrointestinal: 0.9%;<br>Skin: 0.4%;<br>Respiratory: 1.3%<br>Upper respiratory: 0.2%;<br>No treatment with epinephrine; four subjects were discontinued due to asthma worsening |
| Anagnostou (2014), United Kingdom | 49                         | 7–16 years              | Peanut | 6 months | The entire course of OIT<br>Oral pruritus: 6.3%;<br>Abdominal pain: 2.6%;<br>Nausea: 2.2%;<br>Vomiting: 0.75%;<br>Diarrhoea: 0.03%;<br>Urticaria: 0.16%;<br>Angioedema: 0.4%;<br>Erythema: 0.23%;<br>Rhinitis: 0.37%;<br>Wheezing: 0.41%;<br>Laryngeal oedema: 0.01%;<br>Use of inhaled bronchodilator: 0.35%;<br>Use of intramuscular epinephrine: 0.01% |                                                                                                                                                                                                                                                  |

## OIT AND QUALITY OF LIFE

Results from uncontrolled studies suggest that OIT may improve some aspects of life quality such as dietary and social limitations, risk of accidental exposure, and anxiety.<sup>90,91,92</sup> The true impact of OIT on quality of life remains to be determined.

## SELECTED CLINICAL TRIALS OF FOOD OIT

Although numerous studies of food OIT have been conducted to date, only a few adhered to a rigorous design, as recently critically reviewed by meta-analyses.<sup>36,37,39,93</sup> There is tremendous heterogeneity regarding study design, inclusion criteria, dosing schedule, duration of therapy and the approach to evaluating the persistence of the protection following discontinuation of OIT. Table II summarises selected clinical trials of food OIT.

### ORAL IMMUNOTHERAPY COMBINED WITH ANTI-IGE MONOCLONAL ANTIBODY

Anti-IgE monoclonal antibody is a non-allergen-specific

treatment that has been successfully tested as a monotherapy for peanut allergy. In one study, subjects treated with the highest dose of anti-IgE showed an increased dose threshold response for peanut after four months.<sup>94</sup> Pre-treatment with anti-IgE monoclonal antibody has been shown to be effective and the improved safety of food OIT likely by lowering circulating IgE and down-regulating expression of the IgE receptor on antigen presenting cells. Two small pilot studies of milk and peanut OIT combined with omalizumab reported a markedly increased safety of OIT.<sup>22,95</sup> These results have been confirmed by a large, double-blind, placebo-controlled trial with subjects randomised to omalizumab or placebo.<sup>96</sup> Open-label milk OIT was initiated after four months of omalizumab/placebo with escalation to maintenance over 22–40 weeks, followed by daily maintenance dosing through to month 28. At month 28, omalizumab was discontinued, and subjects passing an oral food challenge (OFC) continued OIT for 8 weeks, after which OIT was discontinued with a re-challenge at month 32 to assess

sustained unresponsiveness.

Fifty-seven subjects (7–32 years) were randomised, with no significant baseline differences in age, milk-specific IgE levels, skin-test results, or OFC results. At month 28, 24 (88.9%) omalizumab-treated subjects and 20 (71.4%) placebo-treated subjects passed the 10 g 'desensitisation' OFC ( $p = 0.18$ ). At month 32, sustained unresponsiveness

was demonstrated in 48.1% in the omalizumab group and 35.7% in the placebo group ( $p = 0.42$ ). Adverse reactions were markedly reduced during OIT escalation in omalizumab-treated subjects for percentages of doses per subject, provoking symptoms (2.1% vs 16.1%,  $p = 0.0005$ ), dose-related reactions requiring treatment (0.0% vs 3.8%,  $p = 0.0008$ ) and doses required to achieve maintenance (198 vs 225,  $p = 0.008$ ). In this first randomised, double-blind,

**TABLE II: SELECTED CLINICAL TRAITS IN FOOD ORAL IMMUNOTHERAPY**

| STUDY/SUBJECTS                                                                                                                                                                                                                                                                                                                            | SUCCESS RATE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | IMMUNOLOGIC CHANGES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | SIDE-EFFECTS/COMMENTS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| <b>PEANUT OIT</b>                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Blumchen, 2010 <sup>20</sup><br>n = 23; age 3–14 years<br>Subjects underwent a rush protocol for 1 week and then received OIT for 8 weeks.<br><br>Goal maintenance dose: 500 mg peanut protein daily.                                                                                                                                     | Twenty-two out of 23 (96%) subjects finished the initial rush protocol, but 17 of these subjects did not achieve the goal dose of 500 mg of peanut with rush therapy (they continued on individualised long-term build-up protocols to reach 500 mg).<br><br>Only 14 subjects out of 22 (64%) reached a maintenance dose of at least 500 mg of peanut and completed OIT.<br><br>The median tolerated dose after completion of OIT was 1 g of peanut.                                                                                                                                         | After OIT, all subjects had reductions in IL-5, IL-4, and IL-2 ( $P < 0.001$ ). After discontinuing OIT for 2 weeks, peanut-induced IL-5, IL-4 and IL-2 secretion were stable in most of the subjects.<br><br>After OIT, there was a small reduction of peanut SPT wheal diameter ( $P < 0.05$ ). After discontinuing OIT for 2 weeks, this reduction was no longer evident.<br><br>After OIT, peanut-specific IgG4 levels increased ( $P < 0.001$ ). After discontinuing OIT for 2 weeks, there was a small decrease in specific IgG4 levels ( $P < 0.001$ ).<br><br>Peanut-specific IgE levels as well as total IgE levels did not change with OIT. | The dropout rate of this study was 35% (8 out of 23 subjects). In 4 subjects, OIT was discontinued by the study physician because of adverse allergic reactions. Two subjects dropped out because of compliance, 1 because of a severe infection and 1 was a partial responder who did not qualify for the final challenge.<br><br>Adverse reactions were frequent, particularly during the rush protocol. Of 317 total doses of OIT during the rush protocol, 25 doses (7.9%) were associated with objective symptoms. Of 637 doses of OIT during the long-term build-up protocol, 160 doses (2.6%) were associated with objective symptoms. |
| Varshney, 2011 <sup>71</sup><br>n = 28; age 1–16 years<br>Subjects were randomised 19:9 to OIT or placebo for 48 weeks.<br><br>Goal maintenance dose: 4 000 mg peanut protein daily.                                                                                                                                                      | During the initial day of rapid dose escalation, 26 out of 28 (93%) subjects reached the maximum cumulative dose of 12 mg of peanut protein or placebo.<br><br>Sixteen subjects received the full course of peanut OIT and all tolerated 5 g of peanut protein following OIT.                                                                                                                                                                                                                                                                                                                | Compared to placebo, peanut OIT group showed reductions in SPT size ( $P < 0.001$ ), IL-5 ( $P = 0.01$ ), and IL-13 ( $P = 0.02$ ), and increases in peanut-specific IgG4 ( $P < 0.001$ ). The ratio of forkhead box protein 3 (FoxP3) (high): FoxP3(intermediate) CD4+ CD25+ T cells increased at the time of OFC ( $P = 0.04$ ) in peanut OIT subjects.                                                                                                                                                                                                                                                                                             | Adverse reactions were common, but most reactions were mild. In the active arm, 9 out of 19 subjects (47%) experienced adverse reactions during the initial day escalation. During the build-up phase, adverse reactions occurred following 1.2% of 407 build-up doses. None of the placebo subjects required treatment during initial day escalation or build-up dosing; however, 3 (33%) were treated with epinephrine during the final peanut DBPCFC.                                                                                                                                                                                      |
| Vickery 2013 <sup>71</sup><br>n = 24; age 1–16 years<br>Subjects were treated for up to 5 years with peanut OIT, and then stopped treatment for 1 month to test for sustained unresponsiveness.<br><br>Goal maintenance dose: The protocol was modified over time to permit dose increases to a maximum of 4 000 mg peanut protein daily. | Of the 39 subjects originally enrolled, 24 (62%) completed the protocol and had evaluable outcomes.<br><br>All subjects completing the study successfully ingested 5 000 mg of peanut protein without symptoms during a desensitisation challenge.<br><br>Only 12 out of 24 (50%) successfully ingested 5 000 mg of peanut protein 1 month after stopping OIT and achieved sustained unresponsiveness.<br><br>Of those who failed the 5 000 mg challenge, the median amount of peanut protein ingested cumulatively before the development of symptoms was 3 750 mg (range, 1 500–5 000 mg). | In those who achieved sustained unresponsiveness, subjects had smaller skin test results, lower IgE levels specific for peanut, Ara h 1, and Ara h 2, and lower ratios of peanut-specific IgE/total IgE compared to those who did not achieve sustained unresponsiveness.<br><br>There were no differences in peanut IgG4 levels or forkhead box protein 3 CD4+ CD25+ T cells between these groups.                                                                                                                                                                                                                                                   | This study is the first to demonstrate sustained unresponsiveness after peanut OIT.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| STUDY/SUBJECTS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | SUCCESS RATE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | IMMUNOLOGIC CHANGES                                                                                                                                                                                                                                                                                                                                                      | SIDE-EFFECTS/COMMENTS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| <p>Anagnostou, 2014<sup>18</sup><br/>n = 99; age 7–16 years<br/>Phase 1: Subjects were randomised 1:1 to OIT or control (standard of care food avoidance) for 26 weeks.<br/>Phase 2: Cross over from the control group into OIT for 26 weeks.</p> <p>Goal maintenance dose: 800 mg peanut protein daily.</p>                                                                                                                                                                                                                | <p>84% of subjects receiving OIT were able to ingest 800 mg of daily peanut for 26 weeks in the first phase, and 91% of subjects from the cross over control group were able to ingest 800 mg of daily peanut for 26 weeks during the second phase.</p> <p>Twenty-four of 39 subjects (62%) receiving OIT tolerated 1 400 mg of peanut at the end of the first phase of the study, as compared to 0 of 46 control subjects (P &lt; 0.001).</p>                                                                                                                                                                                                                                                    | <p>After OIT, there was a small reduction in peanut SPT wheal diameter.</p> <p>After 24 weeks of OIT there was an increase in peanut-specific IgE.</p> <p>No significant within-patient differences were identified after treatment for basophil activation (although there was a reduction in MFI and proportion of CD63 at lower peanut concentrations after OIT).</p> | <p>During the first phase of the study, one subject discontinued and 5 withdrew from the OIT arm. Four subjects could not achieve target maintenance dose at 6 months in the OIT arm. In the control group, 4 subjects withdrew and one discontinued.</p> <p>The number and nature of adverse events was similar in both groups after treatment, and most events were mild. The most common adverse event was oral itching, which occurred after 6.3% of all doses.</p>                                                                                                                                                                                                                   |
| EGG OIT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <p>Burks, 2012<sup>17</sup><br/>n = 55; age 5–11 years<br/>Subjects were part of a multicentre double-blind placebo controlled clinical trial.</p> <p>Goal maintenance dose: 2 000 mg egg white powder daily.</p>                                                                                                                                                                                                                                                                                                           | <p>At the 10-month challenge, 22 of 40 subjects (55%) receiving OIT tolerated 5 g of egg-white powder, and 0 of 15 subjects of the placebo group passed (P &lt; 0.001).</p> <p>At the 22 month challenge, 30 of 40 subjects (75%) receiving OIT tolerated 10 g of egg-white powder (were considered desensitised). At the 24 month challenge (6–8 weeks off OIT), 11 of 29 subjects (28%) tolerated 10 g of egg-white powder plus whole egg (were considered to have sustained unresponsiveness). According to the intention-to-treat analysis, 11 of the 40 subjects (28%) in the oral-immunotherapy group passed the oral food challenge at 24 months (P = 0.03, as compared with placebo).</p> | <p>Compared to subjects who received placebo, those who received OIT had a decreased wheal size on SPT, reduced egg-induced basophil activation, and increased egg-specific IgG4 antibody levels over time, whereas no change in egg-specific IgE antibody levels was noted.</p>                                                                                         | <p>All 55 subjects completed the initial-day dose escalation, but 7 subjects withdrew before the maintenance phase (5 in the OIT group and 2 in the placebo group).</p> <p>There were no severe adverse events, and rates of adverse events were highest during the first 10 months of OIT. Adverse events were associated with 25 % of 11 860 doses of OIT and 3.9% of 4 018 doses of placebo.</p> <p>The results of this clinical trial raise concerns about the long term protection (sustained unresponsiveness) afforded by OIT. It remains to be determined whether a higher maintenance dose and longer duration of OIT might improve the rates of sustained unresponsiveness.</p> |
| MILK OIT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <p>Staden, 2007<sup>28</sup><br/>n = 45; age &lt;1–12 years<br/>Subjects were randomised to OIT or elimination diet. Oral tolerance for all subjects was evaluated after a median 21 months (range 11–59 months).</p> <p>Goal maintenance dose: Doses were increased (according to individual tolerance) to a maximum dose of 8 250 mg cow's milk protein or 2 800 mg hen's egg protein. The maintenance phase mandated a minimum daily maintenance dose of 3 300 mg cow's milk protein and 1 600 mg hen's egg protein.</p> | <p>Twenty-five subjects were randomised into milk or egg OIT, and 14 underwent milk OIT. 20 subjects were randomised into an elimination diet, 10 of which were avoiding milk.</p> <p>In the OIT group, 16 of 25 subjects (64%) were able to integrate the food allergen into their diet. Nine of 25 subjects (36%) showed sustained tolerance after a secondary elimination diet, 3 of 25 (12%) showed tolerance with regular intake, and 4 of 25 (16%) were partial responders who never met planned full maintenance dose. In contrast, only 7 of 20 subjects (35%) showed tolerance (P = 0.05).</p>                                                                                           | <p>Allergen-specific IgE levels decreased.</p> <p>Significantly, both in subjects who developed natural tolerance during the elimination diet (P &lt; 0.05) and in those treated with OIT (P &lt; 0.001).</p>                                                                                                                                                            | <p>All subjects in the OIT group had adverse events to some extent; 21 had mild symptoms and 4 had moderate symptoms. In the control group, 5 subjects had mild to moderate adverse events due to inadvertent ingestion of food allergens.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                            |

| STUDY/SUBJECTS                                                                                                                                                                                                                                                                          | SUCCESS RATE                                                                                                                                                                                                                                                                                                                                                                           | IMMUNOLOGIC CHANGES                                                                                                                                                                                                                                             | SIDE-EFFECTS/COMMENTS                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| Skripak, 2008 <sup>26</sup><br>n = 20; age 6–17 years<br>Subjects were randomised 2:1 to OIT or placebo for 13 weeks.<br><br>Goal maintenance dose: 500 mg cow's milk protein daily.                                                                                                    | Nineteen subjects completed treatment (12 receiving OIT and 7 receiving placebo). After OIT, the median cumulative dose of milk inducing a reaction in the active group increased from 40 mg to 5 140 mg, but there was no change in the placebo group (P = 0.0003).                                                                                                                   | Milk-specific IgE levels did not change in either group. Milk IgG levels increased significantly in the OIT group, with a predominant milk-IgG <sub>4</sub> increase.<br><br>End-point titration milk SPT wheal decreased over time (P = 0.0091 from baseline). | Among 2 437 active OIT doses, there were 1 107 reactions (45.4%). Among 1 193 placebo doses, there were 134 reactions (11.2%). Local symptoms were most common.                                                                                                                                                                                                                                                                                  |
| Narisety, 2009 <sup>25</sup><br>n = 15; age 6–16 years<br>Open label follow up to Skripak study, which occurred over 13–75 weeks (median 17 weeks).<br><br>Fourteen subjects were able to escalate daily doses, with maximum doses ranging from 1 000 to 16 000 mg (median, 7 000 mg).  | After 13–75 weeks of open label dosing, challenges were conducted on 13 subjects. Six tolerated 16 000 mg with no reaction, and 7 reacted at 3 000 to 16 000 mg.                                                                                                                                                                                                                       | Milk-specific IgE levels decreased and IgG <sub>4</sub> levels increased in over the follow up period from 3 to 17 months.                                                                                                                                      | Challenges were not performed in 2 subjects because of ongoing reactions with home dose escalations. Adverse reactions were common and unpredictable, but overall rates of reaction decreased over time. In the 2 465 home doses recorded, there were 419 local reactions (17% of doses). Epinephrine was required for 6 (0.2%) of doses in 4 subjects.<br><br>Of note, one subject developed symptoms consistent with eosinophilic esophagitis. |
| Pajno, 2013 <sup>79</sup><br>n = 32; age 4–13 years<br>Subjects who were successfully desensitised with oral immunotherapy were randomised to two maintenance regimens for 1 year: Group A had to ingest 150–200 ml milk daily, and Group B had to ingest 150–200 ml milk twice weekly. | Twenty-nine subjects completed the 12 month study, 15 randomised to daily milk and 14 randomised to twice weekly milk.<br><br>No subjects permanently discontinued their maintenance diet based on adverse events.                                                                                                                                                                     | There were no significant differences in milk-specific IgE, IgG <sub>4</sub> , and SPT reactivity between Group A and B.                                                                                                                                        | Three subjects and their families withdrew during maintenance because of personal problems, not related to the study procedures.<br><br>Adverse events included asthma, oral itching, urticaria, rhinitis and abdominal pain, usually associated with concomitant illness or exercise. There were 8 events in Group A, and 9 events in Group B (no difference between the groups, P = 0.08).                                                     |
| MULTIPLE FOOD OIT                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Begin, 2014 <sup>97</sup><br>n = 40; age 4–46 years<br>Pilot phase I study for multi-food OIT (15 subjects on peanut OIT, 25 subjects on multi-food OIT).<br><br>Goal maintenance dose: 4 000 mg of food protein per allergen daily.                                                    | Rates of reaction per dose did not differ significantly between the two groups (median of 3.3% and 3.7% in multi and single OIT group, respectively; P = 0.31). In both groups, most reactions were mild but two severe reactions requiring epinephrine occurred in each group. Those on multiple food OIT took longer to reach equivalent doses per food (median +4 mo.; P < 0.0001). | In the multi-food group, there was an increase in peanut-specific IgG4 similar to the monotherapy group. Peanut-specific IgE levels were stable after one year.                                                                                                 | This was a proof of concept phase I safety study, and the primary endpoint of the study was occurrence of allergic reactions.<br><br>Over the study period, there were 5 dropouts for reasons which included non-compliance with study medication and change of residence. One subject in the multi-OIT group was unable to increase doses due to eczema flares and was categorised a treatment failure.                                         |

Abbreviations: OIT, oral immunotherapy; SPT, skin-prick test; OFC, oral food challenge.

placebo-controlled trial of omalizumab in combination with food OIT, significant improvements in safety were evident but not in efficacy (desensitisation and sustained unresponsiveness). The optimal duration of co-treatment with omalizumab and OIT needs to be established due to the concerns about the high cost of anti-IgE treatment.

#### OIT WITH MULTIPLE FOODS

A safety trial of a multi-food OIT was conducted in parallel to peanut OIT in subjects with peanut allergy.<sup>97</sup> Forty subjects reacted at the baseline DBPCFC to a maximum cumulative dose of 182 mg of peanut protein; of those, 25 had additional food allergies (eg walnut, cashew, pecan, almond, hazelnut, cow's milk, egg and sesame). OIT with

two foods was done in 24% of the participants, three foods in 32%, four foods in 20% and five foods in 24%. The protocol had three phases: the initial dose escalation day, home dosing with up-dosing every two weeks, and the maintenance phase. The daily maintenance dose was 4 000 mg protein of each allergen, with up to 20 000 mg as a cumulative dose for five-food OIT. Rates of reaction per OIT dose were (median) 3.3% in multi-food OIT and 3.7% in the single OIT group. Most reactions were mild, but two severe reactions requiring epinephrine occurred in each group.

Pre-treatment with omalizumab may also be applicable to multiple-food OIT.<sup>98</sup> In a pilot study, 25 participants, median

age seven years, had failed an initial double-blind placebo-controlled food challenge at a protein dose of 100 mg or less to each food included in OIT. After 16 weeks of pre-treatment with omalizumab, 19 participants tolerated all six steps of the initial escalation day (up to 1 250 mg of combined food proteins), requiring minimal or no rescue therapy. The remaining six were started on their highest tolerated dose as their initial daily home doses. The participants reported 401 reactions per 7 530 home doses (5.3%) with a median of 3.2 reactions per 100 doses. Ninety-four per cent (94%) of reactions were mild; one reaction was severe. The maintenance dose of 4 000 mg protein per allergen was reached at a median of 18 weeks. These results suggest that multi-food OIT combined with omalizumab pre-treatment may be a practical and safe option for patients with multiple-food allergy, pending validation by large and rigorous clinical trials.

### ORAL IMMUNOTHERAPY – RECOMMENDATIONS FOR CLINICAL PRACTICE

The studies of food OIT give hope that an effective interventional treatment for food allergy is within reach. Preliminary data suggest a beneficial treatment effect; however, there cannot be a definitive statement yet regarding efficacy as no study has carried both a treatment and a placebo arm to identical end points. In most published studies to date, the placebo group has been treated differently from the active group (ie followed over time, but not systematically challenged). In addition, significant adverse reactions to OIT are common. Meta-analyses on immunotherapy for milk, egg and peanut allergy pointed out significant limitations of the published studies.<sup>35-37,99</sup> The most recent analyses included all randomised controlled, quasi-randomised controlled, and case-controlled trials of peanut and milk OIT published from 1990 through to January 2012.<sup>37,99</sup> In the meta-analysis of peanut OIT papers, one study only out of 746 fulfilled the Cochrane inclusion criteria.<sup>71</sup> Authors of the *Cochrane Report* concluded that, based on the findings of one small trial, peanut OIT cannot be recommended as a routine treatment for patients with peanut allergy. In the meta-analysis of milk OIT papers, slightly less rigorous criteria were used and 16 records representing five clinical trials were reviewed.<sup>99</sup> The authors concluded that the quality of these trials was low; because no standardised protocols

were used, milk OIT could not be recommended as a routine treatment for patients with milk allergy. However, it is clear that some allergists provide oral immunotherapy for different foods in their practices.<sup>82</sup> Nevertheless, at this time, expert consensus and formal guidelines recommend that food OIT should remain limited to the research setting until properly evaluated for its long-term efficacy, safety and cost-effectiveness.<sup>4,10,12,13,83,84</sup>

### CONCLUSIONS

In the past two decades, food allergy has emerged as an important public health issue on a global scale. The current management of food allergy is restricted to dietary avoidance and no treatment reliably restores permanent oral tolerance to food.<sup>4</sup> Diets containing extensively heated (baked) milk and egg may represent a safer approach to oral immunomodulation applicable to the majority of children with milder phenotype of milk and egg allergy.<sup>57</sup>

OIT alone or in combination with anti-IgE antibody is likely to advance into clinical practice in the more immediate future. However, OIT protocols require further validation in large clinical trials before their incorporation into clinical practice. There is a need to harmonise the protocols for the clinical trials for food immunotherapy to maximise the data quality and allow for better comparison of the outcomes from different studies.<sup>38</sup> OIT with multiple foods, OIT with cross-reactive foods and OIT starting at younger ages (e.g. infants with peanut allergy) are potential future options. In addition to OIT, sublingual and epicutaneous immunotherapy are being evaluated in clinical trials. Modified hypoallergenic peanut molecules are being evaluated regarding their feasibility for clinical trials.<sup>100</sup> Nanoparticles targeting dendritic cells to induce T regulatory cells and to provide slow release of the antigen, as well as oligomannose-coated liposomes (OML) that induce MHC class I-restricted CD8+ T-cell responses, show promise in mouse models of food allergy.<sup>101,102</sup> Immunotherapy with specific peptides represents yet another approach to food antigen-specific immunomodulation.<sup>103,104</sup> These advances in the field of novel therapies for food allergy bring hope for allergy patients that effective therapy is within reach.

### DECLARATION OF CONFLICT OF INTERESTS

The authors have no conflicts of interests to declare.

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